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The synthesis, properties, and applications of *N*-acyl-α-aminoacids

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Abstract. The review gives a systematic account of, and surveys the literature data on, the methods of synthesis, the physical and colloidal properties, and applications of acyl derivatives of aminoacids. The bibliography includes 369 references.

I. Introduction

Aminoacid derivatives, in particular *N*-acyl-α-aminoacids, the molecules of which include the peptide and carboxy-groups (or the sulfo-group in the case of aminosulfonic acids) have aroused continuous interest because of their exceptionally broad spectrum of activity. The presence of the acyl fragment in the molecule imparts hydrophobic properties to these compounds and enables them to exhibit surface-active properties. Aminoacids and higher carboxylic acids (HCA) are used for the manufacture of *N*-acyl-α-aminoacids. The practical application of *N*-acyl-α-aminoacids in industry and in human vital activity merits special attention. They are biologically 'soft' and are readily decomposed by bacteria under natural conditions, which is very important in our era of progressive pollution of the environment by industrial and domestic waste.

The chemistry of aminoacids, including the practical aspects of the chemical synthesis of peptides from which acylaminoacids are obtained, is fairly widely represented in the literature.[1–11] However, there is at present only isolated information about the methods of synthesis of acylaminoacids suitable for industrial application, their properties, and their practical applications.[12–15] The large number of continuously appearing publications on this topic has necessitated a survey of the accumulated information.

This review gives a systematic account and discusses the methods of synthesis of *N*-acyl-α-aminoacids having the general structure $R^1C(O)NR^2[CH(R^3)CO]_nOH$ and the relation between their structure and their physicochemical properties and surface and biological activities.

Since the methods for the acylation of aminoacids by higher carboxylic acids have been described in fair detail in the literature, we shall deal in detail with certain data concerning the kinetics and general mechanisms of acylation by the Schotten–Baumann method and of the activated esters method, which are fairly widely used for the synthesis of the above compounds.

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II. Methods for the acylation of aminoacids

Detailed analysis of the formation of the peptide linkage, carried out, for example, in the monograph of Gershkovich and Kibirev,[16] showed that as a rule the carboxy-group is initially activated in order to increase the electron density on the carbonyl carbon atom of the higher carboxylic acid and this is followed by nucleophilic attack, in the given instance by the amino-group of the aminoacid. Nowadays methods such as the carbodiimide, azide, mixed anhydride, activated esters, and carboxy-anhydride procedures are most widely used for the formation of the peptide linkage. However, these methods are not always effective in the development of a technology for the manufacture of acylaminoacids.

The ability of aminoacids to be acylated is in many respects determined by the nucleophilicity ($pK_a = 2.23 - 4.43$) of the amino groups,[1,7] steric factors, and the acylating capacity of the carboxylic acid derivatives RCOX, which is in its turn determined by the stability of the anion X^-. In terms of their reactivity, the principal types of acylating agents are equivalent to the acidity series (the stability of the anion X^-) and the series based on the rates of their hydrolysis and can be represented by the following sequence:

$$R^1COHal > (R^1CO)_2O \approx R^1COOR^2 > R^1CONR^2_2 > R^1COOH.$$

Hence it is seen that the most effective acylation of aminoacids requires the activation of the carboxy-group in carboxylic acids, for example up to the formation of acid chlorides, anhydrides, activated esters, etc. The overall mechanisms of reactions involving acylation by carboxylic acids and their various derivatives have been investigated quite adequately.[1–8, 16, 17]

The principal methods of synthesis of acylaminoacids suitable for practical application known at the present time are considered below.

1. Acylation by the Schotten–Baumann method

Acylation of aminoacids by HCA chlorides is one of the commonest methods of synthesis of acylaminoacids. It constitutes the basis of the industrial manufacture of a whole series of

products, for example 'medialans' which are derivatives of sarcosine.[18-20] There are various modifications of this method:

$$R^1COCl + H_2NCHR^2COOH \xrightarrow{NaOH} \longrightarrow R^1C(O)NHCHR^2COONa.$$

HCA chlorides with various structures are used as the acylating agents. The reaction is carried out in aqueous solutions, in aqueous organic mixtures containing 30%–50% of an inert water-soluble organic solvent, and in systems comprising two immiscible solvents, one of which is water. It is noteworthy that in the last case, for example in the water–toluene system, the yield of the target product is appreciably reduced.[15]

In the study of the kinetics of the acylation of α-aminoacids by benzoyl chloride in aqueous solutions, it has been shown[21] that the amino-group in the aminoacids investigated has a high reactivity, which is determined by the form in which the acid exists in solution. The forms having free amino-groups, $H_2NCHRCOO^-$ (A) and $H_2NCHRCOOH$ (B), are the most reactive, the activity of form A being higher. The rate of change of the concentration of benzoyl chloride, for example in the acylation of glycine in a water–dioxane mixture (298 K, $c_{H^+} = 1.17 \times 10^{-7}$ M), is described by the following equation when account is taken of its hydrolysis:

$$\frac{dc_b}{d\tau} = k_h c_b + \frac{kK_a}{c_{H^+}} c_b c ,$$

where k_h and k are the hydrolysis rate constant and the rate constant for the acylation of the α-aminoacid in form A by benzoyl chloride, K_a is the acid ionisation constant of the protonated amino-group of the aminoacid, c_b and c are the benzoyl chloride and aminoacid concentrations, and c_{H^+} is the concentration of hydrogen ions. Subject to the conditions $c \gg c_b$ and a constant pH of the reaction medium (the use of a buffer), the observed rate constant (k_o) for the given first-order reaction is calculated by the equation

$$k_o = k_h + \frac{kK_a}{c_{H^+}} c .$$

The constants, calculated by the least squares method (Table 1), show that under the experimental conditions the α-aminoacids do not catalyse the hydrolysis of benzoyl chloride; this is confirmed by the similar rate constants for the hydrolysis of the latter in reactions with various α-aminoacids. The reactivities of the amino-groups of α-aminoacids are analysed in terms of the quantity K_1, which includes the product of k and K_a. The reactivities of the amino-groups of the α-aminoacids investigated are approximately the same with the exception of L-proline and L-glutamine. The study of the hydrolysis kinetics of the chloride of lauric acid under conditions of aminoacid acylation has shown[22] that this reaction proceeds in the kinetic region with $E_a = 12.8 \pm 0.5$ kcal mol^{-1} at temperatures below 30 °C. The kinetic parameters for the acylation of a series of α-aminoacids by benzoyl chloride in aqueous solutions, obtained by Babaev et al.,[23] describe the experimental data satisfactorily (the error does not exceed 5%). However, there is no rigorous correlation between the reactivity of α-aminoacids and their structure.

The methods of synthesis of acylaminoacids via HCA chlorides proved to be effective not only for natural α-aminoacids but also for many others,[20,24] for example for α- and ε-aminohexanoic, α-aminobutyric, α-aminoisobutyric, and iminodiacetic acids as well as *N*-ethyl, *N*-propyl-, and *N*-butylglycine, *N*-methylalanine, and β-alanine.

In the acylation of sarcosine by HCA chlorides, it was found[25] that, in order to increase the quality of the product, it is necessary to maintain rigorously a series of technological process parameters (pH 10.5 ± 0.3, temperature below 30 °C, vigorous stirring during the addition of the acid chloride). In order to isolate the pure substances, the reaction mixture is extracted with ether, washed with water until neutral, dried over sodium sulfate, the solvent is distilled away, and the residue is recrystallised from hexane or petroleum ether.[24] It is recommended that acylsarcosine be neutralised by washing with hot water for 3 h at a temperature 10 °C below its melting point. More prolonged washing of the product under these conditions leads to the hydrolysis of the peptide linkage.

Table 1. The rate constants for the hydrolysis of benzoyl chloride (k_h) and the acylation of α-aminoacids (k_1 and k) and the acid dissociation constants (K) of α-aminoacids at 298 K and $c_{H^+} = 1.17 \times 10^{-7}$ mol litre^{-1}.[21]

α-Aminoacid (pK_a)[a]	$10^3 k_h$/s^{-1}	$k_1 = 10^7(kK_a)$/ s^{-1}	10^{-4} k/litre mol^{-1} s^{-1}
Gly (11.28)	1.93 ± 0.18	4.01 ± 0.23	7.64
DL-Ala (11.46)	1.69 ± 0.09	0.817 ± 0.005	2.35
DL-Val (11.25)	1.89 ± 0.05	2.14 ± 0.02	3.81
DL-Leu (11.09)	1.46 ± 0.15	1.74 ± 0.06	2.14
L-Ile (11.26)	1.92 ± 0.19	2.33 ± 0.08	4.24
L-Pro (12.0)	3.80 ± 1.54	23.0 ± 0.7	230
DL-β-Phe (10.83)	1.66 ± 0.23	3.97 ± 0.08	2.68
L-Gln (10.78)	2.41 ± 0.39	6.45 ± 0.25	3.89

[a] The values of pK_a are quoted to within ±0.02.

Much attention has been devoted to questions of the purification of *N*-acyl-α-aminoacids. One of the effective ways of solving this problem involves the washing of the reaction mass with C_1–C_4 aliphatic alcohols with simultaneous reduction of pH and filtration of the precipitated deposit or the employment of an alcohol–water mixture in the acylation stage.[26,27] These procedures make it possible to obtain acylaminoacids with a purity of 98%–99%.[28] Further development of industrial methods of synthesis of acylaminoacids by the Schotten–Baumann method involves the optimisation of the process and the development of continuous technological production schemes.[29]

Together with the natural and synthetic aminoacids, hydrolysed proteins are an important raw material for the industrial production of acylaminoacids and oligopeptides.[1,18-20,25] The products of the cleavage of the waste from leather (in the tanning of leather) and food industries, products of plant origin (cereal fibrin), microorganism biomass, etc. are as a rule employed as the protein raw material. The protein is usually hydrolysed by boiling in an excess of concentrated hydrochloric acid or alkali.

The industrial manufacture of products based on hydrolysed proteins with the trade name 'Lamepons', and 'Meipons' have been organised using the chlorides of lauric, palmitic, stearic, and oleic acids, as well as mixtures of acids from coconut and tall oils, lipids, and phospholipids.[13,18,30] The industrial methods of synthesis of acylated hydrolysed proteins are based on the Schotten–Baumann reaction in accordance with the following scheme:

$$R^1COCl + H_2NCHR^2CO[NHCHR^3CO]_nNHCHR^4COOH \xrightarrow{NaOH} \longrightarrow R^1CONHCHR^2CO[NHCHR^3CO]_nNHCHR^4COONa,$$

where R^1 = alkylated HCA, and R^2, R^3, and R^4 are fragments present in the α-aminoacids of protein raw materials of different origin.

In practice, the reaction is usually carried out with the gradual addition of HCA chlorides and stirring. A constant pH (9.5) and temperature (20 ± 5 °C) are then maintained.[31,32]

A commercial product with the following composition (%) is obtained under these conditions: acyl derivatives (25.0), initial hydrolysed protein (3.5), HCA (6.0), NaCl (5.0), and water (60.5). The optimum process conditions, making it possible to attain the maximum conversion of HCA chlorides and to obtain a high quality target product in a high yield, have been determined in a number of studies.[29,33-37]

The acylation of aminoalkanesulfonic acids takes place similarly to the reactions with aminoacids. The best known of the industrially produced acylaminoalkanesulfonic acids are derivatives of methyltaurine with the commercial names 'Igepons', 'Metaupons', 'Hostapons', etc. The methods of synthesis of acylmethyltaurine (including the principal industrial method of its preparation) by the Schotten–Baumann reaction, have been described in fair detail in a monograph.[25]

In recent years, studies in this field have been directed to the synthesis of highly concentrated acyltaurines with an increased purity. For example, repeated heating (to 50–90 °C) of the reaction mass containing 30%–60% of moisture, up to 50% of acylmethyltaurine, and 6% of NaCl followed by cooling to 10–30 °C[38] makes it possible to eliminate up to 90% of water from it. Highly pure acyltaurines have been obtained in a high yield in the stoichiometric interaction of HCA chlorides with taurine in an aqueous alcoholic medium.[39] The product, free from the NaCl impurity, has been isolated on heating the reaction mass, from which the NaCl deposit was filtered off and the product was crystallised.[40] A continuous method of synthesis of acyltaurines involving the continuous introduction of measured amounts of HCA chlorides has been developed. The optimum parameters of the technological process (pH 9–10, T = 40–60 °C) make it possible to obtain a highly concentrated pure product with an impurity content < 3%.[29,41-44]

2. The anhydride method

Symmetrical organic acid anhydrides and mixed anhydrides of inorganic acids are used for the acylation of aminoacids. Despite the fact that they are all less reactive than HCA chlorides, their employment for the synthesis of acylaminoacids is fairly important. The amide linkage is formed in this case in accordance with the following scheme:

$$(R^1R^2CO)_2O + H_2NCHR^3COOH \longrightarrow$$
$$\longrightarrow R^1CONHCHR^3COOH + R^2COOH.$$

Symmetrical organic acid anhydrides are preferable to others because they make a wide variety of side reactions avoidable. However, it is not possible to avoid the formation of the corresponding acids from the anhydrides (in stoichiometric proportions). For this reason, mainly the anhydrides of lower carboxylic acids are used in this method. The employment of extremely reactive anhydrides of halogenated acids with electron-accepting substituents, for example trifluoroacetic acid anhydride, for the large-scale production of acylaminoacids is economically unsound.

Aminoacids are as a rule acetylated by acetic anhydride in water or in acetic acid. For glycine and racemic aminoacids,[45-47] the yield of the target product is 89%–92%. Acetylation by acetic anhydride in boiling glacial acetic acid afforded derivatives of DL-alanine,[48] DL-valine,[49] and 4-aminobutyric and 6-aminohexanoic acids.[50] *N*-Alkylaminoacids are acetylated similarly.[51,52] In order to improve the quality of the acetylaminoacids obtained, acetylation by acetic anhydride in ethyl acetate in the presence of the cation-exchange resin K in the H^+-form has been suggested.[53] Together with acetyl chloride, acetic anhydride is widely used for the preparation of acetyl derivatives of aminoalkanesulfonic acids.[54,55] A method for the acetylation of aminoalkanesulfonic acid in the solid phase has been proposed. It makes it possible to obtain extremely pure products in a high yield.[56] It has been demonstrated by liquid chromatography that the product is up to 97% pure and contains about 1.5% of the initial aminosulfonic acid.

A series of acyl derivatives have been obtained by acylating aspartic acid with the anhydrides of alkenyl(alkyl)succinic acids[57] and by acylating taurine with the anhydrides of propionic and butyric acids.[58] HCA (C_8–C_{22}) anhydrides have been used in a series of syntheses.[59]

Mixed HCA anhydrides with sulfuric and carbonic acids are included among effective acylating agents despite the fact that in this case there is a possibility of side reactions. When mixed anhydrides of HCA and sulfuric acid were used at −5 to 40 °C in a water–acetone mixture, acyl derivatives of alanine, lysine, glutamic acid, and peptides were obtained.[60] The products of the acylation of aminoacids by mixed anhydrides of HCA and alkylcarbonic acids [alkyl carbonates? (Translator)] are the corresponding alcohols and carbonic acid together with the acylaminoacids.[61]

3. Method employing esters

Despite the fact that only the activated esters method has found extensive application in the synthesis of peptides, in practice both HCA esters and their activated forms are used to synthesise acylaminoacids. As a rule activated esters are obtained from nitro-, chloro-, and fluoro-phenols. The acylation of aminoacids by HCA esters leads to the simultaneous formation of acylaminoacids and alcohols in accordance with the scheme:

$$R^1COOR^2 + H_2NCHR^3COOH \longrightarrow$$
$$\longrightarrow R^1CONHCHR^3COOH + R^2OH.$$

This reaction is usually catalysed by an equimolar amount of a strong base, for example sodium alkoxide, sodium and lithium tetrahydroaluminates, etc. When this method of acylation of aminoacids or their salts was used, the yield of the target product reached 90%–95%.[62] The yield of the product decreases appreciably in the presence of traces of moisture. Acyl derivatives of α-aminoacids,[63] oligopeptides,[64-66] hydrolysed proteins,[67] and methylpurine[68,69] have been obtained by this method.

Nitrophenyl derivatives have been used to isolate α-aminoacids.[63,70,71] Pentafluorophenyl esters have been used successfully to acylate iminoacids despite the fact that *N*-alkyl substitution and branching at the α- and β-carbon atoms of the aminoacids interfere with the reaction.[72]

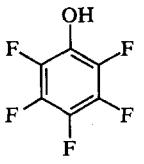
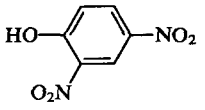
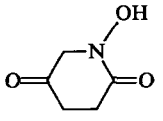
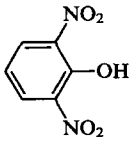
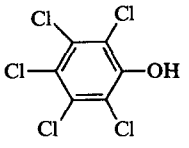
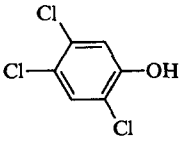
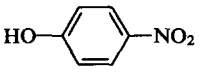
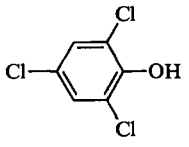
The reagents proposed nowadays for the activation of the carboxy-group and the subsequent formation of the peptide linkage by the activated esters method are as a rule stable during storage and exhibit a high reactivity, which in the case of substituted phenyl esters, for example, is determined by the acidity of their hydroxy-groups and by the type and position of the substituent and may differ by 2–3 orders of magnitude.[16] Pentafluorophenyl and nitrophenyl esters with a nitro-group which does not hinder the access of the amino-component to the electrophilic centre are the most reactive (Table 2, see over). A lower rate of acylation is characteristic of polychlorophenyl esters, which is due to the steric shielding of the electrophilic centre by the chlorine atoms in the *ortho*-positions.

4. Acylation by carboxylic acids

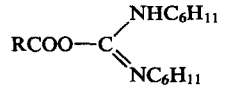
As a rule, aminoacids and their derivatives are not acylated by carboxylic acids at the usual temperatures. As stated above, the occurrence of such reactions under relatively mild conditions is possible only after the preliminary activation of the carboxy-group, for example by means of dicyclohexylcarbodiimide (DCHC).

$$R^1COOH + H_2NCHR^2COOH + C_6H_{11}N{=}C{=}NC_6H_{11} \longrightarrow$$
$$\longrightarrow R^1C(O)NHCHR^2COOH + C_6H_{11}NHC(O)NHC_6H_{11}.$$

Table 2. The rate constants (k) and the times (τ) required for 90% acylation by various activated esters.[16]

R^2	$10^2k/mol^{-1}\ s^{-1}$	τ/min
	40.4 ± 9	2.9
	18.4 ± 3	6.3
	5.4 ± 0.7	21
	1.73 ± 0.2	67
	1.72 ± 0.03	62
	0.3 ± 0.03	385
	0.1 ± 0.01	1088
	0.06 ± 0.002	1856

It has been suggested[73] that aminoacids are acylated in the presence of carbodiimides in accordance with a complex scheme involving the formation in the first stage of an adduct of the HCA and DCHC — *O*-acylurea.



This adduct, in which the carboxy-group is in an activated form, subsequently reacts with the aminoacid, forming an acylaminoacid. Acyl derivatives of glycine, alanine, leucine,[74] phenylalanine, lysine, methionine, glutamic acid,[75] and a number of other aminoacids[76] have been synthesised by this method in the presence of DCHC. It has been suggested that the acylation of HCA in an inert solvent with a calculated amount of carbonyldiimidazole be used to form the peptide linkage.[77] The imidazolide of the acid is formed as an intermediate in the reaction. It is subsequently transacylated to give the target products by reaction with the amino-group.

The synthesis of peptides, in particular of acylaminoacids, employing HCA as the acylating agent is favoured by the introduction into the reaction system of catalytic amounts of various phosphorus compounds: phosphorus chloride,[78] triphenyl phosphite,[79] the anhydrides of alkylphosphonic[80] and dialkylphosphinic[81] acids, derivatives of phenylphosphonic acid,[82] diethylphosphoryl cyanide,[83] diphenylphosphoryl azide,[84] and tetraethyl pyrophosphite.[1] Acylation by carboxylic acids in the presence of diethylphosphoryl cyanide is carried out in the presence of triethylamine.

$$R^1COOH + H_2NCHR^2COOH \xrightarrow[Et_3N]{NCP(O)(OEt)_2} R^1C(O)NHCHR^2COOH$$

The addition of tertiary amines promotes the formation of a carboxylate ion and the esterification reaction, increasing the yield of the target products. Acylaminoacids or peptides have been obtained in high yields (83%–94%) using carboxylic acids and diphenylphosphoryl azide.

$$R^1COOH + H_2NCHR^2COOH \xrightarrow[Et_3N]{N_3PO(OPh)_2} R^1C(O)NHCHR^2COOH$$

The effectiveness of the preliminary activation of the amino-group by tetraethyl pyrophosphite with formation of an amide has been demonstrated for the acylation of aminoacid esters with the aid of HCA.

$$R^1COOH + [(EtO)_2PNHCHR^2COOEt] \longrightarrow R^1C(O)NHCHR^2COOEt$$

The reaction with diethyl phosphorochloridite takes place in accordance with a similar mechanism.[1]

Despite the fact that the reactivity of carboxylic acids as acylating agents is extremely low without their preliminary activation, this method has found fairly extensive applications in practice in the development of technological processes. Acyl derivatives of glycine,[85] α-aminoacids, β-alanine, 6-aminohexanoic acid, and oligopeptides[86] have been obtained by this method. The reaction is carried out as a rule at 160–200 °C under an inert gas atmosphere. Depending on the type of the starting material, the yield of the target product can reach 40%–90% of the theoretical value. Under these conditions, acylaminoacids can be dehydrated with formation of oxazolones.

$$R^1C(O)NHCHR^2COOH \xrightarrow[-H_2O]{\Delta} R^1C\!\left(=N-CHR^2\right)\!-O-C(O)$$

The method of synthesis of basic acylaminoacids, developed by the Ajinomoto Company,[87] involves the interaction of aminoacids with HCA at 100–250 °C in an organic solvent immiscible with water and forming an 'azeotrope with water' under the reaction conditions. The method of synthesis of acylaminoacids proposed by the Dynamit Nobel AG Company has effective technological parameters.[62] The experimental industrial technology for the production of acylaminoacids is based on the acylation of 6-aminohexanoic acid, obtained by the alkaline hydrolysis of ε-caprolactam,[88] and its amination and subsequent acylation by acrylic acid.[89,90] Acyl derivatives of peptides with valuable operating properties have been obtained by the reaction of HCA at 210–250 °C with oligopeptides obtained by

hydrolysing protein materials, in particular leather, bristle, hooves, animal hair, bird feathers, plant proteins, fish waste, and purified proteins such as collagen, casein, and elastin.[91]

Together with the traditional industrial methods for the synthesis of acyltaurides by the Schotten–Baumann acylation, a procedure involving the acylation of a methyltaurine salt by carboxylic acids has been proposed for commercial use.[92]

$$RCOOH + HN(CH_3)CH_2CH_2SO_3Na \xrightarrow[-H_2O]{\Delta} RC(O)N(CH_3)CH_2CH_2SO_3Na$$

A characteristic feature of this method is a higher content of the initial carboxylic acids in the reaction mass. The process is carried out at reduced pressure under inert gases. The corresponding acyl derivatives based on HCA have also been obtained for the sodium salts of *N*-cyclohexyltaurine,[93] *N*-2-hydroxypropyltaurine,[94,95] and methyltaurine.[96]

5. Other methods

Amides and carbon monoxide belong to the class of acylating agents which are rarely used in the synthesis of acylaminoacids but are potentially of practical value. The reaction of an amide with carbon monoxide and an aldehyde or a compound giving rise to an aldehyde takes place in the presence of a catalyst (Cat) in accordance with the scheme

$$R^1C(O)NH_2 + CO + R^2CHO \xrightarrow{Cat} R^1C(O)NHCHR^2COOH.$$

Group VIII transition metals (cobalt is the best) in the form of carbonyls, carboxylates, and various complexes have been proposed as catalysts.[97–100] The reaction is carried out at 50–150 °C, at a carbon monoxide partial pressure of 50–500 atm, in the presence of solvents, preferably alcohols, ethers, and ethyl acetate. The best results in the carbonylation reaction have been achieved with the aid of aliphatic aldehydes and primary amides.[99] As nucleophiles, amides add to the carbonyl group of aldehydes over a wide pH range and the initial product is usually an *N*-acylcarbinolamine $R^1C(O)NHCR^2R^3OH$.[17] When this reaction is carried out at an elevated temperature, the O → N rearrangement is facilitated. Under these conditions, ketones are as a rule less reactive.

A modified version of the above method, involving the replacement of the aldehyde by compounds containing double bonds, has been proposed.[101,102] The reaction is carried out in one stage, which increases its selectivity and rate. Ethers, ketones, and sulfoxides have been proposed as solvents. The highly nucleophilic amide anion, formed under these conditions on treatment with a strong base, undergoes Michael addition to the substituted alkene.

$$R^1C(O)NHR^2 \underset{}{\overset{OH^-}{\rightleftharpoons}} R^1C(O)\bar{N}R^2 \xrightarrow{R^3CH=CHCOOH} R^1C(O)NR^2CHR^3CH_2COOH$$

In practice, acylaminoacids are obtained under these conditions from alcohols and organic halo-derivatives.[103–105] The hydroformylation of an alcohol or halide in the presence of an amide and a catalyst (a Group VIII transition metal) is carried out at 50–200 °C and a pressure of 10–500 atm (a mixture of CO and H_2); the yield of the target product is up to 69%.

The method of synthesis of acylaminoacids by the reactions of oxiranes with amides, carbon monoxide, and hydrogen in the presence of cobalt-containing catalysts and promoting agents is of considerable interest.[106–109] Compounds containing Group I–V metals are employed as promoting agents. Among the diverse methods of synthesis of acyl aminoacids, the hydrogenation of an azlactone by *N*-acetylaminocinnamic acid in the presence of Raney nickel,[110] reactions of aliphatic nitriles with glyoxylic acid,[111] the interaction of an aminoacid salt with gaseous ketene,[112] and the acylation of the aminoacid by the succinimidine ester of the HCA[113] have been mentioned. In the last case, acyl derivatives of glycine, α- and β-alanines, and aspartic acid were obtained. The constant growth of the number of studies published on this topic shows that the methods are extremely promising.[114–118]

The processes based on the interaction of amides with chloro- and hydroxy-alkane sulfonates,[25] for example

$$R^1C(O)NHR^2 + HOCH_2CH_2SO_3Na \xrightarrow{\Delta} R^1C(O)NR^2CH_2CH_2SO_3Na + H_2$$

can also be included among the traditional methods of synthesis of acylaminoalkanesulfonic acids. Derivatives of aminomethanesulfonic[119,120] and aminoethanesulfonic[121–124] acids have been obtained in this way. For example, acylaminoethanesulfonates have been synthesised by the interaction of HCA, urea, and hydroxyethanesulfonates in the presence of an excess of the latter at 180–240 °C.[95,122] The process is distinguished by a high degree of conversion of the starting materials (92%–98%). HCA, amines, and hydroxyalkanesulfonates interact under virtually identical conditions.[125]

It has been suggested that, instead of amides, nitriles should be employed in the synthesis of acylaminoalkanesulfonates.[126–128] Acylaminoalkanesulfonic acids can also be obtained by aminating hydroxyethanesulfonates with subsequent acetylation[129,130] or activation of the aminoalcohols and the sulfonyl chlorination of the amidoalcohols obtained.[131]

One of the possible ways of obtaining acylaminoacids and their derivatives involves the interaction of lactams with HCA and their derivatives such as acid chlorides, anhydrides, esters, etc.[20] The acylation of lactams, for example of ε-caprolactam, by carboxylic acids is carried out at 240–250 °C and a pressure of 16 atm,[132] the target product being obtained with different degrees of oligomerisation of 6-aminohexanoic acid, depending on the ratio of the lactam and the acid taken for the reaction. The interaction of lactams with carboxylic acid esters leads to the formation of the corresponding acylaminoacids in fairly high yields (68%–71%).[133]

It follows from the foregoing that, for the industrial production of acylaminoacids, one may use (together with the acid chloride method, on the basis of which the technologies for the synthesis of virtually all the products of this kind have been developed by foreign companies) methods for their synthesis by the direct condensation of aminoacids with HCA, via carboxylic acid anhydrides, and by the reaction of amides, carbon monoxide, and an alkene (aldehydes, alcohols, and organic halides) are of considerable interest. The disadvantages of each of these procedures were noted above.

III. Properties of acylaminoacids

The properties of acylaminoacids are determined by the presence in the latter of peptide and carboxy-groups and by the conjugation of the lone pair of the nitrogen atom with the π-electrons of the carbonyl group, which leads to the manifestation by the peptide group of the properties of a double bond. The salts of these compounds in highly dilute aqueous solutions (below 10^{-3} M) tend to form micelles. Information about the properties of acylaminoacids has scarcely been treated systematically hitherto and is sometimes published in sources which are not readily available. The individual properties and constants of some of these compounds can be found in a number of communications.[11,14,15,24,25,68,134–140]

The solubility in water of *N*-acylaminoacids, forming colloidal solutions at low concentrations, is in many respects

Table 3. The dissociation constants (pK') and solubilities (P_s) of a series of aminoacids.[1]

Aminoacid	Chemical formula	pK'_1 (α-COOH)	pK'_2 (α-NH_3^+)	pH_i[a]	P_s/g[b]
Glycine	$CH_2(NH_2)COOH$	2.34	9.6	5.97	25.0
α-Alanine	$CH_3(NH_2)COOH$	2.34	9.69	6.00	16.6
Valine	$(CH_3)_2CHCH(NH_2)COOH$	2.32	9.62	5.96	8.8
Leucine	$(CH_3)_2CHCH_2CH(NH_2)COOH$	2.36	9.60	5.98	2.2
Sarcosine	CH_3NHCH_2COOH	2.23	10.01	6.12	
Aspartic acid	$HOOCCH_2CH(NH_2)COOH$	1.88[c]	9.60	2.77	0.5
Glutamic acid	$HOOC(CH_2)_2CH(NH_2)COOH$	2.19[d]	9.67	3.22	0.9
Lysine	$H_2N(CH_2)_4CH(NH_2)COOH$	2.18	8.95[e]	9.59	73.3
β-Alanine	$H_2N(CH_2)_2COOH$	3.60	10.19	6.90	16.6
γ-Aminobutyric acid	$H_2N(CH_2)_3COOH$	4.02	10.40	7.21	6.7
ε-Aminocaproic acid	$H_2N(CH_2)_5COOH$	4.43	10.75	7.60	

[a] pH at the isoelectric point. [b] Solubility in 100 g of water at 25 °C. [c] $pK''_1 = 3.65$. [d] $pK''_1 = 4.25$. [e] $pK''_2 = 10.53$.

Table 4. The solubilities of the sodium salts of certain *N*-acylated aminoacids (determined at the Krafft point).[140]

Aminoacid	Acyl group[a]				
	C_{10}	C_{12}	C_{14}	C_{16}	C_{18}
Glycine	(+) (40)	36 (65)	47 (93)	55 (−)	66 (−)
α-Alanine	(+) (154)	18 (666)	32 (523)	45 (301)	56 (−)
Valine	(+) (109)	(+) (372)	(+) (400)	8 (330)	36 (229)
Leucine	(+) (94)	(+) (299)	(+) (243)	(+) (236)	46 (−)
Sarcosine	(+) (109)	(+) (258)	(+) (273)	2 (229)	33 (229)
Aspartic acid	(+) (47)	(+) (78)	(+) (109)	(+) (169)	46 (154)
Lysine	8 (184)	34 (229)	61 (−)	84 (−)	

[a] The numbers in brackets are concentrations of Ca^{2+} ions in $CaCO_3$ in ppm; (+) indicates that the solutions remain clear at 0 °C; (−) indicates that the solutions become cloudy at 0 °C.

determined by the acid–base properties and structural characteristics of the initial aminoacids $R^1C(O)NR^2(CH_2)_nX$, such as the number and ratio of the polar groups (carboxy- and amino-groups), and the polar and nonpolar R^1 groups. The dissociation constants and solubilities of a number of aminoacids, the *N*-acyl derivatives of which are considered in the present review, are presented in Table 3. In the aminoacid series glycine–α-alanine–valine–leucine, the solubility in water decreases by an order of magnitude with increase in the size of the nonpolar R^1 group, i.e. with increase in their hydrophobicity. Thus, leucine, which contains the relatively large hydrophobic fragment Pr^iCH_2CH, can be extracted by hot n-butanol from its mixture with glycine. The solubilities of the basic α-aminoacids are much higher than those of the mono-carboxylic and acid α-aminoacids. Similar behaviour may also be traced for *N*-acyl derivatives of the same α-aminoacids (Table 4). The Krafft point for ionogenic surfactants characterises the lower temperature limit for the formation of micelles by the latter, because at lower temperatures the solubility of the surfactants is insufficient for the formation of micelles. The data in Table 4 show that the principal factors which determine the Krafft point are the size of the acyl group and the degree of branching of the aminoacid fragment.

The phase transitions from the solid to the liquid state (320–400 K) in acylaminoacids differing in the size of the acyl group have been investigated by IR spectroscopy.[141] It has been shown that, with increase in the number of methylene fragments and with the appearance of side chains in the aminoacid, ΔH_m and ΔS_m† both increase. Thus, for glycine and L-alanine derivatives the appearance of each additional CH_2 group entails an increase in ΔH_m and ΔS_m by 3–5 and 7 kJ mol^{-1} and by 8–10 and 18 J mol^{-1} K^{-1} respectively. Studies on solutions of acylaminoacid esters by spectroscopic methods have shown that they exist in the form of dimeric complexes[142] formed on associative interaction as a result of the formation of hydrogen bonds between the NH and ester CO groups.

† Enthalpy and entropy of fusion (Translator).

1. Spectroscopic properties

The UV spectra of acyl aminoacids are not of special interest to organic chemists because, like the UV spectra of the initial aminoacids and the HCA, they contain weak absorption bands in the region below 215 nm. The presence of a peptide group does not introduce a significant change into the UV spectra of acylaminoacids in this absorption region either.[143]

The IR spectra of acylaminoacids contain characteristic absorption bands of the functional groups C=O and OH (carboxyl), C=O and NH (amide bands I and II), and CH_3-, $-CH_2-$, and =CH– (the hydrocarbon skeleton). The range of the absorption frequencies of these compounds is determined by a number of factors (solvent, suspension medium, possibility of association, etc.) and for this reason Table 5 lists their average

Table 5. Characteristic vibration frequencies of the functional groups in the IR spectra of acylaminoacids.[14,15,144–146]

Functional group	Frequency/cm^{-1}	Type of vibrations
OH	3550–3000	stretching
NH	3460–3350	"
CH_3 and CH_2	2940–2870	"
C=O	1730–1710	"
C=O (amide I)	1685–1645	"
NH (amide II)	1550–1530	deformation

values. It is difficult to make reliable assignments in the high-frequency region of the IR spectra of acylaminoacids because the υ_{NH} and υ_{OH} bands of the corresponding groups in the free and associated states are as a rule observed simultaneously in this region.

^1H and ^{13}C NMR spectroscopy is one of the most important methods for the identification of acylaminoacids, which are polyfunctional compounds.

The ^1H NMR spectra of acylsarcosinate salts have been described in the literature. It has been shown that in aqueous solution acylsarcosinates exist as *cis*- and *trans*-isomers.[147] The presence of an intramolecular hydrogen bond between the amide carbonyl groups and the carboxyl in the *trans*-conformer has been established by NMR spectroscopy. On the basis of the spectra of certain acylaminoacids, general information has been obtained concerning the dependence of the chemical shifts of the amide protons on the dissociation constants of the carboxylic acid (the acylating agent)[148,149] and of the α-protons of the acylaminoacid on the nature of the solvent.[150] ^{13}C NMR spectroscopy has been more vigorously resorted to in recent years in order to investigate acylaminoacids containing long hydrocarbon groups. Thus Bouloussa and Dizabo[151] presented the ^{13}C NMR spectra of the palmitoyl derivatives of glycine, alanine, and glutamic acid, while Newmark and Hill[152] and Gunston[153] described a method for the assignment of the carbon atoms in the α-, β-, and γ-positions relative to the amide carbonyl group

Table 6. The chemical shifts of the signals in the ^1H NMR spectra (400 MHz) of the acylaminoacids $R^1C(O)NR^2(CH_2)_nX$.

Compound	$R^1C(O)-$	R^2	n	X	Solvent	Chemical shift/ppm (rel. to TMS)		
						$CH_2C(O)$	NCH_2	CH_2X
1	$C_{18:1}$	H	1	COOH	$CDCl_3$	2.35 (m)	4.05[a] (m)	4.05[a] (m)
1	$C_{18:1}$	H	1	COOH	CD_3OD	2.77 (m)	4.11[a] (m)	4.11[a] (m)
2	C_{18}	CH_3	1	COOH	$CDCl_3$	2.33 (m)	3.88[a] (s)[b]	3.88[a] (s)
3	$C_{18:1}$	H	2	COOH	$CDCl_3$	2.15 (m)	3.51 (m)	2.56 (m)
3	$C_{18:1}$	H	2	COOH	CD_3OD	2.15 (m)	3.39 (m)	2.47 (m)
4	C_{16}	H	3	COOH	$CDCl_3$	2.34 (t)	3.38 (br.t)	2.25 (t)
5	C_{11}[e]	H	5	COOH	$CDCl_3$	2.32 (m)	3.28 (m)	2.32 (m)
6	C_{12}	H	5	COOH	CD_3OD	2.15 (t)	3.15 (t)	2.28 (t)
7	$C_{18:1}$	H	5	COOH	$CDCl_3$	2.15 (t)	3.15 (t)	2.28 (t)
8	C_{12}	H	5[d]	COOH	CD_3OD	2.15, 2.17 (t)	3.14, 3.15 (t)	2.28 (t)
9	$C_{18:1}$	H	5[d]	COOH	$CDCl_3$	2.16	3.17, 3.19 (br.t)	2.31 (t)
10	$C_{18:1}$	H	5[d]	COOH	$CDCl_3$	2.16 (br.m)	3.19 (br.m)	2.31 (br.m)
11	C_{10}	H	2	SO_3Na	CD_3OD	2.17 (t)	3.58 (t)	2.95 (t)
12	C_{12}	H	2	SO_3Na	CD_3OD	2.15, 2.17 (t)	3.58 (t)	2.95 (t)
13	C_{14}	H	2	SO_3Na	CD_3OD	2.15, 2.17 (t)	3.57 (t)	2.95 (t)
14	C_{16}	H	2	SO_3Na	CD_3OD	2.15, 2.17 (t)	3.57 (t)	2.95 (t)
15	C_{18}	H	2	SO_3Na	CD_3OD	2.15, 2.17 (t)	3.58 (t)	2.95 (t)
16	$C_{18:1}$	H	2	SO_3Na	CD_3OD	2.15, 2.17 (t)	3.58 (t)	2.95 (t)
17	$C_{16}-C_{18:1}$	CH_3	2	SO_3Na	CD_3OD	2.34, 2.44 (t)	3.75 (m)	3.0 (m)

Remarks. The following notation has been adopted: m = multiplet, s = singlet, br.t = broadened triplet, br.m = broadened multiplet, t = triplet. [a]The same methylene group. [b]The chemical shift of the NCH_3 group is 3.02 ppm (s). [c]Undecenoyl. [d]For the compounds $R^1C(O)[NR^2(CH_2)_n]_mX$ (m = 2, 2, and 3) **8**, **9**, and **10**.

Table 7. The chemical shifts (δ) of the signals in the ^{13}C NMR spectra (20 MHz) of the acylaminoacids $R^1C(O)NR^2(CH_2)_nX$.

Compound	$R^1C(O)-$	R^2	n	X	Solvent	δ/ppm (rel. to TMS; the values of $^1J_{CH}$/Hz are given in brackets)				
						$CH_2C(O)$	CH_2X	NCH_2	C(O)	COOH
18	C_{12}	H	1	COOH	CD_3OD	36.8	41.7	41.6	173.1	176.3
19	C_{16}	H	1	COOH	CD_3OD	36.8	41.8[a]	41.8[a]	173.2	176.6
20	C_{18}	H	1	COOH	CD_3OD	36.7	41.7[a]	41.7[a]	173.1	176.5
2	C_{18}	CH_3[b]	1	COOH	CD_3OD	35.1	53.8	53.8 (J = 146)	171.0	177.0
21	$C_{18:1}$	CH_3	1	COOH	$CDCl_3$	35.4	51.9[a]	51.9[a]	176.0	178.0
22	CH_3	$C_{18:1}$	2	COOH	CD_3OD	7	34.6 (J = 127)	36.5, 36.4 (J = 139)	173.3 173.4	175.0
3	$C_{18:1}$	H	2	COOH	CD_3OD	36.5[a]	35.2[a]	37.1	175.1	176.1
7	$C_{18:1}$	H	5	COOH	CD_3OD	37.2	34.8	40.1	176.0	177.3
9	$C_{18:1}$	H	2[c]	COOH	$CD_3OD/CDCl_3$ 1:1	36.0, 36.4	33.7	38.9, 39.0	–	–
23	[d]	H	2	SO_3Na	CD_3OD/D_2O	35.6–35.9	50.4–50.9 (J = 137)	36.6–36.9 (J = 146)	176.0 176.4	
17	$C_{16}-C_{18:1}$	CH_3[e]	2	SO_3Na	CD_3OD/D_2O	33.9	48.6	44.6	175.0	

[a] The same carbon atom. [b]The chemical shift of the CH_3 group is 37.2 ppm (J = 144 Hz). [c]Here the compound is $R^1C(O)[NR_2(CH_2)_n]_mX$ (m = 5). [d] The range of chemical shifts for individual compounds is quoted. [e]The chemical shift of the NCH_3 group is 36.5 ppm.

involving the use of deuterium exchange. NMR spectroscopy has made it possible to establish the nature of the associated species of acylaminoacids in aqueous systems and to show that the formation of their micelles is accompanied by an upfield displacement of the chemical shift for the hydrophilic part of the molecule as a result of conformational rearrangements around the C(O)–N and N–CH_2 bonds.[154]

Measurement of the ^1H and ^{13}C NMR spectra (400 and 20 mHz) for a series of acylaminoacids with long hydrocarbon groups, involving the use of spectrometers with superconducting magnets, which increased the chemical shift resolution, has made it possible to make a reliable assignment of the majority of the signals due to the functional groups of individual compounds and to identify them readily in technical products constituting multicomponent mixtures.[155–165] Typical chemical shifts for certain functional groups in the ^1H and ^{13}C NMR spectra of acylaminoacids are presented in Tables 6 and 7.

2. Chromatographic separation

Despite the fact that the separation of acylaminoacids by gas–liquid chromatography is extremely difficult owing to their relatively high molecular masses and extremely low volatility, the application of this method for the separation of acyl derivatives of, for example, glycine, alanine, α-aminohexanoic and α-aminoheptanoic acids, β-alanine, and the mixture of α-aminoacids produced by the hydrolysis of natural protein materials have been described in the literature.[166–172] High performance liquid chromatography has been very widely used to separate acylaminoacids (see for example, Refs 173–177). The order in which acylaminoacids are eluted is determined both by the nature of the aminoacids and by the structure of the acyl group.

3. Surface-active and bulk-phase properties

Like other anionic surfactants, acylaminoacids form micelles, by virtue of their diphilic structure, over a narrow temperature range exceeding the Krafft point, i.e. the temperature below which micelles are insoluble. The structures of the aminoacids differ from those of the traditional surfactants, for example HCA soaps, by the presence of the peptide groups, which impart to them a number of specific properties. In particular, they exhibit an increased resistance to acids and salts, a greater rigidity, lower pH values of their aqueous solutions, lower critical concentrations for micelle formation (CCM) and Krafft points, and a lower surface activity (G_m), but they have higher minimum surface tensions (σ_{min}).[25,140,178,179] Certain colloidal-chemical properties of acylaminoacids are presented in Table 8.

The available data show that the principal factors determining the Krafft points and CCM are the size of the acyl group and the degree of branching of the aminoacid fragment. The salts of acylaminoacids are less active at the liquid–gas interface than the corresponding HCA salts, where the nature of the formation of their micelles is largely determined by the enhancement of the hydrophobic properties of the molecule owing to the lateral branching at the C_α atom of the aminoacid fragment. This has been confirmed by the minimum surface tensions and the CCM. The CCM for acyl derivatives of α-aminoacids diminishes with increase in the hydrophobicity of the molecules in the following sequence; glycine > α-alanine > valine > leucine.[179–181] The hydrophobicity increases sharply for salts of acyl derivatives of lysine. On the other hand, the salts of acyl derivatives of aspartic acid (a dicarboxylic acid) are more hydrophilic. The contribution of aminoacid side chains to the relative hydrophobicity has been estimated from the CCM for the salts of the lauroyl derivatives of a series of α-aminoacids in a study of the formation of their micelles in various media[182,183] and the authors suggested that the CCM be used as a characteristic of a surfactant, reflecting its hydrophile-lypophile balance (HLB).

The formation of micelles by acylaminoacids is accompanied by a change in certain physical parameters of their molecules, for example by a displacement of the chemical shift of the nuclei of the nucleophilic fragment, which is a consequence of the conformational rearrangements about the C(O)–N and N–CH_2 bonds.[184] It is noteworthy that the mechanisms of micelle formation are very significantly influenced by the type and number of impurities. Thus it has been shown[185] that values of CCM_1–CCM_4 in the range 0.026%–0.12% have been found in a technical product—sodium oleoylmethyltaurinate containing NaCl and NaOH as the main impurities—from the points of inflexion in the isotherm and from the solubilisation of a dye. The different micellar structures, characterised by the four typical concentrations for micelle formation, correspond to spherical and non-spherical (cylindrical) micelles and their aggregates.

The influence of the structure of the acylaminoacid molecules on their surface and bulk-phase properties has been estimated quantitatively by calculation and by correlating the values of σ_{min} derived from experimental σ isotherms.[179] It was shown that this parameter increases steadily with increase in the size of the acyl group, obeying the familiar Duclos–Traube rule, and decreases with increase in the size of the carbon skeleton of the molecule of the initial aminoacid.

Adsorption in a layer with participation of the carboxy- and peptide-groups is characteristic of acylaminoacids. This increases the surface area per molecule in the monomeric layer of the surfactant and decreases its limiting adsorption.[198] It has been shown for acyl derivatives of glycine and alanine[199] that they form a condensed monolayer over the entire range of surface pressures at temperatures of 283.2–308.2 K. Under these conditions, an increase in the size of the side group of aminoacid entails an increase in the area of the monolayer.

4. Hydrophobicity

The hydrophobicity of the molecules of organic compounds is an important property which determines the effectiveness of their activity. In view of this, constant attention has been devoted to the development of methods for the quantitative estimation of hydrophobicity or the HLB. The hydrophobicity of molecules is determined by their structure (each functional group makes a definite contribution in accordance with the values of the fragment constants).[200] Thus the introduction of a hydrocarbon group into the molecule makes it more hydrophobic, whilst the presence in the molecule of a double or triple bond as well as the lone pairs of the oxygen and nitrogen atoms make the compound hydrophilic. Recently it has been suggested that, together with the traditional methods for the instrumental estimation of the HLB, one should employ reversed-phase high performance liquid chromatography.[177] The hydrophobicities of the dodecanoyl derivatives of 17 most important aminoacids have been estimated from their measured chromatographic capacity coefficients and the results have been correlated with calculated data. It was shown that the correlation coefficients for structurally similar acylaminoacids are extremely high (0.978–0.999).

It has been found that the hydrophobic parameters of acylaminoacids determine the colloidal-chemical properties of these compounds and their fungicidal activity. The correlation between the hydrophobic and colloidal parameters for the dodecanoyl derivatives of a series of α-aminoacids[181] is entirely satisfactory, particularly for the CCM and σ_{min}. The results of in vitro tests on acylaminoacids by a standard method in a medium with toxicants acting against agents inducing fungal diseases showed[201] that the fungicidal activity of these compounds is satisfactorily correlated with their hydrophobic parameters, particularly in the case of structurally similar derivatives of α-aminoacids.

Table 8. The melting points (T_m), the Krafft points, CCM, and σ_{min} for aqueous solutions of the sodium salts of the acyl derivatives of a series of aminoacids $R^1C(O)NR^2(CHX)_nY$.[13,20,25,140,156,178–197]

No. of compound	$R^1C(O)$	R^2	X	*n*	Y	T_m/°C[a]	Krafft point/°C[b]	σ (60°C)/ mN m^{-1}	10^{-3} CCM (30 °C)/k mol^{-3}
24	C_{10}	H	H	1	COONa	113	+ (40)	34.5	45.72
18	C_{12}	H	H	1	COONa	117	36 (65)	35.6	12.66
25	C_{14}	H	H	1	COONa	121	47 (93)	35.6	4.30
19	C_{16}	H	H	1	COONa	121	55 (–)	35.4	1.25
20	C_{18}	H	H	1	COONa	127	66 (–)	36.1	0.44
26	C_{10}	H	CH_3	1	COONa	97	+ (154)	33.8	38.60
27	C_{12}	H	CH_3	1	COONa	104	18 (666)	34.5	11.53
28	C_{14}	H	CH_3	1	COONa	109	32 (523)	34.7	3.80
29	C_{16}	H	CH_3	1	COONa	114	45 (301)	34.3	1.23
30	C_{18}	H	CH_3	1	COONa	116	56 (–)	35.0	0.40
31	C_{10}	CH_3	H	1	COONa	36.5	+ (109)	33.8	53.08
32	C_{12}	CH_3	H	1	COONa	45.6	+ (258)	34.0	14.57
33	C_{14}	CH_3	H	1	COONa	52.0	+ (273)	34.2	3.99
34	C_{16}	CH_3	H	1	COONa	60.0	2 (229)	34.2	1.12
2	C_{18}	CH_3	H	1	COONa	71.5	33 (229)	34.1	0.32
35	C_{10}	H	$CH(CH_3)_2$	1	COONa	90	+ (109)	30.0	32.22
36	C_{12}	H	$CH(CH_3)_2$	1	COONa	92	+ (372)	31.0	9.97
37	C_{14}	H	$CH(CH_3)_2$	1	COONa	97	+ (400)	33.3	3.24
38	C_{16}	H	$CH(CH_3)_2$	1	COONa	99	8 (330)	32.1	0.82
39	C_{18}	H	$CH(CH_3)_2$	1	COONa	100	36 (229)	32.4	0.25
40	C_{10}	H	$CH_2CH(CH_3)_2$	1	COONa	109	+ (94)	28.6	19.09
41	C_{12}	H	$CH_2CH(CH_3)_2$	1	COONa	107	+ (229)	29.0	6.09
42	C_{14}	H	$CH_2CH(CH_3)_2$	1	COONa	101	+ (243)	30.0	2.04
43	C_{16}	H	$CH_2CH(CH_3)_2$	1	COONa	91	+ (236)	30.3	0.67
44	C_{18}	H	$CH_2CH(CH_3)_2$	1	COONa	65	46 (–)	29.9	0.22
45	C_{10}	H	$(CH_2)_4NH_2$	1	COONa	113	8 (184)	21.7	1.74
46	C_{12}	H	$(CH_2)_4NH_2$	1	COONa	117	34 (229)	23.8	0.90
47	C_{14}	H	$(CH_2)_4NH_2$	1	COONa	119	61 (–)	22.5	0.27
48	C_{16}	H	$(CH_2)_4NH_2$	1	COONa	122	84 (–)	23.6	0.17
49	C_{10}	H	CH_2COOH	1	COONa	103	+ (47)	39.6	112.20
50	C_{12}	H	CH_2COOH	1	COONa	109	+ (78)	39.3	33.56
51	C_{14}	H	CH_2COOH	1	COONa	115	+ (109)	40.1	13.02
52	C_{16}	H	CH_2COOH	1	COONa	118	+ (169)	40.6	3.69
53	C_{18}	H	CH_2COOH	1	COONa	119	46 (154)	40.8	1.33
54	C_{10}	H	H	5	COONa	58–60	18	44.8	13.0
6	C_{12}	H	H	5	COONa	85–86	29	42.4	6.0
55	C_{14}	H	H	5	COONa	90–91	39	39.6	2.0
56	C_{16}	H	H	5	COONa	99–101	49	38.2	0.6
57	C_{18}	H	H	5	COONa	105–107	61	36.7	0.2
7	$C_{18:1}$	H	H	5	COONa	–	5	32.0	0.3
58	C_{10}	CH_3	H	2	SO_3Na	224–225	0	61.0	–
59	C_{12}	CH_3	H	2	SO_3Na	207–208	1	49.6	8.7
60	C_{14}	CH_3	H	2	SO_3Na	201–203	23	41.4	1.82
61	C_{16}	CH_3	H	2	SO_3Na	187–188	43	40.4	0.43
62	C_{18}	CH_3	H	2	SO_3Na	171–173	58	37.8	–
63	$C_{18:1}$	CH_3	H	2	SO_3Na	162–164	0	39.3	0.29
11	C_{10}	H	H	2	SO_3Na	–	0	61.7	33.0
12	C_{12}	H	H	2	SO_3Na	–	14	50.9	10.1
13	C_{14}	H	H	2	SO_3Na	–	29	42.9	2.1
14	C_{16}	H	H	2	SO_3Na	–	46	41.4	0.55
15	C_{18}	H	H	2	SO_3Na	–	60	39.5	–
16	$C_{18:1}$	H	H	2	SO_3Na	–	0	39.1	0.40

[a] The melting points T_m were taken from Refs 14, 15, 24, 25, 135, 139, 180, 187, 189, 191, and 193. [b] The following notation has been adopted: (+) — pure solutions at 0 °C; the numerals in brackets denote the concentrations of the Ca^{2+} ions in $CaCO_3$ (10^{-4} %).

IV. Practical applications

There are almost no literature data on the practical applications of acylaminoacids, especially on their use as biologically and surface-active substances. A need for such a survey has arisen as a result of the continuous growth in the number of publications devoted to the study of the properties of acylaminoacids and especially their practical applications. Acylaminoacids exhibit different physiological and biological activities and are employed widely in various investigations in biology and biochemistry.[202] The latter include the study of complex membrane proteins, the preparation of liposomal systems, the crystallisation and study of the structures of proteins, etc. The uses of acylaminoacids associated with human vital activity are presented below.

1. Physiologically active agents

The search for new physiologically active agents among acylaminoacids embraces a wide range of compounds, for example acetylenic[203] and fluorine-containing[204–206] aminoacids, and phosphorus analogues of aminoacids.[207] The last exhibit an appreciable biological activity.[208]

Acylaminoacids, in particular derivatives of glycine, ornithine, and aspartic and glutamic acids have been detected in the organisms of certain warm-blooded animals and man.[1] This is due to the fact that they are the final products of the metabolism of proteins or are intermediates in the interconversions of aminoacids and proteins. It has been established experimentally that certain acyl derivatives are metabolised by the intestinal microflora under anaerobic conditions in vitro[209] and in animal tissues,[210] which leads to their deacylation.

The medical industry imposes very rigorous requirements on the chemical compounds employed. In this respect, acylaminoacids are favourable substances because their toxicity is extremely low. For example, LD_{50} = 5000 mg kg^{-1} (rats, administration via the stomach)[211] or 260–460 mg kg^{-1} (mice, intraabdominal administration)[212] for certain acylaminoacids. It was shown experimentally that acylaminoacids can be assimilated by the organism, since they are the starting materials for the synthesis of the organism's lipids and biologically active metabolites, for example arachidonic acid, the principal precursor of prostaglandins.[213]

Acetylcysteine, an active mucolytic agent which is indicated in the treatment of diseases of the respiratory organs, when there is a tendency toward lung haemorrhages, and in bronchial asthma, occupies an important place in the assortment of medicinal drugs.[214–216] Together with the mucolytic activity, acetylcysteine exhibits also an antibiotic activity.[217] The use of this preparation in the treatment of the diseases of the eye cornea[218] and for detoxication in cases of poisoning with methylmercury[219] in combination with haemodialysis has been described.

Effective preparations influencing the central nervous system have been discovered among acylaminoacids. These are derivatives of DL-aspartic[220] and 4-aminobutyric[221] acids, asparagine,[222] and the amides of acylaminoacids.[223] Their effect on the central blood circulation and the systemic arterial pressure, on the content of acetylcholine in various regions of the cerebral cortex, and on the functional disorders of the brain has been noted.

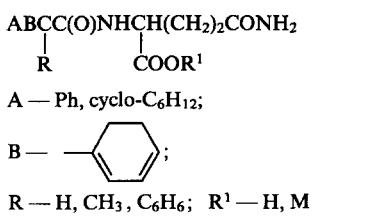
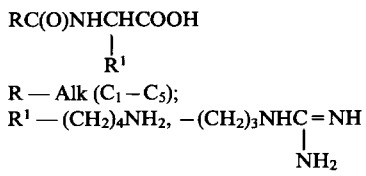
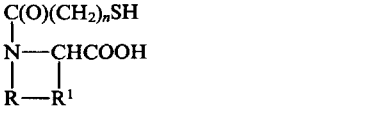
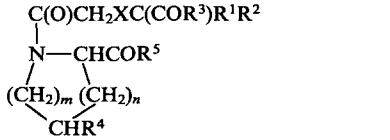
Acylaminoacids occupy a notable place among the rheumatological antiinflammatory and antiulcer preparations.[224–231] They are designed for the treatment of patients for whom the employment of traditional agents is contraindicated. Acylaminoacids do not as a rule induce undesirable side effects. A series of acylaminoacids are the active principles of antihypertonic[232–240] and therapeutic,[61,242] agents, inhibitors of enzymes with angiotensive activity,[235,243–246] and other preparations with many-sided activity.[247–252] The main principles of the selectivity and mechanisms of the action of medicinal drugs, including acylaminoacids, have been described in a monograph.[246] Thus certain acylaminoacids, for example benzoylglycine, are formed as metabolites when benzoic acid is eliminated from the kidneys. A series of benzoyl derivatives of aminoacids and oligopeptides have been used as anions in the study of a model of their transport through membranes.

Acylaminoacids with a complex structure which are the active principles of many medicinal drugs (ampicillin, oxacillin, carbenicillin, ceflorin, folic acid, levomycetin succinate, methotrexate, pantogam, picamilon, phenoxymethylpenicillin, cefazolin, cephalexin, and cephalothin) are included in a handbook.[253] These compounds are antibacterial, neotropic, and antitumour agents which are components of the Group B vitamin complex and participate in the carbohydrate and fat metabolism.

Table 9. Certain medicinal preparations based on *N*-acylaminoacids.

Compound	Chemical formula	Applications	Ref.
Acetylcysteine	$CH_3C(O)NHCHCOOH$ $\quad\quad\quad

Table 9 (continued)

Compound	Chemical formula	Applications	Ref.
Acylglutamine	 A — Ph, cyclo-C_6H_{12}; B — ; R — H, CH_3, C_6H_6; R^1 — H, M	Antiinflammatory agent and preparation for the treatment of diseases of the eye	225
6-(*N*-Acetyl)amino-hexanoic acid	$CH_3C(O)NH(CH_2)_5COOH$	Stimulation of the reparative processes in the healing of wounds and in the knitting of bones	248
Zn salt of 6-(*N*-acetyl)-aminohexanoic acid	$[CH_3C(O)NH(CH_2)_5COO]I_2Zn$	Therapeutic preparation with antiinflammatory and antirheumatic activities.	226
N-Acylaminoacids	 R — Alk (C_1-C_5); R^1 — $(CH_2)_4NH_2$, $-(CH_2)_3NHC(=NH)NH_2$	Antitumour and antiviral agent	249
Acylaminoacid derivatives	$RC(O)XC(O)NR^1CHR^2COOR^3$ R — Ar; R^1, R^2, R^3 — H, Alk (C_1-C_4); X — $-CH(SR^4)CHR^5-$; R^4, R^5 — H, Ac	Hypertonic preparations	232
Sulfur-containing acylaminoacids	$CH(2\text{-}HOC_6H_4)(CH)_2NC(O)ASR$ $SCH_2CHCONHCHR^1COR^2$ R — H, Ac; R^1 — H, Alk, NH_2, COOH, H, S, RS; R^2 — OH, OAlk; A — $-(CH_2)_n-$, $n = 1-3$	Antihypertensive agents	233
N-(Thiopropanoyl)-aminoacids	$C(O)R^1CHCH_2SR$ $NR^2CR^3R^4COOH$ R — Ac; R^1, R^2 — H, Alk; R^3, R^4 — Alk	Preparations with hypertonic activity	234
N-Acylaminoacid amides	$CH(YXR^2)(CH_2)_nSR^1$ $CONR^3CHR^4COR^5$ R^1 — H, Bz, Ac; R^2 — H, Alk, Ac; R^3-R^5 — H, Alk, Ar; R^3, R^4 — $(CH_2)_m$, $m = 3, 4$; X — O, S; Y — (CHR)	Anticonvulsant and soporific agents and depressants of the central nervous system	223
N-(Mercaptoacyl)-aminoacids	 R, R^1 — $(CH_2)_3$, $(CH_2)_4$, CH_2SCH_2; $n = 1-3$	Hypotensive preparation, in particular in the treatment of liver hypertonicity	236
N-(Carboxyacyl)-aminoacid derivatives	 R^1 — Alk, Ar; R^2 — H, Alk, Ar; R^3, R^5 — OH, OAlk, OAr, NH_2 R^4 — OAlk, SAlk; X — CHR, NR $n, m = 0-3$	Preparation for the treatment of hypertonicity	237
N-(Carboxyacyl)-aminoacids	$CHR^3(CH_2)_nC(O)R^4$ $C(O)NR^2CHR^1COOH$ R^1 — H, Alk, Ph, HOC_6H_4, NH_2, HS; R^2, R^3 — H, Alk; n — 1, 2; R^4 — OAlk, OH	Inhibitors of the angiotensive transformation of enzymes	239

Acylaminoacids exhibit antimicrobial and antifungal activities and are used as disinfectants and antiseptic agents in toothpaste, tooth powders, and toilet requisites. These include acyl derivatives of glycine,[254] sarcosine,[13] arginine, histidine, lysine, diaminobutyric acid,[255] and their peptides.[256] The highest activity against Gram-negative bacteria among the homologous acyl derivatives has been discovered for caproylglycine[257] at the pH characteristic of the surface of the skin. Acyl derivatives of glutamic acid and glutamine have been proposed for the inhibition for the activity of bacteriophages[13,258] and are used in the preparation of antibiotics, enzymes, aminoacids, and nucleotides. The ability of acylsarcosinates to inhibit bacterial hexokinase and other acid forming enzymes, protecting thereby the tooth enamel, is widely used for commercial purposes in the manufacture of toothpaste.[20,259,260]

Table 9 presents a list of the medicinal preparations based on *N*-acylaminoacids.

2. Pesticides

Together with natural α-aminoacids and their alkyl derivatives, acylaminoacids exhibit a fairly broad spectrum of biological activity.[261]

Acylaminoacids manifest a fungicidal activity[254,262,263] and regulate the formation of ethene in plants, permitting an increase in the lifetime of cut flowers.[264] These products are effective as preparations against the tobacco mosaic virus and fungal and bacterial diseases of plants.[13,265–267] The stimulation of the growth of the central stem and of the flowering of carnations may be included among the advantages of the compounds indicated.[265–267] They are also capable of destroying the eggs of lice.[268–270] The highest biological activity has been noted for α-alanine derivatives.[261] The esters of acyl derivatives of alanine have found an application as herbicides against wild oats in spring and winter wheat, barley, rape, and pulses,[271–277] and as fungicides against phytophthorosis on tomatoes and potatoes,[278] peronosporosis on tobacco and hops, mildew on grape vine shoots, false mildew on onions,[279] root rot on beetroot, false mildew on potatoes,[280] and phytopathogenic fungi of the class of oomycetes.[281] Acylalanines act selectively on groups of peronosporaceous fungi.[279]

A large series of acylaminoacids with fungicidal activity have been synthesised from glycine, sarcosine, alanine, phenylalanine, valine, norvaline, leucine, proline, threonine, methionine, and α-aminobutyric acid.[13,265–267] Acylaminoacids are active against the diseases of rice (*Piricularia oryzae*)[12,282] and the radiating mildew on cucumbers and are used to combat *Bacterium oryzae, Diaporthe citri,* and *Spraerotheca fuliginca.*[283] Whilst exhibiting effective protecting properties in tests on plants in vivo, their toxicity to warm-blooded animals is low. They are nonphytotoxic and they accelerate the growth of plants. Studies on the mechanisms of the action of acylalanines on the fungal cell have shown that in most cases the synthesis of nucleic acid is retarded. The inhibition of the synthesis of RNA is the primary result of the attack by acylalanines, which has been confirmed by the retardation of the formation of RNA in a number of fungi.[279] The dodecanoyl derivatives of 15 α-aminoacids exhibit a fungicidal activity against fungi giving rise to fungal diseases: *Acterharia solani, Helmirtosporium sativum, Fusarium graminea-kum,* and *Fusarium nivali.*[201] The usual dose of the above preparations is 0.5–10 kg ha^{-1}.[284]

The benzoyl derivatives of alanine, valine, aspartic acid, and other acylaminoacids are effective herbicides.[13,285–287] These compounds proved to be effective in vivo against pathological fungi on plants, whilst they had no in vitro fungicidal activity.[288]

3. Cosmetic and hygienic preparations

The inclusion of acylaminoacids in cosmetic and hygienic preparations is due to their effective dermatological properties, biological compatibility, a low level of the irritant and allergenic activities on the skin, and the manifestation of specific types of biological activity. The use of acylaminoacids as polyfunctional surfactants in cosmetic and hygienic preparations has been described in a number of studies.[12,25,211,289,290]

The specific biological activity of acylaminoacids in cosmetic preparations is manifested by the regulation of the blood circulation in the skin. They are employed in moisturising creams for the treatment of dry skin[292] and for the retention of biologically active substances on the surface of the skin.[293] Acylaminoacids possess an antimicrobial activity against Gram-negative bacteria.[257] Acyl derivatives of a mixture of α-aminoacids have been proposed as a means of stimulating the growth of hair and promoting an increase in the content of soluble protein in the latter.[294] The preparation increases the diameter of growing hair by a factor of 2–3 and has a positive effect on the protein metabolism in the skin, increasing the content of soluble proteins by 25%–50%, which promotes a sharp decrease in defatting and irritant action. The biological activity was estimated from the total amount of soluble proteins (Bailey's method), hair being subjected under these conditions to trichlonometric monitoring by Khrunova's method.[295]

It has been demonstrated experimentally[296] that acyl derivatives of elastin are capable of penetrating deeper into the human skin epidermis compared with other agents, improving the tone and structure of the skin and eliminating fine wrinkles. The introduction of acylaminoacids combined with oligopeptides into a cream[297] has a moisturising and protecting effect on the hair and skin, limits the swellability of hair, reduces the level of irritant action in the presence of surfactants and alkalies, and makes it possible to restore damaged hair.

One of the principal requirements which must be met by modern cosmetics as regards skin care is the prevention of the premature ageing of the skin. For this purpose, deeper studies are necessary on the mechanisms of the ageing and moisturising of the skin and on the metabolic processes occurring in the latter. As a rule, acyl derivatives of hydrolysed protein,[298–300] glutamic acid,[301] and a number of other α-aminoacids[302,303] are included in such preparations in order to impart to them effective moisturising properties, to stimulate metabolic processes, and to maintain the normal water balance in the skin. As substances with a low primary toxicity and a weak side effect on the skin,[304] acylaminoacids have been proposed in recipes for decorative[305] and cleansing cosmetics.[306] They hinder the total removal of fat deposits during the washing of the skin and hair. This is important, since the secretions of the sebaceous glands have a protecting function while increased defatting of hair makes it dry and brittle and leads to the loss of its lustre and silky appearance.

Liquid detergents, shampoos, and gels occupy a leading place in the market of personal hygiene preparations. These preparations contain aminoacids and their derivatives, including acylaminoacids, as the most valuable additives.[13,307,308] In terms of a series of parameters such as the effectiveness of detergent action, degree of elution of aminoacids from the skin during washing, and the solubilisation of the defatting agent, acylaminoacids have a clear advantage over traditional surfactants such as HAC soaps, alkyl sulfates, and alkyl sulfonates.

A series of recipes for shampoos with a low irritant action and improved detergent and foam-forming properties, liquid and solid detergents, and gels incorporating acyl derivatives of β-alanine and acylglutamic acid have been developed.[309–326] Mild shampoos, which cause almost no irritation to the eyes and the skin on the head, for improving the state of hair have been created on the basis of acyl derivatives of hydrolysed proteins.[327–330] The introduction of the latter into recipes for shampoos eliminates the hardness and dullness of hair caused by the deposition of $CaCO_3$ from tap water.[331,332] Dermatologically mild detergents and shampoos with a wide variety of valuable properties from the consumer's point of view contain acyl derivatives of various α-aminoacids.[333–350]

When hair is washed, up to 50% of natural lipids are removed, as a result of which it becomes dry, loses its lustre, and

Table 10. Brief characteristics of certain recipes for cosmetic and hygienic preparations based on *N*-acylaminoacids.

Type of preparation	*N*-Acyl derivatives of aminoacids (mass %)	Consumption properties	Ref.
Shampoo	of glutamic acid		
	(1 – 10)	Preparations with a low irritant activity and improved detergent and foam-forming properties	309, 317, 318
	(20 – 25)	Transparent creamy detergents	310, 320
	or β-alanine		
	(0.5 – 10)	Preparations with improved detergent, foam-forming, and softening properties, which readily wash away fatty dirt, assist in feeding and strengthening hair, and do not irritate the skin and the mucous membranes around the eyes	325, 338
	(25 – 35)	In combination with acylsarcosinates, an effective preparation in the form of a transparent gel	326
	of hydrolysed proteins (3 – 30)	Dermatologically soft preparations for dry and sensitive skin, improving the state of hair, and possessing excellent foam-forming properties and increased stability during storage. These preparations exhibit a satisfactory affinity for the skin and hair, and improve the state of hair, rendering it pleasant to the touch, and preventing its entanglement during drying. They counteract the deposition on hair of water-insoluble salts, preventing the hardness and dullness of hair, and form on the damaged ends of hair a protective film which promotes softening and regenerative properties	327 – 332
	of sarcosine		
	(1 – 10)	Dermatologically soft preparations with high foam-forming and detergent capacities	336 – 338
	(30 – 50)	Transparent gel-like preparations, which do not irritate the skin and eyes	340
	of an aminoacid mixture (5 – 20)	Preparations with high foam-forming and detergent capacities. Therapeutic and healing agents with a low irritant activity containing biologically active additives, for example derivatives of α-pyridone	334, 335 333, 345
Cream	of oligopeptides (0.5 – 8)	Preparations improving the structure of the skin, influencing metabolic processes, promoting a better permeation through the corneous layer of the skin, and smoothing away fine wrinkles	296, 300
	of glutamic acid (0.1 – 12)	Effective preparations with biological activity for the care of ageing skin, improving its moisture-retaining capacity, and stimulating metabolic processes	301 – 303
Cream	of aminoacids (0.1 – 5)	Preparations promoting the restoration of damaged hair, increasing the affinity for the skin and softening and feeding the latter	297, 305
Preparations for hair care	of oligopeptides (0.1 – 3)	Effective preparations for the improvement of the state of hair by restoring its lipid balance, rendering it soft, improving its capacity for being set, and reducing the damage to hair after dyeing and the application of a chemical permanent wave	351, 356, 369
	of aminoacids (0.1 – 10)	Preparations softening leather and hair, imparting lustre to the latter and making it manageable, smooth, fluffy, and elastic. These preparations feed hair effectively, stimulate the occurrence of metabolic processes in it, exert an antistatic effect, improve the setting of hair, promote its growth, and prevent its falling out.	352, 354 – 359, 362 – 366
		The *N*-acylaminoacids in these preparations promote the retention of biologically active substances in hair and enhance blood circulation, thus preventing dandruff and loss of hair	291, 293

is difficult to set. The loss of lipids may be made good with the aid of cosmetics containing various plant extracts, natural lipids, and acyl derivatives of a series of α-aminoacids.[351] Cosmetics for skin and hair care in the form of lotions and sprays containing acyl derivatives of aminoacids and hydrolysed proteins soften hair,[352-362] strengthen it,[363,364] promote its growth,[365] feed it and stimulate metabolic processes in it,[366,367] improve its moisture retaining properties,[360,368] and reduce damage to hair and improve its structure.[369]

N-Acylaminoacids are a valuable cosmetic raw material for effective preparations with a broad spectrum of cosmetic and therapeutic and healing activities on skin and hair (Table 10).

References

1. J P Greenstein, M Winitz *Chemistry of the Amino Acids* (New York: Wiley, 1961) (Translated into Russian; Moscow: Mir, 1965)
2. E Schröder, K Lübke *The Peptides* Vol. 1 (Translated into Russian; Moscow: Mir, 1967)
3. E Schröder, K Lübke *The Peptides* Vol. 2 (Translated into Russian; Moscow: Mir, 1969)
4. *Amino Acids, Peptides and Proteins (Specialist Periodical Reports)* (London: Chemical Society, 1969)
5. P Katsoyanis (Ed.) *Khimiya Polipeptidov* (Chemistry of Polypeptides) (Moscow: Khimiya, 1977)
6. B Weinstein (Ed.) *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins* Vol. 1, 3 (New York: Marcel Dekker, 1971, 1974)
7. E Gross, J Meinhofer (Eds) *The Peptides* Vol. 1–3 (New York: Academic Press, 1979–1981)
8. E Gross, J Meinhofer (Eds) *The Peptides. The Principal Methods for the Formation of Peptide Bonds* (Translated into Russian; Moscow: Mir, 1983)
9. Yu A Ovchinnikov *Bioorganicheskaya Khimiya* (Bioorganic Chemistry) (Moscow: Prosveshchenie, 1987)
10. N V Sidgwick *The Organic Chemistry of Nitrogen* Part 6 (Eds T Millar, H D Springall) (Oxford: Claredon Press, 1966)
11. J H Jones (Ed.) *Amino Acids and Peptides. Review of the Literature Published during 1985* Vol. 18 (London: Royal Society of Chemistry, 1987)
12. M S Sadovnikova, V M Belikov *Usp. Khim.* **47** 357 (1978) [*Russ. Chem. Rev.* **47** 199 (1978)]
13. M Takehara *Yukagaku* **34** 964 (1985)
14. A A Akimova, O I Galakhova *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **30** (6) 144 (1987)
15. E A Smirnova, Yu A Davidovich, S V Rogozhin *Synthesis of Higher N-Acyl Derivatives of Amino Acids: Comparative Analysis* Article deposited at TsNIITEPishcheprom, No. 75, Moscow (1983)
16. A A Gershkovich, V K Kibirev *Khimicheskii Sintez Peptidov* (Chemical Synthesis of Peptides) (Kiev: Naukova Dumka, 1992)
17. D Barton, W D Ollis (Eds) *Comprehensive Organic Chemistry* Vol. 4 (Translated into Russian; Moscow: Khimiya, 1983)
18. H Stüpel *Synthetischewasch und Reingungsmittel* (Stuttgart: Konradin Verlag,1954) (Translated into Russian; Moscow: Goskhimizdat, 1960)
19. A M Schwartz, J W Perry, J Berch *Surface Active Agents and Detergents* (New York: Interscience,1958) (Translated into Russian; Moscow: Izd. Inostr. Lit., 1960)
20. J D Spivack, in *Anionic Surfactants* Part 2 (Ed. W M Linfield) (New York: Marcel Dekker, 1976)
21. L V Kuritsyn, N V Kalinina, M V Moshkova *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **32** (10) 30 (1989)
22. V G Kotlerevskii, V E Kuban, G P Nechesnyuk, V A Kruchinin *Zh. Prikl. Khim.* **49** 1558 (1976)
23. E F Babaev, R G Safarov, M F Bakhmanov, O A Narimanbekov *Kinetics and Mechanism of the N-Acylation of α-Aminoacids in the Salt Form by Benzoyl Chloride* (Baku, 1989) Article deposited at the All-Union Institute of Scientific and Technical Information (VINITI), No. 625, Moscow (1989)
24. E Jungermann, J F Gevecht, I J Krems *J. Am. Chem. Soc.* **78** 172 (1956)
25. S N Faingol'd, A E Kuusk, Kh E Kiik *Khimiya Anionnykh i Amfolitnykh Azotsoderzhashchikh Poverkhnostno-Aktivnykh Veshchestv* (Chemistry of Anionic and Ampholytic Nitrogen-Containing Surface-Active Substances) (Tallin: Valgus, 1984)
26. Jpn. Appl. 63-45 244; *Ref. Zh. Khim.* 18 N 38P (1989)
27. Jpn. Appl. 54-100 317; *Ref. Zh. Khim.* 10 N 72P (1980)
28. US P. 4 293 106; *Ref. Zh. Khim.* 17 N 162P (1982)
29. M Koyil, B Baranowska, B Cybulska *Tenside* **17** 174 (1980)
30. J P Sisley (Ed.) *Encyclopedia of Surface-Active Agents* Vols 1–4 (New York: Chem. Publ., 1961–1964)
31. B Mitev, G Khanzada, in *Proc. of the IVth Int. Congr.* Vol. 1 (London: Gordon and Breach, 1967) p. 379
32. G P Nechesnyuk, V A Kruchinin, T N Trufanova, V I Zhuravleva, V E Kuban *Khim. Promst.* 587 (1987)
33. J W B Methfess *Acta Biol. Med. Ger. B* **26** 1147 (1971)
34. G P Nechesnyuk, M I Volokhina, O D Slapygina, V A Kruchinin, Yu V Logunov, in *V Vsesoyuzn. Konf. Poverkhnostno-Aktivnye Veshchestva i Syr'e dlya Nikh (Tez. Dokl.)* (Abstracts of Reports of the Fifth All-Union Conference on Surface-Active Substances and Raw Materials for Their Production) (Shebekino: VNIIPAV, 1979) p. 57
35. I A Krylov, V I Panfilov, I V Tikhonova, M N Manakov, in *VI Vsesoyuz. Konf. po Poverkhnostno-Aktivnym Veshchestvam i Syr'yu dlya Ikh Proizvodstva (Tez. Dokl.)* (Abstracts of Reports of the Sixth All-Union Conference on Surface-Active Substances and Raw Materials for Their Production) (Volgodonsk: VNIIPAV, 1984) p. 79
36. USSR P. 1 006 481; *Byull. Izobret.* (11) 143 (1983)
37. USSR P. 1 639 051; *Byull. Izobret.* (47) 259 (1992)
38. DDR P. 144 406; *Ref. Zh. Khim.* 16 N 81P (1981)
39. US P. 4 352 759; *Chem. Abstr.* **97** 198 573h (1982)
40. US P. 4 233 229; *Ref. Zh. Khim.* 18 N 78P (1981)
41. DDR P. 131 467; *Ref. Zh. Khim.* 4 R 494P (1979)
42. DDR P. 133 233; *Ref. Zh. Khim.* 17 R 453P (1979)
43. DDR P. 208 800; *Ref. Zh. Khim.* 9 R 489P (1985)
44. DDR P. 255 733; *Ref. Zh. Khim.* 1 R 2 029P (1989)
45. Jpn. Appl. 56-35 176; *Ref. Zh. Khim.* 5 N 63P (1983)
46. Jpn. Appl. 62-178 558; *Chem. Abstr.* **108** 56 621i (1988)
47. S Fisler, D Oana, G Musca *Rev. Chim., Bucharest* **39** 128 (1988)
48. USSR P. 761 455; *Byull. Izobret.* (33) 118 (1980)
49. USSR P. 753 844; *Byull. Izobret.* (29) 111 (1980)
50. US P. 3 796 751; *Ref. Zh. Khim.* 1 N 76P (1975)
51. Fr. P. 2 113 231; *Izobret. Stran Mira* (7) (1972)
52. USSR P. 185 876; *Byull. Izobret.* (18) 34 (1966)
53. USSR P. 1 703 640; *Byull. Izobret.* (1) 112 (1992)
54. US P. 4 487 725 (1981)
55. BRD Appl. 3 219 651; *Ref. Zh. Khim.* 2 N 151P (1985)
56. US P. 4 749 523; *Ref. Zh. Khim.* 12 N 92P (1989)
57. USSR P. 436 077; *Byull. Izobret.* (26) 71 (1974)
58. US P. 3 074 980; *Ref. Zh. Khim.* 22 R 354P (1964)
59. Fr. P. 2 460 295; *Ref. Zh. Khim.* 6 N 84P (1982)
60. Jpn. Appl. 50-088 002; *Chem. Abstr.* **83** 193 730h (1975)
61. Br. Appl. 1 434 217; *Izobret. Stran Mira* (11) (1976)
62. BRD P. 3 003 898; *Ref. Zh. Khim.* 13 N 120P (1982)
63. Jpn. Appl. 55-57 548; *Ref. Zh. Khim.* 17 O 12P (1981)
64. BRD Appl. 2 151 739; *Ref. Zh. Khim.* 17 R 647P (1978)
65. BRD Appl. 2 031 826; *Chem. Abstr.* **74** 75 692p (1971)
66. Pol. Appl. 254 551; *Izobret. Stran Mira* (2) (1988)
67. US P. 4 406 833; *Ref. Zh. Khim.* 14 R 486P (1984)
68. R G Bistline, E S Rothman, S A Serota, A J Stirton, A N Wrigley *J. Am. Oil Chem. Soc.* **48** 657 (1971)
69. US P. 3 745 181; *Ref. Zh. Khim.* 11 R 477P (1974)
70. USSR P. 513 025; *Byull. Izobret.* (17) 80 (1976)
71. K A Kochetkov, Zh S Urmambetova, V M Belikov, Z B Bakasova *Izv. Akad. Nauk SSSR, Ser. Khim.* 2555 (1990)
72. V V Ryakhovskii, S V Agafonov, Yu M Kosyrev *Usp. Khim.* **60** 1817 (1991) [*Russ. Chem. Rev.* **60** 924 (1991)]
73. D Barton, W D Ollis (Eds) *Comprehensive Organic Chemistry* Vol. 10 (Translated into Russian; Moscow: Khimiya, 1986)
74. G Ivaldi, L Arrigo *Giorn. Biochim.* **10** 549 (1961)
75. Jpn. P. 9 131; *Ref. Zh. Khim.* 19 N 317P (1968)
76. USSR P. 694 070; *Byull. Izobret.* (39) 240 (1979)
77. R Paul, G W Anderson *J. Am. Chem. Soc.* **82** 4596 (1960)
78. Jpn. Appl. 47-35 900; *Ref. Zh. Khim.* 11 N 156 (1972)
79. USSR P. 456 804; *Byull. Izobret.* (2) 46 (1975)
80. BRD P. 2 901 843; *Chem. Abstr.* **93** 239 946v (1980)
81. BRD Appl. 3 101 427; *Ref. Zh. Khim.* 18 O 11P (1983)
82. Jpn. Appl. 57-27 103; *Chem. Abstr.* **96** 102 790g (1982)
83. S Yamada, Y Kasai, T Shioiri *Tetrahedron Lett.* **14** 1595 (1973)
84. T Shioiri, K Ninomiya, S Yamada *J. Am. Chem. Soc.* **94** 6203 (1972)
85. USSR P. 405 868; *Byull. Izobret.* (45) 93 (1973)
86. BRD P. 2 004 099; *Chem. Abstr.* **74** 119 426d (1971)
87. Br. Appl. 1 384 982; *Ref. Zh. Khim.* 9 O 8P (1976)
88. A P Mikhalkin, V N Marshalkin, P P Gnatyuk, V A Malii, V N Vlasov *Khim. Promst* 651 (1991)

89. A P Mikhalkin, V V Sudneko, A B Sakhinov, I G Rybalka, in *VIII Vsesoyuz. Konf. Poverkhnostno-Aktivnye Veshchestva i Syr'e dlya Ikh Proizvodstva (Tez. Dokl.)* (Abstracts of Reports at the Eighth All-Union Conference on Surface-Active Substances and Raw Materials for Their Production) (Belgorod: VNIIPAV, 1992) p. 4
90. A P Mikhalkin, V V Sudneko, I G Rybalka, A B Bakhinov *Khim. Promst* 388 (1992)
91. US P. 4 234 475; *Ref. Zh. Khim.* 13 R 439P (1981)
92. L W Burnette, M E Chiddix *J. Am. Oil Chem. Soc.* **39** 477 (1962)
93. E Ebbel *Tenside* **1** 26 (1964)
94. BRD Appl. 2 231 070; *Ref. Zh. Khim.* 2 3R 481 (1974)
95. US P. 3 894 064; *Chem. Abstr.* **80** 82 080q (1974)
96. Jpn. Appl. 60-59 902; *Chem. Abstr.* **98** 142 968i (1983)
97. Br. Appl. 1 325 102 (1973)
98. US P. 3 766 266 SShA; *Ref. Zh. Khim.* 18 N 103P (1974)
99. D Reffet Doctoral thesis, University of Paris, 1982
100. Fr. Appl. 2 523 576; *Ref. Zh. Khim.* 16 N 48P (1980)
101. Fr. Appl. 239 5252; *Ref. Zh. Khim.* 2 N 57P (1980)
102. US P. 2 826 676 (1958)
103. Jpn. Appl. 55-21 737; *Ref. Zh. Khim.* 8 N 23P (1981)
104. Jpn. Appl. 54-117 403; *Ref. Zh. Khim.* 10 O 9P (1980)
105. Jpn. Appl. 55-43 455; *Ref. Zh. Khim.* 13 N 72P (1981)
106. Jpn. Appl. 58-85 845; *Ref. Zh. Khim.* 16 O 7P (1984)
107. US P. 4 497 964
108. BRD Appl. 3 242 374; *Chem. Abstr.* **99** 105 706g (1983)
109. Fr. Appl. 2 516 508 (1983)
110. US P. 4 414 404; *Ref. Zh. Khim.* 16 O 8P (1984)
111. Br. Appl. 1 513 533
112. BRD Appl. 274 1081; *Chem. Abstr.* **91** 108 229z (1979)
113. US P. 4 126 628; *Ref. Zh. Khim.* 12 O 12P (1979)
114. A Paquet *Can. J. Chem.* **54** 733 (1976)
115. Br. Appl. 2 111 982 (1983)
116. I Ojima *J. Mol. Catal.* **37** 25 (1986)
117. I Simidzu *Kagaku to kogy* **39** 370 (1986)
118. K Izawa *Yuki Gosei Kagaku Kyokaishi* **46** 218 (1988)
119. M Debska, A Hpofinger *Przem. Chem.* **43** 359 (1964)
120. USSR P. 195 393; *Byull. Izobret.* (10) 4 (1967)
121. K Teramura *Mem. Fac. Ind. Arts Kyoto Tech. Univ. Sci. Technol.* (8) 53 (1959)
122. BRD P. 2 537 914; *Ref. Zh. Khim.* 7 R 501P (1978)
123. Br. Appl. 1 502 519; *Chem. Abstr.* **87** 23 738o (1977)
124. Fr. Appl. 2 322 133; *Chem. Abstr.* **87** 23 788 (1977)
125. BRD P. 2 537 289; *Ref. Zh. Khim.* 7 R 495P (1978)
126. WO Appl. 84-00 165; *Chem. Abstr.* **100** 157 172p (1984)
127. Jpn. Appl. 55-122 755; *Ref. Zh. Khim.* 4 R 515P (1982)
128. Eur. Appl. 0 112 921; *Chem. Abstr.* **100** 157 177 (1984)
129. Br. Appl. 1 503 280; *Chem. Abstr.* **86** 189 248 (1977)
130. USSR P. 1 051 069; *Byull. Izobret.* (40) 92 (1983)
131. Ch Kimura, K Kashiwaya, K Murai *Jukagaku* **32** 692 (1983)
132. US P. 2 956 068 SShA (1960)
133. BRD P. 1 184 769; *Ref. Zh. Khim.* 17 N 69 (1966)
134. T Suyama, T Toyoda, S Kanao *Jakugaku Zasshi* **86** 967 (1966)
135. S Miyagishi, S Matsumura, K Murata, T Asakawa, M Nishida *Bull. Chem. Soc. Jpn.* **58** 1019 (1985)
136. M Naudet *Bull. Soc. Chim. Fr.* **17** 358 (1950)
137. K Okki, F Tokiwa *Yukagaku* **19** 897 (1970)
138. T Shirai, T Narita, G Yamaguchi, K Arai *Yuki Gosei Kagaku Kyokaishi* **30** 68 (1972)
139. V N Iyer, G N Sheth, V V R Subrahmanyam *J. Indian Chem. Soc.* **59** 856 (1982)
140. V N Iyer, V V R Subrahmanyam *J. Indian Chem. Soc.* **62** 507 (1985)
141. S Miyagishi, S Matsumura, T Asakawa, M Nishida *Bull. Chem. Soc. Jpn.* **59** 557 (1986)
142. S Hara, A Dobashi, V Dobashi *Yuki Gosei Kagaku Kyokaishi* **44** 858 (1986)
143. A I Scott *Interpretation of the UV Spectra of Natural Products* (New York: Pergamon Press, 1962)
144. L J Bellamy *The Infrared Spectra of Complex Molecules* Vols 1, 2 (London: Chapman and Hall, 1975) (Translated into Russian; Moscow: Izd. Inostr. Lit., 1963)
145. Y K Nakanishi *Infrared Absorption Spectroscopy* (Translated into Russian; Moscow: Mir, 1965)
146. *The Aldrich Library of Infrared Spectra* (3rd Edition) (Milwaukee, USA: Charles J. Pouchert, Aldrich Chem. Co., 1981)
147. H Takahashi, Y Nakayama, H Hori, K Kihara, H Okabayashi, M Okuyama *J. Colloid Interface Sci.* **54** 102 (1976)
148. H Konig, in *Neue Methoden zur Analyse von Tensiden* (Berlin: Springer, 1971) p. 75
149. Y Schimohigashi, T Kato, Sh Kang, Y Minematsu, M Waki, N Izumiya *Tetrahedron Lett.* **20** 327 (1979)
150. Y Shimohigashi *Mem. Fac. Sci. Kyushu Univ. C* **13** 135 (1981)
151. O Bouloussa, P Dizabo *J. Labelled Compd. Radiopharm.* **19** 991 (1982)
152. R A Newmark, T R Hill *J. Magn. Reson.* **21** 1 (1976)
153. P D Gunston *Chem. Phys. Lipids* **18** 115 (1977)
154. H Okabayashi, T Yoshida, Y Terada, K Matsushita *J. Colloid Interface Sci.* **87** 527 (1982)
155. A A Fomichev, L V Gorshkova, A P Mikhalkin, in *VII Vsesoyuz. Konf. Poverkhnostno-Aktivnye Veshchestva i Syr'e dlya Ikh Proizvodstva (Tez. Dokl.)* (Abstracts of Reports at the Seventh All-Union Conference on Surface-Active Substances and Raw Materials for Their Production) (Shebekino: VNIIPAV, 1988) p. 44
156. A A Fomichev, A P Mikhalkin, L V Gorshkova, V N Marshalkin *Identification of the Products of the Acylation of 6-Aminohexanoic Acid from NMR Spectra* (Cherkassy 1990) Article deposited at ONIITEKhIM, No. 509 Cherkassy (1990)
157. A P Mikhalkin, V N Marshalkin, A A Fomichev, L V Gorshkova *Sodium Salts of 2-N-Acylaminoethane Sulfonic Acid* (Cherkassy 1990) Article deposited at ONIITEKhIM, No. 229 Cherkassy (1990)
158. Russ. P. 1 602 181; *Byull. Izobret.* (47) 262 (1992)
159. A P Mikhalkin, L V Gorshkova, I G Rybalka, in *VIII Vsesoyuz. Konf. Poverkhnostno-Aktivnye Veshchestva i Syr'e dlya Ikh Proizvodstva (Tez. Dokl.)* (Abstracts of Reports at the Eighth All-Union Conference on Surface-Active Substances and Raw Materials for Their Production) (Belgorod: VNIIPAV, 1992) p. 202
160. A P Mikhalkin, L V Gorshkova, V N Marshalkin, in *VIII Vsesoyuz. Konf. Poverkhnostno-Aktivnye Veshchestva i Syr'e dlya Ikh Proizvodstva (Tez. Dokl.)* (Abstracts of Reports at the Eighth All-Union Conference on Surface-Active Substances and Raw Materials for Their Production) (Belgorod: VNIIPAV, 1992) p. 203
161. Russ. P. 1 740 075; *Byull. Izobret.* (22) 33 (1992)
162. Russ. P. 1 796 614; *Byull. Izobret.* (7) 78 (1993)
163. A P Mikhalkin, L V Gorshkova *Spektry YaMR N-Alkil-, N-Alkanoilproizvodnykh Nekotorykh ω-Aminokislot i Aminosul'fokislot (Ser. Aktual'nye Voprosy Khimicheskoi Nauki i Tekhnologii, Ekologii v Khimicheskoi Promyshlennosti)* [NMR Spectra of *N*-Alkyl- and *N*-Alkanoyl Derivatives of Certain ω-Aminoacids and Aminosulfonic Acids (Ser. Current Chemical, Chemical Engineering, and Ecological Problems in the Chemical Industry), No. 1 (Moscow: NIITEKhIM, 1993)
164. Russ. P. 2 007 388; *Byull. Izobret.* (3) 65 (1994)
165. A P Mikhalkin, L V Gorshkova *Zh. Fiz. Khim.* **69** 865 (1995)
166. E V Sunozova, V Yu Trubnikov, K I Sakodynskii *Gazovaya Khromatografiya Aminokislot* (Gas Chromatography of Aminoacids) (Moscow: Nauka, 1976)
167. A N Korol' *Usp. Khim.* **46** 2264 (1977) [*Russ. Chem. Rev.* **46** 1202 (1977)]
168. S C J Eu, D S H Mak *J. Chromatogr.* **78** 211 (1973)
169. L A Osterman *Khromatografiya Belkov i Nukleinovykh Kislot* (Chromatography of Proteins and Nucleic Acids) (Moscow: Nauka, 1985)
170. R B O'Neill, T Gerritsen *Clin. Chim. Acta* **62** 13 (1975)
171. Russ. P. 2 000 565; *Byull. Izobret.* (33–36) 130 (1993)
172. Russ. P. 2 000 567; *Byull. Izobret.* (33–36) 131 (1993)
173. K G Wahlund, B Edlen *J. Liq. Chromatogr.* **4** 309 (1981)
174. E Busker, J Martens *Fresenius Z. Anal. Chem.* **325** 559 (1986)
175. Shoji Hara *Yakugaku Zasshi* **102** 107 (1982)
176. J Vindevogel, J Dijck, M Verzele *J. Chromatogr.* **447** 297 (1988)
177. A P Mikhalkin, V N Vlasov *Kolloidn. Zh.* **55** 100 (1992)
178. G N Sheth, V V R Subrahamanyam *J. Indian Chem. Soc.* **59** 860 (1982)

179. A P Mikhalkin, A D Korenev, L A Koroleva *Kolloidn. Zh.* **51** 706 (1989)
180. J Beger, R Neuman, A Seib *Tensi de Detergents* **23** 156 (1986)
181. A P Mikhalkin, V N Vlasov *Kolloidn. Zh.* **57** (1) (1995)
182. B Yu Zaslavskii, A A Borovskaya, N N Osipov, Yu A Davidovich, A Yu Lisichkin, S V Rogozhin *Kolloidn. Zh.* **41** 233 (1979)
183. B Yu Zaslavskii, A A Borovskaya, A Yu Lisichkin, Yu A Davidovich, S V Rogozhin *Kolloidn. Zh.* **41** 553 (1979)
184. A P Mikhalkin *Kolloidn. Zh.* **56** 400 (1994)
185. I L Povkh, R V Kucher, I A Shevchuk, A I Serdyuk, Z M Vashun', V G L'vov *Zh. Prikl. Khim.* **51** 1045 (1978)
186. S Miyagishi, Y Ishibai, T Asakawa *J. Colloid. Interface Sci.* **103** 164 (1985)
187. R Yoshida *Yukagaku* **24** 538 (1975)
188. M Takehara, R Yoshida *Yukagaku* **25** 789 (1976)
189. T Suyama, T Toyoda, S Kanoo *Yakugaku Zasshi* **86** 967 (1966)
190. R Yoshida *Yukagaku* **25** 404 (1976)
191. M Takehara, U Moriyuki, J Yoshimura *J. Am. Oil Chem. Soc.* **49** 143 (1972)
192. M Takehara, H Moriyuki, A Arakawa *J. Am. Oil Chem. Soc.* **50** 223 (1973)
193. M Takehara, I Yoshimura, K Takizawa *J. Am. Oil Chem. Soc.* **49** 157 (1972)
194. M Takehara, I Yoshimura, R Yoshida *J. Am. Oil Chem. Soc.* **51** 419 (1974)
195. T Kuwamura, O Aoki, N Suto *Yukagaku* **34** 626 (1985)
196. A P Mikhalkin, L A Koroleva, V N Marshalkin *Some Surface-Active Properties of Sodium Salts of N-Acyl Derivatives of 6-Aminohexanoic Acid — the Base of Flotation Agent AAK* (Cherkassy, 1988) Article deposited at ONIITEKhIM No. 804 Cherkassy (1988)
197. N Parris, I K Weil, M Linfield *J. Am. Oil Chem. Soc.* **49** 649 (1972)
198. A P Mikhalkin, L A Koroleva *Kolloid. Zh.* **54** 123 (1992)
199. K Takahashi, F Tanaka, K Motomura *Bull. Chem. Soc. Jpn.* **57** 944 (1984)
200. R Rekker, H De Kort *Eur. J. Med. Chem.* **14** 479 (1979)
201. V N Vlasov, A P Mikhalkin, A L Chimishkyan *Zh. Fiz. Khim.* **69** 833 (1995)
202. J Neugelauer *A Guide to the Properties and Uses of Detergents in Biology and Biochemistry* (Lucerne: © Calbiochem. Brand Biochemicals, 1987)
203. S A Abdulganeeva, K B Erzhanov *Usp. Khim.* **60** 1318 (1991) [*Russ. Chem. Rev.* **60** 678 (1991)]
204. V P Kukhar', Yu L Yagupol'skii, V A Soloshonok *Usp. Khim.* **59** 149 (1990) [*Russ. Chem. Rev.* **59** 89 (1990)]
205. V P Kukhar', V A Soloshonok *Usp. Khim.* **60** 1680 (1991) [*Russ. Chem. Rev.* **60** 850 (1991)]
206. V P Kukhar', Yu L Yagupol'skii, I I Gerus, M T Kolycheva *Usp. Khim.* **60** 2047 (1991) [*Russ. Chem. Rev.* **60** 1050 (1991)]
207. V P Kukhar', V A Solodenko *Usp. Khim.* **56** 1504 (1987) [*Russ. Chem. Rev.* **56** 859 (1987)]
208. K A Kochetkov, V M Belikov *Usp. Khim.* **56** 1832 (1987) [*Russ. Chem. Rev.* **56** 1045 (1987)]
209. G E Smith, L A Griffiths *Xenobiotica* **4** 477 (1974)
210. Y Endo, Y Oqura *Jpn. J. Pharmacol.* **25** 161 (1975)
211. M Yu Pletnev *Kosmetiko-Gigienicheskie Moyushchie Sredstva* (Cosmetic and Hygienic Detergents) (Moscow: Khimiya, 1990)
212. A F Akhabadze, N B Koroleva, A G Strenkovskaya *Ekspertiza Novykh Kosmeticheskikh Sredstv Razlichnogo Naznacheniya* (Expert Assessment of New Cosmetics for Different Purposes) (Moscow: TsNIITEIPishcheprom, 1975)
213. V T Mazaev, E S Petrova, R V Bobylev, L B Troenkina, A V Kuznetsova *Tr. Mosk. Med. Inst. im. I M Sechenova* 115 (1986)
214. Ya K Gauen, E K Platkais, Ya Ya Putniek, in *Fiziologiya i Patologiya Beremennosti i Detei* (Physiology and Pathology of Pregnancy and Children) Vol. 1 (Riga: Zinatne, 1973) p. 59
215. A Horvath, M Takeres, Gy Deak *Medicamentum* **30** 24 (1974)
216. N Konnadovam, Y Vavrova, J Sŭlova *Folia Marphol., Praga* **31** 250 (1983)
217. H Bürgy *Chemotherapy* **21** 167 (1975)
218. M A Lemp, M Roddy *Ann. Ophthalmol.* **6** 893 (1974)
219. P J Kostyniak, T V Clarkson, P Y Cestero *J. Pharmacol. Exp. Ther.* **192** 260 (1975)
220. T Xoaku *Okayamigakkai Zasshi* **81** 411 (1969)
221. Eur. P. 46 707; *Chem. Abstr.* **97** 5 820e (1982)
222. G Cannizzaro, V La Grutta, M Palazzoadrino *Arch. Int. Pharmacodynam Ther.* **192** 220 (1971)
223. Jpn. Appl. 48-37 024; *Ref. Zh. Khim.* 20 N 311 (1973)
224. P Grellat *Phumatologia* **27** 67 (1975)
225. BRD P. 2 618 936; *Chem. Abstr.* **86** 43 421 (1977)
226. BRD P. 2 901 914; *Chem. Abstr.* **90** 192 550g (1979)
227. Ruman. P. 78 211; *Ref. Zh. Khim.* 21 O 2 210 (1983)
228. Jpn. Appl. 61-1 651; *Ref. Zh. Khim.* 1 O 18P (1987)
229. Eur. Appl. 011 5424; *Chem. Abstr.* **102** 25 030x (1985)
230. BRD P. 2 506 601; *Chem. Abstr.* **84** 15696o (1976)
231. US P. 4 610 983; *Ref. Zh. Khim.* 11 O 25P (1987)
232. US P. 4 435 329; *Ref. Zh. Khim.* 2 O 10P (1985)
233. US P. 4 425 333; *Ref. Zh. Khim.* 3 O 25P (1985)
234. Irish P. 46 875; *Ref. Zh. Khim.* 7 O 9P (1985)
235. BRD P. 2 752 720; *Chem. Abstr.* **89** 147 225y (1978)
236. US P. 4 424 228; *Ref. Zh. Khim.* 1 O 255P (1985)
237. Eur. Appl. 0 115 091; *Chem. Abstr.* **102** 25 042c (1985)
238. BRD Appl. 2 720 996; *Chem. Abstr.* **88** 51 169m (1978)
239. US P. 4 228 184; *Ref. Zh. Khim.* 13 O 22P (1981)
240. Eur. P. 21 883; *Chem. Abstr.* **95** 98 321q (1981)
241. US P. 4 440 788; *Ref. Zh. Khim.* 2 O 12P (1985)
242. BRD P. 2 923 698; *Chem. Abstr.* **93** 47 196d (1980)
243. Eur. P. 4 649; *Chem. Abstr.* **92** 181 655k (1980)
244. J T Suh, J R Regan *Eur. J. Med. Chem.* **20** 563 (1985)
245. T K Komori *Chem. Pharm. Bull.* **35** 2382 (1987)
246. A Albert, in *Selective Toxicity. The Physicochemical Basis of Therapy* Vol. 2 (Translated into Russian; Moscow: Meditsina, 1982) p. 52
247. E Clany, B Jacotot, E C R Patois *Soc. Biol.* **165** 1549 (1971)
248. B G Yasnitskii, E B Dol'berg, A D Spivak *Khim.-Farm. Zh.* **13** (4) 78 (1979)
249. Eur. Appl. 0 069 659; *Chem. Abstr.* **98** 155 213i (1983)
250. Fr. P. 2 564 832; *Ref. Zh. Khim.* 1 O 19P (1987)
251. BRD Appl. 3 003 898; *Chem. Abstr.* **95** 187 672x (1981)
252. US P. 4 681 973; *Ref. Zh. Khim.* 11 O 170P (1989)
253. V G Belikov *Sinteticheskie i Prirodnye Lekarstvennye Sredstva. Kratkii Spravochnik* (Synthetic and Natural Medicines. A Concise Handbook) (Moscow: Vysshaya Shkola, 1993)
254. USSR P. 325 837; *Ref. Zh. Khim.* 24 O 290P (1976)
255. US P. 3 825 560; *Ref. Zh. Khim.* 9 R 492P (1975)
256. H Ito *Yakugaku Zasshi* **94** 1010 (1974)
257. A Alfaloji, J Fourniat, P Bourlioux *Parfumes Cosmet. Arames* **53** 95 (1983)
258. US P. 3 880 718; *Chem. Abstr.* **83** 5 6726x (1975)
259. S H Shapiro, in *Surface-Active Derivatives, Soaps and Detergents.* Part 5 (New York: Marcel Dekker, 1968) p. 115
260. J P Sisley, in *Index des Huiles Sulfonees et Detergents Modernes* Vol. 3 (Paris: Teintex, 1961) p. 121
261. N N Mel'nikov, in *Pestitsidy: Khimiya, Tekhnologiya i Primenenie* (Pesticides: Chemistry, Technology and Applications) (Moscow: Khimiya, 1987) p. 149
262. A Kolbe *Z. Chem.* **27** 215 (1987)
263. B Rigo, C Lespagnol, M Pauly *J. Heterocycl. Chem.* **25** 49 (1988)
264. BRD Appl. 3 528 631; *Ref. Zh. Khim.* 18 O 449P (1987)
265. US P. 3 947 589; *Ref. Zh. Khim.* 24 O 289P (1976)
266. Br. Appl. 2 096 897; *Ref. Zh. Khim.* 17 O 304 (1983)
267. Jpn. Appl. 52-17 093; *Ref. Zh. Khim.* 4 O 330 (1978)
268. US P. 41 28 662; *Ref. Zh. Khim.* 14 O 375P (1979)
269. Jpn. P. 55-34 124; *Chem. Abstr.* **79** 53 049k (1973)
270. Fr. Appl. 2 422 400; *Ref. Zh. Khim.* 23 O 328P (1980)
271. Yu A Baskakov *Zh. Vses. Khim. O-va im. D I Mendeleeva* **29** 22 (1984)
272. K J Kirklan *Weed Sci.* **24** 316 (1976)
273. W A Olsow *Weed Sci.* **25** 355 (1977)
274. S D Miller *Weed Sci.* **27** 91 (1979)
275. B Jeffcoad *Pestic. Sci.* **6** 283 (1975)
276. E Haddack *Weed Sci.* **6** 273 (1975)
277. B Jordan *Weed Sci.* **20** 21 (1977)
278. N M Golyshin *Zh. Vses. Khim. O-va im. D I Mendeleeva* **29** 74 (1984)

279. B A Khaskin *Zh. Vses. Khim. O-va im D I Mendeleeva* **33** 698 (1988)
280. F Schwinn *Mit. Biol. Bundesanst* **178** 145 (1977)
281. E Ammerman, in *Proceedings of the 10th Congress on Plant Protection, Brighton, 1983* Vol. 1, p. 332
282. Jpn. Appl. 52-42 851; *Ref. Zh. Khim.* 7 O 522 (1979)
283. Jpn. Appl. 52-44 369; *Chem. Abstr.* **83** 80 008k (1975)
284. DDR P. 241 350; *Ref. Zh. Khim.* 12 O 426P (1987)
285. Swed. P. 357 736; *Ref. Zh. Khim.* 9 N 429 (1974)
286. Norw. P. 122 188; *Ref. Zh. Khim.* 8 N 662P (1972)
287. US P. 3 840 362; *Ref. Zh. Khim.* 16 O 472P (1975)
288. BRD P. 2 303 228; *Chem. Abstr.* **78** 93 629 (1973)
289. A Domsch, G Schuster *Alvztl. Kosmetol., Ser. B* **6** 524 (1983)
290. M Takehara *Kjemi* **22** 459 (1984)
291. Jpn. Appl. 63-159 308; *Ref. Zh. Khim.* 21 R 2 077P (1989)
292. Eur. Appl. 0 408 448 (1991)
293. Br. P. 1 439 244; *Chem. Abstr.* **86** 60 411v (1977)
294. Russ. Appl. 5 045 347 (1994)
295. A P Khrunova, Yu N Koshevenko, V V Rubina, K I Trukhmanova *Vestn. Dermatol. Venerol.* **3** 14 (1985)
296. Eur. P. 0 283 601; *Ref. Zh. Khim.* 13 R 2 044P (1989)
297. Russ. P. 2 005 469; *Byull. Izobret.* (1) 28 (1994)
298. L V Laine, S I Karal'nik *Kosmeticheskie Sredstva po Ukhodu za Kozhei (Ser. Parfyumerno-Kosmeticheskaya i Efiromaslichnaya prom-st'* [Cosmetics for Skin Care. (Ser. Perfumery and Aromatics Industry)] Vol. 2 (Moscow: TsNIITEIPishcheprom, 1979)
299. Jpn. Appl. 54-163 828; *Ref. Zh. Khim.* 7 R 526P (1981)
300. Jpn. Appl. 61-118 307; *Ref. Zh. Khim.* 18 R 607P (1987)
301. Jpn. Appl. 61-171 405; *Ref. Zh. Khim.* 18 R 626P (1987)
302. Jpn. Appl. 62-138 599; *Ref. Zh. Khim.* 24 R 847P (1988)
303. Jpn. Appl. 62-138 600; *Ref. Zh. Khim.* 24 R 846P (1988)
304. Eur. Appl. 0 102 118; *Chem. Abstr.* **101** 9 127h (1984)
305. Jpn. Appl. 61-105 03; *Ref. Zh. Khim.* 17 R 566P (1987)
306. Jpn. Appl. 61-135 714; *Chem. Abstr.* **105** 210 065p (1986)
307. S I Koral'nik, D A Gabrielyan, L V Laine *Proizvodstvo Shampunei za Rubezhom. (Ser. Parfyumerno-Kosmeticheskaya i Efiromaslichnaya Prom-st')* [Production of Shampoos Abroad (Ser. Perfumery and Aromatics Industry)] Vol. 8 (Moscow: TsNIITEPishcheprom, 1983)
308. F Rabeli *Cosmet. Toilet.* **102** 83 (1987)
309. Jpn. Appl. 61-69 713; *Ref. Zh. Khim.* 6 R 612P (1987)
310. Jpn. Appl. 62-297 398; *Ref. Zh. Khim.* 20 R 2 020P (1989)
311. Jpn. Appl. 60-31 240; *Chem. Abstr.* **103** 63 501e (1985)
312. US P. 4 578 216; *Ref. Zh. Khim.* 22 R 612P (1986)
313. Jpn. Appl. 61-23 959; *Chem. Abstr.* **104** 215 219e (1986)
314. Jpn. Appl. 60-39 316; *Chem. Abstr.* **98** 217 673e (1983)
315. Jpn. Appl. 51-42 603; *Ref. Zh. Khim.* 18 N 132 (1973)
316. Jpn. Appl. 52-10 457; *Ref. Zh. Khim.* 4 R 550 (1978)
317. Jpn. Appl. 61-16 997; *Ref. Zh. Khim.* 13R545P (1987)
318. Jpn. Appl. 61-272 294; *Ref. Zh. Khim.* 20 R 2 018P (1989)
319. Jpn. Appl. 58-35 560; *Chem. Abstr.* **88** 172 289j (1978)
320. Jpn. Appl. 59-230 099; *Ref. Zh. Khim.* 11 R 533P (1986)
321. Jpn. Appl. 60-43 495; *Ref. Zh. Khim.* 20 R 2 021P (1989)
322. US P. 4 578 218; *Ref. Zh. Khim.* 22 R 613P (1986)
323. US P. 4 591498; *Ref. Zh. Khim.* 4 R 621P (1987)
324. Jpn. Appl. 60-132 912; *Ref. Zh. Khim.* 21 R 559P (1986)
325. Jpn. Appl. 61-283 695; *Ref. Zh. Khim.* 12 R 2 031P (1989)
326. Jpn. Appl. 58-113 298; *Ref. Zh. Khim.* 22 R 512P (1984)
327. Jpn. Appl. 61-69 714; *Ref. Zh. Khim.* 7 R 634P (1987)
328. Jpn. Appl. 61-140 515; *Ref. Zh. Khim.* 18 R 647P (1987)
329. Jpn. Appl. 62-298 515; *Ref. Zh. Khim.* 11 R 2 024P (1989)
330. Jpn. Appl. 63-105 000; *Ref. Zh. Khim.* 15 R 2 079P (1989)
331. US P. 3 988 438; *Ref. Zh. Khim.* 14 R 498P (1977)
332. Jpn. Appl. 63-150 212; *Ref. Zh. Khim.* 18 R 2 064P (1989)
333. Jpn. Appl. 62-151 499; *Ref. Zh. Khim.* 6 R 2 013P (1989)
334. Jpn. Appl. 62-263 297; *Ref. Zh. Khim.* 18 R 2 021P (1989)
335. Jpn. Appl. 63-75 096; *Ref. Zh. Khim.* 10 R 2 011P (1989)
336. US P. 4 726 915; *Ref. Zh. Khim.* 6 R 2 020P (1989)
337. US P. 4 772 424; *Ref. Zh. Khim.* 17 R 2 013P (1989)
338. Jpn. Appl. 63-183 519; *Ref. Zh. Khim.* 16 R 2 012P (1989)
339. Jpn. Appl. 58-168 695; *Ref. Zh. Khim.* 22 R 520P (1984)
340. Jpn. Appl. 59-232 194; *Ref. Zh. Khim.* 15 R 649P (1986)
341. US P. 4 478 734; *Ref. Zh. Khim.* 14 R 453P (1983)
342. US P. 4 147 782; *Chem. Abstr.* **90** 192 573s (1970)
343. Eur P. 0 248 297; *Izobret. Stran Mira* **8** (1988)
344. Jpn. Appl. 54-38 604; *Chem. Abstr.* **84** 137 638t (1976)
345. Jpn. Appl. 58-56 399; *Chem. Abstr.* **89** 30 593a (1978)
346. Jpn. Appl. 59-1 435; *Ref. Zh. Khim.* 3 N 59P (1985)
347. Jpn. Appl. 60-46 156; *Chem. Abstr.* **102** 168 720h (1985)
348. Jpn. Appl. 61-2 112; *Chem. Abstr.* **97** 217 583e (1982)
349. T Schoenberg *Soap Cosmet., Chem. Spec.* **62** 36 (1986)
350. J R Hart, E F Levy *Soap Cosmet., Chem. Spec.* **53** 31 (1977)
351. T Schoenberg *Manuf. Chem.* **60** 27 (1989)
352. Jpn. Appl. 59-5 108; *Ref. Zh. Khim.* 6 R 621P (1985)
353. Jpn. Appl. 59-53 677; *Ref. Zh. Khim.* 22 R 690P (1985)
354. Jpn. Appl. 61-152 615; *Ref. Zh. Khim.* 15 R 629P (1987)
355. Jpn. Appl. 60-214 724; *Ref. Zh. Khim.* 6 R 614P (1987)
356. Jpn. Appl. 62-286 911; *Ref. Zh. Khim.* 4 R 2 059P (1989)
357. Jpn. Appl. 59-108 708; *Ref. Zh. Khim.* 19 R 574P (1985)
358. Jpn. Appl. 59-31 706; *Ref. Zh. Khim.* 13 R 607P (1985)
359. Jpn. Appl. 61-229 812; *Ref. Zh. Khim.* 19 R 540P (1987)
360. Jpn. Appl. 63-33 317; *Ref. Zh. Khim.* 17 R 2 050P (1989)
361. Jpn. Appl. 56-12 609; *Ref. Zh. Khim.* 11 R 616P (1982)
362. Eur. Appl. 0 336 265; *Izobret. Stran Mira* (10) (1990)
363. Jpn. Appl. 61-137 808; *Ref. Zh. Khim.* 18 R 649P (1987)
364. Jpn. Appl. 61-155 310; *Ref. Zh. Khim.* 17 R 579P (1987)
365. Jpn. Appl. 61-151 109; *Ref. Zh. Khim.* 16 R 568P (1987)
366. Jpn. Appl. 61-227 515; *Ref. Zh. Khim.* 3 R 566P (1988)
367. Br. Appl. 1 388 760; *Izobret. Stran Mira* (6) (1975)
368. Jpn. Appl. 62-28 913; *Ref. Zh. Khim.* 6 R 2 062P (1989)
369. Jpn. Appl. 63-57 512; *Ref. Zh. Khim.* 8 R 2 092P (1989)