International Review of Science

Amino Acids Peptides and Related Compounds

Organic Chemistry
Series Two
Volume 6

Consultant Editor
D H Hey FRS
Volume Editor
H N Rydon

Butterworths

International Review of Science

Organic Chemistry
Series Two

Volume 6

Amino Acids, Peptides and Related Compounds

Edited by **H. N. Rydon**
University of Exeter

BUTTERWORTHS
LONDON - BOSTON
Sydney - Wellington - Durban - Toronto

THE BUTTERWORTH GROUP

ENGLAND
Butterworth & Co (Publishers) Ltd
London: 88 Kingsway, WC2B 6AB

AUSTRALIA
Butterworths Pty Ltd
Sydney: 586 Pacific Highway, NSW 2067
Also at Melbourne, Brisbane, Adelaide and Perth

CANADA
Butterworth & Co (Canada) Ltd
Toronto: 2265 Midland Avenue, Scarborough, Ontario M1P 4S1

NEW ZEALAND
Butterworths of New Zealand Ltd
Wellington: 26–28 Waring Taylor Street, 1

SOUTH AFRICA
Butterworth & Co (South Africa) (Pty) Ltd
Durban: 152–154 Gale Street

USA
Butterworths (Publishers) Inc
Reading: 161 Ash Street, Boston, Mass., 01867

Library of Congress Cataloging in Publication Data
Main entry under title:
Amino acids, peptides, and related compounds.
(Organic chemistry, series two; v. 6) (International review of science)
Includes index.
1. Amino acids. 2. Peptides. I. Rydon, H. N. II. Series. III. Series: International review of science.
QD245.073 vol. 6 [QD431] 547′.008s [547′.75]
ISBN 0 408 70618 X 75–19374

First Published 1976 and

Typeset, printed and bound in Great Britain by
REDWOOD BURN LIMITED
Trowbridge & Esher

International Review of Science

Organic Chemistry
Series Two

Consultant Editor
D. H. Hey, F.R.S.

Publisher's Note

The International Review of Science is an important venture in scientific publishing presented by Butterworths. The basic concept of the Review is to provide regular authoritative reviews of entire disciplines. Chemistry was taken first as the problems of literature survey are probably more acute in this subject than in any other. Biochemistry and Physiology followed naturally. As a matter of policy, the authorship of the Review of Science is international and distinguished, the subject coverage is extensive, systematic and critical.

The Review has been conceived within a carefully organised editorial framework. The overall plan was drawn up and the volume editors appointed by seven consultant editors. In turn, each volume editor planned the coverage of his field and appointed authors to write on subjects which were within the area of their own research experience. No geographical restriction was imposed. Hence the 500 or so contributions to the Review of Science come from many countries of the world and provide an authoritative account of progress.

The publication of Organic Chemistry Series One was completed in 1973 with ten text volumes and one index volume; in accordance with the stated policy of issuing regular reviews to keep the series up to date, volumes of Series Two will be published between the middle of 1975 and early 1976; Series Two of Physical Chemistry will be published at the same time, while Inorganic Chemistry Series Two was published during the first half of 1975. Volume titles are the same as in Series One but the articles themselves either cover recent advances in the same subject or deal with a different aspect of the main theme of the volume. In Series Two an index is incorporated in each volume and there is no separate index volume.

Butterworth & Co. (Publishers) Ltd.

ORGANIC CHEMISTRY SERIES TWO

Consultant Editor
D. H. Hey, F.R.S., *formerly of the Department of Chemistry, King's College, University of London*

Volume titles and Editors

1 **STRUCTURE DETERMINATION IN ORGANIC CHEMISTRY**
Professor L. M. Jackman, *Pennsylvania State University*

2 **ALIPHATIC COMPOUNDS**
Professor N. B. Chapman, *University of Hull*

3 **AROMATIC COMPOUNDS**
Professor H. Zollinger, *Eidgenössische Technische Hochschule, Zürich*

4 **HETEROCYCLIC COMPOUNDS**
Professor K. Schofield, *University of Exeter*

5 **ALICYCLIC COMPOUNDS**
Professor D. Ginsburg, *Technion-Israel Institute of Technology, Haifa*

6 **AMINO ACIDS, PEPTIDES AND RELATED COMPOUNDS**
Professor H. N. Rydon, *University of Exeter*

7 **CARBOHYDRATES**
Professor G. O. Aspinall, *York University, Ontario*

8 **STEROIDS**
Dr. W. F. Johns, *G. D. Searle & Co., Chicago*

9 **ALKALOIDS**
Professor K. Wiesner, F.R.S., *University of New Brunswick*

10 **FREE RADICAL REACTIONS**
Professor W. A. Waters, F.R.S., *University of Oxford*

INORGANIC CHEMISTRY SERIES TWO

Consultant Editor
H. J. Emeléus, C.B.E., F.R.S. *Department of Chemistry University of Cambridge*

Volume titles and Editors

1 **MAIN GROUP ELEMENTS—HYDROGEN AND GROUPS I–III**
Professor M. F. Lappert, *University of Sussex*

2 **MAIN GROUP ELEMENTS—GROUPS IV AND V**
Dr. D. B. Sowerby, *University of Nottingham*

3 **MAIN GROUP ELEMENTS—GROUPS VI AND VII**
Professor V. Gutmann, *Technical University of Vienna*

4 **ORGANOMETALLIC DERIVATIVES OF THE MAIN GROUP ELEMENTS**
Professor B. J. Aylett, *Westfield College, University of London*

5 **TRANSITION METALS—PART 1**
Professor D. W. A. Sharp, *University of Glasgow*

6 **TRANSITION METALS—PART 2**
Dr. M. J. Mays, *University of Cambridge*

7 **LANTHANIDES AND ACTINIDES**
Professor K. W. Bagnall, *University of Manchester*

8 **RADIOCHEMISTRY**
Dr. A. G. Maddock, *University of Cambridge*

9 **REACTION MECHANISMS IN INORGANIC CHEMISTRY**
Professor M. L. Tobe, *University College, University of London*

10 **SOLID STATE CHEMISTRY**
Dr. L. E. J. Roberts, *Atomic Energy Research Establishment, Harwell*

PHYSICAL CHEMISTRY SERIES TWO

Consultant Editor
A. D. Buckingham, F.R.S., *Department of Chemistry University of Cambridge*

Volume titles and Editors

1 **THEORETICAL CHEMISTRY**
Professor A. D. Buckingham, F.R.S., *University of Cambridge* and Professor C. A. Coulson, F.R.S., *University of Oxford*

2 **MOLECULAR STRUCTURE AND PROPERTIES**
Professor A. D. Buckingham, F.R.S., *University of Cambridge*

3 **SPECTROSCOPY**
Dr. D. A. Ramsay, F.R.S.C., *National Research Council of Canada*

4 **MAGNETIC RESONANCE**
Professor C. A. McDowell, F.R.S.C., *University of British Columbia*

5 **MASS SPECTROMETRY**
Professor A. Maccoll, *University College, University of London*

6 **ELECTROCHEMISTRY**
Professor J. O'M. Bockris, *The Flinders University of S. Australia*

7 **SURFACE CHEMISTRY AND COLLOIDS**
Professor M. Kerker, *Clarkson College of Technology, New York*

8 **MACROMOLECULAR SCIENCE**
Professor C. E. H. Bawn, C.B.E., F.R.S., *formerly of the University of Liverpool*

9 **CHEMICAL KINETICS**
Professor D. R. Herschbach *Harvard University*

10 **THERMOCHEMISTRY AND THERMO-DYNAMICS**
Dr. H. A. Skinner, *University of Manchester*

11 **CHEMICAL CRYSTALLOGRAPHY**
Professor J. M. Robertson, C.B.E., F.R.S., *formerly of the University of Glasgow*

12 **ANALYTICAL CHEMISTRY—PART 1**
Professor T. S. West, *Macaulay Institute for Soil Research, Aberdeen*

13 **ANALYTICAL CHEMISTRY—PART 2**
Professor T. S. West, *Macaulay Institute for Soil Research, Aberdeen*

BIOCHEMISTRY SERIES ONE

Consultant Editors
H. L. Kornberg, F.R.S.
Department of Biochemistry University of Leicester and
D. C. Phillips, F.R.S., *Department of Zoology, University of Oxford*

Volume titles and Editors

1 **CHEMISTRY OF MACRO-MOLECULES**
Professor H. Gutfreund, *University of Bristol*

2 **BIOCHEMISTRY OF CELL WALLS AND MEMBRANES**
Dr. C. F. Fox, *University of California, Los Angeles*

3 **ENERGY TRANSDUCING MECHANISMS**
Professor E. Racker, *Cornell University New York*

4 **BIOCHEMISTRY OF LIPIDS**
Professor T. W. Goodwin, F.R.S., *University of Liverpool*

5 **BIOCHEMISTRY OF CARBO-HYDRATES**
Professor W. J. Whelan, *University of Miami*

6 **BIOCHEMISTRY OF NUCLEIC ACIDS**
Professor K. Burton, F.R.S., *University of Newcastle upon Tyne*

7 **SYNTHESIS OF AMINO ACIDS AND PROTEINS**
Professor H. R. V. Arnstein, *King's College, University of London*

8 **BIOCHEMISTRY OF HORMONES**
Professor H. V. Rickenberg, *National Jewish Hospital & Research Center, Colorado*

9 **BIOCHEMISTRY OF CELL DIFFER-ENTIATION**
Professor J. Paul, *The Beatson Institute for Cancer Research, Glasgow*

10 **DEFENCE AND RECOGNITION**
Professor R. R. Porter, F.R.S., *University of Oxford*

11 **PLANT BIOCHEMISTRY**
Professor D. H. Northcote, F.R.S., *University of Cambridge*

12 **PHYSIOLOGICAL AND PHARMACO-LOGICAL BIOCHEMISTRY**
Dr. H. K. F. Blaschko, F.R.S., *University of Oxford*

PHYSIOLOGY SERIES ONE

Consultant Editors
A. C. Guyton,
Department of Physiology and Biophysics, University of Mississippi Medical Center and
D. F. Horrobin,
Department of Physiology, University of Newcastle upon Tyne

Volume titles and Editors

1 **CARDIOVASCULAR PHYSIOLOGY**
Professor A. C. Guyton and Dr. C. E. Jones, *University of Mississippi Medical Center*

2 **RESPIRATORY PHYSIOLOGY**
Professor J. G. Widdicombe, *St. George's Hospital, London*

3 **NEUROPHYSIOLOGY**
Professor C. C. Hunt, *Washington University School of Medicine, St. Louis*

4 **GASTROINTESTINAL PHYSIOLOGY**
Professor E. D. Jacobson and Dr. L. L. Shanbour, *University of Texas Medical School*

5 **ENDOCRINE PHYSIOLOGY**
Professor S. M. McCann, *University of Texas*

6 **KIDNEY AND URINARY TRACT PHYSIOLOGY**
Professor K. Thurau, *University of Munich*

7 **ENVIRONMENTAL PHYSIOLOGY**
Professor D. Robertshaw, *University of Nairobi*

8 **REPRODUCTIVE PHYSIOLOGY**
Professor R. O. Greep, *Harvard Medical School*

Consultant Editor's Note

The ten volumes in Organic Chemistry in the Second Series of the biennial reviews in the International Review of Science follow logically from those of the First Series. No major omissions have come to light in the overall coverage of the First Series. The titles of the ten volumes therefore remain unchanged but there are three new Volume Editors. The volume on Structure Determination in Organic Chemistry has been taken over by Professor Lloyd M. Jackman of Pennsylvania State University, that on Alicyclic Compounds by Professor D. Ginsburg of Technion-Israel Institute of Technology, and that on Amino Acids, Peptides and Related Compounds by Professor H. N. Rydon of the University of Exeter. The international character of the Series is thus strengthened with four Volume Editors from the United Kingdom, two each from Canada and the U.S.A., and one each from Israel and Switzerland. An even wider pattern is shown for the authors, who now come from some sixteen countries. The reviews in the Second Series are mainly intended to cover work published in the years 1972 and 1973, although relevant results published in 1974 and 1975 are included in some cases, and earlier work is also covered where applicable.

It is my pleasure once again to thank all the Volume Editors for their helpful cooperation in this venture.

London

D. H. Hey

Preface

This volume covers progress in the chemistry of amino-acids, peptides and related compounds* in 1972 and 1973, thus up-dating the Series One volume which dealt with the literature of 1967 to 1971. Some latitude has been allowed, both to provide an adequate background to the work falling within the period covered and to cover those more recent advances whose omission would falsify or distort the picture.

The organisation of this volume differs somewhat from that of its predecessor. Work on amino-acids is dealt with in a single chapter whereas work on linear peptides occupies four, two dealing with structure determination and methods of synthesis, one with the synthesis and structure–activity relationships of important biologically active peptides, and one with studies of conformation. Cyclic peptides occupy two chapters, one devoted to homodetic and the other to heterodetic cyclic peptides. Once again a chapter is devoted to those 'distorted' peptides, the penicillins and cephalosporins. The final chapter is concerned with the biosynthesis of amino-acids, peptides and modified peptides of all kinds, a field in which there is rapid growth. As with the Series One volume, protein and enzyme chemistry have been excluded; these subjects are dealt with in the Biochemistry Series.

I wish to express my thanks to the thirteen authors, all authorities in their field, who have contributed chapters to what I hope will be a useful contribution to a most important field of chemistry.

Exeter H. N. Rydon

* The three-letter abbreviations used for amino-acid residues and substituents are those recommended by the IUPAC–IUB Commission on Biochemical Nomenclature [see (1972). *Biochem. J.*, **126,** 773].

Contents

1 Amino Acids

E. A. BELL and D. I. JOHN
King's College, University of London

1.1 INTRODUCTION

Since the appearance of the first series of the *International Review of Science*, more than forty new amino acids have been isolated from living organisms and their structures determined. The increased use of proton magnetic resonance spectroscopy for the study of these compounds is perhaps the most obvious development in this area. The distribution and biosynthesis of 'known' amino acids continue to be studied and more attention is being given to the biological significance of those amino acids which are not normally found as protein constituents.

For the purposes of this review, those natural amino acids which are widely distributed either as protein constituents (e.g. lysine and serine) or as metabolic intermediates (e.g. ornithine and homoserine) will be referred to as 'usual' amino acids and the remainder (numbering some 300) as 'unusual' amino acids. For a comprehensive review of amino acids which have been unequivocally identified in protein hydrolysates the reader is referred to the excellent article entitled 'The history of the discovery of the amino acids. II' by Vickery[1].

Amongst techniques which have been used for the synthesis of amino acids, traditional methods still predominate. A few novel general procedures which may offer certain advantages over established methods have, however, been reported during the period of review. As has been the case in recent years, asymmetric synthesis continues to be the area of major interest and advancement, but notable achievements have also occurred in the synthesis of labelled compounds, particularly through the development of procedures for prochiral labelling.

In the discussion of syntheses within this chapter, reference will only be made to those methods or compounds which are either interesting or novel.

1.2 RECENTLY DISCOVERED AMINO ACIDS OF NATURAL ORIGIN

The higher plants have continued to prove a rich source of 'unusual' amino acids. The majority of these compounds have been found to occur in the free state or combined as simple derivatives of which the γ-glutamyl derivatives are the most common. In micro-organisms, 'unusual' amino acids occur most frequently as constituents of low molecular weight peptides of the 'antibiotic' type.

The 'unusual' amino acids identified from animal sources are for the most part minor components of protein hydrolysates arising from the modification of one or other of the universally distributed 'protein' amino acids after incorporation of the latter into the protein molecule.

The halogenated aromatic amino acids identified in the proteins of molluscs are perhaps the most surprising find from the animal kingdom.

1.2.1 Neutral aliphatic amino acids

From a New Guinea fungus (tentatively identified as *Boletus* section *Ixacomus* group *nudi*), Rudzats and co-workers[2,3] have isolated 2-amino-4-methylhex-5-enoic acid (1):

$$H_2C{=}CHCH(Me)CH_2CH(NH_2)CO_2H$$
(1)

D-Alanine, previously found in bacterial cell walls[4] and elsewhere, has now been identified as a constituent of higher plants, occurring as the peptide D-alanyl-D-alanine in tobacco leaves[5].

The biosynthesis of β-cyanoalanine (2), which was originally isolated from

$$NCCH_2CH(NH_2)CO_2H$$
(2)

seeds of *Vicia sativa*[6], has now been studied in *Acacia georginae*. It is suggested that β elimination in cysteine, which in the absence of cyanide leads to the formation of pyruvate, in the presence of cyanide leads to the formation of β-cyanoalanine[7].

1.2.2 Hydroxyamino acids

From an antibiotic source, Ohashi and co-workers[8] have isolated β-hydroxyvaline (3) and a novel synthesis has been reported by Berse and Bessette[9].

$$Me_2C(OH)CH(NH_2)CO_2H$$
(3)

Two stereoisomers of (4), viz. (2*S*,4*S*)-(+)-γ-hydroxynorvaline and (2*S*,4*R*)-(−)-γ-hydroxynorvaline, have been isolated from the basidiomycete

$$MeCH(OH)CH_2CH(NH_2)CO_2H$$
(4)

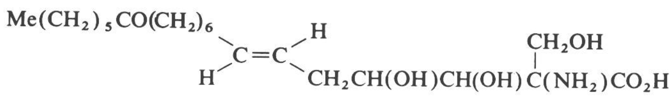
Boletus satanus[10]. A second basidiomycete, *Tricholomopsis rutilans*, has been reported[11] to contain L-2-aminohex-4-ynoic acid (5). The same species has

$$MeC{\equiv}CCH_2CH(NH_2)CO_2H$$
(5)

also been shown[12] to contain both L-*threo* and L-*erythro* forms of 2-amino-3-hydroxyhex-4-ynoic acid (6). An α-hydroxymethyl-α-amino acid with anti-

$$MeC{\equiv}CCH(OH)CH(NH_2)CO_2H$$
(6)

fungal properties tentatively assigned the structure (7) has been isolated from a thermophilic mould[13] and the configuration of the threonine isolated from



(7)

the hydrolysate of a teleomycin-related antibiotic has been established as *threo*[14]. Methods for the separation of the diastereoisomers of threonine and other hydroxyamino acids have been described by Ariyoshi and co-workers[15,16].

From higher plants two new neutral hydroxyamino acids have been characterised, 2-amino-5-methyl-6-hydroxyhex-4-enoic acid (8) from *Blighia unijugata*[17] and (2*S*,3*R*,4*R*)-γ-hydroxyisoleucine (9) from seeds of *Trigonella foenum-graecum*[18].

$$HOCH_2C(Me){=}CHCH_2CH(NH_2)CO_2H$$
(8)

$$MeCH(OH)CH(Me)CH(NH_2)CO_2H$$
(9)

1.2.3 Sulphur-containing amino acids

The isolation of *S*-(2-hydroxy-2-carboxyethanethiomethyl)-L-cysteine (10) from *Acacia georginae*[19] adds to the list of unusual amino acids found in higher plants. Two new substituted homocysteines, *S*-(carboxymethylthio)-homocysteine (11) and *S*-(3-hydroxy-3-carboxypropyl)homocysteine (12), have been found among the compounds excreted by patients suffering from homocystinuria[20].

$$HO_2CCH(OH)CH_2SCH_2SCH_2CH(NH_2)CO_2H$$
(10)

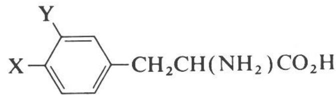
$$RSCH_2CH_2CH(NH_2)CO_2H$$

(11) $R = SCH_2CO_2H$

(12) $R = CH_2CH_2CH(OH)CO_2H$

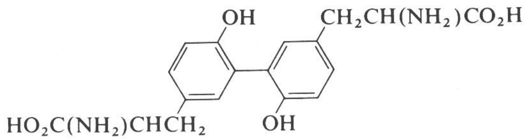
1.2.4 Aromatic and heterocyclic amino acids

New aromatic amino acids which have recently been isolated from higher plants include 3-hydroxymethylphenylalanine (13) and 4-hydroxy-3-hydroxy-methylphenylalanine (14), which have been isolated from the legume *Caesalpinia tinctoria*[21], and L-4-aminophenylalanine (15), which was obtained from another legume, *Vigna vexillata*[22].



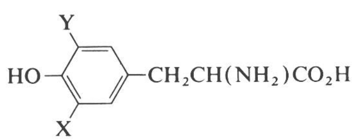
(13) X = H; Y = CH_2OH
(14) X = OH; Y = CH_2OH
(15) X = NH_2; Y = H

'Dityrosine' (16), a compound previously identified chromatographically as a component of alkali soluble connective tissue protein, has now been isolated and its structure confirmed[23].



(16)

The molluscs have been found to synthesise a number of novel halogenated aromatic amino acids; one of these is 3-chlorotyrosine (17), which has been found in hydrolysates of the scleroprotein of *Buccinum undatum* (whelk)[24] and of the cuticle of *Limulus polyphemus* (horseshoe crab)[25]. The same compound has also been found as a component of insect cuticle protein[26]. Both



(17) X = Cl; Y = H
(18) X = Cl; Y = Br
(19) X = Br; Y = H
(20) X = Y = Cl
(21) X = Y = Br

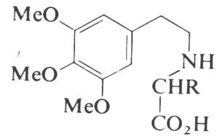
Buccinum undatum[27] and *Limulus polyphemus*[25] also contain 3-chloro-5-bromotyrosine (18), while 3-bromotyrosine (19), 3,5-dichlorotyrosine (20) and 3,5-dibromotyrosine (21) have been found among the hydrolysis products of the *Limulus* scleroprotein[25].

Another halogenated amino acid recently reported[28] is ($\alpha S,5S$)-α-amino-3-chloro-2-isoxazoline-5-acetic acid (22), which has been isolated from the hydrolysate of an antibiotic.

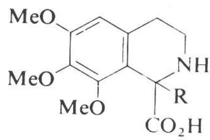
Other recently discovered naturally occurring aromatic amino acids are mescaloxylic acid (23) from the peyote cactus[29] and mescaloruvic acid (24) from the same plant.

Another compound reported from the same laboratory[30] is *O*-methylpeyoxylic acid (25), an amino acid analogue of mescaline, which occurs with the methylated compound (26), corresponding to mescaloruvic acid, in extracts of the peyote cactus.

(22)



(23) R = H
(24) R = Me



(25) R = H
(26) R = Me

1.2.5 Acidic amino acids

From *Gleditsia caspica*, Dardenne *et al.*[31] have isolated (2*S*,3*S*)-3-hydroxy-4-methyleneglutamic acid (28), which was catalytically reduced to give a mixture of (2*S*,4*S*)-4-methylglutamic acid (27) and (2*S*,3*S*,4*S*)-3-hydroxy-4-methylglutamic acid (29), an amino acid which has not been described previously.

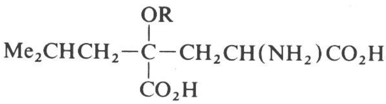
The same species was also found to contain (2*S*,4*R*)-4-methylglutamic acid (27) and (2*S*,3*S*,4*R*)-3-hydroxy-4-methylglutamic acid (29), which has previously been isolated from *Gymnocladus dioicus*[32,33]. In *G. dioicus* the (2*S*,3*S*,4*R*)-3-hydroxy-4-methylglutamic acid is accompanied by a stereoisomer which, on the basis of n.m.r. data, was identified as (2*S*,3*R*,4*R*)-3-hydroxy-4-methylglutamic acid[33]. X-Ray crystallography, however, has led to the conclusion that the correct structure of this isomer is (2*S*,3*R*,4*S*)-3-hydroxy-4-methylglutamic acid[34].

$$HO_2CCH(Me)CH_2CH(NH_2)CO_2H$$
(27)

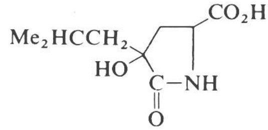
$$HO_2CC(:CH_2)CH(OH)CH(NH_2)CO_2H$$
(28)

$$HO_2CCH(Me)CH(OH)CH(NH_2)CO_2H$$
(29)

Another γ-substituted glutamic acid which has been discovered recently is (2*S*,4*R*)-4-(β-D-galactopyranosyloxy)-4-isobutylglutamic acid (30), the first plant amino acid to be found which contains a sugar moiety attached through an aliphatic hydroxy group. The isolation was made by Larsen and co-workers[35] from the flowers of *Reseda odorata*. On hydrolysis the sugar moiety was removed and a mixture of (2*S*,4*R*)-4-hydroxy-4-isobutylglutamic acid (31) and (3*R*,5*S*)-3-hydroxy-3-isobutyl-2-pyrrolidone-5-carboxylic acid (32) was obtained.

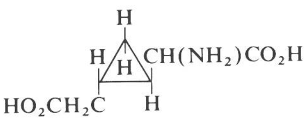


(30) R = Gal
(31) R = H

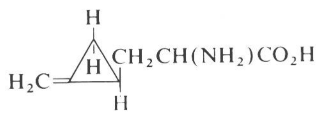


(32)

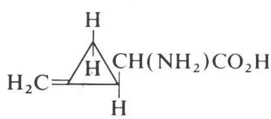
Fowden and co-workers[17] report the occurrence of α-(2-carboxymethylcyclopropyl)glycine (33) in *Blighia unijugata*, an interesting addition to



(33)



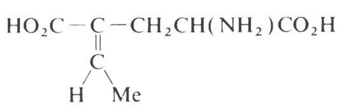
(34)



(35)

hypoglycin (34) and α-(methylenecyclopropyl)glycine (35), which have been found previously in *B. sapida*, another species of the same genus[36,37].

γ-Ethylideneglutamic acid (36) has been isolated from a third plant source



(36)

—the seeds of *Guilandina crista*[38]. The compound was identical in all respects with previous isolates from *Tulipa gesneriana*[39] and *Tetrapleura tetraptera*[40]. The recent development of n.m.r. shift reagents as tools for structural analysis enabled Nulu and Bell[38] to establish unequivocally for the first time that the unsaturated amino acid possesses the *cis* configuration.

In addition to pinnatanine (37), an amide previously isolated from *Staphylea pinnata*[41] and now characterised as N^5-(2-hydroxymethylbutadienyl)-L-*allo*-4-hydroxyglutamine[42], Grove and co-workers have identified a second unusual

(37)