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Advances and Prospects in the Chemistry of Nucleoaminoacids and Nucleopeptides

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The present state of research into the development of methods of synthesis and into properties of aminoacids containing a natural nucleic acid base in the side chain (nucleoaminoacids) as well as the peptides formed from nucleoaminoacids (nucleopeptides) is examined. Attention is concentrated on the description of naturally-occurring representatives of these classes of compounds and on the analysis of prospects for their further investigation and use.
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I. INTRODUCTION

Pyrimidine and purine bases are widely distributed in nature and play an important role in vital processes. They are obligatory structural components of all nucleic acids without exception. Many coenzymes, vitamins, and antibiotics are purine- or pyrimidine derivatives; the pyrimidine ring is the basis of many most important natural condensed systems (pteridines, isoalloxazines, etc.). α-Aminoacids, which constitute the elementary structural units of peptides and proteins and occupy one of the central positions among known natural products, are no less important and are just as widely distributed in biological systems.

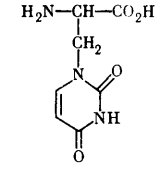
One may claim that pyrimidine and purine derivatives as well as α-aminoacids belong to chemical structures which permeate the entire spectrum of life, starting from viruses and extending to higher animals and man.

The chemical research into the above heterocyclic compounds, on the one side, and α-aminoacids and peptides, on the other, was prosecuted for a long time in isolation and such investigations did not as a rule overlap. Nevertheless, biochemical and molecular biological data undoubtedly indicate the occurrence in biological systems of very intimate interactions, combining these classes of natural products. This has been manifested not only in the study of metabolic pathways involving these structures but also in the detection in nature of various aminoacids (and recently also peptides) derived from pyrimidine and purines.

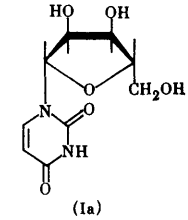
Among the wide variety of pyrimidinyl- and purinyl-aminoacids, *nucleoaminoacids* are of special interest[1]. Here and henceforth this term will be used to designate α-amino-carboxylic acids with pyrimidine or purine nucleic acid bases in the side chain, attached to the aminoacid fragment via the N^1 (pyrimidine) or N^9 (purine) atom.

In conformity with the above definition, the structure of nucleoaminoacids follows unambiguously from the structures of the known nucleic acid bases. If we disregard for the moment the minor nucleic acid bases and confine ourselves to the principal nucleic acid bases (uracil, thymine, cytosine, adenine, and guanine) and if among all the aminoacid fragments only the α-alanine fragment is considered, then typical examples of the class of nucleoaminoacids are β-(N^1-uracilyl)-α-alanine (I), β-(N^1-thyminyl)-α-alanine (II), β-(N^1-cytosinyl)-α-alanine (III), β-(N^9-adeninyl)-α-alanine (IV), and β-(N^9-guaninyl)-α-alanine (V). The three-letter abbreviations for these nucleoaminoacid residues are Ual, Tal, Cal, Aal, and Gal respectively.

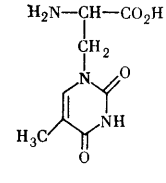
Comparison of the structure of nucleoaminoacids with that of the corresponding nucleosides of the pyrimidine and purine series shows readily that nucleoaminoacids are aminoacid analogues of the natural nucleosides (Ia)–(Va), differing from the latter by the substitution of the pentose (ribose or deoxyribose) residue by the aminoacid fragment:



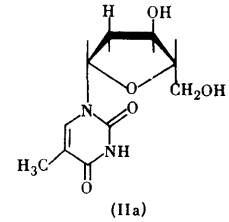
(I)



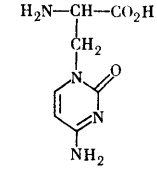
(Ia)



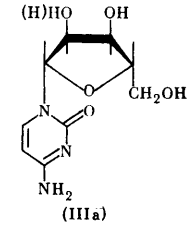
(II)



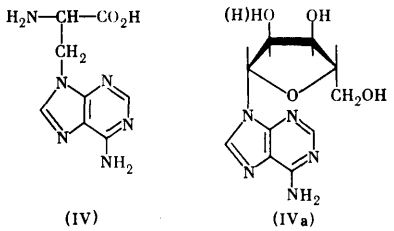
(IIa)



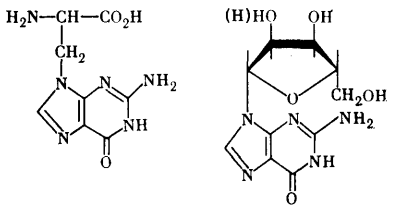
(III)



(IIIa)



(IV) (IVa)

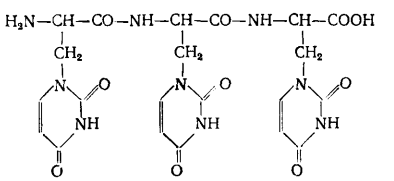


(V) (Va)

When nucleoaminoacid residues are linked together by peptide bonds, *nucleopeptides* are formed[1]. Here and henceforth this term will be used to designate peptides containing nucleoaminoacid residues. Whereas nucleic acid bases in oligonucleotides are attached to the pentose phosphate skeleton, in nucleopeptides the bases form a framework around the peptide chain.

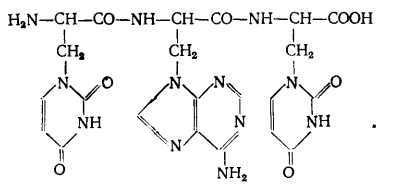
Depending on the qualitative composition, nucleopeptides can in general be divided into three main types: (1) homonucleopeptides; (2) heteronucleopeptides; (3) mixonucleopeptides.

Homonucleopeptides. These are nucleopeptides made up of repeating units of the same nucleoaminoacid. The tripeptide (VI), made up exclusively of β-(N^1-uracilyl)-α-alanine residues, is an example of a homonucleopeptide (the structure of this tripeptide is formulated in an abbreviated form in brackets underneath the formula below):



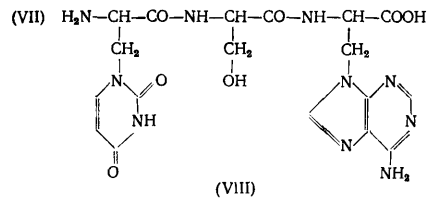
(VI) (H-Ual-Ual-Ual-OH)

Heteronucleopeptides. These are nucleopeptides made up of different nucleoaminoacid residues. The tripeptide (VII), whose composition includes two β-(N^1-uracilyl)-α-alanine residues and one β-(N^9-adeninyl)-α-alanine residue, is a typical example of heteronucleopeptides:



(VII)
(H-Ual-Aal-Ual-OH)

Mixonucleopeptides (synonym—nucleopeptides of the mixed type). These are peptides containing, together with nucleoaminoacid residues, also the residues of other aminoacids (in particular protein aminoacids). The tripeptide (VIII), whose composition includes the residues of β-(N^1-uracilyl)-α-alanine, serine (a protein aminoacid), and β-(N^9-adeninyl)-α-alanine, may serve as an example of a mixonucleopeptide:



(VIII)
(H-Ual-Ser-Aal-OH)

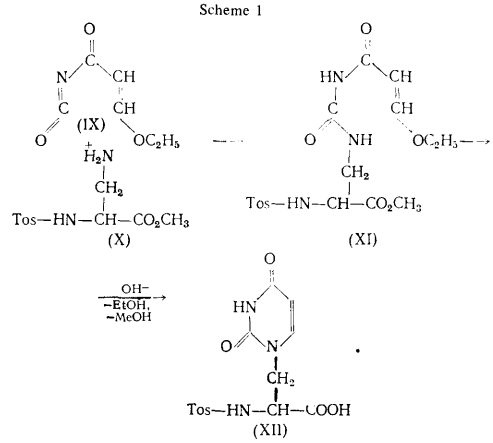
The methods of synthesis and the reactions of nucleoaminoacids are considered below, the methods of synthesis and properties of nucleopeptides are described, and the prospects for the further study and utilisation of nucleopeptides and nucleoaminoacids are discussed.

II. SYNTHESIS OF NUCLEOAMINOACIDS

All the methods of synthesis of nucleoaminoacids known at the present time can be divided by convention into two main groups: (1) methods of synthesis based on reactions in which the pyrimidine or purine ring is formed during the synthesis of the compound: (2) methods of synthesis in which a substituent is introduced into a complete hydropyrimidine or purine.

A typical example of the first group of methods of synthesis of nucleoaminoacids is the synthesis of the N^{α}-tosyl derivative of β-(N^1-uracilyl)-α-alanine [compound (XII)] by Kjaer et al.[2], which is based on the intramolecular cyclisation of the asymmetrically substituted urea (XI), formed on condensation of β-ethoxyacryloyl isocyanate (IX) with methyl α-tosylamino-β-DL-aminopropionate (X) via Scheme 1.

Scheme 1



It must be emphasised that initially the interest of investigators in the development of methods of synthesis of nucleoaminoacids was to a large extent stimulated by the detection of individual representatives of the class of nucleoaminoacids in nature. The first report of the possible presence of naturally-occurring nucleoaminoacids, by the German biochemist Gmelin[3], appeared at the end of 1959. In his study of extracts from the seeds of *Acacia willardiana*, Gmelin detected in them a new aminoacid, which he called "willardiine".

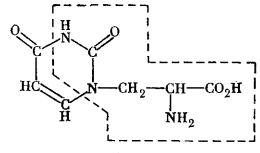
Subsequently Gmelin was able to isolate this aminoacid on a preparative scale and to show that its composition corresponds to the overall formula $C_7H_9N_3O_4.H_2O$. One of the remarkable properties of the new aminoacid was its capacity to absorb ultraviolet light intensely. The study of the ultraviolet absorption spectra of willardiine at different pH showed that they are extremely similar to the corresponding spectra in the near ultraviolet of compounds such as uridine and 1-methyluracil. Investigation of the infrared spectra of willardiine also revealed the presence of characteristic frequencies corresponding to the uracil ring; furthermore, it was concluded that the infrared spectra of willardiine contain absorption bands characteristic of the alanine fragment.

The hypothesis that willardiine may constitute a structure in which the alanine residue is linked to one of the oxygen atoms in the uracil molecule was abandoned when it was established[3] that the new aminoacid is extremely stable and, in particular, does not change on prolonged refluxing with 28% hydrobromic acid. If the alanine residue were linked to one of the oxygen atoms of the uracil molecule, then serine would have been inevitably formed under these conditions, which was not observed.

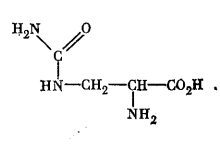
A more detailed study of the ultraviolet absorption spectra of willardiine[3] made it possible subsequently to eliminate from consideration variants of the structure which involved the addition of the alanine residue to the uracil ring via its carbon atoms in the 5- or 6-position and also via the nitrogen heteroatom in the 3-position. The last variant was rejected on the grounds that the ultraviolet spectra of willardiine, recorded at different pH, did not exhibit a bathochromic shift of λ_{max} with increasing alkalinity of the medium, which is known to be a characteristic property of 3-substituted uracils and is not observed in the spectra of 1-substituted uracils[4-6].

As a result of his investigations, Gmelin[3] concluded that willardiine apparently has a structure in which the alanine fragment is linked to the uracil ring and that the most probable point of addition of the alanine chain is the nitrogen heteroatom in the 1-position in the uracil ring. In other words, Gmelin suggested that the new natural aminoacid which he isolated has the structure of L-β-(N^1-uracilyl)-α-alanine (I).[3]

The fact that, long before the discovery of willardiine, a hitherto also unknown acyclic aminoacid was detected in plants of the family of Mimosaceae and was called "albizziine" [7,8] is noteworthy. It was subsequently shown unambiguously to have the structure of L-α-amino-β-ureidopropionic acid (XIII):[9,10]



(I)



(XIII)

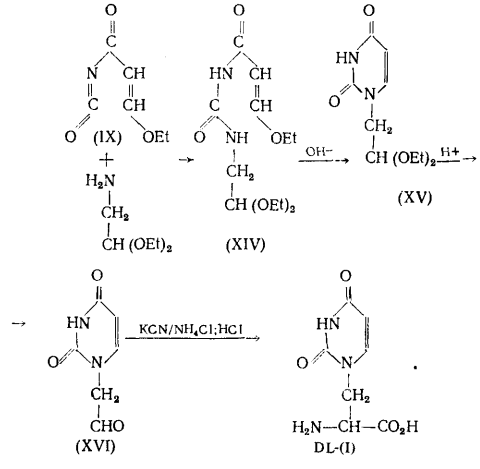
Gmelin was able to demonstrate that albizziine is present together with willardiine in the seeds of *Acacia willardiana*, *Acacia millefolia*, *Acacia lemmoni*, and *Mimosa asperata*.[3] This observation and the evident analogy between the molecular structures of (I) and (XIII) constituted additional arguments in support of structure (I) proposed for willardiine. Furthermore, on the basis of the above observation, Gmelin put forward the hypothesis that albizziine (XIII) can be a bioprecursor of willardiine[3].

All these ideas agree satisfactorily with one another and are consistent with a logical general scheme. However, one must not forget that at that time there was no final and rigorous proof that willardiine does indeed have structure (I). The question of the possible existence of nucleoaminoacids in nature therefore remained open.

The resulting situation was finally clarified when structure (I) of willardiine was demonstrated rigorously in 1961 by unambiguous chemical syntheses of this substance carried out almost simultaneously and independently by two groups of chemists—in Denmark[2] and in England[11,12].

The English investigators initially reported the synthesis of DL-β-(N^1-uracilyl)-α-alanine[11] from β-ethoxyacryloyl isocyanate (IX) which they had obtained previously[13,14]. Treatment of compound (IX) with the diethyl acetal of aminoacetaldehyde led to the formation of the disubstituted urea (XIV), which underwent intramolecular cyclisation on being heated in an aqueous solution of sodium hydroxide, accompanied by the elimination of an ethanol molecule and the formation of N^1-(2′,2′-diethoxyethyl)uracil (XV). Acid hydrolysis of the latter then yielded N^1-uracilylacetaldehyde (XVI), which was introduced into the cyanohydrin synthesis reaction, ensuring the unambiguous formation of DL-β-(N^1-uracilyl)-α-alanine via Scheme 2.

Scheme 2



As was to be expected, apart from the positive response to the ninhydrin test, the compound was able to absorb ultraviolet light intensely. Comparison of the ultraviolet spectra and other characteristics of the synthetic compound (I) and natural willardiine led to the conclusion that the chemical structures of these substances are identical.

Later the English investigators reported the separation of the racemic aminoacid (I) into its optical isomers[12]. For this purpose, the N^{α}-formyl derivative was obtained from the racemic aminoacid (I) and was treated with the dextrorotatory isomer of methylphenylaminomethane. The resulting mixture of diastereoisomeric salts was subjected to fractional crystallisation, which led to the isolation of the laevorotatory isomer of β-(N^1-uracilyl)-α-alanine, whose properties, including the magnitude and sign of the specific optical rotation, proved to be identical with those of natural willardiine[12].

Although these studies did not solve the problem of the absolute configuration of willardiine, they did not leave any doubt about the natural aminoacid being a nucleoaminoacid whose structure is identical with that of compound (I).

The fact that Dewar and Shaw[12] were unable to convert N^1-uracilyl-acetaldehyde (XVI) into compound (I) by the hydantoin method of synthesis[15,16] instead of the cyanohydrin method is noteworthy. This attempt led to the formation of the corresponding 1-hydantoinylmethyluracil; however, this compound proved to be extremely stable and did not hydrolyse even after prolonged heating at 150 °C with 10 *N* hydrochloric acid in a sealed tube[12].

Danish investigators[2] carried out an unambiguous synthesis of β-(N^1-uracilyl)-α-alanine (I) by the somewhat different procedure illustrated in Scheme 1 (see above). They obtained N^{α}-tosyl-DL-β-(N^1-uracilyl)-α-alanine (XII) in an analytically pure state. Further studies showed that this compound is chromatographically identical with the substance obtained on tosylation of natural willardiine[2]. This constituted independent proof that the new natural amino-acid has the structure of β-(N^1-uracilyl)-α-alanine.

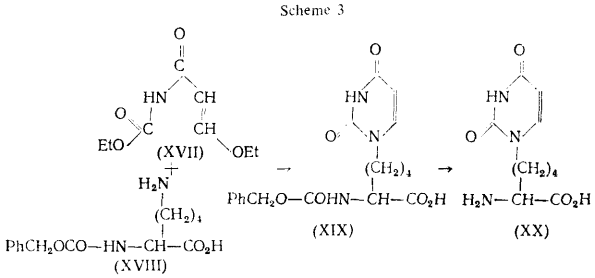
Kjaer et al.[2] studied the possibility of detosylating compound (XII) in order to obtain synthetic DL-β-(N^1-uracilyl)-α-alanine. However, they found that treatment of compound (XII) with sodium in liquid ammonia entails the breakdown of the uracil ring and the appearance of a whole "family" of aminoacids which did not absorb in the ultra-violet, one of which was identified as α,β-diaminopropionic acid. Treatment of the N^{α}-tosyl derivative of willardiine with a solution of hydrogen bromide in glacial acetic acid (for 3 h at 70 °C [17]) results in the complete removal of the protecting tosyl group; however, according to the above author's data[2], this involves extensive racemisation of the free aminoacid formed. When the duration of the detosylation process was reduced to 1 h, the Danish chemists were able to obtain from compound (XII) a substance whose infrared spectrum and specific optical rotation did not differ from those of natural willardiine. However, the yield of the optically active nucleoaminoacid (I) prepared in this way was extremely low (2%).

Thus the above method of preparing β-(N^1-uracilyl)-α-alanine, which solves in principle the problem of the complete chemical synthesis of this natural nucleoaminoacid, does not permit its preparative synthesis in appreciable amounts.

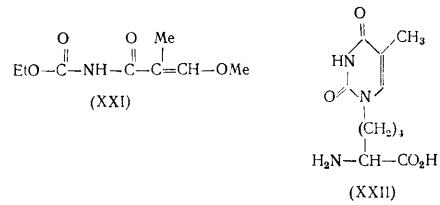
In this connection we should note that the method of synthesis of compound (I) proposed by the English investigators[12] also fails to solve the problem of the preparative synthesis of the nucleoaminoacid β-ethoxyacryloyl isocyanate, which they used as the starting material, is itself difficult to obtain[13,14]. Examination of the entire synthetic pathway leading to compound (IX) from ethyl bromoacetate shows that the yield of the diethyl acetal of N^1-uracilyl-acetaldehyde (XV), which is the key compound in this method of synthesis of β-(N^1-uracilyl)-α-alanine, is only 4% of theoretical.

In 1971 De Koning and Pandit[18] described the synthesis of α-amino-ε-(N^1-uracilyl)-caproic acid (XX) via Scheme 3, which provides for the condensation of 3-ethoxy-*N*-ethoxycarbonylacrylamide (XVII) with N^{α}-benzyloxycarbonyl-lysine (XVIII). α-Amino-N^{α}-benzyloxycarbonyl-ε-(N^1-uracilyl)-caproic acid (XIX) is an intermediate in this synthesis.

Scheme 3

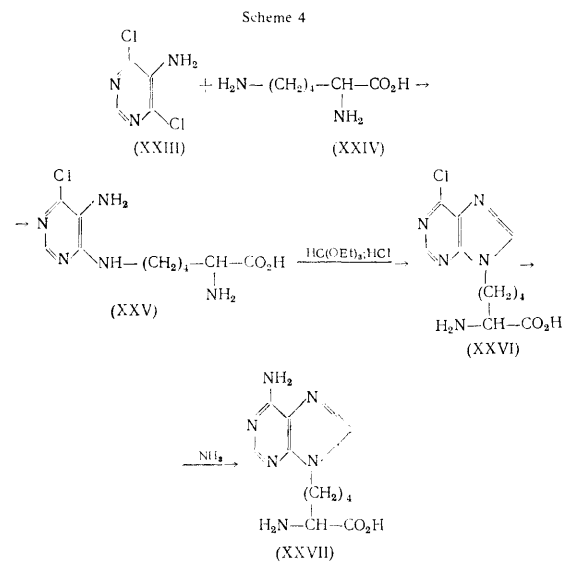


When *N*-ethoxycarbonyl-3-methoxy-2-methylacrylamide (XXI) was used in the condensation stage instead of compound (XVII), α-amino-ε-(N^1-thyminyl)-caproic acid (XXII) was obtained via an analogous scheme. The yield of the racemic nucleoaminoacids (XX) and (XXII) was approximately 40%.



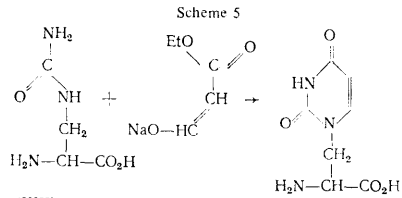
The first group of methods of synthesis also includes that of the synthesis of α-amino-ε-(6-chloro-N^9-purinyl)-caproic acid (XXVI). Compound (XXVI) is the key substance in the synthesis of ε-(N^9-adeninyl)-α-aminocaproic acid (XXVII).[19] A characteristic feature of the synthesis of compound (XXVI) is the formation of the purine ring as a result of the closure of the imidazole ring in the course of the synthesis via Scheme 4. The initial compounds are 5-amino-4,6-dichloro-pyrimidine (XXIII) and lysine (XXIV), while the pyrimidinyl-aminoacid (XXV) is an intermediate.

Scheme 4



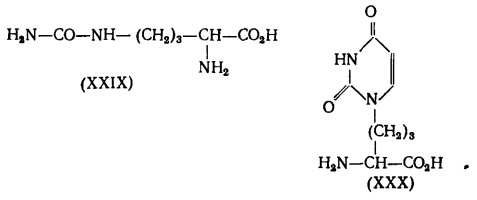
The method of synthesis of compound (I) by the condensation of α-amino-β-ureidopropionic acid (albizziine) with formylacetic ester also belongs to this group[20,21]. The ester is used in the form of the sodio-derivative (XXVIII) and condensation proceeds via Scheme 5.

Scheme 5



If citrulline (α-amino-δ-ureidovaleric acid (XXIX) is used in the analogous condensation instead of albizziine, then α-amino-δ-(N^1-uracilyl)valeric acid (XXX) can be

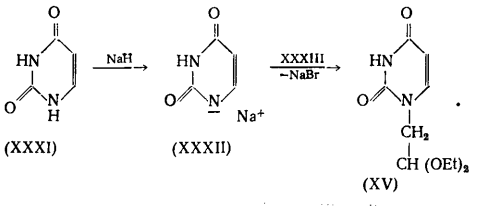
obtained[22]:



(XXIX) (XXX)

A new direct synthesis from uracil (XXXI) of compound (XV), i.e. N^1-(2′,2′-diethoxyethyl)uracil (the diethyl acetal of N^1-uracilylacetaldehyde), already mentioned above (see Scheme 2), was described in 1965.[23] According to these data[23], when compound (XXXI) is treated with sodium hydride in dimethylformamide, the sodio-derivative of uracil (XXXII) is formed initially and, on subsequent heating with 2-bromo-1,1-diethoxyethane (XXXIII), is smoothly converted into N^1-(2′,2′-diethoxyethyl)uracil (XV):

Scheme 6



(XXXI) (XXXII) (XV)

The yield of compound (XV), which is the key substance in the synthesis of nucleoaminoacids, is approximately 40%.

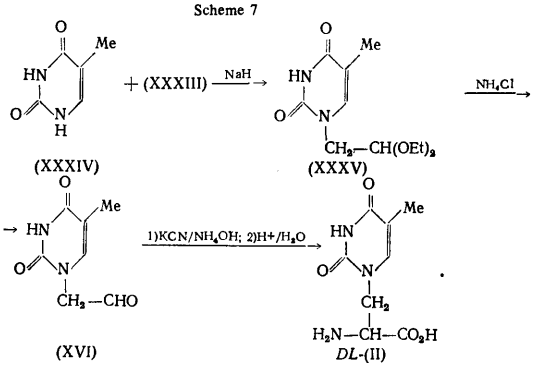
The formation of the N^1,N^3-disubstituted product (XXXV) takes place simultaneously (yield approximately 13%), but this substance can be separated comparatively readily from the desired compound (XV).

In contrast to Shaw and Dewar[11], who used acid hydrolysis, American investigators[23] suggested that the diethyl acetal of N^1-uracilyl-acetaldehyde be converted into free N^1-uracilyl-acetaldehyde by a milder process involving the heating of compound (XV) with an aqueous solution of ammonium chloride. Under these conditions, the yield of compound (XVI) was increased from 40 to 83%. The subsequent introduction of compound (XVI) into the cyanohydrin synthesis reaction makes it possible to obtain readily the racemic nucleoaminoacid (I) on a preparative scale by the scheme already described (Scheme 2).

The above method of synthesis of DL-β-(N^1-uracilyl)-α-alanine (I) was extended to other nucleoaminoacids. In particular, DL-β-(N^1-thyminyl)-α-alanine and DL-β-(N^1-cytosinyl)-α-alanine can be synthesised by this method[24,25].

The synthesis of DL-β-(N^1-thyminyl)-α-alanine is based on thymine (XXXIV) as the starting material and proceeds via the following scheme:

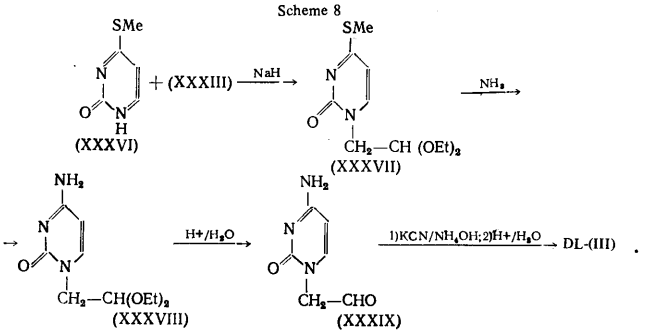
Scheme 7



(XXXIV) (XXXV) (XVI) *DL*-(II)

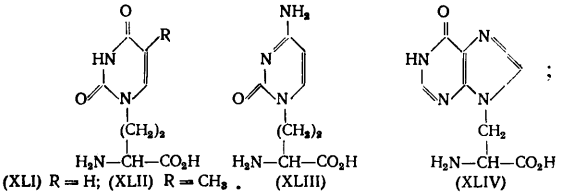
In the synthesis of DL-β-(N^1-cytosinyl)-α-alanine (III) the starting material is 4-methylthio-2-oxodihydropyrimidine (XXXVI):

Scheme 8



(XXXVI) (XXXVII) (XXXVIII) (XXXIX)

The interaction of uracil (XXXI), thymine (XXXIV), and 4-methylthio-2-oxodihydropyrimidine (XXXVI) with the diethyl acetal of γ-chloropropionaldehyde (XL) has also been investigated[25]. It was established that uracil and thymine give rise to both N^1- and N^3-derivatives, which can be readily separated by crystallisation. On the other hand, the exclusive formation of the N^1-isomer was noted in the case of 4-methylthio-2-oxodihydropyrimidine (XXXVI). These investigations led to the synthesis of α-amino-γ-(N^1-uracilyl)-butyric acid (XLI), α-amino-γ-(N^1-thyminyl)-butyric acid (XLII), and α-amino-γ-(N^1-cytosinyl)-butyric acid (XLIII):[25]



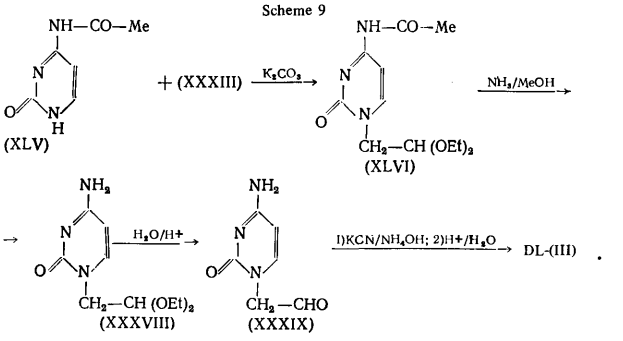
(XLI) R = H; (XLII) R = CH_3. (XLIII) (XLIV)

The reaction of heterocyclic bases with 2-bromo-1,1-diethoxyethane (XXXIII) was extended to the synthesis of a number of aminoacids of the purine series, including β-(N^9-adeninyl)-α-alanine and β-(N^9-hypoxanthinyl)-α-alanine (XLIV).[26,27] A series of β-(amino-N^9-purinyl)-α-alanines, including β-(N^9-guaninyl)-α-alanine, were synthesised with the aid of this reaction[28].

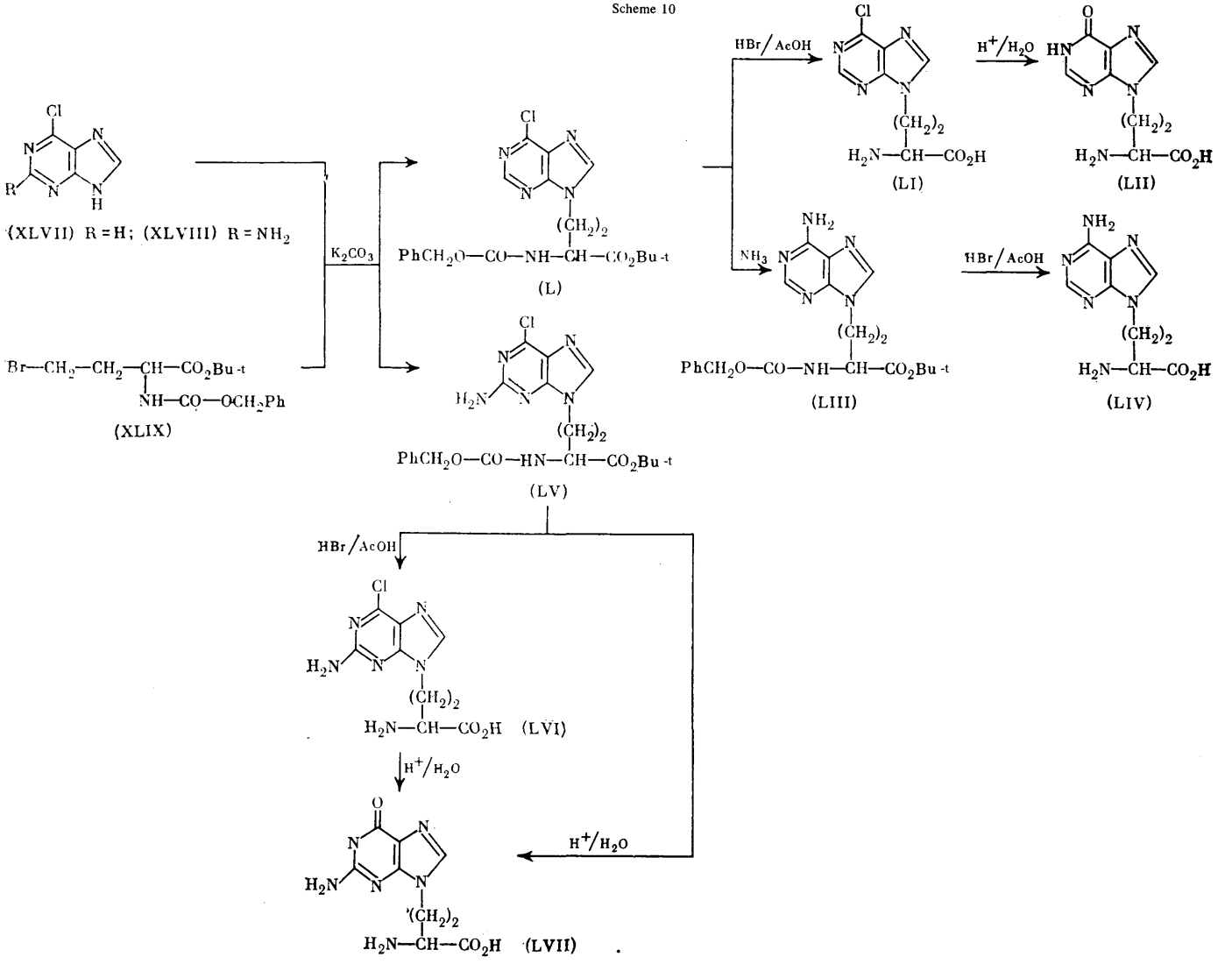
A further improvement of the method of synthesis of nucleoaminoacids based on the reaction of acetals of halogenoaldehydes with heterocyclic bases of the pyrimidine and purine series involved the use of potassium carbonate, proposed by Doel et al.[29], instead of sodium hydride in the alkylation stage. This change significantly simplified the method of synthesis, and, what is particularly important, made it possible to increase the yield of nucleoaminoacids to 50–60%.

Various nucleoaminoacids, including β-(N^1-thyminyl)-α-alanine and β-(N^9-adeninyl)-α-alanine, were synthesised by this modified method. In the synthesis of β-(N^1-cytosinyl)-α-alanine by this procedure, the starting material can be 4-*N*-acetylcytosine (XLV) and the intermediates in this instance are the diethyl acetal of 4-*N*-acetyl-N^1-cytosinylacetaldehyde (XLVI), the diethyl acetal of N^1-cytosinylacetaldehyde (XXXVIII) and, directly, N^1-cytosinylacetaldehyde (XXXIX):

Scheme 9



Scheme 10



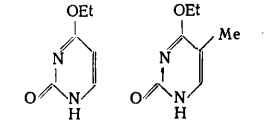
This method is most frequently used nowadays for the synthesis of various nucleoaminoacids, particularly nucleoalanines.

A variant of this method is the synthesis of nucleoaminoacids by the alkylation of pyrimidine or purine bases with the corresponding halogeno-derivatives of protected aliphatic aminoacids. For example, Nollet et al.[30] described the synthesis of a series of nucleoaminoacids of the purine series via Scheme 10, which provides for the use of various 6-chloropurines and potassium carbonate as the starting materials and of t-butyl γ-benzyloxycarbonylamino-α-bromobutyric acid (XLIX) as the alkylating agent. α-Amino-γ-(N^9-hypoxanthinyl)-butyric acid (LII), γ-(N^9-adeninyl)-α-aminobutyric acid (LIV), and α-amino-γ-(N^9-guaninyl)butyric acid (LVII) have been synthesised using this compound[30].

The alkylation reactions proceed with high yields (70 to 88%) in these syntheses and lead to the preferential formation of the N^9-derivatives. Admixtures of the isomeric N^7-derivatives did not exceed 10–11% in all cases and could be readily separated by chromatography on alumina.

Nollet and Pandit[31] also described the synthesis via an analogous scheme of α-amino-γ-(N^1-uracilyl)butyric acid (XLI), α-amino-γ-(N^1-cytosinyl)butyric acid (XLIII), and α-amino-γ-(N^1-thyminyl)butyric acid (XLII).

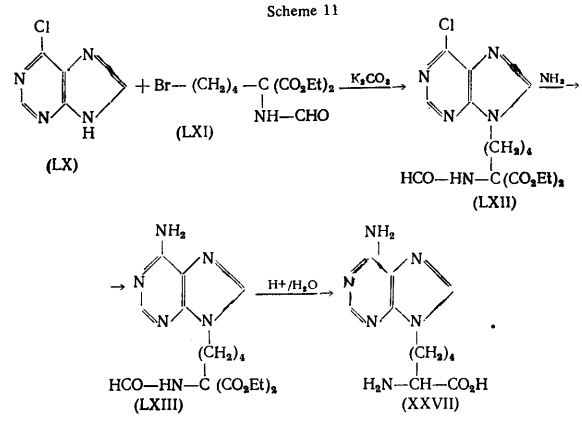
The nucleoaminoacids (XLI) and (XLII) were synthesised from 4-ethoxy-2-oxodihydropyrimidine (LVIII); on the other hand, in the synthesis of the nucleoaminoacid (XLII) the starting material was 4-ethoxy-5-methyl-2-oxodihydropyrimidine (LIX). The alkylation stages in these syntheses were carried out using sodium hydride.



(LVIII) (LIX)

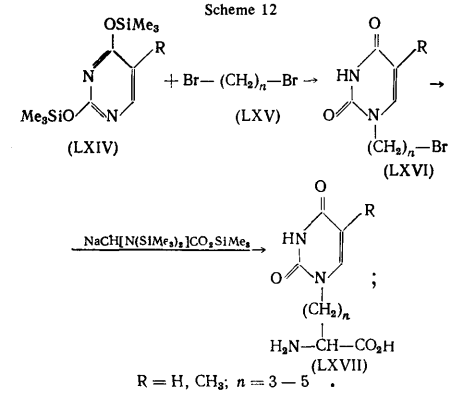
De Koning and Pandit[18] also used halogenoacylaminomalonic esters for the alkylation of heterocyclic bases. In particular, they obtained α-(4-bromobutyl)-α-formylaminomalonic ester (LXI) by the reaction of 1,4-dibromobutane with formylaminomalonic ester and then used it as the alkylating agent in the synthesis of ε-(N^9-adeninyl)-α-aminocaproic acid via the following scheme:

Scheme 11



Another sequence of reactions ensuring the formation of nucleoaminoacids by the alkylation of complete heterocyclic structures has been proposed[32].

Scheme 12

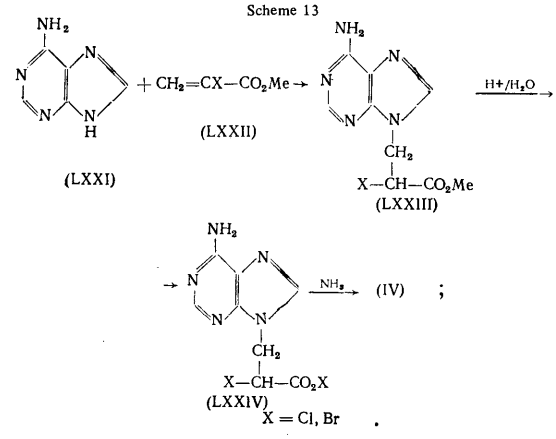


The principle of the method is that the heterocyclic structure is initially treated with an α,ω-dihalogenoalkane and the resulting ω-halogenoalkyl derivative of the pyrimidine or purine series is then converted into the corresponding nucleoaminoacid. The specific stages of this method are indicated in Scheme 12. α-Amino-ε-(N^1-uracilyl)caproic acid (XX) and α-amino-ε-(N^1-thyminyl)caproic acid (XXII), as well as the previously unknown α-amino-δ-(N^1-thyminyl)-valeric acid (LXVIII), α-amino-ω-(N^1-uracilyl)oenanthic acid (LXIX), and α-amino-ω-(N^1-thyminyl)oenanthic acid (LXX) have been synthesised by this method.

Japanese investigators[33] recently reported the synthesis via the alkylation reactions of a special group of nucleoaminoacids in which the pyrimidine or purine ring is linked directly to the α-carbon atom of the aminoacid residue.

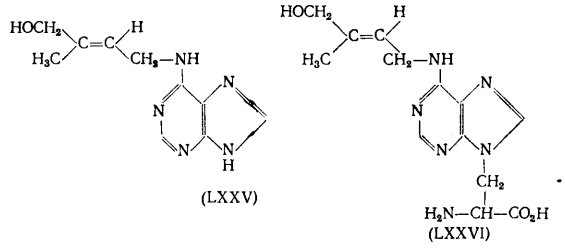
Instead of the alkylation of heterocyclic derivatives, one can use in the synthesis of nucleoaminoacids the reaction involving the addition of the corresponding nucleic acid bases to unsaturated compounds with an activated double bond. The preparation of β-(N^9-adeninyl)-α-alanine via Scheme 13, in which adenine (LXXI) and methyl α-halogenoacrylate (LXXII) are used as the starting materials[34], can serve as an example of such synthesis:

Scheme 13



The methyl ester of the corresponding β-(N^9-adeninyl)-α-halogenopropionic acid (LXXIII) and free β-(N^9-adeninyl)-α-halogenopropionic acid (LXXIV) are intermediates in this synthesis. The addition of adenine to methyl α-halogenoacrylate takes place with 80–85% yield, which ensures a fairly high overall yield of the nucleoaminoacid.

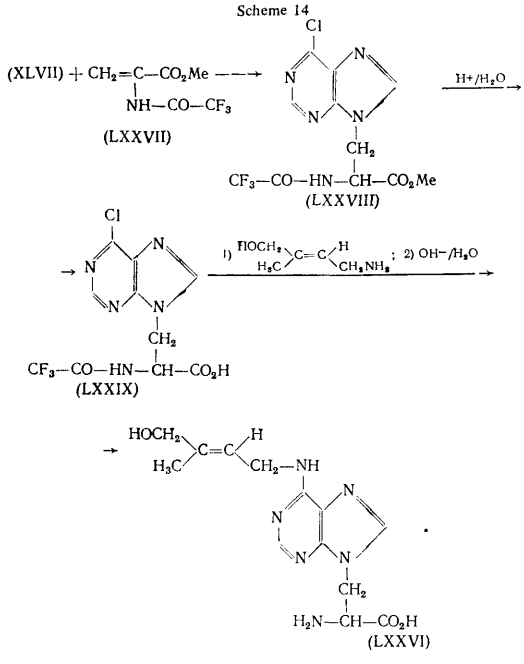
An analogous scheme can be used successfully also in the synthesis of other nucleoaminoacids of the purine series. Thus the method has been employed[35] to synthesise lupinic acid (LXXVI), which is a natural purine nucleoaminoacid. Lupinic acid was first isolated by Australian investigators[35,36] from prickly lupin (*Lupinus angustifolius*) and can be regarded as the N^9-alanine derivative of the familiar phytohormone zeatin (LXXV):



(LXXV) (LXXVI)

Lupinic acid can be regarded just as reasonably as a derivative of the nucleoaminoacid (IV) with the substituent in the exocyclic 6-aminogroup. Racemic lupinic acid has been synthesised via the following scheme[35]:

Scheme 14



(LXXVII) (LXXVIII) (LXXIX) (LXXVI)

The overall yield of compound (LXXVI) was approximately 5% (relative to the initial 6-chloropurine).

III. PROPERTIES OF NUCLEOAMINOACIDS

All the nucleoaminoacids known at present are colourless crystalline substances in a free state with high melting points. The solubilities of nucleoaminoacids in water are various and depend both on the nature of the nucleic acid base and on the length of the hydrocarbon chain linking the nucleic acid base to the α-carbon atom of the nucleoaminoacid. Nucleoaminoacids are almost insoluble in non-polar organic solvents. As typical amphoteric compounds, nucleoaminoacids are as a rule readily soluble in acid and alkaline aqueous solutions.

The ultraviolet spectroscopy occupies a special place in the study of the structures and physical properties of nucleoaminoacids (both naturally-occurring and synthetic). In many instances this technique makes it possible to solve convincingly and unambiguously the important problem of the cycloaddition of the aminoacid fragment to the nucleic acid base. Thus in the case of substituted uracils and analogous compounds of the pyrimidine series the large bathochromic shift of λ_{max} in the ultraviolet spectra of alkaline solutions of the test substances is characteristic of N^3-substituted derivatives. On the other hand, there is virtually no bathochromic shift in the spectra of the isomeric N^1-substituted derivatives in alkaline media[4-6,22].

NMR,[37,38] infrared spectroscopy[2,12,39], and mass spectrometry[35,36] are also useful in the solution of structural problems in the chemistry of nucleoaminoacids.

All the nucleoaminoacids give a positive response to tests with ninhydrin and other reagents forming characteristic coloured products on interaction with α-aminoacids. The chemical reactions of nucleoaminoacids can be divided into those involving the α-amino-group, the α-carboxy-group, and the nucleic acid base. The reactions of the first two types have now been particularly widely investigated. Methods of synthesis of N^{α}-protected nucleoaminoacids, in particular N^{α}-benzyloxycarbonyl-[40,41] and N^{α}-t-butoxycarbonyl-nucleoaminoacids[42-44] as well as nucleoaminoacid esters (including methyl, ethyl, and t-butyl esters[30,31,43,45]), amides[46], and hydrazides[45] have been developed on the basis of these studies. The synthesis of various activated esters of N^{α}-protected nucleoaminoacids (in particular, *p*-nitrophenyl, pentachlorophenyl, pentafluorophenyl, *N*-hydroxysuccinimido, and other esters) has also been achieved[45-47].

Takemoto et al.[48] obtained in a high yield and characterised the *N*-carboxyanhydride of β-(N^1-uracilyl)-α-alanine. The formyl[12], tosyl[2], *o*-nitrobenzenesulphenyl[44], 2,4-dinitrophenyl[45], and acetyl[49] derivatives of nucleoaminoacids have also been described in the literature.

The bromination and chlorination of certain nucleoaminoacids of the pyrimidine series in the 5-position in the pyrimidine ring by bromine and *N*-chlorosuccinimide respectively have also been studied[24].

Microbiological transformations as well as the chemical nature of the resulting products have been studied for certain nucleoaminoacids[52]. In particular, it has been established that a strain of *Microbacterium sp.* can utilise only the L-forms of compounds (I) and (II) as well as certain other nucleoaminoacids. This involves in the first place the oxidative deamination of the nucleoaminoacids and then the cleavage of the bond between the nitrogen atom in the 1-position in the pyrimidine ring and the β-carbon atom of the alanine fragment. Uracil, thymine, as well as the corresponding α-ketoacids of the pyrimidine series, which are apparently the precursors of the free nucleic acid bases formed, have been found among the microbiological transformation products of nucleoaminoacids.

IV. SYNTHESIS OF NUCLEOPEPTIDES

The reactions of peptide synthesis in solution, the methods of synthesis of peptides on insoluble polymeric carriers, as well as polycondensation reactions of carboxyl-activated derivatives of nucleoaminoacids can be used to synthesise nucleopeptides.

The synthesis of nucleopeptides in solution requires the preliminary solution of many special problems due to the

specific features of the chemical structures of nucleoaminoacids. The direct transfer to the synthesis of nucleopeptides of the traditional methods of the usual peptide synthesis, disregarding the characteristic features of the structure and reactivity of nucleoaminoacids, is in most cases relatively ineffective. At the same time there is much in common between the synthesis of nucleopeptides in solution and the usual peptide synthesis. In particular, as in the synthesis of normal peptides, made up of protein aminoacid residues, in the synthesis of nucleopeptides one must have at one's disposal the corresponding protected and activated derivatives of nucleoaminoacids, as well as reliable methods for the formation of peptide bonds between individual nucleoaminoacid residues.

The benzyloxycarbonyl and t-butoxycarbonyl groups are most often used in the synthesis of nucleopeptides in solution for the temporary protection of the α-aminogroup. In order to protect the carboxy-group, the nucleoaminoacids are first converted into esters (the methyl and ethyl esters are most often employed).

The carboxyl of the *N*-protected nucleoaminoacid used as the carboxy-component in nucleopeptide synthesis can be activated by the mixed anhydride or activated ester method as well as the azide and carbodi-imide methods.

Using the above protecting groups and methods of activation, a series of nucleopeptides incorporating the β-(N^1-uracilyl)-α-alanine residue have been synthesised[40,41]. The simplest representative of the family of homonucleopeptides—β-(N^1-uracilyl)-α-alanyl-β-(N^1-uracilyl)-α-alanine (LXXX)—was also obtained for the first time by this procedure. The syntheses of a series of oligonucleopeptides containing the α-amino-ε-(N^1-uracilyl)caproic acid (XX) and α-amino-ε-(N^1-thyminyl)caproic acid (XXII) residues[50], as well as other nucleoaminoacid residues of the pyrimidine and purine series[43,44,53,54] have been achieved analogously.

An example of the synthesis of nucleopeptides using insoluble polymeric carriers is provided by the synthesis of an oligonucleopeptide containing a monotonic block comprising nine repeating residues of compound (I).[55] The chloromethylated styrene–1% divinylbenzene copolymer was used as the insoluble carrier and the condensing agent was *N*,*N*′-dicyclohexylcarbodi-imide.

The nucleopeptide was separated from the polymeric carrier by hydrazinolysis. An oligonucleopeptide containing a monotonic block of repeating residues of compound (IV) has been synthesised via a similar scheme[56].

It is noteworthy that the synthesis of nucleopeptides on insoluble polymeric carriers involves many difficulties characteristic of the solid-phase synthesis of the usual peptides made up of protein α-aminoacid residues[57,58].

The polycondensation reactions of carboxyl-activated derivatives of nucleoaminoacids can be used to synthesise both homo- and hetero-nucleopeptides.

Homonucleopeptides containing the residues of nucleoaminoacids (I) or (II) have been synthesised by the polycondensation of the *p*-nitrophenyl esters of the nucleoaminoacids[59]. The molecular weight of the homonucleopeptides obtained is approximately 2000 according to sedimentation analysis and gel filtration data. Homonucleopeptides containing repeating units of nucleoaminoacids (XXII) or (XXVII) have been synthesised analogously[50]. Their yields were 85–90% and the molecular weight of the homonucleotide made up repeating nucleoaminoacid (XX) residues reached 5%.

Together with the polycondensation of *p*-nitrophenyl esters of nucleoaminoacids, the analogous reaction using the pentachlorophenyl esters of nucleoaminoacids has also been studied[46]. Compared with the *p*-nitrophenyl esters, the pentachlorophenyl esters of nucleoaminoacids are more reactive and make it possible to obtain longer homonucleopeptide chains.

Takemoto et al.[48] reported the synthesis of homonucleopeptides containing repeating residues of β-(N^1-uracilyl)-α-alanine from the *N*-carboxyanhydride of the same nucleoaminoacid. Aliphatic amines (in particular, mono-, di-, and tributylamines) were used as the initiators of the polycondensation reaction[48]. The same workers also reported the synthesis of mixonucleopeptides containing the residues of β-(N^1-uracilyl)-α-alanine and γ-benzylglutamic acid[48].

An important new stage in the study of nucleopeptides has been the development of methods of synthesis of hitherto unknown stereoregular nucleopeptides made up of optically pure, and not racemic, enantiomeric nucleoaminoacids. A necessary condition for the synthesis of stereoregular nucleopeptides was the development of preparative methods of synthesising the optical isomers of nucleoaminoacids.

The first attempts to obtain L-β-(N^1-uracilyl)-α-alanine were made by Kjaer and Knudsen[2] and Dewar ahd Shaw[12]. Kjaer and Knudsen[2] started with the optically active derivative of α,β-diaminopropionic acid. However, as already mentioned above, the difficulties arising in the stage involving the removal of the N^{α}-protecting groups prevented these investigators from obtaining L-β-(N^1-uracilyl)-α-alanine in preparative amounts. Dewar and Shaw[12] attempted to separate racemic β-(N^1-uracilyl)-α-alanine into optical isomers by forming diastereoisomeric salts with optically active bases. The latter consisted of the dextrorotatory enantiomer of α-methylphenylamine and natural laevorotatory brucine. However, these attempts were also unsuccessful as regards the preparative scale of the synthesis of optical isomers of nucleoaminoacids.

It was not until 1975–1976 that preparative methods for the synthesis of nucleoaminoacid enantiomers were developed. A special series of studies established that nucleoaminoacid racemates can be separated into optical isomers with the aid of the stereoselective enzymatic hydrolysis of the N^{α}-acyl derivatives of D,L-nucleoaminoacids by pig kidney acylase (I) [49] or plant acylase[51]. The possibility of using chymotrypsin for the stereoselective hydrolysis of racemic nucleoaminoacid esters was also demonstrated.

The use of the above methods made it possible for the first time to obtain the optical isomers of various nucleoaminoacids on a preparative scale. Using individual enantiomers of nucleoaminoacids, methods were then developed for the synthesis of protected and carboxyl-activated derivatives of optically active nucleoaminoacids, which led to the possibility of synthesising also stereoregular nucleopeptides. For example, the corresponding N^{α}-t-butoxycarbonyl derivatives and pentachlorophenyl esters have been synthesised from the L- and D-isomers of the nucleoaminoacid (I). They were made to undergo the polycondensation reaction, which yielded stereoisomeric homonucleotides made up of repeating L- (I) or D- (I) residues[60].

Various stereoisomeric mixonucleopeptides—in particular water-soluble stereoregular nucleopeptides of the mixed type made up of regularly alternating residues of compound L- (I)—have also been synthesised by an analogous procedure[61].

An important recent discovery has been the detection of naturally-occurring nucleopeptides of a mixed type. The isolation of two new willardiine peptides from the seeds of *Fagus silvaticus* has been reported[62,63]. The structures of γ-L-glutamyl-L-β-(N^1-uracilyl)-α-alanine (LXXXI) and γ-glutamylphenylalanyl-β-(N^1-uracilyl)-α-alanine (LXXXII) respectively have been proposed for the above peptides on the basis of a study of their chemical and spectroscopic

properties[62]. In view of the very limited amount of the second compound, the authors were unable to determine the stereochemical configuration of the aminoacid residues in this nucleotripeptide. The question of the synthesis of these new natural products also remained open.

Both problems were subsequently solved. Firstly, the total synthesis of the nucleopeptide (LXXXI) was carried out[64]. Secondly, authentic γ-L-glutamyl-L-phenylalanyl-L-β-(N^1-uracilyl)-α-alanine was synthesised. The natural nucleopeptides proved to be identical with the synthetic specimens[64]. Thus it can be regarded as proved that all three aminoacid residues in the nucleotripeptide (LXXXII) have the L-configuration.

V. PROPERTIES OF NUCLEOPEPTIDES

In a free state nucleopeptides are colourless crystalline or amorphous substances with high and as a rule non-characteristic melting points. The solubility of nucleopeptides in water varies within wide limits and depends on the nature of the aminoacid residues and on the length of the nucleopeptide chain. There is an overall tendency towards a decrease of the solubility of nucleopeptides in water with increase of the length of the nucleopeptide chains. Free nucleopeptides are almost insoluble in non-polar salts. Comparatively short nucleopeptides dissolve satisfactorily in aqueous solutions of acids and alkalies. The solubility of nucleopeptides of the mixed type can be regulated within wide limits by introducing "solubilising inserts" into the nucleopeptide chain. Thus water-soluble nucleopeptides of a mixed type can be obtained by introducing the residues of hydrophilic α-aminoacids (in particular serine, lysine, glutamic acid, etc.) into the nucleopeptide chain. The properties of long nucleopeptide chains have so far been inadequately investigated.

Short nucleopeptides can be used to prepare longer nucleopeptide chains either by the stepwise growing of the chain or by employing fragment polycondensation methods. At the same time short nucleopeptides are not only important intermediates but are also of independent interest, because these compounds can exhibit certain general properties characteristic of nucleopeptide structures.

One of these general properties is the interaction of the side groups in nucleopeptides. In nucleopeptides made up exclusively of nucleoaminoacid residues there is a possibility of observing the interaction between the corresponding nucleic acid bases. On the other hand, in nucleopeptides of the mixed type, incorporating various protein and non-proteinogenic aminoacid residues, together with those of nucleoaminoacids, the interaction of the nucleic acid bases with the side chains of aromatic and heterocyclic aminoacids merits attention.

Comparative study of the ultraviolet and ^{1}H NMR spectra of aqueous solutions of oligonucleopeptides incorporating the residues of nucleoaminoacid (I) as well as the residues of this nucleoaminoacid and phenylalanine showed[38] that secondary structures, stabilised by intramolecular hydrophobic stacking interactions, are formed in such nucleopeptides.

VI. PROSPECTS FOR THE STUDY OF NUCLEOAMINOACIDS AND NUCLEOPEPTIDES

The synthesis and investigation of nucleoaminoacids and nucleopeptides are of undoubted interest. Nucleoaminoacids are necessary for the synthesis of nucleopeptides. The latter can have unique properties, the unusual nature of which is determined by the combination, within the framework of a single molecule, of the peptide skeleton characteristic of proteins and of heterocyclic bases characteristic of nucleic acids.

Interesting effects can be expected as a result of the superposition and interaction of the system of hydrogen bonds characteristic of the polypeptide chain and the system of hydrogen bonds characteristic of nucleic acids and bases. An important structural factor, namely the hydrophobic stacking interaction between the heterocyclic bases, should also be added to the structure-forming factors playing a cardinal role in biopolymers.

In nucleopeptides the nucleic acid bases are attached to the nitrogen atom of the peptide skeleton in the 1- and 9-positions (in the pyrimidine and purine bases respectively). These are the positions at which the nucleic acid bases are attached to the pentose phosphate skeleton in polynucleotides. Thus the nucleic acid bases in nucleopeptides retain in an unchanged form all the structural elements necessary for the formation of specific mutually complementary hydrogen bonds between the complementary bases.

The distances between neighbouring nucleic acid bases in regular nucleopeptides are identical and equal to the translation along the chain by one nucleoaminoacid residue.

The combination of the above structural features of nucleopeptides creates the necessary and sufficient conditions for the occurrence of numerous intermolecular cooperative contacts between the nucleopeptide chains. These contacts must be similar to those which arise in the interaction of the corresponding polynucleotide chains. As a result of the cooperative nature of the process, each interaction of the pair of complementary bases increases the probability of subsequent contacts. Ultimately one may foresee the possibility of complementary interactions between different nucleopeptide chains, carrying complementary nucleic acid bases, corresponding to the canonical nucleoaminoacid pairs Aal-Tal (Aal-Ual), Gal-Cal, etc.

Complementary interactions of the above type can also take place intramolecularly, i.e. between different sections of the same nucleopeptide chain if the sequence of the alternating nucleoaminoacid residues in these sections of the nucleopeptide chain ensures the possibility of the formation of complementary pairs of nucleic acid bases.

The possibility of the occurrence of the analogous complementary interactions between nucleopeptide and polynucleotide chains and also between nucleopeptides and oligonucleotides is of especial interest. Complementary interactions can also take place when polynucleotides come into contact with nucleoaminoacids and short nucleopeptides.

All these factors suggest that it may become possible to employ nucleopeptide structures for the specific interference with nucleic acid–protein interactions, which play the most important role in vital phenomena.

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