mixture). The evaporation of the benzene and $CHCl_3$ fractions yielded 12.3 g (40.1%) of 1-[3-(N-phenyl-N-methylsulfonamido)propyl]-2-oxo-4,6-dimethyl-1,2-dihydropyrimidine (XXI) in the form of an amorphous powder, which is not subject to recrystallization. The melting point of the purest sample was 92-95°C.

CONCLUSIONS

The reaction of the Na salts of hydroxypyrimidines with N-phenyl-N-methyl-ω-chloroalkylsulfonamides results in the formation of mixtures of N- and O-alkylation products.

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AMINO ACIDS AS CH ACIDS.

13. C-ALKYLATION OF BIS[(N-CARBETHOXYMETHYL)-SALICYLIDENEAMINO]COPPER

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The synthesis of amino acids on the basis of metallic complexes of Schiff bases of glycine [1-4] is governed to a considerable extent by the possibility of increasing the CH acidity of the methylene group of the glycine fragment. The replacement of the negatively charged carboxyl group by a neutral carbethoxyl group should favor the stabilization of the carbanion formed and an increase in its concentration in the reacting system, creating more favorable conditions for alkylation. In the present work we investigated the reaction of bis[(N-carbethoxymethyl)salicylideneamino]copper (I) with a number of alkylation agents.

DISCUSSION

We investigated the reaction of I with alkylating agents differing in nature. The reactions were carried out in the presence of bases, i.e., under conditions which facilitate the acidic dissociation of the proton of the glycine fragment (scheme 1). As expected, the reactivity of the methylene fragment of the glycine as a CH acid increases sharply in the transition from copper salicylideneglycinate to I. For example, the reaction of I with acetaldehyde or benzaldehyde results in the formation of threonine and phenylserine, while the reaction of copper salicylideneglycinate with acetaldehyde under the same conditions does not even produce traces of threonine, and 99% of the glycine is recovered. Our attempts to effect the alkylation of salicylideneglycinate complexes with gramine or its quaternary salt

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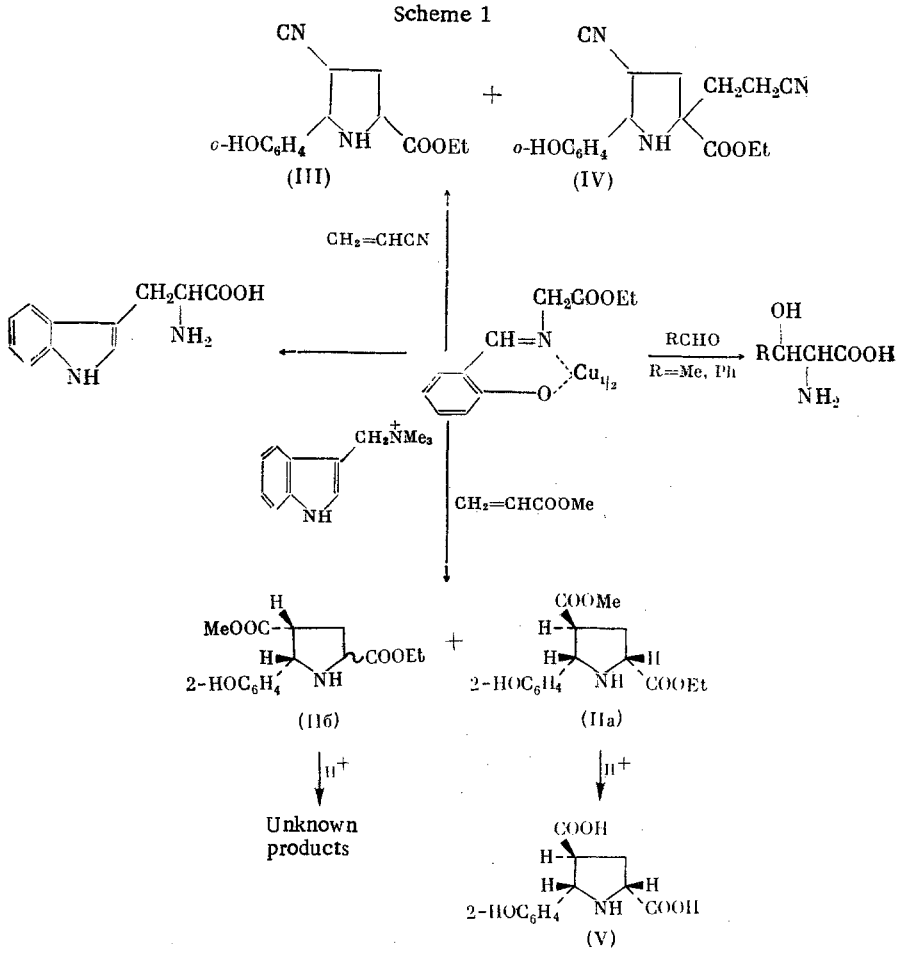
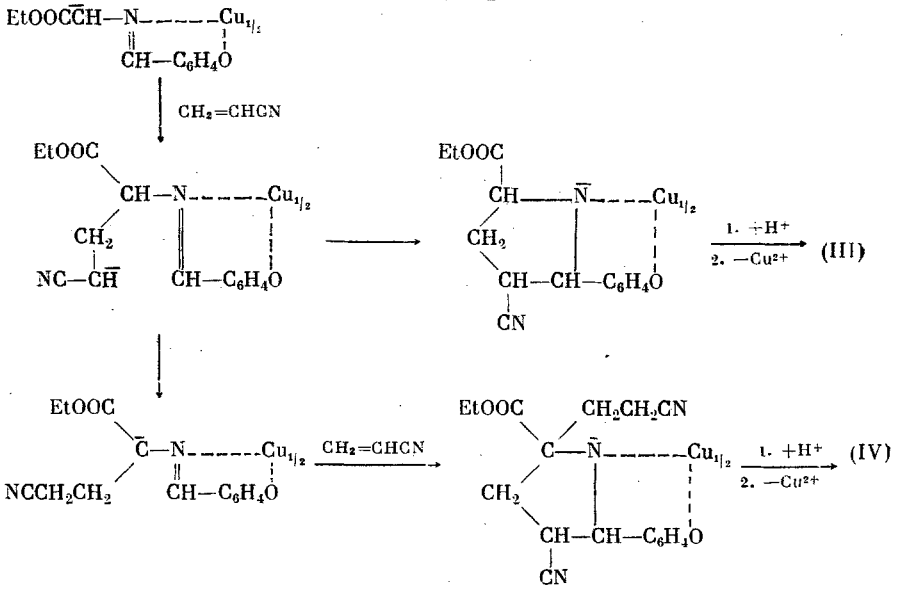
Scheme 1



Scheme 2



have so far been without results. The use of I in the reaction with graminium methiosulfate has led to some success: Tryptophan has been obtained in a very small yield.

The reaction of I with methyl acrylate produces a mixture of products, from which the two stereoisomers of the ethyl ester of 5-(2'-hydroxyphenyl)-4-carbomethoxyproline (IIa and IIb) could be isolated by preparative chromatography. Condensation with acrylonitrile produces a mixture of the ethyl esters of 5-(2'-hydroxyphenyl)-4-cyanoproline (III) and 5-(2'-hydroxyphenyl)-2-(2"-cyanoethyl)-4-cyanoproline (IV).

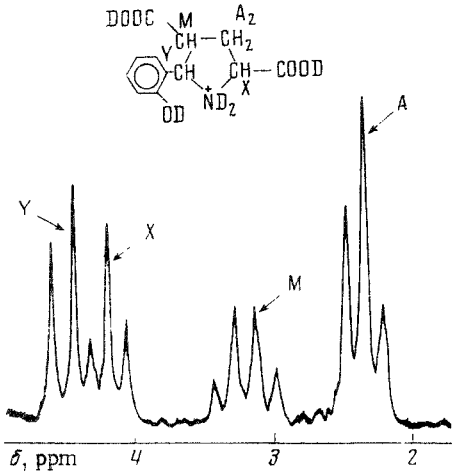


Fig. 1. Proton magnetic resonance spectrum of 5-(2'-hydroxypropyl)-4-carboxyproline (proline system). The solvent was a D_2O—CF_3COOH mixture.

Thus, the intramolecular cyclization following the addition of I to olefins containing an activated double bond is apparently a common phenomenon. This allows us to consider this reaction as a method for the synthesis of 4-substituted 5-(2'-hydroxyphenyl)prolines. The most likely mechanism for the process is the addition of the carbanion of I to the activated double bond followed by the addition of a new carbanion center to the double bond of the Schiff base (Scheme 2). The usual addition of the first molecule of acrylonitrile according to the Michael reaction followed by the addition of the second molecule with cyclization occurs, in all likelihood, during the formation of IV. The addition of the second molecule of acrylonitrile after cyclization is unlikely, since the conversion of the double CN bond into a single bond should sharply lower the CH acidity of the remaining α proton.

Compounds IIa and IIb each have three asymmetric centers and, in principle, can exist in the form of four diastereomers. The products isolated have narrow melting ranges and, according to the data on silica gel and cellulose in various buffer systems, are individual compounds. This is also supported by the unexpectedly simple nature of their PMR spectra. Figure 1 presents the PMR spectrum of V, which was obtained by hydrolysis of IIa, in a D_2O—CF_3COOH system. It might be expected that the protons of the proline system will be manifested by a multiplet characteristic of an ABMXY spin system even in the case of one isomer. In a first approximation the observed spectrum may be interpreted as a first-order A_2MXY spectrum, in which $\delta_{A_2} = 2.4$, $\delta_M = 3.2$, $\delta_X = 4.2$, $\delta_Y = 4.5$ ppm, $J_{AX} = J_{AM} = 7.3$ and $J_{MY} = 9.3$ Hz, and the remaining spin—spin coupling constants are close to zero. This spectrum supports the trans arrangement of the carboxyl groups in the case of IIa and thus of V, since the chemical equivalence of the two protons on C^3 can be realized only in that case. In the PMR spectrum of IIb the signal of the CH_3 in the carbomethoxyl group is shifted 0.4 ppm toward a stronger field relative to the signal of the same group in the IIa isomer. This finding is apparently the result of the screening of the carbomethoxyl group by the phenyl ring in IIb. Consideration of the Dreiding model shows that such screening is far more effective when the MeOOC and 2-HOC_6H_4 groups are in cis positions than when they are in trans positions. It may, thus, be assumed that in IIb the substituents at the C^4—C^5 bond are in cis positions and that in IIa they are in trans positions. Thus, the data obtained make it possible to establish the configuration of IIa: The COOMe and COOEt groups are in the trans positions, as are the protons at the C^4—C^5 bond.

The results obtained allow us to hope that the use of metallic complexes of the Schiff bases of esters of glycine with salicylaldehyde will greatly expand the set of amino acids that can be synthesized according to the pathway which imitates pyridoxal catalysis.

EXPERIMENTAL

The analysis of the amino acids was carried out on an Hitachi KLA-3B amino-acid analyzer. The PMR spectra were recorded on a Perkin—Elmer R-12 spectrometer with a TMS internal standard.

In order to determine the glycine content in the original I, a weighed sample of the complex has treated with H_2S in a slightly acidic aqueous solution, the CuS precipitate was filtered, and the filtrate was extracted with ether in order to remove the salicylaldehyde,

evaporated to a minimum volume, dissolved in 6 N HCl, and boiled for 1 h. After the evaporation, the amino acid was isolated on a Dowex 50 resin (H^+ form). The glycine yield was 80% of the theoretical. The yields of all the products are given as calculated for the actual glycine content in I.

The mixing of the reactants and all the reactions prior to the moment when the process was interrupted by an addition of acid were carried out in an atmosphere of dry Ar freed of O_2.

Condensation of I with Acetaldehyde. A 0.451 mmole portion of CH_3CHO was disssolved in 5 ml of anhydrous pyridine, 0.11 mmole of I were added, the mixture was held at ∿20°C for 1 h, and 6 N HCl was added until there was a weakly acidic reaction. The composition of the complex, the hydrolysis, and the isolation of the amino acids were carried out precisely as in the case of the determination of the glycine content in I. The total yield of the threonine diastereomers was 66%, the threo/allo ratio was 3:1, and the glycine residues amounted to 5%.

Condensation of I with Benzaldehyde. A 0.25 mmole portion of C_6H_5CHO was dissolved in 5 ml of abs. anhydrous pyridine, 0.11 mmole of I were added, the mixture was held at 45°C for 1.5 h, and the reaction was interrupted by an addition of HCl. The subsequent treatment was carried out in analogy to that described above. The total yield of the phenylserine diastereomers was 43.5%, and the glycine residues amounted to 50%.

Reaction of I with Graminium Methiosulfate. A 0.12 mmole portion of graminium methiosulfate and 0.11 mmole of I were added to 5 ml of DMFA. Three portions of sodium hydride (totaling 0.166 mmole) were added at 30 min intervals with stirring at 60°C. A 0.1 N HCl solution was added 30 min after the addition of the last portion, and the Cu was removed with the aid of H_2S. The solution was evaporated to dryness, and the residue was dissolved in 1 N NaOH and boiled for 1 H, extracted with ether, and introduced into a column with Dowex 50 (H^+ form). After the removal of the amino acids from the resins, the presence of tryptophan was proved by the data from TLC on cellulose in a 10:10:5:2 butanol—acetone—ammonia—water buffer system. The yield of tryptophan was 5.3% according to the data from the amino acid analysis and the spectrophotometry [5].

Condensation of I with Methyl Acrylate. A 36 mmole portion of freshly redistilled methyl acrylate, 43.4 mmole of pyridine, and 10.5 mmole of I were added to 320 ml of freshly redistilled anhydrous DMFA. The mixture was left to stand for 5 h at ∿20°C, the reaction was interrupted, and the Cu and salicylaldehyde were removed as described in the foregoing. Then 1 N NaOH was added to a weakly alkaline reaction, and the mixture was extracted several times with ether and then with $CHCl_3$. The combined organic layer was evaporated in a rotary evaporator, and the low-boiling fraction was distilled from the oil remaining in a vacuum (∿12 mm). According to the data from TLC on silica gel, the solid residue is a (∿1:3) mixture of the two diastereomers of the ethyl ester of 5-(2'-hydroxyphenyl)-4-carbomethoxyproline (IIa and IIb) with insignificant admixtures of other products. The total yield of IIa and IIb was ∿57%.

The mixture was chromatographed on Silica Gel M. Woelm-3440, the eluent was 20:19:16:10:5 chloroform—benzene—ether—THF—CH_3COOH, and the fraction containing IIa and IIb was collected. After the evaporation, the product was dissolved in ether, NH_3 was bubbled through in order to separate the product from the acetate, and the ammonium acetate precipitate was removed. A mixture of IIa and IIb was obtained from the filtrate after the evaporation.

The stereoisomers were separated by repeated crystallization from ether. Compound IIb precipitates predominantly in crystalline form, while IIa remains in the mother liquid. The melting point of IIa is 88°C and that of IIb is 108—110°C. The mass spectra of both isomers contain a peak at m/e 293. Found for IIa: C, 61.2; H, 6.0; N, 4.8%. Calculated for $C_{15}H_{19}O_5N$: C, 61.4; H, 6.5; H, 4.8%. The UV spectra of IIa and IIb (3:1 ethanol—water) have maxima at 278 and 280 nm, respectively ($\varepsilon_{(IIa)} = 2600$, $\varepsilon_{(IIb)} = 2640$). The IR spectra of IIa and IIb are practically identical. PMR spectrum of IIa (in $CDCl_3$, δ, ppm): 1.25 (t, 3H, CH_3 group in C_2H_5O), 3.65 (s, 3H, CH_3O), 6.7-7.4 (m, 4H, 2-OC_6H_4), 2.4 (m, 2H, CH_2 in the proline ring), 3.1 (q, 1H, C^4), 4.55 (d, 1H, C^5), and 4.2 (m, 3H, C^2 and CH_2 in the C_2H_5O group).

The most significant difference between the PMR spectra of IIb and IIa is the position of the signal for the methoxy-group protons, which is shifted 0.4 ppm toward higher fields in the case of IIb.

Hydrolysis of IIa. A sample of IIa was dissolved in 6 N HCl, and the solution was boiled for 1.5 h, evaporated to dryness, and dried in a vacuum. The product consisted of 5-(2'-hydroxyphenyl)-1-carboxyproline hydrochloride (V). Found: C, 47.7; H, 4.74; H, 4.15%. Calculated for $C_{12}H_{14}NO_5Cl \cdot H_2O$: C, 47.3; H, 5.25; N, 4.6%. PMR spectrum (in D_2O—CF_3COOH, δ, ppm): 2.4 (t, 2H, CH_2), 3.2 (q, 1H, C^4), 4.2 (t, 1H, C^2), 4.5 (d, 1H, C^5), and 6.2-6.8 (m, 2-OC_6H_4). The last signal overlaps the signal of HOD.

According to the data from the PMR spectra, the hydrolysis of IIb under analogous conditions is accompanied by profound changes in the proline system. The structure of the resultant products is presently being investigated.

Condensation of I with Acrylonitrile. A 9 mmole portion of I and 27 mmole of acrylonitrile were added to 100 ml of anhydrous pyridine, and the mixture was stirred for 2 h at ∿20°C and then left to stand overnight in a refrigerator. The solution was diluted twice with water, an equivalent amount of ethylenediaminetetraacetic acid was added, and then the solution was extracted with ether. The ethereal extract was dried with K_2CO_3, the ether was driven off in a rotary evaporator, and the low-boiling fraction was distilled from the oil obtained in a vacuum (∿12 mm). The solid residue was recrystallized from a 1:1 ethanol—benzene mixture. The product consisted of 1.5 g of a mixture of the ethyl esters of 5-(2'-hydroxyphenyl)-4-cyanoproline (III) and 5-(2'-hydroxyphenyl)-2-(2"-cyanoethyl)-4-cyanoproline (IV) (∿1.5:1). The total yield was 37%.

This mixture was chromatographed on Silica Gel M. Woelm-3440, the eluent was 10:13:5:5 $CHCl_3$—C_6H_6—ether—CH_3COOH, and two fractions were obtained. The second fraction obtained after the evaporation of the solvent was dissolved in absolute ether, NH_3 was bubbled through the solution, and the ammonium acetate precipitate was removed. Compound III with mp 132-134°C was obtained from the filtrate after the evaporation of the ether. Mass spectrum: m/e 260. PMR spectrum (in pyridine-d_6, δ, ppm): 1.2(t, 3H, CH_3 in the C_2H_5O group), 6.75-7.55 (m, 4H, 2-OC_6H_4), 2.6 (t, 2H, CH_2 in the proline ring) 3.55 (q, 1H, C^4), 4.85 (d, 1H, C^5), and 4.15 (m, 3H, C^2 and CH_2 in the C_2H_5O group).

After evaporation of the solvent, the first fraction yielded IV, mp 131.5-133.5°C. Mass spectrum: m/e 313. PMR spectrum (in pyridine-d_6, δ, ppm): 1.21 (t, 3H, CH_3 in the C_2H_5O group), 4.26 (q, 2H, CH_2 in the C_2H_5O group), 7.0-7.9 (m, 4H, 2-OC_6H_4), 2.6 (m 4H, CH_2 in the proline ring and CH_2 in the side chain), 3.1-3.6 (m, 3H, C^4, and CH_2CN), and 4.86 (d, 1H, C^5).

CONCLUSIONS

1. The ethyl ester of glycine in the copper complex of the Schiff base with salicylaldehyde is significantly more reactive than glycine in the copper complex of N-salicylideneglycinate.

2. Aldehydes are added under mild conditions to bis[(N-carbethoxymethyl)salicylideneamino]copper, resulting in the formation of β-hydroxyamino acids.

3. The reaction of bis[(N-carbethoxymethyl)salicylideneamino]copper with olefins with an activated double bond proceeds according to a scheme involving a Michael condensation followed by intramolecular cyclization, which results in the synthesis of 4-substituted 5-(2'-hydroxyphenyl)proline systems.

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