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Acetylenic amino acids

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ABSTRACT. The methods of synthesis, application, and mechanisms of the biological action of α- and γ-amino acids containing an acetylene residue in the molecule that gives rise to the specific ability of these compounds to deactivate irreversibly certain enzymes are reviewed.

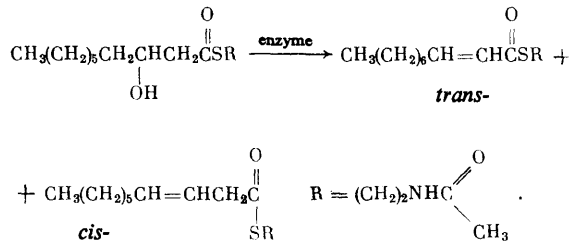
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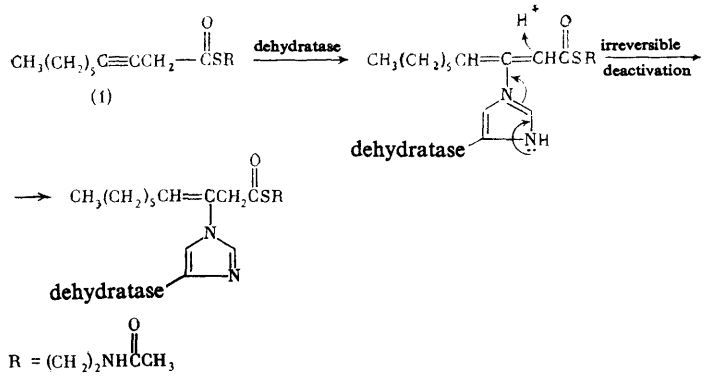
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I. Introduction

The growing interest in unsaturated amino acids is stimulated by their potential biological activity as specific irreversible enzyme inhibitors. A study of the action mechanism of these inhibitors shows that they contain functional groups which when treated with enzymes form new highly reactive groups. The latter immediately interact with nucleophiles in the active sites of the enzymes, as a result of which covalent compounds are formed between inhibitors and enzymes, leading to inhibition of the activity of the latter. Thus, the enzymes catalyse their own deactivation, which is also known as "suicidal" deactivation, while the compounds that cause the suicidal deactivation are called "suicide substrates".[1–5] It is found that compounds that contain carbon–carbon triple bonds act on enzymes that catalyse isomerisation, oxidation, elimination, and transamination. Thus acetylenic ketones inhibit dehydrogenases and aldolases, acetylenic amines inhibit monoamine oxidases bound to flavin, and acetylenic hydroxyacids inhibit lactate dehydrogenases.[4,6] The fundamental chemical principles of the action of acetylenic compounds appear to be mainly derived from the fact that they can be converted enzymically to conjugated allenes. The latter are strong Michael acceptors, whereas the former are not very chemically reactive.[7] A typical example of highly specific deactivation of this type is the irreversible suppression of β-hydroxydecanoyl thioester dehydratase by 3-decynoyl *N*-acetylcysteamine (1). This enzyme plays an important part in the synthesis of unsaturated fatty acids and catalyses the reversible conversion of hydroxydecanoyl thioesters to α,β-*trans*- and β,γ-*cis*-unsaturated compounds:



On treatment with the enzyme, amide (1) isomerises to an allene which reacts with histidine at the active site of the enzyme, causing the irreversible deactivation of the latter.[8]



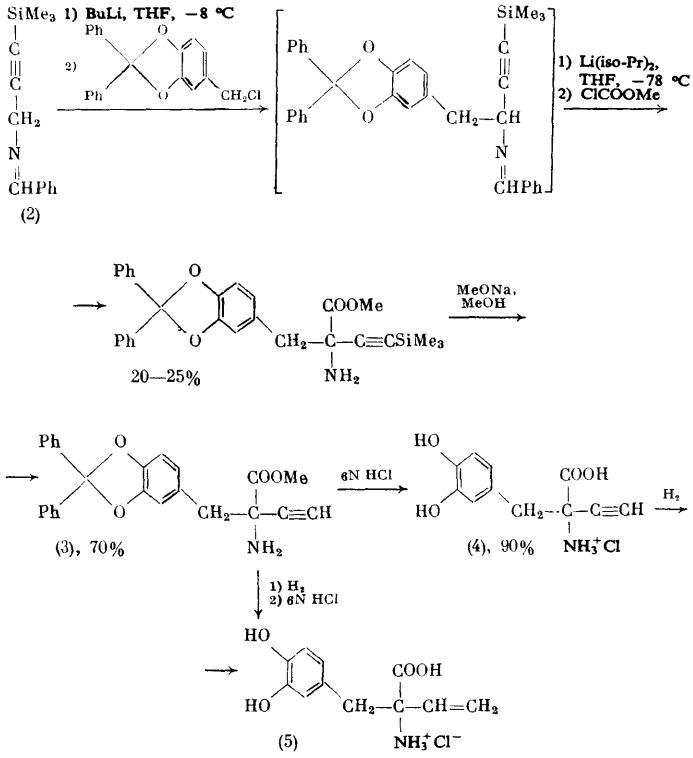
II. α-Amino acids

1. α-Ethynyl-α-amino acids

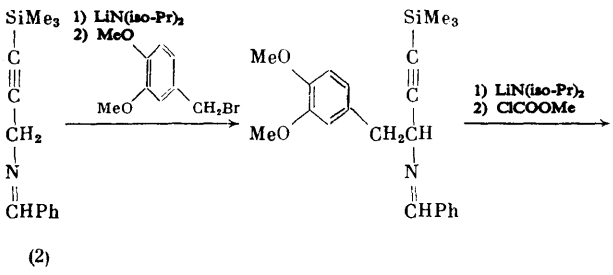
In 1977 α-ethynyl-3,4-dihydroxyphenylalanine (4) and α-vinyl-3,4-dihydroxyphenylalanine (5), which were the first examples of α-substituted α-amino acids with an unsaturated function on the quaternary α-carbon atom, were synthesised.[9] These analogues of dihydroxyphenylalanine (DOPA) proved to be inhibitors of DOPA decarboxylase.

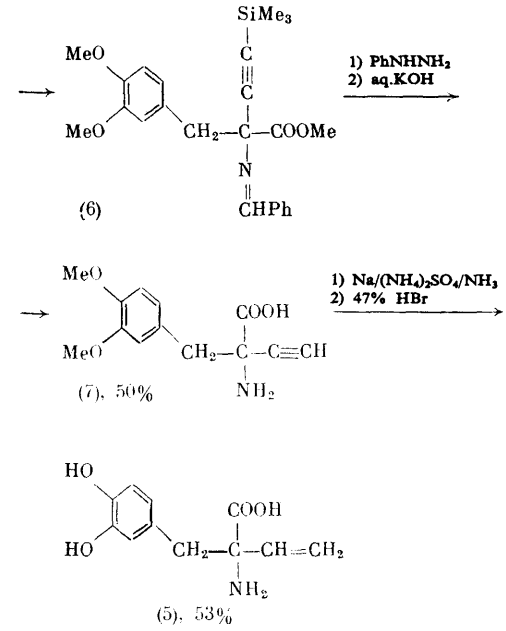
In order to obtain amino acids (4) and (5), Taub and Patchett[9] alternately introduced protected 3,4-dimethoxyphenylmethyl and carboxyl functions into the propargyl synthon (2). A diphenylmethylene group, which is stable during chromatography on silica gel but is readily removed by mild acid treatment, was used to protect the base-sensitive catechol function. After removal of the

protecting groups the acetylenic amino acid (4) was obtained with an overall yield of 13–16% [based on the initial synthon (2)]. On partial hydrogenation of the protected amino ester (3) followed by acid hydrolysis as in the case of (3) → (4) it was possible to obtain the hydrochloride of α-vinyl-α-amino acid (5) with a yield of about 70% [based on amino ester (3)].



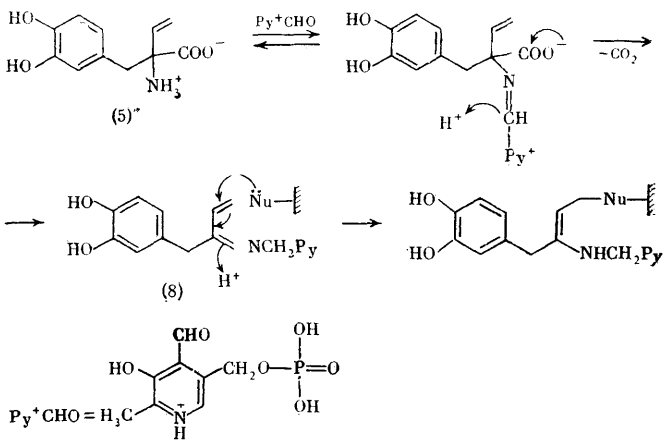
At almost the same time Metcalf and Jung reported[10] their own variant of the synthesis of amino acids (4) and (5), which differed from the above in that the regioselective alkylation of aldimine (2) was carried out with 3,4-dimethoxybenzyl bromide. In order to generate an anion from aldimine (2) use was made of lithium diisopropylamide, which can avoid the dialkylation that occurs to a considerable degree when n-butyllithium is used as the base. The benzyl and trimethylsilyl protecting groups were removed by successive treatment of the imine ester (6) with phenylhydrazine and an aqueous solution of potassium hydroxide. The acetylenic amino acid (7), which was obtained with a 50% overall yield based on 3,4-dimethoxybenzyl bromide, was subsequently reduced with sodamide and treated with 47% hydrobromic acid, and after neutralisation α-vinyl-DOPA (5) was isolated.





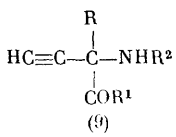
By using 3,4-isopropylidenedioxybenzyl bromide instead of 3,4-dimethoxybenzyl bromide for the regioselective alkylation of aldimine (2), it was possible to obtain the acetylenic amino acid (4) with an overall yield of 24%.

Metcalf and Jung[10] examined the possible mechanism of deactivation of DOPA decarboxylase by β,γ-unsaturated α-amino acids in the case of α-vinyl-DOPA (5). The process is initiated with the formation of a Schiff base between the amino acid and the coenzyme of the decarboxylase—pyridoxal phosphate. After decarboxylation of the Schiff base the vinylimine (8) is formed, which reacts with the nucleophile of the active site of the enzyme to form a strong covalent bond, resulting in irreversible deactivation of the latter. The authors assumed that α-acetylene-DOPA also deactivates the carboxylase by the same mechanism.



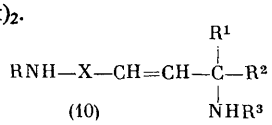
By successive alkylation and acylation of the carbanions obtained from 3-trimethylsilylpropyne-2-ylbenzaldimine (2) with various electrophilic reagents, Metcalf et al.[10–24] obtained a large number of α-ethynyl-α-amino acids and their esters, amides, thioesters, thioamides, lactams, and other derivatives (9),[10–16] (10),[17–19]

and (11),[20–24] which can be used as reagents to combat pathogenic viruses, bacteria, and fungae, as stimulants of the nervous systems, antidepressants, tranquillisers, agents for treating Parkinsonism, rheumatoid arthritis, carcinoid syndromes, bronchospasmatic conditions in asthmatics, manic disorders, and other conditions induced by high levels of 5-hydroxytryptamine and other polyamines that play an important part in cell division and growth, since compounds (9)–(11) are irreversible inhibitors of the decarboxylases that participate in the formation of polyamines from the corresponding amino acids.



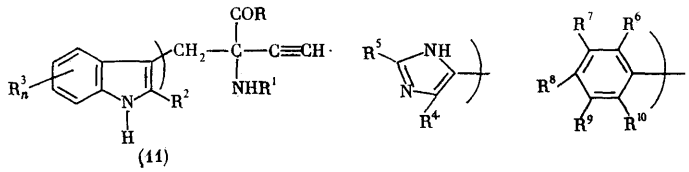
(9)

R = $MeS(CH_2)_2$, $PhCH_2S(CH_2)_2$, (*S*)-(5-desoxyadenosynyl-5)-*S*-methylthionethyl, $H_2NC(=NH)NH(CH_2)_3$, $R^3NH(CH_2)_n$, $n = 3,4$, R^3 = H, Alk, CO_2Alk, $C(O)CH(NH_2)R^4$, R^4 = H, Alk, CH_2Ph; R^2 = H, C(O)Alk, CO_2Alk; R^1 = OH, OAlk, CO_2Alk, NH_2, $N(Alk)_2$.



(10)

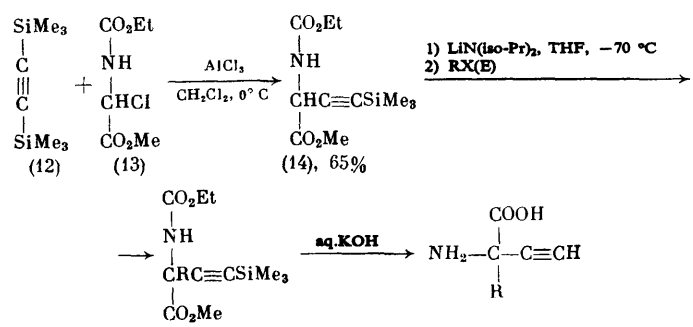
X = CH_2, $(CH_2)_2$, CH=CH, CHMe; R = H, $C(=NH)NH_2$, CO_2Alk, $C(=O)CHR^4NH_2$; R^1 = $CH=CH_2$, C≡CH; R^2 = H, CO_2H, CO_2Alk; R^3 = H, C(=O)Alk, CO_2Alk; R^4 = H, Alk, CH_2Ph, $CH_2C_6H_4$—OH-*n*.



(11)

R = OH, OAlk, NH_2, R^1 = H, C(=O)Alk, CO_2Alk; R^2 = H, Me; R^3 = H, OH, OAlk, CO_2Alk, Hal, Me; $n = 1,2$; R^4, R^5 = H, Hal, $Alk(C_{1-4})$; R^6–R^{10} = H, Me, Et, t-Bu, Cl, F, OR^{11}, R^{11} = H, $Alk(C_{1-8})$, $C(=O)Alk(C_{1-6})$, C(=O)Ph, $C(=O)Alk(C_{1-6})Ph$.

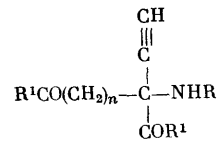
As a continuation of studies on the synthesis and properties of derivatives of α-acetylenic α-aminoacids, Casara and Metcalf[25] developed another general method for their synthesis by regioselective alkylation of a common synthon—the urethane (14), which was readily obtained in 65% yield by amidoalkylation of bis(trimethylsilyl)acetylene (12) under conditions of the Friedel–Crafts reaction.



(12) (13) (14), 65%

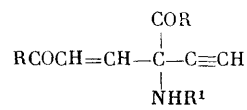
R = CH_2Ph (75%), $CH_2CH=CH_2$ (70%), $(CH_2)_5Me$ (60%).

By changing the initial amide (13) and varying the electrophiles (E), Metcalf et al.[26–29] increased the number of amino acids and their derivatives synthesised by the same method to include (15) and (16), which irreversibly inhibit glutamic acid decarboxylase, stimulate the activity of the nervous system, and have bactericidal activity.



(15)

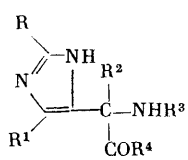
R = H, R^2CO; R^2 = $Alk(C_{1-4})$, $OAlk(C_{1-4})$, H_2NCHR^3CO; R^3 = H, Alk, CH_2Ph, $CH_2C_6H_4$—OH-*n*; R^1 = OH, OAlk, NR^4R^5; R^4 = R^5 = H, Alk, $NHCHR^6CO_2H$; R^6 = H, Alk, CH_2Ph, $CH_2C_6H_4$—OH-*n*; $n = 1 \div 3$.



(16)

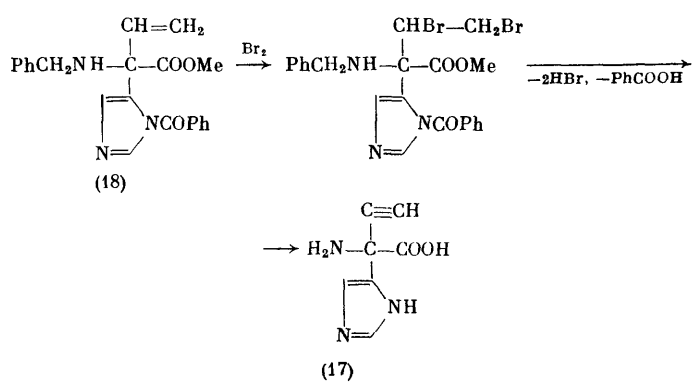
R = OH, OAlk, NR^2R^3(R^2, R^3 = H,Alk), $NHCHR^4CO_2H$(R^4 = H, Alk, $CH_2C_6H_4$—OH-*n*); R^1 = H, Alk, CH_2Ph, $CH_2C_6H_4$—OH-*n*.

In synthesising the amino acid derivatives (17), which exhibit antihistamine activity, Metcalf and Jung[30,31] introduced the acetylene function by successive bromination and didehydrobromination of histidine derivatives of amino acids with protected amine and acid functions (18).



(17)

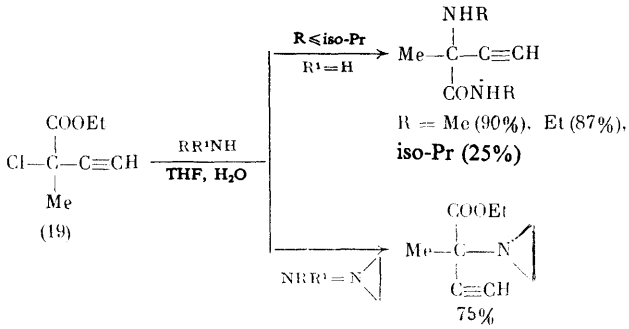
R = R^1 = H, F, Cl, Br, I, $Alk(C_{1-4})$; R^2 = $CH=CH_2$, C≡CH; R^3 = H, CO_2R^5(R^5 = Alk (C_{1-4})); NH_2CHR^6CO(R^6 = H, $Alk(C_{1-4})$, $CH_2C_6H_5$, $CH_2C_6H_4$—OH-*n*); R^4 = OH, OAlk. (C_{1-8}), NR^7R^8(R^7, R^8 = H, $Alk(C_{1-4})$, $NHCHR^9CO$(R^9 = H, $Alk(C_{1-4})$, $CH_2C_6H_4$—OH-*n*))



(18)

(17)

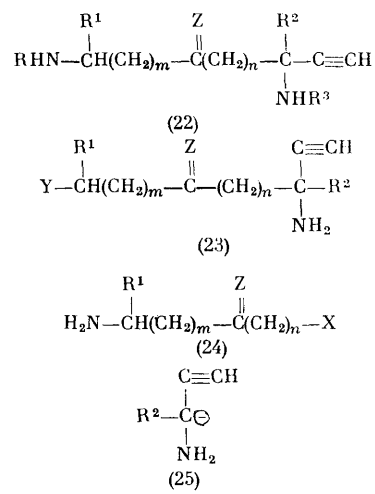
In 1983 Dugat and Verny[32] suggested another approach to derivatives of α-ethynyl-α-amino acids starting from ethyl 2-chloro-2-methyl-3-butynoate (19).



The simplest α-ethynyl-α-amino acid — 2-amino-3-butynoic acid (20), which Metcalf and Jung were not able to obtain[10] — was first isolated by Kuroda et al.[33] in its *L*-form from a cultural liquid of *Streptomyces*, and it is produced by the microorganisms *Streptomyces catenulae*. It appeared to be unstable in aqueous solution so it was isolated and determined by the authors as its acetyl derivative (21).[34] It is an antibiotic that is active towards Gram-positive bacteria and inhibits alanine racemase.

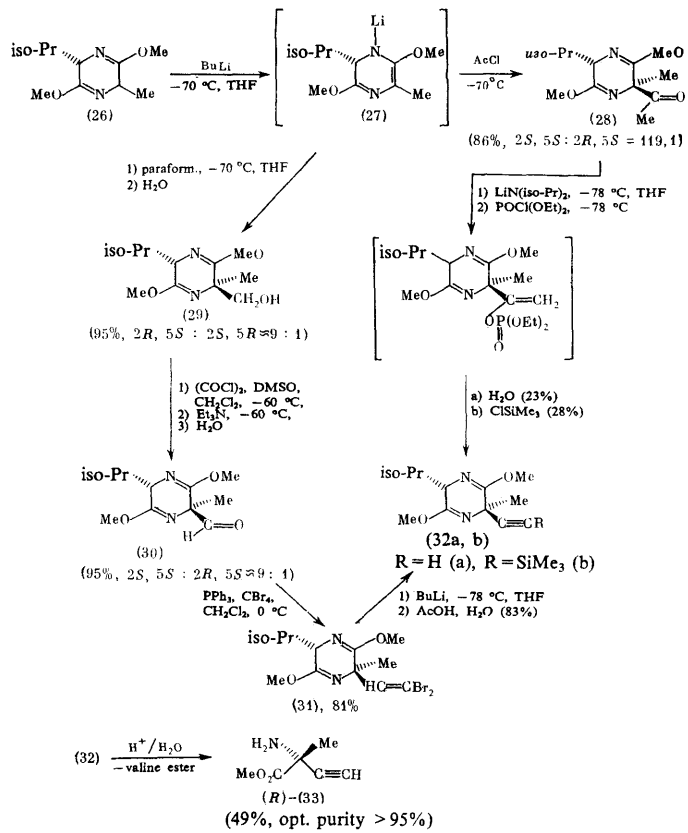


α,δ-Diamino-α-ethynyl-α-amino acids and their derivatives (22), which deactivate amino acid decarboxylase, have been proposed by Gerhard and Van Dorsselaer as antitumour agents.[35]



R = H, $R^4C=O$ (R^4 = Alk, Ph, Ph—Alk), residue of *L*-amino acid, R^1 = H, Alk; *m*, *n* = 0, 1 (*m*+*n* = 1); Z = O, CH_2; R^2 = H, $R^5C=O$ (R^5 = OH, when R = R^3 = H, R^5 = OAlk, NR^6R^7, where R^6, R^7 = H, Alk, residue of *L*-amino acid); R^3 = H (R = H, R^3 = H), $R^4C=O$; Y = Br, Cl, I, TsO, MsO; X = Br, Cl, I.

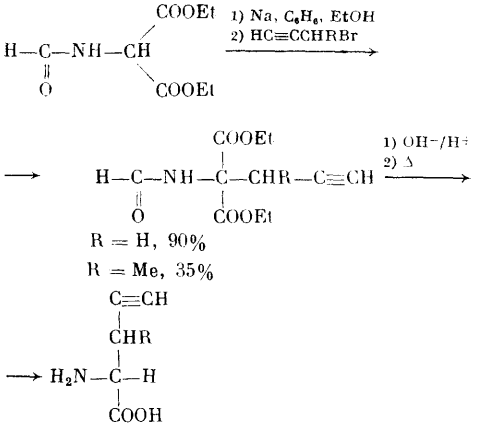
Compound (22) was obtained by either amination of the phthalimide derivatives of compounds (23) with hydrazine or methylamine followed by treatment with strong acid or reaction of amines (24) with the carbanion (25). At the same time the acetylene and amino groups in (23)—(25) were protected in a suitable manner.



In 1988 Schöllkopf et al., starting from the cyclic bislactim diether of *L*-valine and alanine (26), carried out the asymmetric synthesis of (*R*)-α-ethynylalanine (33) — a potential suicidal inhibitor of glutamic acid decarboxylase — in two ways.[36] A key stage of the first method was the regio- and stereo-selective acetylation of the *N*-lithiated ether (27) to the 2-acetyl-2,5-dihydropyridine (28) with a 90% excess of the (2*S*, 5*S*)-enantiomer. Compound (28) was converted by phosphorylation and subsequent hydrolysis or trimethylsilylation to 2-ethynyldihydropyrazines (32a, b), acid hydrolysis of which gave (*R*)-α-ethynylalanine (33) with an overall yield of 10—12% based on the initial ether (26). In the second method treatment of the lithiated bislactim ether (27) with paraformaldehyde followed by hydrolysis gave the alcohol (29) with an optical purity of 90%, which was oxidised with a mixture of oxalyl dichloride and dimethyl sulphoxide to the aldehyde (30). A Wittig reaction of the latter with triphenylphosphine dibromomethylene gave the 2-dibromoethylene-2,5-dihydropyrazine (31), which was converted by dehydrobromination and acid hydrolysis to the 2-ethynyldihydropyrazine (32a) in higher yield but with slightly lower stereoselectivity than in the first case. When the other enantiomer of the initial bislactim ether (26) is used it is possible to obtain the (*S*)-enantiomer of α-ethynylalanine in a similar manner.

2. α-Propargyl-α-amino acids

The first known example of α-propargyl-α-aminoacids was propargylglycine (34a), which was prepared in 1949 by Gershon et al.[37] from sodium formamidomalonate during research on active bactericidal agents amongst glycine analogues. The same authors subsequently reported the propargylglycine homologue—2-amino-3-methylpentynoic acid (34b).[38]



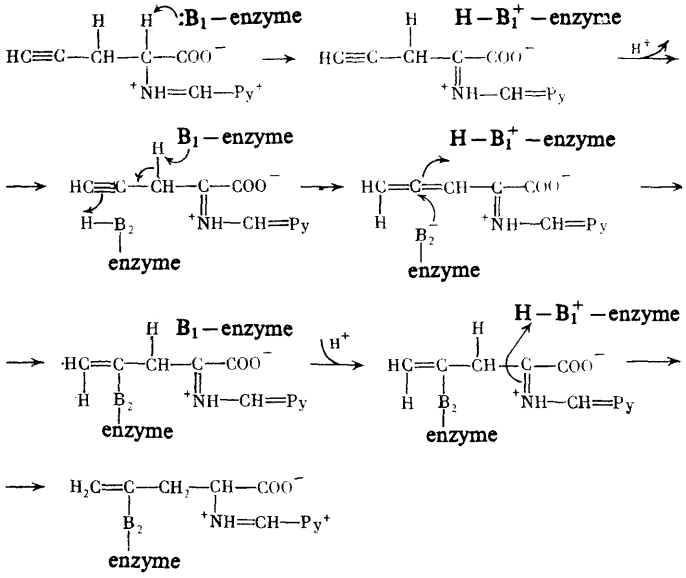
(34a, b)

R = H (a), 89%

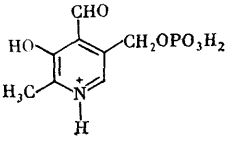
R = Me (b), 71%

It transpired that both amino acids (34a, b) actively inhibit the growth of yeast *Saccharomyces cerevisiae* and mould *Erchérihia* [Eschericia?] *coli* microorganisms.

In 1971 Scannel et al.[39] found that *L*-propargylglycine can be obtained microbiologically from cultivation of *Streptocetes*. As a result of fundamental biochemical studies by Walsh, Abeles, Marcotte, et al.,[40–45] it was established that inhibition of the growth of bacteria[41,43] and fungae[45] by propargylalanine is caused by its ability to deactivate irreversibly the enzymes bound to pyridoxal phosphate as the coenzyme—γ-cystathionase,[40,42] cystathionine γ-synthetase, methionine γ-lyase,[43] *L*-alanine transaminase, and others[44]—which take part in the biosynthesis or metabolism of the corresponding amino acids, and hence to disrupt the growth and development of cells, tissues, and complete organisms. As a result of a study on the suicidal deactivation of rat liver γ-cystathione with α-propargylglycine labelled with ^{14}C, ^{2}H, and ^{3}H isotopes, a mechanism for the process was put forward.[40,42] According to this mechanism, after bonding of the amino group of propargylglycine with the aldehyde group of the coenzyme, one of the bases (B_1) of the active site of γ-cystathionase by reacting alternately with the hydrogen atoms of the α- and β-carbon atoms of propargylglycine catalyses the isomerisation of the Schiff base and rearrangement of the acetylene residue to a highly reactive allene.[40,42] The authors assume that one of the acid groups of the active site of the enzyme ($H-B_2$) assists the formation of the allene by protonating the δ-carbon atom of the propargylglycine residue. It is very probable that after deprotonation, a base (B_2) adds to the allene, forming a covalent bond between enzyme and deactivator. A study of the hydrolysis products of the adduct between deactivator and enzyme showed that cysteine and tyrosine residues in the active site of the enzyme act as nucleophiles (and bases) forming a covalent bond with the deactivator. However, the authors do not exclude the possibility that the number of bases involved in the process may in fact amount to more than two.

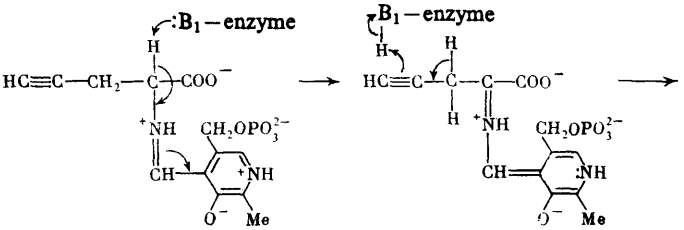


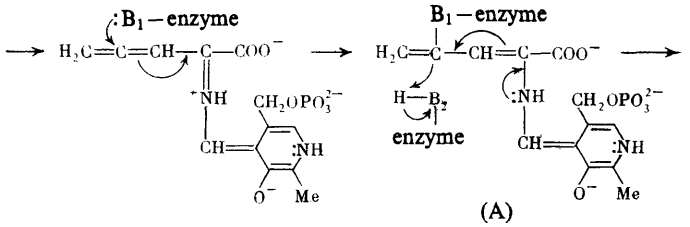
where Py^+-CHO is pyridoxal phosphate bound to the enzyme:



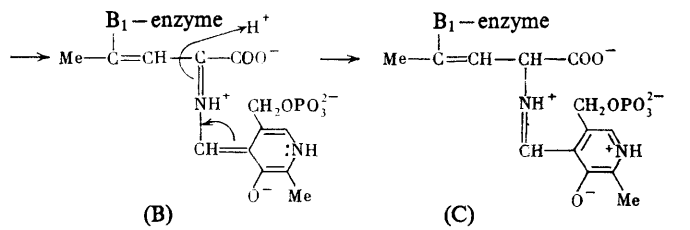
and B_1 and B_2 are bases (or nucleophiles) at the active site of the enzyme.

It is possible that the sequence of action of bases B_1 and B_2 is somewhat different to that described above. Johnston et al.[43] put forward a modified mechanism for the deactivation by *L*-propargylglycine of two enzymes—cystathionine γ-synthetase and methionine γ-lyase—from different types of bacteria. The main stages of this mechanism are the same as for the above, namely: reaction of propargylglycine with the coenzyme (pyridoxal phosphate), isomerisation of the acetylene residue of bound propargylglycine to an allene group with the participation of a minimum of two bases (or nucleophiles: B_1 and B_2) in the active site of the enzyme, and final protonation of the α-carbon atom of the deactivator, possibly through proton exchange with the solvent. The main difference from the previous mechanism is that Johnston et al.[43] assume that isomerisation of the γ,δ-double bond of the deactivator in adduct (A) to a β,γ-double bond occurs. As a result the final adduct mainly has structure (B) (according to the visible absorption spectra of the adduct between methionine γ-lyase and the deactivator) or (C) (in the case of cystathionine γ-synthetase.



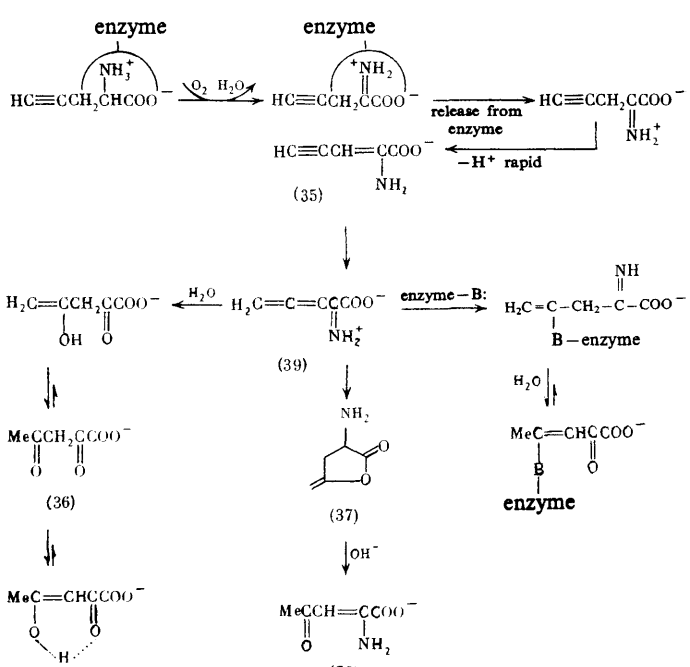


(A)



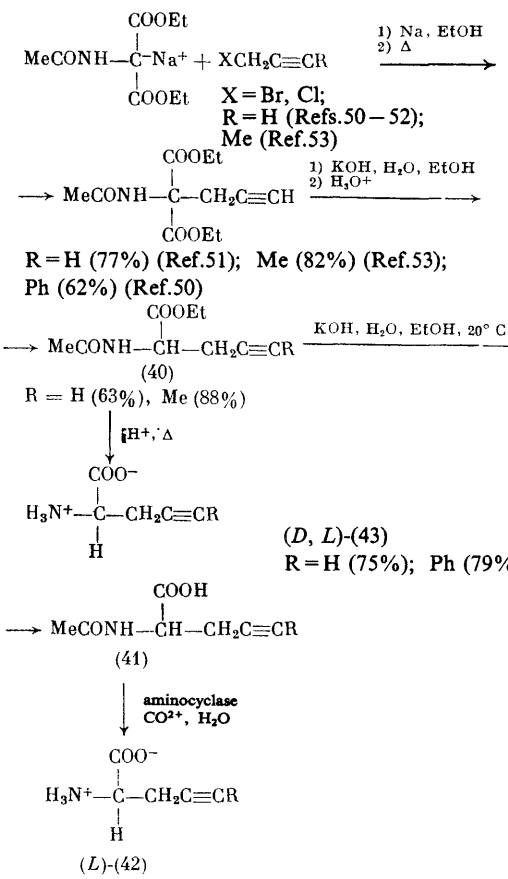
(B) (C)

The action of *D*- and *L*-propargylglycine on *D*- and *L*-amino acid oxidases bound to flavin as the coenzyme has been studied in detail.[46–49] It was established that *D*-propargylglycine is oxidised by a *D*-oxidase to the 2-aminopent-2-en-4-ynoate (35), which is then converted to acetopyruvate (36) or to the iminodiene lactone (37), and the latter after treatment with alkali gives 2-amino-4-oxo-2-pentenoate (38). Compounds (35) and (38) form charge transfer complexes with a *D*-amino acid oxidase and act as noncovalent inhibitors. However, after oxidation of propargylglycine the activity of the oxidase is not completely regenerated by the usual methods. Therefore, it was assumed by the authors that the enzyme undergoes not only reversible modification but also irreversible (covalent) modification as a result of the reaction of a nucleophilic residue (B:) in the active site of the enzyme with a highly reactive metabolite of propargylglycine, which may be the conjugated allenimino acid (39).



B—nucleophile of active site of enzyme

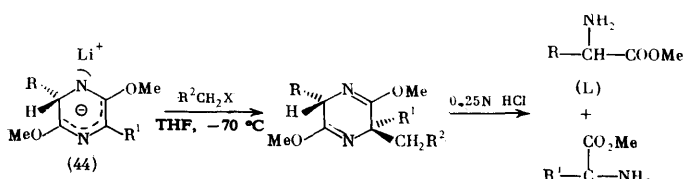
In biochemical studies use is made not only of *L*-propargylglycine obtained microbiologically[39] but also of racemic *D,L*-propargylglycine synthesised by the Gershon method modified by different authors.[50–53] Stereospecific hydrolysis of the acetamide group of the *D,L*-acetamide (41) by pig kidney aminoacylase in the presence of cobalt acetate or chloride gives *L*-propargylglycine (42). The *D*-form of the ethyl ester of the amino acid acetamide (41) is isolated from the filtrate.[53]



R = H (80%) (Ref.52); Me (86%) (Ref.53).

On conventional acid hydrolysis of the racemates of the acetamide ethyl esters (40), the corresponding amino acids (43) are obtained in a racemic form.

Diastereoselective alkylation of the lithiated bislactim ethers (44) followed by hydrolysis of the resulting intermediates was carried out by Schöllkopf et al.[54–59] for the asymmetric synthesis of the methyl esters of (*R*)-α-propargylglycine (45a) and certain other β-acetylenic α-amino acids (45b–d).



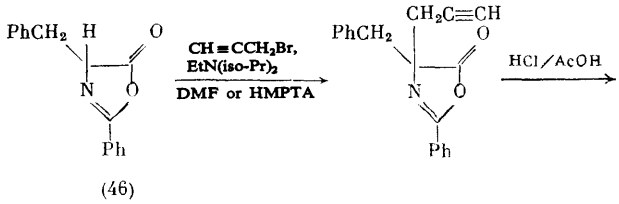
(45a–d)

Amino ester (45)	R	R^1	R^2	Yield, %	Optical Purity, %	Refs.
a	iso-Pr	H	C≡CH	52	60–65	[54]
a	t-Bu	H	C≡CH	59	95	[55–58]
b	iso-Pr	H	C≡CPh	86	95	[54–57]
c	iso-Pr	Me	C≡CH	–	95	[56–58]
d	iso-Pr	$(CH_2)_2PO(OEt)_2$	C≡CH	83	95	[59]

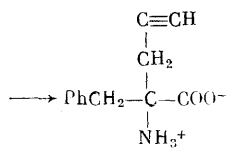
In 1984 O'Donnell et al.[60] demonstrated the possibility of obtaining α-propargylglycine (34a) in good yield (68%) by propargylation of the Schiff base of ethyl glycinate with diphenyl ketone in acetonitrile in the presence of potash and tributylammonium bromide as a phase transfer catalyst.

Propargylglycine is not used solely as a suicidal inhibitor of enzymes:[40–41] it has been used to establish the chemical structure of the active sites of enzymes[61,62] and also to synthesise tritium-labelled norleucine-containing peptides[52,53] and other novel peptides.[63]

The original synthesis of α-propargylphenylalanine (47) by reaction of propargyl bromide with the oxazoline (46) in the presence of a tertiary amine in dimethylformamide or hexamethylphosphoric triamide has been reported.[64]

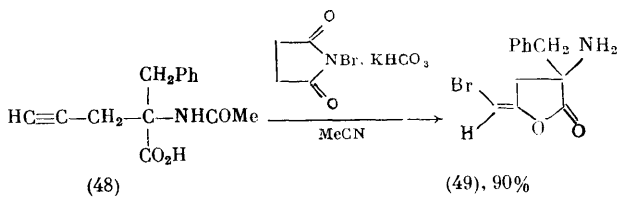


(46)

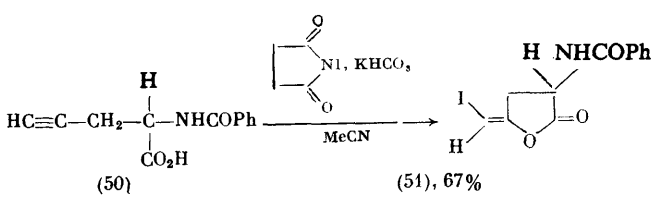


(47) 25%

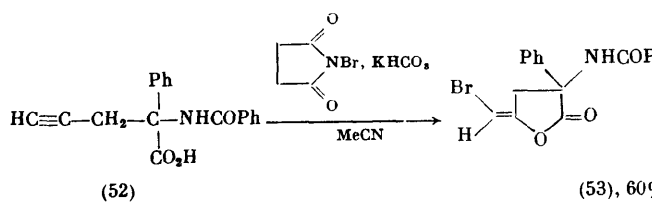
Katzenellenbogen et al.[65] subsequently used amides of propargylphenylalanine (48), propargylglycine (50), and propargylphenylglycine (52) for the synthesis of the five-membered lactones (49), (51), and (53), which proved to be inhibitors of serine protease.[65]



(48) (49), 90%

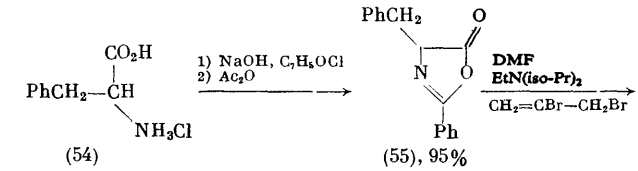


(50) (51), 67%

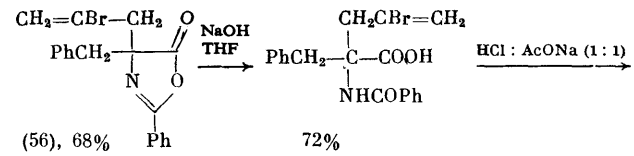


(52) (53), 60%

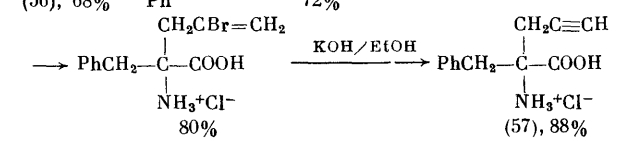
The synthesis of propargylphenylalanine was carried out by the authors in three ways. In the following scheme is depicted the method in which the 2-bromo-2-propenyl group, which was introduced into the 2-benzyloxazolone (55) obtained by reaction of phenylalanine hydrochloride with benzoyl chloride, was used as the propargyl synthon. After three-stage hydrolysis of the alkylated oxazoline (56) in different media propargylphenylalanine (57) was isolated with a total yield of 33% [based on phenylalanine (54)].



(54) (55), 95%

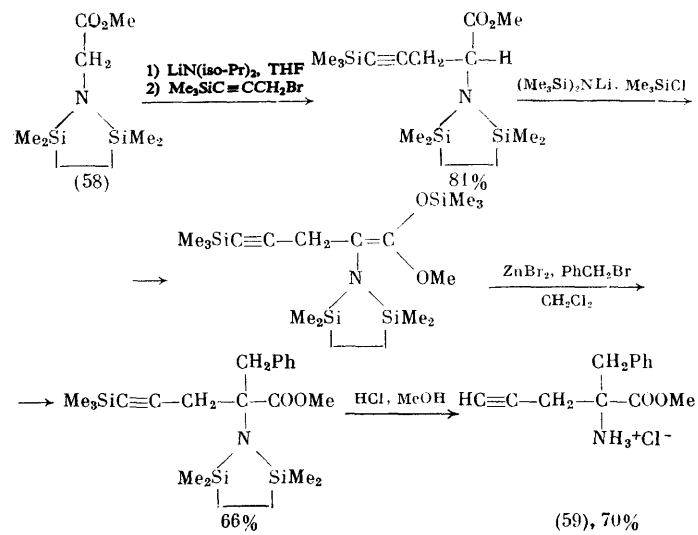


(56), 68% 72%



(57), 88%

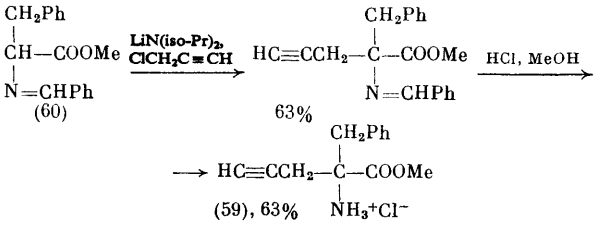
Alternative approaches to propargylphenylalanine (57) include the selective alkylation of the suitably protected α-amino acid derivatives (58) and (60). In the first method the adduct of methyl glycinate and 1,1,4,4-tetramethyldichlorosilylethylene (58) was first alkylated with 1-bromo-3-trimethylsilyl-2-propyne in the presence of lithium diisopropylamide and then benzylated under Friedel–Crafts conditions. After acid hydrolysis the methyl ester of propargylphenylalanine hydrochloride was isolated with an overall yield of 37%.



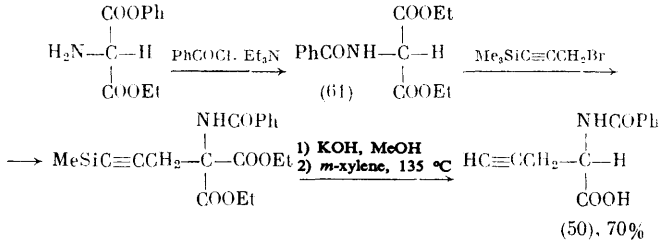
(58) 66% (59), 70%

In the second method the benzylidenimine of phenylalanine methyl ester (60) after treatment with lithium diisopropylamide at −78 °C was alkylated with 1-chloro-2-propyne. After removal of the benzylidene protecting group by acid hydrolysis, the methyl ester

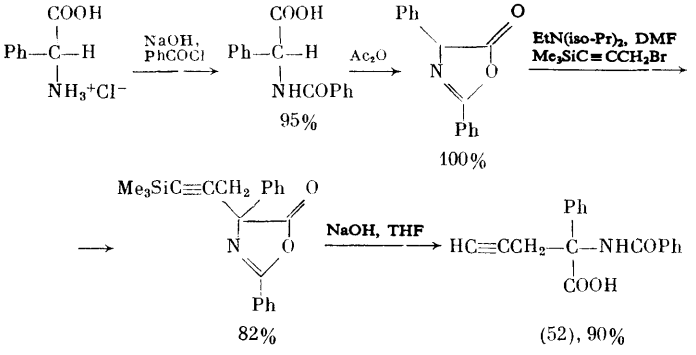
of propargylphenylalanine hydrochloride (59) was isolated with a total yield of 38%.



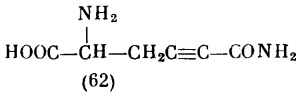
Sofia et al.[65] used the method of Gershon for the synthesis of propargylglycine benzamide (50), namely, diethyl malonate benzamide (61) was alkylated with 1-bromo-3-trimethylsilyl-2-propyne:



The benzamide of propargylphenylglycine (52) was synthesised using the methods described above in the following way:

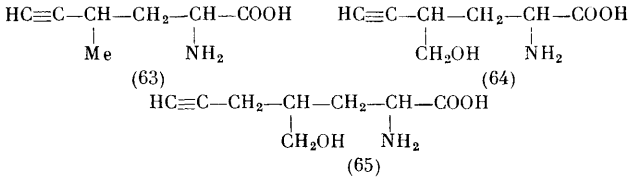


The carbamoyl derivative of propargylglycine—2-amino-5-carbamoyl-4-pentynoic acid (62)—has been isolated by Japanese biochemists from a cultural liquid of *Streptomyces* bacteria, which are capable of producing this antibiotic.[66]

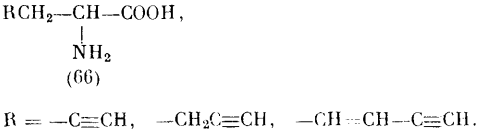


3. γ-Ethynyl-α-amino acids

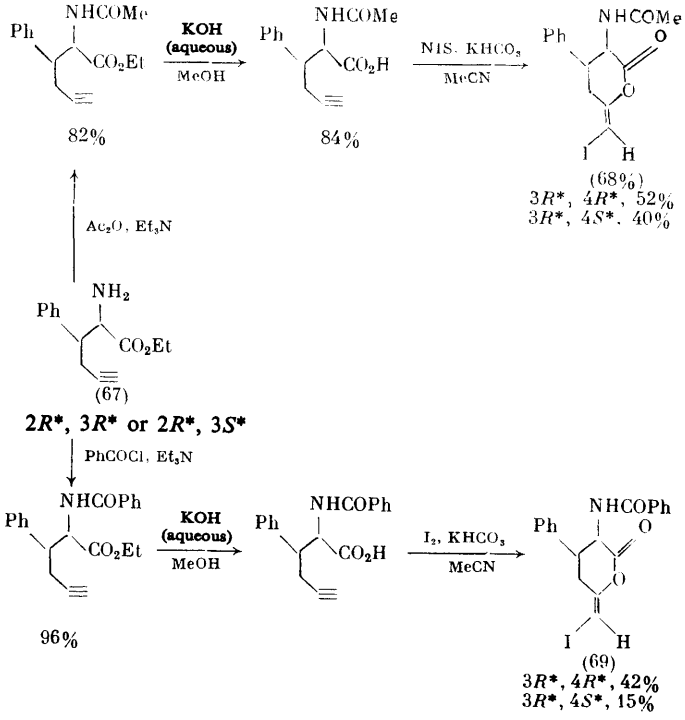
Information about γ-ethynyl-α-amino acids is limited. The isolation of two γ- and one δ-ethynyl-α-amino acids (63)–(65) from seeds of *Euphoria longan* plants was reported.[67]

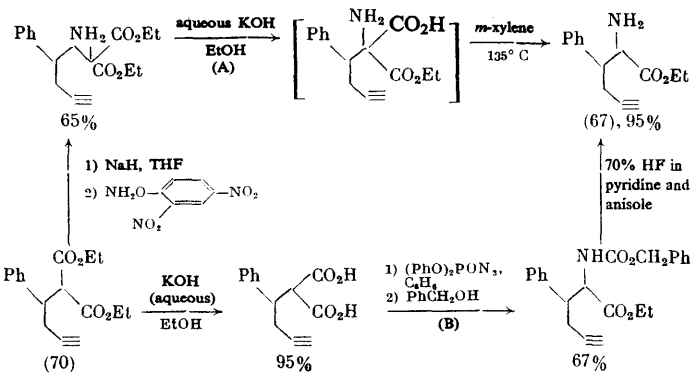


Several acetylene-containing amino acids of the type (66) were later isolated by extraction from a culture of *Basidomycetes* (for example, *Amanita Pseudoporphria*).[68]



In synthesising the iodomethylidenetetrahydro-2-pyranones (68) and (69), which, like the five-membered lactones (49), (51), and (53) described above,[65] act as irreversible inhibitors of serine protease, Sofia and Katzenellenbogan[69] used as the starting compound ethyl 2-amino-3-phenyl-5-hexynoate (67), which after protection of the amine group with acetyl or benzoyl functions underwent hydrolysis and iodolactonisation.



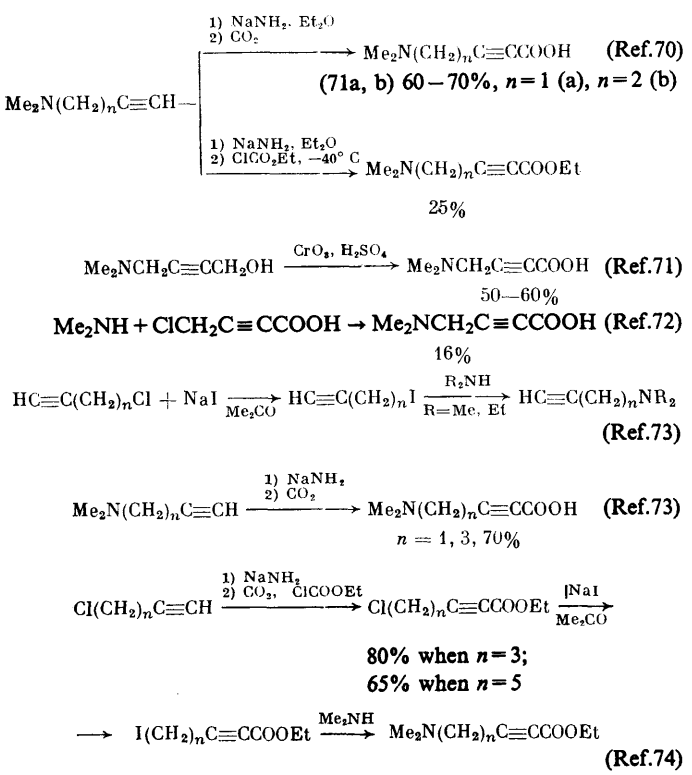


The γ-ethynyl-α-amino acid ethyl ester (67) was synthesised from the substituted malonate ester (70) either by successive amination and decarboxylation (route A) or by a modified Curtius rearrangement (route B).[69]

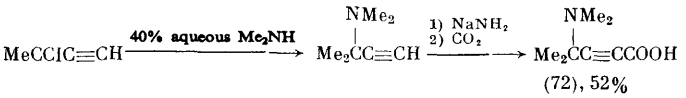
III. γ-Amino acids

1. α-Acetylenic γ-amino acids and their derivatives

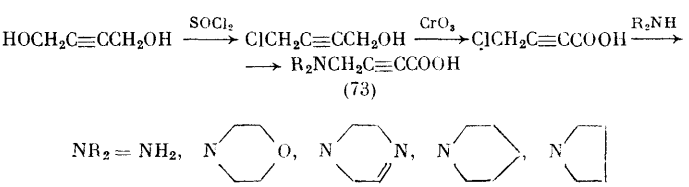
The first syntheses of α-acetylenic γ-, δ-, and ε-amino acids date back to the late 1950s when Olomucki and Marszak[70–74] put forward several methods for the preparation of 4-dimethylamino-2-butynoic acid (71a), its homologues, and esters, without touching on the question of their possible biological activity.



Subsequently Hennion and Perrino,[75] in studying the synthesis and conversions of certain α-acetylenic tertiary amines, obtained 4,4-dimethyl-4-dimethylamino-2-butynoic acid (72).

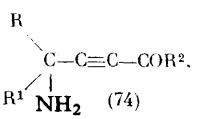


Bert and Johnston[76] in 1972 were the first to consider the biological activity of α-acetylenic γ-amino acids. They synthesised 4-aminotetrolic acid (73) and some of its derivatives as simple conformationally strained analogues of the neuromediator—γ-aminobutanoic acid (GABA)—in order to establish a correlation between the structure and activity of γ-amino acids.



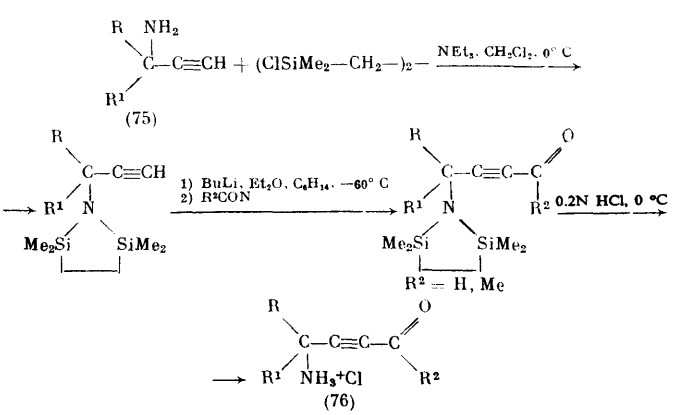
All of the γ-amino acids (73) that were synthesised proved to be inhibitors of the stimulation of central neurons, but they were weaker than GABA.

In the middle of the 1980s the aminoacetylenecarbonyl compounds (74), amongst which were amides of γ-carbon atom-substituted analogues of γ-aminobutynoic acid, were proposed[77] for the therapeutic treatment of alcoholism.



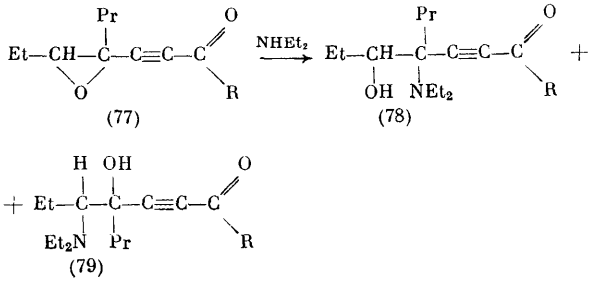
R and R^1 are hydrocarbon or heteroatomic hydrocarbon groups, R + R^1 is a cycloalkylene or heterocycloalkylene group, R^2 = H, Alk, NH_2.

They were synthesised from the acetylenic amines (75), by replacing the acetylenic hydrogen with an aldehyde, carbonyl, or amide function after initial protection of the amino group. Subsequent acid hydrolysis under mild conditions gave the hydrochlorides (76) of compounds (74).



Some of the hydrochlorides (76) exhibited antitumour properties.[77]

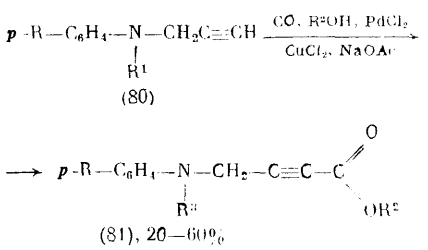
By aminating the epoxyacetylenic acid derivatives (77), Larionov et al.[78] in 1985 synthesised certain esters and amides of α-acetylenic hydroxyamino acids (78) and (79). The biological activity of the latter was not studied.



(77) (78) (79)

R = OMe, NEt_2

It was recently demonstrated by the present authors that for the synthesis of *N*-substituted α-acetylenic γ-amino acid esters in sufficient yield for preparative purposes, it is possible to utilise the oxidative alkoxycarbonylation of acetylenic amines (80) with carbon monoxide in alcohols under conditions of homogeneous catalysis by palladium chloride.[79,80]



(80) (81), 20–60%

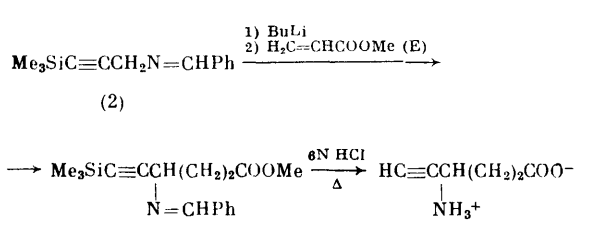
R = H, Cl; R^2 = Me, Et; R^3 = Me, $CH_2C{\equiv}CCOOMe$.

The amino esters (81) exhibit weak fungicidal and antistaphylococcal activity.

2. γ-Ethynyl-γ-amino acids

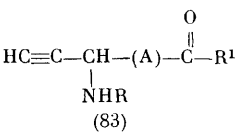
γ-Ethynyl analogues of GABA have attracted the attention of research workers because they have proved to be active inhibitors of GABA α-ketoglutarate transaminase from mammalian brain. Therefore they have very considerable potential for application in therapy as psychotropic agents. Metcalf and Jung[81,82] put forward a possible mechanism of their action which is similar to that described above for other irreversible enzyme inhibitors containing an acetylene function.[40,42,43]

The first example of this class of amino acids—4-amino-5-hexynoic acid (82) was obtained by alkylation of the protected aldimine (2), used subsequently for the synthesis of α-ethynyl-α-amino acids.[9,10]



(2) (82), 53%

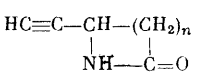
By varying the electrophilic reagent (E), Metcalf and Jung[83–86] obtained a large group of γ-amino acids (83) and their lactams (84) in racemic and enantiomerically pure forms. Some of these compounds had a beneficial effect in the treatment of functional disorders of the nervous system caused by Parkinsonism, chorea, epilepsy, alcohol syndrome, psychoses related to schizophrenia, manic depression, and hyperkinesia. Other compounds had hypothermal, myorelaxant, cholinergic, antibacterial, anticonvulsive, analgesic, sedative, and tranquillising activity.



(83)

R = Alk, $C(O)Alk(C_{1-4})$, $OC(O)Alk(C_{1-4})$, $C(O)CHR^2$, NH_2

R^2 = H, $Alk(C_{1-4})$, CH_2Ph, $CH_2C_6H_4OH$-*p*;



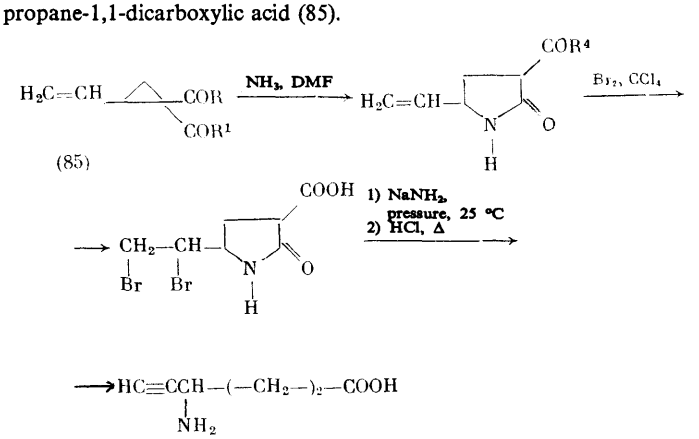
(84) *n* = 2, 3

R^1 = H, $AlkO(C_{1-8})$, NR^3H, R^3 = $Alk(C_{1-4})$, $NHCHCOOH$ (R^4);

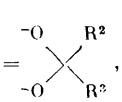
R^4 = H, $Alk(C_{1-4})$, CH_2Ph,

$CH_2-C_6H_4-OH$-*p*; A = $-CH(R^5)-$, R^5 = H, $Alk(C_{1-4})$, Ph, *o*-, *m*-, *p*-$C_6H_4-R^6$, R^6 = Hal, $OAlk(C_{1-4})$, $Alk(C_{1-4})$.

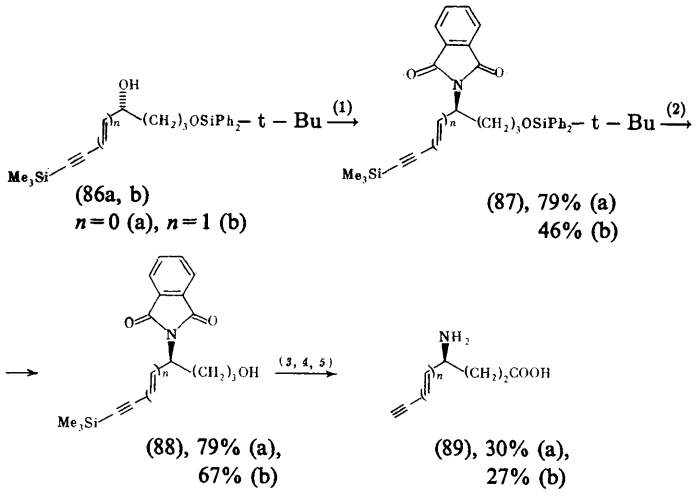
Gittos and Letertre proposed another route for the synthesis of 4-amino-5-hexynoic acid (82)—from derivatives of 2-vinylcyclopropane-1,1-dicarboxylic acid (85).



(85) (82)

R, R^1 = $OAlk(C_{1-4})$, R + R^1 = , R^2, R^3 = $Alk(C_{1-4})$.

R^4 = OH, NH_2, **O–Bu-t.**



(*1*) Ph_3P, phthalimide, diethyl azodicarboxylate, THF, room temperature, 19 h;
(*2*) HF–pyridine (3 equiv.), THF, room temperature, 19 h;
(*3*) $(COCl_2)$, DMSO, Et_3N, CH_2Cl_2, −78 °C, then Jones reagent (2 equiv.);
(*4*) $H_2N-NH_2.H_2O$, EtOH, refluxing, 10 min;
(*5*) $Bu_4N^+F^-.3H_2O$, THF, −10 °C, 20 min.

In 1989 Tabor et al.[88] carried out the enantioselective synthesis of (*S*)-γ-acetylene-γ-aminobutyric acid (89a) and its vinyl analogue—(*S*)-*trans*-γ-butenynyl-γ-aminobutyric acid (89b)—with greater than 95% enantiomeric purity by phthalimide substitution of the homochiral alcohols (86a, b) followed by desilylation of the imides (87a, b), oxidation of the imidoalcohols (88a, b), and removal of the phthalimide and trimethylsilyl protecting groups.

IV. Various mono- and poly-acetylene -containing amino acids

In addition to the information given above on the synthesis and biological properties of α- and γ-amino acids, there are separate reports in the literature on the preparation of certain other acetylenic and polyacetylenic amino acids.

Dumont et al.[89] synthesised the diacetylenic amino acids (90) by reaction of acetylenic amines or amides with haloacetylenic acids.

$$R^1R^2N(CH_2)_n-C\equiv CH + BrC\equiv C(CH_2)_n-COOH \xrightarrow[EtNH_2]{Cu^I} \longrightarrow R^1R^2N(CH_2)_nC\equiv CC\equiv(CH_2)_m-COOH,$$

$R^1 = H$, Me, COH; $R^2 = H$, Me; $n = 1$–6; $m = 2, 4$. (90)

When this reaction was carried out with primary amines, the amino group was first protected by formylation, and after formyl derivatives (90) were obtained, R^1 = HCO, R^2 = H, they were deformylated with caustic soda to the corresponding amino acids (90), $R^1 = R^2 = H$.[89]

Acid hydrolysis of nitriles of *N*-alkynylamino acids (91) gave the corresponding amino acids (92) in 90% yield.[90]

$$R-\underset{\displaystyle R^1}{\overset{\displaystyle C\equiv CH}{\overset{|}{C}}}-NH-(CH_2)_2-CN \xrightarrow{HCl,\ Et_2O} R-\underset{\displaystyle R^1Cl^-}{\overset{\displaystyle C\equiv CH}{\overset{|}{\overset{+}{C}}}}-NH_2-(CH_2)_2-COOH,$$

(91) (92), 90%

R = R^1 = Me, Et; R = Me, R^1 = Et.

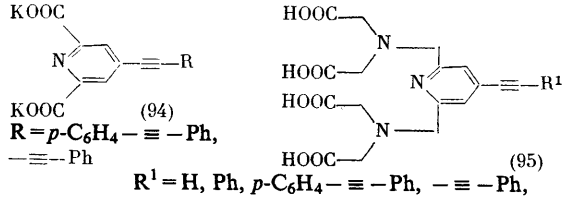
Ahmed et al.[91] isolated the polyacetylenic amino acids (93) from cultures of *Fayodia bisphaerigera* fungae. The structure of the acids was reliably established by a range of physicochemical studies and by counter-synthesis.

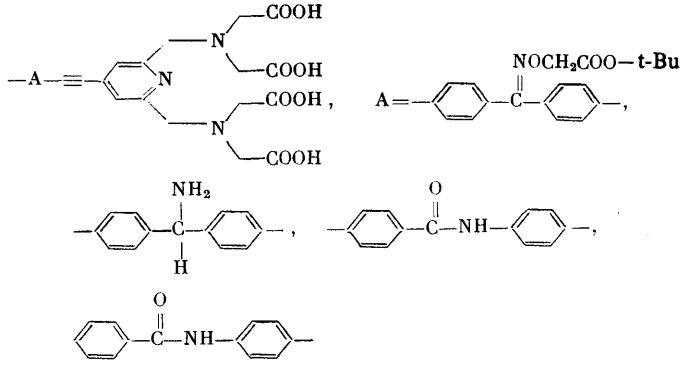
trans-HO–CH_2–CH=CH–$(C\equiv C)_3$–COX, (93)

X = OMe, NHCHRCOOMe, R = H, Me.

In recent years amino acid derivatives containing an acetylene residue in the molecular structure have attracted the attention of research workers as complexing agents and as synthons for the derivation of novel compounds with interesting and useful properties.

Takalo, Hänninen, et al.[92–94] in a multistage synthesis obtained a number of polyconjugated derivatives of ethynylated pyridinecarboxylic acids (94) and pyridinaminocarboxylic acids (95) in order to study the spectroscopic properties of their metal complexes.

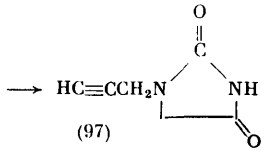




The alkyl esters of *N*-propargyl-*N*-alkoxycarbonylglycine (6) were used[95] to obtain 1-propargyl-2,4-dioxoimidazolidine (97)—an intermediate in the synthesis of pyrethroid insecticides and acaricides

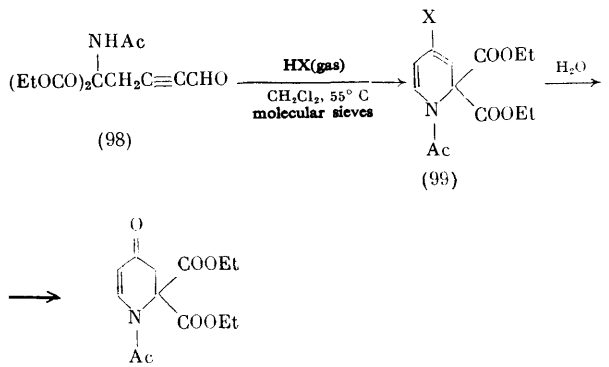
$$HC\equiv CCH_2-\underset{\displaystyle (96)}{\overset{\displaystyle CH_2COOR^1}{\overset{|}{N}}}-COOR + NH_3 \xrightarrow[atm.pressure]{0-100^\circ C} \longrightarrow$$

$$\longrightarrow HC\equiv CCH_2\overset{\displaystyle CH_2COOR^1}{\overset{|}{N}}-COOR \xrightarrow[2)\ H^+,\ H_2O]{1)\ NaOMe,\ \Delta}$$



R, R^1 = Alk(C_{1-4})

It was found by Roduit and Wyler[96] that the propargylacetylaminomalonic acid derivatives (98) readily cyclise, forming dihydropyridines (99), which are then hydrolysed to trihydropyridones (100). Dihydropyridines are known to be widely used in pharmacology and in biological studies.



(100), up to 85%

X = Cl, Br

This review of information in the literature on amino acids of various structures that contain an acetylene residue in the molecule, obtained by both chemical and microbiological methods, provides an indication of the extensive possibilities of using these compounds as biologically active agents whose specific physiological action is mainly due to their ability to modify irreversibly the active sites of certain enzymes by disrupting the chain of biochemical reactions of vital amino acids. Acetylenic amino acids are also used as synthons for the preparation of various compounds that have properties with useful practical applications.

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