# 1
# Amino Acids

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## 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.

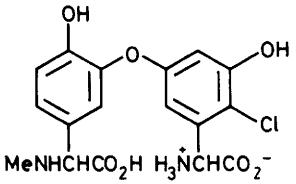
3.2 New Natural Amino Acids.- Xylem sap of Pisum sativum contains an amino-chlorobutanoic acid $C_4H_8NO_2Cl$;[21] while further structural studies can be expected for this compound, more complete assignments have been reported for $N^{\delta}$-(1-carboxyethyl)-L-ornithine from Streptococcus lactis grown in ornithine-supplemented media.[22] Synthesis of this compound from poly(L-ornithine) or $N^{\alpha}$-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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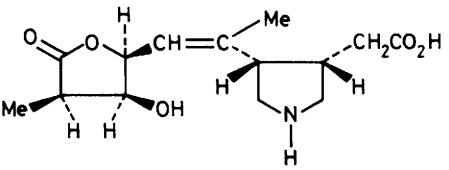

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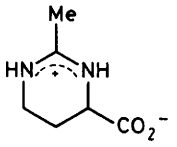

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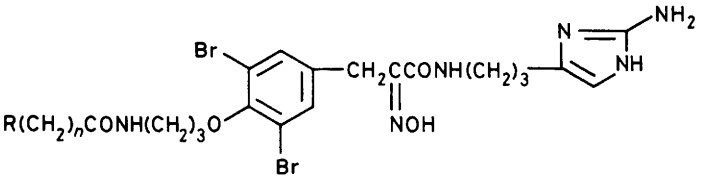

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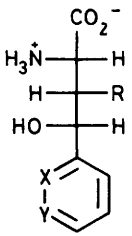

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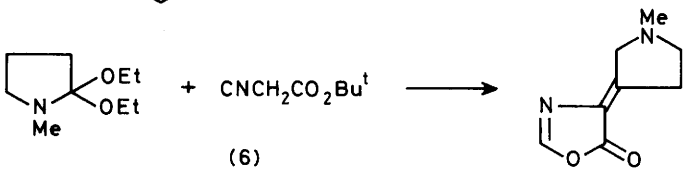

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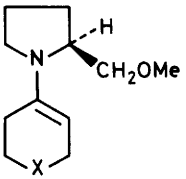

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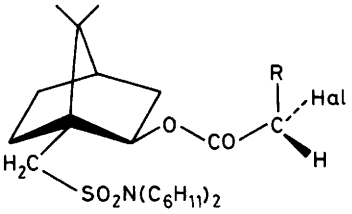

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in yeast acospore wall protein in previously unknown racemic and meso forms.[28] Hydrolysis of proteins that have been chemically modified through azo-coupling of lysine residues releases the modifed residues unaltered when $MeSO_3H$ is used, but when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

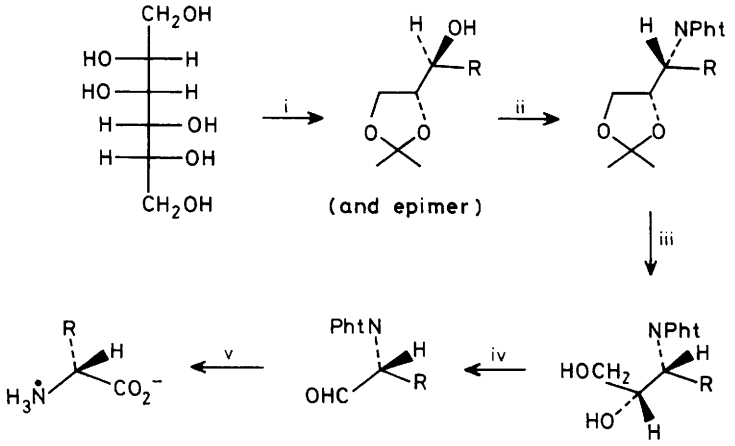
details: $R^1R^2C{=}CHCH_2OH + AcNH_2 + CO + H_2 \rightarrow R^1R^2CHCH_2CH(NHAc)CO_2H$ under mild conditions through the use of the catalyst system $HRh(CO)(PPh_3)_2 + Co_2(CO)_8$.[50]

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]

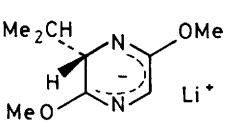
Chiral heterocyclic compounds are being worked hard for the present purpose, with the bislactim ethers (e.g. 9) derived from L-valylglycine di-oxopiperazine having been in use by Schollkopf's group for several years. Chlorination by $Cl_3CCCl_3$ followed by reaction with a malonic ester gives β-carboxy-D-aspartic 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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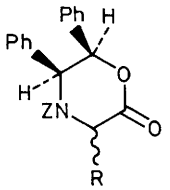


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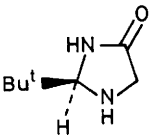


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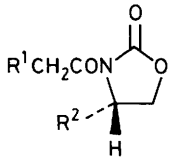


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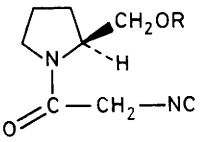



(13)

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]

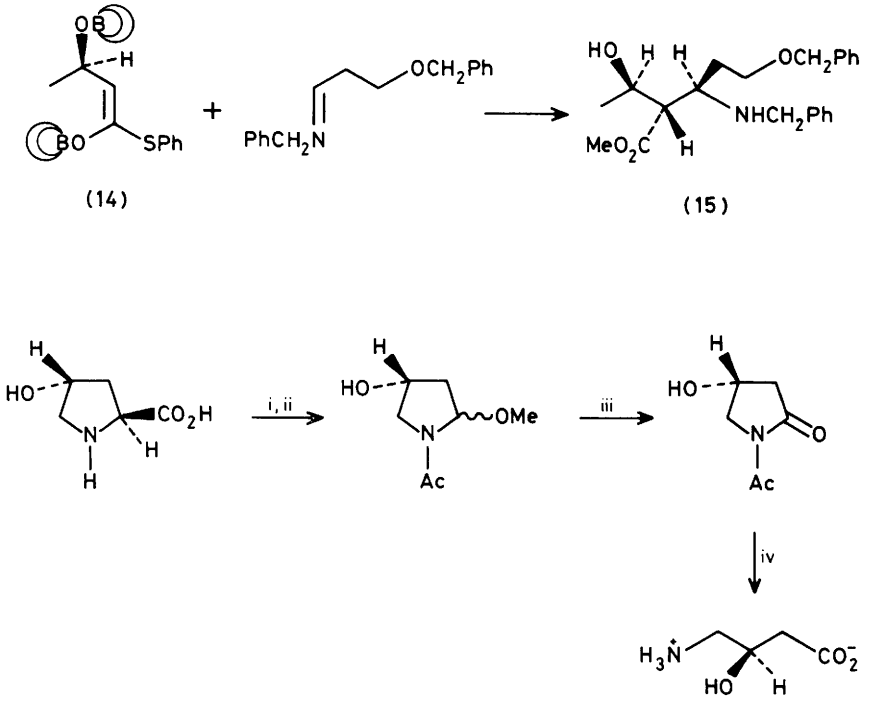
Conventional experiments, repeating the earliest laboratory demonstrations, have been described for photolysis of $CH_4$ with HCN, $CO_2$, and other simple compounds;[92] of HCHO with aqueous $K_4Fe(CN)_6$;[93] and electric discharge studies with $CH_4$, $N_2$, $H_2O$, $NH_4^+$ and metal salts;[94] and 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]

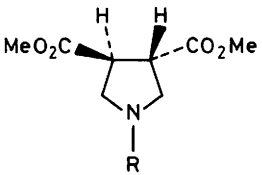
Several of the papers discussed in other sections (synthesis and reactions of amino acids) lead incidentally to the synthesis of natural amino acids, and a full appraisal of syntheses achieved should take in these other Sections.

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]




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

**Scheme 2**

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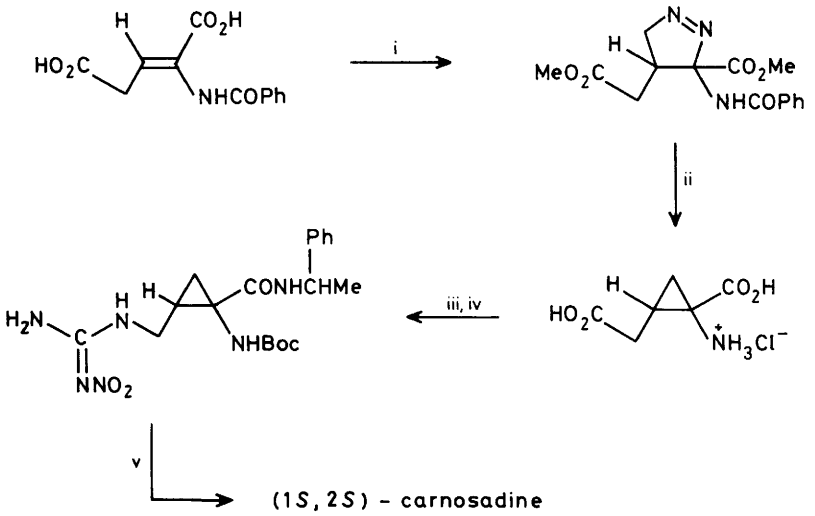
1-aminocyclopropanecarboxylic acid (through the use of methyl 4-bromo-2-phthalimidobutyrate, a compound more generally useful in synthesis as shown by syntheses of DL-phosphinothricin and DL-2-amino-4-phosphonobutyric acid);[101] and carnosadine (1-amino-2-guanidinomethylcyclopropane-1-carboxylic acid) 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]

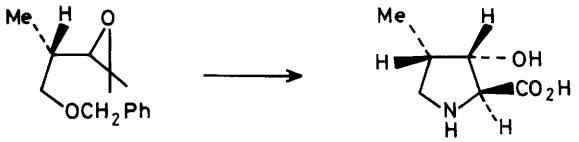
Proline and its analogues feature prominently in the recent literature, with syntheses[105,143] of some amino acids (17)-(19) of the echinocandins employing largely conventional routes from starting materials shown; synthesis of (2S,4S)-4-phenylproline, notable for the retention of configuration observed 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)-$N^{\epsilon}$-(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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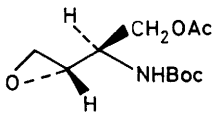

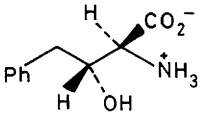

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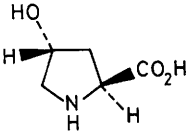

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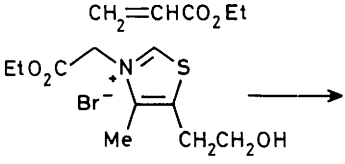

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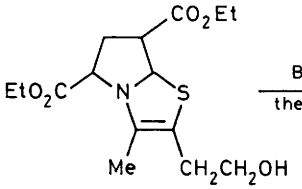
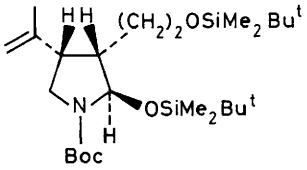
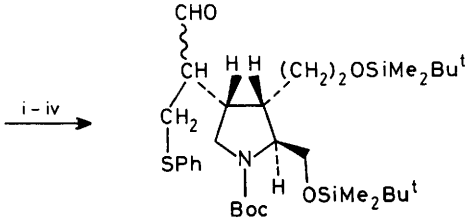
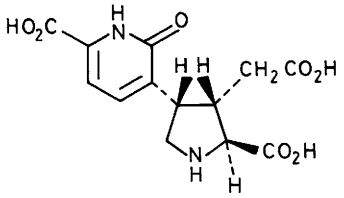


prolines



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





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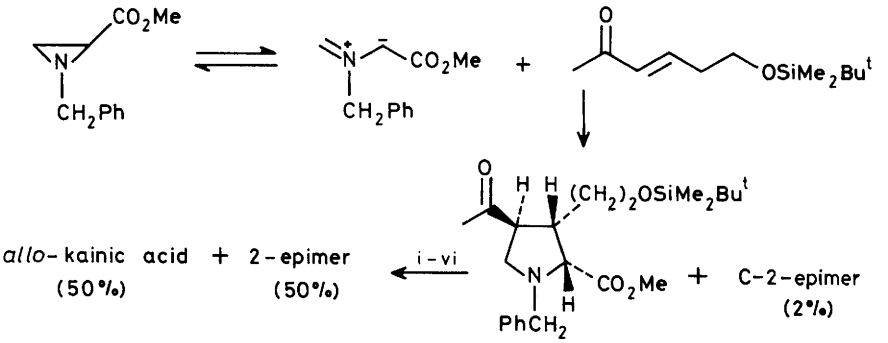
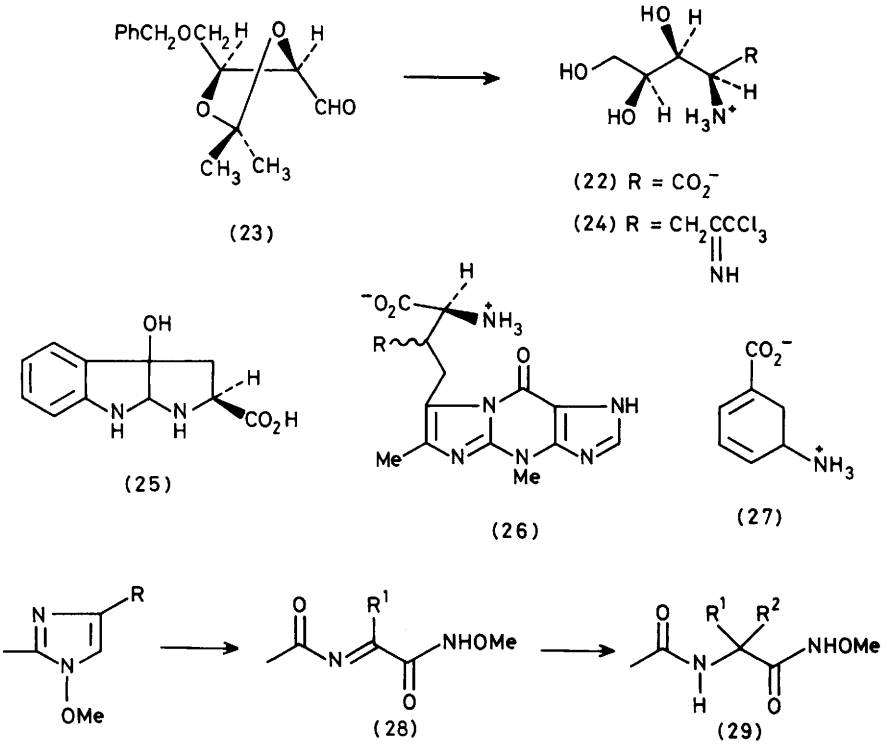
Reagents: i, *m*-chloroperbenzoic acid; ii, Li tetramethylpiperidide; iii, $MnO_2$; iv, PhSH; v, construction of 3-(*o*-picolyl) ring; vi, oxidation of desilylated intermediate to the tricarboxylic acid; vii, rearrangement of the pyridine *N*-oxide; viii, Boc removal

**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]

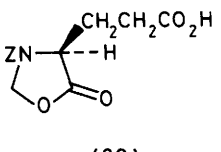
Uses of readily available L-amino acids for the synthesis of elusive analogues continue to be well represented, a further illustration of the versatility of L-glutamic acid being its use in the synthesis of (S)-$H_3\overset{+}{N}CH_2CH(OH)CH_2CH_2CO_2H$ via (S)-5-carboxybutyrolactone (elaboration of 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 $\gamma$-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 $\beta$-halogenoaspartic acids through $\beta$-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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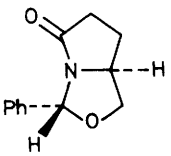

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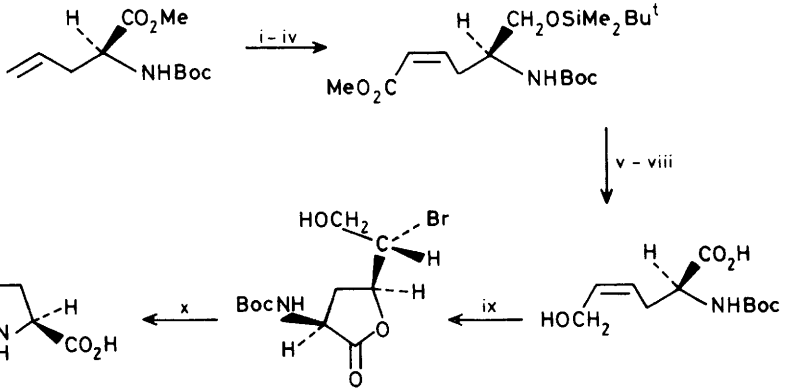
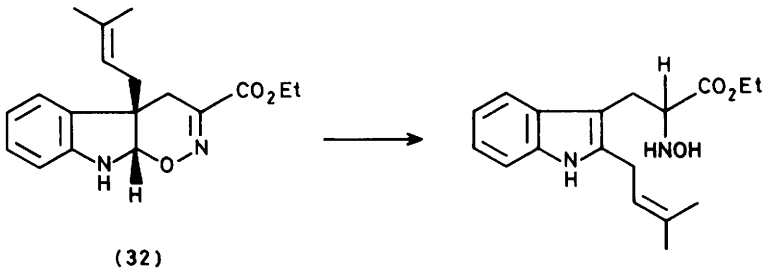



Reagents: i, $LiAlH_4$ ;ii, TBDMSCl ; iii, $O_3$ ; iv, Wittig synthesis; v, DIBAL reduction ; vi, $Ac_2O$ ; vii, oxidation; viii, 0.5 M-NaOH; ix, NBS ; x, deprotection

**Scheme 6**



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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 (seeVol.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]

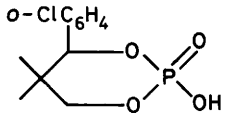
A number of papers on 6-[$^{18}$F]-dopa synthesis (and its use for tracing dopamine metabolism in the brain by positron tomography[179]) has appeared, employing $^{18}F_2$ with 6-trimethylsilyl-3,4-dimethyldopa ethyl ester as its N-salicylidene derivative[180] or direct reaction of the amino acid with $AcO^{18}F$ (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]



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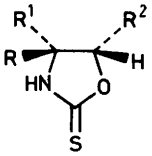

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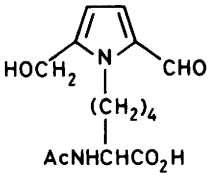

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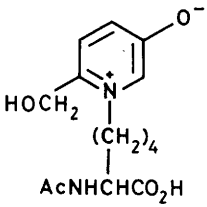

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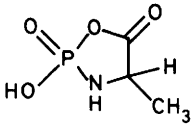

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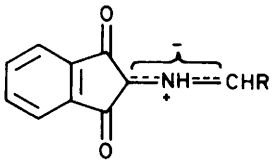

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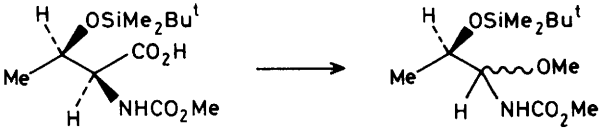

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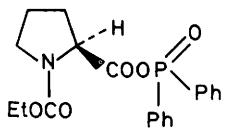

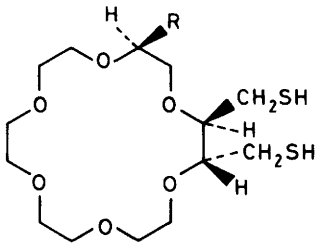

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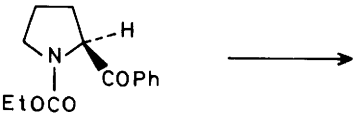


(42)

and N-acetyl-DL-phenylalanine (as its pentylammonium salt)[192] has been achieved. Again, any rational link between structure and tendency towards preferential crystallization still seems elusive.

Chromatographic and related methods are often useful since they are direct, and economical of time. Many of the analytical methods (Sections 7.1, 7.4) for determining enantiomer ratios can be scaled up for preparative separations, in principle. Another example of the use of the simplest chiral stationary phase, cellulose, has been reported: the preparative separation of enantiomers of N-(2,4-dinitrophenyl)amino acids.[193] Pirkle has developed an application of long-chain esters of N-(2-naphthyl)-L-valine attached to silica as stationary phase for the resolution of DL-amino acid 3,5-dinitrobenzamides[194] and the reverse approach, resolution of N-acyl-DL-amino acid esters on a chiral stationary phase prepared from N-(3,5-dinitrobenzoyl)-L-leucine or D-phenylglycine.[195] The thorough study is being rewarded with very substantial separation factors in some cases, and has more recently been extended to N-(2-naphthyl)alanine alanine esters.[196] A chiral stationary phase formed by immobilizing bovine serum albumin has been used in exploratory studies of resolution of N-acetyl-DL-amino acid derivatives.[197]

Other physical methods of resolution include a promising observation that macroporous acrylic polymers, when prepared so that the architecture of the polymer becomes chiral through what is described as a 'coulombic' influence by D-phenylalanine ethyl ester (or its L-isomer), show a modest resolution capability towards DL-phenylalanine ethyl ester when used in column chromatography.[198] L-Tryptophan is adsorbed more strongly than its D-isomer on silica coated with membranes formed by plasmolysis of (+)-camphor,[199] and a distantly related basis applies to the resolution of racemates over polystyrene-supported liquid membrane carrying a chiral crown ether,[200] and through electrophoresis in a chiral electrolyte.[201]

Uses of enzymes in resolution of DL-amino acids are: α-chymotrypsin (aromatic amino acid esters);[202] aminopeptidase from Pseudomonas putida (homomethioninamide);[189] and hog renal acylase (trifluoroalanine;[203] see also refs. 172,173). A review has appeared[204] dealing with uses of L-aminoacylases and N-acyl-L-lysine amidohydrolase in resolution of DL-amino acids. Microbial sources of enzymes such as these may themselves be used for the same purpose, an example being preferential degradation of L-isomers of N-acetyl-DL-tryptophan and N-benzoyl-DL-alanine (Nocardia restrictus) and of the D-isomer of N-acetyl-DL-tryptophan ethyl ester (Arthrobacter oxydans; the L-isomer is preferentially hydrolyzed by Nocardia corallina).[197]

Some enzymic methods involve the 'destruction' of one enantiomer to achieve resolution of a DL-amino acid (though none of the examples in the preceding paragraph are in this category). The differential degradation of enantiomers of an amino acid by radiation is a topic that has featured in the literature for many years, because of its relevance to the ascendancy of L-amino

acids in biological systems. Polarized electrons arising from $^{90}Sr$ - $^{90}Y$ β-decay cause some 10% greater degradation of solid D-alanine than of its L-analogue, as shown by e.s.r. spectral analysis of radical yield.[205] Results such as these have been claimed, and disputed, over the years; but persuasive attempts continue to be made to the effect that each member of a pair of enantiomers is of slightly different energy due to parity-violating weak neutral current perturbation of ground-state electronic energy.[206] The result of this, in energy content, is that the existence of L-amino acids is favoured to the extent of approximately $10^{-14}$ J $mol^{-1}$,[206] too small an amount to have led to the present situation.[207] A new type of chiral interaction, expressed in the relative affinities for enantiomeric amino acids towards water[208] or the coupling of the magnetic moment induced by the chiral interaction with the Earth's magnetic field,[209] has been proposed.

## 5 Physical and Stereochemical Studies of Amino Acids

5.1 Crystal Structures of Amino Acids and Their Derivatives.- While there is a predominant 'fact-gathering' motive to many of the reported crystal structures of these compounds, there are examples of experimental verification of calculated molecular parameters, and of comparison of information with that obtained by solid-state n.m.r. spectrometry.

Amino acids for which more accurate data than those in the literature have been determined are L-leucine[210] and D-enantiomers of methionine and tyrosine.[211] L-Citrulline dihydrate,[212] salts formed between L-arginine and D-aspartic acid or D-glutamic acid,[213] DL-homocysteine thiolactone perchlorate,[214] and p-fluoro-DL-[2,3,5,6-$^2H_4$]phenylalanine[215] have also been studied, the last-mentioned example assisting the interpretation of the solid-state n.m.r. spectrum.

Amino acid derivatives subjected to X-ray analysis are N-monochloroacetylglycine and the αα-di-ethyl and -di-propyl homologues,[216] and various αα-dimethylglycine (alias α-aminoisobutyric acid) derivatives.[217] The parameters found for the proline and hydroxyproline moieties in their simple derivatives correlate well with those deduced from conformational energy calculations.[218] NN'-Bis(L-phenylalanyl) hydrazide[219] and dimethyl N-phthaloyl-4-bromo-DL-glutamate[220] and unsaturated derivatives (Z)-N-benzoyl-αβ-dehydroleucine[221] and (Z)-4-benzylidene-2-methyloxazolin-5-one[222] have been studied.

5.2 Nuclear Magnetic Resonance Spectrometry.- Conformational information has been inferred from n.m.r. studies of amino acid adenylate anhydrides of amino acids with hydrophobic side-chains.[223] At low pH in dilute solutions, the side-chain is shown to participate in the same type of intercalative interaction with the adenine ring that has already been established for aromatic side-chains. N-Acetyl t-butyl-DL-valinate has provided a surprising example of

discrimination of one enantiomer in favour of another, in studies of this racemate to which small additions of one enantiomer were made (i.e. $[D] \neq [L]$). It was found that $CCl_4$ solutions showed n.m.r. non-equivalence due to the formation of N-H ····· O=C hydrogen-bonded diastereoisomeric dimers.[224]

$^1H$-, $^{19}F$-, and $^{31}P$-N.m.r. has been used in estimations of enantiomeric purity for (S)-[2-$^2H$]-glycine as its (-)-N-camphanyl derivative;[67] of amino acids derivatized with Mosher's acid (2-trifluoromethyl-2-methoxyphenylacetic acid);[225] and methylthiophosphoric di-amides formed between an amino acid ester and $MeP(S)Cl_2$.[226] In the last-mentioned example the derivatives consist of a mixture of racemate with two meso isomers due to the chirality at both carbon and phosphorus centres, that show well resolved $^{31}P$ singlets which, on integration, give a direct measure of optical purity.[226]

$^2H$-N.m.r. nuclear relaxation rates for aqueous solutions over a wide pH range reveal details of molecular dynamics of [$\gamma$-2,2-$^2H_2$]aminobutyric acid, [2-$^2H$]-DL-glutamic acid, and [2-$^2H$]-DL-lysine.[227] A similarly targetted study[228] has been made of polycrystalline [4,4-$^2H_2$]-DL-proline and of [2,3,5,6-$^2H_4$]-p-fluoro-DL-phenylalanine,[215] assisted in the latter case with a detailed X-ray crystal structure determination.

$^{13}C$-N.m.r. study of L-histidine prepared in differently protonated forms from solutions of various pH illustrates further the increasing interest in the finer details of the solid-state behaviour of amino acids.[229] Homonuclear coupling is revealed by the magic-angle technique for solid-state glycine zwitterion labelled at both carbon atoms by $^{13}C$ that can be interpreted in terms of rotamer composition. Different crystalline forms of DL-, D-, and L-methionine are conformationally pure, but each contains a different conformation,[230] as yet undefined.

$^{17}O$-N.m.r. of solutions of L-alanine and L-proline in $^2H_2O$ - dimethyl sulphoxide provide unique information on the hydration states of the carboxy group.[232] Two water molecules are hydrogen-bonded in neutral and basic solutions, and a third is involved in acidic media. In dimethyl sulphoxide solutions the solute appears to exist in the dimeric form. $^{17}O$-N.m.r. data have been reported for the labelled L-tyrosine isotopomers.[233]

5.3 Optical Rotatory Dispersion and Circular Dichroism.- While routine applications for assignments of absolute configuration continue to be excluded, even the two papers selected are based on well established principles. The c.d. of N-2,4-dinitrophenyl-L-amino acids carrying a polycyclic aromatic side-chain shows a negative Cotton effect centred at 400 nm,[234] in accordance with the rule linking chirality with sign of longest-wavelength Cotton effect. On this basis, the laevorotatory isomer of 3-(9-anthryl)alanine is assigned the D-configuration. An interesting example of the power of the technique is the discovery of induced Cotton effects by tryptophan, tyrosine and phenylalanine into gossypol.[235] Solutions at pH 7.6 show negative c.d. at 424-426 and 300 nm, and positive c.d. centred at 355 nm, indicating weak complex

formation between the aromatic moieties in the amino acids and the pigment.

5.4 Mass Spectrometry.- In contrast with the preceding Section, this is well supplied with innovative papers associated with the rapid progress in instrumentation. Again, routine mass spectrometric analysis is excluded, and mention of a study of the N-trifluoroacetyl derivative of n-butyl $^{2}$H-leucinate to establish positions of the label[236] is made to give the reader an indication of the sort of material which, although worthy and useful, is based on established principles and supported by standard textbook coverage and not covered further here.

A curious observation has been published[237] to the effect that c.i.m.s. of enantiomers of an amino acid derivative can show characteristic differences when (+)-amyl alcohol is a constituent of the reagent gas. The implication that this might be exploited to permit mass spectrometric assignment of absolute configuration to an amino acid is sure to be followed up. The c.i.m.s. technique has been applied to N-2,4-dinitrophenylamino acid esters, leading to very simple negative-ion spectra in which the molecular ion is the base peak.[238]

Various fast-atom bombardment studies, mostly in the tandem mode, have been reported for amino acids. These provide improved spectra for problem cases (argininosuccinic acid and citrulline as their n-butyl esters,[239] L-carnitine [240]) but also give more insight into fragmentation processes more generally. Two isomeric immonium ions formed from N-isobutylglycine and N-methylvaline by f.a.b. can be distinguished by their collision-induced fragmentation characteristics and therefore mixtures containing them can be analyzed.[241] In terms of structure determination of an 'unknown' amino acid, the characteristic fragmentation patterns permit an unequivocal distinction to be made between C- and N-alkylated isomers.

Unimolecular reactions of metastable cluster ions formed by f.a.b. of amino acids have been interpreted to provide an order of relative proton affinities: Arg > His > Lys > Trp.[242]

5.5 Other Spectroscopic Studies.- The pattern for preceding Sections (exclusion of routine papers) continues here. Observations from readily accessible methods that appear to provide novel insights include reduction of the molar absorptivity of bilirubin by all common amino acids except arginine[243] and indications from calorimetric and infrared spectrometric studies that proline aggregation in aqueous solutions may account for a role for this amino acid in stabilizing biological macromolecules under reduced water stress (Vol.18, p.26).[244] An extraordinary technique in which molecules are cooled to near absolute zero in supersonic beams has been applied to tryptophan, so that it could be shown that two conformers exist under these conditions.[245] The conclusion was drawn from electronic spectra with the implication that there must be two gas-phase conformations of this amino acid of essentially identical energy.

Considerable progress is being made with Raman spectroscopic techniques, and the literature

on amino acids is duly reflecting this. Surface-enhanced Raman spectra of amino acids[246] adsorbed on silver have been interpreted to show that both amino and carboxy functional groups are points of adsorption. Ultraviolet excitation resonance Raman spectroscopy can provide finer details of structure - spectra relationships. An application to aromatic[247,248] and heteroaromatic[247,249] amino acids includes observations that nitration of tyrosine shifts the spectral features and abolishes its 200nm excited Raman spectrum, and that a similar effect is observed for the 218nm excitation feature of tryptophan as a result of (2-hydroxy-5-nitro)-benzylation.[247]

More convential Raman spectroscopic study has been incorporated with infrared and n.m.r. analysis of conformational equilibria for thiazolidine-4-carboxylic acid and its 2- and/or 5-methyl derivatives.[250]

5.6 Other Physical Studies.- Papers collected for this Section range from simple observations on purely physical phenomena to applications of physical methods other than spectroscopic for determination of data. In the former category, the observations usually relate to certain biological models, and include adsorption studies (intercalation of L-histidine, L-lysine, and L-arginine in γ-zirconium phosphate,[251] phenylalanine - cyclodextrin[252] and cyclomaltohexose[253] inclusion complexes) and radiation protection (N-acetylcysteine[254] and zinc aspartate[255]). The effect of tyrosine on reducing critical micellar concentrations of bile salts[256] and an effect of proline (see also ref. 244) in increasing the area occupied by membrane phospholipid molecules[257] have been reported.

A fascinating study[258] of transport of L-amino acids employs an oil layer between two aqueous layers, one of which contains a chiral detergent and the other contains the amino acids. As followed by changes in the electric potential across the aqueous layers, which varied with time in a pattern that is characteristic of the detergent chirality, the transport behaviour could be interpreted as a novel method to determine chirality. A related transport study through an ion-exchange membrane to which a potential gradient is applied has been modelled on the biological cell membrane system.[259]

Fundamental physical parameters have emerged from studies of N-acetyl-L-prolinamide and N-acetyl-N-methyl-L-alaninamide in binary mixtures, in terms of interpreting the excess free energy of the mixtures and their enthalpic virial coefficients to show interactions between solute molecules.[260] A related objective, the estimation of transfer free energies of amino acid side-chains from water to N-methylacetamide, similarly aims to extend knowledge on aspects of interactions that occur within proteins.[261] Simpler methods can be used to determine the hydrophobicity of amino acid side-chains, but vapour pressure measurements[262] may have only limited validity.[263] Dissociation constants of amino acids can be determined[264] by the ionophoretic technique; a simple interpretation of the variation of electrophoretic

mobility with pH of the electrolyte shows results in "fair agreement" with those of other methods. The related isotachophoretic indexes vary with pH and this has been interpreted to give absolute mobility values and $pK_a$ values for 26 amino acids.[265] An equally simple method based on polarimetric measurements yields protonation microconstants for L-amino acids.[266]

The long-running interest in interactions between amino acids and DNA continues with interpretations of simple physical data on mixtures.[267]

The polarographic behaviour of L-pyrrolidine-2-carboxylic acid and its lead(II) and cadmium(II) complexes[268] and of DL-norleucine[269] has been described.

5.7 Molecular Orbital Calculations.- Continuing an interest covered at the end of the preceding Section, calculations have been presented[270] for the binding energies of amino acid side-chains to O-6 and N-7 of guanine and adenine . Allowed molecular conformations for Pirkle's chiral stationary phases (see refs. 194-196) have been computed for one specific case, viz. 3,5-dinitrobenzoyl-L-alaninamide linked to silica through the amide nitrogen atom with a $-(CH_2)_3-$ group.[271] Because force field parameters for aromatic nitro groups do not yet exist, these authors have based their computations on the 3,5-di-formylbenzoyl analogue, and have concluded that the chiral stationary phase presents chiral recognition through an anti conformation of the methine hydrogen at the chiral centre relative to the benzoyl carbonyl group.[271]

Support for spectroscopic studies is provided by calculations of lower electronic energy levels for the glycine zwitterion, which are in good agreement with the spacing implied by absorption spectra.[272]

## 6 Chemical Studies of Amino Acids

6.1 Racemization.- Kinetic studies for racemization of representative L-amino acids at 142°C in aqueous solutions of differing pH yield the 6 absolute rate constants that correspond with each ionic species for catalysis by $H_3O^+$ and $OH^-$.[273] The heterogeneous-catalyzed racemization of L-alanine (a strong base anion exchanger substituted with 5-sulphosalicylaldehyde as the $Cu^{++}$ salt) has also been studied kinetically.[274]

The use of a racemase is still the province of very few groups, but the catalyzed 2-$^1$H - 2-$^2$H exchange by α-amino-ε-caprolactam racemase in $^2H_2O$ will be an attractive labelling method in certain cases.[275]

The exploitation of amino acid racemization for dating of relatively young fossil samples has given cause for concern due mainly to the uncertainties of effects, particularly catalytic, of the medium in which the fossil was located. A further problem, of course, is the chance that the amino acids being studied may have accumulated in the sample over time, from the

environment, and it has been pointed out[276] that there might be evidence on the absolute indigeneity of the amino acids arrived at by considering the proportions of the stable isotopes for carbon and nitrogen in the amino acids from the fossil, in relation to those of other amino acids collected at the fossil site. Major discordances have been reported between dates determined by aspartic acid racemization and those from accelerator mass spectrometric $^{14}C$ analysis, for bone samples,[277] and the sources of error in the amino acid dating method are concluded to be the uncertainties outlined above. Another factor that is perhaps unlikely to have arisen is the acceleration of the racemization of aspartic acid residues in eye lens protein that accompanies accelerated aging by X- or $\gamma$-irradiation.[278] Isoleucine epimerization has been used in dating of nine outcrop raised marine deposits through analysis of epimer ratios for sediment shells (Glycymeris violascens and Glycymeris glycymeris), leading to dates for three marine terraces of 120 000, 200 000, and 350 000 y that agree with estimates derived from $^{230}Th$ - $^{234}U$ decay.[279] Another way of using isoleucine racemization takes account of changes at both chiral centres.[280] The application referred to in the preceding sentence is based on epimer formation at the $\alpha$-carbon, for which the half-life (the time taken to reach a D-alloisoleucine to L-isoleucine ratio of about 0.4) is between $10^5$ - $10^7$ y. The other stereoisomers result from $\beta$-epimerization, and rates for this process have been measured in $H_2O$ at 250°C.[280] All four stereoisomers were found in ancient biogenic carbonates, so $\beta$-epimerization might be an index of value in the study of such samples.

6.2 General Reactions of Amino Acids.- This title is used to collect recent advances in reactions involving the amino and carboxy functional groups of amino acids.

A regular feature of this section is heterocyclic synthesis through the Maillard reaction between amino acids and carbohydrates and other reactions leading to heterocyclic ring formation. In the simplest combination in the Maillard reaction, between glycine and D-glucose, N-butylacetamide and N-butylformamide are formed as well as pyrroles (twelve such products as well as 5,6,7,8-tetrahydroindolizin-6-one and its 8-hydroxymethyl derivative are formed in the reaction of hydroxyproline and arabinose or erythrose[281]), suggesting that an early stage in the reaction creates dicarbonyl compounds.[282] There is some conflict between two reports, in one of which lysine is stated to react with glucose to yield the pyrrole (36),[34] while in the other the product is claimed to be the 1-alkyl-3-oxidopyridinium betaine (37).[283] Synthesis of (36) appears to have settled the point but further consideration may be called for, in view of the numerous products commonly found in such reactions. Fluorescent 1,4-dihydropyridines are formed in the Michael addition of malondialdehyde and a simple aldehyde with an amino acid,[284] and $\alpha$-chymotrypsin catalyzes the formation of fluorescent products between amino acid amides and 1-methyl-3,4-dihydro-$\beta$-carboline-3-carboxylic acid methyl ester.[285] 2-Methoxy-2,4-diphenyl-3(2H)-furanone has been proposed[286] as a useful alternative reagent

for fluorescent derivative formation with amino acids (the reagent is closely similar to fluorescamine).

Well established heterocyclic syntheses are based on the reaction of both amino and carboxy groups, and a new example involves the condensation of alanine with sodium cyclotriphosphate at pH 10 -12, to give (38) as well as the phosphonamide $(HO)_2P(O)NHCHMeCO_2H$.[287] Curiously, β-alanine gives $(HO)_2P(O)OP(O)(OH)OP(O)(OH)NHCH_2CH_2CO_2H$ under these conditions. Oxazolin-5-ones form easily from N-acylamino acids and can be converted into α-acylaminoalkyl β-difluoroalkyl ketones[288] and benzamidoalkyl mono-, di-, and trifluoromethyl ketones[289] by a modified Dakin-West reaction with appropriate acyl chlorides or acid anhydrides. Oxazolinones may be intermediates in oxidative decarboxylation of N-acylglycine using $KO_2$[290] or lead tetra-acetate.[291] Yields of amides are modest in these reactions, the side-products in the latter case being the N-formyl and N-acetoxymethyl amides.[291]

2-Cyclohexen-1-one is a better catalyst than di-t-butyl peroxide for the decarboylation of amino acids;[292] 'peroxidizing methyl linoleate' brings about the standard Strecker degradation of amino acids,[293] a classic example of which (reaction with ninhydrin) is now shown to involve the 1,3-dipole (39).[294] The methaneiminium methylide $CH_2\overset{+}{=}NHCH_2^-$ (more correctly represented in a delocalized structure; cf. (39)) is formed by decarboxylative condensation of glycine with formaldehyde.[295] In both these studies, evidence for the assertions comes from trapping experiments using simple dipolarophiles.

Studies of the kinetics of oxidative degradation of amino acids by familiar oxidants continue to fascinate a number of research groups.[296] Metabolic oxidation, exemplified by a study using Raja erinacea liver mitochondria,[297] is a broader topic outside the scope of this Chapter.

Oxidation of amino acids with Fremy's salt converts amino acids successively into hydroxy- and keto-acids without oxidative decarboxylation[298] (a number of the other oxidants described in ref. 296 bring about the same conversion). α-Hydroxy acids are formed from amino acids by reaction with $HNO_2$ with high, but not complete, stereospecificity.[299,300] However, the useful chiral synthon (S)-3-hydroxybutyrolactone is available from L-aspartic acid through straightforward elaboration of (S)-malic acid that forms from the amino acid with $HNO_2$.[300]

Photolytic decarboxylation of N-acetyl-N-nitroso-amino acids is accompanied by N-N cleavage.[301] These facts needed unravelling since the eventual products are 1,2,4-oxadiazoles formed between the initially formed N-acetylimines and $NO^-$.

The final example of decarboxylation in this year's review is accomplished by electrolytic methoxylation, a useful entry to chiral amines since the resulting N,O-acetal (e.g. (40) from a protected L-threonine) undergoes $TiCl_4$-catalyzed substitution with high diastereoselectivity.[87] Scheme 2 uses the same decarboxylation process in an alternative synthesis.[86]

*A distantly related asymmetric synthesis, the Rh(I)-chiral phosphine-catalyzed hydrogenation*

of N-(α-ketoacyl)amino acid esters, is a useful route to chiral α-hydroxy acids.[302]

N-Substitution reactions of amino acids providing synthetically valuable derivatives have been reported: N-maleyl and N-dichloromaleylamino acids;[303] Boc- and Z-amino acids prepared using benzotriazol-1-yl carbonates,[304] and through the usual reagent for preparation of Boc derivatives ($Boc_2O$: reactions of $^{17}O$-labelled amino acids with this reagent in MeOH or DMF occur without loss of the label);[305] and use of Fmoc N-succinimidoyl ester for the preparation of Fmoc-amino acids.[306] N-Benzyloxycarbonylamino acids and allyloxycarbonyl analogues can be converted into triethylallyloxycarbonyl analogues, through reaction with triethylsilane (not the N-triethylsilyl analogues as reported earlier), and, using t-butyldimethylsilane and 0.05 equiv. $Pd(OAc)_2$, into the t-butyldimethylsilyloxycarbonyl analogues.[307] Palladium-catalyzed hydrostannolysis by $Bu_3SnH$ of allyl- and allyloxycarbonylamino acid derivatives offers a novel, very mild, deprotection method.[308]

A novel variation of the Bucherer reaction of amino acids enables a preparation of L-N-(2-naphthyl)amino acids to be conducted conveniently and on a sufficiently large scale for the development of chiral stationary phases from them.[309] The method is essentially a condensation reaction of the L-amino acid, 2-naphthol, and $NaHSO_3$ in aqueous media at pH 8.

Kinetic studies have been reported for the reaction of trinitrobenzenesulphonic acid with amino acids[310] and for the nitrosation of proline, cysteine, and sarcosine.[311] A corresponding study of the formation of N-acetyl-$N^{in}$-nitrosotryptophan also covers the kinetics of the de-nitrosation process.[312]

Direct esterification procedures based on the enhanced ambident reactivity of the amino acid zwitterion with an alkyl halide rely on the much higher proportion of zwitterion in DMSO in comparison with $H_2O$.[313] Isolated examples of simple esterification in this way in aqueous solutions[314] have appeared in the literature. The thoughtful article by Hughes, Bergam and Grabowski, though mainly concerned with spectroscopic determination of $pK_a$ values of amino acids in DMSO, will stimulate further attempts to simplify direct esterification. Rates of esterification of 5'-adenosine monophosphate by N-acetylamino acids differ greatly for amino acids with A as the middle letter of their anticodons (Phe > Leu > Val > Ile) but not for others.[315]

Ester hydrolysis is represented in a comparison of uncatalyzed and $Cu^{++}$-promoted reactions of p-nitrophenyl glycinate.[316] The major crop of papers concerns enantioselective hydrolysis, catalyzed by chirally substituted polyethylene imines (benzoyloxycarbonyl-DL-phenylalanine p-nitrophenyl ester),[317] imidazole in chiral reversed micelles (a series of amino acid p-nitrophenyl esters),[318] and N-benzoyloxycarbonyl-L-Phe-L-His-L-Leu-OH (N-dodecanoyl-DL-phenylalanine p-nitrophenyl ester).[319] A comparison is made in the last-mentioned study with the diastereoselectivity of cleavage of N-benzyloxycarbonyl-DL-Pro-L-Pro-$OC_6H_4NO_2$ by a functional iodosobenzoate surfactant showing that both processes respond similarly to dimensions of the coaggregate micellar systems.[319] Chiral crown ethers (**41**) show modest chiral recognition

in thiolysis of DL-amino acid p-nitrophenyl esters.[320]

Simple exchange of anion has been described for amino acid benzyl ester toluene-p-sulphonates, leading to the corresponding hydrochlorides.[321]

Other manipulations of the carboxy function of amino acids have been reported for formation of Fmoc-amino acid chlorides from the acids using $SOCl_2$ in $CH_2Cl_2$ (and the use of 4-piperidylmethylamine for Fmoc cleavage),[322] formation of N-alkylhydroxamate esters by reaction with $ClCH{=}\overset{+}{N}Me_2\ Cl^-$ and N-methylmorpholine, followed by reaction of a hydroxylamine to displace the leaving group: $RCO_2H \rightarrow RCO_2CH{=}\overset{+}{N}Me_2\ Cl^- \rightarrow RCONR'OH$,[323] and the reduction of esters to aldehydes[324] and N-ethoxycarbonyl-L-proline to the phenylmethanol (42) by $H^-$ - selectride reduction of the phenylketone derived (93% e.e.) by Grignard addition to the mixed anhydride.[325]

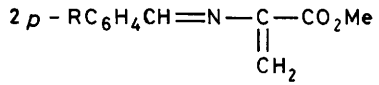
6.3 Specific Reactions of Amino Acids. Side-chain manipulations described here are also, incidentally, often useful methods for the conversion of one amino acid into another.

Aliphatic side-chains in N-benzoylamino acid methyl ester undergo slower H-abstraction with N-bromosuccinimide (a source of $Br^\cdot$ under irradiation in $CCl_4$) than glycine.[326] Ethylene formation from 1-aminocyclopropanecarboxylic acid can be accomplished *in vitro* through $Mn^{2+}$ catalyzed degradation by $H_2O_2$[327] and through lipoxygenase-catalyzed oxidation.[328] In the latter study the atoms of the cyanide ion that results are C-1 and N-1.[328]

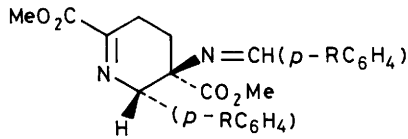
$\alpha\omega$-Aminodicarboxylic acids can be formed from cyclic $\alpha$-amino acids through an improved $RuO_4$-oxidation, followed by hydrolysis of the resulting lactam.[329] The related formal dehydrogenation of proline under physiological conditions, giving pyrrol-1-ine-5-carboxylic acid, involves catalytic transfer of $H^-$ via NADP(H).[330] Other unsaturated side-chain studies include unusual cyclodimerization of Schiff bases (43)→(44)[331] and selective reduction by DIBAL hydride + $BF_3.Et_2O$ of $\alpha\beta$-unsaturated $\gamma$-amino acid esters (readily available from $\alpha$-amino acids) to give corresponding allylic alcohols.[332]

Pyrolysis of cysteine at 130 - 220° during 30 - 120 min in a sealed glass tube gives $NH_3$ and cystine as major identified products, while at 180° for longer periods thiophen, $Et_2S_2$, 4-ethyl-2-methylpyridine, di- and tetramethylthiolans, 1,2-dithiane, and N-ethylacetamide are formed.[333] The sulphur-containing amino acids yield $SO_4^{--}$ through heating in water or HCl (the highest conversion occurring in 1M HCl), particularly readily for cysteine.[334] This surprising result, so long undiscovered, implies that analyses of sulphated proteins or glycoproteins may need correction of the sulphate figure to take account of contributions from these amino acids.

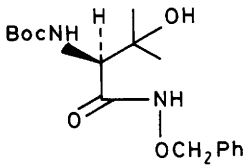
L-Lysine and L-ornithine bis (N-nitrososulphonamide)s undergo regioselective N-nitrososulphonamide - sulphonate rearrangement to give N-toluene-p-sulphonyl-L-proline and -pipecolic acids, respectively.[335] The near-relative amino acid, asparagine, undergoes adduct formation with $H^{13}CHO$ that enables $^{13}C$-n.m.r. detection of free asparagine in potato.[336]

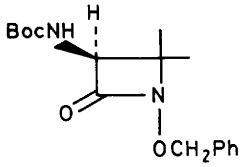

2 p - RC6H4CH=N—C—CO2Me
CH2

(43)


MeO2C
N=CH(p-RC6H4)
N
CO2Me
H
(p-RC6H4)

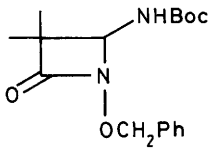
(44)


BocNH
H
OH
NH
O
OCH2Ph

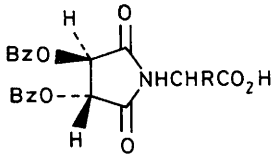

BocNH
H
N
O
OCH2Ph

(45)

+


NHBoc
N
O
OCH2Ph

(46)


H
O
BzO
NHCHRCO2H
BzO
H
O

(47)

A $^{15}N/^{14}N$ kinetic isotope effect has been established in the transamination of aspartic acid by α-ketoglutaric acid.[337] L-Serine is represented in preparation of its O-trimethylsilyl-$N^{\alpha}$-trifluoroacetyl diethylamide,[338] in conversion into an oxetanone under Mitsunobo conditions[339] (see also Vol.18, p.32; these conditions also convert $N^{\alpha}$-Boc β-hydroxy-L-valine O-benzyl hydroxamate into azetidinones (45) and (46)[340]). L-Serine has been used as a substrate for attack by HO• in $H_2O$ at pH 3 - 7, leading to $\cdot CH(OH)CH(CO_2^-)NH_3^+$ and thence to $NH_4^+$ and $OCH\dot{C}HCO_2^-$.[341] In the last-mentioned study, corresponding products were found in reactions of HO• with threonine.

Migration of a 4-substituent in the aromatic moiety of [ring-$^2H_5$]-L-phenylalanine to position 3 or 5 (the NIH shift) occurs in vivo (species: man) in hydroxylation to L-tyrosine.[342] The redox condensation system consisting of an alkanol with $Ph_3P$ - diethyl azodicarboxylate (the Mitsunobo reagent) brings about O-alkylation of tyrosine.[343] Iron(III) complexes catalyze the $H_2O_2$ oxidation of DOPA at pH 7.[344]

Substitution reactions of the indole moiety of tryptophan include a surprising $N^{in}$-acylation by aldehydes in aqueous media at pH 6.8, which can also lead to $N^{in}$-(1-hydroxyalkyl) adducts, but no reaction occurs with ketones.[345] The $N^{in}$-proton can also be substituted by the 3,4-dihydroxyphenyl group through reaction in acidic media with o-benzoquinone.[346] Indole C-hydroxylation can be accomplished in aqueous media with $FeSO_4$ and ascorbic acid;[347] the more extensive result usually observed with such 'Udenfriend reagents' ($Fe^{++}$/EDTA/ascorbic acid/$O_2$) is melanin formation, both from tryptophan and 'melanin-like' material from tyrosine.[348]

6.4 Non-Enzymic Models of Biochemical Processes Involving Amino Acids.- Spectroscopic evidence has been interpreted to derive binding constants for L-tryptophan to the Trp repressor of E.coli.[349] Disulphide bonds of proteins of lysosomes are more likely to undergo thiolysis by cysteine in vivo, rather than alternative thiols.[350]

These papers indicate a general rationale for this Section, but this Chapter contains several overlapping Sections so that certain topics that might have been located here have, instead, found an alternative relevant destination.

6.5 Effects of Electromagnetic Radiation on Amino Acids.- A group of papers dealing with relatively drastic treatment of aliphatic amino acids is a regular feature of this Section. This year this topic is represented by e.s.r. and ENDOR studies of X-irradiated single crystals of DL-proline hydrochloride (yielding radicals through α-deprotonation and ring cleavage),[351] X-ray-or γ-ray-accelerated racemization of aspartyl residues in proteins,[278] and autoradiolysis in solid D- and L-$^{14}$C-leucine resulting in β-radiation-induced decarboxylation.[352] E.s.r. analysis of the autodecomposition products reveals a 10% larger concentration of radicals in the D-leucine samples, a figure identical with that for D- and L-alanine irradiated with

polarized electrons produced during $^{90}Sr$ - $^{90}Y$ $\beta$-decay.[205]

Ultraviolet photolysis of N-acetylamino acids liberates free radicals through amide cleavage, and causes decarboxylation;[353] these substrates do not provide satisfactory models for the u.v. photolysis of peptides and proteins.[353] Arginine is degraded into aspartic acid, serine, norvaline, ornithine, urea, and $NH_3$ through u.v.-stimulated $H_2O_2$ oxidation;[354] in this system u.v. irradiation alone or $H_2O_2$ alone causes no degradation.

Extension of studies of one-electron oxidation of DOPA and cysteinylDOPAs through pulse radiolysis of aqueous solutions has been described.[355] Azide radicals formed from $NaN_3$ in the conditions yield unstable quinones and dopachromes. Electron-donating groups in substituted phenylalanines and tyrosine accelerate lumiflavin-sensitized photo-oxidation;[356] the formation of 'dityrosine' through $^{60}Co$-$\gamma$-irradiation of aqueous tyrosine solutions can be detected by characteristic fluorescence at 410 nm.[357] The fluorescence of tyrosine itself in acidic solutions has been thoroughly investigated.[358]

An interesting variation of what has become a routine area of study is the observation that tryptophan radicals cause oxidation of tyrosine in aqueous solutions of any pH, while tyrosine radicals achieve the corresponding effect on tryptophan only in strongly acidic or strongly alkaline solutions.[359] Tryptophan free radicals involving the indole moiety can be 'repaired' by anti-oxidants.[360] Photo-oxidation of tryptophan in aqueous solutions gives cis- and trans-3$\alpha$-hydroperoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylic acid as primary products through singlet-$O_2$ formed by red-light irradiation in the presence of sulphonated phthalocyanine - metal chelates.[361] Another pathway may be involved in the case of the Mn complex, but the tricyclic photoproduct is common to many other such studies, e.g. dye-sensitized photo-oxygenation at pH 3.6 - 7.1.[362] However, the indole-opened product, kynurenine, o-$HCONHC_6H_4COCH_2CH(CO_2^-)NH_3^+$, is formed in these conditions at pH 7.7 - 8.4.[362] 3-Indolecarboxaldehydes are formed by u.v. degradation of the side-chain of protected tryptophans in acid media through oxidation by pyrimido[5,4-g]pteridine N-oxide, with the corresponding protected glycine as accompanying product.[363] This new cleavage mode may account for the accumulation of 3-indolecarboxaldehyde in animals and plants. Another intriguing role for tryptophan is presumed in interpretation of visible light activation of retinal in bacteriorhodopsin followed by energy transfer to tryptophan revealed by fluorescence emission at 350 nm.[364] Five photolysis products, two unidentified accompanying kynurenine, N-formylkynurenine, and tryptamine, form in laser-irradiated (337 nm) aqueous tryptophan.[365] Radiolysis gives kynurenine and 5-hydroxtryptophan.[366] An e.s.r. study of photoionization products of tryptophan formed in media containing spin-traps to intercept hydrated electrons has been published.[367]

## 7 Analytical Methods

7.1 Gas-Liquid Chromatography.- Despite the continuing surge in h.p.l.c. analytical methods, there is no diminution in the volume of papers describing g.l.c. analysis.

Derivativization is an essential first step in the sample preparation stage of g.l.c. analysis of amino acids, and the novelty of procedures detailed here can be inferred from the extent of the discussion. Silylation is chosen only by a minority of workers, but the fact that t-butyldimethylsilyl derivatives are some 10000 times more stable than their trimethylsilyl analogues[368] will attract some to follow leaders using N-methyl-N-t-butyldimethylsilyltrifluoroacetamide as derivatization reagent for amino acids. Already[369] their use in analyses of glutamine and asparagine avoids problematical side-reactions that generate pyroglutamic acid and deaminated artefacts. Standard silylation practice has been employed in g.l.c. - m.s. analysis of phenylalanine and tyrosine that have been variously $^2$H-labelled,[370] though N-trifluoroacetylated pentafluorobenzyl esters were also used in this study. N-Trifluoroacetylation[371-373,22] and N-heptafluorobutyroylation[374-379,21] remain the most widely used procedures that follow esterification with pentafluorobenzyl alcohol,[370] isobutanol,[371,374-379,21] n-butanol,[372,22] n-propanol.[373] N-Pentafluorobenzoylation is preferred by some workers.[379] Arenesulphonyl derivatives are rarely used, but a novel example is of 1-dibutylamino-5-naphthalenesulphonyl derivatization, followed by trimethylsilylation for an attack on the analytical problem posed by the existence of more than 90 ninhydrin-positive compounds in the urine of healthy subjects, only about 46 of which have been identified previously.[380]

The amino acids that have benefitted from these and other g.l.c. analytical studies[381-385] include various aminobutyric acids,[373] including a new chlorine-substituted homologue found in xylem sap of Pisum sativum,[21] pipecolic acid,[382] 3-methylhistidine,[371,381] $N^5$-(1-carboxyethyl)ornithine,[22] cysteic acid,[383] (employing the N-isobutoxycarbonyl or dibutylsulphamoyl methyl ester or dibutylamide derivatives), and cysteinesulphinic acid.[384]

Some of the papers cited here include some appraisal of practical innovations (stability of the stationary phase "Supelcoport",[376] applicability of an N-selective detector,[377] and fused-silica capillary columns[385]). Creatinine has been established as a major problem of interference in g.l.c. of amino acids in urine.[374]

Estimation of enantiomer ratios by g.l.c. of derivatized amino acids over chiral stationary phases (polysiloxanes treated with chiral derivatives[386-388] including acylated L-phenylalanine t-butyl ester as a novel enantiomer discriminant) has continued, with applications for aspartic acid in aged human eye lens protein hydrolysates[386] and asparagine in ancient samples.[387]

7.2 Ion-Exchange Chromatography.- Automated ion-exchange amino acid analysis has been reviewed,[389] and precautions in sample preparation[389,390] including de-salting[391] have

been discussed. Brief reference can be made to representative applications of the amino acid analyzer: for analysis of crosslinking amino acids and 5-hydroxylysine from hydrolyzed elastin and collagen;[392] an independent study of pyridinoline and its 2'-deoxy analogue;[393] lysine content of fermentation products;[394] 3-methylhistidine;[395] and tryptophan.[396]

7.3 Thin-Layer Chromatography.- Quantitative analysis by t.l.c. is a more reproducible technique than it once was, due to the availability of more homogeneous materials and to improvements in practical aspects.[397]

The use of tin(IV) arsenosilicate as a cation-exchange t.l.c. medium for analysis of amino acids may have some advantages, since aromatic and acidic amino acids show greater mobility than on silica gel while basic amino acids stay at the origin.[398] Other non-routine papers give detailed data on t.l.c. of methylated lysines and arginines,[399] interpretation of t.l.c. mobility to yield an order of lipophilicity of amino acids,[400] identification of amino acids as their 4,4-dimethylamino-azobenzene-4'-naphthalenesulphonyl derivatives,[401] and estimation of optical purity through t.l.c separation of enantiomers on chirally modified silica gel.[402,403] Commercially available 'Chiralplates'® consist of reverse-phase silica gel impregnated with $Cu^{++}$ and a chiral proline derivative, operating on the ligand-exchange principle.[403]

7.4. High-Performance Liquid Chromatography.- A number of reviews have appeared on this vigorously expanding topic, two of a general nature[404,405] and two dealing with pre-column derivatization with o-phthaldialdehyde.[406,407] One covers also electrochemical detectors as they are used in amino acid analysis.[407]

Aspects of experimental technique are covered in a study of the use of alkanesulphonate salts as mobile-phase additives[408] and laser-induced fluorescence detection for o-phthaldialdehyde - mercaptoethanol derivatives and their naphthalenedialdehyde analogues.[409] This sensitive method allows the detection of between 4 and 15 femtomoles of the o-phthaldialdehyde derivatives or 200 - 500 amol amounts of the naphthalenedialdehyde analogues. Several orders of lower magnitude are therefore becoming possible, in relation to current levels around 10 pmol for the o-phthaldialdehyde derivatives using commercial instrumentation.

Deamination of L-amino acids by an L-amino acid oxidase creates a change in ionic strength, and amino acids in h.p.l.c. eluent can be estimated by the conductimetric approach with an immobilized enzyme detector.[410] Crown ether-containing mobile-phase separation parameters for amino acids[411] and improved separations using ammonium tungstophosphate-coated silica gel[412] have been explored.

Familiar subdivisions of the topic appear in the current literature, with some waxing and *waning of emphasis*. o-Phthaldialdehyde - mercaptoethanol occupies the pre-eminent position now, for pre-column derivatization reagent.[413-424] In one of these examples, the

necessity to cleave imino acids by HOCl to generate the fluorophore leads to post-column reaction for detection of proline and hydroxyproline.[420] Two other applications use wholly post-column derivatization following ion-exchange h.p.l.c. for assays of $N^{\epsilon}N^{\epsilon}N^{\epsilon}$-trimethyllysine[425] and S-methylmethionine.[426] Few papers describe the use of ninhydrin, but those that do adopt the usual post-column mode.[427,428] Harduf advocates colorimetry at 405nm and considers it advantageous to avoid switching detector wavelengths, as is common practice.[428]

The other burgeoning application is the direct phenylthiocarbamoylation by phenylisothiocyanate that appears to have been fully developed and side-reactions well understood.[429-439] An excellent short account of the method[436] will inform new and hesitant users. 1 pmol levels of 1-aminocyclopropanecarboxylic acid in apple tissue have been located by the method,[430] so it certainly compares favourably from this point of view with the o-phthaldialdehyde method. A novel combination of the two methods has been used for the assay of proline and hydroxyproline after pre-column derivatization with o-phthaldialdehyde and separation of the derivatives, followed by phenylthiocarbamoylation of the unreacted imino acids.[439]

Electrochemical detection is featured in an increasing proportion of h.p.l.c. studies of amino acids,[440-445] these papers covering homocysteine,[440] cystine,[441] methionine,[442] tyrosine,[443] and tryptophan,[444,445] and detection limits can be as low as 1 ng.[442]

Phenylthiohydantoins, whether they arise from sequencing or are prepared directly from amino acids (e.g. 3-nitrotyrosine + 0.5M HCl + PhNCS, room temp. during 24 h[446]), continue to offer satisfactory h.p.l.c. characterisation of amino acids.[447-453] 4'-(NN-Dimethylamino)azobenzenethiohydantoins form the basis of one of these papers, accompanied by their 4'-sulphonate analogues;[453] all the other papers involve the phenylthiohydantoins themselves.

Dansylamino acids[454-457] and their close analogues (dabsylamino acids[458]) are extending their long service in the context of analysis and characterization at about 20 pmol levels,[454] although laser fluorimetric detection permits $10^{-16}$ mol levels to be reached.[456]

Alternative derivatives are those formed with 4-chloro-7-nitrobenzofurazan[459,460] and with its 4-fluoro analogue,[461] p-bromophenacyl esters from amino acid betaines,[462] Fmoc amino acids,[463] and xanthydrol derivatization of N-acetyl-L-glutamine.[464] Fluorescent 1,$N^6$-etheno derivatives are formed from the reaction between decarboxylated S-adenosylmethionine and $ClCH_2CHO$,[465] and the innate fluorescence of o- and m-tyrosines at 305 nm ($\lambda_{excit.}$ 275 nm) has also been used in detection of these amino acids during h.p.l.c.[466]

The amino acids on which these and other[467-470] h.p.l.c. papers have focussed, if not stated as part of the preceding narrative, are: tryptophan[444,445,467] and its radiolytic decomposition products,[366] methylated lysines, arginines, histidines, and methionine;[381,415,426,457] O-phosphoserine, threonine and tyrosine,[417] γ-carboxyglutamic acid,[417] glutamic acid,[417] $^{32}$P-phosphorylated amino acids,[468] histidine and its 1- and 3-methyl derivatives,[419] phenylalanine and

tyrosine,[424] S-adenosylmethionine,[469,470] arginine,[428] asparagine and glutamine,[431] tyrosine O-sulphate,[433] 4-fluorophenylalanine,[434] hydroxyproline and proline.[437,439]

Losses during protein hydrolysis have been accepted for many years as the price to pay for convenient and reliable methods for most of the amino acids. Cysteine, labelled with 4-(amino sulphonyl)-7-fluoro-[2.1.3]-benzoxadiazole while bound within the protein, is released using 6M-hydrochloric acid and then derivatized for h.p.l.c. analysis. Although methionine is largely destroyed by this milder acid hydrolysis, lysine is quantitatively recovered.[461]

Determination of enantiomer ratios by h.p.l.c. has been based on three main variations: the most common approach is the use of a chiral stationary phase,[471-476] with the use of chiral mobile phases becoming more widely used.[477-479] The classical approach in which the enantiomer mixture is converted into a pair of diastereoisomers through reaction with a chiral reagent is also valid, and dibenzoyl-L-tartaric anhydride has been used for this purpose to give the imides (47).[480] A further example of the formation of diastereoisomeric mixtures has been provided in the context of the well established o-phthaldialdehyde derivatization method. If N-acetyl-L-cysteine is used as thiol co-reactant, instead of the usual mercaptoethanol, then optically impure amino acids will yield corresponding proportions of diastereoisomeric iso-indoles that can be estimated by h.p.l.c. over achiral stationary phases.[478]

Pirkle's group is studying potential chiral stationary phases in a most thorough manner (see also refs. 194-196) and has described their use with enantiomeric purity determinations for α- and β-substituted β-alanines.[471] Silica gel made chiral through bonding to a D-phenylglycine derivative[472] also continues existing studies, and has been used with N-(3,5-dinitrobenzoyl)amino acid isopropyl esters. A chiral naphthylamine stationary-phase approach[473] and bovine serum albumin bonded to silica[474] also exploit the same general principle, the latter being a detailed study showing the particular suitable N-substituent for each amino acid (e.g. o-carboxybenzoyl for DL-alanine, phthaloyl for threonine).[474] The ligand-exchange principle (as used in t.l.c. resolution, ref. 392), in which an L-amino acid is bonded to the stationary phase and chelated to $Cu^{++}$, continues to develop satisfactorily, e.g. for the resolution of perfluoro-α,α-dialkyl glycines.[475,476] The same principle with mobile phases containing L-arginine - $Cu^{++}$[477] and either L-proline or L-histidine with $Cu^{++}$[478] has been used for the resolution of N-dansyl amino acids. N-Acetyl-L-valine t-butylamide has been used as a chiral hydrogen-bonding additive to the nonaqueous phase in silica-gel chromatography for the resolution of N-acetyl-amino acid t-butyl esters.[479]

A further category of h.p.l.c. enantiomer analysis employs a micropolarimeter-cum-refractive index detector at the outlet of a normal (achiral) h.p.l.c. column.[481] The sensitivity claimed (50ng - 2 μg) can only refer to compounds whose pure enantiomers have large specific rotations, and the method operates best only for samples that are close to maximum optical purity.

7.5 Fluorescence Methods.- The o-phthaldialdehyde method is covered in the context of its coupling with h.p.l.c., in the preceding section. Its reliability is assurable only under standardized procedures since degradation of the 1-alkythio-2-alkyliso-indoles occurs during and after derivatization. An important observation,[482] that degradation is strongly accelerated by excess o-phthaldialdehyde, implies the use of minimum reagent (or gradual addition). The low picomole detection limit for these derivatives has been underlined,[483] compared with about 3 nmol limits for the ninhydrin colorimetric method.

2,3-Naphthalenedicarboxaldehyde[409] reacts to give 2-substituted 1-cyanobenzo[f]iso-indoles by condensation with amino acids and $CN^-$;[484] the highly fluorescent derivatives will no doubt be taken up in competition with the o-phthaldialdehyde method for amino acid analysis.

The inherent fluorescence of certain amino acid side-chains has been mentioned in the preceding Section, and fluorescence energy acceptance by 4'-aminophenylalanine[485] might be useful in analysis of this amino acid.

Fluorimetric analysis of amino acids has been reviewed.[486]

7.6 Other Analytical Methods.- Dansylamino acids have been separated by paper electrophoresis[487] and by isoelectric focussing in immobilized pH gradient phases.[488]

7.7 Determination of Specific Amino Acids.- Most of the methods described here are specific because enzymatic assays are involved or because of colorimetry (in its broadest sense) derived from characteristic functional-group reactions for particular amino acids.

Three L-glutamic acid assays based on either L-glutamine synthetase[489] or L-glutamic acid dehydrogenase[490,491] include novel coupling with a second enzyme system - a reductase and luciferase that generate luminescence proportional to the amino acid,[490] and a transaminase that generates NADH in an enzyme electrode system.[491] One of these permits assay down to 100 pmol.[491] Arginase cleavage of L-arginine into ornithine and urea and assay of the urea by standard methods[492] illustrate conventional methodology, and immobilized bacteria - $pO_2$ sensor assay of L-tryptophan,[493] L-lysine α-oxidase electrode,[494] and other immobilized enzyme methods for L-amino acids[495] illustrate another strand of established methodology. An improved radioenzymic carnitine assay has been reported.[496]

Cysteine colorimetry using Ellman's thiol reagent can be inaccurate when surfactants are also present.[497] Another sort of interference applies to HOCl cleavage of 1-aminocyclopropane-carboxylic acid into ethylene, thought to be a specific reaction - but ethanol can also undergo cleavage to the same product.[498] Other presumed inocuous organic compounds, such as aliphatic amines, result in low ethylene yields from the amino acid.[498] Standard colorimetry is represented by Chloramine-T degradation of hydroxyproline (see also Vol.17, p.39)[499] and N-bromosuccinimide substitution of tryptophan (using a stopped-flow technique).[500] Analysis

of S-methylmethionine and S-adenosylmethionine in plant tissue down to 100 pmol levels has been accomplished through a dual-isotope dansylation procedure, depending on separation of the amino acids on phosphocellulose followed by thermal degradation to homoserine and estimation of the derived [$^{3}$H]dansyl[$^{14}$C]homoserine.[501]

Authoritative recent reviews of assay of specific amino acids are contained in refs 6 and 8.

## REFERENCES


1 IUPAC-IUB Newsletter, Biosci.Rep., 1986, 6, 121; Hoppe Seylers Biol.Chem., 1986, 367, 1.

2 H.C.J.Ottenheijm and J.D.M.Herscheid, Chem.Rev., 1986, 86, 697.

3 J.Martens, Chem.-Ztg., 1986, 110, 169.

4 W.Ye, Shengli Kexue Jinzhan, 1986, 17, 187 (Chem.Abs., 1987, 106, 4234).

5 F.J.R.Hird, Comp.Biochem.Physiol., B: Comp.Biochem., 1986, 85B, 285.

6 Methods Enzymol., 1985, 113; e.g. R.A.Hartline, p.639: α-Amino-adipic acid.

7 Proceedings of the 5th USSR-FRG Symposium on Peptides and Proteins, eds. W.Voelter, E.Bayer, Yu.A.Ovchinnikov, and V.T.Ivanov, W.de Gruyter, Berlin, 1986; 9th American Peptide Symposium, eds.C.M.Deber, V.J.Hruby, and K.D.Kopple, Pierce, Rockford, 1985.

8 Methods of Enzymatic Analysis, 3rd Edition, eds. H.U.Bergmeyer, J.Bergmeyer, and M. Grassl, Verlag Chemie, Weinheim, in 12 Volumes (1983-1986): e.g. G.Livesey and P.Lund, Assay of Branched Chain Amino Acids, Vol. 8, p.318; A.Hinkkanen and K.Decker, Vol.8, p.329, Assay of D-amino acids.

9 'Amino Acids', in: Neuromethods, Vol.3, eds. A.Boulton, G.B.Baker, and J.D.Wood. Humana Press, Clifton, N.J., 1985; 'Chemistry and Biochemistry of the Amino Acids'; ed. G.C.Barrett, Chapman & Hall, London, 1985.

10 V.N.Kovalev and A.N.Komissarenko, Khim.Prir.Soedin., 1985, 724.

11 J.T.Romeo and L.A.Swain, J.Chem.Ecol., 1986, 12, 2089.

12 M.Samada, T.Miyano, and S.Iwadare, J.Antibiot., 1986, 39, 304.

13 T.R.Bosin, S.Krogh, and D.Mais, J.Agric.Food Chem., 1986, 34, 843.

14 E.V.Grishin, T.M.Volkova, A.S.Arseniev, O.S.Reshetova, V.V.Onoprienko, L.G.Magazanik, S.M.Antonov, and I.M.Fedorova, Bio-org.Khim., 1986, 12, 1121.

15 J.L.Corbin, B.H.Marsh, and G.A.Peters, Phytochemistry, 1986, 25, 527.

16 B.S.Vold, L.E.Kraus, V.G.Rimer, and R.C.Coombes, Cancer Res., 1986, 46, 3164.

17 P.W.Jeffs, G.Chan, L.Mueller, C.DeBrosse, L.Webb, and R.Sitrin, J.Org.Chem., 1986, 51, 4272.

18 G.H.Fisher, N.M.Garcia, I.C.Payan, R.Cadilla-Perezrios, W.A.Sheremata, and E.H. Man, Biochem.Biophys.Res.Commun., 1986, 135, 683.

19 A.V.Klotz, J.A.Leary, and A.N.Glaser, J.Biol.Chem., 1986, 261, 15891.

20 M.E.Marsh, Biochemistry, 1986, 25, 2392.

21 G.Fortier and S.L.Mackenzie, Biochem.Biophys.Res.Commun., 1986, 139, 383.

22 J.Thompson, M.A.Curtis, and J.P.F.Miller, J.Bacteriol., 1986, 167, 522.

23 M.Maeda, T.Kodama, T.Tanaka, H.Yoshizumi, K.Nomoto, T.Takemoto, and T.Fujita, Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 1985, 616 (Chem.Abs., 1986, 104, 183260).

24 W.Schuh, H.Puff, E.A.Galinski, and H.G.Trueper, Z.Naturforsch.C: Biosci., 1985, 40C, 780.

25 Y.Ikeda, S.Kondo, D.Ikeda, K.Yokose, H.Funitani, T.Ikeda, M.Hamada, M.Ishizuka, T.Takeuchi, and H.Umezawa, J.Antibiot., 1986, 34, 476.

26 S.Yuasa, Clin.Chim.Acta, 1986, 160, 331.

27 S.Yuasa, Biochem.Biophys.Acta, 1987, 540, 93.

28 P.Briza, G.Winkler, H.Kalchhauser, and M.Breitenbach, J.Biol.Chem., 1986, 261, 4288.

29 G.J.Pielak, S.Gurusiddaiah, and J.I.Legg, Anal.Biochem., 1986, 156, 403.

30 S.H.Rahnema and B.T.Leurer, J.Anim.Sci., 1986, 63, 603.

31 H.Wu, H.Nakamura, J.Kobayashi, Y.Ohizumi, and Y.Hirata, Experientia, 1986, 42, 855.

32 W.A.Koenig, H.Hahn, R.Rathmann, W.Hass, A.Keckeisen, H.Hagenmaier, C.Bormann, W.Dehler, R.Kurth, and H.Zaehner, Liebigs Ann.Chem., 1986, 407.

33 Y.H.Paik and P.Dowd, J.Org.Chem., 1986, 51, 2910.

34 R.Miller and K.Olsson, Acta Chem.Scand., Ser.B, 1985, B39, 717.

35 L.S.Payne and J.Boger, Synth.Commun., 1985, 15, 1277.

36 C.R.Creveling and K.L.Kirk, Biochem.Biophys.Res.Commun., 1985, 130, 1123.

37 D.S.Kemp and T.P.Curran, J.Org.Chem., 1986, 51, 2377.

38 N.A.Sasaki, J.L.Morgat, and P.Potier, Int.J.Pept.Protein Res., 1986, 27, 360.

39 O.Tiba and C.G.Overberger, Polym.Sci.Technol.(Plenum), 1985, 31, 419.

40 H.J.Reich, C.P.Jasperse and J.M.Renga, J.Org.Chem., 1986, 51, 2981.

41 D.Ferroud, J.P.Genet, and R.Kiolle, Tetrahedron Lett., 1986, 27, 23; M.Joucla, M. El Goumzili, and B.Fouchet, Ibid., p.1677; M.Joucla and M. El Goumzili, Ibid., p.1681.

42 C.Herdeis and A.Dimmerling, Arch.Pharm., 1986, 319, 473.

43 C.F.Stanfield, W.L.Cody, and V.J.Hruby, J.Org.Chem., 1986, 51, 5153.

44 P.A.Krasutzkii, I.G.Semenova, M.I.Novikova, A.G.Yurchenko, N.A.Leont'eva, and T.V.Veselovskaya, Khim.Farm.Z., 1985, 19, 825; P.A.Krasutskii, I.G.Semenova, M.I. Novikova, and A.G.Yurchenko, Zh.Org.Khim., 1985, 21, 1905.

45 F.Effenberger, U.Burkard, and J.Willfahrt, Liebigs Ann.Chem., 1986, 314.

46 D.Mandler and I.Willner, J.C.S.Chem.Commun., 1986, 851; J.C.S.Perkin II, 1986, 805.

47 T.Sasaki, K.Mori, and M.Ohno, Synthesis, 1985, 280.

48 S.Ram and R.E.Ehrenkaufer, Synthesis, 1986, 133.

49 Y.M.Goo and Y.B.Lee, J.C.S.Chem.Commun., 1986, 1247; S.Y.Choi and Y.M.Goo, Arch.Pharmacol.Res., 1986, 9, 45.

50 S.S.Yuan and A.M.Ajami, J.Organomet.Chem., 1986, 302, 255.

51 C.Gennari, L.Colombo, and G.Bertolini, J.Amer.Chem.Soc., 1986, 108, 6394.

52 W.Oppolzer and R.Moretti, Helv.Chim.Acta, 1986, 69, 1927.

53 K.Pullachipatti and R.W.Woodard, Synth.Commun., 1986, 16, 337.

54 M.Calmes, J.Daunis, R.Jacquier, G.Nkusi, J.Verducci and P.Viallefont, Tetrahedron Lett., 1986, 27, 4303; J.P.Genet, D.Ferroud, S.Juge, and J.R.Montes, Ibid., p.4573.

55 S.Ikegami, T.Hayama, T.Katsuki, and M.Yamaguchi, Tetrahedron Lett., 1986, 27, 3403.

56 J.M.McIntosh and R.K.Leavitt, Tetrahedron Lett., 1986, 27, 3839.

57 S.K.Phadtare, S.K.Kamat, and G.T.Panse, Indian J.Chem., Sect.B, 1985, 24B, 811.

58 R.Kober, K.Papadopoulos, W.Miltz, D.Enders, W.Steglich, H.Reuter, and H.Puff, Tetrahedron, 1985, 41, 1693.

59 W.Oppolzer, R.Pedrosa, and R.Moretti, Tetrahedron Lett., 1986, 27, 831.

60 C.Wandrey and B.Bosrow, Biotekhnol.Biotekh., 1986, 8.

61a A.Dureault, C.Greck, and J.C.Depezay, Tetrahedron Lett., 1986, 27, 4157.

61b J.Mulzer, A.Augermann, B.Schubert, and C.Seilz, J.Org.Chem., 1986, 51, 5294.

62 T.G.Hansson and J.O.Kihlberg, J.Org.Chem., 1986, 51, 4490.

63 L.Duhamel, S.Fouquay, and J.-C.Plaquevent, Tetrahedron Lett., 1986, 27, 4975.

64 U.Schöllkopf, H.J.Neubauer, and M.Hauptreif, Angew.Chem., 1985, 97, 1065.

65 U.Schöllkopf, U.Busse, R.Lonsky, and R.Hinrichs, Liebigs Ann.Chem., 1986, 2150.

66 P.J.Sinclair, D.Zhai, J.Riebenspies, and R.M.Williams, J.Amer.Chem.Soc., 1986, 108, 1103.

67 R.M.Williams, D.Zhai, and P.J.Sinclair, J.Org.Chem., 1986, 51, 5021.

68 J.D.Aebi and D.Seebach, Helv.Chim.Acta, 1985, 68, 1507.

69 R.Fitzi and D.Seebach, Angew.Chem., 1986, 98, 363.

70 D.Seebach, D.D.Miller, S.Mueller, and T.Weber, Helv.Chim.Acta, 1985, 68, 949.

71 D.Seebach and A.Fadel, Helv.Chim.Acta, 1985, 68, 1243.

72 D.A.Evans and A.E.Weber, J.Amer.Chem.Soc., 1986, 108, 6757.

73 D.A.Evans, T.C.Britton, R.L.Dorow, and J.F.Dellaria, J.Amer.Chem.Soc., 1986, 108, 6395.

74 L.A.Trimble and J.C.Vederas, J.Amer.Chem.Soc., 1986, 108, 6397.

75 Y.Yamamoto, M.Kirihata, I.Ichimoto, and H.Ueda, Agric.Biol.Chem., 1985, 49, 2191.

76 Y.Iko, M.Sawamura, and T.Hayashi, J.Amer.Chem.Soc., 1986, 108, 6405.

77 (a) F.Piacenti, P.Frediani, U.Matteoli, G.Menchi, and M.Bianchi, Chem.Ind.(Milan), 1986; 68; 53; (b) U.Nagel and E.Kinzel, Chem.Ber., 1986, 119, 3326; (c) H.Brunner and M.Kunz, Chem.Ber., 1986, 119, 2868; (d) W.S.Knowles, J.Chem.Educ., 1986, 63, 222; (e) A.Kinting and H.W.Krause, J.Organometal.Chem., 1986, 302, 259; (f) M.Yamashita; M.Kobayashi, M.Sugiura, K.Tsunekawa, T.Oshikawa, S.Inokawa, and H.Yamamoto, Bull.Chem.Soc.Jpn., 1986, 59, 175; (g) V.A.Pavlov, A.A.Voloboev; L.S.Gorshkova, and E.I.Klabunovskii, Doklady Akad.Nauk, S.S.S.R., Ser.Khim., 1985, 283, 1206; (h) F.Alario, Y.Amrani, Y.Colleniille T.P.Dang, J.Jenck, D.Morel, and D.Sinone, J.C.S.Chem.Commun., 1986, 202; (i) U.Nagel and E.Kinzel, Chem.Ber., 1986, 119, 1731.

78 H.Aoyagi, F.Horike, A.Nakagawa, S.Yokote, N.Park, Y.Hashimoto, T.Rata, and N.Izumiya, Bull.Chem.Soc.Jpn., 1986, 59, 323.

79 E.I.Klabunovskii, E.I.Karpeiskaya, E.S.Levitina, L.F.Godunova, and L.N. Kaigorodova, Izvest.Akad.Nauk S.S.S.R., Ser.Khim., 1985, 2157.

80 E.S.Levitina, L F Godunova, L.N.Kaigorodova, E. I.Karpeiskaya, E.I.Klabunovskii, and D.D.Gogoladze, Izvest.Akad.Nauk S.S.S.R., Ser. Khim., 1986, 925.

81 C.J.Sih, W.R.Shieh, C.S.Chen, S.H.Wu, and G.Girdankas, Ann.N.Y.Acad.Sci., 1986, 471, 239.

82 A.Yu.Bogdanov, A.A.Zharov, and V.M.Zhubin, Izvest.Akad.Nauk S.S.S.R., Ser. Khim., 1986, 250.

83 H.Oelschlager, J.Ogorka, and I.Kolbeck, Arch.Pharm.(Weinheim), 1986, 319, 488.

84 T.Iimori, Y.Ishida, and M.Shibasaki, Tetrahedron Lett., 1986, 27, 2153.

85 J.D'Angelo and J.Maddaluno, J.Amer.Chem.Soc., 1986, 108, 8112.

86 P.Renaud and D.Seebach, Synthesis, 1986, 424.

87 P.Renaud and D.Seebach, Angew.Chem., 1986, 98, 836.

88 M.Joucla and J.Mortier, J.C.S.Chem.Commun., 1985, 1566.

89 B.N.Khare, C.Sagan, H.Ogino, B.Nagy, C.Er, K.H.Schram, and E.T.Arakawa, Icarus, 1986, 68, 176.

90 C.N.Matthews, Polym.Prepr.(Am.Chem.Soc., Div.Polym.Chem.), 1986, 27, 103.

91 T.Sakata and K.Hashimoto, Nouv.J.Chim., 1985, 9, 699.

92 K.J.Zahnle, J.Geophys.Res., D: Atmos., 1986, 91D, 2819.

93 V.K.Tiwari and R.K.Sharma, Himalayan Chem.Pharm.Bull., 1985, 2, 32.

94 K.Kobayashi and C.Ponnamperuma, Origins Life, 1985, 16, 57.

95 W.Wang, K.Kobayashi, and C.Ponnamperuma, Beijing Daxue Xuebao, Ziran Kexuban, 1984, 36 (Chem.Abs., 1986, 104, 163985).

96 K.Yonaha and K.Soda, Adv.Biochem.Eng./Biotechnol., 1986, 33, 95; J.Plachy, Chem. Prum., 1986, 36, 432; C.Wandrey, NATO ASI Ser., Ser.C, 1986, 178 (Enzymes as Catalysts in Organic Synthesis), p.263; ed.M.P.Schneider, Reidel, Dordrecht, 1986; I.Chibata, T.Tosa, and T.Sato, Biotechnol.Ser., 1985, 5, 37; T.Nagasawa and H.Yamada, Progr.Ind. Microbiol., 1986, 24 (Biotechnology of Amino Acids Production), 217; T.Nagasawa and H.Yamada, Appl.Biochem.Biotechnol., 1986, 13, 147; D.Xu, Gongye Weishengwu, 1986, 16, 25 (Chem.Abs., 1986, 105, 207510); B.Zhang and Y.Tan, Zhongguo Tiaoweipin, 1986, 1 (Chem.Abs., 1986, 105, 22942); L.F.Kurganova, A.D.Neklyndov, and Yu.E.Bartoshevich, Antibiot.Med.Biotekhnol., 1986, 31, 385.

97 V.Vojtisek, T.Guttmann, M.Barta, and J.Netrval, Biotechnol.Bioeng., 1986, 28, 1072.

98 T.K.Lee and H.Y.Hsaio, Enzyme Microb.Technol., 1986, 8, 523.

99 Progr.Ind.Microbiol., Vol.24 (Biotechnology of Amino Acids Production); K.Araki, p.247 (histidine); S.Komatsubara and M.Kisumi, p.233 (isoleucine, valine, and leucine); I.Chibata, T.Tosa, and T.Kakimoto, p.224 (alanine); Y.Morinaga and H.Yamada, p.207(serine); I.Shiio, p.188 (tryptophan); and H.Tanaka and K.Soda, p.183 (methionine).

100 T.Ohta, S.Nakajima, Z.Sato, T.Aoki, S.Hatanaka, and S.Nozoe, Chem.Lett., 1986, 511.

101 E.W.Logusch, Tetrahedron Lett., 1986, 27, 5935.

102 T.Wakamiya, Y.Oda, H.Fujita, and T.Shiba, Tetrahedron Lett., 1986, 27, 2143.

103 R.Wiesendanger, B.Martinoni, T.Boller and D.Arigoni, J.C.S.Chem.Commun.,1986, 238.

104 R.Wiesendanger, B.Martinoni, T.Boller, and D.Arigoni, Experientia, 1986, 42, 207.

105 N.Kurokawa and Y.Ohfune, J.Amer.Chem.Soc., 1986, 108, 6041.

106 J.K.Thottathil and J.L.Moniot, Tetrahedron Lett., 1986, 27, 151.

107 G.A.Kraus and J.O.Nagy, Tetrahedron, 1985, 41, 3537.

108 K.Konno, K.Hashimoto, Y.Ohfune, H.Shirahama, and T.Matsumoto, Tetrahedron Lett., 1986, 27, 607; K.Konno, K.Hashimoto, H.Shirahama, T.Matsumoto, and Y.Ohfune, Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 1985, 252 (Chem.Abs., 1986, 104, 206969).

109 P.DeShong and D.A.Kell, Tetrahedron Lett., 1986, 27, 3979.

110 J.C.Dho, G.W.J.Fleet, J.M.Peach, K.Prout, and P.W.Smith, Tetrahedron Lett., 1986, 27, 3203.

111 B.P.Bashyal, H.-F.Chow, and G.W.J.Fleet, Tetrahedron Lett., 1986, 27, 3205.

112 F.Effenberger and U.Burkard, Liebigs Ann.Chem., 1986, 334; U.Burkard, I.Walther, and F.Effenberger, Ibid., p.1030.

113 A.J.Ozinskas and G.A.Rosenthal, J.Org.Chem., 1986, 51, 5047; K.Barlos, D.Papaioannou, and C.Sanida, Liebigs Ann.Chem., 1986, 287.

114 A.K.Saksena, R.G.Lovey, V.M.Girijacallabhan, A.K.Ganguly, and A.T.McPhail, J.Org.Chem., 1986, 51, 5024.

115 R.I.Cogan and D.E.Rivett, J.Chromatogr., 1985, 348, 421.

116 X.Gu, B.Pan, and Y.Gao, Huaxue Xuebao, 1985, 43, 675 (Chem.Abs., 1986, 104, 149363).

117 T.Itaya, N.Watanabe, and A.Mizutani, Tetrahedron Lett., 1986, 27, 4043.

118 H.Hiemstra, W.J.Klaver, and W.N.Speckamp, Tetrahedron Lett., 1986, 27, 1411.

119 B.H.Lipshutz, B.Huff, and W.Vaccaro, Tetrahedron Lett., 1986, 27, 4241.

120 J.A.Bajgrowacz, A.El Hallaoui, R.Jacquier, C.Pigiere, and P.Viallefont, Tetrahedron, 1985, 41, 1833.

121 M.C.Pirrung and G.M.McGeehan, J.Org.Chem., 1986, 51, 2103.

122 T.Moriya, M.Seki, H.Kubota, and K.Matsumoto, ChemExpress, 1986, 1, 157.

123 K.Drauz, A.Kleemann, J.Martens, P.Scherberich, and F.Effenberger, J.Org.Chem., 1986, 51, 3494.

124 T.C.Ho, B.Gopalan, and J.J.Nestor, J.Org.Chem., 1986, 51, 2405.

125 J.K.Thottathil, J.L.Moniot, R.H.Mueller, M.K.Y.Wong, and T.P.Kissick, J.Org.Chem., 1986, 51, 3140.

126 H.Haber, H.Buchholz, R.Sukale, and H.G.Henning, J.Prakt.Chem., 1985, 327, 51.

127 C.Herdeis, Synthesis, 1986, 232.

128 R.Labia and C.Morin, J.Org.Chem., 1986, 51, 249.

129 J.M.Girodeau, C.Agouridas, M.Masson, R.Pineau, and F.Le Goffic, J.Med.Chem., 1986, 29, 1023.

130 M.G.Bock, R.M.DiPardo, and R.M.Friedinger, J.Org.Chem., 1986, 51, 3718.

131 M.Akhtar, M.A.Cohen, and D.Gani, J.C.S.Chem.Commun., 1986, 1290.

132 S.Lee, Y.Kodera, K.Noda, H.Aoyagi, T.Kato, and N.Izumiya, Bull Chem.Soc.Jpn., 1986, 59, 493.

133 C.Scolastico, E.Conca, L.Prati, G.Guanti, L.Banfi, A.Berti, P.Farina, and U.Valcavi, Synthesis, 1985, 850.

134 Yu.L.Yagupolskii, V.A.Soloshonok, and V.P.Kukhar, Zh.Org.Khim., 1986, 22, 517.

135 A.L.Castelhano, S.Horne, R.Billedeau, and A.Krantz, Tetrahedron Lett., 1986, 27, 2435.

136 S.Sawada, T.Nalayama, N.Esaki, H.Tanaka, K.Soda, and R.K.Hill, J.Org.Chem., 1986, 51, 3384.

137 D.H.R.Barton, D.Crich, Y.Herve, P.Potier, and J.Thierry, Tetrahedron, 1985, 41, 4347.

138 H.Braxmeier and G.Kresze, Synthesis, 1985, 683.

139 T.Seethaler and G.Simchen, Synthesis, 1986, 390.

140 G.Chipens, V.A.Slavinskaya, D.Kreile, D.Sile, A.Strautina, D.Eglite, and E.Kh. Korchagova, Latv.P.S.R. Zinat.Akad.Vestis, Kim.Ser., 1985, 661.

141 R.D.Allan, G.A.R.Johnston, and R.Kazlauskas, Aust.J.Chem., 1985, 38, 1647.

142 R.D.Allan, H.W.Dickenson, G.A.R.Johnston, R.Kaslauskas, and H.W.Tran, Aust.J. Chem., 1985, 38, 1651.

143 Y.Ohfune, K.Hori, and M.Sakaitani, Tetrahedron Lett., 1986, 27, 6079.

144 T.Hvidt, O.R.Martin, and W.A.Szarek, Tetrahedron Lett., 1986, 27, 3807.

145 K.Takahashi, K.L.Kirk, and L.A.Cohen, J.Labelled Compd.Radiopharm., 1986, 23, 1.

146 R.Plate and H.C.J.Ottenheijm, Tetrahedron Lett., 1986, 27, 3755; R.Plate, A.W.G. Theunisse, and H.C.J.Ottenheijm, J.Org.Chem., 1987, 52, 370.

147 A.J.Pearson, P.R.Bruhn, and S.Y.Hsu, J.Org.Chem., 1986, 51, 2137.

148 S.R.Wilson and L.A.Jacob, J.Org.Chem., 1986, 51, 4833.

149 R.S.Phillips and L.A.Cohen, J.Amer.Chem.Soc., 1986, 108, 2023.

150 F.M.F.Chen and L.Benoiton, Biochem.Cell Biol., 1986, 64, 182.

151 T.B.Andersen, P.B.Rasmussen, I.Thomsen, S.O.Lawesson, P.Joergensen, and P.Lindhardt, Liebigs Ann.Chem., 1986, 269.

152 T.Nakagawa, Y.Hasegawa, H.Tanaka, M.Chikuma, H.Sakurai, M.Nakayama, Ganryu Aminosan, 1985, 8, 55 (Chem.Abs., 1986, 105, 186085).

153 P.Serapinowski, Synthesis, 1985, 926.

154 K.Ramalingam and R.W.Woodard; Carbohydr.Res., 1985, 142, 123.

155 J.Martens, K.Guenther, and M.Schickedanz, Arch.Pharm.(Weinheim), 1986, 319, 461.

156 S.Natelson, Anal.Biochem., 1986, 156, 31.

157 J.C.Kaner, S.Erickson-Viitanen, H.R.Wolfe, and W.F.DeGrado, J.Biol.Chem., 1986, 261, 10695.

158 Z.S.Arnold, Pol.J.Chem., 1985, 59, 837.

159 J.Wityak, V.A.Palaniswamy, and S.J.Gould, J.Labelled Compd.Radiopharm., 1985, 22, 1155.

160 J.Oehlke, M.Bienert, H.Niedrich, H.J.Zoepfl, and P.Franke, J.Labelled Compd. Radiopharm., 1986, 23, 935.

161 K.Tatsumoto, R.P.Reddy, and A.E.Martell, Can.J.Chem., 1986, 64, 2053.

162 C. J.Easton and N.G.Findlay, J. Labelled Compd.Radiopharm., 1985, 22, 667.

163 J.R.Dormoyand B.Castro, Synthesis, 1986, 81.

164 Z.Dokuzovic, N.K.Roberts, J.F.Sawyer, J.Whelan, and B.Bosnich, J.Amer.Chem.Soc., 1986, 108, 2034.

165 E.Santaniello, R.Casata, and A.Manzocchi, J.C.S.Perkin II, 1985, 2389.

166 T.E.Walker, C.Metheny, C.B.Storm, and H.Hayden, J.Org.Chem., 1986, 51, 1175.

167 H.Parnes and E.J.Shelton, Int J.Pept.Protein Res., 1986, 27, 289.

168 D. You and G.Fan, Hejishu, 1985, 28.

169 R.Cao, G.Fan, and Y.Zhang, Hejishu, 1985, 55 (Chem.Abs., 1986, 105, 209356).

170 C. Ducrocq, A.Righini-Tapic, R.Azerad, J.F.Green, P.A.Friedman, J.P.Beaucourt, and B.Rousseau, J.C.S.Perkin I, 1986, 1323.

171 R.L.Baxter and E.M.Abbot, J.Labelled Compd.Radiopharm., 1985, 22, 1211.

172 K.H.Rohm and R.L. Van Etten, J.Labelled Compd.Radiopharm., 1985, 22, 901.

173 S.S.Yuan and A.M.Ajami, J.Labelled Compd.Radiopharm., 1985, 22, 1309.

174 N.D.Ledford, P.C.Gibbs, H.B.Wood, and M.Barfield, Org.Prep.Proced.Int., 1986, 18, 263.

175 J.M.Bolster, W.Vaalburg, P.H.Elsinga, M.G.Woldring, and H.Wynburg, Appl.Radiat. Isot., 1986, 37, 985.

176 K.Ishiwata, T.Ido, H.Sato, R.Iwata, K.Kawashima, K.Yanai, S.Watanuki, H.Ohtomo, and K.Kogure, Eur.J.Nucl.Med., 1986, 11, 449 (Chem.Abs., 1986, 105, 93710).

177 M.R.Kilbourn, Int.J.Nucl.Med.Biol., 1985, 12, 345.

178 K.Horsley, I.Havasy, E.Rybosova, K.Kosta, and P.Javorsky, Folia Vet., 1986, 29, 9 (Chem.Abs., 1987, 106, 63769).

179 G.Firnau, E.S.Garnett, R.Chirakal, S.Sood, C.Nahmias, and G.Schrobilgen, Appl. Radiat.Isot., 1986, 37, 669.

180 M.Diksic and S.Farrokhzad, J.Nucl.Med., 1985, 26, 1314.

181 M.J.Adam, J.R.Grierson, R.J.Thomas, and S.Jivan, Appl.Radiat.Isot., 1986, 37, 877.

182 R.Chirakal, G.Firnau, and E.S.Garnett, J.Nucl.Med., 1986, 27, 417.

183 M.Argentini and R.Weinreich, Radioakt.Isot.Klin.Forsch., 1986, 17, 39.

184 H.H.Coenen, W.Bodsch, K.Takahashi, A.Hossmann, and G.Stoecklin, Nuklearmedizin, Suppl.(Stuttgart), 1986, 22, 600.

185 K.Ogawa, J.Saito, K.Taki, and T.Nozaki, Kitasato Arch.Exp.Med., 1985, 58, 37.

186 T.Shiraiwa, Y.Sado, K.Sakaguchi, A.Ikawa, and H.Kurokawa, Nippon Kagaku Kaishi, 1985, 1734.

187 M.Yamada and K.Okawa, Bull.Chem.Soc.Jpn., 1985, 58, 2889.

188 J.Viret, H.Patzelt, and A.Collet, Tetrahedron Lett., 1986, 27, 5865.

189 B.K.Vriedema, W. ten Hoeve, H.Wynburg, R.M.Kellogg, W.H.J.Boesten, E.M.Meijer, and H.E.Schoemaker, Tetrahedron Lett., 1986, 27, 2045.

190 Y.Nagao, T.Kumagai, S.Yamada, E.Fujita, Y.Inoue, Y.Nagase, S.Aoyagi, and T.Abe, J.C.S.Perkin I, 1985, 2361.

191 T.Shiraiwa, H.Miyazaki, S.Konishi, and H.Kurokawa, Nippon Kagaku Kaishi, 1985, 1577 (Chem.Abs., 1986, 105, 24592).

192 H.Miyazaki, T.Shiraiwa, and H.Kurokawa, Nippon Kagaku Kaishi, 1986, 87.

193 T.Fukuhara, M.Itoh, M.Isoyama, A.Shimada, and S.Yuasa, J.Chromatogr., 1986, 354, 325.

194 W.H.Pirkle and T.C.Pochapsky, J.Amer.Chem.Soc., 1986, 108, 352.

195 W.H.Pirkle, T.C.Pochapsky, G.S.Mahler, and R.E.Field, J.Chromatogr., 1985, 348, 89.

196 W.H.Pirkle and T.C.Pochapsky, J.Amer.Chem.Soc., 1986, 108, 5627.

197 S.Allenmark, B.Borngren, and H.Bosen, Enzyme Microb.Technol., 1986, 8, 404.

198 B.Sellergren, B.Ekberg, and K.Mosbach, J.Chromatogr., 1985, 347, 1.

199 Y.Osada, F.Ohta, A.Mizumoto, M.Takase, and Y.Kurimura, Nippon Kagaku Kaishi, 1986, 866 (Chem.Abs., 1986, 105, 173416); 873 (Chem.Abs., 1986, 105, 173417).

200 T.Yamaguchi, K.Nishimura, T.Shinbo, and M.Sugiura, Chem.Lett., 1985, 1549.

201 E.Gassmann, J.E.Kuo, and R.N.Zare, Science, 1985, 290, 813.

202 R.Sheardy, L.Liotta, E.Steinhart, R.Champion, J.Rinker, M.Planutis, J.Salinkas, T.Boyer, and D.Carcanague, J.Chem.Educ., 1986, 63, 646.

203 J.W.Keller and B.J.Hamilton, Tetrahedron Lett.,1986, 27, 1249.

204 J.Plachy, Chim.Prum., 1986, 36, 597.

205 E.Conte, G.Fanfani, M.Pieralice, R.Amerotti, and A.D'Addabbo, Origins Life, Evol. Biosphere, 1986, 17, 51.

206 G.E.Tranter, Mol.Phys., 1985, 56, 825; J.Theor.Biol., 1986, 119, 467.

207 L.Keszthelyi, Fiz.Sz., 1986, 36, 73.

208 G.Gilat, Chem.Phys.Lett., 1985, 121, 9.

209 G.Gilat and L.S.Schulman, Chem.Phys.Lett., 1985, 121, 13.

210 M.Coll, X.Solans, M.Font-Altaba, and J.A.Subirana, Acta Crystallogr., Sect.C: Cryst. Struct.Commun., 1986, C42, 599.

211 B.Khawas, J.Appl.Crystallogr., 1986, 19, 410.

212 P.Toffoli, N.Rodier, and J.Astoin, Bull.Soc.Chim.Fr., 1986, 119.

213 C.G.Suresh, J.Ramaswamy, and M.Vijayan, Acta Crystallogr., Sect.B: Struct.Sci., 1986, B42, 473.

214 K.S.McCully, E.R.Boyko, and G.B.Carpenter, Chem.-Biol.Interact., 1985, 56, 121.

215 Y.Hiyama, J.V.Silverton, D.A.Torchia, J.T.Gerig, and S.J.Hammond, J.Amer.Chem. Soc., 1986, 108, 2715.

216 G.Valle, G.M.Bonora, C.Toniolo, P.M.Hardy, M.T.Leplawy, and A.Redlinski, J.C.S. Perkin II, 1986, 885.

217 G.Valle, C.Toniolo, and G.Jung, Liebigs Ann.Chem., 1986, 1809.

218 V.N.Balaji, M.J.Rao, S.N.Rao, S.W.Dietrich, and V.Sasisekharan, Biochim.Biophys. Res.Commun., 1986, 140, 895.

219 Z.Urbanczyk-Lipkowska, J.W.Krajewski, P.Gluzinski, A.W.Lipkowski, and G.Argau, J.Mol.Struct., 1986, 140, 151.

220 V.Kh.Kravtsov, V.N.Biyushkin, T.I.Malinovskii, I.M.Bukrina, V.P.Krasnov, and I.V. Alekseeva, Doklady Akad.Nauk S.S.S.R., 1986, 288, 884.

221 V.Busetti, D.Ajo, and A.Vittadini, Acta Crystallogr., Sect.C: Cryst.Struct.Commun., 1986, C42, 1178.

222 A.Aubry, G.Boussard, and M.Marraud, Angew.Chem., 1986, 98, 443.

223 J.C.Lacey, L.M.Hau, D.W.Mullins, and C.L.Watkins, Origins Life, Evol.Biosphere, 1985, 16, 151; J.C.Lacey, D.W.Mullins, and C.L.Watkins, J.Biomol.Struct.Dyn., 1986, 3, 783.

224 A.Dobashi, N.Saito, Y.Motoyama, and S.Hara, J.Amer.Chem.Soc., 1986, 108, 307.

225 W.E.Hull, K.Seeholzer, M.Baumeister, and I.Ugi, Tetrahedron, 1986, 42, 547.

226 B.L.Feringa, B.Strijtveen, and R.M.Kellogg, J.Org.Chem., 1986, 51, 5484.

227 Y.Van Haverbeke, R.N.Muller, and L.Vander Elst, Magn.Reson.Chem., 1986, 24, 284.

228 S.K.Sarkar, P.E.Young, and D.A.Torchia, J.Amer.Chem.Soc., 1986, 108, 6459.

229 M.H.Frey and S.J.Opella, J.Magn.Reson., 1986, 66, 144.

230 E.M.Menger, S.Vega, and R.G.Griffin, J.Amer.Chem.Soc., 1986, 108, 2215.

231 L.E.Diaz, F.Morin, C.L.Mayne, D.M.Grant, and C.J.Chang, Magn.Reson.Chem., 1986, 24, 167.

232 A.Spisni, E.D.Gotsis, and D.Fiat, Biochim.Biophys.Res.Commun., 1986, 135, 363.

233 H.Eckert and D.Fiat, Int.J.Pept.Protein Res., 1986, 27, 613.

234 M.Kawai, T.Matsuura, Y.Butsugan, S.Egusa, M.Sisido, and Y.Imanishi, Bull.Chem.Soc. Jpn., 1985, 58, 3047.

235 A.G.A.Rao, Int.J.Pept.Protein Res., 1986, 27, 380.

236 T.Dai, J.Zhang, W.Zhou, and Z.Xia, Hejishu, 1985, 24 (Chem.Abs., 1986, 105, 209537).

237 S.Hua, Y.Chen, L.Jiang, and S.Xue, Org.Mass Spectrom., 1986, 21, 7.

238 T.D.Williams, L.Vachon, and R.J.Anderegg, Anal.Biochem., 1986, 153, 372.

239 D.S.Millington, D.A.Maltby, and C.R.Roe, Clin.Chim.Acta, 1986, 155, 173.

240 A.Liquori, G.Sindona, and N.Uccella, J.Amer.Chem.Soc., 1986, 108, 7488.

241 K.Eckart and H.Schwarz, Biomed.Environ.Mass Spectrom., 1986, 13, 641.

242 G.Bojesen, J.C.S.Chem.Commun., 1986, 244.

243 M.S.Iqbal, M.A.Shad, R.H.Tariq, M.Arif, and M.I.Akhtar, J.Pure Applied Sci., 1985, 4, 13.

244 A.S.Rudolph and J.H.Crowe, Biophys.J., 1986, 50, 423.

245 T.R.Rizzo, Y.D.Park, L.Peteanu, and D.H.Levy, J.Chem.Phys., 1985, 83, 4819.

246 J.S.Suh and M.Moskovits, J.Amer.Chem.Soc., 1986, 108, 4711; I.R.Nabiev and G.D. Chumanov, Biofizika, 1986, 31, 183.

247 D.S.Caswell and T.G.Spiro, Biochim.Biophys.Acta, 1986, 873, 73.

248 S.A.Asher, M.Ludwig, and L.R.Johnson, J.Amer.Chem.Soc., 1986, 108, 3186.

249 D.S.Caswell and T.G.Spiro, J.Amer.Chem.Soc., 1986, 108, 6470.

250 H.E.Howard-Lock, C.J.L.Lock, M.L.Martins, P.S.Smalley, and R.A.Bell, Can.J.Chem., 1986, 64, 1215.

251 T.Kijima and S.Ueno, J.C.S.Dalton Trans. 1986, 61.

252 S.Takahashi, E.Suzuki, and N.Nagashima, Bull.Chem.Soc.Jpn. 1986, 59, 1129.

253 F.H.Kuan, Y.Inoue, Y.Miyata, and R.Chujo, Carbohydr.Res., 1985, 142, 329.

254 N.J.Tarbell, M.Rosenblatt, D.A.Amato, and S.Hellman, Radiother.Oncol., 1986, 7, 77.

255 G.L.Floersheim and P.Floersheim, Br.J.Radiol., 1986, 59, 597.

256 C.O.Mills, G.H.Martin, and E.Elias, Biochim.Biophys.Acta, 1986, 876, 677.

257 A.S.Rudolph, J.H.Crowe, and L.M.Crowe, Arch.Biochem.Biophys., 1986, 245, 134.

258 K.Yoshikawa, T.Omachi, Y.Matsubara, and H.Kourai, Biophys.Chem., 1986, 24, 111.

259 K.Alonso, Biochim.Biophys.Acta, 1986, 860, 484.

260 G.M.Blackburn, T.H.Lilley, and P.J.Milburn, J.Solution Chem., 1986, 15, 99.

261 S.Damodaran and K.B.Song, J.Biol.Chem., 1986, 261, 7220.

262 J.L.Fauchere and V.Pliska, Trends Biochem.Sci.,(Pers.Ed.), 1986, 11, 70.

263 R.Wolfenden, Trends Biochem.Sci., (Pers.Ed.), 1986, 11, 70.

264 S.Singh, D.Gupta, H.L.Yadava, P.C.Yadava, R.K.P.Singh, and K.L.Yadava, Z.Phys.Chem.(Leipzig), 1986, 267, 1008; S.Singh, D.Gupta, A.K.Singh, B.N.Tiwan, Y.Kumar, and K.L.Yadava, Bull.Soc.Chim.Fr., 1986, 218.

265 T.Hirokawa, T.Gojo, and Y.Kiso, J.Chromatogr., 1986, 369, 59.

266 R.Benhallan, E.Collange, and M.R.Paris, Bull.Soc.Chim.Fr., 1985, 1159.

267 J.L.Campos, J.Portugal, J.A.Subirama, and R.Mayer, J.Mol.Biol., 1986, 187, 441.

268 R.S.Saxena and A.Gupta, J.Chem.Soc.Pak., 1986, 8, 359.

269 R.S.Saxena, S.K.Dhawan, and A.Gupta, J.Chem.Soc.Pak, 1986, 8, 391.

270 A.M.Sapse and D.C.Jain, Int.J.Quantum Chem., 1986, 29, 23.

271 K.B.Lipkowitz, D.L.Malik, and T.Darden, Tetrahedron Lett., 1986, 27, 1759.

272 N.Sukumar and G.A.Segal, J.Amer.Chem.Soc., 1986, 108, 6880.

273 R.Baum and G.G.Smith, J.Amer.Chem.Soc., 1986, 108, 7325.

274 Yu.N.Belokon, V.I.Tararov, T.F.Saveleva, and V.M.Belikov, Makromol.Chem., 1986, 187, 1077.

275 S.A.Ahmed, N.Esaki, H.Tanaka, and K.Soda, Biochemistry, 1986, 25, 385.

276 M.H.Engel and S.A.Macko, Nature (London), 1986, 323, 531.

277 P.Ennis, E.A.Noltmann, P.E.Hare, P.J.Slota, L.A.Payen, C.A.Prior, and R.E.Taylor, Radiocarbon, 1986, 28, 539.

278 N.Fujii, I.Tamanpo H.Joshima, M.Kashima, and K.Harada, J.Radiat.Res., 1986, 27, 103.

279 C.Bartolini, C.Bosi, G.Belluomini, and L.Delitala, Boll.Soc.Geol.Ital., 1984, 103, 485 (Chem.Abs., 1986, 105, 171363).

280 J.L.Bada, M.Zhao, S.Steinberg, and E.Ruth, Nature (London), 1986, 319, 314.

281 R.Tressl, K.G.Gruenewald, E.Kersten, and D.Rewicki, J.Agric.Food Chem., 1986, 34, 347.

282 F.Hayase, J.B.Kim, and M.Hato, Agric.Biol.Chem., 1985, 49, 2337.

283 O.Pachmayr, F.Ledl, and T.Severin, Z.Lebensm.-Unters.Forsch., 1986, 182, 294.

284 V.Nair, R.J.Offerman, and G.A.Turner, J.Amer.Chem.Soc., 1986, 108, 8283.

285 A.Skalli, M.Pugniere, M.A.Coletti-Previero, J.Torreilles, and A.Previero, Int.J.Pept. Protein Res., 1986, 28, 1.

286 H.Nakamura, K.Takagi, Z.Tamura, R.Yoda, and Y.Yamamoto, Nippon Kagaku Kaishi, 1986, 1017 (Chem.Abs., 1986, 105, 164191).

287 M.Tsuhako, A.Nakajima, T.Miyajima, S.Ohashi, H.Nariai, and I.Motooka, Bull.Chem. Soc.Jpn., 1985, 58, 3092.

288 M.Kolb and B.Neises, Tetrahedron Lett., 1986, 27, 4437.

289 M.Kolb, J.Barth, and B.Neises, Tetrahedron Lett., 1986, 27, 1579.

290 M.Lissel and A.Gau, Z.Naturforsch., B: Anorg.Chem., Org.Chem., 1986, 418, 367.

291 A.P.Gledhill, C.J.McCall, and M.D.Threadgill, J.Org.Chem., 1986, 51, 3196.

292 M.Hashimoto, Y.Eda, Y.Osanai, T.Iwai, and S.Aoki, Chem.Lett., 1986, 893.

293 T.Uematsu, Y.Akaike, and K.Ishii, Nihon Daigaku Nojuigakubu Gijutsu Kenkyu Hokaku, 1986, 30.

294 R.Grigg, J.F. Malone, T.Mongkolaussavaratana, and S.Thianpatanagul, J.C.S.Chem. Commun, 1986, 421.

295 O.Tsuge, S.Kanemasa, M.Ohe, and S.Takenaka, Chem.Lett., 1986, 973.

296 M.L.Bishnoi, S.C.Negi, and K.K.Banerji, Oxid.Commun., 1986, 9, 95; S.Mittal, V. Sharma, and K.K.Banerji, J.Chem.Res., Synop., 1986, 264; V.S.Rao, B.Sethuram, and T.N.Rao, Oxid.Commun., 1986, 9, 11; P.S.Radhakrishnamurti, B.M.Sasmal, and D.P. Patnaik, Indian J.Chem., Sect.A, 1986, 25A, 69; V.K.Sharma, K.Sharma, A.P.Payasi, and P.S.Tiwari, Z.Phys.Chem., 1986, 267, 821; M.L.Bishnoi and K.K.Banerji, Tetrahedron, 1985, 41, 6047; V.K.Sharma, K.Sharma, and A.P.Payasi, Monatsh.Chem., 1986, 117, 1041; K.C.Gupta and K.K.Gupta, J.Chem.Soc.Pak., 1985, 7, 155; M.K.Reddy and E.V. Sundaram, Indian J.Chem., Sect.A, 1986, 25A, 471.

297 C.D.Moyes, T.W.Moon, and J.S.Ballantyne, J.Exp.Zool., 1986, 237, 119.

298 A.Garcia-Raso, P.M.Deya, and J.M.Saa, J.Org.Chem., 1986, 51, 4205.

299 V.Schurig, U.Leyrer, and D.Wistuba, J.Org.Chem., 1986, 51, 242.

300 S.Henrot, M.Larcheveque, and Y.Petit, Synth.Commun., 1986, 16, 183.

301 Y.L.Chow and J.S.Polo, J.C.S.Perkin II, 1986, 727.

302 K.Tani, E.Tanigawa, Y.Tatsuno, and S.Otsuka, Chem.Lett., 1986, 737.

303 M.Augustin and W.Mueller, J.Prakt.Chem., 1985, 327, 789, 857.

304 S.Kim, J.I.Lee, and K.K.Yi, Bull.Chem.Soc.Jpn., 1985, 58, 3570; S.Kim and H.Chang, Bull.Korean Chem.Soc., 1986, 7, 703.

305 E.Ponnusamy, U.Fotadar, A.Spisni, and D.Fiat, Synthesis, 1986, 48.

306 P.B.W.Ten Kortnaar, B.G.Van Dijk, J.M.Peeters, B.J.Raaben, P.J.H.M.Adams, and G.I.Tesser, Int.J.Pept.Protein Res., 1986, 27, 398.

307 M.Sakaitani, N.Kurokawa, and Y.Ohfune, Tetrahedron Lett., 1986, 27, 3753.

308 F.Guibe, O.Dangles, and G.Balavoine, Tetrahedron Lett., 1986, 27, 2365.

309 W.H.Pirkle and T.C.Pochapsky, J.Org.Chem., 1986, 51, 102.

310 E.G.Sarantonis, E.P.Diamandis, and M.I.Karayannis, Anal.Biochem., 1986, 155, 129.

311 J.Casado, A.Castro, J.R.Leis, M.Mosquera, and M.E.Pena, J.C.S.Perkin II, 1985, 1859.

312 A.Castro, E.Iglesias, J.R.Leis, M.E.Pena, J.Vazquez Tato, and D.L.H.Williams, J.C.S. Perkin II, 1986, 1165.

313 D.L.Hughes, J.J.Bergam, and E.J.J.Grabowski, J.Org.Chem., 1986, 51, 2579.

314 H.N.Rydon and J.E.Willett, in "Peptides: Proceedings of the Fifth European Peptide Symposium", ed. G.T.Young, Pergamon Press, Oxford, 1963, p.23; see also G.C.Barrett, Ibid., p.55.

315 D.W.Mullins and J.C.Lacey, J.Mol.Evol., 1986, 23, 76.

316 R.W.Hay and A.K.Basak, J.C.S.Dalton Trans., 1986, 39.

317 N.Kahana, I.Barness, and G.H.Posner, J.Polmer Sci., Polym.Lett.Ed., 1986, 24, 41.

318 R.Andriananampisoa, B.Boyer, G.Lamaty, and J.P.Roque, J.C.S.Chem.Commun., 1986, 597.

319 R.Ueoka, Y.Matsumoto, T.Yoshino, T.Hirose, R.A.Moss, K.Y.Kim, and S.Swarup, Tetrahedron Lett., 1986, 27, 1183.

320 S.Sasaki, M.Kawasahi, and K.Koga, Chem.Pharm.Bull., 1985, 33, 4247.

321 F.M.F.Chen and N.L.Benoiton, Int.J.Pept.Protein Res., 1986, 27, 221.

322 L.A.Carpino, B.J.Cohen, K.E.Stephens, S.Y.Sadat-Aalee, J.H.Tien, and D.C.Langridge, J.Org.Chem., 1986, 51, 3732.

323 L.Nakonieczna, M.Milewska, T.Kolasa, and A.Chimiak, Synthesis, 1985, 929.

324 G.Cipens, V.A.Slavinskaya, D.Sile, D.Kreile, E.Kh.Korchagova, A.Strautina, L.Kruming and A.Krikis, Latv.P.S.R.Zinat.Akad.Vestis, 1985, 516.

325 K.Soai and A.Ookawa, J.C.S.Chem.Commun., 1986, 412.

326 C.J.Easton and M.P.Hay, J.C.S.Chem.Commun., 1986, 55.

327 S.J.Stegink and J.N.Siedow, Physiol.Plant., 1986, 66, 625.

328 M.C.Pirrung, Biochemistry, 1986, 25, 114.

329 S.Yoshifuji, K.Tanaka, T.Kawai, and Y.Nitta, Chem.Pharm.Bull., 1985, 33, 5515.

330 C.H.Hagedorn and J.M.Phang, Arch.Biochem.Biophys., 1986, 248, 166.

331 G.Wulff and H.Boehnke, Angew.Chem., 1986, 98, 101.

332 T.Moriwake, S.Hamano, D.Miki, S.Saito, and S.Torii, Chem.Lett., 1986, 815.

333 H.Takano and K.Shirai, Nihon Daigaku Nojuigakubu Gijitsu Kenkyu Hokoku, 1986, 37.

334 J.N.Cogburn and J.A.Schiff, Physiol.Veg., 1985, 23, 849.

335 M.Iwata and H.Kuzuhara, Chem.Lett., 1985, 1941.

336 R.P.Mason, J.K.M.Sanders, and M.J.Gidley, Phytochemistry, 1986, 25, 1567.

337 S.A.Macko, M.L.F.Estep, M.H.Engel, and P.E.Hare, Geochim.Cosmochim.Acta, 1986, 50, 2143.

338 G.Michael, Z.Chem., 1985, 25, 371.

339 S.E.Ramer, R.N.Moore, and J.C.Vederas, Can.J.Chem., 1986, 64, 706.

340 W.A.Slusarchyk, T.Dejneka, J.Goufoutas, W.H.Koster, D.R.Kronenthal, M.Malley, M.G.Perri, F.L.Routh, J.E.Sundeen, E.R.Weaver, R.Zahler, J.D.Godfrey, R.H.Mueller, and D.J.Von Langen, Tetrahedron Lett., 1986, 27, 2789.

341 G.Behrens and G.Koltzenburg, Z.Naturforsch., C: Biosci., 1985, 40C, 785.

342 W.D.Lehmann and H.C.Heinrich, Arch.Biochem.Biophys., 1986, 250, 180.

343 K.Barlos, M.Lampropoulou, V.Marmatas, D.Papaioannou, and S.Patrianakou, Liebigs Ann. Chem., 1986, 1407.

344 B.Pispisa and A.Palleschi, Macromolecules, 1986, 19, 904.

345 G.Saito, A.Okitani, F.Hayase, and H.Kato, Agric.Biol.Chem., 1986, 50, 2315.

346 S.Narasimhan and P.J.Vithayathil, Indian J.Biochem.Biophys., 1986, 23, 215.

347 J.Gartz, Pharmazie, 1985, 40, 811.

348 D.P.Chakraborty, S.Roy, A.K.Chakraborty, and K.Rakshit, I.R.C.S.Med.Sci., 1986, 14, 940 (Chem.Abs., 1987, 106, 14783).

349 A.N.Lane, Eur.J.Biochem., 1986, 157, 405.

350 J.B.Lloyd, Biochem.J., 1986, 237, 271.

351 W.H.Nelson and P.K.Carpenter, J.Phys.Chem., 1985, 83, 2153.

352 R.K.Tokay, B.Norden, J.O.Liljenzin, and A.Andersson, J.Radioanal.Nucl.Chem., 1986, 104, 337.

353 D.J.T.Hill, J.H.O'Donnell, P.J.Pomery, and A.K.Whittaker, Poly.Photochem., 1986, 7, 13.

354 A.S.Ansari, I.A.Khan, and R.Ali, J.Radiat.Res., 1985, 26, 321.

355 T.Ambler, E.J.Land, M.R.Chedekel, K.V.Subbarao, and T.G.Truscott, Biochim.Biophys Acta, 1985, 843, 49.

356 F.Rizzuto, J.D.Spikes, and G.D.Coker, Photochem.Photobiophys., 1986, 10, 149.

357 G.Boguta and A.Dancewicz, Nukleonika, 1985, 30, 47.

358 W.R.Laws, J.B.A.Ross, H.R.Wyssbrod, J.M.Beechem, L.Brand, and J.Sutherland, Biochemistry, 1986, 25, 599.

359 J.Butler, E.J.Land, W.A.Pruetz, and A.J.Swallow, J.C.S.Chem.Commun., 1986, 348.

360 S.V.Jovanovic and M.G.Simic, J.Free Radicals Biol.Med., 1985, 1, 125.

361 R.Langlois, H.Ali, N.Brasseur, J.R.Wagner, and J.E.Van Lier, Photochem.Photobiol., 1986, 44, 117.

362 M.Nakagawa, Y.Yokoyama, S.Kato, and T.Hino, Tetrahedron, 1985, 41, 2125.

363 M.Sako, K.Shimada, K.Hirota, and Y.Maki, Tetrahedron Lett., 1986, 27, 3877.

364 H.J.Polland, M.A.Franz, W.Zinth, W.Kaiser, and D.Oesterhelt, Biochim.Biophys.Acta, 1986, 851, 407.

365 R.F.Borkman, L.B.Hibbard, and J.Dillon, Photochem.Photobiol., 1986, 43, 13.

366 K.Stulik, V.Pacakova, M.Weingart, and V.Vlasakova, J.Chromatogr., 1986, 354, 449.

367 M.Hoebecke, E.Gandin, and Y.Lion, Photochem.Photobiol., 1986, 44, 543.

368 C.J.Biemann, C.M.Kinoshita, J.A.Marlett, and R.D.Steele, J.Chromatogr., 1986, 357, 330; see also T.P.Mawhinney, R.S.R.Robinett, A.Aralay, and M.A.Madson, J.Chromatogr., 1986, 358, 231.

369 G.Fortier, D.Tenaschuk, and S.L.Mackenzie, J.Chromatogr., 1986, 361, 253.

370 T.Hayashi, Y.Minatogawa, S.Kamada, M.Shimamura, H.Naruse, and Y.Iida, J.Chromatogr., 1986, 380, 239.

371 V.A.Rogozkin, A.I.Krylov, L.N.Meleshchenko, and A.T.Alekseev, Ukr.Biokhim.Zh., 1986, 58, 62.

372 G.Chen, M.Cai, H.Zhuo, and X.Zong, Sepu, 1986, 4, 56 (Chem.Abs., 1985, 104, 221536).

373 G.Gamerith and H.Brantner, J.Chromatogr., 1986, 355, 273.

374 D.Labadarios, I.M.Moodie, and G.S.Shephard, J.Chromatogr., 1986, 382, 237.

375 D.Labadarios, G.S.Shephard, E.Botha, L.Jackson, I.M.Moodie, and J.A.Burger, J.Chromatogr., 1986, 383, 281.

376 I.M.Moodie, G.S.Shephard, and D.Labadarios, J.Chromatogr., 1986, 362, 407.

377 S.L.Mackenzie, J.Chromatogr., 1986, 358, 219.

378 S.L.Mackenzie, D.Tenaschuk, and G.Fortier, J.Chromatogr., 1986, 367, 181.

379 J.M.Yeung, G.B.Baker, and R.T.Coutts, J.Chromatogr., 1986, 378, 293.

380 M.Matsumoto, Y.Inoue, T.Kuhara, K.Nojima, E.Kubota, and I.Matsumoto, Iyo Masu Kenkyukai Koenshu, 1985, 10, 135.

381 H.Faure, C.Boujet, G.Fouillet, J.Marcak, B.Aguillanin, and A.Favier, Spectra 2000, 1986, 111, 44.

382 G.A.Van den Berg, H.Breukelman, H.Elzinga, J.M.F.Trijbels, L.A.H.Monnens, and F.A.J.Muskiet, Clin.Chim.Acta, 1986, 159, 229.

383 H.Kataoka, K.Ohishi, N.Inoue, and M.Makita, Bunseki Kagaku, 1986, 35, 389 (Chem.Abs., 1986, 104, 221534); H.Kataoka, K.Ohishi, and M.Makita, J.Chromatogr., 1986, 354, 482.

384 H.Kataoka, K.Chishi, J.Imai, and M.Makita, Bunseki Kagaku, 1986, 35, 518 (Chem.Abs., 1986, 105, 75203)

385 D.Labadarios, I.M.Moodie, J.Burger, and G.S.Shephard, HRC CC, J.High Resolut.Chromatogr., Chromatogr.Commun., 1986, 9, 555.

386 P.J.M.Van der Oetelaar, L.E.C.Van Beijsterveldt, J.R.C.M.Van Beckhoven, and H.J. Hoenders, J.Chromatogr., 1986, 386, 135.

387 B.Brassat, P.E.Hare, C.Ponnamperuma, and W.Thiemann, J.Chromatogr., 1986, 354, 474.

388 G.Palla, A.Dossena, and R.Marchelli, J.Chromatogr., 1985, 349, 9.

389 A.P.Williams, J.Chromatogr., 1986, 373, 175.

390 E.A.Izatullaev, T.D.Talbaev, T.N.Mamirova, and Zh.K.Urbisinov, Vopr.Piran, 1986, 64 (Chem.Abs., 1986, 104, 221629).

391 G.C.Mills, J.Chromatogr., 1986, 355, 193.

392 C.G.Zarkadas, G.C.Zarkadas, C.N.Karatzas, A.D.Khalili and N.Quang, J.Chromatogr., 1986, 378, 67.

393 T.Ogawa and Y.Kawanishi, J.Chromatogr., 1986, 354, 495.

394 A.Bordons, Biotechnol.Lett., 1986, 8, 411.

395 W.L.Fitch, J.E.Watson, and J.C.King, Anal.Biochem., 1986, 154, 632.

396 E.A.Izatullaev and Zh.K.Urbisinov, Lab.Delo, 1986, 118.

397 C.F.Poole and S.Khatib, in "Quantitative Analysis using Chromatographic Techniques", ed. E.Katz, Wiley, Chichester, 1987, p.193.

398 K.G.Varshney, S.Anwar, and A.A.Khan, Anal.Lett., 1986, 19, 543.

399 T.Cserhati, B.Bordas, and E.Tyihak, J.Chromatogr., 1986, 365, 289.

400 G.Gullner, T.Cserhati, B.Bordas, and M.Szogyi, J.Liq.Chromatogr., 1986, 9, 1919.

401 T.Wolski, W.Golkiewicz, Z.Grodzicki, and G.Bartuzi, Chem.Anal.(Warsaw), 1985, 30, 291.

402 E.Neuzil, A.M.Lacoste, and F.Denois, Biochem.Soc.Trans., 1986, 14, 642.

403 K.Gunther, J.Martens, and M.Schickedanz, Angew.Chem.Int.Ed., 1986, 25, 278.

404 Z.Deyl, J.Hyanek, and M.Horakova, J.Chromatogr., 1986, 379, 177.

405 I.Maurer-Fogy, Oesterr.Chem.Z., 1986, 87, 36.

406 K.Athman and A.Bosserhoff, in "Modern Methods of Protein Chemistry", ed. H.Tschesche, Vol.2, de Gruyter, Berlin, 1985, p.155.

407 W.Jacobs, Curr.Sep., 1986, 7, 39.

408 T.A.Walker and D.J.Pietrzyk, J.Liq.Chromatogr., 1985, 8, 2047.

409 M.C.Roach and M.D.Harmony, Anal.Chem., 1987, 59, 411.

410 D.W.Taylor and T.A.Nieman, J.Chromatogr., 1986, 368, 95.

411 T.Nakagawa, A.Shibukawa, A.Kaihara, T.Itamochi, and H.Tanaka, J.Chromatogr., 1986, 353, 399.

412 P.G.Desideri, L.Lepri, L.Merlini, and L.Checchini, J.Chromatogr., 1986, 370, 75.

413 H.S.Sista, J.Chromatogr., 1986, 359, 231.

414 B.V.R.Sastry, V.E.Janson, M.Horst, and C.C.Stephan, J.Liq.Chromatogr., 1986, 9, 1689.

415 K.S.Park, S.Y.Hong, H.W.Lee, S.Kim, and W.K.Paik, Arch.Pharmacol.Res., 1986, 9, 15.

416 Q.Zhao, H.Lin, W.Zhu, H.Liu, Y.Cai, and S.Ye, Sepu, 1986, 4, 201 (Chem.Abs., 1986, 105, 205639).

417 R.W.Etheridge and M.J.Glimcher, Calcif.Tissue Int., 1986, 39, 239.

418 J.M.Leah, T.Palmer, M.Griffin, C.J.Wingad, A.Briddon, and V.G.Oberholzer, J.Inherited Metab.Dis., 1986, 9, 250.

419 G.Ali Qureshi, A.Gutierrez, and J.Bergstroem, J.Chromatogr., 1986, 374, 363.

420 N.Nimura and T.Kimoshita, J.Chromatogr., 1986, 352, 169.

421 R.Dawson, J.Kalbfleisch, G.Liebezeit, C.A.Llewellyn, R.F.C.Mantoura, F.Moreau, and S.A.Poulet, Oceanis, 1985, 11, 521.

422 H.Garza-Ulloa, R.Garza Cantu, and A.M.Canales Gaja, J.Am.Soc.Brew.Chem., 1986, 44, 27.

423 F.Boudah, K.Abdeddaim and M.Guermouche, Dev.Food Sci., 1986, 12, 683 (Chem.Abs., 1986, 105, 22952).

424 R.A.Roesel, P.R.Blankenship, and F.A.Hommes, Clin.Chim.Acta, 1986, 156, 91.

425 P.E.Minkler, E.A.Erdos, S.T.Ingalls, R.L.Griffin, and A.L.Hoppel, J.Chromatogr., 1986, 380, 285.

426 J.P.Dufour, J.Am.Soc.Brew.Chem., 1986, 44, 1.

427 J.Macek, L.Miterova, and M.Adam, J.Chromatogr., 1986, 364, 253.

428 Z.Harduf, J.Chromatogr., 1986, 363, 261, 428.

429 K.L.Stone and K.R.Williams, J.Chromatogr., 1986, 359, 203.

430 D.Lanneluc- Sanson, C.T.Phan, and R.L.Granger, Anal.Biochem., 1986, 155, 322.

431 L.E.Lavi, J.S.Holcenberg, D.E.Cole, and J.Jolivet, J.Chromatogr., 1986, 377, 155.

432 R.F.Ebert, Anal.Biochem., 1986, 154, 431.

433 D.L.Christie, R.M.Hill, K.Isakow, and P.M.Barling, Ana .Biochem., 1986, 154, 92.

434 M.P.Gamcsik, Anal.Biochem., 1986, 154, 317.

435 S.Shoji, M.Ichikawa, T.Yamaoka, T.Funakoshi, and Y.Kubota, J.Chromatogr., 1986, 354, 463.

436 S.A.Cohen, B.A.Bidlingmeyer, and T.L.Tarvin, Nature (London), 1986, 320, 769.

437 V.Semensi and M.Sugumaran, LC-GC, 1986, 4, 1108 (Chem.Abs., 1986, 105, 237767).

438 P.S.L.Janssen, J.W. Van Nispen, P.A.T.A.Melgers, H.W.M.Van der Bogaart, R.L.A.E. Hamelinck, and B.C.Goverdi, Chromatographia, 1986, 22, 345; P.S.L.Janasen, J.W. Van Nispen, P.A.T.A.Melgers, H.W.M.Van der Bogaart, G.W.M.Van Aalst, and B.C.Goverdi, Ibid., p.351.

439 K.Yaegaki, J.Tonzetich, and A.S.K.Ng, J.Chromatogr., 1986, 356, 163.

440 S.B.Thomson and D.J.Tucker, J.Chromatogr., 1986, 382, 247.

441 D.C.Sampson, P.M.Stewart, and J.W.Hammond, Biomed.Chromatogr., 1986, 1, 21.

442 K.Iriyama, M.Yoshiura, and T.Iwamoto, J.Liq.Chromatogr., 1986, 9, 2955.

443 D.J.Edwards, D.Sorisio, S.Knopf, and S.Mujumdar, J.Chromatogr., 1986, 383, 142.

444 A.Lagana, A.Liberti, C.Morgia, and A.M.Tarola, J.Chromatogr., 1986, 378, 85.

445 N.Narasimhachiri, J.Liq.Chromatogr., 1986, 9, 2223.

446 A.Lilova, T.Kleinschmidt, P.Nedkov, and G.Braunitzer, Hoppe Seylers Biol.Chem., 1986, 367, 1055.

447 M.Simmaco, D.Barra, and F.Bossa, J.Chromatogr., 1985, 349, 99.

448 C.Chen amd G.Xi, Sepu, 1985, 2, 276 (Chem.Abs., 1986, 104, 125899).

449 V.K.Sarin, Y.Kim, and J.L.Fox, Anal.Biochem., 1986, 154, 542.

450 J.L.Menth and J.L.Fox, Anal.Biochem., 1986, 154, 478.

451 B.L.Johansson and K.Isaksson, J.Chromatogr., 1986, 356, 383.

452 C.Fonck, S.Frutiger, and G.J.Hughes, J.Chromatogr., 1986, 370, 339.

453 V.Stocchi, L.Cucchiarini, G.Piccoli, and M.Magnani, J.Chromatogr., 1985, 349, 77.

454 N.B.Levina, Kh.G.Muradov, and I.V.Nazimov, Bioorg.Khim., 1986, 12, 165.

455 F.J.Marquez, A.R.Quesada, F.Sanchez-Jiminez, and I.Nunez de Castro, J.Chromatogr 1986, 380, 275.

456 B.G.Belen'kii, V.A.Mostovnikov, S.V.Nechaev, A.F.Lobazov, and I.V.Nazimov, Zh.Prikl.Spektrosk., 1986, 44, 511.

457 R.Garcia, W.R.Hiatt, S.Jasinski, and P.S.Sypherd, Appl.Environ.Microbiol., 1986, 51, 1355.

458 J.Vendrell and F.X.Aviles, J.Chromatogr., 1986, 358, 401.

459 W.C.Sessa, R.L.Rodgers, and O.Chichester, J.Chromatogr., 1986, 382, 258.

460 H.Hughes, L.Hagen, and R.A.L.Sutton, Clin.Chem.(Winston-Salem), 1986, 32, 1002.

461 T.Toyooka, H.Miyano, and K.Imai, Biomed.Chromatogr., 1986, 1, 15.

462 S.Konosu, A.Shinagawa, and K.Yamaguchi, Nippon Suisan Gakkaishi, 1986, 52, 869.

463 S.Einarsson, S.Folestad, B.Josefsson, and S.Lagerkvist, Anal.Chem., 1986, 58, 1638.

464 U.Hellmann, J.Luederwald, and M.Neuhäuse Fresenius Z.Anal.Chem., 1986, 325, 290.

465 J.Wagner, Y.Hirth, N.Clavecie, and C.Danzin, Anal.Biochem., 1986, 154, 604.

466 S.Ishimitsu, S.Fujimoto, and A.Ohara, J.Chromatogr., 1986, 378, 222.

467 E.Rocchi, F.Farina, M.Silingardi, G.Casalgrandi, E.Gaetani, and C.F.Laurer, J.Chromatogr., 1986, 380, 128.

468 V.P.Kumarev, R.L.Mitina, and T.M.Morozova, Bioorg.Khim., 1986, 12, 54.

469 T.Masuda, T.Gomi, and M.Fujioka, Ganryu Aminosan, 1985, 8, 21 (Chem.Abs., 1986, 105, 186919).

470 H.Gourdeau, R.Lavoie, J.H.Grose, and L.Belanger, Anal.Biochem., 1986, 158, 64.

471 O.W.Griffith, E.B.Campbell, W.H.Pirkle, A.Tsipouras, and M.H.Hyun, J.Chromatogr., 1986, 362, 345.

472 H.Berndt and G.Krueger, J.Chromatogr., 1985, 348, 275.

473 R.Daeppen, V.R.Meyer, and H.Arm, J.Chromatogr., 1986, 361, 93.

474 B.Bomgren and S.Allenmark, J.Liq.Chromatogr., 1986, 9, 667.

475 H.Engelhardt, T.Koenig, and S.Kromidas, Chromatographia, 1986, 21, 205

476 J.W.Keller and K.O.Dick, J.Chromatogr., 1986, 367, 187.

477 S.H.Lee, T.S.O, and K.S.Park, Taehan Hwahakhoe Chi, 1986, 30, 216.

478 S.Lam, J.Chromatogr., 1986, 355, 157.

479 A.Dobashi and S.Hara, J.Chromatogr., 1985, 349, 143.

480 T.Kolasa and M.J.Miller, J.Org.Chem., 1986, 51, 3055.

481 B.H.Reitsma and E.S.Yeung, J.Chromatogr., 1986, 362, 353.

482 W.A.Jacobs, M.W.Leburg, and E.J.Madaj, Anal.Biochem., 1986, 156, 334.

483 X.Luo, Z.Yu, and X.Wang, Shengwu Huaxue Yuo, Shengwu Wuli Jinzhan, 1986, 58 (Chem.Abs., 1986, 105, 75224).

484 R.G.Carlson, K.Srinivasachan, R.S.Givens, and B.K.Matuszewski, J.Org.Chem., 1986, 51, 3978.

485 A.Jankowski and P.Dobryzycki, Photochem.Photobiol., 1986, 44, 159.

486 H.Nakamura, Yahugaku Kenkyu no Shinpo, 1986, 2, 43 (Chem.Abs., 1987, 106, 63720).

487 A.R.Hayman and D.O.Gray, J.Chromatogr., 1986, 370, 194.

488 A.Bianchi-Bosisio, P.G.Prighetti, N.B.Egen, and M.Bier, Electrophoresis, 1986, 7, 128.

489 T.Iida, N.Iijima, M.Hisatomi, and T.Mitamura, Denki Kagaku, oyobi Kogyo Butsuri Kagaku, 1986, 54, 290 (Chem.Abs., 1986, 105, 93729).

490 V.M.Fosse, J.Kolstad, and F.Fonnum, J.Neurochem., 1986, 47, 340.

491 F.Schubert, D.Kirstein, F.Schneller, R.Appelqvist, L.Gorton, and G.Johansson, Anal. Lett., 1986, 19, 1273.

492 R.Faby, Gartenbauwissenschaft, 1986, 51, 47.

493 B.J.Vincke, M.J.Devleeschouwer, and G.J.Patriarche, J.Pharm.Belg., 1985, 40, 357.

494 J.S.Yang, Han'guk Saenghwa Hakhoechi, 1986, 19, 13 (Chem.Abs., 1986, 105, 73132).

495 J.M.Dicks, W.J.Aston, G.Davis, and A.P.F.Turner, Anal.Chim.Acta, 1986, 182, 103.

496 G.Cederblad and P.Harper, Clin.Chem. (Winston-Salem), 1986, 32, 2117.

497 J.L.Parra, L.J.Sanchez, and J.J.Garcia Dominguez, Tenside, Surfactants, Deterg., 1986, 23, 36.

498 M.Nieder, W.K.Kip, and S.F.Yang, Plant Physiol., 1986, 81, 156.

499 Y.Nagatani, Y.Muto, H.Sato, and M.Iijima, Yakugaku Zasshi, 1986, 106, 41 (Chem.Abs., 1986, 104, 144952).

500 M.Ohnishi and K.Hiromi, Anal.Sci. 1985, 1, 89.

501 P.K.Macnicol, Anal.Biochem., 1986, 158, 93.