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Amino Acids and Peptides

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Amino Acids and Peptides

Volume 19

A Specialist Periodical Report

Amino Acids and Peptides

Volume 19

A Review of the Literature Published during 1986

Senior Reporter

J. H. Jones, *University of Oxford*

Reporters

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P. M. Hardy, *University of Exeter*
R. W. Hay, *University of Stirling*
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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 monographs[1] 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 Keenan[2] 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 edition[3] 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 argued[4] (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 Roth[3] conclude their book is sound: 'Stay tuned, the data flow fast'.

Balliol College, Oxford *John Jones*
July 1987

References

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 Pharmocology', 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.

Contents

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.

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)-hydroxypent-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 $-NH(CH_2)_3NH(CH_2)_3NH(CH_2)_5NH-$, 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-[9-(β-D-ribofuranosyl)purin-6-ylcarbamoyl]-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 "histidinobutyrine" crosslinks could also be hunted for.

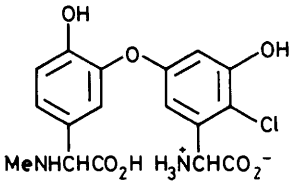
3.2 New Natural Amino Acids.- Xylem sap of Pisum sativum contains an amino-chlorobutanoic acid $C_4H_8NO_2Cl$;[21] while further structural studies can be expected for this compound, more complete assignments have been reported for N^{δ}-(1-carboxyethyl)-L-ornithine from Streptococcus lactis grown in 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 domoilactone B (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. Ectothiorhodispira 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 finding[26] 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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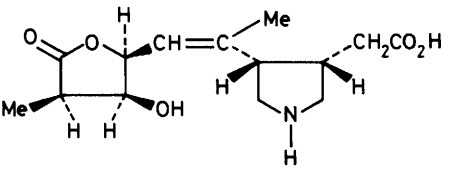

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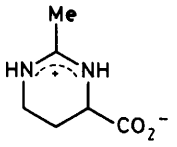

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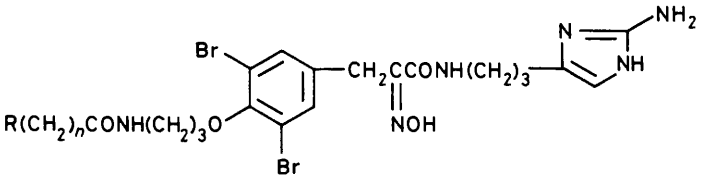

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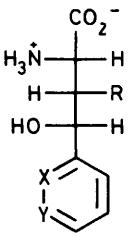

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X = CH , Y = N , R = Me
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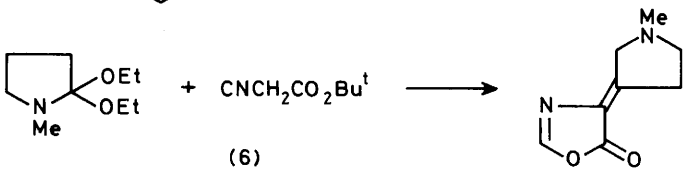

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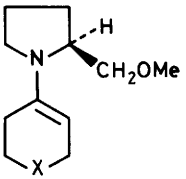

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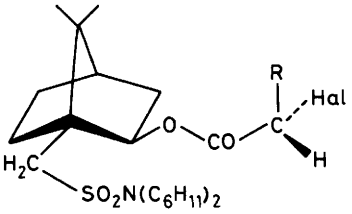

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in yeast acospore wall protein in previously unknown racemic and meso forms.[28] Hydrolysis of proteins that have been chemically modified through azo-coupling of lysine residues releases the modifed residues unaltered when $MeSO_3H$ is used, but when 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 ruminate 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 purea.[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.

Acylaminomalonates, Ac- or Z-$NHCH(CO_2Et)_2$,[33-39] and other glycine derivatives, e.g. $Ph_2C{=}NCH_2CO_2Me$,[40,41] are alkylated by alkenes,[33,41] alkyl halides,[34-38,40] or αβ-unsaturated aldehydes (Michael addition leading to Z/E-3-ethylproline[39]). Analogous alkylation of 'azlactones' continues in use;[80,145] a new azlactone synthesis[42] uses the glycine derivative t-butyl isocyanoacetate (6) in a condensation that is closely analogous to the standard use of (6) for the synthesis of αβ-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-acid[44] or amines with triflates of α-hydroxyacids.[45] In the latter study based on (S)-lactic acid derivatives, decreasing reactivity of various leaving groups ($MeCHRCO_2Et$: R = $CF_3SO_3 \gg Br > MeSO_3 > TolSO_3 > Cl$) is accompanied by increasing tendency towards racemization and elimination.[45] Reductive amination of α-keto-acids using NADH and NADPH with NH_3 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, $PhNO + (Me_3SiO)_2C{=}CR^1R^2 \rightarrow PhNHCR^1R^2CO_2H$, involves $LiAlH_4$ 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

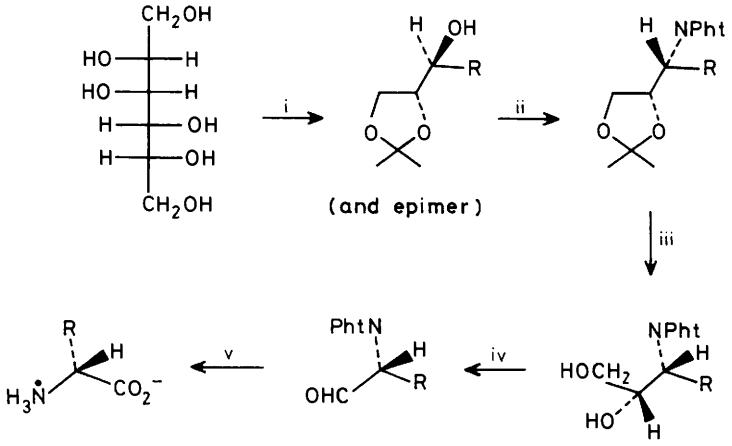
details: $R^1R^2C{=}CHCH_2OH + AcNH_2 + CO + H_2 \rightarrow R^1R^2CHCH_2CH(NHAc)CO_2H$ under mild conditions through the use of the catalyst system $HRh(CO)(PPh_3)_2 + Co_2(CO)_8$.[50]

4.2 Asymmetric Synthesis of α-Amino Acids. Electrophilic amination by BocN=NBoc of chiral silylketene acetals[51] and of camphane esters[52] 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 glycinate [56]), 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-alloisoleucine[59] and L-t-leucine.[60] Other examples of chiral auxiliaries[3] 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 debenzylation, 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]

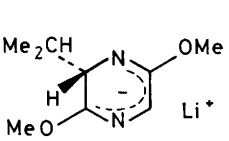
Chiral heterocyclic compounds are being worked hard for the present purpose, with the bislactim ethers (e.g. 9) derived from L-valylglycine di-oxopiperazine having been in use by Schollkopf's group for several years. Chlorination by Cl_3CCCl_3 followed by reaction with a malonic ester gives β-carboxy-D-aspartic acid diesters,[64] while more conventional alkylation methods lead to γ-diethoxyphosphinyl-L-butyrine.[65] The oxazinone (10) from erythro-αβ-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 example[67] in which displacement of the bromine substituent is brought about by $^2H_2$ has been described, leading to (S)-chiral glycine.

Seebach's exploitation of the enantioselectivity accompanying alkylation of lithium



Reagents: i, Established route; ii, Mitsunobu reaction (DEAD, Ph_3P), phthalimide; iii, H_3O^+; iv, $Pb(OAc)_4$; v, oxidation, deprotection

Scheme 1



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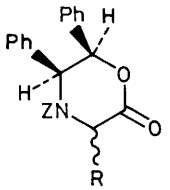

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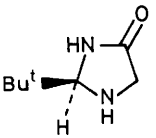

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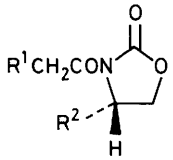

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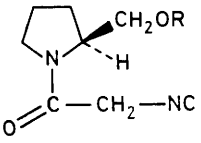


(13)

enolates of imidazolidines (11; see also Vol.18, p. 5) has been extended to other examples,[68-71] including analogous oxazolidinones.[70,71] Condensation of pivalaldehyde with glycinamide gives (11), which can be resolved in the conventional way using (S)-$PhCH(OH)CO_2H$,[69] while use of an L-amino acid in the condensation gives the oxazolidinone corresponding to (11) with a cis relationship between the 2-t-butyl group and the 4-substituent.[71] Use of an N-alkanoyl oxazolidinone (12) as a chiral glycine synthon for the synthesis of N-methyl-β-hydroxy amino acids through syn-diastereoselective aldol addition of the stannous enolate of (12; $R^2 = {}^nBu$) has been illustrated for N-methyl-3-hydroxy-4-methyloct-6-enoic acid, an unusual α-amino acid in cyclosporin.[72] The novel aminating agents BocN=NBoc[73; cf. 51,52] and $RO_2CN{=}NCO_2R$[74] react with near-100% stereoselectivity with (12) in the form of its Li enolate, the resulting (S)-hydrazino acids being hydrolysed (LiOH), deblocked, and hydrogenolyzed (H_2/Ni) to give the amino acids. N-Isocyanoacetyl-L-prolinol derivatives (13) have served the corresponding purpose in syntheses of enantiomers of α-disubstituted amino acids.[75]

Aldol reactions ($CNCH_2CO_2Me$ + RCHO)[76] and hydrogenations of 2-acylaminocrotonates[77] show a wide range of enantio- and diastereoselectivities with the influence of chiral catalysts. Bis(cyclohexylisocyanide)gold(I) tetrafluoroborate and an (R)-ferrocenylphosphine are very effective in this respect for the aldol reaction,[76] while a range of chiral Rh(I) phosphines of familiar types has shown mixed ability (less than 26%,[77a] 100%[77b]). 'Asymmetric hydrogenation' (H_2 can be replaced by 80% aqueous HCO_2H[77c]) has been reviewed in relation to the commercial synthesis of L-dopa.[77d] Closely related studies have been described for the hydrogenation of alkylidene derivatives of glycyl-L-alanine dioxopiperazine,[78] leading to L-amino acids in better than 94% e.e., and α-nitrocaprolactam catalyzed by $PdCl_2$-(S)-phenylethylamine (giving L-lysine in only 11% e.e.);[79] aminolysis of 2-methyl-4-(4-acetylaminobutyl)oxazolin-5-one with (S)-phenylethylamine gives mainly the L-lysine-containing diastereoisomer.[80]

A review has appeared[81] concerning applications of enzymes in asymmetric synthesis.

4.3 Synthesis of β- and Higher Homologous Amino Acids.- These systems can be made available through standard methods of introduction of amine and carboxy functional groups, and there are few characteristic routes.

Addition of ammonia to αβ-unsaturated acids at 15-30 Kbar yields β-amino acids.[82] An alternative conventional approach to these compounds, exemplified in the synthesis of 3-amino-3-(2-nitrophenyl)propionic acid from o-nitrobenzaldehyde, malonic acid, and NH_4OAc in AcOH, offers a 'one-pot' procedure.[83] Asymmetric synthesis is illustrated in the threo-selective condensation of Z-(O-vinyloxy)boranes with imines (14)→(15).[84] The addition of a chiral primary amine to an αβ-unsaturated ester at 5-15 Kbar is generally highly enantioselective, especially so in the case of 8-(2-naphthyl)menthylamine (better than 99%).[85]

Seebach has taken up the procedure for decarboxylative electrochemical methoxylation of amino acids (see Vol. 17, p. 26) to provide a conversion of (2S,4R)-hydroxyproline into (R)-3-amino-3-hydroxybutanoic acid ("GABOB"), as shown in Scheme 2.[86,87]

Proline isomers (16) can be prepared by cyclization of azomethine ylides formed between alkenes, amines, and formaldehyde.[88]

4.4 Prebiotic Synthesis Models for Amino Acids.- A number of enterprising experiments have been described under this heading in recent Volumes of this Report. These are joined by an account of the formation of the polymer "Titan tholin" by continuous d.c. discharge through N_2 and CH_4 (9:1) at 0.2 mbar pressure.[89] This mixture and energy source simulates the turbulent cloud-top atmosphere of Jupiter's moon; hydrolysis of the polymer with 6M-hydrochloric acid leads to glycine, aspartic acid, alanine, and β-alanine, with 12 other amino acids in lesser proportions. A review has appeared[90] covering HCN polymers as a potential prebiotic source of amino acids.

An efficient system for the synthesis of amino acids that may be relevant to the primordial scene is the ammonolysis of keto-acids in aqueous ammonia, mediated by visible light and dyes.[91]

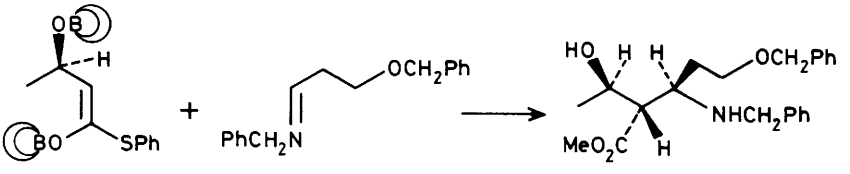
Conventional experiments, repeating the earliest laboratory demonstrations, have been described for photolysis of CH_4 with HCN, CO_2, and other simple compounds;[92] of HCHO with aqueous $K_4Fe(CN)_6$;[93] and electric discharge studies with CH_4, N_2, H_2O, NH_4^+ and metal salts;[94] and similar mixtures also including PH_3.[95] Amino acids are formed in all these cases.

4.5 Synthesis of Protein Amino Acids and Other Naturally Occurring α-Amino Acids.- As in previous Volumes, there is insufficient space here for the ever more voluminous literature concerning enzymic synthesis of protein amino acids. This important area can only be acknowledged through representative citations here, but it is well served with reviews[96] and is accessible through Section 16 (Fermentation and Bio-industrial Chemistry) of Chemical Abstracts.

Selected papers[97,98] and a compendium[99] describe the use of immobilized cells of Alcaligenes metalcaligenes for the synthesis of L-aspartic acid from ammonium fumarate;[97] mixed enzymes (serine hydroxymethyltransferase with β-tyrosinase) for the synthesis of L-tyrosine from glycine and phenol;[98] and individual treatment of the microbiological production of each of the protein amino acids.[99]

Several of the papers discussed in other sections (synthesis and reactions of amino acids) lead incidentally to the synthesis of natural amino acids, and a full appraisal of syntheses achieved should take in these other Sections.

Simple aliphatic α-amino acids that have received attention are (S)-2-cyclopropylalanine, a constituent of the mushroom Amanita virgineoides (synthesis from L-allylglycine);[100]



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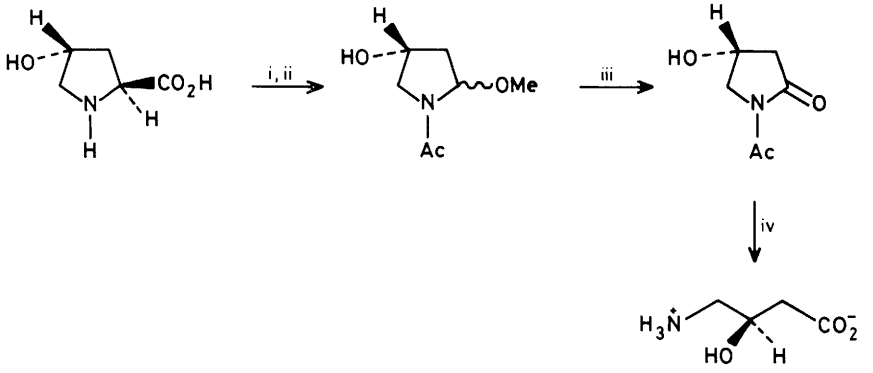
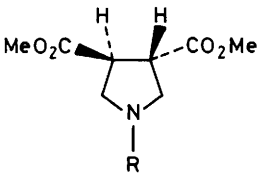


Reagents: i, e, MeOH, carrier electrolyte; ii, Ac_2O; iii, AcO_2H; iv, 4M–HCl

Scheme 2



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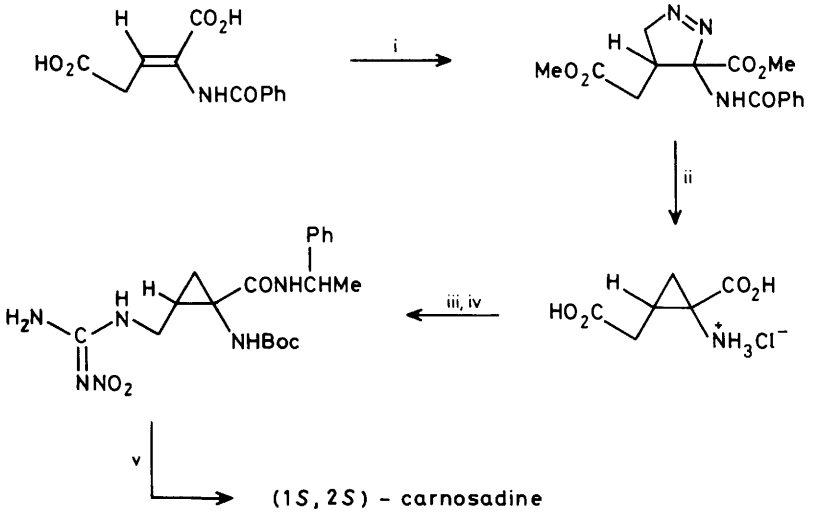
1-aminocyclopropanecarboxylic acid (through the use of methyl 4-bromo-2-phthalimidobutyrate, a compound more generally useful in synthesis as shown by syntheses of DL-phosphinothricin and DL-2-amino-4-phosphonobutyric acid);[101] and carnosadine (1-amino-2-guanidinomethylcyclopropane-1-carboxylic acid) from Z-(N-benzoyl)-αβ-dehydroglutamic acid (Scheme 3).[102] Numerous studies, mainly biosynthetic as far as chemical interest is concerned, have continued to appear for 1-aminocyclopropanecarboxylic acid, including an interesting proof that synthesis from S-adenosyl-[4-$^2H_2$]-L-methionine through the use of 1-aminocyclopropanecarboxylic acid synthase involves inversion of configuration at C-2.[103] In an extension of this project, in which ^{2}H-n.m.r. played a key role, a 1:1 mixture of (3S,4R)-[3,4-$^2H_2$]-(2S)-adenosylmethionine and its (3R,4R) isomer was converted into a 1:1 mixture of the two meso isomers of 1-aminocyclopropanecarboxylic acid labelled by ^{2}H. This is consistent with the inversion of configuration at C-4 that implies direct nucleophilic displacement of the sulphonium grouping.[104]

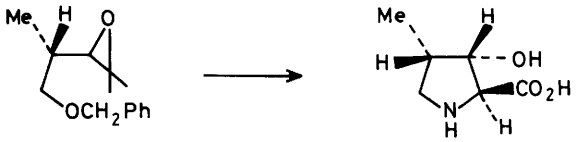
Proline and its analogues feature prominently in the recent literature, with syntheses[105,143] of some amino acids (17)-(19) of the echinocandins employing largely conventional routes from starting materials shown; synthesis of (2S,4S)-4-phenylproline, notable for the retention of configuration observed in displacement of the corresponding 4-tosyloxyproline with lithium diphenylcuprate;[106] and a general synthesis employing 1,3-dipolar cycloaddition of an N-alkyl thiazolium salt (20) to an αβ-unsaturated ester leading to 4-ethoxycarbonylprolines.[107] Acromelic acid A (21), the toxic principle of the poisonous mushroom Clitocybe acromelalga, has been synthesised from L-α-kainic acid (Scheme 4).[108] The allo isomer accompanying kainic acid (opposite configuration at the isopropenyl-substituted carbon atom) as neuroexcitatory amino acids in the alga Diginea simplex Ag., has been synthesised through the dipolar cycloaddition to an azomethine ylide that has become a favoured strategy in this area of stereoselective synthesis (Scheme 5).[109] Hydroxylated prolines (22) and analogous pipecolic acids have been synthesized enantiospecifically from D-ribonolactone[110] and from D-glucuronolactone,[111] respectively. In the former case, introduction of the azide grouping at C-2 of D-ribonolactone occurs with retention of configuration, surprisingly, and routine elaboration of the resulting compound gives the D-proline derivative (2R,3S,4R)-dihydroxyproline. A similar strategy leads to (2S,3R,4R,5S)-trihydroxypipecolic acid and its (2R) epimer and bulgecinine [alias (2S,4S,5R)-4-hydroxy-5-hydroxymethylproline].[111]

Highly stereoselective syntheses have been described for L-saccharopine, (2S,5'S)-N^{ϵ}-(1,3-dicarboxypropyl)lysine, and related N-carboxyalkylamino acids ('opines'; see Vol. 18, p. 1) through aminolysis of triflates of chiral hydroxy-acids.[112,45] Other simple aliphatic amino acids synthesised recently include L-canaline (O-amino-L-homoserine)[113] and polyoxamic acid (22; from the threose derivative (23) through Overman - Claisen rearrangement of the derived



Reagents : i, CH_2N_2, MeOH; ii, hν; 6M – HCl; iii, MeOH, H^+; Boc_2O; NH_3; Br_2/NaOH; iv, ZCl; (*R*)-(+)-$PhCHMeNH_2$; DCCI; H_2 – Pt; 3,5-dimethyl-1-nitroguanyl-pyrazole; v, H_2 – Pd; 6M-HCl

Scheme 3



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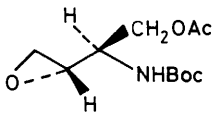

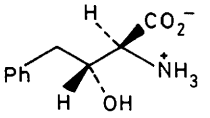

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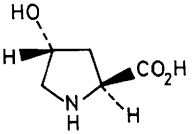

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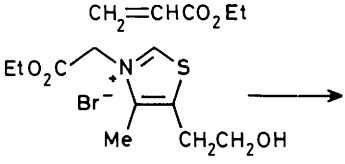

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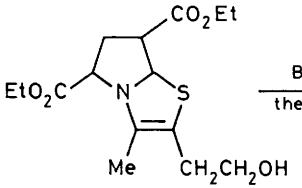
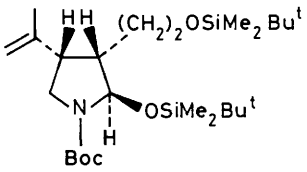
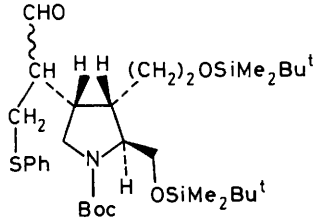


prolines

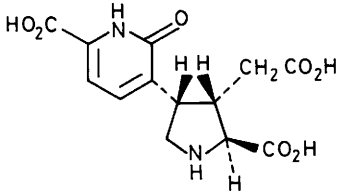


from L-α-kainic acid by $LiAlH_4$ reduction of *N*-Boc dimethyl ester and silylation

i - iv



v - viii



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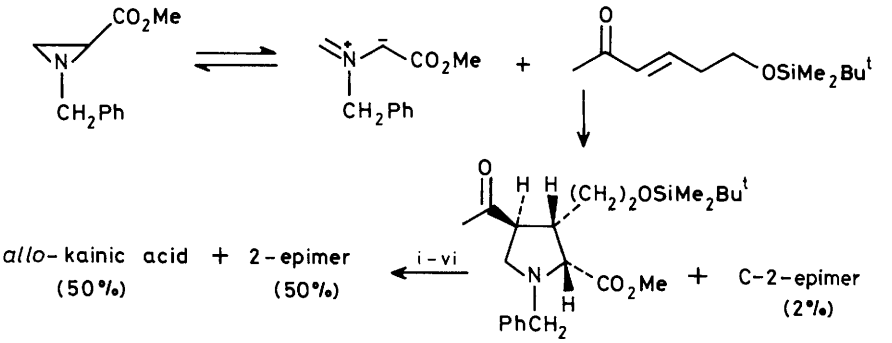
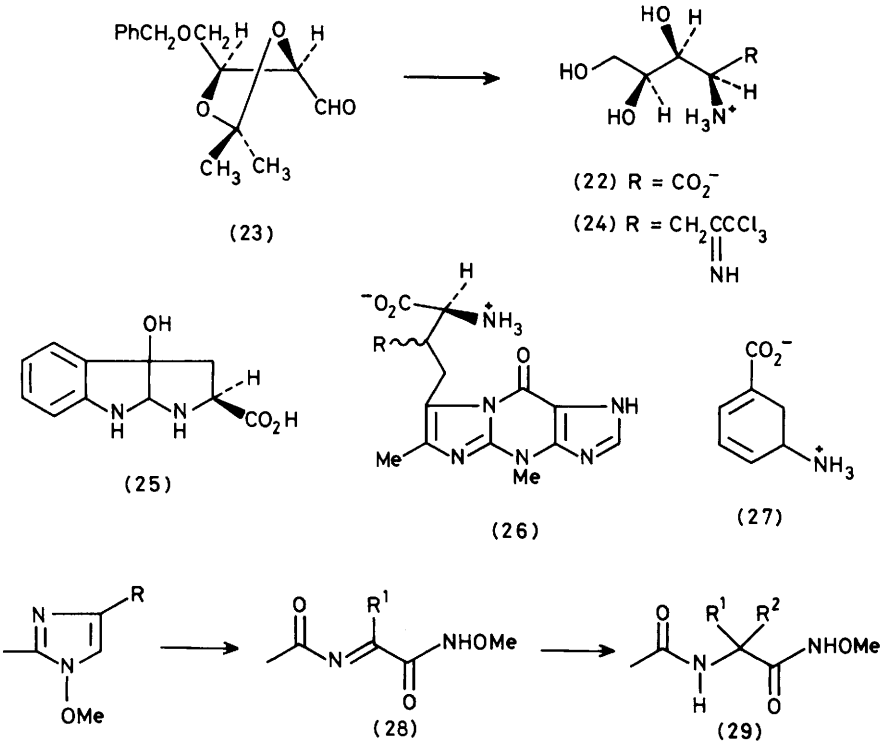
Reagents: i, *m*-chloroperbenzoic acid; ii, Li tetramethylpiperidide; iii, MnO_2; iv, PhSH; v, construction of 3-(*o*-picolyl) ring; vi, oxidation of desilylated intermediate to the tricarboxylic acid; vii, rearrangement of the pyridine *N*-oxide; viii, Boc removal

Scheme 4



Reagents: i, PPh_3CH_2; ii, F^-; iii, CrO_3-acetone; iv, CH_2N_2; v, $ClCOOCHClCH_3$; vi, NaOH, for C-2-epimerization

Scheme 5



imine (24)).[114]

Aromatic and heterocyclic amino acids featured in the recent literature include tryptathionine, formed between cysteine and the pyrrolo[2,3-b]indole (25);[115] quisqualic acid, synthesized from β-chloroalanine[116] (see also Vol. 18, p.16); and the extraordinary wybutine (26; R = H) a fluorescent minor base from yeast tRNA, whose oxygenated derivative (R = OH or R = COOH) has been located in animal and plant sources. Disagreement has arisen over structural details obtained with minute amounts of the materials, and synthesis of (2S,3S)-β-hydroxywybutine and its 2S,3R isomer has identified one or other of these as 'most likely' structure.[117] The natural GABA-T inhibitor gabaculine (Streptomyces toyocaensis) is now available through a fifth synthesis that is conceptually different from its predecessors, all of which have been based on the functionalization of a cyclohexenecarboxylic acid. 5-Ethoxypyrrolid-2-one was N-silylated and its 3-phenylsulphenyl derivative was alkylated with 5-iodo-1-trimethylsilylpent-2-yne. Desilylation in HCOOH was accompanied by ring closure to a 7-azabicyclo[3.2.1]oct-2-ene from which gabaculine was secured through straightforward elaboration,[118] as the racemate (27).

4.6 Synthesis of α-Alkyl Analogues of Protein Amino Acids.- Reference is made elsewhere in this Chapter to the title compounds (e.g. refs 47, 53). Acylimines are a novel source,[119] adding organometallic compounds to give αα-disubstituted N-acylglycinamides in good yields when the amide function is methoxylated (28)→(29). The starting materials are formed by singlet oxygenation of corresponding imidazoles.[119]

4.7 Synthesis of Other Aliphatic Amino Acids.- Later Sections deal with side-chain functionalized amino acids, and this Section discusses close relatives of protein amino acids.

Side-chain extension of protected γ-iodobutyrine (prepared from homoserine) through nucleophilic displacement by a lithium dialkyl cuprate offers a general entry to long-chain homologues.[120] A different carbon-carbon bond-forming strategy, used for the synthesis of (1R, 2S)-2-methyl-1-aminocyclopropane-1-carboxylic acid,[121] was the outcome of consideration of other established methods for this type of amino acid. It was concluded that condensation of 1,2-dibromopropane with ethyl isocyanoacetate was the method of choice in this case.

Friedel-Crafts acylation of benzene by ethyl N-methoxycarbonyl-L-aspartate through the side-chain carboxy group leads to (S)-phenacylglycine derivatives.[122]

Several proline analogues have been synthesized through demonstrations in a crop of papers of the potential of new methods for this category. 5,5-Dichloro-L-pyrrolidinecarboxylic esters formed from corresponding L-pyrrolines as N-chlorocarbonyl derivatives by reaction with $COCl_2$ can be converted into proline esters in 78% overall yield by dehydrochlorination followed by hydrogenation.[123] cis-5-Alkyl-[124] and trans-4-cyclohexyl-prolines have been

synthesized from N-benzyloxycarbonyl-L-glutamic acid and from L-pyroglutamic acid, respectively, deriving their absolute configurations from that of the starting materials. Ring closures, in the former case to the oxazolidinone (30), which on ammonolysis undergoes ring opening and reclosure to the prolinamide, and in the latter case to the bicyclic derivative (31), which is formed from benzaldehyde and the hydroxymethylpyrrolidone derived from L-pyroglutamic acid, are crucial to each route.[125] The chiral lithium enolate from (31) is alkylated by cyclohexyl bromide and elaborated through conventional methods into the L-proline analogue. Photocyclization of secondary amines $PhCOCHR^1CH_2NRCHR^2CO_2R^3$ yields mixtures of cyclopropanones and 3-hydroxyprolines.[126]

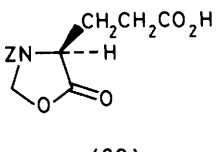
Uses of readily available L-amino acids for the synthesis of elusive analogues continue to be well represented, a further illustration of the versatility of L-glutamic acid being its use in the synthesis of (S)-$H_3\overset{+}{N}CH_2CH(OH)CH_2CH_2CO_2H$ via (S)-5-carboxybutyrolactone (elaboration of the carboxy group into CH_2NH_2).[127] Other aliphatic amino acids with well separated functional groups include 2,3-diaminopropanoic acid, prepared as its N^2-Boc-N^3-benzyl ester through addition of benzylamine to Boc-dehydroalanine methyl ester,[128] and unsaturated $\alpha\varepsilon$-diaminopimelic acids carrying γ-methyl, methylene, or chloro substituent.[129] At the other end of the scale, the aminoglycines, e.g. $BocNHCH(NHZ)CO_2H$, can be prepared from Z-hydroxyglycines (i.e. ZNH_2+ glyoxylic acid) through conversion into the sulphide with Pr^iSH and reaction with $BocNH_2$ and $HgCl_2$.[130]

4.8 Synthesis of Halogenoalkyl Amino Acids.- An enzyme-catalyzed route is to be seen as unusual in this area, and conversion of halogenofumaric acids into β-halogenoaspartic acids through β-methylaspartase-mediated addition of NH_3 is a valuable entry to (2S,3R) isomers.[131]

The usual method for introducing a halogen substituent into an amino acid, remembering the relatively easily modified incumbent functional groups, is through side-chain unsaturation via hydrogen halide addition to a derived oxirane. This approach has been used in a synthesis of (2S,3R,4R)-4-chloro-3-hydroxyproline from the protected 3,4-dehydroproline,[132] and for a synthesis of 4-fluoro-L-threonine.[133] In this latter case, stereospecific introduction of the halogen substituent into a chiral oxirane derived from benzyl 4-hydroxybut-2-enyl ether was followed by construction of the amino acid through standard general methods.[133]

Separate routes to threo and allo isomers of $\gamma\gamma\gamma$-trifluorothreonines have been reported, reduction of $CF_3COC(=NOMe)CO_2Et$ and hydrolysis giving the allo isomer, and hydrolysis of 4-trifluoromethyloxazolin-2-one-5-carboxylic acid giving the threo isomer.[133] $\beta\beta\beta$-Trifluoroalanine has been prepared by azidolysis of $FCOCH(CF_3)CO_2Me$ and hydrolysis of the resulting isocyanate.[134]

4.9 Synthesis of Amino Acids with Unsaturated Side-Chains.- A general amino acid



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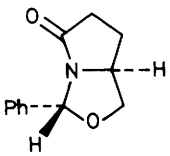

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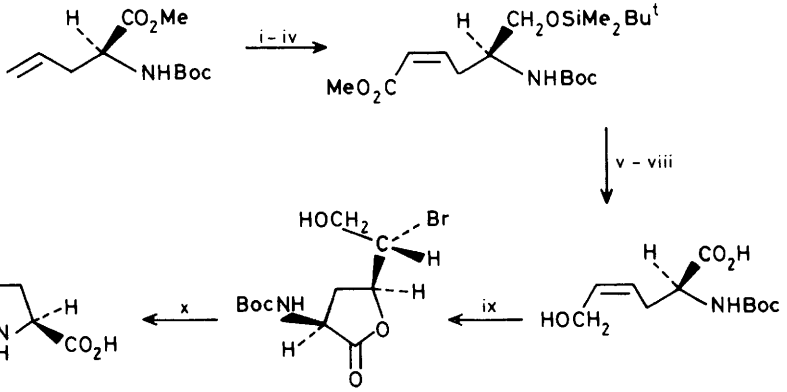
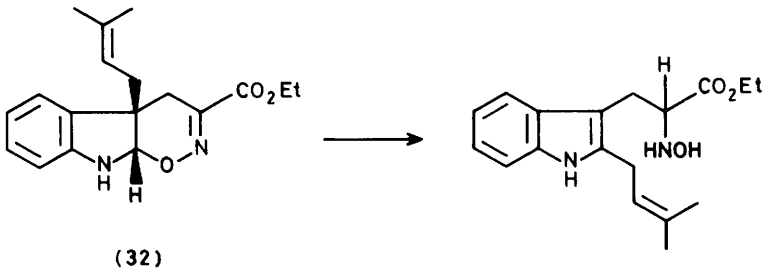


Scheme 6



(32)

(33)

synthesis employing a cationic glycine synthon, $ZNHCHClCO_2Me$, has been applied to a synthesis of vinylglycine and other $\beta\gamma$-unsaturated amino acids,[135] through condensation with organomagnesium reagents. Differently based routes include alkylation of diethyl acetamidomalonate with $Me_3SiC{\equiv}CSO_2Ph$ followed by sulphone cleavage, a method that permits stereospecific labelling at each vinyl proton,[136] and an alternative (see V ol.17, p.13) route to optically pure L-vinylglycine from L-glutamic acid.[137] The latter method involves successive Hunsdiecker reaction ($CO_2H \rightarrow Br$) and conversion into the 2-pyridyl selenide, followed by oxidative elimination (O_3).[137] Another acetamidomalonate route leads to β-methyleneglutamic acid through alkylation by the allene $H_2C{=}C{=}CHCO_2Et$;[33] yet another leads to 2-amino-4-hexynoic acid.[38]

Allylglycines $R^2SO_2NHCH(CO_2Bu)CHR^2CR^3{=}CHR^4$ are formed from an N-sulphinylsulphonamide RSO_2NSO and glyoxylate ester through an ene reaction with an alkene.[138]

2-Aminocrotonates ('dehydro-amino acids') have received attention over many years, and the novel eliminative route from $CF_3CON(SiMe_3)CH(CO_2Me)CHRSiMe_3$ should offer entry to new examples of this class carrying sensitive side-chains.[139] The synthesis of 'dehydroprolines' has been reviewed.[140]

Higher homologous unsaturated amino acids , like their saturated analogues, are generally prepared through standard methods for the introduction of either amine or carboxy group into the otherwise complete structure. Gabriel synthesis of $PhtCH_2C{\equiv}CCO_2H$ and partial reduction and deblocking ($EtNH_2$) gives (Z)-$H_3\overset{+}{N}CH_2CH{=}CHCO_2H$;[141] Schmidt rearrangement of (E)-$(HO_2CCH_2CH{=})_2$ yields (E)-5-aminopent-3-enoic acid;[142] the double bond can be moved into conjugation with E/Z isomerization through the use of a strong base. Corresponding alkynes have been formed through the same amination approach.[142]

4.10 Synthesis of Hydroxyalkyl Amino Acids.- Ohfune's group continues to provide elegant syntheses of uncommon amino acids (see also ref.105), especially hydroxylated derivatives, and the 'halolactonization' approach by which (S)-allylglycine is converted into (19) has been used with other alkenyl amino acids.[143] (-)-Bulgecinine has been provided with another synthesis using this approach (Scheme 6), and the general nature of this route was illustrated for several β-hydroxy-α-amino acids from 2-amino-4-pentenoic acid derivatives.[143] The same systems can be prepared through condensation of aldehydes or ketones with [N,N-bis(trimethylsilyl)-amino]ketene bis(trimethylsilyl)acetal, a method that avoids the use of a strong base.[144] The key intermediate $(Me_3Si)_2NCH{=}C(OSiMe_3)_2$ is readily available by reaction of glycine with Me_3SiNEt_2 followed by conversion into the lithium enolate and silylation (Me_3SiCl).

4.11 Synthesis of Amino Acids with Aromatic or Heteroaromatic Side-Chains.- Syntheses from familiar (azlactone)[145] and novel $[CH_2{=}C(N{=}O)CO_2Et]$[146] alanine derivatives have been

described for 2-fluoro-L-histidine and 2-substituted tryptophans, respectively. Rearrangement is observed in the ring-opening of the 2-(dimethylallyl)indole - nitrosoalkene adduct (32) to give the N-hydroxy tryptophan homologue (33), after reduction of the precursor oxime using trimethylaminoborane and HCl in ethanol.[146]

Modification of the side-chains of readily available amino acids (O-phenylation of N-acetyl-L-tyrosine methyl ester [NaH and C_6H_6-$Mn(CO)_3$],[147] iodination of p-trimethylsilylphenylalanine with I_2/Ag^+ to give p-iodophenylalanine,[148] and radical halogenation of protected tryptophans to give 2-halogenation products[149]) continues a long series of papers over the years in the same vein.

4.12 Synthesis of N-Substituted Amino Acids.- The problems of synthesis of simple N-alkyl amino acids from the amino acids themselves have been largely overcome in recent years, and a synthesis of $N^{\epsilon}N^{\epsilon}N^{\epsilon}$-trimethyllysine from a suitably protected starting material is illustrative of the general approach.[150]

4.13 Synthesis of Amino Acids containing Sulphur or Selenium.- General methods have been applied to the synthesis of ββ-dialkyl cysteines through reaction of P_4S_{10} with an N-formyl dehydroamino acid ester[43] and preparation of selenocysteines through alkylation of a Schiff base of methyl glycinate with bromomethyl selenides.[40]

Other papers under this heading describe modifications of amino acids in straightforward ways. 5-Thioxoproline can be prepared from pyroglutamic acid through reaction with Lawesson's reagent.[151] Cysteine is the starting material for the synthesis of bis(S-cysteinyl)selenide using selinite anion as reagent,[152] and homocysteine for the preparation of S-adenosylhomocysteine through reaction of the derived N-TFA disulphide methyl ester with adenosine and Bu_3P;[153] and of S-(N^6N^6-dimethyladenosyl)-L-methionine from 6-chloro-9-(β-D-ribofuranosyl)purine by reaction with Me_2NH to give 5'-chloro-5'deoxy N^6N^6-dimethyladenosine, the synthesis being completed by methylation of the resulting homocysteine analogue.[154] DL-5,5-Dimethyl-4-thiazolidinecarboxylic acid has been prepared from DL-penicillamine and formaldehyde.[155]

4.14 Amino Acids Synthesized for the First Time.- The following, additional to other new amino acids named elsewhere in this Chapter, have been prepared through routine methods: 2-amino-4-alkenoic acids;[41] cyclopropylglycines;[41] (2S,9S)-2-amino-8-oxo-9,10-epoxydecanoic acid;[55] 1-adamantylglycines and 2-adamantylalanines;[44] 1,3-bis(2-glycinyl)adamantanes;[44] (2R,5R)-5-hydroxymethylproline;[37] DL-homolysine;[35] 1-amidinylpyro-L-glutamic acid;[156] p-benzoyl-L-phenylalanine;[157] 3'-carboxy-D-phenylalanine, and its 4'-methyl- and 4'-hydroxy analogues;[158] 4'-methoxy-3'-formylphenylalanine and its oxime;[158] and 2'-, 5'- or 6'-fluorodopas.[36]

4.15 Synthesis of Labelled Amino Acids.- Many of the methods described here are standard general methods, but others illustrate novel solutions to problems of synthesis of selectively labelled amino acids. As in previous Volumes, the coverage is in a sequence of increasing atomic number of the labelled atom.

Addition of $^2H_2$ to 2-cyanoethyl acetamidomalonic acid diethyl ester gives [5,5-$^2H_2$]-DL-ornithine after conventional elaboration.[159] Catalyzed halogen exchange between $^2H_2$ and N-acetyl-4-chloro- and -iodo-L-phenylalaninamides competes unfavourably with exchange with ^1H (from H_2O) and scrambling is also observed.[160] Catalyzed β-deuteriation of GABA and homoserine requiring pyridoxal and its 5'-phosphate[161] and direct substitution of the halogen atom in N-benzoyl-3-chloro-L-valine methyl ester by ^2H[162] are processes that do not suffer side-reactions. NaB^2H_4 is the source of the label in Boc-[4,4-$^2H_2$]-L-proline, prepared from hydroxy-L-proline via the oxo analogue (RuO_4 - $NaIO_4$) through[4-^2H]-hydroxy-L-proline and the iodo analogue (Ph_3P/diethyl azodicarboxylate/MeI).[163] Chiral ^2H-glycine features in an exchange study involving a chiral cobalt(II) N-2-picolinylglycine complex and ^2H_2O[164] and also results from L-glutamic acid subjected to enzymic and chemical degradation in the presence of ^2H_2O.[165]

Various ^2H, ^{13}C, ^{15}N, and ^{18}O isotopomers of L-tyrosine have been prepared from the correspondingly labelled phenol and L-serine through the use of β-tyrosinase,[166] and the L-phenylalanines derived from them by chemical degradation have also been described.

Processes analogous to some of those described above have led to ^3H-labelled amino acids, namely addition of $^3H_2$ to L-2-amino-4-hexynoic acid,[38] to a protected dehydro-2-fluoro-histidine,[145] and a protected dehydro-3-(2-naphthyl)alanine.[167] ^3H - Halogen exchange has been employed for the preparation of [4'-^3H]-DL-phenylalanine from p-chlorophenylalanine,[168] [2,5-$^3H_2$]-L-histidine from 2,5-di-iodo-L-histidine,[169] and [4-^3H]-L-glutamic acid.[170] Pd-Catalyzed exchange of $^3H_2$ was used in these studies,[168,169] and NaB^3H_4 was employed in the case of labelled glutamic acid, where curiously only the (2S,4S)-4-halogenoglutamic acid (as its dimethyl ester) underwent satisfactory ^3H - halogen exchange.[170] The diastereoisomer was obtained, however, by the alternative enzymatic exchange method.[170]

^{13}C-Formaldehyde has been extended to $EtO_2CCH_2{}^{13}CHO$ via 1,3-dithian and used in the Strecker synthesis giving the labelled aspartic acid.[171] The [1,4-$^{13}C_2$]-L-aspartic acid isotopomer is obtainable through aspartase-catalyzed addition of ammonia to [1,4-$^{13}C_2$]-fumaric acid[172] and the [4-^{13}C]-L-aspartic acid from an acetamidomalonate synthesis.[172] Acylase mediates the conversion of the intermediate cyanomethyl derivative into β-[^{13}C-cyano]-L-alanine in this route.[172] The amidocarbonylation synthesis of amino acids has been used only rarely in syntheses of labelled compounds, a recent example being [1-^{13}C]-L-isoleucine;[173] cobalt(II) acetate-catalyzed condensation of acetamide, (RS)-EtCHMeCHO, and ^{13}CO in the presence of hydrogen is followed by resolution of the resulting N-acetylamino acid using

hog renal acylase.[173] o-[Carboxy-^{13}C]-phenylalanine has been prepared from o-bromotoluene and $^{13}CO_2$, followed by conversion of the resulting labelled o-toluic acid into the o-[carboxy-^{13}C]benzyl bromide and use in the acetamidomalonate synthesis.[174]

^{11}C-Labelled amino acids are worthwhile targets only if rapid synthesis and use in metabolic and transport studies is ensured, because of the short half-life of this isotope. A 30 minute synthesis of isocyanoacetic acid ($CNCH_2Li$ + $^{11}CO_2$) has been reported,[175] opening up some options for use in synthesis of [1-^{11}C]amino acids. S-Adenosyl-[^{11}C]-L-methionine has been prepared from the labelled methionine and rat liver extract.[176] The general field of [^{11}C]-amino acid synthesis has been reviewed.[177]

Purification of [^{15}N]-amino acids, prepared through standard procedures from $^{15}NH_3$, by anion-exchange preparative chromatography has been achieved.[178]

A number of papers on 6-[^{18}F]-dopa synthesis (and its use for tracing dopamine metabolism in the brain by positron tomography[179]) has appeared, employing $^{18}F_2$ with 6-trimethylsilyl-3,4-dimethyldopa ethyl ester as its N-salicylidene derivative [180] or direct reaction of the amino acid with $AcO^{18}F$ (less than 8% yield)[181] or with $HB^{18}F_4$ (high yield).[182] Introduction of ^{18}F into 5-amino-3,4-dimethoxybenzaldehyde through the Schiemann reaction, followed by the elaboration of the aldehyde group into the alanyl moiety through standard methods, provides a satisfactory route to 5-[^{18}F]-dopa.[183] Direct fluorination of phenylalanine with $^{18}F_2$ gives a mixture of o-, m- and p-^{18}F derivatives.[184]

Incorporation of ^{73}Se from $^{73}SeO_2$ into selenomethionine can be accomplished by *Saccharomyces cerevisiae* and *E.coli*.[185]

4.16 Resolution of DL-Amino Acids.- While this Section is at least as well endowed with useful recent literature as in previous Volumes of this Report, and therefore surprisingly lengthy for such a well researched topic, there are also papers discussed elsewhere in this Chapter on the analytical resolution of amino acids.

Chemical and physical techniques to achieve the separation of enantiomers continue to be based on familiar principles. Adduct formation of DL-amino acids with L-phenylalanine is strongly enantioselective in a number of cases, permitting D-amino acids to be crystallized out in 75 - 100% optical purity.[186] More reliable general methods have been used for the resolution of DL-*threo*-β-hydroxyvaline and its DL-*erythro* isomer via L-tyrosinehydrazide salt formation,[187] of *cis*-3-ethyl-DL-proline and its DL-*trans* isomer by (+)-dibenzoyltartaric acid salt formation,[39] of tert-leucine by (+)-camphor-10-sulphonic acid,[188] and of homomethionine through salt formation with the chiral phosphoric acid (34).[189] Derivative formation between DL-amino acids and (35) is followed by separation of the resulting diastereoisomers and removal of the chiral 'handle' with $NaBH_4$, in an efficient resolution method.[190]

Preferential crystallization resolution of N-acetyl-DL-phenylglycine (as its NH_4^+ salt)[191]