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Industrial Applications of Amino-acids

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Aspects of the use of amino-acids in various branches of industry—as food additives and surface-active agents, in the production of polymeric materials, in electrochemical manufacture, etc.—are surveyed on the basis of works of reference and the patent literature up to 1975. A list of 273 references is included.

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I. INTRODUCTION

During recent years the manufacture of amino-acids has been actively developed throughout the world (Table). Their chief consumers, ensuring a steady demand, have been the food industry, in which sodium glutamate is used as a flavour intensifier, and lysine as an additive to increase the nutritional value of bread, animal husbandry, and poultry farming, where lysine, tryptophan, threonine, and methionine are used to increase the food value of protein feeds.

World production of amino-acids (1974).

Product	Annual production, tonnes	Method*
Sodium *L*-glutamate monohydrate	200 000	M, X
L-Methionine	50 000	X
L-Lysine monohydrochloride	20 000	M
L-Tryptophan	20	X
L-Threonine	20	X
Glycine	2 000	X

*M = microbiological; X = chemical.

The present review does not cover such well known fields of application as animal husbandry, parenteral feeding, etc., on which a vast review literature exists. Special attention is paid to less well known trends—the possible use of amino-acids in pharmacology and cosmetics, as food additives and surface-active agents, in the synthesis of polymeric materials, as pesticides, in the electrochemical industry, etc. Several fields of application have not been developed because of the very high cost of amino-acids, due mainly to the low volume of production. The recognition of new consumers will help to increase production and thereby ensure the comprehensive application of amino-acids.

II. THE FOOD INDUSTRY

The chief consumer of amino-acids at the present time is the food industry. Problems of the enrichment of food products with indispensable amino-acids and of balancing the diet (i.e. adding the missing amino-acids to low-quality proteins) have been widely discussed in the Soviet [1-3] and foreign [4-8] literature, so that we will not dwell on them. Food products can be enriched with lysine, threonine (rice, wheat, sorghum, etc.), tryptophan (maize, wheat). and methionine (soya-bean and peanut flour). However, the balancing of cereal products with pure amino-acids (other than lysine) has not yet found widespread application in the food industry [3], although it improves the nutritional properties of vegetable protein. *L*-Threonine and *L*-tryptophan have not yet found practical application for product enrichment, yet vigorous research has been undertaken on the possible use of these important saturated amino-acids, which is prevented by their high price. Among possible fields of application of these and other amino-acids are babyfoods [1], enrichment of low-calorie food [1,6,9-11], dietetic feeding [12-15], and special diets for cosmonauts [16].

While possessing extremely interesting and diverse properties, amino-acids have come to find application in the food industry, as microbiological and chemical methods for obtaining them have developed, mainly as seasonings, to confer taste and aroma on food products, and as antioxidants.

The main requirement to be met by various kinds of food additives is that they should not be toxic. In the opinion of many experts amino-acids, being together with proteins natural constituents of food products, fully satisfy this requirement. Many publications have appeared, including Refs. 17–19, on the determination of the degree of toxicity of amino-acids.

Glutamic acid has become the most widely used in the food industry: salt sodium glutamate is commonly employed as an effective taste intensifier. It is widely used to improve the taste of meat and vegetable dishes [20], as a mixture with table salt, and for modifying the taste of synthetic sweetening agents [21]; in many countries it is added to all products during canning, freezing, or prolonged storage [3,20]. The patent literature suggests that the boundaries of its application continue to be extended [22-28]; in Japan its production has formed the starting point for industrial methods of obtaining amino-acids, and has stimulated vigorous research on the application of other amino-acids in this way.

In fact many amino-acids possess their own unique flavour and are important elements in the taste of food products. These properties of individual amino-acids have been studied by many investigators and in especial

detail by groups under the leadership of Yoshida [29] and of Solms [30,31]. The usual pure amino-acids were found to be respectively tasteless or with a barely perceptible taste (*D*-alanine, *D*- and *L*-arginine, *D*- and *L*-aspartic acid, *D*-glutamic acid, *L*-histidine, *D*- and *L*-isoleucine, *D*- and *L*-lysine, *D*- and *L*-proline, *D*- and *L*-serine, *D*- and *L*-threonine, and *D*- and *L*-valine), sweet (in order of diminishing sweetness—*D*-tryptophan, *D*-histidine, *D*-phenylalanine, *D*-tyrosine, *D*-leucine, *L*-alanine, and glycine), bitter (in order of diminishing bitterness—*L*-tryptophan, *L*-phenylalanine, *L*-tyrosine, and *L*-leucine), and "sulphurous" (*D*- and *L*-cysteine and *D*- and *L*-methionine); *D*-isomers of bitter amino-acids are usually sweet. *L*-Aspartic and *L*-glutamic acids exhibit a sour taste, but when neutralised their solutions have a pleasant flavour; their *D*-isomers are tasteless. These results confirm the relation between the taste and the configuration of amino-acids. The taste is assumed to be due to "three-point" stereospecific adsorption on taste receptors in the surface of the tongue [7].

The majority of methyl, ethyl, benzyl, and t-butyl esters of α-amino-acids have a bitter taste or are tasteless. However, the hydrochloride of the t-butyl ester of *L*-alanine possesses an intensely sweet taste: a given weight is equivalent in sweetness to ~75 times that weight of sucrose [32].

The taste of a product is determined not only by the amino-acids but also by its content of mononucleotides (such as inosinic and guanylic acids), organic acids, sucrose, and inorganic acids. Peptides and metabolites of amino-acids (such as betaine and creatine) promote complexity, the "bouquet" of flavour sensations. A great contribution to the taste of plant products is made by glutamic acid, and also by other amino-acids, organic acids, and sucrose. Free amino-acids present in certain foodstuffs may completely determine the taste; in other products amino-acids or their mixtures either strengthen the taste or supply body to it [7,33,34]. The buffering properties of amino-acids also influence flavour [34]. A required taste sensation can be matached by combining various chemical substances, including amino-acids. At the present time amino-acids can be used to strengthen and improve the flavour characteristics of many food products. However, only monosodium glutamate and glycine have found practical application for these purposes.

Glycine is a typical example of sweet amino-acids, exhibiting a "refreshing" sweetness equivalent in intensity to that of sucrose. At the present time it is widely used in the Japanese food industry for the manufacture of seasonings, non-alcoholic drinks, soups, marinades, various fish products, and delicatessen (0.1–1% in amount depending on the type of product) [7,35–38]. It not only serves as sweetening agent but also creates the foundation of a taste or improves the flavour, by mitigating bitterness and saltiness. It is used also for the modification of artificial products to remove an unpleasant aftertaste.

Amino-acids and mononucleotides act synergistically with respect to taste: the effect of the flavouring agent sodium inosinate is strengthened by the addition of sodium monoglutamate. The synergistic effect of mononucleotides is evident also in combination with sodium *L*-aspartate, *L*-asparagine, and glycine, which is used in recipes for seasonings to improve the taste of foodstuffs and drinks [36,39–41].

Patent information has appeared on such taste-improving agents as *L*-lysine palmitate [42] and glutamylglycylserine [43].

A wide search is being made for new sweetening agents, especially those of peptide character. The taste of peptides is independent of the type of component amino-acids, being determined by the overall structure of the peptide. Dipeptides formed by sweet amino-acids are generally tasteless, whereas peptides containing residues of bitter amino-acids all, without exception, have a bitter taste. In 1969 the discovery was reported [44] of the methyl ester of *L*-aspartyl-*L*-phenylalanine, possessing a sweet taste (sweeter than sucrose by a factor of 150). Investigations on the dependence of taste on structure have shown that a dipeptide must contain aspartic acid to be sweet. Many sweetening agents have since been patented, representing various modifications of this dipeptide [14,45,46]; they can be used for dietary products (e.g. for diabetics). The methyl esters of *L*-aspartyl-*O*-t-butyl-*L*-serine and *L*-aspartyl-*O*-t-pentyl-*L*-serine are sweeter than sucrose by factors of 130–200, and similar to the latter in the character of the sweet taste, have no odour or unpleasant aftertaste, and can be used to improve the flavour of chocolate, confectionery, tea, farinaceous products, fruit juices, etc. [47,48] Much information has been published on the possible application as sweetening agents of both peptide and non-peptide derivatives of aspartic acid [12,14,44–53]. Either *D*- or *DL*-tryptophan can be used as synergist, intensifying the sweetness of saccharin and eliminating its inherent unpleasant aftertaste [45,53,54].

One of the chief reactions producing aroma in almost all food products is Maillard's, consisting in the interaction of the amino-groups of peptides, amino-acids, and proteins with the glycosidic hydroxyl of sugars. This reaction is especially important when the aroma results from heating the food, e.g. bread or meat [55]. According to Tressl [56] several hundred aromatic compounds, many formed by reactions between amino-acids and reducing sugars, have been identified in the aroma of products that have been subjected to heat. Thus, although most individual amino-acids are odourless, when heated with other compounds they yield odours that are specific to the given type of amino-acid. Herz and Shallenberger [57] studied the aroma produced when certain amino-acids were heated with glucose at 100 and 180°C for 1 h, and found that glycine, proline, methionine, valine, and arginine yielded the odours respectively of caramel, bread, potatoes, chocolate, and burnt sugar.

As early as the 1960s it was noted that the Maillard reaction offered great prospects of "synthesising" food odours [20], and attention has now been paid to its utilisation. Since the decisive role of the reaction is indicated by the appearance of the aroma of bread from valine, leucine, proline, and lysine in model experiments, it is recommended that a mixture of these amino-acids or the products obtained by heating the mixture with saccharides should be added to improve the flavour and aroma of farinaceous confectionery, and proline mixed with dihydroxyacetone in bread manufacture [58,59]. Valine and phenylalanine have already been used in Japan to improve the aroma of rice pastry. *L*-Lysine is added to coffee (10–70 mg/100 ml) for the same purpose [60]. It has been proposed [61] to introduce amino-acids (arginine, leucine, valine, lysine, etc.) together with dihydroxyacetone into tobacco, on the view that during curing they react with the latter to form aldehydes, which confer agreeable properties on the smoke.

Lysine, ornithine, histidine, arginine, aspartic acid, alanine, valine, leucine, isoleucine, and proline can serve as active ingredients of various deodorants for food

products[62-64]. The specific odour of rice that has been stored for a long time can be removed by adding *L*-cysteine, *L*-lysine, and *L*-histidine[65]. Thus the definite influence of amino-acids on taste and aroma has led various investigators to make repeated attempts to improve the organoleptic indices of food products.

For several years Miyake et al. studied the influence of basic amino-acids on the taste properties of meat products. They showed that the organoleptic characteristics (tenderness, taste, odour) were improved by treating raw meat with basic amino-acids, especially arginine[66]. Patents have appeared on the use of histidine, lysine, cystine, and arginine to improve the quality of meat and fish products[67,68]. In the manufacture of sausages from the meat of warm-blooded animals or fish the fat distribution and the gelatinisation of the products are improved by the addition of 0.1–1% of a *D*-amino-acid (alanine, arginine, cysteine, etc.)[69].

Individual amino-acids and their mixtures can be introduced into compositions simulating the taste and odour of natural foodstuffs. Cysteine and cystine are important constituents in the creation of "meaty" odours, and are introduced into compositions possessing the taste of meat[7,20,27,70]. Monosodium *L*-glutamate must also be present to produce a fully "meaty" odour and flavour[26,27,70,71]. For example, a mixture of a hexose and a pentose is heated with cysteine or cystine in the presence of water to give compounds having the taste of meat. They are mixed in definite proportions with the hydrolysate of a vegetable protein, monosodium glutamate, sucrose, alanine, glycine, and a mixture of inosine and guanyl monophosphates. Heating the mixture alone and together with fats produces the flavours of soup and of gravy respectively[70]. Pentoses such as ribose and xylose are more active than are hexoses. Methionine is used to make a flavouring with the smell and taste of potatoes[72]. Such synthetic compositions will become especially timely in the future in connection with the production of artificial foods[26,27,70-74].

The development of the food industry has entailed an increasing demand for large quantities of antioxidants. The antioxidising properties of methionine have been known for a long time; it is widely used in edible oils and fats, in which a strong effect is apparent, with a favourable influence on the organoleptic indices of the product[75,76]. Progress has now been made in the use of other amino-acids for these purposes.

Soboleva and her coworkers[77] studied the antioxidant properties of several amino-acids in soft and hard margarine, vegetable oil, and butter. All the amino-acids used tended to inhibit oxidising processes in fats, but the efficiency of a particular amino-acid depended considerably on the type of fat. *DL*-Lysine, *DL*-tryptophan, and *DL*-methionine are effective antioxidants for the fatty base of soft and hard margarine; *L*-arginine hydrochloride, *DL*-tryptophan, *L*-cysteine, and *DL*-methionine for vegetable cooking fat; and *L*-arginine hydrochloride, *L*-asparagine, *DL*-norleucine, and especially methionine for butter. The introduction of synergists improves the antioxidant properties of amino-acids: mixtures with chemical antioxidants—butoxytoluene and butoxyanisole—are more effective than are the individual components.

Glycine is a good antioxidant for such emulsifiers as mono- and di-glycerides. Several amino-acids were studied in model experiments using methyl linoleate[78]. The best results were obtained with histidine and tryptophan, which can be added to powdered milk to preserve it from the most frequent defect of milk products—the "oxidised" aftertaste resulting from the autoxidation of milk fat[78,79]. Individual amino-acids, their derivatives, and various compositions with other compounds have been patented for use as antioxidants[38,80-83]. Lipids in food can be freed from rancidity by adding a salt of a basic amino-acid (such as lysine) and phytic acid[82]. Alkyl esters of aspartylphenylalanine $HOOC.CH_2.CH(NH_2).CO.NH.CH(CH_2C_6H_5).COOR$ (where R = CH_3, C_2H_5) are readily soluble in oils and fats, cause neither an unpleasant odour nor discoloration when heated, and can be used as antioxidants and emulsifiers for foodstuffs[83]. *N*-Acetylmethionine has a stronger antioxidant effect than methionine in cooking oil[84].

Many investigators have studied the antioxidant action of the coloured products formed by the Maillard reaction, first reported for melanoidins[85]. The coloured products formed from amino-acids and reducing sugars play an important part in stabilising fats against oxidation[86]. As a threose, dihydroxyacetone is more reactive towards amino-acids than are pentoses and hexoses, and therefore Ito et al.[87] have compared (in a model system) the antioxidant activity of the coloured products obtained with dihydroxyacetone, glucose, and xylose respectively. This shows strong variation with the sugar and with the amino-acid. The most active sugar (the threose dihydroxyacetone) gives products exerting the greatest antioxidant effect. Among amino-acids the best results are shown by methionine, leucine, isoleucine, and valine. Products obtained from certain amino-acids and dihydroxyacetone are far more effective than butoxyanisole. These results enabled compositions prepared from dihydroxyacetone and amino-acids such as alanine, leucine, histidine, methionine, phenylalanine, threonine, and tryptophan to be recommended as food antioxidants for oils and fats[88].

Glycine, alanine, lysine, ornithine, arginine, and glutamic and aspartic acids react with sugars (glucose, fructose, etc.) under certain conditions (pH 11–13 at 100–120°C) to give food colorants having an antioxidant effect, adsorbing oxygen, and inhibiting lipoxidase[89].

Cysteine is able to occupy a special position in the food industry because of its mercapto-group and hence specific physicochemical properties. Laboratory and industrial research on *L*-cysteine and *L*-cystine has shown that their introduction into many foodstuffs (meat and meat products, milk products, bread, farinaceous confectionery, etc.) has a considerable favourable effect. These amino-acids show great promise for stabilising the quality of foodstuffs—for slowing down enzymic browning reactions, stabilising ascorbic acid, retarding the autoxidation of fats, strengthening the effect of food preservatives, and also aromatising foodstuffs[90-97]. In Japan it is permissible to add cysteine as antioxidant to natural fruit juices. Cysteine is effective against the browning of foodstuffs, since it suppresses the formation of coloured compounds (melanoidins) by reducing intermediate products; or else free radicals formed from cysteine inactivate the intermediates. Since free cysteine is readily oxidised, it is normally used in the form of the relatively stable hydrochloride. During storage of a natural fruit juice ascorbic acid, being a reductant and hence opposing browning reactions, is gradually oxidised, with browning and decrease in the nutritional value of the product. This can be prevented by adding cysteine hydrochloride. A stable food antioxidant containing equimolecular proportions of ascorbic acid and cysteine has been patented[93].

According to various authors cysteine as a reductant can also be used to improve the baking process (improve the rheological properties of the dough) and the quality of

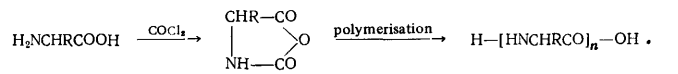
the bread[90,94-97]. Use together with ascorbic acid alone or mixed with potassium bromate gives a bread of improved structure, flavour, and aroma in a shorter time (this has already been introduced into practice in the USA, England, and Japan). Cysteine is considered to make the dough softer, by rapid reaction with gluten accompanied by cleavage of S–S bonds, while the oxidant slowly restores the elasticity, forming new S–S cross-links. Sulphur-containing amino-acids—methionine, *L*-cysteine, *L*-cysteinyl-*L*-cysteine—have been recommended for enriching phosphorylated starch, which serves as a gelling agent in foodstuffs and drinks[98].

The storage of perishable foodstuffs is one of the most important problems facing the food and canning industry. Glycine can be used to lengthen the storage life to fish products: addition of 1–2% (to improve taste and aroma) revealed that the growth of slime-forming bacteria was suppressed for some time. It is assumed that glycine inhibits biosynthesis of the cell walls of such bacteria, e.g. *Bacillus subtilis*[99]. A proposed deodorant for the oral cavity contains a reaction product of copper gluconate and glycine[100]. Derivatives obtained by the reaction of *L*-, *DL*- and *D*-glutamic acid with alkylamines and alcohols have been patented[101] for the protection of products from damage by micro-organisms. Increased storage life in the preservation of various foodstuffs—meat, fish, etc.—has been claimed[102] for the addition of a lauroyl-amino-acid (-leucine, -glycine). A method has been developed[103] for preserving foodstuffs by forming a coating from a prolamine and an amino-acid (alanine).

The list of amino-acids permitted as food additives in Japan comprises[104] *DL*-alanine, *L*-arginine-*L*-glutamate, sodium *L*-aspartate monohydrate, *L*-glutamic acid, sodium *L*-glutamate monohydrate, glycine, *L*-histidine hydrochloride monohydrate, *L*-isoleucine, *L*-lysine hydrochloride, *L*-lysine *L*-aspartate, *L*-lysine *L*-glutamate dihydrate, *DL*- and *L*-methionine, *L*-phenylalanine, *DL*- and *L*-threonine, *DL*- and *L*-tryptophan, and *L*-valine. Those permitted in the USA are[105] *LL*- and *L*-alanine, *L*-arginine, *L*-arginine hydrochloride, *DL*-aspartic acid, *L*-cystine, *L*-glutamic acid, ammonium *L*-glutamate, sodium *L*-glutamate monohydrate, potassium *L*-glutamate, *L*-glutamic acid hydrochloride, glycine, *DL*- and *L*-isoleucine, and *DL*- and *L*-leucine, *L*-lysine hydrochloride, *DL*- and *L*-methionine, *DL*- and *L*-phenylalanine, *L*-proline, *DL*- and *L*-serine, *L*-threonine, *DL*- and *L*-tryptophan, *L*-tyrosine, and *L*-valine.

III. USE OF AMINO-ACIDS IN THE SYNTHESIS OF POLYMERS

Polyamino-acids are usually obtained by the polymerisation of *N*-carboxyanhydrides prepared by the action of carbonyl chloride on the amino-acids:



Their skeletal structure resembles that of proteins, but their properties differ greatly from those of natural proteins, since they contain only one kind of amino-acid. Although various copolymers have already been synthesised, as yet they are of no practical value. Nevertheless, the structures of polyamino-acids are similar to those of such natural proteins as silk and leather, and therefore are regarded as suitable materials for the production of synthetic fibres and leather. Their use as raw material for synthetic fibres, films, and coatings of vinyl leathers was suggested by Woodward 20 years ago[7]; but these materials were then uneconomic as silk substitutes. Later glutamic acid became widely used in the Japanese food industry, and the development of methods for producing it more cheaply led to the use of polyglutamates as coatings for artificial leathers.

Poly(methyl *L*- and *D*-glutamate) are obtained by polymerisation of the *N*-carboxyanhydrides of γ-methyl *L*- and *D*-glutamates, prepared by treating the glutamates with carbonyl chloride in the presence of an appropriate polymerisation initiator in a suitable solvent[106-109]. The resulting polymer is soluble in halogenated hydrocarbons and has a highly regular linear structure, forming right-handed and left-handed α-helices from the initial *L*- and *D*-anhydrides respectively.

Two types of polymers based on γ-methyl glutamate (PGS—in the form of a solution in both cases, since PGS becomes insoluble after removal of the solvent, and moulding requires the direct use of a solution of the polymer)—unmodified PGS (commercial designation PLG) and modified PGS (PLG-N)[106-109]—which can be used e.g. for manufacture of artificial leather, synthetic fibres, and films for edible packings, are manufactured in Japan. Wet spinning gives a fibre closer than other synthetic fibres to natural silk in appearance and "feel", similar in strength and elongation, and surpassing it in resistance to weathering[107,110]. The practical value of PGS is evident in the usual application of an approximately 10% solution to coat the surface of vinyl leathers, which then become very closely similar to natural leather, highly resistant to heat, water, chemicals, and dirt, with good dyeability and several other valuable properties[109,111]. All this has resulted in the widespread use of such leathers in the manufacture of handbags, suitcases, furniture, clothing, and footwear.

Research on the preparation and properties of polyamino-acids is being vigorously pursued: polymerisation conditions[108,112,113] and effective moulding methods[110,114] are being worked out, and polymers based on other amino-acids—e.g. aspartic acid[111,115-117], glycine[115], alanine[118,119], and lysine[115,119,120]—have been synthesised. Many papers have appeared on the preparation of copolymers of amino-acids, which opens up great opportunities for modifying the properties of the resulting materials. The copolymer of γ-methyl *L*-glutamate with 1% of *L*-methionine, obtained from the corresponding *N*-carboxyanhydrides, will give a fibre of enhanced strength in comparison with the fibre without added methionine[121]. Several copolymers of *L*-leucine with *L*-cystine varying in composition and molecular weight have been synthesised[122], from which fibres have been obtained by wet spinning. X-Ray diffraction and infrared spectroscopy indicate that the fibres comprise α-helices with cystine bridges. The mechanical properties show strength and elasticity not inferior to those of wool. In contrast to wool fibres, however, whose modulus of elasticity increases appreciably at deformations $> 20\%$, these synthetic fibres develop plasticity in this range of deformations.

Modification of poly-*D*-glutamic acid and poly-*L*-aspartic acid with styrene gives resins suitable for the production of a silklike fibre with enhanced alkali resistance[123]. Copolymers of *DL*-methionine and *L*-leucine form flexible films able to transmit water vapour slowly. Oxidation of the methylthioethyl groups by hydrogen peroxide to methylsulphonium groups strengthens the hydrophilic properties of these films, the rate of passage of

vapour through a film increasing rapidly with the number of groups oxidised. The permeability of such films to carbon dioxide and oxygen is strongly dependent on the ratio of methionine to leucine. The above properties are of interest in connection with possible use of the films in various prostheses, in particular in artificial kidneys [124].

The main trend in improving the quality of synthetic polymeric materials is chemical modification of their structure. A great variety of materials having special properties, not present in the usual natural and synthetic fibres, can be obtained in virtue of the physical and chemical structural peculiarities of various modifications of polyamino-acids. Such properties include enhanced stability to chemical reagents and various physical factors, the ability to be resorbed in functioning tissues of the organism, etc. The modified polymers may find application in many branches of science and technology, such as medicine, foodstuffs, the pharmaceutical industry, etc. Films or fibres from polymers containing acid groups (poly-*L*-glutamic acid) modified with di-isocyanates become semipermeable and water-resistant, which is very important for their use in dialysis or surfery [125]. Threads for surgical sutures are obtained from readily hydrolysable fibre- and film-forming polymers based on amino-acids and hydroxy-acids [126] $[NH.CH(CH_3).COO.C(CH_3)_2.CO]_n$, $[NH.CH(CH_2C_6H_5).COO.[CH_2]_2.CO]_m$, etc.

A very important property of polyamino-acids is their non-toxicity and inertness towards the tissues of the macro-organism. On the other hand, the production of polymers possessing biological activity—antimicrobial, anti-inflammatory, anaesthetic—is of great interest. Polyamino-acids impregnated with bactericides, antiseptics, and antibiotics in various dressings and emergency remedies are very convenient for the prophylaxis and treatment of open wounds and skin diseases [127,128].

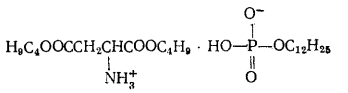
Medicinal preparations have recently become widely used in which coatings protect the contents of a tablet from the environment (moisture, air, light), prevent irritation of the stomach by mucosa by the medicinals, localise the action of the latter, etc. A protective coating for medicinal preparations has been developed from a copolymer of glutamic acid and an alkyl glutamate: it is odourless, sufficiently stable to the action of the gastric juices, and readily soluble in weakly acidic or neutral media [129].

Amino-acids and their derivatives can also fulfil various functions as additives to synthetic polymers and resins: they act as stabilisers, plasticisers, hardening accelerators, etc. [130-142] The copolymerisation of acrylonitrile (or methacrylonitrile) with $\alpha\beta$-unsaturated acids (e.g. itaconic) in the presence of glutamic acid and asparagine yields a water-soluble resin suitable as a binder or a modifier for paints and adhesives [130]. Because of their amphoteric character, amino-acids (glycine, lysine, aspartic acid) can be used to accelerate the hardening of phenol–formaldehyde resins [131]. To improve the resistance to sticking of goods from optically active γ-esters of glutamic acid, its *N*-substituted ethers may be added as plasticisers, possessing good compatibility with the base [132].

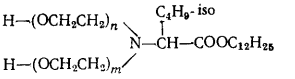
Glycine is used to increase the adhesion of silicone rubber to metal surfaces [136]. A γ-ethyl *L*-glutamate–*DL*-alanine copolymer coating has been proposed to eliminate tackiness, due to migration of the plasticiser, in moulded goods made of plasticised poly(vinyl chloride) [137]

During recent years considerable attention has been paid in synthetic-fibre plants not only to the usual finishing methods (washing, removal of impurities, drying) but also to treatment of the fibres with surface-active agents, which confers optimum frictional properties. Amino-acid derivatives can be used for this purpose [138].

One of the most serious defects of synthetic and acetate fibres is their great tendency to become electrified, which increases the adsorption of dust and creates difficulties in use. Surface-active salts of diesters (e.g. butyl) of aspartic and glutamic acids with monophosphates containing a single higher alkyl group

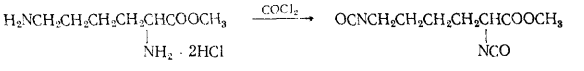


have been investigated for the purpose of lowering and removing the static charge on synthetic fibres. The electrifiability of nylon and polyester fibre was considerably diminished after treatment with a 0.4% methanolic solution of the quaternary ammonium salt formed by dibutyl aspartate with dodecyl hydrogen phosphate [139]. Amino-acid derivatives that dissolve readily in polyalkenes were prepared and studied with the aim of improving the antistatic properties of the latter. Thus the product of the condensation of dodecyl-leucine with oxiran



proved an excellent antistatic agent for polyethylene [140]. Derivatives of amino-acids may serve as antistatic agents for the most diverse synthetic polymers—polyamide, polyester, polyacrylonitrile, poly(vinyl chloride), polyalkene, etc. [141,142]

Finally, a very important possibility is the use of diamino-acids such as lysine and ornithine as raw material for polyamides or for the di-isocyanates employed in the manufacture of polyurethanes. The latter are obtained on the large scale by polymerising polyisocyanates (di- or poly-functional) and polyols containing at least two hydroxy-groups (e.g. glycols, polyethers, polyesters, etc.). They are widely used for the production of adhesives, foam plastics, protective coatings, and artificial leather. The action of carbonyl chloride on the dihydrochloride of the methyl ester of *L*-lysine in *o*-dichlorobenzene at 150°C followed by distillation yields methyl 2,6-di-isocyanatohexanoate, a liquid having a high boiling point [143]:



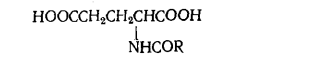
The decisive factor in assessing the toxicity of different di-isocyanates is their volatility. Being less volatile, the above di-isocyanate is less toxic than tolylene di-isocyanate, a fact of importance for the manufacture of polyurethanes.

IV. SURFACE-ACTIVE DERIVATIVES OF AMINO-ACIDS

Introduction of a hydrophobic moiety into one or other of the two hydrophilic functional groups in an amino-acid—amino and carboxy—will yield two types of surface-active compounds—anion-active and cation-active.

N-Acylamino-acids obtained by the action of chlorides of higher aliphatic acids belong to the first class. The initial amino-acids are most often aspartic (*N*-alkylaspartic) and especially glutamic (*N*-alkylglutamic) [144-147].

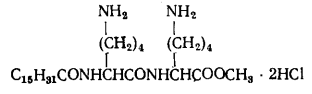
The surface tension, the film-forming and emulsifying power, and the pH of such surface-active compounds can be modified by varying the length of the carbon chain of the acyl group (usually C_{8-22}) and the number of alkaline components used to neutralise the carboxyls. The aliphatic acids most frequently employed are lauric, stearic, oleic, and palmitic. The best surface-active properties are possessed by *N*-acylglutamates [147,148]



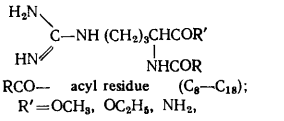
all acyl residue (C_8—C_{22}).

N-Lauroyl-*L*-glutamate salts exhibit better wetting, emulsifying, and dispersing properties than does the widely used sodium dodecanesulphonate [147]. The monosodium salt gives better results than does the disodium salt of the *N*-acylglutamate in model experiments with carbon blacks and powdered iron(III) and titanium(IV) oxides.

Esters of amino-acids obtained by the action of higher alcohols are cation-active surfactants, examples being the tetradecyl esters of glycine, serine, and aspartic acid, as well as dioctyl and dioctadecyl aspartates [149,150]. Cationic detergents, predominantly amines and quaternary ammonium salts, disturb membrane permeability and are highly active towards both Gram-positive and Gram-negative bacteria, which makes them useful in certain special applications, as disinfectants and antiseptics [151]. Several cationic surface-active derivatives of basic amino-acids, e.g. the hydrochloride of the methyl ester of palmitoyl-*L*-lysyl-*L*-lysine



are also strongly bactericidal [152]. Arginine derivatives (their salts and esters) having the formula



exert an antimicrobial and antifungal action, and can be used as disinfectant and antiseptic agents in dental powders, toothpastes, toilet lotions, etc. [153,154] The sodium salt of lauroylsarcosine, possessing a strong bactericidal effect together with good foaming power, is widely used in Japan for such purposes [7].

Amphoteric surface-active compounds have been prepared from alanine and from aspartic and glutamic acids [155]. A considerable number of publications have appeared on the possible use of surface-active derivatives of amino-acids in various wetting agents, emulsifiers, dispersants, bactericides, etc. [156-163] These derivatives merit special attention in connection with the growing contamination of the environment by industrial and domestic refuse, since they are biologically "soft", readily decomposed by bacteria under natural conditions. Wetting agents based on amino-acid derivatives, while possessing essentially the same wetting power as soap, do not have the two main defects of the latter: they are not harmed by acids or by hard water. Examples of possible applications of surface-active derivatives of amino-acids are given below. Thus wetting compositions in solid form have been proposed, containing as active component a salt of an *N*-acylated amino-acid [157]. Sodium, potassium, and ammonium salts of water-soluble amines are used, or salts of basic amino-acids, e.g. lysine or ornithine. *N*-Acylaspartic and *N*-acylglutamic acids can be employed both in optically active and in racemic forms. Several papers have appeared on the application of *N*-acylglutamates [158,159] and derivatives of aspartic acid [160,161] in cosmet products. *N*-Acyl-*N*-alkyl-β-alanine salts $RCONR'CH_2CH_2COOX$ (in which RCO represents a C_{8-22} acyl residue, R' a straight-chain or branched C_{1-8} (cyclo)alkyl, and X hydrogen, an alkali metal, ammonium, or an aminoethanol or a bis- or tris-hydroxyethylamine radical) are present in wetting agents [162] and liquid shampoos [163] possessing good surface-active properties and foam-forming and wetting power.

Reaction of an aliphatic glycerol monester with glutamic (better with *L*-glutamic) and pyroglutamic acids under reduced pressure at 200°C yields odourless and tasteless surface-active compounds [164].

N-2'-Hydroxyethylglycines $HOCH_2CH_2NRCH_2COOH$ (where R = CH_2CH_2OH, CH_3, C_4H_9) have been recommended [165] as a base for detergents. From glycine have been obtained [138] new *N*-carboxymethylamides of perfluorocyclohexanecarboxylic acid $C_nH_{2n+1}ACONHCH_2COOH$, where A represents the perfluorocyclohexane ring and $n = 0-4$, whose sodium, potassium, or ammonium salts are used as surface-active agents in the polymerisation of fluorinated alkenes and of acrylates. They are present to the extent of 0.001–0.002% in polishing mixtures. The potassium salt of *N*-ethyl-*N*-perfluoro-octanesulphonylglycine has been introduced as a levelling agent into a liquid composition for cleaning floors [166], to ensure the formation of a semilustrous, polished, and dust-resistant film on the surface.

Detergent compositions on derivatives of aspartic acid (e.g. the sodium salts of *NN*-biscarboxymethylaspartic acid) are claimed [167] to possess the same cleansing power as those containing sodium tripolyphosphate. A proposed method for obtaining *N*-decanoylamino-acids and peptides (employed as surface-active and bactericidal agents) involves esterification of decanoic acid with 3-hydroxypyridine or 8-hydroxyquinoline followed by treatment of the esters with aqueous solutions of sodium or potassium salts of amino-acids or peptides [168]. A mixture of salts of *N*-alkanoylamino-acids (e.g. an *N*-alkanoyl-*L*-valine salt), an *N*-hydroxyalkylamide, and a salt of phenol [sic: "carboxylic acid salt" in Ref. 169—Ed. of Translation] gives a detergent composition of low toxicity and better wetting power than standard compositions [169].

V. OTHER FIELDS OF APPLICATION

1. Electrochemistry

Amino-acids have not yet found practical application in electrochemistry, apparently because of their high cost, but quite a number of patents have been granted on their possible use. They serve as complexing agents, and also have a good buffering effect on the electrolyte, thereby ensuring its stability and the production of high-quality deposits. The patent literature suggests that the use of amino-acids for the electrochemical production of various coatings and alloys has many advantages. Special attention has been paid to glycine [170-191], which increases the rate of electrodeposition by factors of 5–6 when present in the electrolytes. In the formation of a chromium–cobalt alloy glycine keeps the pH within the range 0.5–1; [170] its use in solution for the application of lead

selenide coatings to dielectric materials makes it possible to obtain uniform, firmly adherent layers without activation of the substrate [171].

Good-quality palladium–nickel alloy deposits can be obtained only over a narrow range of current densities from an electrolyte containing palladium and nickel chlorides together with ammonia. This disadvantage is removed by adding glycine to the electrolyte [173]. The composition of the alloy and the deposition conditions in the presence of this amino-acid have been studied in detail [174]. Palladium-plating electrolytes can be based [175] on glycine and ethylenediaminetetra-acetic and diethylenetriaminepenta-acetic acids, which form palladium complexes differing in stability. The electrolytes are nontoxic and stable, enabling high-grade metal deposits to be obtained. The throwing power of the electrolytes has been studied, the physicochemical characteristics of the deposits are presented, the rules for obtaining high-quality deposits are elucidated, and electrolytes are proposed for palladium-plating (glycine content 44 g litre^{-1}). Good palladium deposits are obtained at a certain pH. [175]

Glycine is used together with Trilon B as a complexing agent in the deposition of nickel–tin [176] and nickel–tin–molybdenum [177] alloys. It serves as complexing agent in chemical nickel plating [178,179]. In the application of cobalt [180] and ruthenium [181] its use tends to stabilise the solution and diminish the porosity of the coating. In combination with cadmium oxide and ammonium chloride glycine increases the stability and the throwing power of the electrolyte used to obtain finely crystalline cadmium–tin alloy deposits [184]. Bright, dense chromium–cobalt alloy deposits, adhering well to the substrate and possessing high abrasion and corrosion resistance, can be obtained [185] from an electrolyte containing glycine and sodium dodecyl sulphate (respectively 50–250 and 0.05 g litre^{-1}). The electrolyte is stable in operation, and its composition can be adjusted by adding a previously prepared complex of the chromium compound and the amino-acid.

In a process for obtaining an iron–nickel–chromium alloy similar in composition to the chromium–nickel stainless steel Kh18N9 glycine is introduced into an electrolyte containing potassium chrome alum together with nickel and iron sulphates, in order to increase the buffer capacity of the electrolyte, raise the pH of hydration of chromium, and increase the thickness of the coating [186].

Glutamic acid hydrochloride is recommended for use with ammonium chloride at elevated temperatures below the melting point for the cleaning of gold alloys containing small quantities of tin, indium, germanium, antimony, and silicon [192]. A patent has appeared on the application of glutamic acid as a hydrotropic agent for increasing the throwing power of the electrolyte in the electrodeposition of zinc and other metals [193].

A chromium–nickel alloy can be obtained from an electrolyte containing the sulphates together with an amino-acid, e.g. cysteine [194]. This has great disadvantages over other processes, since chromium contents of 10–90% can be obtained depending on the electrolyte concentration and the electrolysis schedule. Furthermore, the proposed electrolyte enables this alloy to be obtained at room temperature, which improves the working conditions considerably. During recent years research has been undertaken in the USSR on copper-plating electrolytes containing various complexing and surface-active additives, including amino-acids, with the aim of replacing the poisonous and unstable cyanide electrolytes [195].

2. Photography

Reports have appeared on the possibility of using amino-acids in photography; mainly cysteine and cystine are recommended. To accelerate the one-stage photoprocess the amino-acids are introduced (together with 5-mercapto-1-phenyltetrazole as antifogging agent and ascorbic acid as accelerator) into the processing formulation containing metol, quinol, and sodium sulphite, carboxymethylcellulose, thiosulphate, and hydroxide. In the presence of 5-mercapto-1-phenyltetrazole cystine or cysteine improves the quality of the positive image, by increasing the maximum density and ensuring neutrality of tone [196].

Cysteic acid or a derivative can be added also for stabilisation purposes and to eliminate bronzing in the receiving layer of the positive material for the one-stage photographic process, which includes a latex—a copolymer of butadiene and methyl methacrylate—silicic acid, and an activator [197].

The use of cysteine hydrochloride has been patented as an agent for controlling the colour of images in developers not containing metol, amidol, *N*-benzyl-*p*-aminophenol, or *p*-aminophenol. Good results are obtained by the use of developers containing *NN*-diethyl-*p*-phenylenediamine, kojic acid, and cysteine hydrochloride in certain proportions [198].

Double salts of compounds $HS[CH_2]_nCH(NHR)COR'$ (where $n = 1-4$; R = H, or a lower or substituted acyl; and R′ = OH, a lower acyloxy-group or a substituted amino-group) have been proposed to improve development and sensitometric characteristics in diffusion developers for half-tone print negatives [199]. The introduction of cysteine, its hydrochloride, cysteinylglycine, or *N*-methylcysteine hydrochloride into a devloper containing quinol as main component enhances appreciably the maximum density while preserving the same minimum density (fog) on development under the usual conditions [199]. Cysteine can also serve as chemical sensitiser of the negative or positive emulsion layer in the planographic printing plates employed in lithography [200].

Arginine and its salts have been suggested for rapid development of the latent image in a silver-halide emulsion film containing at least one developer [201]. Several surface-active derivatives of aspartic acid have been prepared and studied [202,203]. A series of *N*-alkyl-*N*-sulphosuccinyl derivatives of aspartic acid, possessing a branched structure and containing several hydrophobic and hydrophilic groups, show high wetting and emulsifying power. Disodium diethyl *N*-decyloxypropyl-γ-sulphosuccinylaspartate meets most closely the requirement for the washing of photographic emulsions [203].

3. Pesticides

Losses in agriculture due to pests, weeds, and plant and animal diseases are extremely high, approximately one-third of all agricultural production. Chemical plant-protection agents are widely used to diminish them, and intensive research is being undertaken to find new preparations, whose application is not only an important condition for eliminating the huge losses but also one of the most economic ways of intensifying agriculture [204]. Derivatives of such an important class of biologically active natural compounds as amino-acids have been the subject of numerous investigations on these lines. The

demands on pesticidal preparations have increased sharply during recent years: they should not leave harmful residues in the environment, and their toxicity towards warm-blooded animals and man should be low. Amino-acids are of definite interest in this connection, since they are readily biodegradable, and their decomposition products are non-toxic.

The most diverse derivatives of many amino-acids have been investigated as weed-killers. Among all the known physiologically active compounds aryloxyalkanoic acids are the most highly active towards plants. Individual members of this group have found wide practical application as agents in the struggle against weeds (in high concentrations) and as growth stimulants (in low concentrations). Many derivatives of amino-acids have been described, one of the commonest herbicides in this series being 2,4-dichlorophenoxyacetic acid (2,4-D). These derivatives were obtained by reaction between the acetyl chloride and the amino-acid in the presence of sodium hydroxide or pyridine. When the herbicidal effect was tested, 2,4-dichlorophenoxyacetyl-*D*-amino-acids were found to be almost inactive, although the corresponding *DL*- and *L*-derivatives approached 2,4-D in activity[205,206].

Glycine derivatives that are nitrogen analogues of aryloxyacetic acids—*N*-2,4- and *N*-2,5-dichlorophenylglycines, *N*-2,4-dinitrophenylglycine, *N*-*o*- and *N*-*p*-chlorophenylglycines and *N*-phenyl-, *N*-*p*-hydroxyphenyl-, *N*-*p*-carboxyphenyl-, and *N*-1′-naphthyl-glycines—exhibit herbicidal activity. However, replacing the ethereal oxygen in phenoxyacetic acid by an imino-group lowers the activity by factors of 3–5.[205] Glycine often serves as initial compound for the production of herbicides, e.g. aminophosphonate[207] or *N*-phosphonomethylglycines[208].

Derivatives of *N*-benzoylalanine may serve as selective herbicides[209,210]. Novel amino-acid derivatives—*NN*-disubstituted alanines $R_nC_6H_{5-n}N(R'Y(COR''$, where R = Hal, Alk, AlkO, n = 0–5, R′ = Alkylene, R″ = Alk, AlkO, Ar, ArOAlkylene, and Y = COOH, *N*-mono- or *NN*-disubstituted NH_2CO—can be used[211] in any way known for herbicides, as solutions, dusts, and wettable powders, alone or mixed with other active components, with or without the use of surface-active dispersants or emulsifiers. A formulation containing a synergistic mixture of the ethyl ester of *N*-benzoyl-*N*-3,4-dichlorophenylalanine and 2,4-dichlorophenyl *p*-nitrophenyl ether has been claimed[212].

Substances used to remove leaves from various cultivated plants—termed defoliants—are closely related to herbicides. Not only compounds involved in the biosynthesis of *L*-lysine—pyridine-2,4-, -2,5-, and -2,6-dicarboxylic acids—but also *L*-lysine itself can form the basis of products that accelerate the fall of leaves from trees[213].

The action of amino-acid derivatives on the germination and growth of a plant depends on whether the latter is di- or mono-cotyledonous[214]. Thus *N*-benzoyl-*L*-aspartic acid and *N*-benzoyl-*L*-valine inhibit the germination of rice, and *N*-α-phthaloylacetyl-*L*-methionine retards that of horseradish. Phenacetyl-α-leucine slows down the early stage in the germination of dicotyledons, but does not affect monocotyledons. The mechanism of such inhibition is regarded as consisting in suppression of the action of lipase: the energy necessary for germination ceases to be supplied from the fats[215].

Several attempts have been made to use amino-acids as plant-growth regulators. Tryptophan, being a precursor of indolylacetic acid (a heteroauxin)—a true phytohormone—effectively accelerates the growth of plants[216].

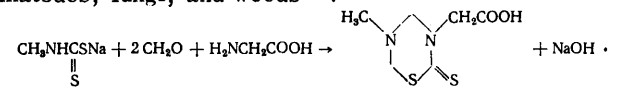
L- and *DL*-Methionine, its metal (e.g. calcium and barium) salts, and its aliphatic (e.g. ethyl) esters have proved efficient growth stimulants for cucumbers, tomatoes, kidney beans, apple and orange trees, etc.[217] Watering cucumber seedlings with a solution containing proline together with uracil (each 1%) stimulates their growth and then increases the yield. A more concentrated solution of the same amino-acids (up to 30%) is a fertiliser for rice shoots[218].

Products containing *N*-purin-6′yl-*L*-phenylalanine, -cysteine, or -threonine as active component have been patented as new plant-growth regulators. Preparations based on these compounds prevent the decomposition of chlorophyll, increase leaf size, and accelerate plant growth[219]. Cysteine hydrochloride is a component of a preparation which stimulates the growth of maize, tomato seedlings, and fruit-tree saplings[220].

Many derivatives of amino-acids have been suggested as fungicides. Preparations based on glutamine derivatives $RNHCOCH_2CH_2CH(NHR)COOH$, where R = H or a lower alkyl, have been successfully used against diseases of citrus plants[221]. These products are non-toxic and are ineffective *in vitro*. Threonine and its *N*-formyl and *N*-benzoyl derivatives have the same effect[222]. The dodecyl ester of valine and other higher alkyl (tetradecyl, octadecyl, etc.) esters of various amino-acids have been patented as fungicides and bactericides for field-crop cultivation and horticulture[223,224].

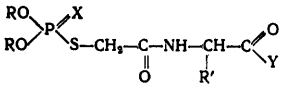
Investigation of the fungicidal action of higher aliphatic *N*-acyl derivatives of amino-acids (their sodium salts and methyl and ethyl esters) and of esters of amino-acids with higher alcohols has shown many of them to be effective *in vivo* against the most common disease of rice *Piricularia oryzae*, although they exhibit no activity *in vitro*; prophylactic use gives the greatest effect[224,225]. Since these amino-acid derivatives have low toxicity and are readily biodegradable, they fully deserve attention as agricultural chemicals that do not pollute the environment. It has been reported[226] that salts of alkylamines with such amino-acids as glycine, alanine, and pyroglutamic acid have proved effective against the diseases of rice. Several *N*-phenylacetyl- and *N*-naphth-1′-ylacetyl-amino-acids (derivatives of glycine, *L*-alanine, *L*-serine, *DL*-methionine, etc.) have been claimed[227] as bases for fungicidal preparations. Copper and nickel salts of amino-acids (valine, methionine, threonine, etc.) have been suggested[228] for use against diseases of citrus plants and rice. These salts are stable in water and have low toxicity towards warm-blooded animals; they are readily obtained by the action of copper sulphate and nickel dichloride respectively on the amino-acid in the presence of ammonia, an alkali-metal carbonate, or a strong base. In another patent[229] copper salts of *D*- and *L*-glutamic and *L*-aspartic acids or mixed copper salts of these acids and di- or tri-basic acids, such as phthalic or benzene-1,3,5-tricarboxylic acid, added to increase the stability of the preparations, are recommended for the struggle against duckweed and pathogenic fungi[229].

Glycine is used in the preparation of the thiadiazine-thione fungicide tetrahydro-5′-methyl-2′-thionothiadiazin-3′-ylacetic acid, which satisfactorily suppresses nematodes, fungi, and weeds[204]:



The main trend of research on insecticides is to find effective products that are less toxic to mammals than are current preparations. Recently Mastryukova et al.[230]

have made detailed studies on a novel type of selective insecticides and acaricides comprising derivatives of phosphoro-thiolic and -thiolothionic acids containing residues of amino-acids, their esters, and their methylamides



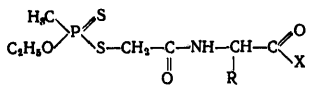
X=O, S; Y=OH, OC_2H_5, $NHCH_3$;

R=CH_3, C_2H_5, $NHCH_3$; R′=H, CH_3, iso-C_3H_7,

iso-C_4H_9, $CH_2C_6H_5$, n-C_6H_7, $CH_2C_6H_4OH$, $CH_2CH_2SCH_3$ etc.

The thio-organophosphorus compounds obtained, containing residues of acylated amino-acid derivatives, are either anticholinesterases (when X = O) or are converted into cholinesterase inhibitors by enzymic oxidation (X = S). The authors started from the view that the selectivity of such preparations may be based on differences in the sensitivity of arthropods and warm-blooded animals to the action of cholinesterase inhibitors and also on differences in the metabolic processes to which insecticides are subjected in the two types of organisms. In the first case it would probably be very significant whether or not the preparation is complementary to the active centre of the choline esterases or choline receptor. Examination of the physiological activity of these compounds showed that both their toxicity and their selectivity is strongly dependent on the nature of the amino-acids forming part of the molecule. Thus the β-alanine derivative (R = C_2H_5, Y = S) is a relatively strong insecticide comparable with Thiophos and a quite weak acaricide; the α-alanine derivative (R = C_2H_5, R′ = CH_3, Y = S) is a strong acaricide (like Thiophos) and only a moderate insecticide. The corresponding valine derivative (R = C_2H_5, R′ = iso-C_3H_7, Y = S) has still more marked acaricidal properties (twice as strong as Thiophos), but is almost devoid of insecticidal effect [230]. Derivatives of amino-acid methylamides (Y = $NHCH_3$) are more toxic to warm-blooded animals than are the corresponding esters. The selectivity of the action on arthropods is less marked in this series, although all the compounds are somewhat stronger acaricides. Great prospects are opened up for seeking selective preparations in this series [230].

Thio-organophosphorus compounds containing amino-acid fragments do not leave harmful residues in the environment, since the products of their decomposition and metabolism (acids of phosphorus, glycollic and thioglycollic acids, and biogenic amino-acids) are non-toxic. Methods have been developed for synthesising this series of compounds from salts of the corresponding thio-acids of phosphorus and chloroacylated derivatives of various amino-acids [231-233]. The same workers [234] investigated the analogous series of methylphosphonothiolothionates

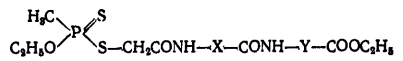


R=H, CH_3, iso-C_3H_7, iso-C_4H_9, $CH_2CH_2SCH_3$; X=OH, OC_2H_5

which are characterised more by acaricidal activity. However, they are usually more active insecticides and acaricides than are the corresponding phosphorodithioates and, of course, more toxic to warm-blooded animals. Thus changing from the dithiophosphate derivative of the ethyl ester of glycine to the corresponding dithiophosphonate involves increases in animal toxicity and in acaricidal and aphicidal effects by factors of 5.3, 40, and 30 respectively. The compounds obtained include active insecticides and acaricides having moderate toxicity towards animals [234].

Compounds obtained by adding dialkyl hydrogen thiophosphates to esters of *N*-acylated cysteine also possess insecticidal properties [235-237].

The next step on these lines was to study a series of derivatives of *O*-ethyl hydrogen methylphosphonodithioate containing in the detachable moiety of the insecticide a peptide fragment comprising residues of two amino-acids [238]



X and Y=CH_2, CH_2—CH_2, CH(CH_3), CH(C_3H_7-iso)

on the assumption that formation of a dipeptide group in the side-chain may affect the specificity of sorption of these compounds by increasing the complementarity of the peptide fragment to the active centre of the enzyme [238]. Preparations of this series proved to be inferior to dithiophosphonates containing a single amino-acid residue, both in general insecticidal action and in selectivity, despite the slightly lower animal toxicity. It was concluded that further modification of the products with the accumulation of amino-acid residues was pointless [238].

In view of the rapidly increasing demands on pesticides, and also substantial difficulties involved in introducing them, the Reviewers feel that special interest attaches to the possible use of amino-acids as additives improving the properties of products already in use in agriculture. Thus it has been recommended to add aspartic acid and its salts to organophosphorus, organochlorine, and carbamate insecticides to stimulate the growth of the treated plants and remove the phytotoxic effect of the preparations [239]. Tryptophan stabilises the unstable cyclic *o*-hydroxybenzyl phosphate insecticides [240]. Arginine and its salts increase the solubility of the plant-growth stimulant gibberellin A_3 in aqueous solutions, which considerably expands the boundaries of its possible application [241]. Gibberellins may find practical application for the cultivation of ornamental plants and of grapes [204].

Derivatives of glutamic and aspartic acids may serve as stabilisers for dichlorovinyl dimethyl phosphate (DDVP, Dichlorophos), which during recent years has found widespread application in the fight against various harmful insects and mites in agriculture and public health [242]. Aspartic acid and methionine have been patented as stabilisers in fungicidal compositions [243].

The efficiency of insecticides is often enhanced by combination with attractants, which enable certain types of pests and the loci of infection to be detected in good time, so that measures can be taken to prevent their further dissemination. Use of such mixtures enables the resistance of insects to be overcome, eliminates the need to treat vast areas, diminishes the consumption of insecticides, and lowers the infectiousness of water, soil, and food products, while leaving certain useful species unaffected. The most common food baits are protein hydrolysates, whose mixtures with insecticides are employed against Eastern, Mediterranean, Natal, and Mexican fruit-flies, etc. [244] Addition of the protein hydrolysates increased the efficiency of the insecticides by factors of 3–12. The greatest effect was achieved by adding brewer's yeast or casein and yeast hydrolysates to the insecticides [244]. Many orders of insects, especially Diptera, respond to individual amino-acids, which apparently serve as nourishment. Glutamic acid is an effective attractant for the Mediterranean fruit-fly [244]. Lysine,

while being an attractant for mosquitoes, attracts also Mexican, Eastern, Mediterranean, and melon flies. In the campaign against fruit-flies in the Hawaiian Islands it was observed that certain amino-acids are necessary for abundant egg-laying, which is promoted by acid and enzymic hydrolysates [244].

4. Motor-fuel Additives

To prevent the formation of deposits in the carburettors of interna-combustion engines it is proposed [245] to add to petrol 0.0005–0.1% of asparagine derivatives $R'NHCOCH_2.CH(NHR)COOH$, where R and R′ represent secondary and tertiary hydrocarbon radicals up to C_{22}. These compounds possess anticorrosive and dispersive properties, preventing carbonisation and icing [246–248]. Substituted amides of aspartic acid combined with succinates of diethylenetriamine, triethylenetetramine, and tetraethylenepentamine act as ashfree dispersing agents in the form of additives to hydraulic fluids [249].

5. Cosmetics

The buffering action of amino-acids, helping to maintain the normal functioning of the skin (by controlling the pH), the protective effect against bacteria, and the surface-active properties of amino-acid derivatives, as well as the favourable physiological action, have enabled amino-acids to be introduced into cosmetics.

In hair colorants it is recommended that ammonia could be replaced by arginine carbonate [250] or by glycine, *L*-alanine, or valine mixed with ammonium carbonate [251]. The use of 0.1–20% of arginine carbonate in hair-bleaching formulations diminishes the injury to the hairs while achieving the same bleaching effect as with formulations containing 9% of ammonium hydroxide [252].

Amino-acids are used in creams and hair conditioners as nutrients, improving the sheen and conferring softness. An especially favourable effect on hair is exerted by cysteine, on whose derivatives many papers have appeared in this connection. Like thioglycollic acid, cysteine and its derivatives can be used as reductants in cold [253,254] and permanent [255] waving. Derivatives or cysteine $RSCH_2CH.(NHR)COOH$ and methionine $RS[CH_2]_2CH(NHR)COOH$, where R = $HOCH_2CH_2$ or $NH_2CH_2CH_2$, have been proposed in various formulations ensuring a better, grease-free appearance of the hair [256]. Derivatives of cysteine and cysteamine may form the basis for shampoos against dandruff [257]. For the treatment of seborrhoea and other diseases characterised by enhanced secretion of sebum, formulations have been patented containing as active component the compound $RSCH_2CH(NH_2)COOH$ [where R = $(C_6H_5)_3C$, $(C_6H_5)_2CH$, $C_6H_5CH_2$, $HOOC[CH_2]_{2-4}$, [258] $HOOC[CH_2]_{1-2}$, and their salts with inorganic and organic acids) [259] or cystine derivatives [260]. Other patents have appeared on cysteine derivatives that can be used in cosmetics [261–263].

A proposed hair lacquer is based on salts (alkali-metal or amine) of poly-α-amino-acids (polyaspartic and polyglutamic) [122].

Great attention is paid in cosmetology to the so called natural moisturising factor (NMF).[7] It was shown not long ago that skin dryness is due not to loss of liquids from the horny layer, as had been thought previously, but to loss of NMF, which plays an important part in the retention of water. Since the main components of NMF are free glycine, threonine, alanine, aspartic and glutamic acids, serine, and pyrrolidonecarboxylic acid, the use in cosmetics of various amino-acids, their derivatives, and protein hydrolysates is based on control of the normal functioning of the skin. Patents have appeared on the application of enzymic hydrolysates of lactalbumin [264] and plankton [265], and on the use of condensates of amino-acids and sugars as nutrients and moisturising agents [266]. Amino-acids are present as moisturising and antiseptic agents in skin creams and toothpastes [153,154,267].

Aspartic acid and its derivatives have diverse applications in cosmetics [161,268–271]. Thus a salt of the acid can be used in photosensitive pigments for the treatment of keratodermatitis [269]. Addition to cosmetic preparations of aspartic acid or its derivatives together with vitamin B_6 is effective in preventing drying of the skin and for counteracting ageing [270].

A disadvantage of amino-acids with respect to their use in cosmetics is their hydrophilic character, which hinders their imbibition by skin. Their absorption can be improved by combining their use with alkaloids [272].

Surface-active derivatives of amino-acids can be applied fn the most diverse cosmetic products [149,150,154,158,163,268]. Derivatives of glutamic acid

$$M^+[OOCCH_2CH_2—CH(NHCOR)COO^-]H$$

where M = Na, Li, $(C_2H_5)_4N$ and RCO is a C_{12-18} aliphatic acyl, possess several cosmetically valuable properties [158]. Apart from the excellent wetting and foaming power, *N*-acylglutamates do not irritate the skin, since their pH of 5.5–6.5 is similar, whereas a solution of ordinary soap is slightly alkaline. They are more effective than the latter for hard water, have an antimicrobial effect, and readily undergo biological degradation without polluting the environment. Sodium acylglutamates are used as foundations or components in shampoos, detergents, etc. They can be usefully added to various domestic synthetic detergents obtained from petroleum or alcohols to mitigate their irritant action on the skin (e.g. in kitchen products). Detergent compositions containing salts of *N*-acylglutamic acids and betaines have a favourable action on skin and possess good cleansing power [159]. Butyl *N*-acylglutamates *L*-$RNHCH(COOC_4H_9)CH_2CH_2.COOC_4H_9$ (where R represents lauroyl, miristoyl, or stearoyl) are recommended for use in lip salve [273].

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