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**Amino Acids
and Peptides**
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Amino Acids and Peptides

Volume 19

A Review of the Literature Published
during 1986

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Preface

We have not been made aware of any major general works on the chemistry of amino acids and peptides, although there has of course been the usual crop of specialist monographs¹ and symposium proceedings. On the other hand, there have been two noteworthy texts covering the pharmacological background which provides the principal justification and motivation for a large part of the chemical effort surveyed in these Specialist Periodical Reports. In their 'Principles of Endocrine Pharmacology', Thomas and Keenan² give clear and up-to-date (at mid-1985) accounts of the functions and pharmacology of hypothalamic hormones, the anterior pituitary hormones, the posterior pituitary hormones, parathyroid hormone, calcitonin, and insulin. The fifth edition³ of a well-known introduction to neuropharmacology is also commended: it has a most stimulating discussion of the neuroactive peptides. This is an area of great complexity, which increases relentlessly with the discovery of new peptide factors and activities, and it will be a long time before all the pieces of the puzzle fall into place. It is already clear that the interpretation of the roles of the neuropeptides will lead towards an understanding of the workings of the brain and provide a basis for the rational design of drugs for use in neurological and psychiatric disorders. Quite a lot can be said about what the neuropeptides can do in experimental systems, but what are they for in Nature? At first it was thought that they were like the neurotransmitters of classical pharmacology. Now they are generally regarded as modulators of neural activity - a high sounding but imprecise phrase, like a politician's answer to a tricky question. But there is room for speculation and hypothesis at a fundamental level here, and it has been argued⁴ (in a new journal which looks like one which should be watched) that 'peptides are an overelaborated form of messenger for engaging in the relatively simple informational events associated with neurotransmission', and suggested that there may be other functions, to do with nerve growth and development.

The advice with which Cooper, Bloom, and Roth³ conclude their book is sound: 'Stay tuned, the data flow fast'.

Balliol College, Oxford
July 1987

John Jones

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1. Note especially The Peptides, 1985, 7 (ed. V. J. Hruby, Academic Press, New York, etc.: deals with the study of peptide conformations and interactions, in relation to drug design, by c.d., fluorescence, theoretical, and n.m.r. methods) and T. Wieland, 'Peptides of Poisonous Amanita Mushrooms', Springer, New York, etc., 1986.
2. J. A. Thomas and E.J. Keenan, 'Principles of Endocrine Pharmacology', Plenum Medical Book Company, New York and London, 1986.
3. J. R. Cooper, F. E. Bloom, and R. H. Roth, 'The Biochemical Basis of Neuropharmacology', 5th Edn., Oxford University Press, New York and Oxford, 1986.
4. J. S. Morley, Drug Design and Delivery, 1986, 1, 47. This new journal is published by Harwood Academic Publishers GmbH.

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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1 Amino Acids

BY G. C. BARRETT

1 Introduction

The coverage is predominantly derived from the chemical literature, though much of the interest in the amino acids lies in their biological context. The list of references at the end of this Chapter (p.40) reveals many citations from biological journals and secondary sources, however. The 'cut-off point' as far as this Chapter is concerned is to exclude coverage of the distribution of amino acids and metabolic and biosynthetic aspects and biological roles.

2 Textbooks and Reviews

Reviews of a specialist nature are cited in the appropriate Sections of this Chapter. This Section lists more general references: a supplementary list of nomenclature recommendations (IUPAC-IUB) covers selenium-containing amino acids;¹ N-hydroxyamino acids;² L-proline and L-hydroxyproline as chiral auxiliary agents in asymmetric synthesis;³ historical account of the discovery of γ -aminobutyric acid;⁴ and arginine with special emphasis on evolutionary and metabolic aspects.⁵ Monographs and compendia include a volume entitled 'Glutamate, Glutamine, and Related Compounds' that contains authoritative coverage of many other amino acids of similar functionality;⁶ Proceedings volumes;⁷ comprehensive analytical coverage;⁸ and more broadly based texts.⁹

3 Naturally Occurring Amino Acids

3.1 Occurrence of Known Amino Acids.- This Section includes examples of unusual occurrence of simple, familiar amino acids, either in the free form or in a non-peptide coupling.

D-Leucine is found, not merely in trace amounts, in aerial parts of Coronilla varia and in seeds of Coronilla scorpioides.¹⁰ S-(β -Carboxyethyl)cysteine is the major free amino acid (up to 2.9% dry weight) in seeds of several Calliandra species, and survives in leaves of these plants at early stages of germination.¹¹ Since this derivative is moderately insecticidal, young plants have chemical defence against at least some of their natural adversaries.

Culture media of Streptomyces cattleya contain (2S)-amino-(3R)-hydroxy-pent-4-ynoic acid (" β -ethynyl serine").¹² The detection of 1,2,3,4-tetrahydro- β -carboline-3-carboxylic acid in beer and wine has been reported;¹³ it is accompanied by its 1-methyl homologue.

Argiopine, a fortuitously named ion-channel blocking agent from the spider Argiope iobata,

contains arginine and asparagine linked through their carboxy groups by the polyamine moiety $-\text{NH}(\text{CH}_2)_3\text{NH}(\text{CH}_2)_3\text{NH}(\text{CH}_2)_5\text{NH}-$, the side-chain amide being substituted by a 2,4-dihydroxyphenylacetic acid grouping.¹⁴

3.2 Uncommon Amino Acids in Peptides and Proteins. - This would be a much larger section if it covered the title comprehensively; it is restricted to representative citations.

The aquatic fern Azolla caroliniana contains (N^γ -L-glutamyl-D-amino)phenylpropanoic acid.¹⁵ The modified nucleoside N^γ -[9-(β -D-ribofuranosyl)purin-6-ylcarbomoyl]-L-threonine occurs in the urine of patients with certain types of breast cancer and may be of diagnostic value in this context.¹⁶

Hydrolysis of the glycopeptide antibiotic aricidin A gives (2R,2'S)-actinoidinic acid (as a mixture of two atropisomers) and the phenylglycine derivative (1).¹⁷ More familiar but still uncommon amino acids reported as substituents of proteins are D-aspartic acid in myelin and myelin basic protein;¹⁸ γ -N-methyl asparagine in allophycocyanin;¹⁹ and histidinoalanine, a crosslinking residue in a Macrocallista nimbosa protein.²⁰ This crosslink is surmised to derive from non-enzymic condensation of phosphoserine and histidine residues,²⁰ though since this protein also contains phosphothreonine this conclusion would be more plausible if analogous "histidinobutyryne" crosslinks could also be hunted for.

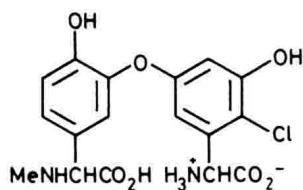
3.2 New Natural Amino Acids. - Xylem sap of Pisum sativum contains an amino-chlorobutanoic acid $\text{C}_4\text{H}_9\text{NO}_2\text{Cl}$;²¹ while further structural studies can be expected for this compound, more complete assignments have been reported for N^δ -(1-carboxyethyl)-L-ornithine from Streptococcus lactis grown in ornithine-supplemented media.²² Synthesis of this compound from poly(L-ornithine) or N^α -benzyloxycarbonyl-L-ornithine gave a 1:1 mixture of diastereoisomers, one of which was identical with the natural material.

Seven new amino acids have been found in the red alga Chondria armata,²³ but the information from Chemical Abstracts is limited to domoic acid (2) and two palitoxin analogues. The strongly insecticidal properties of these amino acids towards cockroach will ensure the availability of more complete information on this research. Ectothiorhodospira halochloris yields ectoine (3), shown by X-ray analysis to exist in the zwitterionic form.²⁴

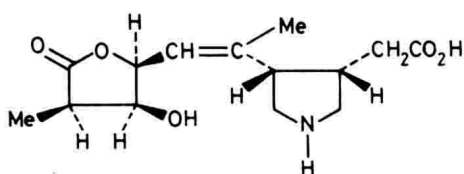
An unusual type of derivative, D- β -lysylmethanediamine, occurs in Streptomyces nashvillensis.²⁵

The earlier finding²⁶ that α -amino- γ , δ -dihydroxyadipic acid is a constituent of normal human urine is now corrected;²⁷ it is an artefact from boiling urea and D-glucuronolactone with 6M hydrochloric acid.

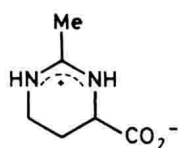
3.3 New Amino Acids from Hydrolysates. - This Section covers new amino acids found in peptides and proteins and related condensation products. 2,2'-Bityrosine has been detected



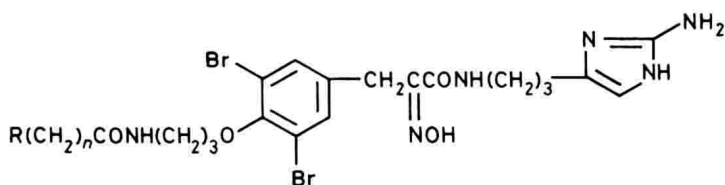
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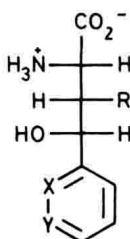
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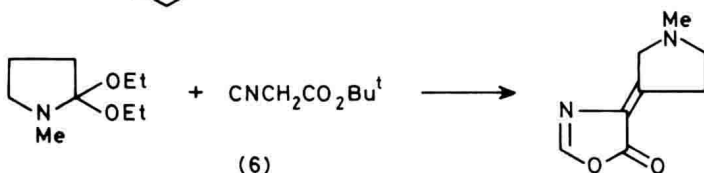
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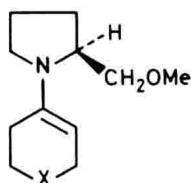
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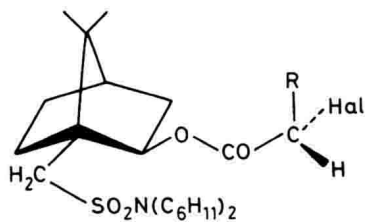
(5) $\text{X} = \text{N}, \text{Y} = \text{CH}, \text{R} = \text{Me}$
 $\text{X} = \text{CH}, \text{Y} = \text{N}, \text{R} = \text{Me}$
 $\text{X} = \text{N}, \text{Y} = \text{CH}, \text{R} = \text{H}$



(6)



(7)



(8)

in yeast ascospore wall protein in previously unknown racemic and meso forms.²⁸ Hydrolysis of proteins that have been chemically modified through azo-coupling of lysine residues releases the modified residues unaltered when MeSO_3H is used, but when aqueous HCl is used for the hydrolysis α -amino- ϵ -hydroxycaproic acid and α -amino- ϵ -chlorocaproic acid are formed.²⁹

2-Aminoethylphosphonic acid, claimed to have been found in hydrolysates of ruminant stomach contents, is thought to be a mis-interpretation.³⁰

Lipopurealins A (4; R = Me, $n = 12$) and homologues B (4; R = i Pr, $n = 11$) and C (4; R = Me, $n = 14$) are novel bromotyrosine derivatives from the marine sponge *Psammaplysilla pura*.³¹ Nikkomycin from *Streptomyces tendae* releases three novel amino acids (5) on hydrolysis, whose structures have been confirmed by synthesis.³²

4 Chemical Synthesis and Resolution

4.1 General Methods of Synthesis of α -Amino Acids. - This Section collects together those papers that illustrate the use of standard methods (the objectives of these papers are mentioned elsewhere in this Chapter), and also the development of alternative methods. Several papers in the following Section on Asymmetric Synthesis describe the use of standard general methods.

Acylaminomaltonates, Ac- or Z-NHCH(CO₂Et)₂,³³⁻³⁹ and other glycine derivatives, e.g. Ph₂C=NCH₂CO₂Me,^{40,41} are alkylated by alkenes,^{33,41} alkyl halides,^{34-38,40} or $\alpha\beta$ -unsaturated aldehydes (Michael addition leading to Z/E-3-ethylproline³⁹). Analogous alkylation of 'azlactones' continues in use;^{80,145} a new azlactone synthesis⁴² uses the glycine derivative *t*-butyl isocyanacetate (6) in a condensation that is closely analogous to the standard use of (6) for the synthesis of $\alpha\beta$ -dehydro amino acids through reaction with aldehydes or ketones.⁴³

Several methods exist for the amination of carboxylic acid derivatives, either employing ammonia with an α -halo-acid⁴⁴ or amines with triflates of α -hydroxyacids.⁴⁵ In the latter study based on (S)-lactic acid derivatives, decreasing reactivity of various leaving groups (MeCHR₂CO₂Et; R = CF₃SO₃ \gg Br > MeSO₃ > TolSO₃ > Cl) is accompanied by increasing tendency towards racemization and elimination.⁴⁵ Reductive amination of α -keto-acids using NADH and NADPH with NH₃ has been given a novel aspect in the use of photoinduced regeneration of the reducing agent.⁴⁶

The use of nitrosobenzene for the introduction of a nitrogen functional group into a silyl enol ether, PhNO + (Me₃SiO)₂C=CR¹R² \rightarrow PhNHCR¹R²CO₂H, involves LiAlH₄ reduction of the intermediate adduct.⁴⁷ Nitro-alkanoate esters are reduced by catalyzed hydrogen transfer (ammonium formate and Pd-C).⁴⁸

The hydrolysis of α -aminonitriles to corresponding amides is markedly catalyzed by thiols; for example 2-mercaptoethanol leads to 90% conversion in 17 hours at room temperature in aqueous solution at pH 6.5.⁴⁹

Further study of the amidocarbonylation of allylic alcohols has led to improvements in

details: $R^1R^2C=CHCH_2OH + AcNH_2 + CO + H_2 \rightarrow R^1R^2CHCH_2CH(NHAc)CO_2H$ under mild conditions through the use of the catalyst system $HRh(CO)(PPh_3)_2 + Co_2(CO)_8$.⁵⁰

4.2 Asymmetric Synthesis of α -Amino Acids. Electrophilic amination by BocN=Nboc of chiral silylketene acetals⁵¹ and of camphane esters⁵² leads to α -hydrazino acids. These are readily reduced (H_2/Pt) to α -amino acids and provide valuable new routes as alternatives to well established methodology. In the latter category, the 'asymmetric Strecker synthesis' in which (S)-1-phenylethylamine is condensed with NaCN and $PhCH_2COMe$ to give (R)- α -methyl phenylalanine,⁵³ numerous examples of alkylation of glycine derivatives ($Ph_2C=NCH_2CO_2Me$) and allyl acetate catalyzed by a chiral Pd catalyst,⁵⁴ $(MeS)_2C=NCH_2CONR^1R^2$ where $-NR^1R^2$ is a chiral 2,5-bis(methoxymethyl)pyrrolidine,⁵⁵ and the D-camphor imine of t-butyl glycinate⁵⁶, and analogous Schiff bases ($RCH=NCHMePh + BrCN \rightarrow RCH(CN)NBrCHMePh$,⁵⁷ and $PhCON=CHCO_2R +$ enamines (7)⁵⁸) provide a range of optical efficiency. While modest enantioselectivity (up to 57%⁵⁴) is frequently obtained, some of these methods are exceedingly enantio- and diastereoselective (better than 97%,⁵⁵ 100%⁵⁸), alkylation by enamines being postulated to proceed via a Diels-Alder-like transition state.⁵⁸

Amination processes of a conventional type are involved in the reaction of α -halogeno-10-sulphonamido-isobornyl esters (8) with NaN_3 ⁵⁹ and of α -keto-acids mediated by polymer-bound NADH and leucine dehydrogenase.⁶⁰ Both lead to nearly 100% enantioselective syntheses of a variety of simple aliphatic L- α -amino acids including L-alloisoleucine⁵⁹ and L-t-leucine.⁶⁰ Other examples of chiral auxiliaries³ are D-mannitol (conversion into diaziridines, thence to N-toluene-p-sulphonyl-L- α -aminobutyric acid,^{61a} or conversion into (R)-phthalimido-aldehydes and D-amino acids: Scheme 1^{61b}). (R,R)-Tartaric acid has been used for the preparation of N-Boc-L-erythro- β -benzyloxyaspartate through partial debenzoylation, then conventional stages.⁶² Enantioselective protonation of lithium enolates by chiral acids alters the optical purity of an amino acid, the extent determined by the lithium counter-ion.⁶³

Chiral heterocyclic compounds are being worked hard for the present purpose, with the bislactim ethers (e.g. 9) derived from L-valylglycine di-oxopiperazine having been in use by Schollkopf's group for several years. Chlorination by Cl_3CCl_3 followed by reaction with a malonic ester gives β -carboxy-D-aspartic acid diesters,⁶⁴ while more conventional alkylation methods lead to γ -diethoxyphosphinyl-L-butyryne.⁶⁵ The oxazinone (10) from erythro- $\alpha\beta$ -diphenyl- β -hydroxyethylamine enantiomers is a useful electrophilic glycine synthon when R = Br (prepared from 10; R = H by reaction with N-bromosuccinimide) that reacts with carbon nucleophiles.^{66,67} The (-) isomer after alkylation in this way gives L- α -amino acids through hydrolysis and hydrogenolysis;⁶⁶ one example⁶⁷ in which displacement of the bromine substituent is brought about by H_2 has been described, leading to (S)-chiral glycine.

Seebach's exploitation of the enantioselectivity accompanying alkylation of lithium