RUSSIAN CHEMICAL REVIEWS
Uspekhi Khimii

June 1967

U.D.C. 547.466

ADVANCES IN THE SYNTHESIS OF UNSUBSTITUTED AMINO-ACIDS

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Recently there has been a considerable increase of interest in the synthesis of biologically important amino--acids, due to the fact that these amino-acids are ceasing to be objects of theoretical studies only and are becoming available as products of industrial manufacture and are widely used in the food industry and in agriculture. Since the number of studies published recently in this field is fairly large, their critical review is essential.

The present review is concerned with the synthesis of eight unsubstituted amino-acids: valine, leucine, isoleucine, phenylalanine, threonine, lysine, methionine, and tryptophan. A review on the synthesis, degradation, and racemisation of yet another important amino-acid, glutamic acid, was published in 1963.[1] Since the detailed review of the literature on the synthesis of amino-acids in the book of Greenstein and Winitz[2] covers the original literature up to 1958, we shall consider in detail only later studies which appeared up to the middle of 1965 and also some work published in the second half of 1965. Earlier work will be quoted for the purpose of exposition. Initially we shall describe general methods of synthesis and then specific methods for each individual amino-acid, starting with monoaminomonocarboxylic acids and then continuing with more complex acids. Since the usual chemical syntheses yield racemic amino-acids, the separation of the DL-forms into optical isomers is of primary importance. Among the reviews dealing with this problem, there is one which was published relatively recently[3]. However, all these reviews describe only individual aspects of the problem and are to a large extent obsolete.

GENERAL METHODS OF SYNTHESIS

The simplest general method of the synthesis of all amino--acids is the ammonolysis of the corresponding α-halogeno--substituted acids. The amination reaction itself presents no difficulties and the applicability of this reaction is restricted solely by the availability of the α-halogeno-acids. Until recently the halogeno-derivatives of aliphatic acids only were available. In 1956–1959 Nesmeyanov, Freidlina, and coworkers developed a new method for the synthesis of α- and ω-chlorocarboxylic acids and their derivatives with other functional groups based on the telomerisation of ethylene[4,5]. $\alpha\alpha\alpha\omega$-Tetrachloroalkanes, obtained in the radical--chain telomerisation of ethylene and carbon tetrachloride, are converted into amino-acids according to the following general mechanism:

$$CCl_3CH_2(CH_2)_nCl \xrightarrow[SbCl_5]{FeCl_3,\ AlCl_3} CCl_2=CH(CH_2)_nCl \xrightarrow{HX}$$

$$\rightarrow CCl_2=CH(CH_2)_nX \xrightarrow[(CH_3COO)_2Hg]{Cl_2/H_2SO_4,\ CH_3COOH\ or} HOOCCHCl(CH_2)_nX \xrightarrow{NH_3} \underset{\displaystyle NH_2}{\overset{\displaystyle |}{HOOCCH}}(CH_2)_nX,$$

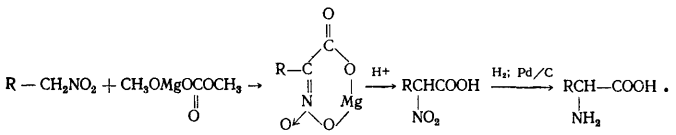
where X is the substituent and n ranges from 0 to 15.

The following amino-acids were obtained in this way: phenylalanine (X = C_6H_5, n = 1), glutamic acid (X = COOH, n = 2), and lysine and ornithine [X = $C_6H_4(CO)_2N$, n = 4 and 3]; the phthalic acid group was removed by hydrolysis with concentrated hydrochloric acid. Ammonolysis of $\alpha\omega$-dichlorovaleric acid (X = Cl, n = 3) yields proline[7-9].

α-Nitro-acids and their derivatives constitute another convenient intermediate for the synthesis of α-amino-acids. In 1952 Weisblatt and Little outlined the principal ways of using nitroacetic ester for the synthesis of α-amino-acids: (1) alkylation of nitroacetic ester with alkyl halides, alkylarenesulphonates, and alkyl sulphates in the presence of alkaline catalysts, with carbinols in the presence of boron trifluoride, and with substituted dialkylamines and quaternary ammonium bases; (2) condensation of nitroacetic ester by reaction of the Knoevenagel type with aldehydes

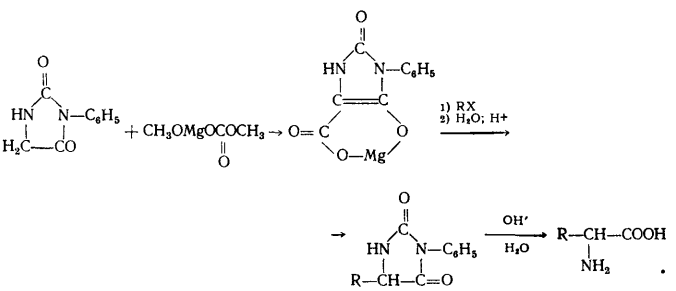
and ketones in the presence of the appropriate catalysts; (3) addition of nitroacetic ester to substances containing an activated double bond. After the introduction of the required substituents, the nitro-group is reduced and the ester is hydrolysed[10]. These workers and a number of other investigators developed, on the basis of nitroacetic ester, methods for the synthesis of tryptophan[11], threonine[12,13], leucine[14], glutamic acid[15], glycine[16,17], α-aminobutyric acid[13], and other amino-acids. Interest in nitroacetic ester has recently increased appreciably in connection with the development of a simple method for its preparation from nitromethane and alkali[18]. Nitromalonic ester has also been used for the preparation of tryptophan[19-21], proline[22], ornithine[23], and glutamic acid[24]. Valine[25,26], leucine[26], isoleucine[27], and the *O*-methyl ester of threonine[26] have been obtained by the reduction of the esters of substituted α-nitroacrylic acids. The α-nitro-ϵ-lactams of these acids[28] can apparently be used as intermediates in the synthesis of $\alpha\omega$-diamino-acids.

For the preparation of α-nitro-acids, Finkbeiner proposed a reaction involving the carboxylation of primary nitro-paraffins with methoxymagnesium methyl carbonate in dimethylformamide[29-32]:



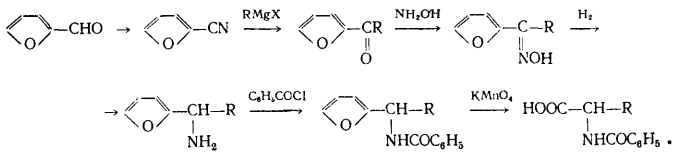
The chelate structure of the magnesium salt of the α-nitro-acid formed stabilises the molecule. The free nitro-acid is isolated by acidification and then reduced to the amino-acid. DL-Alanine, DL-α-aminobutyric acid, and DL-norvaline were obtained in this way from nitroethane, 1-nitropropane, and 1-nitrobutane in yields of 46, 34, and 42% respectively, relative to the nitro-paraffin; the authors state that the conditions used were not optimum[29].

The general synthesis of amino-acids by the carboxylation and alkylation of phenylhydantoin was achieved with the aid of methoxymagnesium methyl carbonate:



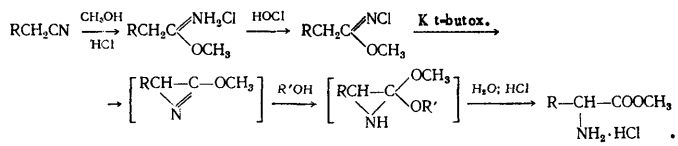
The following amino-acids were obtained by this procedure (the amino-acid and the alkylating agent are listed, the percentage yield with respect to 3-phenylhydantoin being indicated in brackets): valine, isopropyl bromide (38); leucine, isobutyl bromide (46); phenylalanine, benzyl chloride (97); tryptophan, gramine (53); proline, 1,3-dibromopropane (45); lysine *N*-(4-bromobutyl)phthalimide (45); glutamic acid, the sodium salt of β-chloropropionic acid (30).[33,34]

In 1958 Terent'ev and Gracheva suggested that furfural be used as a cheap raw material for the preparation of amino-acids[35]. Furfural is converted into a ketone which is in turn converted into the corresponding oxime, the latter being reduced to the amine with zinc in acetic acid. The amino-group is then protected by acylation, the furan ring is oxidised with alkaline permanganate, and the acyl derivative of the amino-acid is obtained, the free acid being isolated after hydrolysis:



The *N*-benzoyl derivatives of the following aliphatic amino-acids were obtained in this way: leucine, alanine, norvaline, norleucine, α-aminobutyric acid, and α-amino-isoheptanoic acid [R = $CH_2CH_2CH(CH_3)_2$]. When *N*-benzoyl-isopropylfurylamine is oxidised, the valine derivative cannot be isolated[36]. In addition, *N*-benzoylaspartic acid and proline were obtained from the furan derivatives[37]. β-Amino-acids are obtained by the condensation of furfural and nitro-alkanes with subsequent reduction of the nitro-group with lithium aluminium hydride and the oxidation of the furan ring[38]. The aldol condensation of furfural with alkyl methyl ketones, accompanied by the hydrogenation of the unsaturated ketone, ammonolysis, and oxidation, yields γ-amino-acids[39].

Baumgarten proposed a very interesting method for the conversion of nitriles into α-amino-acids. The reaction proceeds as follows:



Partial hydrolysis of the nitrile yields the hydrochloride of the methyl imino-ester, which is converted into the *N*-chloro-imino-ester by chlorination. The latter undergoes rearrangement into the methyl ester of the amino-acid hydrochloride under the action of potassium t-butoxide. The rearrangement is a special case of the conversion of *N*-dichloro-s-alkylamines into α-amino-ketones. The following amino-acids were obtained from nitriles (the percentage yields with respect to the nitrile are indicated in brackets): phenylalanine (44), leucine (59), alanine (51), glycine (51), norvaline (21), and phenylglycine (51).[40]

We think it desirable to consider in the general section the following widely known synthetic methods for amino-acids.

1. Syntheses based on malonic, acetamidomalonic, cyanoacetic, and acetoacetic esters.

2. The azlactone method for the synthesis of aromatic amino-acids and the related procedures which are based on the principle involving the utilisation of the mobility of the hydrogen atoms of the activated methylene group (condensation of aldehydes with dioxopiperazines, hydantoins, etc.).

3. The cyanohydrin method (the Strecker synthesis).

4. The applications of the Schmidt method in the synthesis of amino-acids.

The new variants and the most important examples of the application of these methods will be examined in fair

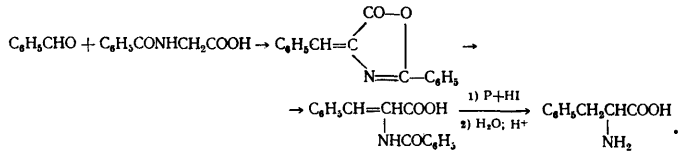
detail in connection with the description of the procedures for the preparation of the individual amino-acids.

The problems associated with the synthesis of mixtures of amino-acids from the simplest carbon and nitrogen compounds under the action of various physical factors (temperature, irradiation, ultrasonic vibrations, electric discharge, etc.) are outside the scope of this review.

Phenylalanine

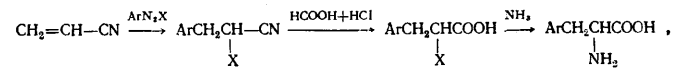
The principal methods for the synthesis of phenylalanine are at the same time the general methods for the preparation of other aromatic and aliphatic monoaminomonocarboxylic acids. Therefore in the subsequent consideration of the syntheses of valine, leucine, and isoleucine we shall refer to the reactions described in this section.

The method proposed by Erlenmeyer (known as the Erlenmeyer synthesis) for the synthesis of aromatic amino-acids by the condensation of benzaldehyde (or other aromatic aldehydes) with hippuric acid is widely known. The azlactone formed hydrolyses and after reduction and liberation of the amino-group phenylalanine is obtained[41]:



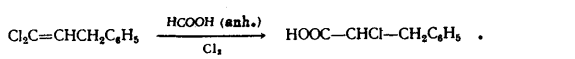
The yield of phenylalanine is 63–67% with respect to the azlactone[42] or 55% with respect to hippuric acid[43]. When acetylglycine is used instead of hippuric acid, the yields reach 72%.[44-46] Various modifications of this method are known, consisting in the condensation of benzaldehyde with heterocyclic compounds containing an active methylene group: hydantoin[47-50], dioxopiperazine[51], 1-benzoyl-2-mercaptohydantoin[52,53], 2-mercaptothiazolone[54,55], and rhodanine[56]. Reduction and hydrolysis of the resulting benzylidene derivatives yields amino-acids.

The application of the Meerwein reaction proved extremely fruitful in the synthesis of aromatic amino-acids, in particular phenylalanine and tyrosine[57-61]. A very convenient method for the preparation of α-halogeno-β-arylpropionic and β-arylisobutyric acids, based on the halogenoarylation of acrylic acid derivatives, was developed, which made it possible to find a general method for the synthesis of DL-β-phenylalanine and its derivatives from acrylonitrile and methyl methacrylate[59,60]:



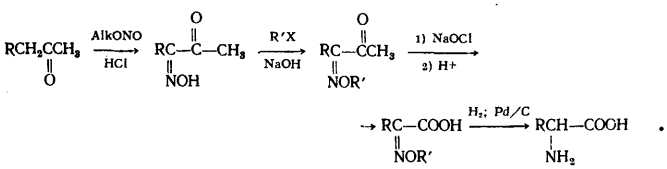
where X = Cl or Br.

α-Chloro-β-phenylpropionic acid was obtained in 40% yield; when it was aminated with aqueous ammonia, the yield of phenylalanine was 40–42%, the use of liquid ammonia increasing the yield of the amino-acid to 80%. The halogenoarylation of acrylic acid with subsequent amination gave phenylalanine with an overall yield of 10% with respect to aniline[61]. Another method for the preparation of α-chloro-β-phenylpropionic acid was proposed by Freidlina and coworkers:



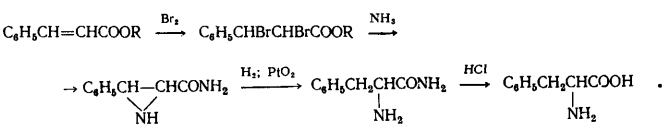
The acid, isolated in 63% yield, was subjected to ammonolysis with an excess of aqueous ammonia under pressure, the product being phenylalanine in 77% yield[7].

Monoaminomonocarboxylic acids can be obtained from alkyl ethyl ketones via α-hydroxyimino-ketones by the following mechanism:

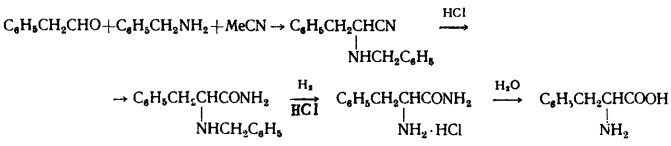


The methyl ketone is nitrosated with alkyl nitrite or an alkali metal nitrite, the ketone oxime being alkylated with diethyl sulphate. Hoffmann degradation of the α-alkoxyimino-ketone gives the α-alkoxyimino-acid, which is reduced to the amino-acid. In this way it was possible to obtain phenylalanine from methyl β-phenylethyl ketone in 50–53% yield, alanine from ethyl methyl ketone in 14 and 32% yield, and valine from isobutyl methyl ketone in yields of 34 and 31%.[62-65] In addition, tyrosine, norleucine, 3,4-dihydroxyphenylalanine, and phenylglycine were also obtained[66].

Interesting reactions occur in the preparation of phenylalanine from cinnamic esters. The cinnamic acid ester is converted into the ester of αβ-dibromo-β-phenylpropionic acid by treatment with bromine. The product obtained when this ester is treated with an excess of 25% solution of ammonia under pressure was initially incorrectly assumed to be the amide of α-amino-β-phenylacrylic acid [$C_6H_5CH=CC(NH_2)CONH_2$].[67] Later it was shown that the compound is in fact a derivative of aziridine[68]. Hydrogenation of the intermediate product with subsequent hydrolysis gives phenylalanine in 25% yield with respect to the ester of αβ-dibromo-β-phenylpropionic acid[69]:



The synthesis of phenylalanine by the Strecker method was achieved by Erlenmeyer[70] in 1882 but has not been used since. In 1963 a modification of the method was proposed for the preparation of alanine, valine, leucine, and phenylalanine, consisting in the initial reaction of the aldehyde, metal cyanide, and benzylamine (instead of ammonia); the resulting (*N*-benzyl)amino-nitrile is hydrolysed to the amine, the benzyl group is removed by hydrogenation, and the amino-acid is obtained after hydrolysis[71]:



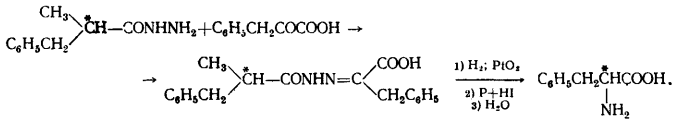
The methods for the preparation of phenylalanine with the aid of malonic, cyanoacetic, and acetoacetic esters and their derivatives are distinguished by their great variety. New modifications of these methods are being proposed by investigators also at the present time. Since a complete description of these syntheses would be unduly cumbersome and their exclusion from the review would render the range

of syntheses of unsubstituted amino-acids incomplete, we have confined ourselves to a Table in which the key features of the syntheses are given and other amino-acids obtainable by the same method are indicated.

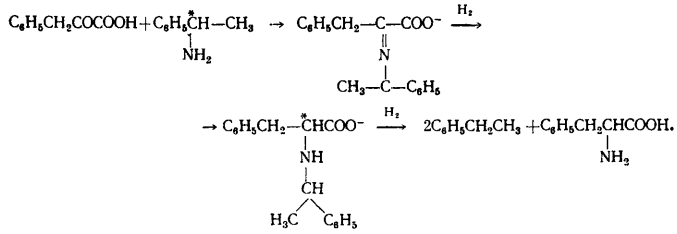
Reductive amination of phenylpyruvic acid with hydrogen and ammonia in the presence of the palladium catalyst is a reaction analogous to the reduction of oximes and phenylhydrazones of α-keto-acids[93]. Reductive amination is particularly convenient for the synthesis of phenylalanine labelled at the nitrogen[94]. A series of Japanese patents describe the reductive amination of phenylpyruvic, pyruvic, and oxoglutaric acids in the presence of various complex cobalt salts[95-97] and also with sodium borohydride[98]. The cobalt complexes were used in the preparation of phenylalanine by the hydrogenation of α-acetamidocinnamic acid[99].

The preparation of phenylalanine, leucine, and α-aminobutyric acid by the Grignard reaction has been noted. However, the yields of the amino-acids did not exceed 5–10%.[100]

Several methods have been proposed for the preparation of optically active phenylalanine (and also valine, alanine, and glutamic acid) by the reaction of substances containing an optically active group in the molecule, with formation of a new centre of asymmetry. However, the asymmetric yield is usually low. For example, the product of the condensation of the hydrazide of an optically active acid with an α-keto-acid is reduced and then decomposed, a compound with a new centre of asymmetry being obtained[101]:



The optical isomers of phenylalanine, alanine, and valine were obtained by the catalytic hydrogenation of the corresponding α-keto-acids in the presence of D(+)- and L(-)-α-methylbenzylamine:



The asymmetric centre of the amino-acid arises in the stage involving the hydrogenation of the Schiff base. The degree of asymmetry thus introduced depends on the structure of the initial substances and the properties of the catalyst[102]. The preparation of L-phenylalanine by the hydrogenation of α-acetamidocinnamic acid in the presence of Pd/C and small amounts of L-methionine[103] has been described. Akabori suggested that optically active amines and amino-acids be obtained with the aid of an asymmetric hydrogenation catalyst, consisting of a reduced protein–palladium complex prepared by the adsorption of $PdCl_2$ on fibres of silk fibroin. L-phenylalanine was obtained in this way from the ethyl ester of α-acetoxyiminophenylpropionic acid[104].

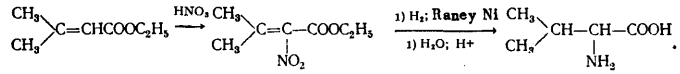
TABLE.

Starting material	No. of stages	Total yield, %	Other amino-acids obtained by the same method	Refs.
$C_6H_5CH_2CH(COOK)COOC_2H_5$	4	—		72
$CH_2(COOC_2H_5)_2$	4	31—36		73,74
$BrCH(COOC_2H_5)_2$	3	64		75
$C_6H_5CH_2CH(COOC_2H_5)_2$	2	60		76
$RCONHCH(COOC_2H_5)_2$	2			
$R=C_6H_5$		64		77
$R=CH_3$		60	histidine, leucine	78
$R=H$		60	aspartic and glutamic acids	79
$R=H$		75	norleucine, aspartic acid, and tyrosine	80
$RCONHCH(CONH_2)_2$ $R=C_6H_5$; CH_3	3	73—77	leucine, histidine, glutamic acid, and norleucine	81
$CNCH(NHCOCH_3)CONH_2$	3	77	valine, leucine, glutamic acid, and norleucine	82
$CN-CH(NHCOCH_3)-COOC_2H_5$	2	62	tryptophan, histidine, methionine, valine, and leucine	83
$CN-CH(CH_2C_6H_5)-COOC_2H_5$	2	30		76
$CN-CH_2COOC_2H_5$	5	18	valine and tyrosine	84
$CN-CH(NHCOCH_2C_6H_5)-COOCH_3$	2		leucine, methionine, and valine	85
$CH_3COCH(CH_2C_6H_5)COOC_2H_5$	3	54	alanine and aspartic and glutamic acids	86
То же	2	79		87
То же	2	68	alanine, leucine, isoleucine, methionine, valine, and tyrosine	88—92

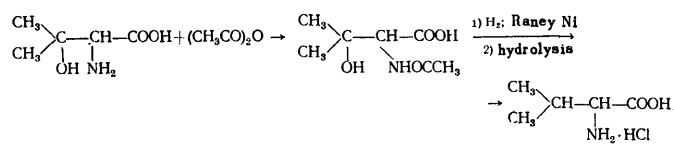
Valine

Valine is obtained most simply by the ammonolysis of α-halogenoisovaleric acid. When ammonia is allowed to act on α-bromoisovaleric acid, the yields of valine reach 78%;[105] treatment of the acid with hexamethylenetetramine results in almost quantitative yields of valine[74,106].

Various modifications of the Strecker synthesis have been examined by Gaudry[107]. Valine is obtained from isopropylmalonic ester in about 70% yield by the Schmidt reaction in a single stage[108]. The hydrogenation of the ethyl ester of ββ-dimethyl-α-nitroacrylic acid with subsequent hydrolysis results in the formation of valine in a yield of about 50%:[25,26]



The application of the Akabori method (see below) to the synthesis of valine merits attention. The *N*-acetyl derivative of hydroxyvaline obtained by the condensation of acetone with copper glycinate is reduced in the presence of Raney nickel, valine being obtained in 80% yield[109]:



A number of studies described in the preceding sections are also relevant to the synthesis of valine[33,62-65,82-85,88]. The failure in the attempt to obtain valine (and isoleucine) from furan derivatives[36] and also by the alkylation of the amides of acylaminomalonic acids[81] is probably due to steric hindrance.

Leucine

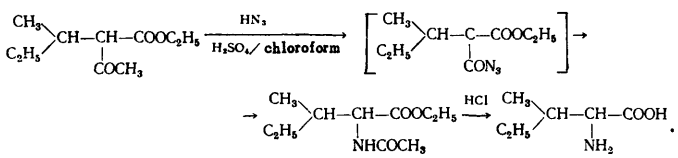
All the classical methods for the synthesis of amino-acids have been used in the preparation of leucine: amination of α-halogeno-derivatives of isocaproic acid with ammonia or hexamethylenetetramine, the Strecker synthesis from isovaleric aldehyde, and the syntheses with the aid of acetoacetic and malonic ester derivatives. Recently a number of new modifications have been proposed for the preparation of leucine [10,14,26,33,36,71,78,81-83,85,88,100,108].

Isoleucine

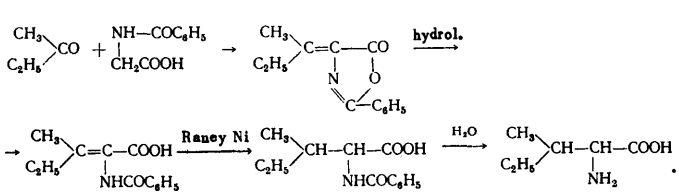
The difficulties in the synthesis of isoleucine are caused in the first place by the presence in this compound of two asymmetric carbon atoms, and hence of diastereoisomeric forms, and in the second place by the steric hindrance due to the large size of the s-butyl group. So far no methods are available for directed synthesis whereby isoleucine free from alloisoleucine could be obtained. The most favourable isoleucine : alloisoleucine ratio obtainable during synthesis is 3 : 1.

A 49% yield (after recrystallisation) of a mixture of racemic diastereoisomers containing 89% of DL-isoleucine was obtained by the bromination and amination of s-butylmalonic ester [110]. The use of acetamidocyanoacetic ester gives a 40% yield of the product with an isoleucine : alloisoleucine ratio of 3 : 1. [111] The mixture of diastereoisomers, obtained in a yield of about 60% in the reduction of the oxime of the ethyl ester of ethylmethylpyruvic acid [112] and also of its phenylhydrazone [88], contains up to 66% of isoleucine.

When isoleucine is synthesised by the Schmidt reaction, one obtains from s-butylacetoacetic ester a 40–50% yield of a mixture of racemic diastereoisomers, from which 72% of DL-isoleucine can be isolated [113,114]:



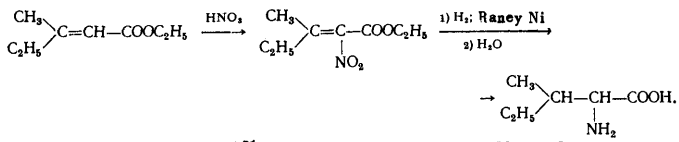
When s-butylmalonic acid is used in the same reaction as the starting material, the yield of the racemic mixture is 66%. [108] Certain modifications of the cyanohydrin synthesis make it possible to obtain a mixture of racemates containing more than 60% of isoleucine [115-117]. Attempts have been made to find stereospecific methods for the synthesis of isoleucine. 4-s-Butylidene-2-phenyloxazol-5-one, formed when ethyl methyl ketone was allowed to act on hippuric acid, was separated into two isomers by hydrolysis with alcoholic alkali. However, the subsequent reduction and hydrolysis of the *N*-benzoyl derivative of s-butylideneglycine involve partial inversion of configuration, and therefore the product contains only 78% of DL-isoleucine [113,118]:



In the preparation of isoleucine from the optically active D-isopentyl alcohol (by its oxidation to the aldehyde followed by synthesis using the cyanohydrin method) one obtains approximately equal amounts of L-isoleucine and D-alloisoleucine, which can be separated by crystallisation [119-121].

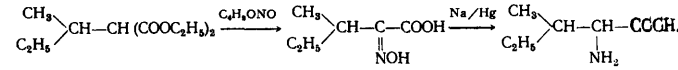
Two methods have been proposed for the conversion of s-butylcyanoacetic ester into isoleucine. The first is the Darapskii method (a modification of the Curtius rearrangement). In this case the ethoxycarbonyl group is converted into the amino-group ($COOC_2H_5 \rightarrow CONHNH_2 \rightarrow CON_3 \rightarrow \rightarrow NHCOOC_2H_5 \rightarrow NH_2$) and the carboxyl is obtained by the hydrolysis of the cyano-group. The second method is Hoffmann degradation ($CN \rightarrow CONH_2 \rightarrow NH_2$), which consists in the conversion of the cyano-group into the amino-group. The initial s-butylcyanoacetic ester has two asymmetric carbon atoms and is a mixture of racemic diastereoisomers, one of which predominates. Thus, the ratio of diastereoisomers in the resulting isoleucine depends on the method by which s-butylcyanoacetic ester is converted into isoleucine. (The investigators concerned suggest that there is no inversion of configuration in the amination and hydrolysis.) Indeed, when a non-purified ester obtained by the hydrogenation of the ethyl ester of α-cyano-β-ethyl-β-methylacrylic acid made from ethyl methyl ketone and cyanoacetic acid is used, the first method yields 60% of isoleucine in the mixture with an overall yield of the racemic diastereoisomers of 55%, while the second method gives 40% of isoleucine with an overall yield of 50%. [122,123] However, if the initial ester is made by the alkylation of cyanoacetic ester with s-butyl bromide, Darapskii's method gives 42% of isoleucine (overall yield 32%) [124] and the Hoffmann method gives about 60%. Consequently the ratio of the diastereoisomers in the initial s-butylcyanoacetic ester is not the same in the different methods of its preparation.

The amide of s-butylcyanoacetic acid is converted into isoleucine by the Hoffmann method in a single stage with a yield of 46%. [125] The yield of isoleucine obtained from the amide of s-butylmalonic acid is 74%. [126] s-Butylideneacetic acid prepared from ethyl methyl ketone and bromoacetic acid by the Reformatskii reaction can be converted into isoleucine in two ways. The first involves the usual operations: hydrogenation, bromination in the α-position, and ammonolysis. Isoleucine is then obtained in 32% yield, the isoleucine : alloisoleucine ratio being 71 : 29. The second procedure involves nitration with 81% nitric acid free from nitrogen oxides, followed by reduction:

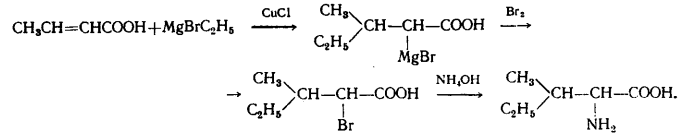


The yield is about 20% and the isoleucine : alloisoleucine ratio is 77 : 23.

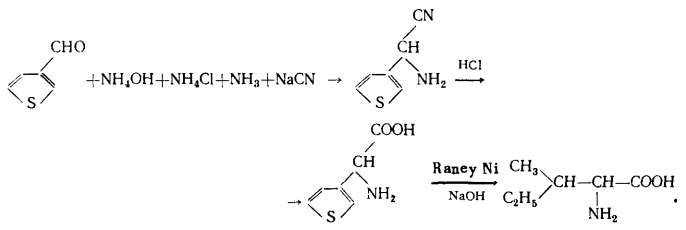
Isoleucine is formed in the reduction of α-hydroxyimino-β-methylvaleric acid obtained by the nitrosation of s-butylmalonic ester with butyl nitrite [114]:



A synthesis of isoleucine from crotonic acid using a Grignard reagent has been proposed recently [127]. It involves the following mechanism:



An interesting study has been made of the preparation of isoleucine from thiophen. 3-Thienylglycine obtained from thiophen-3-aldehyde by the Strecker method is subjected to reductive desulphurisation with Raney nickel, an equimolar mixture of DL-isoleucine and DL-alloisoleucine being obtained with an overall yield of 23%:

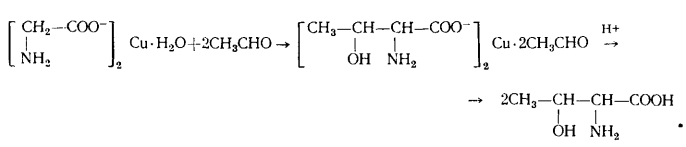


The 3-thienylglycine was separated into the optical isomers. Desulphurisation of the L-isomer gives a 21.5% yield of a product containing more than 50% of L-alloisoleucine. The investigators suggest that the conformation of the molecule adsorbed on the catalyst is stereochemically more favourable for the formation of the *allo*-form [128]. We shall see below, in the examination of the methods of synthesis of threonine, that those involving catalytic hydrogenation result in the preferential formation of the *allo*-isomer.

Threonine

The characteristic features of the chemical synthesis of threonine (α-amino-β-hydroxybutyric acid) are due to the necessity to introduce into the molecule both the amino- and the hydroxy-group. In the threonine molecule there are two centres of asymmetry (as in isoleucine) and therefore there exist two diastereoisomeric forms, of which only the L-*threo*-form is the natural amino-acid.

At the present time one may regard as the best the method of synthesis of threonine proposed by Akabori, which consists in the Knoevenagel condensation of the copper complex of glycine with acetaldehyde in the presence of alkaline reagents [129]:



In this reaction the complexed copper successfully combines the functions of activating the hydrogen atom in the methylene group and of protection of the amino-group. Since the copper complex of allothreonine is much more soluble than the threonine complex, the mixture of copper threoninates obtained in the reaction is convenient for the separation of the diastereoisomers [130-133]. The free amino-acids are isolated by the decomposition of the complex with hydrogen sulphide or on an ion-exchange resin. The amount of DL-threonine in the reaction product exceeds by a factor of two the amount of DL-allothreonine. This is virtually the principal value of the Akabori method, since other methods serve essentially for the preparation of allothreonine and the inversion of allothreonine into *threo*-threonine with thionyl chloride gives rise to additional difficulties and is not adequately effective [134,135].

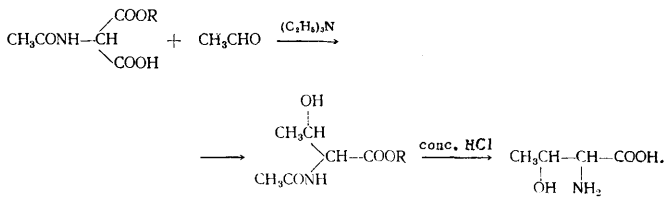
The undoubted advantages of the method described above include the small number of stages (two stages, including the isolation of the free amino-acid), good yields, speed, availability of the starting materials, and the possibility of regenerating the copper. A large number of papers and patents are devoted to the development of this method of preparing threonine. The principal results of these investigations are as follows. (1) The use of methanol as the solvent instead of water improves the yields and favours the formation of a purer crystalline product; (2) when the reaction is carried out under more severe conditions (elevated temperature, higher alkalinity of the medium), and the content of the *threo*-form in the product increases, but the overall yield falls (it has been shown that the copper complex of threonine is more stable under severe conditions than the complex of the *allo*-form); (3) the addition of pyridine increases the overall yield [129,136-143].

There is a patent describing the preparation of threonine (*threo* : *allo* = 3 : 1) by the reaction of copper glycinate with vinyl acetate in an aqueous medium in the presence of potassium carbonate [144].

Akabori investigated the reaction of acetaldehyde with cobalt triglycinate, which exists in two isomeric forms (α and β). The overall yield of the isomeric threonines, particularly with the β-form of the complex, is poorer than with copper glycinate, but the ratio of the *threo*- and *allo*--forms is more favourable (7.6 instead of 2.9). The poorer yield may be due to the much greater stability of cobalt glycinate compared with copper glycinate, and the change in the ratio of the *threo*- and *allo*-forms with temperature and duration of the reaction confirms that the stability of the cobalt threoninates is different [145]. An attempt has been made to obtain optically active threonine with the aid of the optically active cobalt complex of the type L-$[Co(EH)_2GLY]I_2$, where EH is ethylene- or propylene--diamine. The asymmetric yield of threonine was only about 8%. [146-148]

The possibilities of the Akabori methods are not restricted to the preparation of threonine. The use in this reaction of formaldehyde and other aldehydes and ketones and also of copper alaninate (instead of the glycinate) makes it possible to obtain a wide variety of α-amino-β-hydroxy--acids [109,149-154].

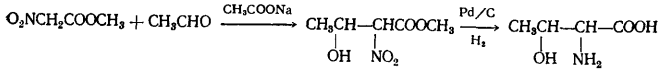
Recently a relatively simple general method has been proposed for the synthesis of α-amino-β-hydroxy-acids by the condensation of aldehydes with acetamidomalonic acid or its half-ester, which is a modification of King's method [155] (preparation of serine by the condensation of formaldehyde with ethyl acetamidomalonate):



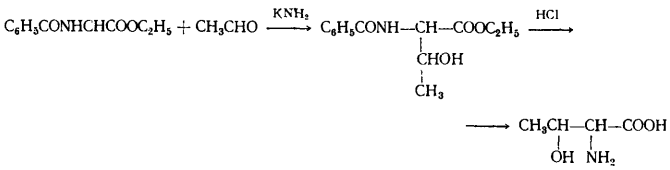
When R = H, serine is obtained in 50.4% yield and when R = CH_3, 53% of threonine consisting of 95% of the *allo*--form and 5% of the *threo*-form is obtained [156,157].

The synthesis of threonine based on nitroacetic ester is fairly simple and convenient. Methyl nitroacetate condenses smoothly with acetaldehyde, methyl α-nitro-β--hydroxybutyrate being obtained Its hydrogenation over

5% palladium on charcoal in a methanol–acetic acid mixture gives an equimolar mixture of the diastereoisomeric threonines with an overall yield of 66%:

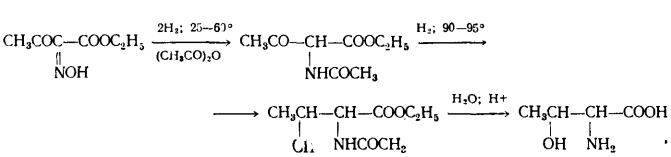


The reduction of α-nitrocrotonic acid in the presence of Raney nickel in methanol results, together with the normal reduction to α-aminobutyric acid, in the addition of methanol to the double bond and subsequent reduction to *O*-methylthreonine [13]. There are a number of patents describing syntheses of threonine. A 52% yield of threonine (the ratio of the *threo*- and *allo*-forms is not indicated) was obtained by the condensation of ethyl hippurate with acetaldehyde in the presence of alkali metal amides [158]:

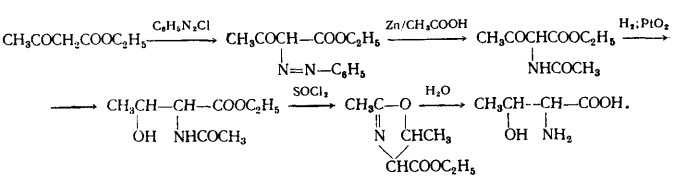


In another synthesis glycine and paraldehyde are condensed in dilute alcoholic solution of hydrochloric acid [159]. The treatment of the Schiff base obtained from aminoacetonitrile and formaldehyde with acetaldehyde followed by hydrolysis probably also yields threonine [160].

The syntheses of threonine from acetoacetic ester derivatives with a nitrogen-containing group in the α-position (=NOH or $=NOC_2H_5$; [161-163] $NHCOCH_3$; [170] $-N=NC_6H_5$ or $-NH-N(C_6H_5)(COCH_3)$ [164-169]) are based on the catalytic hydrogenation of the nitrogen-containing group to the amino-group and of the carbonyl group to the hydroxy-group. The reduction is performed in one or two stages (the nitrogen-containing group is reduced first and then the carbonyl group). The reaction involves 3–4 stages, but the amount of the *threo*-form in the mixture of epimers, which is obtained as a rule in a high yield, does not exceed 30–40% in the most favourable cases, the usual percentage being not more than 15–20. For example, threonine is obtained in an overall yield of about 70% from α-hydroxyiminoacetoacetic ester, the ratio of the *threo*- and *allo*-forms being 21 : 79: [162]

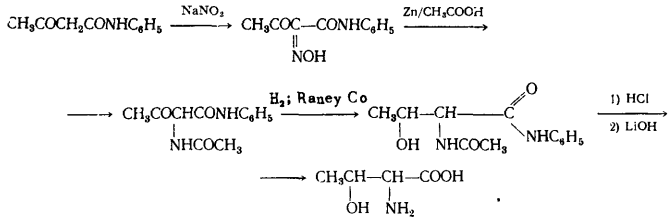


The preparation of threonine via the α-phenylazoacetoacetic ester has been investigated in detail:



After hydrogenation the product contains 80–85% of the *allo*-form of the ethyl ester of *N*-acetylthreonine. Under the action of thionyl chloride the configuration is inverted and a mixture containing 83% of DL-threonine is produced. The overall yield is 57%. [164]

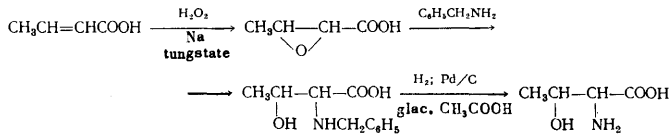
The use of a stereospecific hydrogenation catalyst, Raney cobalt, to increase the content of the *threo*-form in the mixture of diastereoisomers obtained by the reaction



has been described. The reaction products contain 56% of *threo*-threonine [171].

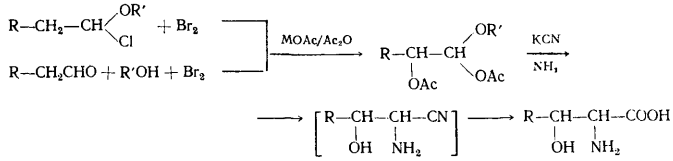
The first practical method of preparing threonine, which is also a general method for the preparation of α-amino-β-hydroxy-acids, was developed by Carter [172,173]. Its principle consists in the addition of hypobromous acid to unsaturated acids. It was established that this reaction takes place in only one way, with formation of α-bromo-β-hydroxybutyric acid (the second isomer, α-hydroxy-β-bromobutyric acid, does not form), which can be converted by amination into threonine, consisting mainly of the *allo*-form. Carter was the first to demonstrate the existence of threonine diastereoisomers, separated the epimeric racemates, isolated natural threonine, and investigated the interconversions of the *threo*- and *allo*-forms via the azlactone [174]. Modifications of this method are used for the synthesis of allothreonine [175-177].

The possibility of the selective synthesis of diastereoisomeric α-amino-β-hydroxy-acids has been demonstrated recently. Pure allothreonine was obtained in an overall yield of 50% by the following reaction [178]:



The epoxy-ring is opened in this process exclusively with the formation of the α-amino-β-hydroxy-acid, without admixtures of the α-hydroxy-β-amino-acid. Furthermore, ring opening takes place in such a way that the initial *trans*-form of the acid gives only *erythro*-isomers and the *cis*-form gives only *threo*-isomers. Unfortunately, the preparation of *threo*-threonine by this procedure has not been described; however, pure *threo*- and *erythro*-isomers of β-hydroxy-DL-aspartic acid have been obtained from maleic and fumaric acids [179].

Until recently Strecker's method for the synthesis of α-amino-β-hydroxy-acids has not been used, except for serine, since under the conditions of this reaction higher hydroxy-aldehydes isomerise to hydroxy-ketones. However, when acylal ethers of α-hydroxy-aldehydes are used, the reaction is successful:



M = Na for R containing up to three carbon atoms and M = Ag for R containing more than three carbon atoms. The yields

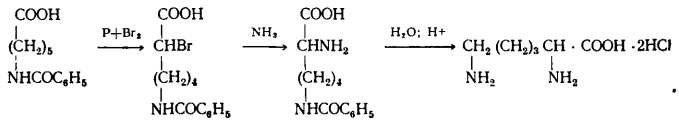
are 60–80% for R ranging from CH_3 to C_4H_9 and 45–60% for R ranging from C_5H_{11} to $C_{10}H_{21}$, i.e. are in general higher than is usual in the Strecker synthesis [180,181]. α-Alkoxypropionaldehyde is converted into threonine in 44% yield with the ratio *threo* : *allo* = 3 : 2. [182]

At the present time there are a number of fairly reliable methods for the quantitative and semi-quantitative estimation of the diastereoisomeric threonines in a mixture. These methods include paper chromatography [146], infrared spectroscopy [183], and gas–liquid chromatography [184,185].

Lysine

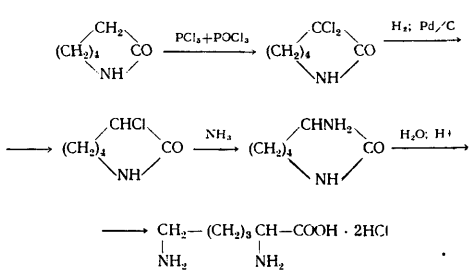
The problem of the chemical synthesis of lysine (αω-diaminocaproic acid) continues to attract the attention of many investigators. Among the methods available at present for the synthesis of lysine there are some which have been developed in detail and others which only provide a guideline for further research. To facilitate the exposition, the data have been grouped as follows: (1) syntheses of lysine from ε-aminocaproic acid derivatives, in particular from caprolactam; (2) syntheses based on telomerisation products; (3) syntheses by the cyanohydrin method; (4) other methods.

ε-Benzoylaminocaproic acid and caprolactam are the traditional starting materials for the synthesis of lysine. The at first sight simple problem, the introduction of only one amino-group into the α-position of an otherwise "finished" molecule, has been solved over a period of almost sixty years. In one of the first syntheses of lysine ε-benzoylaminocaproic acid was obtained in a three-stage synthesis from *N*-benzoylpiperidine and then converted into lysine as follows:

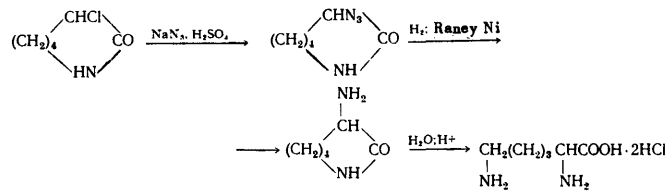


Although this synthesis is still extremely imperfect, it served as the basis for further studies [186]. Initially, caprolactam served as the starting material for the preparation of ε-benzoylaminocaproic acid. In many of the subsequent investigations improved methods of halogenation [187,188] and ammonolysis were employed (in particular bromination was replaced by chlorination with sulphuryl chloride) [189]. Rational utilisation of these advances made it possible to increase the yield of lysine from 23 to 68% with respect to caprolactam [190].

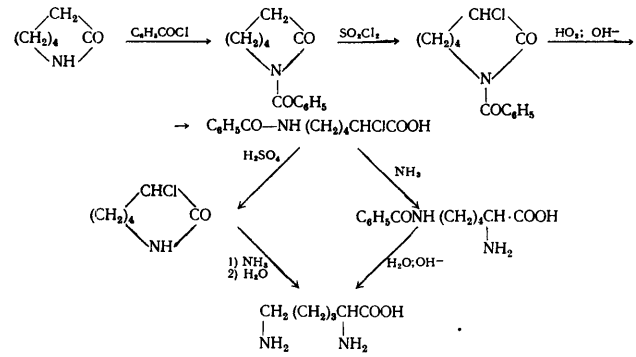
Later the attention of investigators was attracted to the possibility of direct halogenation and amination of caprolactam. It was found that in this case a complication arises in the halogenation, since two halogen atoms are introduced simultaneously into the caprolactam molecule, and in order to obtain α-chloro-ε-caprolactam it is necessary to reduce the dihalogeno-derivative formed initially:



A fundamental study has been made of the conditions of the chlorination and bromination of both caprolactam itself and its acetyl derivative, the conditions of the ammonolysis of α-halogeno-ε-caprolactam with aqueous and liquid ammonia in the presence of various salts, and the conditions of the hydrolysis of α-amino-ε-caprolactam. When optimum conditions are provided, the yield of lysine amounts to about 50% with respect to ε-caprolactam [191–193]. α-Amino-ε-caprolactam and then lysine can be obtained with the same yield by the reduction and subsequent hydrolysis of α-azido-ε-caprolactam [194,195]:

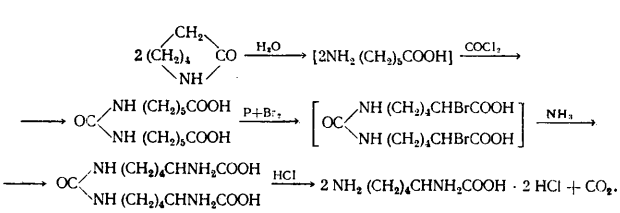


In contrast to ε-caprolactam, *N*-benzoyl-ε-caprolactam can be monochlorinated in the α-position. Then one obtains by alkaline hydrolysis ε-benzamido-α-chlorocaproic acid, whose subsequent conversion into lysine can be achieved in two ways:



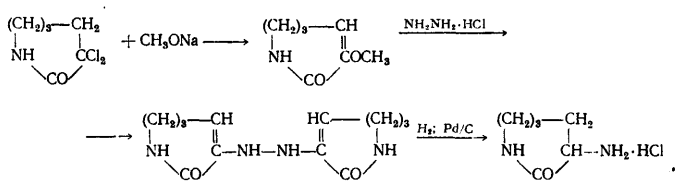
Amination with subsequent hydrolysis gives lysine in an overall yield of 73% and debenzoylation followed by hydrolysis and amination gives a 60% yield of lysine [196].

Apart from these procedures developed in detail, a number of modifications have been outlined, whereby it is possible to avoid certain difficulties in the existing syntheses, but these procedures require further development. For example, a new method has been proposed for the protection of the amino-group in aminocaproic acid with the aid of phosgene:

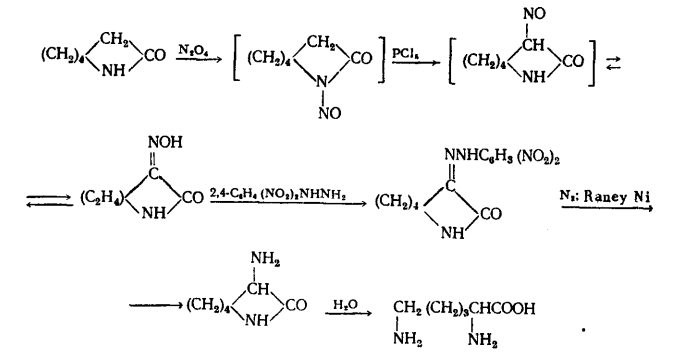


The overall yield of lysine is only 11%. [197,198]

A patent describes a method for the preparation of α-amino-ε-caprolactam from αα-dichloro-ε-caprolactam and hydrazine hydrochloride by the following mechanism[199]:

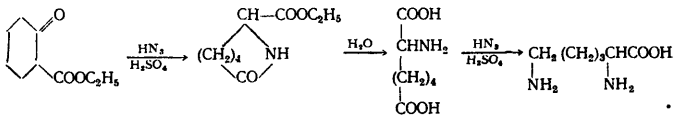


It has been shown that lysine can be synthesised via α-hydroxyiminocaprolactam. Treatment of caprolactam with nitrogen tetroxide gives an *N*-nitroso-compound, which rearranges into α-hydroxyimino-ε-caprolactam under the action of phosphorus pentachloride. The product is converted into the dinitrophenylhydrazone of α-oxo-ε-caprolactam from which α-amino-ε-caprolactam is obtained after hydrogenation:



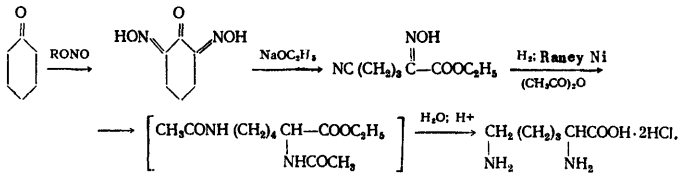
This fundamentally new reaction makes it possible to eliminate the halogenation stage[200,201].

The Schmidt reaction has been used in an interesting way for the preparation of lysine from 2-ethoxycarbonylcyclohexanone:



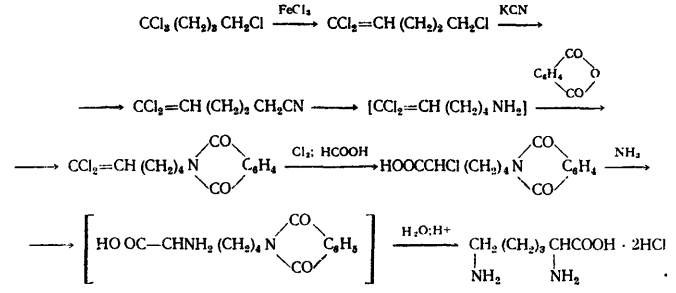
The overall yield is 60%. Only the ω-carboxy-group reacts[202].

It has recently been stated that α-nitro-ε-caprolactam can be used as the starting material for the synthesis of lysine[28]. An original procedure involving the use of cyclohexanone in the synthesis of lysine, which has been developed by Ferris, includes three stages: (1) preparation of 2,6-dihydroxyiminocyclohexanone by the nitrosation of cyclohexanone with alkyl nitrites in ether containing hydrochloric acid; (2) reaction of 2,6-dihydroxyiminocyclohexanone with sodium ethoxide in alcohol in the presence of acetic anhydride (Beckmann rearrangement of the "second kind")[203,204] with formation of the ethyl ester of 5-cyano-2-hydroxyiminovaleric acid; (3) hydrogenation of this ester in the presence of Raney nickel in acetic anhydride containing sodium acetate with subsequent hydrolysis using hydrochloric acid. The overall yield of lysine monohydrochloride is 63%:[205-208]

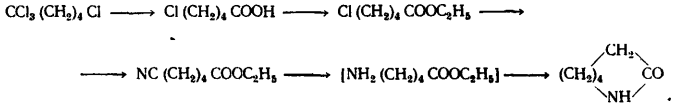


In a similar way ornithine was obtained from cyclopentanone and 4-methyl-lysine from 4-methylcyclohexanone[209,210].

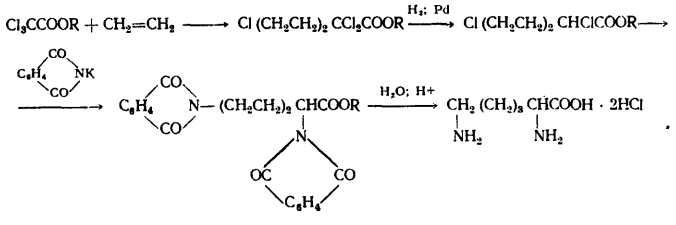
New possibilities arose in the field of synthesis of amino-acids and in particular lysine in connection with the telomerisation reaction. As already stated, ααaω-tetrachloroalkanes, which have now become available, serve as the starting material for the preparation of various amino-acids. The following procedure has been proposed for the synthesis of lysine from ααaω-tetrachloropentane[6,7,211,212]:



The overall yield of lysine is 44%. It has also been suggested that ε-caprolactam be obtained from tetrachloropentane[213]:

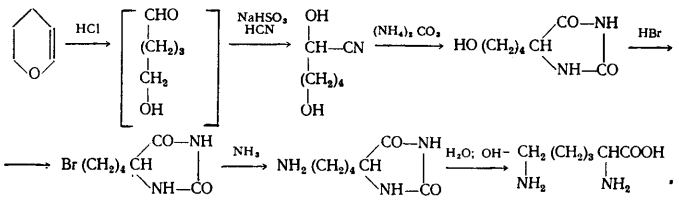


The ε-caprolactam is then converted into lysine, by the already known mechanism, via *N*-benzoylcaproic acid. One of the principal products of the telomerisation reaction of ethylene and trichloroacetic acid is ααω-trichlorocaproic acid — a new starting material for the synthesis of lysine. Hydrogen is substituted for one of the chlorine atoms in the α-position by hydrogenation and then the remaining α- and ω-chlorine atoms are replaced by amino-groups with the aid of potassium phthalimide:

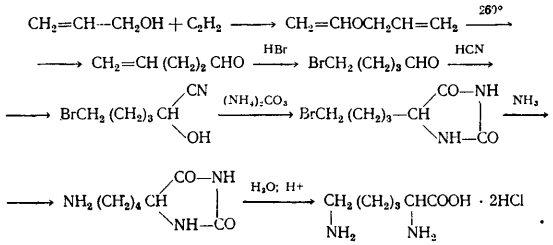


The yield of lysine is 53% with respect to the ester of ααω-trichlorocaproic acid. Simple ammonolysis is recommended for technical synthesis. This method undoubtedly merits attention in view of its exceptional simplicity and the availability of the starting materials[214].

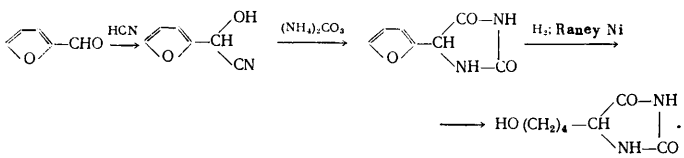
The oldest methods include the synthesis of lysine by the cyanohydrin method. Here one must mention the Gaudry method, which has also been studied by other investigators:



The initial dihydropyran is converted by the action of hot dilute hydrochloric acid into δ-hydroxyvaleric aldehyde, from which 5-(4-hydroxybutyl)hydantoin is obtained by treatment with hydrogen cyanide and ammonium carbonate. The next stages are replacement of the hydroxy-group by a halogen and ammonolysis; acid or alkaline hydrolysis complete the synthesis. The yield of the product is 30–40%.[215,216] Modifications of this method make it possible to obtain up to 51% of lysine[217]. The search for a readily available raw material for the preparation of the aldehyde component is being continued. Thus a patent describes the preparation of lysine (and other amino-acids) via vinyl ethers[218]:



5-(4-Hydroxybutyl)hydantoin can be obtained from the readily available furfural:

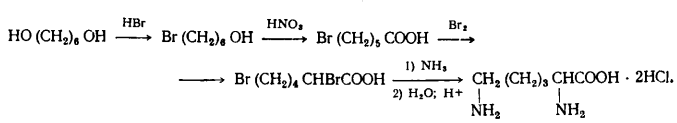


The hydantoin is then converted into lysine by the method described above. The total yield is 32%.[219]

Lysine can be obtained from piperidine in the following way. *N*-Chloropiperidine, formed when piperidinium acetate is acted upon by calcium or sodium hypochlorite, is dehydrohalogenated by booling with alcoholic alkali. The reaction product, the α-trimer of 2,3,4,5-tetrahydropyridine, is treated with ammonium carbonate, hydrogen cyanide, and water, lysine being isolated after purification on an ion-exchange resin[220].

Malonic ester synthesis has been widely used for the preparation of lysine. The use of malonic[221,222] and acetamidomalonic[223-225] esters has been described. δ-Bromovaleric acid[222], γ-chlorobutyronitrile[221], 1-bromo-4-chlorobutane[223], and acrolein[224,225] have served as components in these syntheses. The yields of lysine reach in some cases 30–40%[222] and even 55%.[223]

When hexane-1,6-diol is used as the starting material, it is possible to obtain lysine by the following simple operations:



The overall yield is 38%. The greatest difficulties in the synthesis are associated with the selective replacement of a hydroxyl by a halogen and the oxidation of the primary alcohol group to the carboxyl[227].

α-Aminogluconic acid can be converted into 5-hydroxylysine, the reduction of which gives lysine itself[228]. In the synthesis of lysine by the Finkbeiner method the chelate complex of 3-phenylhydantoin and methylmagnesium bromide can be alkylated with *N*-(4-bromobutyl)phthalimide[33,34].

Attempts have recently been made to obtain L-lysine by the Kolbe electrochemical reaction. A mixture of the monomethyl ester of *N*-phthaloyl-L-glutamic acid and *N*-phthaloyl-β-alanine was electrolysed in dimethylformamide. After appropriate treatment L-lysine was obtained in amounts which so far are only of theoretical importance[226].

In conclusion it is appropriate to mention that L-lysine for food and fodder additives can be obtained by combining chemical synthesis with stereospecific microbiological synthesis. For example, diaminopimelic acid prepared from ethoxydihydropyran is converted with the aid of *Bacillus sphaericus* into L-lysine. This method is also suitable for the separation of synthetic DL-lysine into optical isomers[229]. A combination of chemical and biological syntheses has been proposed by Ferris and coworkers. 2-Hydroxyiminoadipic acid is obtained by the hydrolysis of 5-cyano-2-hydroxyiminovaleric acid [synthesised from 2,6-di(hydroxyimino)-cyclohexanone]. This substance is added to a nutrient medium containing baker's yeast, lysine being isolated after fermentation[230].

Tryptophan

The chemical synthesis of tryptophan can be conveniently examined using the following classification of methods proposed by Hellmann in his review published in 1949.[231]

I. Syntheses from compounds containing the indole ring.

a. Condensation of indole-3-aldehyde with compounds containing an active methylene group.

b. Alkylation of esters of acylamino- and nitro-acids with gramine and diethylaminomethylindole.

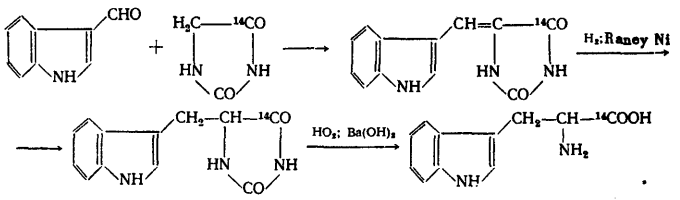
c. Alkylation of indole with various reagents.

II. Syntheses involving the formation of the indole ring.

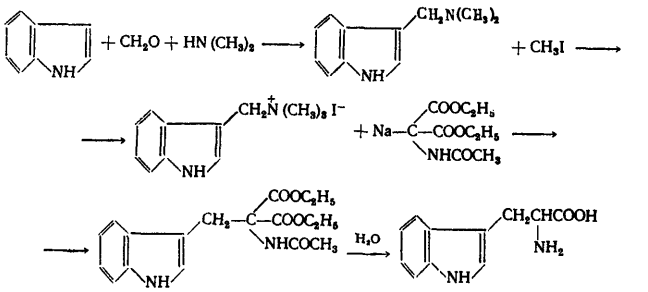
The syntheses of the first group, in particular the alkylation with gramine, have been studied extensively and are sufficiently simple for the preparation of tryptophan under laboratory conditions.

The preparation of tryptophan by the condensation of indole-3-aldehyde with benzoylglycine (the azlactone method) is

not used at the present time. The condensation of indole-3-aldehyde with hydantoin is used for the synthesis of tryptophan labelled at the carboxyl[232]:

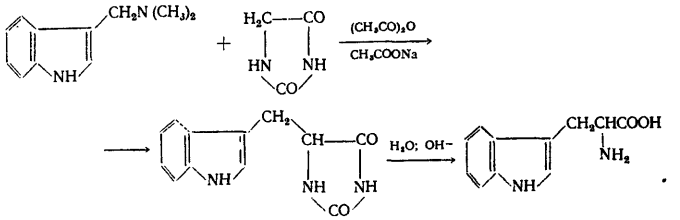


Gramine (dimethylaminomethylindole), obtained by the Mannich reaction from indole, formaldehyde, and dimethylamine, is widely used in tryptophan syntheses. For example, tryptophan can be obtained by the following reaction from acetamidomalonic ester and gramine[233,234]:

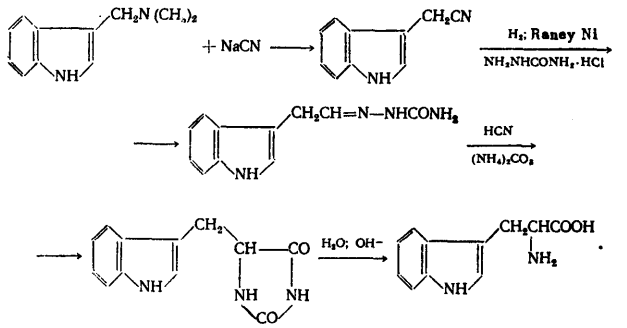


The yields of tryptophan reach 66% with respect to indole[235,236]. When formamidomalonic ester is used instead of acetamidomalonic ester and diethylaminomethylindole instead of gramine, the yield of tryptophan increases to 90%.[237] The following esters have also been alkylated with gramine in the same way (the percentage yields with respect to gramine are indicated in brackets): acetylcyanoacetic (71, with respect to indole)[83], acetamidoacetoacetic[238], acetoacetic (58)[239,240], cyanoacetic (22)[239], nitroacetic (45)[10,11], and nitromalonic (77)[19].

Gramine has been used in the synthesis of tryptophan hydantoin[241]:



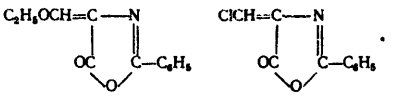
β-Indolylacetonitrile, obtained in quantitative yield by the alkylation of cyanide salts with gramine, serves as a new starting material in the synthesis of tryptophan:



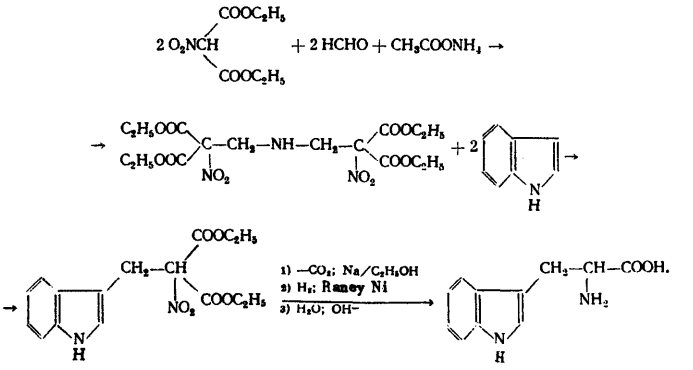
The semicarbazone of β-indolylacetaldehyde is prepared by the reduction of 3-indolylacetonitrile in the presence of semicarbazide. The semicarbazone is obtained as the *syn*-isomer, which on standing is converted into the more stable *anti*-isomer. The *syn*-isomer is more reactive and is converted into hydantoin in 66% yield, while the yield of hydantoin from the *anti*-isomer is 38%. The hydantoin is hydrolysed in the usual way and tryptophan is isolated in an overall yield of 33% with respect to gramine[242].

Gramine has been used as the alkylating agent in the preparation of tryptophan by the Finkbeiner method[33].

The procedures for the preparation of tryptophan in which indole is the starting material are simpler, since the necessity for the synthesis of gramine is eliminated. Alkylation of indole by a Mannich base derived from piperidine, formaldehyde, and formamidomalonic ester followed by hydrolysis and decarboxylation gives tryptophan in 71% yield[243]. A new method for the preparation of azlactones by the alkylation of indole with 4-ethoxymethylene-2-phenyl-5-oxazolone[244] and 4-chloromethylene-2-phenyl-5-oxazolone[245] makes it possible to obtain tryptophan in two stages with yields up to 75%:

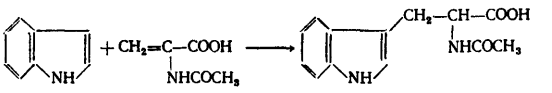


The key reaction in a new synthesis of tryptophan based on nitromalonic ester is the alkylation of indole with 1,1,5,5-tetraethoxycarbonyl-1,5-dinitro-3-azapentane — a Mannich base obtained from nitromalonic ester, formaldehyde, and ammonia:



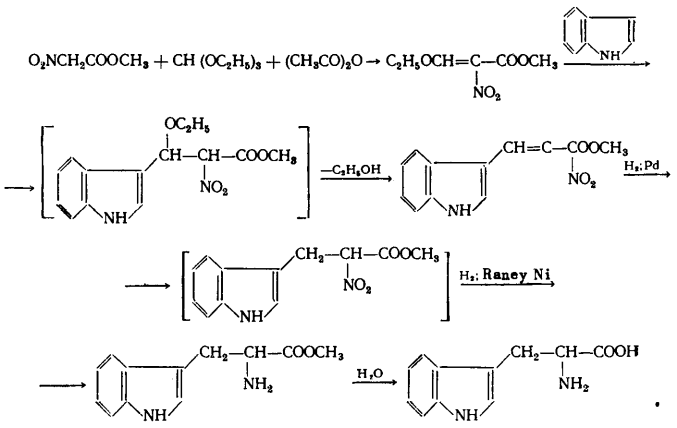
The decarboxylation, reduction of the nitro-group, and hydrolysis are carried out without isolating the intermediates. The overall yield with respect to indole is 50%.[20,21]

A simple method for the synthesis of *N*-acetyltryptophan in 57.7% yield consists in the addition of indole to α-acetamidoacrylic acid:

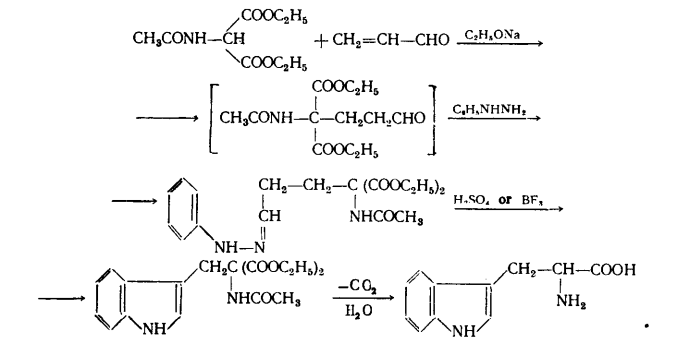


N-Acetyl-2-methyltryptophan and *N*-acetyl-7-methyltryptophan were obtained similarly[246].

Tryptophan has been obtained in 45% yield with respect to indole by an original method based on nitroacetic ester, using ethoxynitroacrylic acid as an intermediate[247]:

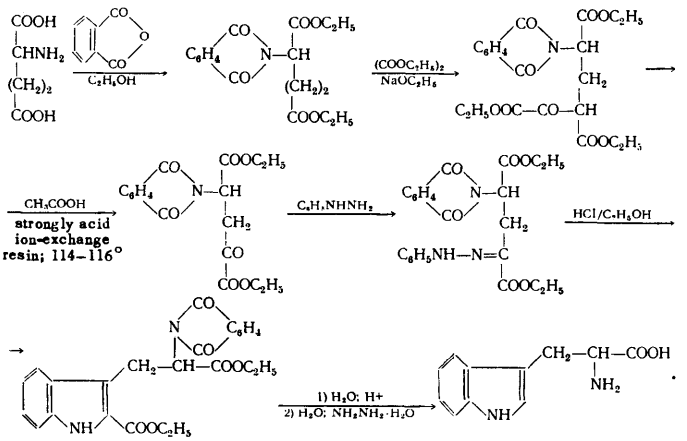


In all the cases examined the indole ring is introduced as such into the molecule, i.e. essentially each synthesis is only a partial synthesis of tryptophan. The Fischer reaction made it possible to perform the complete synthesis of tryptophan from starting materials not containing indole. The condensation of acetamidomalonic ester with acrolein must be regarded as the most successful procedure of this kind. The condensation product is treated with phenylhydrazine and the resulting phenylhydrazone is cyclised:



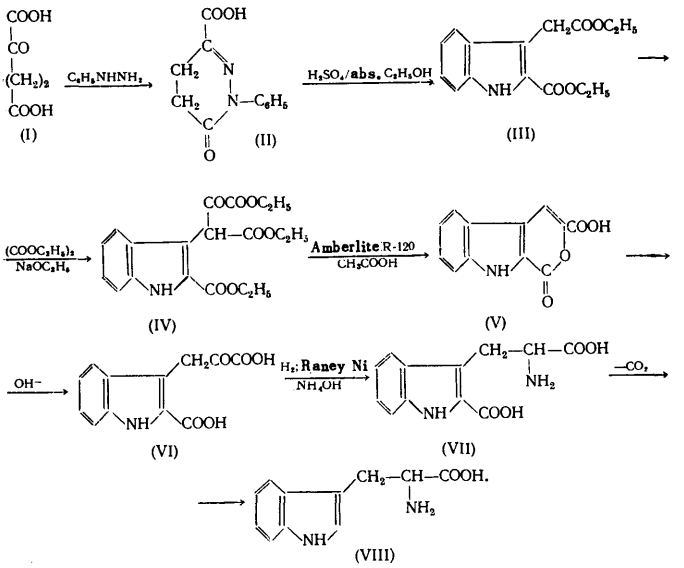
The overall yield with respect to acetamidomalonic ester is 43%.[248-250] Ion-exchange resins can be used as catalysts of the condensation of acrolein with acetamidomalonic ester and the cyclisation of phenylhydrazone[251].

In 1961 an attempt was made to prepare optically active tryptophan from optically active L-glutamic acid by the reaction

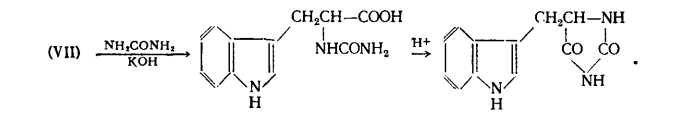


However, the attempt was unsuccessful, since racemisation takes place in the condensation with diethyl oxalate in an alkaline medium[252].

Another similar method is the synthesis of tryptophan from oxoglutaric acid, which includes seven stages with an overall yield of 35% (with respect to the initial acid)[253]:



A modification, starting with the conversion of the intermediate pyrone derivative (V), has been described in a patent[254]. Compound (V) is converted into β-(2-carboxy-3-indolyl)pyruvic acid (VI), which is reductively aminated to β-(2-carboxy-3-indolyl)-α-aminopropionic acid (VII). Further conversion of compound (VII) takes place by the mechanism



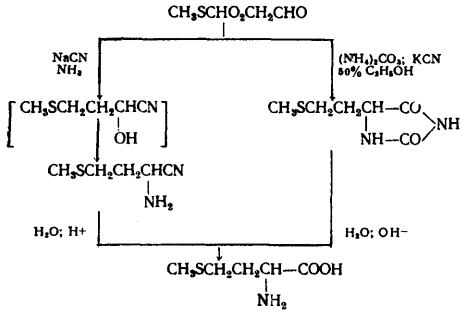
The hydantoin is hydrolysed and tryptophan is obtained in 50% yield. There is also a patent concerning the decarboxylation of compound (VII).[255] Tryptophan hydantoin can be obtained by the condensation of the phenylhydrazone of β-(hydantoin-5-yl)propionaldehyde. The latter was prepared by the reduction of 5-(β-cyanoethyl)hydantoin in the presence of phenylhydrazine[256,257].

Methionine

Methionine (α-amino-γ-methylthiobutyric acid) is the most important source of sulphur and plays an exceptionally important role in metabolism. The methods for the synthesis of methionine have not changed significantly in recent years. At the present time there are three fairly thoroughly developed procedures for the synthesis of methionine: (1) the cyanohydrin method; (2) syntheses with the aid of esters; (3) syntheses based on butyrolactone. The cyanohydrin method must be regarded as the most convenient and the most suitable for industrial manufacture. The starting material is β-methylthiopropionaldehyde which is obtained in good yield by the catalytic addition of methanethiol to acrolein[258,259]:

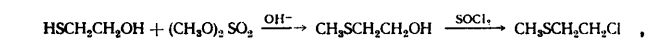
$$CH_3SH + CH_2{=}CHCHO \rightarrow CH_3SCH_2CH_2CHO$$

β-Methylthiopropionaldehyde is converted into methionine via an aminonitrile[258-263] or via hydantoin[250,259,264]:



If the reaction is performed at atmospheric pressure, the process via hydantoin gives best results (the total yield with respect to acrolein is 60%).[264] The application of pressure makes it possible to obtain in high yield α-amino-γ-methylthiobutyronitrile, the hydrolysis of which gives methionine. The yield of methionine is 82%,[260] but according to other data it is almost quantitative[262].

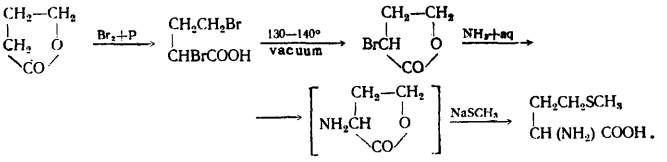
In the synthesis of methionine based on acetic and malonic ester derivatives α-chloro-β-methylthioethane, obtained from ethylene monothioglycol,



is used as the alkylating agent. The yield varies from 70 to 90% depending on the purity of the starting material[265]. Acetamidocyanoacetic[88], phenylacetamidocyanoacetic[85], acetamidomalonic[266], formamidomalonic[267], and phthalimidomalonic[265,268] esters were alkylated with α-chloro-β-methylthioethane. The alkylated esters were then converted by simple operations (hydrolysis, decarboxylation) into the amino-acid, the yields varying from 24 to 60%.

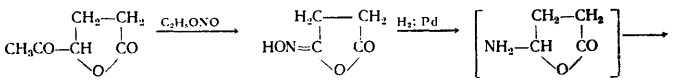
The phenylhydrazone of γ-methylthio-α-oxobutyric acid, obtained by the action of phenyldiazonium chloride on (β-methylthio)ethylcyanoacetic ester, gives a 49% yield of methionine on reduction with zinc in hydrochloric acid[89]. The ethyl ester of (β-methylthio)ethylcyanoacetic acid has been converted into methionine by the Darapskii method ($-COOC_2H_5 \rightarrow CONHNH_2 \rightarrow CON_3 \rightarrow NHCOOC_2H_5 \rightarrow NH_2$).[124]

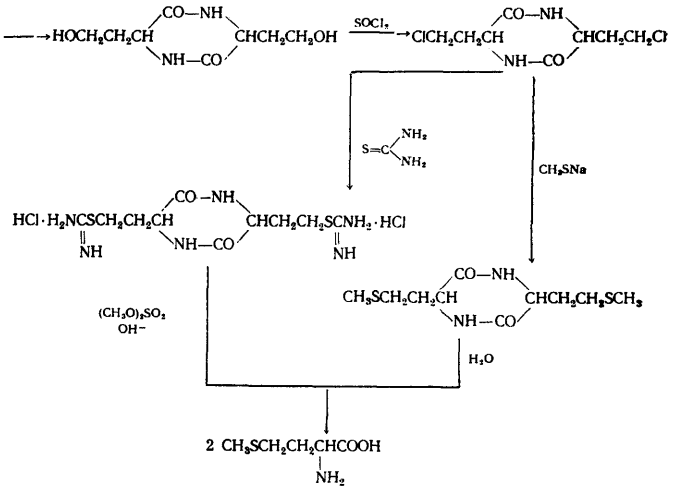
Butyrolactone can be converted into methionine in several ways. The simplest method includes four stages:



The total yield is 37%.[269]

In the free state α-amino-γ-butyrolactone readily dimerises with the formation of dioxopiperazine, which can serve as an intermediate in the synthesis of methionine:

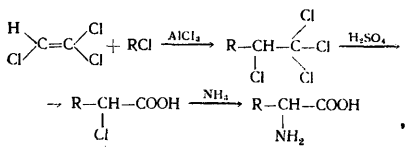




The total yield of the amino-acid when the methylthio-group is introduced with the aid of sodium methylsulphide amounts to 24% with respect to the butyrolactone[270]; 36% of methionine is obtained via the thiuronium salt[271]. α-Amino-γ-butyrolactone can be converted into α-amino-γ-hydroxybutyric acid and then into methionine by the halogenation of the hydroxy-group and the replacement of the halogen by CH_3S. The amino-group is protected by benzoylation[272] or the hydantoin is obtained[273].

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During the preparation of this review for printing, several papers on the synthesis of essential amino-acids were published. Baumgarten and coworkers continued the study of the general method for the preparation of α-amino-acids from imino-esters[274] which they proposed earlier[40]. A general method for the synthesis of α-amino-acids by the carboxylation and alkylation of hydantoin was put forward by Finkbeiner[275]. A new synthesis of DL-isoleucine and DL-valine from trichloroethylene and alkyl chlorides takes place as follows:



where R = $CH_3-CH-CH_3$ or $CH_3-CH-C_2H_5$. DL-Isoleucine and DL-alloisoleucine are obtained in a ratio of 35 : 65.[276]

Perekalin et al. suggest that the dihydrochloride of lysine be obtained from butadiene and nitroacetic ester. Butadiene is nitrohalogenated, the resulting halogenonitrobutene is alkylated with ethyl nitroacetate, and then the ethyl ester of 2,5-dinitrohex-4-enoic acid is reduced with hydrogen in the presence of acid palladium and hydrolysed with hydrochloric acid[277].

A new modification of the Akabori method[278] for the preparation of threonine was put forward. An increase in the amount of alkali used in the reaction made it possible to reduce the reaction time to 30 min and to reduce the temperature. The threonine : allothreonine ratio in the reaction product is 41 : 9, the overall yield of the diastereoisomers being 86%.

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U.D.C. 546.263

CARBON SUBOXIDE IN ORGANIC SYNTHESIS

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I. INTRODUCTION

Carbon suboxide C_3O_2 (dioxoallene, dioxopropadiene), discovered by Diels in 1906, is a very unusual compound with four cumulative double bonds. The first investigations of Diels and coworkers [1] showed that it should be regarded as an internal dianhydride of malonic acid. Like methylene, carbon suboxide should be included, in principle, among the few "key compounds", and the study of its chemical properties will undoubtedly lead to the discovery of new and specific methods of organic synthesis.

Although carbon suboxide was actually discovered before keten, it has been much less investigated. Nevertheless malonic addition reactions occupy a fairly important position in practical organic chemistry. The malonyl radical is known to be incorporated in many biologically active compounds: barbiturates, pyrazolidinediones, substituted esters and amides of malonic acid, etc.

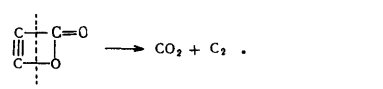
Nowadays, in the practical application of malonic addition reactions malonic acid, diethyl malonate, and malonyl dichloride are used. Compared with these compounds, carbon suboxide has a number of advantages, which consist in high yields of the desired products, their relative purity, and in the specificity of the reactions which take place only when carbon suboxide is used.

There exists no general review of the literature in which the reactivity of carbon suboxide with respect to various classes of chemical compounds is considered systematically. Grauer's review [2] published in 1960 covers the literature up to 1956 only and is far from complete. Of the earlier work, one may mention the paper of Vol'kenshtein [3], who more than thirty years ago drew attention to the promising possible applications of carbon suboxide. Recently carbon suboxide has been increasingly attracting the attention of investigators both in the Soviet Union and abroad.

The aim of the present article is to describe the present state of the chemistry of carbon suboxide, a knowledge of which may prove of interest to chemists working in the field of organic synthesis.

II. THE STRUCTURE AND PHYSICOCHEMICAL PROPERTIES OF CARBON SUBOXIDE

Until comparatively recently the structure of the C_3O_2 molecule remained controversial, which was to a large extent due to the difficulty of obtaining sufficiently pure carbon suboxide. Diels proposed the linear structure of 1,3-dioxopropadiene for carbon suboxide [1]. Most of the investigators working with carbon suboxide support this view, mainly on the basis of the methods of preparation of carbon suboxide — from malonic acid and its derivatives. Hypotheses have also been put forward that carbon suboxide can exist as the lactone of β-hydroxypropiolic acid [4]. Attempts were made to confirm this structure by the value of the dipole moment allegedly found for carbon suboxide [5], and also by its thermal decomposition to C_2 and CO_2: [6]



These views are in conflict with the molar refraction and molar dispersion of carbon suboxide [7,8].

Numerous electron diffraction [9-12] and spectroscopic studies in the last decades established that carbon suboxide has an acyclic structure [13]. Infrared and Raman spectra [13-22] and also its ultraviolet spectra [23] have been investigated. The interatomic distances and the valence angles in the suboxide molecules were calculated from these data:

C=C	C=O
1.28±0.15Å	1.16±0.015Å

Thus the C=C bond in carbon suboxide is shorter than in alkenes (1.34 Å) and in keten (1.32 Å). [24] The length of the C=O bond is close to the interatomic distance in the carbonyl group of keten (1.17 Å) and in chloro- and fluoro-carbonyl compounds (1.18 and 1.17 Å), [25,26] but differs significantly from the length in aliphatic ketones (1.22–1.24 Å). [26]

Vol'kenshtein [27], who explained this shortening of the interatomic distance by the pronounced displacement of the electron cloud towards the oxygen atoms, suggested that the C_3O_2 molecule be represented thus: O=C=C=C=O.