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Aminoacids as the Amine Component in the Mannich Reaction

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The review is devoted to the aminomethylation of the CH-, NH-, and the PH-acid residues by aminoacids. Data are presented on the biological activities of certain Mannich bases derived from aminoacids.
The bibliography includes 132 references.

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I. INTRODUCTION

Mannich aminomethylation consists in the compensation of the substrate R–H containing at least one active hydrogen atom (alkyl ketones, phenols, various heterocycles, etc.) with formaldehyde (more rarely with other aldehydes) and primary or secondary amines (or ammonia):

$$R{-}H + CH_2O + HN\langle \rightarrow R{-}CH_2{-}N\langle \quad .$$

The great flexibility in the choice of reagents, the wide variety of possibilities for other reactions of the Mannich bases, and mild conditions have made the Mannich reaction one of the important methods of modern organic chemistry.

There is an extensive literature on studies of the Mannich reaction, in particular fundamental reviews and monographs[1-7]. However, aminomethylation by aminoacids as a special case of this comprehensively investigated reaction has so far been inadequately dealt with in the literature.

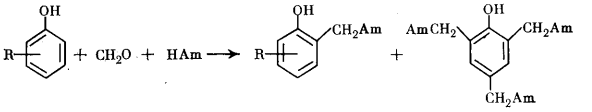
It is known that Mannich bases have a wide spectrum of biological activity[8]. Many of them have found applications in medicine. Thus the hydrochlorides of 4-(n-propoxy)- and 4-(n-butoxy)-β-piperidinopropiophenones (falicaine and dyclonine) are used as local anesthetics[9-11] and the hydrochloride of 4,α-dimethyl-β-piperidinopropiophenone (mydocalm) serves as an anticonvulsant[12]. Certain aminomethyl derivatives of tetracycline (morphocycline, glycocycline, lymecycline) are used in medical practice together with other tetracyclines[13,14]. Antibacterial activity has been observed also in many other Mannich bases[15-19].

The results of studies during the last 10–15 years indicate anti-inflammatory and pyretic[20,21], spasmolytic[22], adrenolytic[23], H-cholinolytic[12,23-25], and analgesic[26-28] properties of aminomethyl derivatives of ketones, phenols, and various heterocycles. Certain coumarin derivatives stimulate the activity of the respiratory and nervous systems[29]. On the other hand, aminoacids, being an inseparable component of the living organism, have become recently the subject of profound investigation from the standpoint of biological properties. Among synthetic derivatives of aminoacids, anti-inflammatory, antipyretic[30-38], antiviral and antibacterial[32,34,39-46], hypotensive[47-53], anti-tumour[32,36,38,46,54-57], and analgesic[33] substances as well as substances acting on the surface nervous system[34,58,59] have been found. As a consequence of this, the biological properties of Mannich bases obtained when the amino-residue is replaced by an aminoacid residue are of special interest.

The aim of the present review is to survey the available literature data on the aminomethylation of various organic compounds by aminoacids in particular CH-, NH-, and PH-acid residues as well as the data on the biological activity of certain Mannich bases derived from aminoacids.

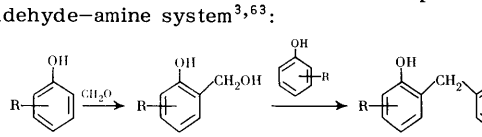
II. AMINOMETHYLATION OF CH-ACID RESIDUES

The first communications on aminomethylation by aminoacids refer to phenols[60,61].† When phenols were condensed with formaldehyde and aminoacids, both the usual aminomethyl derivatives of phenols (I, a and b) and polymeric compounds with benzene rings linked by methylene groups were obtained[60]:

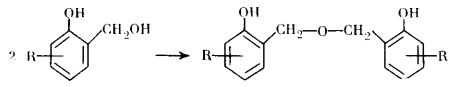


Am = Gly, Ala, Leu, and other aminoacids.

Bearing in mind that phenols are capable of condensing with formaldehyde, apart from the Mannich reaction it is necessary to consider a further two possible pathways [reactions (1) and (2)] in the three-component phenol–formaldehyde–amine system[3,63]:



(1)

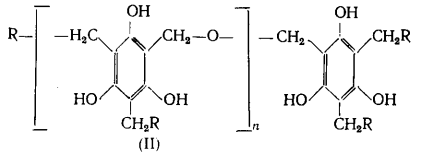


(2)

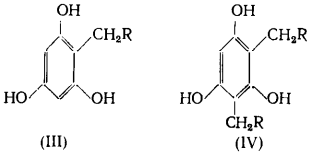
† The Mannich reaction between phenol, iminodiacetic acid, and formaldehyde has also been investigated[62].

Scheme (1) explains the formation of polymeric compounds described in a patent[60].

Later a reaction between aminoacids[64] (particularly glycine), polyhydric phenols, and formaldehydes was investigated#. It has been shown on the basis of ultraviolet and infrared spectroscopic data that the most probable structure of the condensation product is (II):



(II)



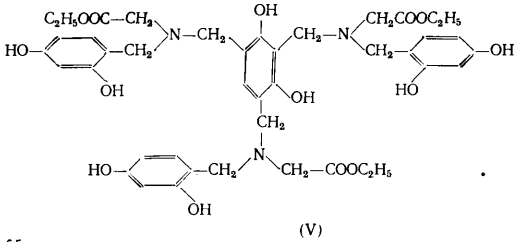
(III) (IV)

R=NHCH$_2$COOH

Structure (II) corresponds to the condensation product of phloroglucinol, glycine, and formaldehyde taken in proportions of 1:2:6. The possibility of the formation of products (III) and (IV) has also been demonstrated.

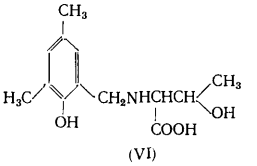
Apart from glycine, other aminoacids as well as di- and tri-peptides have also condensed with phloroglucinol. Thus, according to Gringras and Sjostedt[64], glycine and lycine react with phloroglucinol and formaldehyde to the extent of 90%, the degree of reaction of aspartic acid is 70%, while alanine and leucine react to the extent of 50%.

Data have been published[61] on the aminomethylation of resorcinol by both amines and aminoacid derivatives. In contrast to piperidine and morpholine which led to trisaminomethyl derivatives of type (Ib), ethyl glycinate reacts with resorcinol and formaldehyde to form a product with the tentative structure (V):



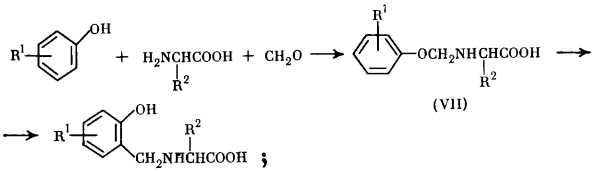
(V)

Blass[65] reported the synthesis of the Mannich base (VI)—a derivative of threonine and 2,4-dimethylphenol (yield 67%):



(VI)

As expected, substitution takes place at the *o*-carbon atom of the benzene ring. It has been suggested[66-68] that the aminomethylation takes place initially at the phenolic hydroxyl with formation of the product (VII), which subsequently, on heating to 80–100 °C or under the influence of inorganic acids at 50–60 °C, isomerises to the *C*-aminomethyl derivative (VIII):



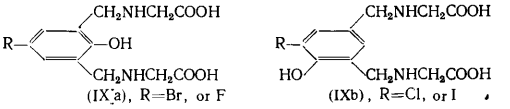
(VII)

(VIII).

R^2=H; R^1= *p*-Cl, *p*-Br, or *o*-(*m*-, *p*-)OH;
R^2=CH$_3$; R^1=H, *o*-(*m*-, *p*-)CH$_3$, *p*-iso-C$_3$H$_7$, *p*-t-C$_4$H$_9$, or *p*-t-C$_5$H$_{11}$.

However, this mechanism was not confirmed in subsequent studies[69,70].

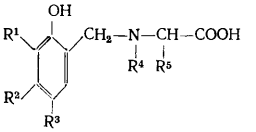
In the presence of a twofold excess of formaldehyde and glycine, 2,6- and 4,6-bis(carboxymethylaminomethyl)phenols (IX) were obtained[68]:



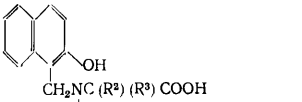
(IXa), R=Br, or F (IXb), R=Cl, or I

2,4,6-Trihalogenophenols and *o*-nitrophenol do not undergo the Mannich reaction with aminoacids under these conditions[68].

The synthesis of Mannich bases derived from phenols, naphthols, and certain aminoacids has been described[71]:



(X)



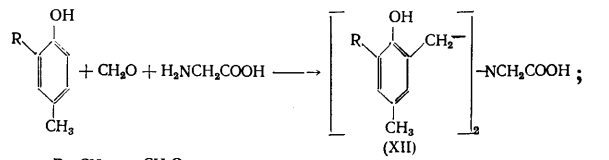
(XI)

(a) R^1=H, R^2=CH$_3$O; R^3=OH; R^4=H, or CH$_3$; R^5=H, or CH$_2$CH$_2$SCH$_3$;
(b) R^1=CH$_3$; R^2=H; R^3=CH$_3$; R^4=H, or CH$_3$, R^5=H, CH$_3$, CH$_2$COOH, CH$_2$OH, or CH$_2$CH$_2$SCH$_3$;
(c) R^1=CH$_3$O; R^2=R^5=H; R^3=CH$_3$, CHO, COOH, or CH$_3$O; R^4=H, or CH$_3$;
(d) R^1=Cl; R^2=R^5=H; R^3=Cl, R^4=CH$_3$.

(a) R^1=H; R^2=CH$_3$, or CH$_2$OH R^3=H, or CH$_3$;
(b) R^1=CH$_3$; R^2=R^3=H.

The authors showed that 2,4-dimethylphenol reacts with formaldehyde and a number of aminoacids (glycine, glutamic acid, alanine, serine, and methionine) to form *N*-benzyl derivatives. Sarcosine condenses successfully with formaldehyde and 2,4-dimethyl-, 2-methoxy-4-methyl-, and 2,4-dichlorophenols.

The reaction of glycine and formaldehyde with 2,4-dimethyl- and 2-methoxy-4-methyl-phenols leads to *N*,*N*-bisbenzyl derivatives (XII)[71]:



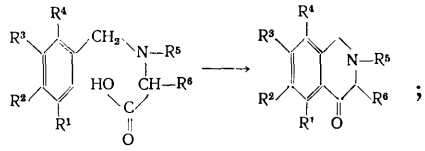
(XII)

R=CH$_3$, or CH$_3$O.

N-Benzylaminoacids (XIII) have been cyclised to derivatives of 1,2-dihydro-4(3*H*)-isoquinolone (XIV)[72]. In particular *N*-(2-hydroxy-3-methoxy-5-methylbenzyl)sarcosine (XIII)

On the basis of the similarity of the ultraviolet spectra of "cross-linked" ("bridged") products formed from gelatin and the products of the Mannich reaction involving aminoacids and peptides, the authors[64] concluded that the reaction mechanisms are similar.

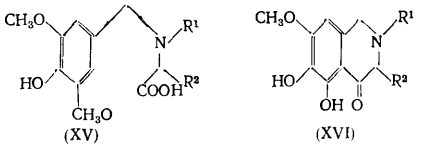
readily cyclises in the presence of sulphuric acid to form 1,2-dihydro-8-hydroxy-7-methoxy-2,5-dimethyl-4(3*H*)-isoquinolone (XIV):



(XIII) (XIV)

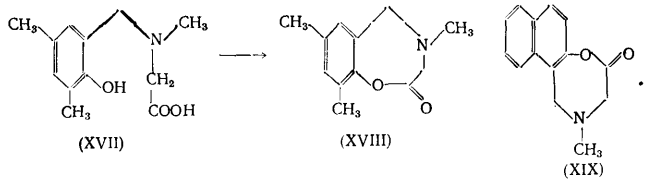
$R^1=R^5=CH_3$; $R^2=R^6=H$; $R^3=CH_3O$, $R^4=OH$.

In the cyclisation of *N*-(4-hydroxybenzyl-3,5-dimethoxy)-sarcosine (XV, $R^1 = CH$, $R^2 = H$) and *N*-(4-hydroxybenzyl-3,5-dimethoxy)alanine (XV, $R^1 = H$, $R^2 = CH_3$) the methoxy-group in the 3-position hydrolyses simultaneously with formation of compound (XVI):



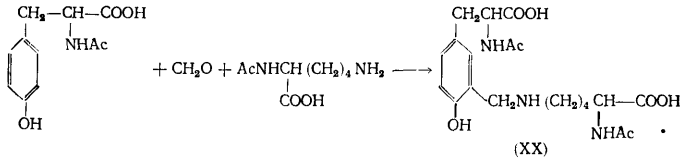
(XV) (XVI)

ortho-Substituted phenolic Mannich bases of type (XVII) are capable of being lactonised in the presence of thionyl chloride with formation of benzoxazepins (XVIII). 1,2-Dihydro-2-methylnaphtho[1,2-*f*]-1,4-oxazepin-4(3*H*)-one (XIX) has been obtained in a similar fashion to compound (XVIII)[72]:



(XVII) (XVIII) (XIX)

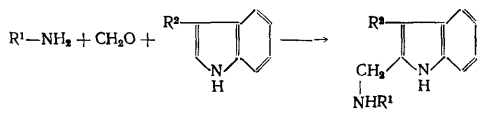
Sometimes the aminoacid itself can serve as the CH-acid component. Thus tyrosine, being a phenol derivative, condenses with formaldehyde and lycine to form the "bridged" compound (XX): Lys-CH_2-Tyr[73] (the α-amino-groups of both aminoacids are protected):



(XX)

The above interaction of aminoacids with formaldehyde and phenol[65] can be regarded as a model of this type of reaction (aminoacid-1-formaldehyde-aminoacid-2). A series of model "cross-linked" systems have been obtained[74,75]. 2,4-Dimethylphenol (model of tyrosine), 3-methylindole§ (model of tryptophan), and alkylamides¶ (models of glutamine and asparagine) have been used as models of aminoacids.

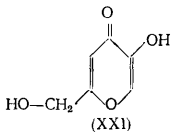
§ However, the indole fragment of tryptophan undergoes the Mannich condensation predominantly as the CH-acid component[77]:



¶ See the next Section for the details of the interaction of aminoacids with amides.

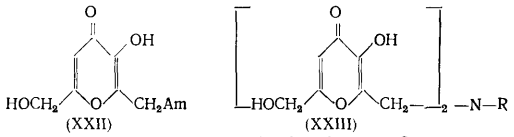
The position of the methylene group has been determined by ^{13}C NMR, which constitutes a convenient non-destructive method for the determination of the location of cross links in peptides treated with formaldehyde.

Thus the possibility of using the Mannich reaction for the synthesis of *C*-aminomethyl compounds in which the amino-fragment is an aminoacid has been demonstrated in relation to phenols. However, it has been suggested[76] that the aminomethylation of phenols by aminoacids involves experimental difficulties (long reaction time and the difficulty of isolating the final products) and cannot be used to synthesise the corresponding aminomethyl derivatives. Nevertheless it was shown[76] that kojic acid (5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one) (XXI), which is structurally similar to phenol, can be successfully condensed with formaldehyde and a number of aminoacids: glycine, sarcosine, valine, leucine, isoleucine, methionine, and taurine.



(XXI)

The formation of the mono-derivative (XXII) has been noted for all the aminoacids investigated; glycine and taurine, in which both amino-hydrogen atoms are substituted with formation of compound (XXIII), are an exception:



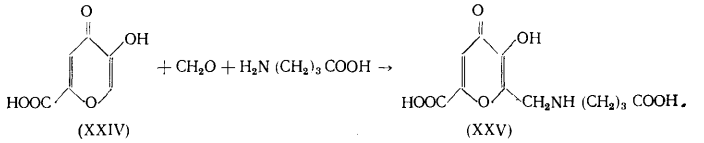
(XXII) (XXIII)

R=CH_2COOH, or $(CH_2)_2SO_3H$.

As was to be expected, aminoacids of different structures condense with formaldehyde and CH-acid components with different degrees of ease. The best results have been achieved in the aminomethylation of kojic acid by valine: heating for 50 min leads to an 80% yield of the final product[76]. This finding and also the lack of differences in the aminomethylation with leucine and isoleucine can be readily accounted for by steric factors.

O'Brien et al.[76] were unable to obtain the aminomethyl derivatives of kojic acid with asparagine, glutamine, aspartic, and glutamic acids, phenylalanine, and tyrosine. They believe that the main reason for the failure of the reaction with phenylalanine and tyrosine is their insolubility in the reaction mixture. In the case of dibasic acids (glutamic and aspartic) the second carboxy-group apparently exerts an inhibiting influence.

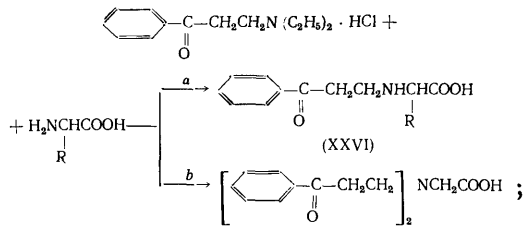
The aminomethyl derivative (XXV) has been obtained by the condensation of γ-aminobutyric acid with formaldehyde and comenic acid (XXIV)[78]:



(XXIV) (XXV)

There are contradictory data in the literature on the aminomethylation of acetophenones. Thus it has been suggested[79] that the Mannich reaction with acetophenones and α-aminoacids hardly occurs and the corresponding aminomethyl

derivatives (XXVI) and (XXVII) have been obtained by the reaction

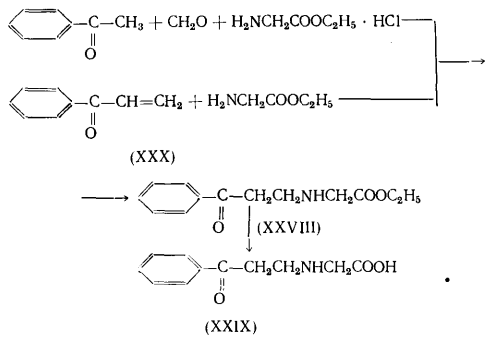


(XXVI)

(XXVII)

a:R=CH_3, CH_2COOH, CH_2CONH_2, $CH_2C_6H_5$;
b:R=H.

However, the ethyl ester[80] of *N*-β-benzoylethylglycine (XXVIII) has been obtained (albeit with a low yield) by the direct condensation of acetophenone, formaldehyde, and the hydrochloride of ethyl glycinate:



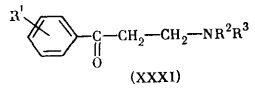
(XXX)

(XXVIII)

(XXIX)

N-β-Benzylethylglycine (XXIX) has been obtained by the hydrolysis of compound (XXVIII). Both products have also been synthesised by specific synthesis from acrylophenone (XXX) and glycine or its ethyl ester[80].

Although one of the convenient methods of synthesising β-aminoketones (derived from α-aminoacids) is in fact the Mannich reaction, many β-substituted aminopropiophenones having the general formula (XXXI) have been obtained by an exchange reaction[81]. The possibility of the aminomethylation of acetophenones by aminoacids via the Mannich reaction has been demonstrated only in relation to *N*-[β-(*o*-hydroxybenzoyl)ethyl]glycine[81]:

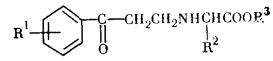


(XXXI)

(a) R^2=H; R^3=CH_2COOH; R^1 = *o*-HO, *o*-NH_2, *o*-CH_3O, *o*-C_3H_7O, *o*-iso-C_3H_7O, or *o*-(*m*-, *p*-)C_4H_9O;
(b) R^2=H; R^3=CH (CH_3) COOH (L-, DL-), CH ($CH_2CH_2SCH_3$) COOH (D-, L-, DL-), or CH (CH_2OH) COOH (L-, DL-); R^1 = *o*-HO; *o*-NH_2^*,
(c) R^2=H; R^3=CH [CH (CH_3)$_2$] COOH (D-, L-); R^1=*o*-HO (DL-); *o*-HO, *o*-CH_3O, *p*-Cl, *o*-(*m*-, *p*-)NH_2^*, CH_3CONH^*, *m*-(*p*-)CH_3NH^*, *p*-$C_4H_9NH^*$, *p*-CH_3COO^*, or *o*-(*m*-)Cl^*;
(d) R^2=H; R^3=C (CH_3) ($CH_2CH_2SCH_3$) COOH (DL-); R^1 = *o*-HO, or *p*-HO^*;
(e) R^2=H; R^3=CH [CH_2CH (CH_3)$_2$] COOH (D-, L-); R^1=*o*-HO, *p*-CH_3CONH^*, or *p*-$C_3H_7CONH^*$;
(f) R^2=H; R^3=CH [CH (OH) CH_3] COOH (D-, L-, DL-); R^1 = *o*-HO, *o*-NH_2^*, or *p*-iso-$C_3H_7O^*$;
(g) R^2=H; R^3=CH (CH_2) $CH_2SCH_2CH_3$) COOH (DL-); R^1 = *o*-HO, or *o*-CH_3O^*;
(h) R^2=CH_3; R^3=CH_2COOH; R^1 = *o*-(*m*-)HO, *m*-C_2H_5O, or *p*-C_3H_7COO;
(i) R^2=CH_3; R^3=CH [CH (CH_3)$_2$] COOH; R^1 = *p*-CH_3O^*;
(j) R^2=CH_3; R^3=CH [CH_2CH (CH_3)$_2$] COOH; R^1 = *o*-HO^*;
(k) R^2=C_2H_5; R^3=CH_2COOH; R^1 = *o*-HO;
(l) R^2 = iso-C_3H_7; R^3=CH [CH_2CH (CH_3)$_2$] COOH; R^1 = *o*-HO^*;
(m) R^2=C_4H_9; R^3=CH_2COOH; R^1 = *o*-HO.

† The optical forms of the aminoacid residues are not indicated.

Certain β-aminoketones (XXXII) derived from glycine, alanine, and valine have been synthesised by the Mannich condensation[71]:

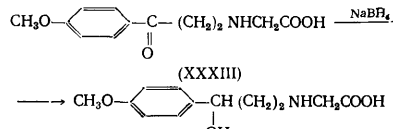


(XXXII)

(a) R^1=R^2=H, R^3=C_2H_5;
(b) R^1=4-CH_3O, R^2=H, CH_3, or $(CH_3)_2$ CH, R^3=H;
(c) R^1=4-HO-3-CH_3O, R^2=H, R^3=C_2H_5;
(d) R^1=3-NO_2, R^2=H, R^3=CH_3;
(e) R^1=3, 4, 5-$(CH_3O)_3$, R^2= H, R^3=C_2H_5 .

The authors achieved the best results using a mixture of cyclohexane and t-butyl alcohol as the solvent.

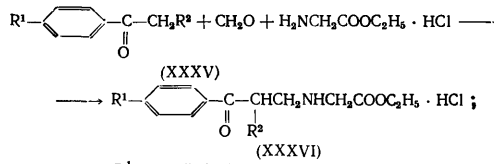
N-[β-(*p*-methoxybenzoyl)ethyl]glycine (XXXIII), obtained by the hydrolysis of the ethyl ester (XXXII, R^1 = 4-CH_3O, R^2 = H, R^3 = C_2H_5), was reduced with sodium tetrahydroborate to the corresponding alcohol (XXXIV)[71]:



(XXXIII)

(XXXIV)

The ethyl esters of *N*-(β-benzoylethyl)-, *N*-[β-(*p*-alkoxybenzoyl)ethyl]-, and *N*-[β-(*p*-halogenobenzoyl)ethyl]-glycines (XXXVIa, R^2 = H) and α-phenyl derivatives of some of them (XXXVIb, R^2 = C_6H_5) have been obtained by the condensation of 4-substituted acetophenones and benzyl phenyl ketones (XXXV) with formaldehyde and ethyl glycinate[82,83]:

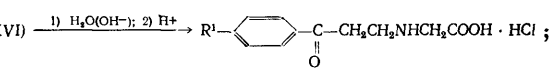


(XXXV)

(XXXVI)

R^1 = H, Alkyl, Cl, or Br.

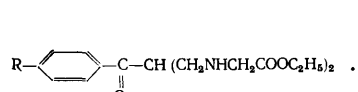
A number of *N*-[β-(*p*-alkoxybenzoyl)ethyl]glycines (XXXVII) have been synthesised by the hydrolysis of the corresponding ethyl esters (XXXVI)[82]:



(XXXVII)

R^2=H, R^1=H, or alkoxy.

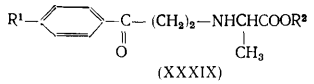
The authors[82] concluded that the aminomethylation of acetophenones with free glycine, as shown by Cymerman-Craig et al.,[79] does not in fact occur. However, condensation with the hydrochloride of ethyl glycinate instead of the free acid takes place in 20–30% yield. It has been shown that, apart from compound (XXXVI), the reaction leads to the formation also of bisethoxycarbonylmethylaminomethyl derivatives of acetophenones (XXXVIII):



(XXXVIII)

Agababyan et al.[83] published data on the aminomethylation of 4-substituted acetophenones with α-alanine. It was shown that, depending on the reaction conditions and the

reactant ratio, the yields of the aminoketones (XXXIX) vary significantly:

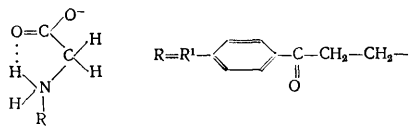


(XXXIX)

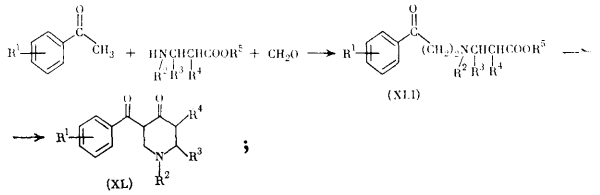
(a) R^2=H; R^1=H, CH_3O, C_2H_5O, C_3H_7O, iso-C_3H_7O, C_4H_9O, Cl, or Br;
(b) R^2=C_2H_5; R^1=C_3H_7O.

Thus, after refluxing for 10 h in ethanol (1:1:1 ratios of the reactants comprising 4-substituted acetophenone, paraformaldehyde, and alanine) at pH 6–7, the yield of the reaction product does not exceed 10–12%, whereas at pH 1–2 and for the same reaction time the yield increases to 28–30%. A change in the reactant ratios (twofold excess of acetophenone and formaldehyde) increases the yields to 30% (at pH 6–7) and 50% (pH 1–2). The replacement of ethanol by dioxan and the use of iron(III) chloride as the catalyst did not increase the yield of the final product. Certain aminoketones (XXXIX, R^1 = H, Br, iso-C_3H_7, or n-C_4H_9) have also been obtained by an exchange reaction[83].

The infrared spectra of *N*-[β-(p-alkoxybenzoyl)ethyl]glycines, their hydrochlorides (XXXVII), and ethyl esters (XXXVIa) have been investigated[84]. It has been established that the secondary amino-group is present only in the esters. In the hydrochlorides (XXXIX) the ketone oxygen forms an intermolecular hydrogen bond with the hydroxy-group of the carboxyl. It has been shown that the length of the alkoxy-group does not affect the intramolecular and intermolecular interactions. It has been suggested that the aminoacid fragment has a cyclic structure:



The Mannich reaction between acetophenones and α-aminoacid esters has been described[85]. The condensation products were further cyclised with sodium hydride to 3-benzoyl-4-piperidinones (XL):



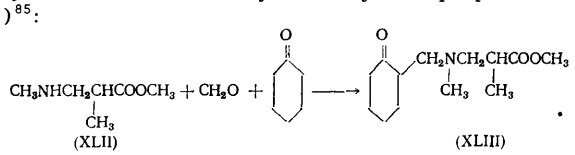
(XLI)

(XL)

(a) R^1=H, or CH_3O; R^2=CH_3, or C_2H_5; R^3=H, or CH_3; R^4=H, or CH_3; R^5=CH_3, or C_2H_5;
(b) R^1=CH_3; R^2=R^4=R^5=CH_3; R^3=H;
(c) R^1=Cl; R^2=R^3=CH_3; R^4=H; R^5=C_2H_5.

The stability of the ketoaminoesters (XLI) varies with their structure; *N*-methyl-substituted Mannich bases are more stable than the *N*-ethyl-substituted derivatives. It has been shown that esters with the methyl group in the α-position cyclise more readily than the esters with the methyl group in the β-position[85].

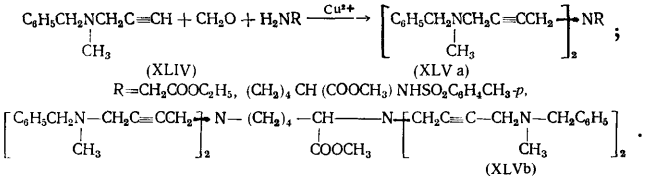
For comparison, a Mannich base has also been obtained from cyclohexanone and methyl β-methylaminopropionate (XLII)[85]:



(XLII) (XLIII)

However, the aminomethylation product (XLIII) could not be cyclised.

Acetylene derivatives have also been used as the CH-acid residues in the Mannich reaction. Aminomethylation of pargyline (*N*-methyl-*N*-propargylbenzylamine) (XLIV) with glycine or lysine derivatives yielded the corresponding Mannich bases (XLV)[86]:

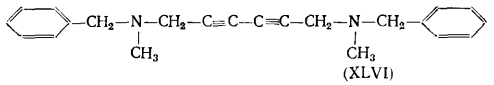


(XLIV) (XLV a)

R=$CH_2COOC_2H_5$, $(CH_2)_4CH(COOCH_3)NHSO_2C_6H_4CH_3$-*p*,

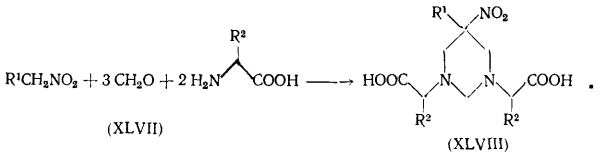
(XLVb)

The reaction was carried out at pH 6 in the presence of a catalyst—copper(II) chloride. At pH 9 or 4 pargyline does not react with the amino-component and formaldehyde, being oxidised to compound (XLVI):



(XLVI)

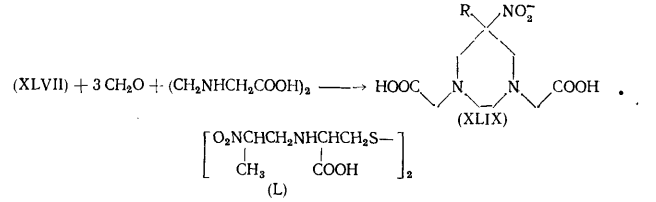
An interesting example of the Mannich reaction is that with nitroalkanes and aminoacids[87]. The hydrogen atoms in compound (XLVII) next to the nitro-group are very mobile, which promotes the cyclocondensation of this compound with two aminoacid molecules and three formaldehyde molecules to form the hexahydropyrimidine (XLVIII):



(XLVII) (XLVIII)

Glycine, β-alanine, valine, leucine, isoleucine, serine, threonine, phenylalanine, and methionine have been used successfully in this reaction (the lowest yield, in the reaction with phenylalanine, is 20%; in the remaining cases it is 60–80%).

In an analogous cyclisation reaction, Roth and Ergenzinger[87] obtained 6-nitro-1,4-diazacycloheptane-1,4-dicarboxylic acids (XLIX) from ethylenediamine-*N*,*N*′-diacetic acid. On the other hand, cysteine condenses with nitroethane and formaldehyde like a normal diamine, with formation of compound (L)—the "normal" Mannich base:



(XLIX)

(L)

However, cysteine does not undergo the Mannich condensation, since the reaction with formaldehyde leads to a cyclic product—thiazolidinecarboxylic acid[87,88].

III. AMINOMETHYLATION OF NH-ACID RESIDUES

Numerous studies[89–95] have been made on the interaction of aminoacids with formaldehyde and compounds containing nitrogen and mobile hydrogen atoms. This applied initially to the amine–formaldehyde–amide and amine–formaldehyde–guanidine coupling reactions, which have been studied by Fraenkel-Conrat and Olcott[91]. It was shown that, over a wide pH range at room temperature, formaldehyde can form

methylene bridges between the amino-group and the primary amide or guanidine NH_2 groups:

$$R^1{-}NH_2 + CH_2O + H_2N{-}C(=O){-}R^2 \longrightarrow RNH{-}CH_2{-}NH{-}C(=O){-}R^2 \ ;$$
$$R^1{-}NH_2 + CH_2O + H_2N{-}C(=NH){-}NHR^2 \longrightarrow RNH{-}CH_2{-}NH{-}C(=NH){-}NHR^2 \ . \qquad (3)$$

Neutral or acid media are preferable for reaction (3) between aminoacids and amides and between amines and amides respectively. The authors[91] explain this difference by the rapid formation of the cyclic trimers of the amines and formaldehyde in alkaline media. In order to confirm finally the condensation of aminoacids with formaldehyde and amides, the products of the interaction of alanine and proline with formaldehyde and acetamide were isolated.

Before the communication of Fraenkel-Conrat and Olcott[91], the mechanism of reaction (3) was studied inadequately. The authors[91] believe that, like the Mannich reaction, reaction (3) can be regarded as the condensation of a primary or secondary amine (in relation to alanine and proline), formaldehyde, and the NH-acid component—the primary amide group. According to Einhorn[96], an amidohydroxymethyl compound is formed initially. However, according to Fraenkel-Conrat and Olcott[91], despite the fact that the addition of formaldehyde to the primary amide group does indeed occur (this is also indicated by other data[94,95]), it is much slower than the "cross-linking" reaction, i.e. the formation of a methylene "bridge". It has been shown experimentally that the amidohydroxymethyl compound is incapable of subsequent condensation with the amine[91]. Thus reaction (3) proceeds in two stages:

$$R^1{-}NH_2 + CH_2O \xrightarrow{a} R^1NHCH_2OH \ ;$$
$$R^1NHCH_2OH + H_2NCOR^2 \xrightarrow{b} RNHCH_2NHCOR^2 + H_2O \ .$$

The interaction of the amino-group and the aminoacid with formaldehyde# is proved by a number of facts: the decrease of the pH of the reaction mixture and the change in the optical rotation of solutions of the L-aminoacid mixed with formaldehyde. The above two-stage mechanism is also confirmed by the change in the optical rotation of the mixture consisting of an optically inactive amide, an optically active amine, and formaldehyde[89].

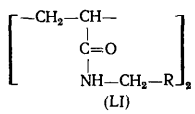
Whereas primary amide groups react with formaldehyde comparatively readily[94], secondary amides as well as peptide groups do not react with amines and formaldehyde under similar conditions[91,95].

On the basis of indirect data, some workers have also concluded that the methylene bridge is formed via a reaction of the Mannich type when proteins are treated simultaneously with formaldehyde and glycine[97] or other aminoacids[98]. The tanning effect of formaldehyde is mainly associated with similar reactions. It has been shown that, in a mixture with formaldehyde, aminoacids with a longer molecule act as less active tanning agents than glycine[98].

Apart from the free amide or guanidine groups, the NH group of indole is involved in the "cross-linking" reactions[73] (the aminomethylation of the α-carbon atom of indole was mentioned above[77]).

As already mentioned, aminoacids undergo a Mannich type reaction with NH-acid substrates such as amides; a number of studies have been made on reactions of this kind[106-110].

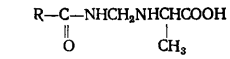
In particular, a number of communications report the synthesis of polymeric Mannich *N*-bases of type (LI) from *N*-hydroxymethylacrylamide, a free aminoacid, and methylenebisacrylamide[107] or from the acrylamide–methylenebisacrylamide copolymer, formaldehyde, and an aminoacid[108]:



(LI)

Here R is a residue of the optically active aminoacid, including L-proline and L-phenylalanine.

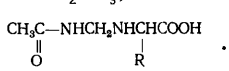
Complexes of polymeric Mannich *N*-bases with copper(II) or nickel(II) salts have been suggested for the resolution of aminoacids into optical isomers[106-108]. The synthesis of alanine derivatives (LII) has been reported[109]:



(LII)

R=CH_3, C_6H_5, 4-$O_2NC_6H_4$, 2-HOC_6H_4, 2,5-$(HO)_2C_6H_3$, or $C_6H_5CH(OH)$.

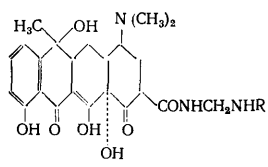
Aminomethyl derivatives of acetamide (LIII) have been obtained by the reaction of the latter with formaldehyde and certain aminoacids, namely valine [R = $CH(CH_3)_2$], norvaline (R = $CH_2CH_2CH_3$), phenylalanine (R = $CH_2C_6H_5$), and α-aminobutyric acid (R = CH_2CH_3)[110]:



(LIII)

Under these conditions, glycine, β-alanine, and α-aminobutyric acid form a mixture of products which has not been separated.

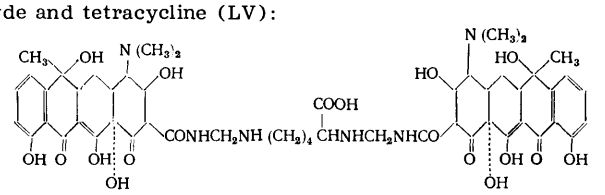
The majority of studies on the aminomethylation of NH-acid compounds have dealt with tetracyclines[14,111-116]. Condensation of aminoacids with formaldehyde and tetracyclines involves the amide group (the Einhorn reaction) with formation of aminomethyl derivatives of tetracycline (LIV):



(LIV)

R=CH_2COOH, $CH(CH_3)COOH$, $CH(CH_2C_6H_5)COOH$, $CH[(CH_2)_3NH_2]COOH$, $CH[CH_2CH(CH_3)_2]COOH$, $CH[CH(CH_3)CH_2CH_3]COOH$, $CH[(CH_2)_4NH_2]COOH$, $CH\left[(CH_2)_3NH{-}C(=NH){-}NH_2\right]COOH$, $CH(CH_2CH_2SCH_3)COOH$, or $(CH_2)_nCOOH$ (n=3—10).

The results of the aminomethylation of tetracycline by aminoacids such as glycine, α-alanine, phenylalanine, ornithine, and arginine indicate unambiguously the formation of monoaminomethyltetracyclines (LIV)[111,112]. However, it has been shown for lysine that the condensation involving the second amino-group is also possible[113] and that the bis-derivative (LV) is formed in the presence of an excess of formaldehyde and tetracycline (LV):

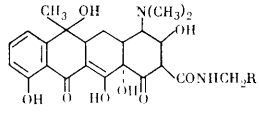


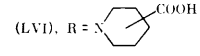
(LV)

The authors[113] emphasise that not more than two formaldehyde molecules react with lysine.

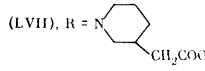
Numerous studies on this problem have now been carried out[99-105].

Among aminomethyl derivatives of tetracycline, compounds (LIV) with R = $(CH_2)_nCOOH$ and n = 3–10 have been obtained in high yields (up to 87–94% for n = 3–5)[114]. A derivative of γ-aminobutyric acid (n = 3) has also been described[115,116]. A synthesis of aminomethyl derivatives of tetracycline (LVI) and (LVII), in which the amino-fragment consists of residues of piperidine-3(4)-carboxylic and piperidine-3-acetic acids, has been proposed[116]:





(LVI), R =



(LVII), R =

IV. AMINOMETHYLATION OF PH-ACID RESIDUES

PH-acid residues—phosphorus and organophosphorus acids and their derivatives—are also used in the condensation reaction with aminoacids and formaldehyde. Like α-aminomethylphosphonic acids[117], *N*-phosphonomethylglycines have been obtained by a reaction of the Mannich type[118–122]. The *N*-phosphonomethylglycines widely used in practice as herbicides are largely obtained by other procedures[123–126].

N-Phosphonomethylglycine (LVIII) has been obtained by the condensation of dialkyl phosphonate [dialkyl halogen phosphite?] with formaldehyde and glycine followed by the hydrolysis of the resulting dialkyl ester of *N*-phosphonomethylglycine (LIX)[118]:

$$(RO)_2P(O)H + CH_2O + H_2NCH_2COOH \xrightarrow{NaOH} \underset{(LIX)}{(RO)_2P(O)CH_2NHCH_2COOH} \xrightarrow{H_2O(H^+)} \underset{(LVIII)}{(HO)_2P(O)CH_2NHCH_2COOH}.$$

The reaction between phosphorous acid, formaldehyde, and glycine taken in proportions of 2:2:1, leads to the formation of *N*,*N*-bis(phosphonomethyl)glycine (LX) (the authors used a different name—*N*-carboxymethyl-*N*,*N*-bismethylphosphonic acid)[119]. In contrast to compound (LIX), obtained at a low temperature in an alkaline medium[118], compound (LX) was synthesised at 110 °C in the presence of hydrochloric acid:

$$2H_3PO_3 + 2CH_2O + H_2NCH_2COOH \xrightarrow{HCl} \underset{(LX)}{HOOC-CH_2N[CH_2P(O)(OH)_2]_2}.$$

The mechanism of the acid dissociation of *N*-carboxymethyl-*N*,*N*-bismethylphosphonic acid has been studied and the structure of its anionic forms has been established[119].

N-Protected glycines condense with phosphorous acid and formaldehyde to form compounds of the type of Mannich bases. Thus *N*-hydroxy-*N*-phosphonomethylglycine (LXI) has been synthesised from *N*-hydroxyglycine[120]:

$$HO-NHCH_2COOH + H_3PO_3 \xrightarrow{CH_2O} \underset{(LXI)}{HOOCCH_2-\underset{\displaystyle OH}{\underset{|}{N}}-CH_2P(O)(OH)_2}.$$

The condensation of the ethyl ester of *N*-benzylglycine takes place analogously. Having removed the benzyl group, *N*-phosphonomethylglycine (LXIII) can be obtained from *N*-benzyl-*N*-phosphonomethylglycine (LXII)[121]:

$$C_6H_5CH_2NHCH_2COOC_2H_5 + CH_2O + H_3PO_3 \xrightarrow{H_2O} \underset{\displaystyle CH_2P(O)(OH)_2}{\underset{|}{C_6H_5CH_2NCH_2COOH}} \xrightarrow{HBr} \underset{(LXIII)}{HOOC-CH_2-NHCH_2P(O)(OH)_2}.$$
(LXII)

Di(carboxymethylaminomethyl)phosphinic acids have also been synthesised by the Mannich reaction[127]:

$$2C_6H_5CH_2NHCH_2COOH + 2CH_2O + H_2P(O)OH \longrightarrow \underset{(LXV)}{\left[\begin{array}{c}HOOC-CH_2-\underset{\displaystyle CH_2C_6H_5}{\underset{|}{N}}-CH_2\end{array}\right]_2P(O)OH} \longrightarrow \underset{(LXIV)}{[HOOC-CH_2NHCH_2]_2P(O)OH}.$$

Compound (LXIV), obtained by the debenzylation of the condensation product (LXV) with palladium, was converted into various salts.

Using iminodiacetic acid as the amino-component in the Mannich reaction, compound (LXVI) has been obtained by the mechanism[128]

$$CH_3-P(OH)(CH_2-N(CH_2COOH)_2) \xrightarrow[3)\ \text{ion-exchange resin}]{1)\ H_2SO_4,\ 2)\ H_2O_2} \underset{(LXVI)}{CH_3-\overset{\displaystyle O}{\overset{\|}{P}}(OH)CH_2NHCH_2COOH}.$$

V. BIOLOGICAL PROPERTIES OF MANNICH BASES DERIVED FROM α-AMINOACIDS

It has been shown[81] that many β-aminoketones derived from aminoacids such as glycine, alanine, valine, serine, methionine, leucine, threonine, ethionine, and α-methylmethionine as well as various salts based on the carboxy- and amino-groups exhibit a high bactericidal activity. The broad spectrum of the bactericidal activity (against both gram-positive and gram-negative micro-organisms) as well as their fungicidal activity suggest the possibility of using this group of β-aminoketones in various branches of industry (for example, the textile and paper industries).

The anti-inflammatory and antipyretic properties of *N*-[β-(*p*-substituted benzoyl)ethyl]glycines, alanines, and the ethyl esters of some of them have been investigated[82,83]. Comparison of the antipyretic and anti-inflammatory properties of the hydrochlorides of the ethyl esters of *N*-[β-(*p*-substituted benzoyl)ethyl]glycines[82] showed that the hydrochloride of ethyl *N*-[β-(*p*-isobutoxybenzoyl)ethyl]glycinate, introduced intra-abdominally in a dose of 50 mg kg^{-1}, exhibits an anti-inflammatory and an antipyretic activity. However, these properties of the preparation were not shown after peroral administration in doses of 50, 100, and 200 mg kg^{-1}.[82]

It has been noted that compounds (XXXVI), (XXXVII), and (XXXIX) have a low toxicity.

The influence of β-aminoketones derived from alanine and glycine, compounds (XXXIX) and (XXXVI) with R = Cl or Br, on the coronary blood circulation has also been studied[83]. Among these, only *N*-[β-(*p*-nitrobenzoyl)ethyl]alanine (XXXIX, R = NO_2) exhibits a weak coronary artery expanding activity. Compared with a series of *N*-[β-(*p*-alkoxybenzoyl)ethyl]- and *N*-[β-(*p*-halogenobenzoyl)ethyl]-alanines (XXXIX, R = alkoxy-group, Cl, or Br) shows that the introduction of the nitro-group in the *p*-position in the benzene ring leads to the appearance of vasodilatory activity.

Three compounds of the series of *N*-[β-(*p*-alkoxybenzoyl)-ethyl]glycines with various substituents (XXXVI, R = C_3H_7O, C_4H_9O, or iso-C_4H_9O) have been tested for their anti-tumour activities. The last two compounds exhibit an anti-tumour activity against Erlich adenocarcinoma (53 and 50% suppression of tumour growth respectively has been observed).

Like tetracycline itself, its aminoacid derivatives are of considerable interest as antibacterial agents. In contrast to other antibiotics of the tetracycline group, the aminomethyl

derivatives (*N*-pyrrolidino- and *N*-morpholino-methyltetracyclines, known as reverin and morphocycline) and, particularly, the aminoacid derivatives (glycino- and lysino-methyltetracyclines—glycocycline[13] and lymecycline§) dissolve much more readily in water. Thus lymecycline is 5000 times more soluble than tetracycline[130]. In terms of their antibacterial activity, aminomethyl derivatives are similar to tetracycline[129–132]. Furthermore parenteral administration of lymecycline does not give rise to local secondary responses, frequently observed when tetracycline is administered[14]. Comparison of reverin and glycocycline showed that, while their therapeutic effects (following intravenous administration) are similar, the latter is preferable because of the absence of side effects[131].

As stated above, *N*-phosphonomethylglycines were used as highly effective herbicides[121–126], fungicides, and plant growth regulators[127].

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