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Amino Acids and Peptides

Volume 18

A Review of the Literature Published during 1985

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Amino Acids and Peptides

Volume 18

Preface

Our syllabus and approach are as in the previous volume, but we have been obliged to submit to the discipline of producing camera-ready copy for the first time. The formulae have been drawn for us by the R.S.C., but the layout of the text has been our own responsibility. Some of us are novices at this art form, and crave indulgence accordingly.

The most notable relevant book[1] published during 1985 is edited by our colleague John Davies. It is largely a derivative work, drawn from the 1982 edition of the 'Dictionary of Organic Compounds', but the entries have all been reviewed and updated where necessary, and some three hundred completely new ones have been added. There are getting on for two thousand all told, and perhaps ten thousand literature citations. The compilation, which is arranged alphabetically, gives physical, chemical, and bibliographic data on all the important amino acids and peptides. The amino acids of proteins have very full entries, and their principal protected derivatives also appear individually. The rarer amino acids are covered as well, together with nearly all known dipeptides; higher peptides are listed if they are of biological or pharmaceutical importance. Coverage extends not only to peptide antibiotics, including β-lactams, but also to natural products such as the peptide alkaloids.

A number of valuable monographs have appeared on biological aspects of amino acid and peptide chemistry. Although aimed at advanced biomedical students, readers of this Report will also find them useful as introductory background reading. Bender's well-known 'Amino Acid Metabolism'[2] is now out in a second edition. Wallis, Howell, and Taylor's 'The Biochemistry of the Polypeptide Hormones'[3] has a chapter on each main class of peptide

hormone and will be very helpful to any chemist entering the field. So will 'Immunology'[4] by Roitt, Brostoff, and Male, which is remarkable for its profuse, clear, and elegant diagrams.

Balliol College, Oxford
July 1986

John Jones

References

1. 'Amino Acids and Peptides', ed. J.S. Davies, Chapman and Hall Ltd., 1985.
2. D.A. Bender, 'Amino Acid Metabolism', 2nd Edn., John Wiley and Sons Ltd., 1985.
3. M. Wallis, S.L. Howell, and K.W. Taylor, 'The Biochemistry of the Polypeptide Hormones', John Wiley and Sons Ltd., 1985.
4. I. Roitt, J. Brostoff, and D. Male, 'Immunology', Gower Medical Publishing Ltd., 1985.

Abbreviations

Abbreviations for amino acids and their use in the formulation of derivatives follow, with rare exceptions, the 1983 Recommendations of the I.U.P.A.C.-I.U.B. Joint Commission on Biochemical Nomenclature, which are reprinted as an Appendix in Volume 16 of this title. Exceptions and additions are defined in the text as they occur.

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Amino Acids

BY G. C. BARRETT

1 Introduction

All major sub-divisions of amino acid science are represented in this Chapter as in previous Volumes of this Specialist Periodical Report (formerly named 'Amino acids, Peptides, and Proteins'), though with some waxing and waning as topic areas develop or become exhausted. The emphasis continues to reside in chemical studies but covers the biological literature to the extent that chemical and analytical studies are included there.

2 Textbooks and Reviews

Reference texts[1] and compendia of data[2,3] include the second supplementary list of amino acid derivatives that are useful in peptide synthesis (taking in the literature to the end of 1982).[3] Other topics reviewed include 1-aminocyclopropanecarboxylic acid,[4] synthesis of N-methylamino acids,[5] applications of uncommon amino acids in natural-products synthesis,[6] the role of S-adenosylhomocysteine[7] and of L-ergothioneine,[8] and boron analogues of amino acids[9] including p-borono-L-phenylalanine.[10]

3 Naturally Occurring Amino Acids

3.1 Occurrence of Known Amino Acids.- Close relatives of the common amino acids are covered here, and no attempt is made to review the routine literature of the distribution of well-known amino acids.

The first natural appearance of methionine sulphoximine is reported;[11] it is the toxic principle of Chestis glabra. L-DOPA-3-Sulphate has been located in the brown alga Ascophyllum nodosum,[12] and α-hydroxymethylserine, not previously reported to be a natural product, has been found in Vicia pseudo-orobus.[13]

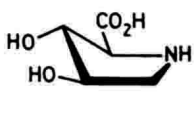
N-Substituted amino acids continue to arise in a variety of systems: N-trimethylalanine at the N-terminus of myosin light chains,[14] L-pyrrolidone-2,4-dicarboxylic acid in the muscle of the mollusc abalone Haliotis discus hannai,[15] and 3R,4R-dihydroxy-L-proline (1), present in virotoxins.[16] (1), like (+)-3,4,5-trihydroxypipecolic acid (2) from Baphia seeds,[17] competitively inhibits cattle β-D-glucuronidase.[16] Leucinopine, one of a group of N-(1-carboxyalkyl)amino acids often categorized as 'opines', has been shown[18] to possess the L-threo stereochemistry; in other words, this amino acid, N-(1,3-dicarboxy-

propyl)leucine, has the '$\underline{L}^{glu}$-,$\underline{L}^{leu}$-' configuration and in this respect is unique amongst the other opines octopine ('$\underline{D}^{ala}$-,$\underline{L}^{arg}$-'), nopaline ('$\underline{D}^{glu}$-,$\underline{L}^{arg}$-'), and succinamopine ('$\underline{D}^{glu}$-,$\underline{L}^{asn}$-').[18]

Plant, fungal, and microbial sources of less common amino acids: Asplenium unilaterale (4-hydroxy-L-2-aminopimelic acid as well as D-2-aminopimelic acid and trans-3,4-dehydro-D-2-aminopimelic acid),[19] Dactylosporangium aurantiacum (L-threo-β-hydroxyaspartic acid, previously only found in Arthrinium and in various Streptomycetes),[20] and Amanita pseudoporphyria (L-2-aminopent-4-ynoic acid and L-2-aminopent-4-enoic acid, L-2-aminohex--4-ynoic acid and L-2-aminohept-4-en-6-ynoic acid, as well as L-2-amino-4-chloropent-4--4-enoic acid and L-2-aminohexa-4,5-dienoic acid as previously reported).[21] Another cyclic tetrapeptide from Helminthosporium carbonum has been described,[22] containing a 2-amino-8-oxo-9,10-epoxydecanoic acid residue. L-Phenylalanine and its 3S-methyl homologue (3) occur as their N-acetyl derivatives esterified with the unusual 8R-hydroxy-9S-methyl oxiranyl-2E,4Z,6E-decatrienoic acid as AK-toxins I and II from Alternaria alternata pear fungus (black spot disease).[23]

Cross-linking amino acid residues in mammalian proteins continue to attract interest, a recent citation referring to the identification of pyridinoline in Type 1 collagen.[24]

3.2 New Natural Amino acids.- New aliphatic α-amino acids include 2S-aminohex-5-ynoic acid (from Cortinarius claricolor var. tennipes),[25] D_s-erythro-2-amino-4-ethoxybutanoic acid (from the edible mushroom Lyophyllum ulmarium),[26] erythro-γ-hydroxyhomo-L-arginine (from the seed of Lonchocarpus costaricaensis; the threo diastereoisomer is already known to be a natural product),[27] and the sulphate ester of trans-4-hydroxypipecolic acid (seeds of Peltophorum africanum).[28] This is the first naturally occurring sulphate ester of a non-protein amino acid to be reported. The bulgecins contain O-glycosylated 5-hydroxymethyl-4-hydroxyproline amides (4; R = glycosyl residue).[29,86] 'Dealanylalahopcin' (5), found with alahopcin in Streptomyces albulus cultures, is (2S,3R)-2-amino-4-formyl-3-(hydroxyaminocarbonyl)butyric acid[30] (wrongly named as the 4-(hydroxyaminocarbonyl)acid in the original paper). A high level of interest in N-(1-carboxyalkyl)amino acids (the 'opines'; see listing in preceding Section) is reflected in three new examples from the 1985 literature: crown-gall tumours incited by Agrobacterium tumefaciens produce agropine and related mannityl opines and leucinopine and in addition large amounts of a new member of the family N-{(1S)-1-carboxy-2-carbamoylethyl}-(S)-glutamic acid ('LL-succinamopine').[31a] The D,L-diastereoisomer having been isolated previously from the same source, this is the first example of the natural occurrence of epimeric opines. The other two new opines are N-(1-carboxyethyl)-L-methionine[31b] and a phosphorylated example (agrocinopine A) secreted by healthy crown-gall cells induced by the same bacterium.[32]



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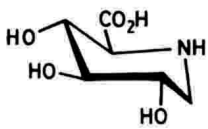

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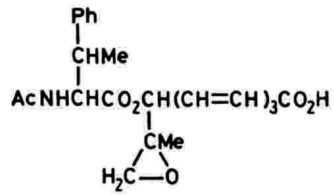

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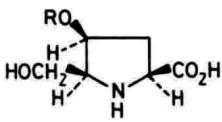

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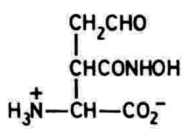

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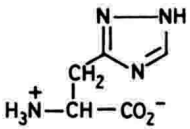

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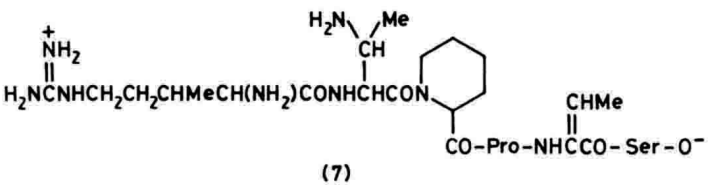

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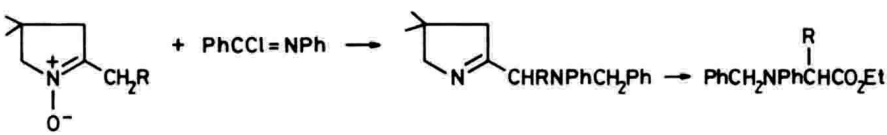

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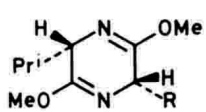
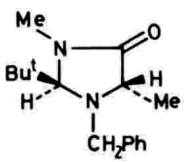


(9) R = H

(10) R = Me



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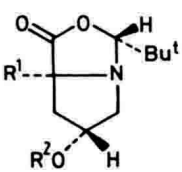

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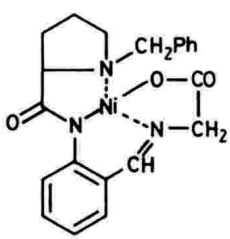

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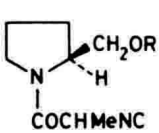

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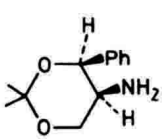

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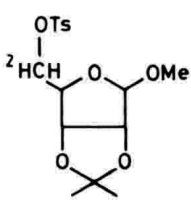

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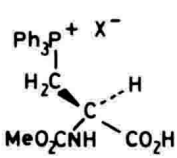

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Streptomyces KM-10329 produces β-(1,2,4-triazol-3-yl)-L-alanine (6).[33]

3.3 New Amino acids from Hydrolysates.- This section specifically refers to natural products that in principle or in practice can release new amino acids on hydrolysis.

Lavendomycin from Streptomyces lavendulae is an unusual peptide (7) containing some close analogues of common amino acids.[34]

Carzinophilin contains (2S,3S)-4-amino-2,3-dihydroxy-3-methylbutanoic acid.[35]

4 Chemical Synthesis and Resolution of Amino Acids

4.1 General Methods of Synthesis.- The major standard methods, mostly of many years' standing, continue to be fully used. It is not necessary to do more than cite most of these with literature references (recent review coverage is available[36]), and some further details of the synthetic objectives are given in later sections of this Chapter. The alkylation methods in which the side chain of the α-amino acid is put in place include alkylation of acetylaminomalonates[37] and other glycine derivatives $(MeS)_2C{=}NCH_2CO_2Et$,[38] $Ph_2C{=}NCH_2CO_2Et$,[39,40] $PhCH{=}NCH_2CO_2Et$,[41] $CNCH_2CO_2Et$,[42] and azlactones.[43]

Alkylation of methyl 2-acetamidoacrylate with a Grignard reagent in the presence of copper(I) iodide gives moderate yields of 3-substituted alanines,[44] and N-alkylamino acid esters, benzaldehyde, and alkenes react in refluxing toluene to give prolines.[45] The latter process involves cycloaddition to intermediate azomethine ylides.

Strecker synthesis of α-amino nitriles[46,47] involving reaction of an aldehyde, a secondary amine, and Me_3SiCN in MeOH can be accomplished within less than 5 minutes, thus providing some assistance in the synthesis of α-amino acids labelled with short-lived radioactive isotopes.[47] Dehydrogenation of aliphatic secondary amines by phenylseleninic acid (or its anhydride), under mild conditions in the presence of NaCN or Me_3SiCN, is a new route to α-amino nitriles.[48]

A full paper has been published on the synthesis of N-acyl α-amino acids through the isomerization - amidocarbonylation of allylic alcohols by primary amides and H_2 with carbon monoxide, using a homogeneous binary catalyst system $HRh(CO)(PPh_3)_3$ with $Co(CO)_8$ or $Fe_2(CO)_9$: $R^1R^2C{=}CR^3CH_2OH + RCONH_2 \longrightarrow R^1R^2CHR^3CH(NHCOR)CO_2H$.[49]

A new amino acid synthesis adding to the group of methods in which the amino function is introduced into an alkanoic acid (or a precursor of it) has been reported.[50] Ethanolysis of the pyrroline formed after reaction of the corresponding N-oxide (8) with N-phenylbenzimidoyl chloride yields an N-phenyl-N-benzylamino acid ethyl ester, from which the various N and C substituents can be removed by standard methods.

4.2 Asymmetric Synthesis.- Further examples have accumulated in the literature during 1985 to extend established methods in the amino acid area. The already voluminous output of Schöllkopf and co-workers, based on the alkylation of bis-lactim ethers (9) derived from piperazine-2,5-diones, has been augmented to include syntheses of D-tryptophan methyl ester and (R)-α-methyltryptophan methyl ester,[51] and other alkylation processes in which very high diastereoselectivity is achieved.[52-56] One of these[54] deals with asymmetric synthesis of D-threonine through reaction of acetaldehyde with the $Ti(NMe_2)_3$ complex of the bis-lactim ether. Another is concerned with the synthesis of chiral deuteriated α-aminoisobutyric acid through reaction of the bis-lactim ether (10) with C^2H_3I.[56]

Further results from Seebach's group[57-59] on the alkylation of chiral enolates with what has been called 'self-reproduction of the centre of chirality' – i.e. the incoming group takes the place of the proton that is substituted – confirm the high (>90%) diastereoselectivity that accompanies this approach. Enantiomerically pure pivalaldehyde aminals (11) derived from N-benzyl-L-alanine can be alkylated and elaborated into (R)- or (S)-α-methylDOPA, depending on the cis or trans orientation, respectively, of the aminal.[57] Other α-methyl analogues prepared in this study in high optical purity include α-methyl-L-methionine and α-methyl-L-valine. Pivalaldehyde N,O-acetals (12) from O-acyl-4-hydroxy-L-proline[58] and the corresponding compound from L-thiazolidine-4-carboxylic acid[59] have also been studied in what is clearly the start of a programme seeking to understand the relationship of structure to carbanion stereochemical integrity, in which the alkylating agent no doubt plays a role.[279]

Highest optical purity was observed in the stereoselective synthesis of L-aspartic acid through alkylation of a di-alkyl malonate with N-benzyloxycarbonyl-L-alanyl-2-chloroglycine methyl ester, followed by hydrolysis, when the malonate carried bulky alkyl groups.[60]

Other studies based on recent pioneering work include alkylation of chiral nickel(II) complexes, to yield either D-serine in better than 80% enantiomeric excess, using 0.2M NaOMe as base, but L-serine in 80-98% enantiomeric excess, using NEt_3,[61] when the complex (13) formed between N-benzyl-L-proline N-arylamide and the contiguous glycine Schiff base is alkylated with formaldehyde. A less puzzling result is seen for the corresponding alanine complex, used[62] for the preparation of α-methyl amino acids in optically pure form after separation of diastereoisomers over silica gel.

Alternative asymmetric synthesis of α-methyl amino acids has been established[63] but in much lower enantiomeric excess (31.7% for the R-enantiomer) when the alanine-based isonitrile (14) participates in Michael addition to acrylonitrile. Variable results (10-45% enantiomeric excess of the R-enantiomer)were obtained in the corresponding reaction with methyl acrylate, in relation to the asymmetric synthesis of α-methyl-D-glutamic acid and α-methyl-D-ornithine.[63]