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Advances in the Synthesis and Manufacture of α-Aminoacids

E.N.Safonova and V.M.Belikov

The review deals with the existing industrial chemical methods for the manufacture of aminoacids as well as new methods and new versions of the existing methods for their synthesis. Much attention has been devoted to methods of asymmetric synthesis of aminoacids, including homogeneous asymmetric hydrogenation. Enzymatic methods for the synthesis of certain aminoacids from chemical raw materials are examined. The literature of the last 7-8 years is mainly considered. The bibliography includes 385 references.

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I. INTRODUCTION

Together with the continuous search for new methods of synthesising aminoacids, during the last 7–8 years the existing methods have been investigated further and those which are most convenient for practical application have been selected and developed. This approach has been dictated by the colossal and rapidly growing need for aminoacids in various branches of the world's economy.

Major advances have been made in the field of asymmetric synthesis avoiding the need for the optical resolution of racemic aminoacids, which has been and still remains one of the greatest disadvantages of the chemical methods for the synthesis of aminoacids.

In terms of their biological value, aminoacids can be divided into two groups—non-essential aminoacids which the animal and human organism can synthesise at a sufficient rate to build up its own proteins and essential aminoacids which it cannot synthesise. The organism can obtain essential aminoacids only from outside in the form of food. If an essential aminoacid is missing from food or its amount is insufficient, the protein cannot be synthesised; this entails emaciation and death of the organism. For this reason, there is a need to balance the diet, i.e. to add the missing aminoacids to the less valuable [second class] proteins, which increases their nutrient value. Animal feed has been successfully balanced in animal husbandry by the addition of the missing methionine and lysine[1,2]. In the food industry grain products have not so far been balanced on a large scale by the addition of pure aminoacids, although this procedure does improve the nutrient properties of plant protein and hence increases the amount of first class protein suitable for use in food. The latter is particularly important, since a real possibility has arisen of meeting the rapidly growing requirements for food protein without altering the nature of the diet and organoleptic properties of the products[3,4]. Nevertheless at the present time the main consumption of aminoacids in the food industry comes from the employment of sodium glutamate as a powerful taste-improving agent. In many countries it is added to all products which are to be preserved, frozen, or stored for a long time; it is used in communal and domestic catering as a mixture with table salt[5,6]. Compositions imitating the taste and smell of food products are also made up of a mixture of aminoacids[3,7].

Aminoacids are also successfully employed in medicine. After severe operations, burns, and in other stress states, the human organism is unable to assimilate proteins in an amount necessary for regenerative processes, which impairs the state of the patient. In such cases aminoacid feeding is resorted to either in the usual way or by the introduction of a solution of aminoacids directly into the bloodstream. The excellent therapeutic effect achieved in such cases has given rise to a considerable requirement for aminoacid mixtures. Children suffering from phenylpyruvate oligophrenia are fed a mixture of aminoacids free from phenylalanine.

Table 1 (Belikov[1]).

Aminoacid	Amount manufactured, tonnes per year	Method of preparation
L-Glutamic acid	180000	Microbiol., chemical
DL-Methionine	32000	Chemical
L-Lysine	8000	Microbiol.
Glycine	2000	Chemical
L-Tryptophan	20	Chemical
L-Threonine	20	Microbiol., chemical

Certain individual aminoacids, both present in and absent from natural proteins, are employed in medicine. Thus methionine is used in the cirrhosis and fat infiltration of the liver, in dystrophy, and in atherosclerosis. Glutamic acid is mainly used in the treatment of diseases of the central nervous system: schizophrenia, epilepsy, psychoses, shock, etc. γ-Aminobutyric acid and its derivatives are widely used for these purposes. Until recently the only treatment for Parkinson's disease was surgical intervention in the region of the brain. An effective therapeutic agent—3,4-dihydroxyphenylalanine (DOPA) (plus its derivatives)—has now been found. The requirement for this aminoacid is very great.

Aminoacids are used as the starting materials for the synthesis of polypeptides, many of which are very active

physiologically, and also for the synthesis of other medicinal preparations.

Finally aminoacids have also found technical applications. When they are introduced into a polycondensation process, the resulting oligomers, while lacking the biological activity of proteins, nevertheless resemble them in structure and imitate some of their important physical properties. Artificial wool, silk, and leather are widely manufactured in this way, and are not inferior in their properties to the natural materials. The total world manufacture of aminoacids in 1972 is characterised approximately by the figures quoted in Table 1.

The relative contributions of aminoacids to various branches of the economy can be demonstrated using Japan as an example, where the manufacture of aminoacids has developed to the greatest extent:

The structure of the applications of aminoacids in Japan

Food industry	65%
Animal husbandry	18%
Medicine	15%
Others	2%

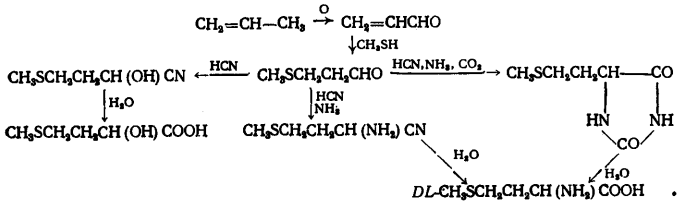
The world requirement for aminoacids increases by 10% annually[1].

II. INDUSTRIAL CHEMICAL SYNTHESES

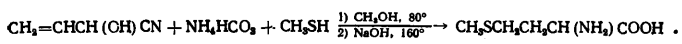
1. Methionine

The chemical synthesis of methionine, an aminoacid mainly consumed in poultry farming, has been most thoroughly developed[1,2,8]. Methionine is unique in its biological properties. Its L- and D-isomers are assimilated to equal extents by the organism. Moreover, the replacement of the amino-group by the hydroxy-group does not affect its nutrient properties. The hydroxy-analogue of methionine is manufactured in the USA. The manufacture of DL-methionine has begun in the USSR. It is also manufactured in the German Federal Republic, France, and Japan. The scale of the manufacture of methionine is greater than that of any other essential aminoacid[9].

The starting material for the synthesis is propene—a petroleum cracking product. Propene is oxidised to a acrolein, which is converted by a series of reactions into racemic methionine:



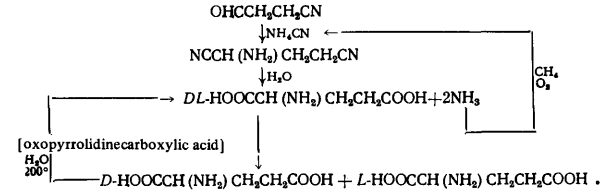
The sequence of reactions can be altered: cyanoallyl alcohol is initially obtained from acrolein and is then converted into highly pure DL-methionine in 80% yield[10]:



A number of other modifications and improvements of the basic process have been proposed[11-23].

2. Glutamic Acid

The raw material for the industrial manufacture of L-glutamic acid is acrylonitrile, obtained by the oxidative ammonolysis of propene. The reaction of acrylonitrile with carbon monoxide and hydrogen is carried out at an elevated temperature and pressure in the presence of $Co_2(CO)_8$ with formation of β-cyanopropionaldehyde, which also serves as the raw material in the synthesis of tryptophan. The subsequent reactions can be represented by the following scheme:

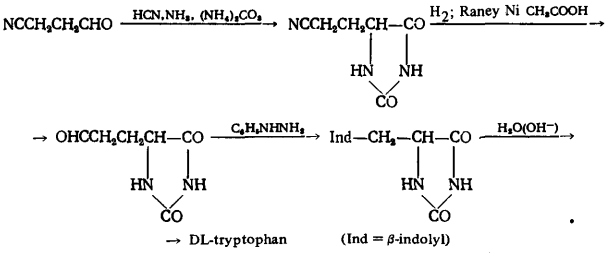


The racemic glutamic acid is resolved into its optical isomers by continuous selective crystallisation. This operation is based on the fact that the solubility of DL-glutamic acid in solutions of its salts (for example, its hydrochloride or its ammonium salt) is almost twice the solubility of the optical isomers. As a result, saturated solutions of DL-glutamic acid are supersaturated with respect to the optical isomers. The introduction of a seed of the L-isomer induces its crystallisation. The optical purity of the resulting L-glutamic acid is 95%.

After neutralisation, the monosodium salt of L-glutamic acid is obtained with an optical purity of 99.8%; it is used as an anabolic agent (to increase weight). The D-isomer of glutamic acid racemises at 200°C and is recycled[5,6]. The synthesis[24-40], cleavage[5,6,41,42], and racemisation[5,6,43] processes have been developed with careful allowance for possible complications, side reactions, and the possibility of the utilisation and reutilisation of the components and waste products of the synthesis. About 1200 tonnes of L-glutamic acid were obtained in Japan in 1972.[1]

3. Tryptophan

The industrial synthesis of tryptophan from β-cyanopropionaldehyde was achieved in Japan by the Ajinomoto Company[8,44-46]:

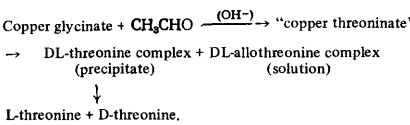


The overall yield of DL-tryptophan amounts to about 60%.[46] It is resolved into optical isomers also by the selective crystallisation of the ammonium[47] or zinc[48] salt of *N*-acetyl-DL-tryptophan, a procedure which is also used to purify DL-tryptophan[49-51].

4. Threonine

The synthesis of DL-threonine by the condensation of copper glycinate with acetaldehyde, which was proposed

in 1957,[52] proved to be the most convenient for the industrial manufacture from the standpoint of the raw material, yield, and economy. It is at present used in Japan[8]:



The complex "copper threoninate" formed consists mainly of the DL-threonine complex. The DL-allothreonine complex obtained simultaneously is much more soluble in water, which makes it possible to separate the diastereoisomers by filtration[53-56]. Several versions of the synthesis have been developed on the basis of this scheme[57-60].

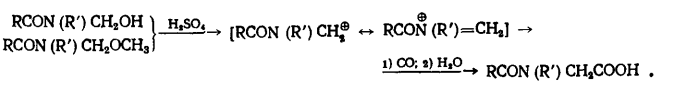
Selective crystallisation is used for the resolution of DL-threonine into optical isomers, as for glutamic acid[8]. The DL-allothreonine and D-threonine formed in the synthesis and after resolution into optical isomers are converted into L-threonine by a number of procedures. Thus L-threonine can be obtained from D-threonine by stereospecific reactions in which the formation of oxazoline derivatives plays an important role[61]. The same derivatives can be used to convert DL-allothreonine into DL-threonine[62,63]. Furthermore, the isomerisation of the copper complex of allothreonine in an alkaline medium in the presence of acetaldehyde leads to an equilibrium mixture of the allothreonine and threonine complexes, with the latter predominating[57,64]. Under these conditions, D-threonine may racemise into a mixture of DL-threonine and DL-allothreonine with inversion at both asymmetric atoms[8].

5. Glycine

In connection with the development of industrial methods for the synthesis of aminoacids by incorporating completed α-aminoacid fragments using glycine and its acyl derivatives, the requirement for these has increased. This is indicated by the large number of patents dealing with the development of new methods for the synthesis of glycine and its derivatives from available raw materials and also with the improvement of the existing methods.

The existing process for the manufacture of glycine from monochloroacetic acid and ammonia in the presence of hexamethylenetetramine and ammonium ions can be carried out continuously with a rational utilisation of the waste and a yield of 96.5%.[65-69] The interaction of monochloroacetic acid with the ammine complexes $[Cu(NH_3)_4]SO_4.H_2O$, $[Co(NH_3)_6](NO_3)_3$, $[Ni(NH_3)_6](NO_3)_2$, and $[Zn(NH_3)_4]SO_4.3H_2O$ yields the corresponding metal glycinates, which can be used in the synthesis of aminoacids[70].

Another process has been developed in which glycine is synthesised from formaldehyde, hydrogen cyanide, and ammonia (by the Strecker or Bucherer–Bergs methods)[71,72]. The resulting aminoacetonitrile can be converted into pure glycine via an oxazole derivative by the reaction with acetone[73]. Glycine can be obtained in 77% yield by the hydrolysis of hydantoin[74,75]. An 80–96% yield of glycine is obtained by the oxidation of acrylonitrile in the presence of tungstic acid or tungsten heteropolyacids[76]. Glycine synthesised by the oxidation of monoethanolamine in the presence of CuO and KOH is used in the synthesis of threonine[58]. *N*-Acylglycines can be obtained by treating hydroxymethyl and alkoxymethyl derivatives of various amides with carbon monoxide in 100% sulphuric acid:



Usually R′ = H and the yields are between 20 and 88%.[77-79] Apart from their ready conversion into the free aminoacid, *N*-acylglycines can be used for the synthesis of peptides[80] and also as one of the components of the azlactone synthesis[81].

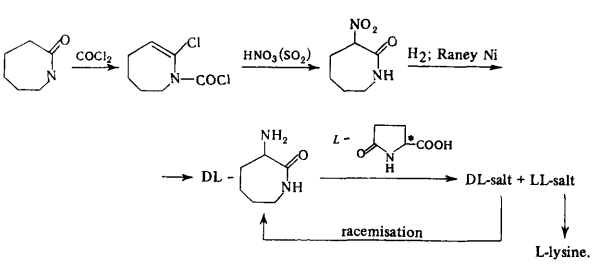
6. Aspartic Acid

DL-Aspartic acid is manufactured from ammonium fumarate or maleate, maleic anhydride being used as the starting material for the synthesis of the latter. A solution of ammonium maleate (or fumarate) in aqueous NH_4Cl with added ammonia (pH ~ 7.5) is heated for 75 min at 180°C. DL-Aspartic acid is isolated at the isoelectric point in 79% yield. The mother liquors and imino-$\alpha\alpha'$-disuccinic acid formed as a by-product are returned to the process[82]. Different versions of this synthesis have been described[83-89].

The method of asymmetric synthesis of L-aspartic acid from ammonium fumarate in a continuous process with the aid of microbial aspartase fixed in a polyacrylamide gel has been recommended for its industrial manufacture[90]. A 1 M solution of ammonium fumarate at pH 8.5 in the presence of $MnCl_2$ is passed through a 5 × 100 cm column filled with the carrier and the fixed enzyme at a rate of 160 ml h^{-1} at 37°C. After the usual treatment, pure crystalline L-aspartic acid is obtained in 95% yield. The enzyme retains its full activity for 7–8 days, but in the subsequent 22–23 days its activity falls to 25%.

7. Lysine

The chemical synthesis of lysine from ϵ-caprolactam has been achieved on an industrial scale in Holland[2,8]:



The resolution into isomers was carried out at the DL-α-aminocaprolactam stage by the crystallisation of the diastereoisomeric salt with L-pyroglutamic acid[2].

A number of patents deal with problems associated with the manufacture of lysine from ϵ-caprolactam. Methods have been described for the formation of α-halogeno-derivatives of ϵ-caprolactam[91,92], including those employing phosgene[93-96], and for their subsequent conversion into DL-lysine[97-100]. Procedures have been developed for the preparation and purification of α-amino-ϵ-caprolactam[101,102], for the resolution of the racemate[103-107], for the racemisation of optically active forms[108,109], and for hydrolysis with formation of lysine[110-117].

8. 3-(3,4-Dihydroxyphenyl)Alanine (DOPA)

Interest in 3,4-dihydroxyphenylalanine arose comparatively recently in connection with the observation of its therepeutic activity against one of the commonest severe nervous disorders in the elderly—Parkinson's disease[118]. Only the L-form has a therapeutic effect. The present requirement for this aminoacid is very great. L-DOPA is obtained by extraction with methanol from broad beans (*Vicia faba*): 1 kg of beans yields 18.7 g of L-DOPA.[119]

The development of a method for homogeneous asymmetric hydrogenation (see above) served as a basis for the experimental manufacture of L-DOPA. It is synthesised by the hydrogenation of 4-hydroxy-3-methoxyacetamidocinnamic acid, obtained by the azlactone synthesis from vanilline. The optical yield reaches 90%. Rhodium complexes with asymmetric *o*-anisylmethylcyclohexylphosphine are used as the catalyst[120-122]. This process is the first asymmetric chemical synthesis of an aminoacid on an industrial scale.

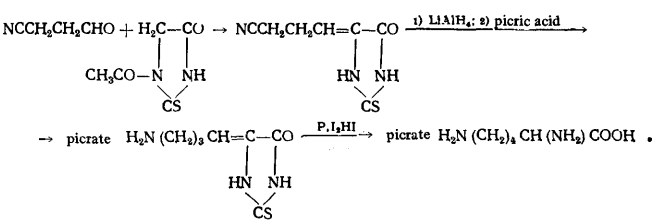
9. β-Alanine

The industrial synthesis of this important natural β-aminoacid[123] involves the addition of an excess of ammonia to acrylonitrile[124,125]. The process is carried out continuously, the yield of β-alanine exceeding 95%.[126] Acrylic acid[127,128] or acrolein[129] can be used instead of acrylonitrile. β-Alanine is used in the synthesis of pharmacological preparations, in particular of panthothenic acid[127] and also in the synthesis of polyamides[130].

III. METHODS FOR THE PREPARATION OF AMINOACIDS

1. From Unsaturated Compounds

Unsaturated compounds—acrylonitrile, acrolein, methyl acrylate, vinyl acetate, butadiene, ethylene, etc.—are widely used for the synthesis of aminoacids. The hydroformylation reaction constitutes a promising method for their conversion into aminoacids and has already been achieved on an industrial scale. The aldehydes or their derivatives obtained in this reaction are subsequently converted into aminoacids by the cyanohydrin or hydantoin syntheses. The industrial syntheses of L-glutamic acid and L-tryptophan from β-cyanopropionaldehyde, obtained by the hydroformylation of acrylonitrile[8], have already been discussed. An attempt has been made to employ this aldehyde also in the synthesis of lysine. It could not be condensed with hydantoin, hippuric acid, or rhodanine, but 1-acetyl-2-thiohydantoin proved to be suitable for this purpose. After the reduction of the condensation product with $LiAlH_4$ and hydrolysis, DL-lysine picrate was obtained in 18% yield with respect to β-cyanopropionaldehyde[131]:



The synthesis of *N*-acylaminoacids from aldehydes (or directly from olefins) and amides has been achieved with the aid of the hydroformylation reaction[132]:

$$RCHO + CH_3CONH_2 + CO \rightarrow RCH(NHCOCH_3)COOH.$$

Since the reaction of an aldehyde, amide, and carbon monoxide catalysed by $Co_2(CO)_8$ proceeds under conditions similar to those in the hydroformylation of olefins, a single-stage conversion of an olefin into an *N*-acylaminoacid is possible:

$$RCH=CH_2 + CH_3CONH_2 + 2CO + H_2 \rightarrow RCH_2CH_2CH(NHCOCH_3)COOH.$$

The reaction is carried out at 110–150°C, 150 atm of CO, and 50 atm of H_2 in 10–80 min. The solvents are dioxane, ethyl acetate, and acetic acid. *N*-Acetyl derivatives of the following aminoacids have been obtained in this way (the percentage yields are indicated in brackets): glycine (26), alanine (68), α-aminobutyric acid (46), valine (70), phenylalanine (56), α-amino-γ-cyanobutyric acid (58), the γ-monomethyl ester of glutamic acid (70), and methionine (64). Benzamide and the amide of lauric acid have been used in place of acetamide. The application of this method in the synthesis of acylglycines was discussed above[77-79]. Carbonylation of Schiff bases yields polypeptides and aminoacids:

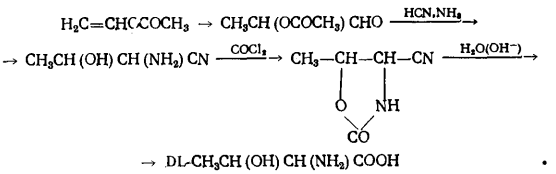
$$R'N=CHR + CO \rightarrow [R'NCH(R)CO-]_n \xrightarrow{H_2O} R'NHCH(R)COOH.$$

Alanine has been obtained in this way with R = CH_3 and R′ = H.[80]

DL-Glutamic acid can be synthesised in 88% yield from the dimethylacetal obtained by the hydroformylation of methyl acrylate in the presence of methanol[133]:

$$CH_2=CHCOOCH_3 \rightarrow (CH_3O)_2CHCH_2CH_2COOCH_3 \xrightarrow{HCN,\ H_2O} \rightarrow NCCH(OH)CH_2CH_2COOCH_3 \xrightarrow[2)\ H_2O(H^+)]{1)\ NH_4OH} DL\text{-}HOOCCH(NH_2)CH_2CH_2COOH.$$

An interesting synthesis of threonine from α-acetoxypropionaldehyde, obtained by oxo synthesis from vinyl acetate, has been described:



A mixture of 91% of DL-threonine and 9% of DL-allothreonine is obtained in 30% yield[134].

The diacetate derived from α-acetoxyacetaldehyde can be used in the synthesis of DL-serine:

$$H_2C=CHOCOCH_3 \xrightarrow{Br_2} CH_2BrCHBrOCOCH_3 \xrightarrow{(CH_3CO)_2O} CH_3OCOCH_2CH(OCOCH_3)_2 \xrightarrow{NaCN,NH_3} CH_3OCOCH_2CH(NH_2)CN \xrightarrow{H_2O(H^+)} CH_2(OH)CH(NH_2)COOH.$$

The yield of DL-serine is 78%.[135] DL-Serine can be obtained via hydantoin by treating the triacetate with NaCN and $(NH_4)_2CO_3$.[136] A mixture of DL-threonine and DL-allothreonine has been obtained in the same way from propenyl acetate in 64% yield[135].

DL-Glutamic acid is obtained by cyanohydrin synthesis from acrolein:

$$H_2C=CHCHO \xrightarrow{HCN,\ NH_3} [NCCH_2CH_2CH(NH_2)CN] \xrightarrow{H_2O(OH^-)} \rightarrow HOOCCH(NH_2)CH_2CH_2COOH.$$

Acrolein homologues can be used in the synthesis of glutamic acid homologues[137-139]. Various α-amino-β-hydroxyacids are obtained from αβ-unsaturated acids

via epoxy-compounds[140-146]. Thus *E*-crotonic acid yields DL-threonine[140]:

$$E\text{-}CH_3CH{=}CHCOOH \xrightarrow{H_2O_2;\ Na_2WO_4} \textit{trans}\text{-}CH_3CH\text{—}CHCOOH \xrightarrow{HCl} \underset{O}{\diagdown\diagup}$$

$$\rightarrow \textit{erythro}\text{-}CH_3CH(OH)CH(Cl)COOH \xrightarrow{NH_3} CH_3CH(OH)CH(NH_2)COOH\ .$$

The bromohydrin of crotonic acid can be converted into DL-threonine by reaction with urotropine[147] or by photochemical ammoniolysis[148]. These studies constitute a development of Carter's method[149,150].

DL-Methionine can also be obtained from crotonic acid. On treatment with C_2H_5OH and $(C_2H_5)_3N$, the acid chloride is converted into the ester with simultaneous migration of the double bond to the $\beta\gamma$-position; this is followed by the addition of CH_3SH, bromination with $P_2Br_2Cl_4$, amination, and hydrolysis. The yield of DL-methionine relative to crotonic acid is 32.5%.[151]

A number of intermediates formed in the synthesis of DL-serine from methyl acrylate or acrylonitrile have been described[152-155]. DL-Glutamic acid is obtained in 30% yield by the cyanoethylation of *N*-acylaminoacetonitriles[156] and also in 40% yields by the cyanoethylation of 2-phenyl-5-oxazolone (azlactone)[157]. Considerable amounts of β-alanine and DL-aspartic acid are obtained from the waste products in the manufacture of acrylonitrile by the oxidative ammonolysis of propene after a simple treatment[158]. The addition of dichloroacetic acid esters to butadiene yields $\alpha\epsilon$-dichlorohexenoic acid esters, which are converted by ammoniolysis, hydrogenation, and hydrolysis into DL-lysine[159,160]. Butadiene has been used to synthesise lysine via the nitro-derivative[161-164]. Various aminoacids can be obtained from the polychloroalkane formed in the telomerisation of ethylene with carbon tetrachloride[165] or trichloroacetic acid[166].

2. From Ketones

Monoaminomonocarboxylic acids can be obtained from methyl alkyl (or aryl alkyl) ketones in several ways via α-hydroxyiminoketones:

$$\begin{array}{l} \xrightarrow{Zn/CH_3COOH} RCH(NHCOCH_3)COCH_3 \xrightarrow{O_2(HCl)} (C) \\ RCH_2COCH_3 \xrightarrow{R'ONO} RC(=NOH)COCH_3 \xrightarrow{NaBrO} RC(=NOH) \xrightarrow[(A)]{H_2;\ Raney\ Ni;} RCH(NH_2)COOH \\ \quad\downarrow (C_2H_5O)_2SO_2 \qquad\qquad\quad \downarrow COOH \qquad\qquad\quad \uparrow H_2;\ Pd/C\ \ (B) \\ \quad\downarrow \qquad\qquad\qquad\quad RC(=NOC_2H_5)COCH_3 \xrightarrow{NaClO} RC(=NOC_2H_5)COOH \end{array}\ .$$

The following products were obtained [the method of preparation, R, and the percentage yield relative to the ketone (in brackets) are indicated]: *A*, $C_6H_5CH_2$ (53);[167] *B*, $C_6H_5CH_2$ (40);[168,169] *C*, $C_6H_5CH_2$ (-);[170] *A*, p-$CH_3OC_6H_4CH_2$ (46); *A*, 3,4-$CH_2O_2C_6H_3CH_2$ (45); *A*, C_6H_5 (44);[171] *B*, CH_3 (15);[168,169,172] *C*, CH_3 (80, with respect to the oxime)[170,173]; *B*, i-C_3H_7 (31—34.4);[168,169,172] *C*, i-C_3H_7 (-);[170] *B*, $CH_3(CH_2)_3$ (51—63);[172] *C*, s-C_4H_9 (-).[170,173]

In addition, the methylene group in methyl ketones can be halogenated, the halogen replaced by an amino-group, and the product oxidised by atmospheric oxygen. DL-Valine and DL-alanine have been obtained in this way[174]:

$$CH_3COCH_2R \xrightarrow{Br_2} CH_3COCHBrR \xrightarrow{NH_3;\ CH_3OH} [CH_3COCH(NH_2)R] \xrightarrow{O_2;\ HCl} \rightarrow \text{DL-}RCH(NH_2)COOH\ .$$

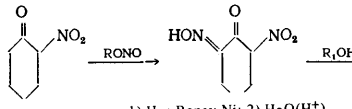
(R=CH_3; i-C_3H_7)

Acetylacetamide, obtained from diketen, is used as the starting material for the synthesis of a wide variety of aminoacids[175,176]:

$$CH_3COCH_2CONH_2 \xrightarrow{RBr} CH_3COCH(R)CONH_2 \xrightarrow{KOBr} CH_3COCH(R)NH_2 \xrightarrow{O_2} \rightarrow RCH(NH_2)COOH\ .$$

R- S-C_4H_9; i-C_4H_9; $C_6H_5CH_2$; $CH_3SCH_2CH_2$; $HOOCCH_2CH_2$.

The nitrosation of cyclic ketones is used in the synthesis of DL-lysine from cyclohexanone[177-179] and nitrocyclohexanone[180-184]:



$$\xrightarrow{R_1OH;\ NaOH} O_2N(CH_2)_4C(=NOH)COOR_1 \xrightarrow{1)\ H_2;\ Raney\ Ni;\ 2)\ H_2O(H^+)} H_2N(CH_2)_4CH(NH_2)COOH\ .$$

3. Carboxylation of Amines

Several studies have been made on the introduction of the carboxy-group into the amine molecule:

$$RCH_2NH_2 + 2H_2O_2 \xrightarrow{Na_2WO_4} RCH{=}NOH \xrightarrow{2NaHSO_3} RCH(NH_2)SO_3Na \xrightarrow{NaCN} RCH(NH_2)CN \xrightarrow{H_2O(H^+)} RCH(NH_2)COOH\ .$$

On treatment with bisulphite, RCH(NHOH)SO_3Na is probably formed as an intermediate and is then reduced to the amine by the excess bisulphite. Alanine, serine, and phenylalanine have been obtained in yields of 71, 68, and 75% respectively[185]. It is desirable to employ readily available amines in the synthesis of aminoacids by this procedure. The interaction of the sodium salt of a sulphonic acid with KCN for the introduction of the carboxy-group has also been used in the synthesis of α-methyl-DOPA.[186]

Isonitriles obtained in a preliminary step from amines have been carboxylated:

$$\begin{array}{l} RCH_2NH_2 \rightarrow RCH_2NC \xrightarrow[NaH]{OC(OC_2H_5)_2} RCH(NC)COOC_2H_5 \xrightarrow{1)\ H_2O(H^+);\ 2)\ H_2OOH^-} \\ \quad\downarrow \rightarrow RCH_2NHCHO \uparrow \\ \rightarrow RCH(NH_2)COOH\ . \end{array}$$

Diethyl carbonate in dimethylformamide (DMF) in the presence of NaH was used as the carboxylating agent. The following percentage yields with respect to the isonitrile (in brackets) were obtained for different R: C_6H_5 (57); 4-$CH_3OC_6H_4$ (54); 4-$CH_3C_6H_4$ (51); 4-Cl—C_6H_4 (56); 3.4-$(CH_2O_2)C_6H_3$ (60); 2-furyl (55); H (32). Dimethyl carbonate and also ethyl chloroformate or CO_2 in the presence of butyl-lithium can be used as carboxylating agents. Conditions for the reaction with aliphatic amines, with the exception of methylamine, have not been found[187,188]. DL-Valine was obtained in 46% yield by treating a solution of isobutylamine in a mixture of dioxane and 35% HCl with 30% hydrogen peroxide, the reaction system being simultaneously bubbled with CO_2 at 30°C for 1.5 h. DL-Alanine was obtained similarly from ethylamine[189]. The direct carboxylation of amines, in particular methylamine, by formic acid, formates, or carbon dioxide is carried out under the influence of γ- or ultraviolet radiation. The yields are low[190].

4. From Nitroacetic Acid Esters

Nitroacetic acid esters O_2NCH_2COOR (R = CH_3 or C_2H_5), obtained from nitromethane, provide an almost

universal starting material for the synthesis of α-amino-acids. The method is based on the exceptional reactivity of the methylene group of the nitroacetic acid ester due to the presence of adjoining nitro- and ester groups. The nitroacetic acid ester contains a potential α-aminoacid grouping: different substituents are introduced into its molecule and the nitro-group is then reduced to the amino-group[191].

A general scheme for the synthesis of aminoacids from nitroacetic acid esters was published in 1969.[3] The most extensive studies in recent years dealt with the synthesis of tryptophan and phenylalanine. Attention was concentrated on reduction of β-substituted α-nitropropionates and α-nitroacrylates which are formed as intermediates.

The reduction of β-indolyl-α-nitropropionic acid esters does not present much difficulty and proceeds smoothly in both catalytic[192] and electrochemical[193] processes. The β-indolyl-α-nitropropionate, obtained by heating the gramine salt of the nitroacetic acid ester, yields DL-tryptophan after reduction of the nitro-group and hydrolysis[194]:

$$\mathrm{IndCH_2N(CH_3)_2 + O_2NCH_2COOC_2H_5 \rightarrow [gramine\ salt\ of\ NAE] \xrightarrow{110^\circ}}$$
$$\rightarrow \mathrm{IndCH_2CH(NO_2)COOC_2H_5 \xrightarrow{H_2;\,Raney\ Ni} IndCH_2CH(NH_2)COOC_2H_5 \rightarrow}$$
$$\xrightarrow{\mathrm{H_2O/C_2H_5OH(OH^-)}} \text{DL-tryptophan}$$

(Ind = β-indolyl; NAE = nitroacetic acid ester).

The reduction of aromatic derivatives of α-nitroacrylic acid is more difficult[192,195,196].

β-Indolyl-α-nitroacrylates have been obtained in two ways: by the condensation of indole with β-alkoxy-α-nitro-acrylates (without condensing agents)[195,197] and also by the condensation of indole-3-aldehyde with nitroacetic acid esters in the presence of acid catalysts[196,198,199]:

$$\left.\begin{array}{l}\mathrm{IndH + C_2H_5OCH{=}C(NO_2)COOCH_3}\\ \mathrm{IndCHO + O_2NCH_2COOC_2H_5 \xrightarrow{HCl,\ SOCl_2,\ AlCl_3}}\end{array}\right\} \rightarrow \mathrm{IndCH{=}CH(NO_2)COOR}\ .$$

Ind = β-indolyl)

The use of alkaline catalysts leads mainly to isoxazoline *N*-oxides[200]. The reduction of β-indolyl-α-nitroacrylates in the presence of Raney nickel in alcohol proceeds with considerable charring[196]. The best results were obtained using two successive hydrogenation stages: initially in the presence of palladium black and then in the presence of Raney nickel[195]. In the first stage β-indolyl-α-nitro-acrylate is partially converted (52%) into β-indolyl-α-nitropropionate ester, which is then readily hydrogen-ated to the tryptophan ester. Together with the catalytic procedure, a method was developed for the electrochem-ical reduction of β-indolyl-α-nitroacrylacrylate in aqueous alcoholic and aqueous dioxane mixtures at pH 1–3 in the presence of metals with a high hydrogen overvoltage. The yield of DL-tryptophan reaches 60%.[201,202] The characteristics of the electrochemical reduction were elucidated by polarography and electrolysis at a controlled potential. It was found that both electrochemical and catalytic reduction proceed in steps, but the saturated nitro-ester is not formed; the principal intermediate in the reduction reaction is the oxime[203,204]. The inadequate yield of the desired product can be accounted for by the instability of the oxime and also of the initial β-indolyl-α-nitroacrylate and other intermediates in the acid medium[193].

Electrochemical reduction of α-nitrocinnamic acid ester gives a 65% yield of DL-phenylalanine. Higher yields could not be achieved owing to the instability of the initial ester and the intermediates under the experimental conditions[193,205,206].

The catalytic reduction of phenyl nitroacrylates was carried out in alcoholic solutions[207], but the process may be complicated by the addition of the alcohol to the double bond and other side reactions[208–211]. On the other hand, β-isopropyl-ββ-dimethyl-, and β-ethyl-β-methyl-α-nitro-acrylates are hydrogenated in the presence of Raney nickel in methanol, yielding respectively DL-leucine, DL-valine, and DL-isoleucine[212,213]. Steric factors probably play a role in these reactions and the rate of hydrogenation exceeds the rate of addition of methanol[212].

Nitroacetic acid ester has been used to synthesise DL-lysine from butadiene:

$$\mathrm{H_2C{=}CH{-}CH{=}CH_2 \xrightarrow{N_2O_4,\ I_2} O_2NCH_2CH{=}CHCH_2I \xrightarrow{O_2NCH_2COOC_2H_5}}$$
$$\rightarrow \mathrm{[O_2NCH_2CH{=}CHCH_2CH(NO_2)COOC_2H_5 \xrightarrow{1)\ H_2;\ Pd/C;\ 2)\ H_2O(H^+)}} \text{DL-lysine}\ .$$

The yields were about 20% and about 70% in the condensa-tion and reduction stages respectively[161–164].

A number of aminoacids have been obtained by the *C*-alkylation of methyl nitroacetate by alkyl halides in aprotic dipolar solvents via the mechanism:

$$\mathrm{RX + O_2NCH_2COOCH_3 \xrightarrow{CH_3ONa} RCH(NO_2)COOCH_3 \xrightarrow{1)\ H_2;\ Raney\ Ni;\ 2)\ H_2O(H^+)}}$$
$$\rightarrow \mathrm{RCH(NH_2)COOH}\ .$$

The resulting nitro-esters are isolated in the form of crystalline ammonium salts, are hydrogenated for 1 h at 20°C and 3–3.5 atm, and the product is hydrolysed with 6 *N* HCl.[214,215]. The following products were obtained in this way (the yields are given with respect to nitro-acetic acid ester): DL-aspartic acid, 55% (90%[215]); DL-glutamic acid, 73.5% (83%[215]); DL-alanine, 63%; DL-valine, 13.5%; DL-phenylalanine, 40%; DL-αα-di-aminobutyric acid, 3.8%; DL-ornithine, 18.5%; DL-lysine, 12%.

Methods for the synthesis of γ-aminoacids, some of which have a sedative effect on the nervous system, have been developed on the basis of nitroacetic acid ester[216].

5. From Aliphatic, Aromatic, and Heterocyclic Compounds and Other Aminoacids

A new method for the preparation of α-aminoacids from carboxylic acids in a single stage consists of the amination of α-lithio-lithium salts of *O*-alkylhydroxylamines in hexametapol at −15°C:

$$\mathrm{RCH_2COOH \xrightarrow{LiN(n\text{-}C_3H_7)_2} RCHLiCOOLi \xrightarrow{NH_2OR'} R\ CH(NH_2)CCOH}\ .$$

The yields of phenylglycine and valine reached 55.5 and 33.9% for a 32.8% conversion of the initial acid. Best results are obtained with *O*-methylhydroxylamine[217].

DL-DOPA is obtained by the hydrolysis of 5-(3,4-iso-propylenedioxybenzyl)hydantoin, which is synthesised in five stages from 4-methylcatechol[218]. Lysine has been obtained from cyanobutyraldehyde by hydantoin synthesis with subsequent hydrogenation and hydrolysis[219,220]. A number of papers deal with the details of the hydrolysis of the hydantoins derived from various aminoacids. The hydrolysis is carried out as a rule under alkaline condi-tions in an autoclave with periodic release of the excess pressure[74,75,221–223]. A number of other improvements have been proposed to the cyanohydrin synthesis[224,225].

The hydroxylation of the aromatic ring is used for the synthesis of aminohydroxyacids. Thus L-DOPA is

obtained in about 50% overall yield from the methyl ester of *N*-acetyl-L-tyrosine[226]:

$$L\text{-}4\text{-}HOC_6H_4CH_2\overset{*}{C}H(NH_2)COOCH_3 \xrightarrow{(CH_3CO)_2O} \rightarrow L\text{-}4CH_3OCOC_6H_4CH_2\overset{*}{C}H(NHCOCH_3)COOCH_3 \xrightarrow{AlCl_3} \xrightarrow{AlCl_3} \rightarrow L\text{-}3,4\text{-}(CH_3CO)(OH)C_6H_3CH_2\overset{*}{C}H(NHCOCH_3)COOCH_3 \xrightarrow{1)\ H_2O_2,\ NaOH;\ 2)\ HBr} \rightarrow L\text{-}3,4\text{-}(OH)_2C_6H_3CH_2\overset{*}{C}H(NH_2)COOH.$$

Hydroxylation of the methyl ester of *N*-acyl-L-tyrosine by benzoyl peroxide gave L-DOPA in about 35% overall yield[227,228].

The hydroxy-group was introduced into the *N*-acyl-L-tyrosine molecule by reaction with atmospheric oxygen in the presence of Fe^{2+} and enediol compounds (ascorbic acid)[229]. Proline reacts with atmospheric oxygen in aqueous solutions on irradiation with ultraviolet or visible light in the presence of semiconducting metal oxides and sulphides. Proline is then converted into hydroxyproline in 1.5 h in 52% yield[230].

Methods have been proposed for the chlorination[231,232] of ω-benzoylaminocaproic acid, the ammoniolysis of the resulting chloro-derivatives[233], and subsequent hydrolysis[234,235], the overall process leading to DL-lysine. These reactions have been examined in detail in the present author's earlier review[191]. Diaminopimelic acid derivatives can serve as lysine precursors. Thus α-cyanopimelic acid diamide was converted into DL-lysine by the Hofmann rearrangement with subsequent hydrolysis[236].

A series of fairly complicated reactions permit the conversion of furfural into DL-glutamic acid[237,238]. Glutamic acid can serve as the starting material for the synthesis of other aminoacids. Thus L-proline and *N*-methyl-L-proline can be obtained from L-glutamic acid[239].

Optically active ornithine (D or L) can be obtained from optically active glutamic acid (D or L) in seven stages with an overall yield of 40%.[240] In its turn, each of the optically active forms of ornithine can serve as the starting material for the synthesis of L- and D-proline[241,242] and L-arginine can be obtained from L-ornithine in virtually one stage[243,244]. DL-Serine and its derivatives are used for the synthesis of DL-cystine[245-248]. L-Tyrosine can be converted into L-phenylalanine by the reduction of the *O*-tosylate[249,250].

6. From Simple Gases

In connection with the problem of the chemical evolution and the origin of life on earth, experiments were begun in 1953 on the non-biological synthesis of aminoacids under conditions simulating "earth's primary atmosphere". It was shown that aminoacids are formed comparatively readily from gaseous methane–water–ammonia mixtures in the presence or absence of hydrogen under the influence of various physical factors. These may be electrical discharges, irradiation, with visible and ultraviolet light as well as with hard ionising radiation, heating, and exposure to ultrasonic waves. Numerous experiments resulted in the formation of twelve of the natural aminoacids and various mechanisms for their formation from gaseous mixtures and certain other simple compounds, which had been synthesised beforehand under the same conditions, have been proposed[251-256]. In all experiments of this kind the yields of aminoacids are extremely low[251]. However, a method was recently patented where a mixture of methane, ethane, ammonia, and water in argon is subjected to the action of a shockwave and cooling by rapid expansion. A mixture of glycine, alanine, valine, and leucine is then obtained with 36% conversion with respect to ammonia[257].

7. From Glycine Derivatives

a. On the basis of isocyanoacetic acid esters. A familiar method for the alkylation of α-*N*-acylaminomalonic esters has been used to synthesise tryptophan[258,259], lysine[260], and glutamic acid[261]. Isocyanoacetic acid ester can be converted into higher homologues by alkylation in a similar manner. The isocyano-group is then converted into the formylamino-group and the aminoacid is obtained after hydrolysis. DL-Tryptophan was obtained in this way in 49% overall yield[262]:

$$IndCH_2N(CH_3)_3I + C{=}NCH_2COOCH_3 \xrightarrow{NaH} IndCH_2CH(N{=}C)COOCH_3 \rightarrow \xrightarrow{CH_3COOH,\ CH_3OH} IndCH_2CH(NHCHO)COOH \xrightarrow[(OH^-)]{H_2O/CH_3OH} \text{DL-tryptophan}.$$

(Ind = β-indolyl)

The reaction of isocyanoacetic acid ester with alkyl halides or tosylates cannot be stopped at the monoalkylation stage[263]. α-Amino-β-hydroxyacids can be obtained by the reaction of isocyanoacetates with aldehydes[264]:

$$C{=}NCH_2COOCH_3 + C_6H_5CHO \xrightarrow{(C_2H_5)_3N} C_6H_5CH(OH)CH(N{=}C)COOCH_3 \rightarrow \xrightarrow{1)\ CH_3OH(HCl);\ 2)\ H_2O(OH^-)} C_6H_5CH(OH)CH(NH_2)COOH.$$

The methyl ester of DL-DOPA was obtained by the same procedure in 83% yield from methyl isocyanoacetate and the dibenzyl ether of 3,4-dihydroxybenzaldehyde:

$$C{=}NCH_2COOCH_3 + 3,4\text{-}(C_6H_5CH_2O)_2C_6H_3CHO \xrightarrow{t\text{-}C_4H_9OK} \rightarrow 3,4\text{-}(C_6H_5CH_2O)_2C_6H_3\underset{\displaystyle O^-K^+}{\underset{|}{C}}HCH(N{=}C)COOCH_3 \xrightarrow{CH_3OH/H_2O(HCl)} \rightarrow 3,4\text{-}(C_6H_5CH_2O)_2C_6H_3CH{=}\underset{\displaystyle NH_2\cdot HCl}{\underset{|}{C}}{-}COOCH_3 \xrightarrow{H_2;\ Pd/C} 3,4\text{-}(OH)_2C_6H_3CH_2\underset{\displaystyle NH_2\cdot HCl}{\underset{|}{C}}HCOOCH_3.$$

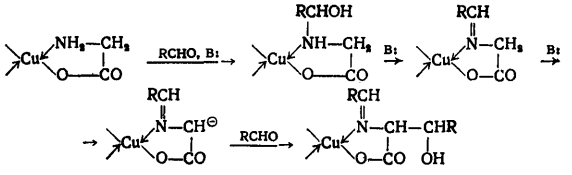
3,4-Methylenedioxy- and 3,4-dimethoxy-benzaldehydes can be used in the reaction. In this case the methylene or methyl groups are removed with BBr_3 after treatment of the isocyano-group and hydrogenation[265]. The report of the above investigation contains a reference to the possibility of obtaining a wide variety of aminoacids by this procedure. A partial asymmetric synthesis of α-methyl-DOPA, which is used as a hypotensive agent, involving the *C*-alkylation of α-isocyanopropionic acid esters by optically active alcohols, has been proposed[266].

The synthesis of silicon- and tin-containing aminoacids from ethyl *NN*-bis(trimethylsilyl)glycinate and the corresponding alkyl halides has been achieved; the reaction with carbonyl compounds yields α-amino-β-hydroxyacids[267].

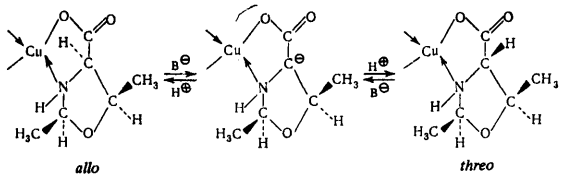
The sodio-derivative of this ester was used to synthesise 2-amino-6-nitrocaproic acid, which is used in peptide synthesis as a protected lysine derivative[268].

b. On the basis of glycine bound in a complex. Alkylation of glycine complexes by aldehydes and certain ketones permits the synthesis of a number of α-amino-β-hydroxyacids[269-277]. The akabori reaction, giving in a single stage threonine with an excess of the *threo*-form, is typical[52]. The study of the reaction mechanism showed that the intermediate reactive species is probably a copper complex of the Schiff base of the aminoacid and the aldehyde, which has a sufficiently acid C–H group for the formation of a carbanion in an alkaline medium and for its further reactions[278-280].

The reaction of copper glycinate with aldehydes proceeds as follows:



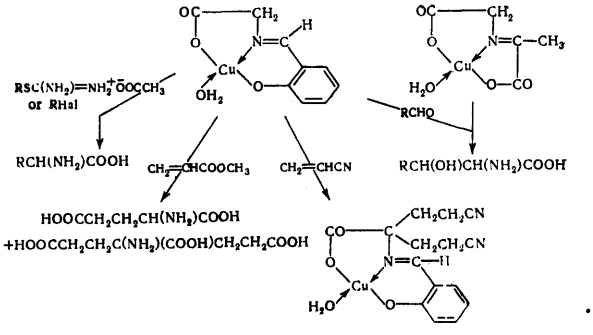
An X-ray diffraction study of crystalline copper threoninate ($C_{12}H_{20}O_6N_2Cu.2H_2O$) showed that the complex has a tetracyclic structure in which two five-membered rings are formed by the bonds between the aminoacids and copper and a further two oxazoline rings are formed by the intramolecular nucleophilic addition of the alkoxide ion to the C=N double bond[281,282]. The less hindered configuration of the substituents in the complex corresponds to the *threo*-form, which is the reason for the stereospecificity of the Akabori reaction and also for the conversion of the *allo*-form of the complex into the *threo*-form in an alkaline medium[57,58,278]:



allo *threo*

Thus, apart from being involved in the synthesis, the aldehydes plays the same role in the Akabori reaction that the pyridoxal molecule plays in alkylation processes catalysed by pyridoxal-dependent enzymes[283,284].

Further development of these studies led to the discovery of chemical systems which not only simulated certain aspects of enzymatic reactions but also gave rise to processes, which do not occur in the living organism. Such systems are the complexes of the Schiff bases of salicylaldehydes and aminoacids with transition metal ions. Salicylaldehyde plays the role of pyridoxal, preventing alkylation at the nitrogen atom[285] and increasing the reactivity of the C—H bond of the aminoacid, while the metal atom imparts in addition a rigidity to the system, which is ensured in nature by the enzyme protein. This permitted asymmetric synthesis with the aid of these systems[286]. The use of salicylaldehyde[283,284,287-289] and pyruvic acid[279,288,289,291] permitted the synthesis under mild conditions of threonine and other α-amino-β-hydroxyacids. In addition, the methylene group of glycine was alkylated by the reaction of alkyl halides[288] and acrylonitrile[285] with copper salicylidene- and 1-carboxy-ethylidene-glycinates and by the reaction of the latter with aldehydes. The alkylation of glycine bound in the complex can be represented by the following scheme:



The reaction with aldehydes has been most thoroughly investigated. Copper salicylideneglycinate was alkylated by aldehydes in water at about 25°C at pH 7.0—8.0. The following aminoacids were obtained by this procedure (the percentage yield and the ratio of the *threo*- and *erythro*-forms are indicated in brackets): threonine [89, (31—34)/(66—69)]; phenylserine [45, (79—84)/(21—26)]; hydroxyaspartic acid (51, 64/36), and serine (2.6, -).[283] The reaction of copper 1-carboxyethylideneglycinate with aldehydes was carried out in an atmosphere of nitrogen, in water or in methanol, at 25—30°C in a moderately alkaline medium. More than ten aliphatic, aromatic, and heterocyclic α-amino-β-hydroxyacids were obtained in this way, including serine, threonine, β-hydroxyleucine, and β-hydroxy-β-phenylalanine in yields of 28, 82, 75, and 67% respectively[179,280].

Copper salicylideneglycinate is alkylated by alkyl halides in dimethylformamide (DMF) at 65°C in the presence of KOH with formation of low yields of alanine, valine, leucine, isoleucine (traces), phenylalanine, and aspartic acid[288]. The alkylation of copper(II) or cobalt(II) salicylideneglycinate by thiuronium salts having the general formula $RSC(NH_2)=NH_2^+ CH_3COO^-$ in acetic acid in the presence of sodium acetate gives particularly good results. The yields of phenylalanine, aspartic acid, and glutamic acid obtained by this method are 50—60%.[292]

The interaction of copper salicylideneglycinate with methyl acrylate in water at 35°C and pH 11.4 in the course of 15 min results in the formation of 46% glutamic acid and 17% of 4-amino-4-carboxypimelic acid with a residue of 35% of unreacted glycine. When 1-carboxyethylideneglycinate is employed, similar results are obtained, but the contribution of side processes (deamination, decarboxylation) increases[284,289]. The above results show that, by employing glycine complexes, it is not only possible to simulate natural process but also to achieve processes which do not occur in nature, and this leads to new ways of synthesising aminoacids.

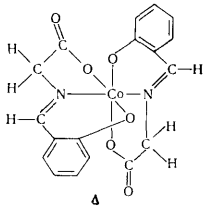
Inert octahedral cobalt(III) complexes such as sodium bis-(*N*-salicylideneglycinato)cobaltate, which have a fairly acid C—H group, can also be used for the *C*-alkylation of glycine by acrylonitrile, acetaldehyde, and methacrylate. The resulting inert complexes of the reaction products can be readily reduced electrochemically to labile cobalt(II) complexes, which dissociate into the aminoacid, salicylaldehyde, and Co^{2+}. The mixture is separated with the aid of ion-exchange resins. A significant advantage of the cobalt(III) complexes is the absence of side processes (bisalkylation, alkylation at the nitrogen atom) in the reaction with methyl acrylate. This results in the formation of glutamic acid in a single stage and in a high yield[293,294].

Cobalt(III) complexes are also interesting because they exhibit dissymmetry due to the rigid fixation of the ligands in the octahedron and also the asymmetry of the ligands themselves. The possibility, in principle, of employing dissymmetric mixed cobalt(III) complexes for the asymmetric synthesis of aminoacids was demonstrated in the synthesis of threonine (asymmetric yield 8%)[295] and alanine (asymmetric yield 14%)[296]. These syntheses are examined in detail in Morrison and Mosher's book[297]. The stereoselectivity of the reactions of cobalt(III) complexes with glycine Schiff bases permitted their employment for the asymmetric synthesis of aminoacids, i.e. essentially for the simulation of the stereospecificity of natural enzymes. For this purpose, potassium bis-(*N*-salicylideneaminoalkylcarboxylato)cobaltate was resolved into optical isomers, the absolute configurations of which were estab-

lished on the basis of circular dichroism spectra, ^1H NMR, and reactivity[298].

The reaction of Δ-isomers (−530) or Λ-isomers (+530) of potassium bis-(*N*-salicylideneglycinato)cobaltate with acetaldehyde (water, pH 11.2, acetaldehyde : complex = 100 : 1, temperature 12°C, time 6 h) is stereospecific with formation of L(*S*)- or D(*R*)-threonine respectively:

$$H_2NCH_2COOH + o\text{-}HOC_6H_4CHO + Co^{3+} \xrightarrow{\text{brucine}}$$



$$\xrightarrow[e^{\ominus}]{CH_3CHO} CH_3\overset{*}{C}H(OH)\overset{*}{C}H(NH_2)COOH + Co^{2+} + o\text{-}HOC_6H_4CHO$$

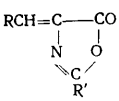
	O.P.
L(3*R*, 2*S*)-threonine	45%
L(3*S*, 2*S*)-allothreonine	65%

The overall yield is 86% and the ratio *threo* : *allo* = 1.25.[286]

The replacement of one of the ligands in the complex with the absolute Δ-configuration of the glycine residue by the (*S*)-valine residue results in the formation of (*S*)-threonine with an asymmetric yield reaching 82%.[298] When account is taken of the synthetic possibilities of these complexes[293,294] and of a series of studies on their properties[298-300], the above approach to the problem of asymmetric synthesis of aminoacids can prove extremely fruitful.

c. On the basis of *N*-acylglycines.

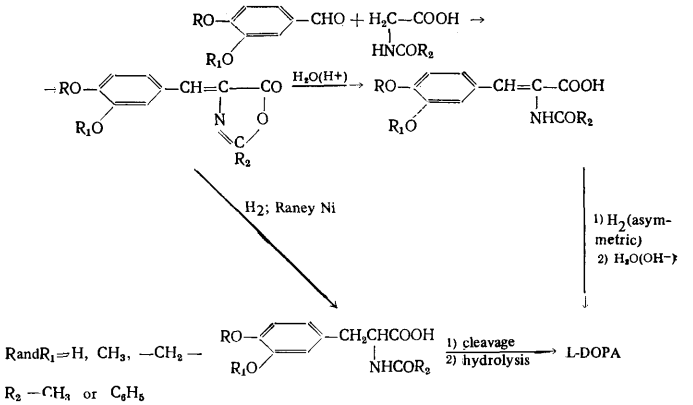
N-Acylglycines are employed as compounds containing the α-aminoacid fragment in the synthesis of aminoacids by the azlactone method. In the classical version azlactones are obtained by the reaction of acylglycine with aromatic aldehydes in the presence of acetic anhydride. Hydrolysis or alcoholysis of the azlactone yields α-acylaminoacrylic acid or its ester, whose subsequent reduction and hydrolysis lead to the aminoacid[81]. Later it was shown that the reaction can also be carried out with aliphatic aldehydes and ketones[301]. It proved possible to achieve the catalytic reduction of azlactones in an alkaline medium, omitting the conversion stage into α-acylaminoacrylic acids. The resulting α-acylaminoacid amides are hydrolysed smoothly to the α-aminoacids:



$$\xrightarrow{1)H_2;\ \text{Raney Ni};\ 2)NH_3,\ \text{alcohol}} RCH_2CH(NHCOR')CONH_2 \xrightarrow{36\%\ HCl}$$

$$\rightarrow RCH_2CH(NH_2)COOH \quad .$$

The following aminoacids were obtained in this way (the percentage yield with respect to the azlactone is indicated in brackets): phenylalanine (84); tyrosine (78); 3,4-dimethoxyphenylalanine (64); 4-hydroxy-3-methoxyphenylalanine (46.5); valine (75); isoleucine (62); leucine (54); and certain other aminoacids[302]. The reduction of azlactones by hydrogen obtained as a result of the catalytic decomposition of HCOOH gave rise to the formation of *N*-acylaminoacids (derivatives of phenylalanine, tryptophan, and valine) in 85—93% yield[303]. The application of the method to the synthesis of cystine[304] and histidine[305] also gives good results. 4-Hydroxy-3-methoxy-,[306-309] 3,4-dihydroxy-,[310] 3,4-dimethoxy-,[311,312] and 3,4-methylenedioxy-benzaldehydes[313] have been used to synthesise L-DOPA by the azlactone method. The corresponding azlactones can be converted into L-DOPA in two ways. The first consists of the catalytic[306,310] or electrochemical[309] reduction of the azlactone with subsequent enzymatic separation[309] of the optical isomers of the β-aryl derivatives of *N*-acylalanines (DOPA precursors) via diastereoisomeric salts with acid[314] or alkaline[306-308,311-313,315] agents and also by selective crystallisation[316-318]. The hydrolysis of the corresponding L-isomers leads to L-DOPA.



The second procedure involves the hydrolysis of the azlactones with subsequent asymmetric catalytic hydrogenation of the resulting *N*-acylaminoacrylates in the presence of homogeneous dissymmetric phosphine—rhodium catalysts. This new method of asymmetric synthesis can probably be used for the industrial manufacture of optically active aminoacids from unsaturated precursors[120,319].

IV. ASYMMETRIC SYNTHESIS

1. Homogeneous Asymmetric Hydrogenation

The catalytic hydrogenation of unsaturated aminoacid precursors with the aid of dissymmetric catalysts has evident advantages over syntheses employing chiral agents to induce a new asymmetric centre—by the saving achieved as a result of the elimination of the expensive optically active starting material, the simplicity of the operations, and the minimal number of side reactions. Until recently, studies in this field concerned the modification of heterogeneous metallic catalysts with various chiral agents in order to make them stereospecific. The degree of asymmetric synthesis in hydrogenation using such catalysts is as a rule low or sometimes poorly reproducible results are obtained[297,320-323].

A new fruitful approach to this problem became possible as a result of two advances in the last decade: the discovery of homogeneous catalytic hydrogenation of olefins with the aid of rhodium(I) complexes with phosphine ligands[324] and the development of procedures for the synthesis of chiral phosphines[325,326]. The application of rhodium complexes with chiral phosphines as homogeneous catalysts for the hydrogenation of *N*-acylaminoacrylic acids permitted the asymmetric synthesis of α-aminoacids with a high degree of stereospecificity[120,319,327,328] and in high yields. The effect of the structure and the optical purity of the chiral phosphine and also of the hydrogenation conditions on the stereospecificity of the catalyst was investigated by Knowles et al.[120,327]. The results are in Table 2.

Table 2 shows that the employment of *o*-anisylmethylcyclohexylphosphine with 95% optical purity leads to a

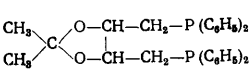
product with 85–90% optical purity, i.e. almost complete stereoselectivity is achieved. The optically pure enantiomer can be obtained by a single recrystallisation.

Table 2 (Knowles et al.[327]). Substrates: 3-(CH_3O)-4-$(OH)C_6H_3CH{=}C(NHCOC_6H_5)COOH$ (I) and 3-(CH_3O)-4-$(CH_3OCO)C_6H_3CH{=}C(NHCOCH_3)COOH$ (II).

Substrate	Phosphine $R_1{-}P(R_2)R_3$			Optical purity of product, %	
	R_2	R_3	R_3	OU, %	
I	*m*-$CH_3OC_6H_4$	CH_3	C_6H_5	80	1[b]
	o-$CH_3OC_6H_4$	C_6H_5	i-C_3H_7	80	1[b]
	CH_3	C_6H_5	i-C_3H_7	90	28[b]
	CH_3	C_6H_5	n-C_3H_7	90	28[b]
	C_6H_{11}	CH_3	C_6H_5	75	32[b]
	o-$CH_3OC_6H_4$	CH_3	C_6H_5	95	58[a]
	o-$CH_3OC_6H_4$	C_6H_{11}	CH_3	95	87[c]
	o-$CH_3OC_6H_4$	C_6H_{11}	CH_3	95	90[d]
II	*o*-$CH_3OC_6H_4$	CH_3	n-C_3H_7	95	20[b]
	o-$CH_3OC_6H_4$	CH_3	C_6H_5	95	55[a]
	o-$CH_3OC_6H_4$	C_6H_{11}	CH_3	90	77[e]
	o-$CH_3OC_6H_4$	C_6H_{11}	CH_3	95	85[c]
	o-$CH_3OC_6H_4$	C_6H_{11}	CH_3	95	87[d]

[a] Methanol, 5 atm, 50°C, with one equivalent of NaOH, substrate: catalyst = 3000 : 1;
[b] Methanol, 5 atm, 25°C; [c] 95% ethanol, H_2 at 500 mmHg;
[d] as for c with 2-propanol; [e] as for a with 0.05% of triethylamine instead of one equivalent of NaOH.

Acyl derivatives of α-aminoacids of the (*S*)-series (l-series) are obtained when (+)-phosphine–rhodium catalysts are used. The employment of catalysts with (-)-phosphine promotes the formation of aminoacids of the unnatural (*R*)-series (D-series)[120,319]. Kagan and Dang studied the hydrogenation of a series of *N*-acylaminoacrylic acids in the presence of a catalyst based on the bisphosphine derivative of natural (+)-tartaric acid[319,328].

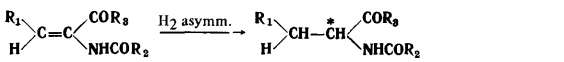

"Kagan's diphosphine".

The data for the asymmetric hydrogenation of *N*-acylaminoacrylic acid derivatives using homogeneous rhodium catalysts based on (+)-*o*-anisylmethylcyclohexylphosphine (A) and Kagan's (-)-diphosphine (B) are summarised in Table 3.

Table 3 shows that the hydrogenation of aromatic systems with chiral phosphine–rhodium catalysts leads to *N*-acylamino-derivatives of L-phenylalanine, L-3,4-dihydroxyphenylalanine, and L-tryptophan in a high optical yield. The above investigations led to the development of a method for the synthesis of L-DOPA from 4-hydroxy-3-methoxybenzaldehyde (vanillin) and its industrial manufacture on its basis has begun[120–122]. The results obtained with aliphatic aminoacid derivatives are more modest, but the limited number of systems investigated precludes definite conclusions at present. Under the conditions adopted, 4-benzylidene-2-methyloxazolone and 5-benzylidenehydantoin are not hydrogenated, although the catalyst retains its activity[319]. This is somewhat unexpected, since azlactones (see end of previous section) are capable of being reduced in the presence of heterogeneous catalysts to *N*-acylaminoacid amides[302].

Comparative characteristics of the catalysts show that both systems have high stereoselectivities, although catalyst B gives higher optical yields with *N*-acetyl derivatives, while in the presence of A the replacement of the acetyl group by the benzoyl group does not affect the stereoselectivity[120,319].

Table 3.



Groups			Catalyst	substrate / rhodium	Chemical yield, %	Optical purity, %	Configuration	Refs.
R_1	R_2	R_3						
C_6H_5	CH_3	OH	A	0.05[a]	—	85	*S*(*L*)	120
C_6H_5	CH_3	OH	B	30	80	72	*R*(*D*)	319, 328
C_6H_5	CH_3	OH	B	100	86	70	*R*(*D*)	319
C_6H_5	CH_3	OH	B	540	95	72	*R*(*D*)	319
C_6H_5	CH_3	OCH_3	B	150	90	55	*R*(*D*)	319
C_6H_5	CH_3	OH_2	B	75	72	71	*R*(*D*)	319
C_6H_5	C_6H_5	OH	A	0.05[a]	—	85	*S*(*L*)	120
C_6H_5	C_6H_5	OH	B	200	96	65	*R*(*D*)	319
3-(C_3O)-4-$(CH_3OCO)C_6H_3$	CH_3	OH	A	0.05[a]	—	88	*S*(*L*)	327
3-(CH_3O)-4-$(OH)C_6H_3$	C_6H_5	OH	A	0.05[a]	—	90	*S*(*L*)	327
3, 4-$CH_2O_2C_6H_3$	CH_3	OH	B	50	95	79	*R*(*D*)	319
p-Cl—C_6H_4	CH_3	OH	A	0.05[a]	—	77	*S*(*L*)	120
p-HO—C_6H_4	CH_3	OH	B	100	92	80	*R*(*D*)	319
p-HO—C_6H_4	CH_3	OH	B	80	95	62	*R*(*D*)	319
N—Ac—Ind	CH_3	OH	A	0.05[a]	—	80	*S*(*L*)	120
H	CH_3	OH	A	0.05[a]	—	60	*S*(*L*)	120
H	CH_3	OH	B	—	—	68	*R*(*D*)	328
i-C_3H_7	C_6H_5	OH	B	75	98	22	*R*(*D*)	319

[a] The amount of metal is expressed as a percentage.

Catalysts for asymmetric homogeneous hydrogenation can be obtained by mixing $[Rh(hexa\text{-}1,5\text{-}diene)Cl]_2$ or $RhCl_3.3H_2O$ with two molecules of a chiral ligand and brief preliminary hydrogenation[120]. The most convenient initial form of the catalyst consists of solid derivatives of the type $[Rh(diene)L_2]^+BF_4^-$, which are stable in air and which readily adsorb hydrogen to form the active catalysts. The latter apparently has an octahedral structure with two stable phosphine linkages. Hydrogen, the substrate, the solvent, and the reaction product are present in dynamic equilibrium in the remaining four coordination sites.



In a complex of this type there is a stereospecific (*cis*-addition) intramolecular transfer of hydrogen to the olefinic double bond with formation of a saturated compound. If the ratio phosphine : rhodium > 2, the complex loses its catalytic activity. The bonds between rhodium and a large number of phosphine molecules probably prevent simultaneous coordination with the olefin[319]. The structural correspondence between the substrate and the ligand is of first importance for high stereospecificity in hydrogenation. The hydrogenation stereoselectivity of the catalyst based on *o*-anisylmethylcyclohexylphosphine is promoted by the methoxy-group, which forms a hydrogen bond with the acylamino-group, thereby determining the relative positions of the substrate and the ligand in the reaction complex. In addition, the methoxy-group, which is a planar ligand, does not form a stable bond with the metal and does not affect its coordination with the other reacting molecules[120]. The high stereospecificity of the catalyst based on Kagan's diphosphine is due to the coordination rigidity of the diphosphine–rhodium chelate, which is increased as a result of the *trans*-configuration of the acetamide ring[319].

The rhodium(I)—neomenthyldiphenylphosphine system [based on natural (-)-menthol] has been used to hydrogenate *E*-β-methylcinnamic acid. This resulted in the formation of (+)-methylhydrocinnamic acid with an optical purity of 61% and in 80% chemical yield[329]. The employment of this catalyst for the hydrogenation of acylaminoacrylic acid would be interesting, since the enamide group in the substrate has been found to have a favourable effect on the steric course of the reaction[319].

2. Method of Asymmetric Induction†

The most extensive studies on the asymmetric synthesis of aminoacids by the reductive transamination of ketoacids with subsequent hydrogenolysis have been carried out by Hiskey and Northrop[330,331] and by Harada and coworkers[332-337]:

$$RCOCOOR' + R^*NH_2 \rightarrow RC(=NR^*)COOR' \xrightarrow{H_2;\ Pd/C} R\overset{*}{C}H(NHR^*)COOR' \rightarrow$$
$$\xrightarrow{1)\ H_2;\ Pd(OH)_2/C;\ 2)\ H_2O\ (H^+)} R\overset{*}{C}H(NH_2)COOH + R^*H + R'H\ .$$

[R* = ArCH(NH₂) AlK; R' = H, Na, C_2H_5, or (-)-menthyl.]

The following aminoacids were obtained in this way (R and the percentage optical purity are indicated): CH_3, 40—80; C_2H_5, 32—42; i-C_3H_7, 28; $C_6H_5CH_2$, 5—14; C_6H_5, 24—30; $HOOCCH_2$, 45—58; $HOOCCH_2CH_2$, 6—56. The configuration of the newly formed asymmetric centre corresponds to the configuration of the chiral amine employed. The two groups of investigators used different methods for the treatment and isolation of the products and for this reason their results, while in general comparable, differ somewhat. The results of the investigations have been discussed in detail in reviews[297,320]. Attempts have been made in recent studies to elucidate the influence of temperature[338-340] and of the solvent[341,342] on the degree of asymmetric synthesis in these reactions.

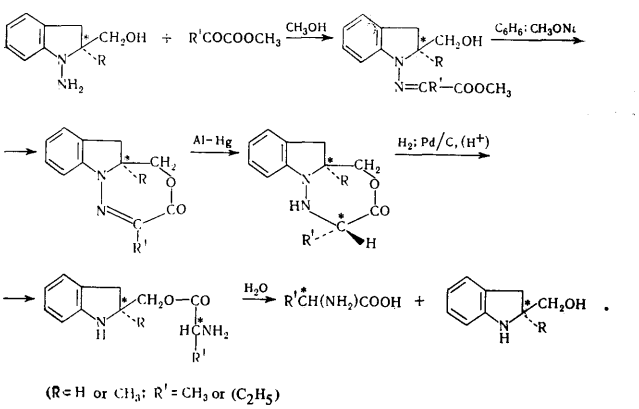
The same method was used to synthesise optically active dipeptides from the esters of the azomethine derivatives of *N*-(α-oxoacyl)-α-aminoacids:

$$CH_3C(=NCH_2C_6H_5)CONHCH(R)COO(i\text{-}C_4H_9) \xrightarrow{H_2;\ Pd/C}$$
$$\rightarrow CH_3\overset{*}{C}H(NH_2)CONHCH(R)COO(i\text{-}C_4H_9).$$

Here the aminoacid residue plays the role of the chiral agent and the L(S)-aminoacid induces a new asymmetric centre with L(S)-configuration when the group R is larger than CH_3. The groups R and the optical purities expressed as percentages were as follows: CH_3, 64; C_2H_5, 42; i-C_3H_7, 32; i-C_4H_9, 39; $C_6H_5CH_2$, 25; $CH_3COOC_4H_9$-i, 25; C_6H_5, 0.[343]

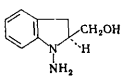
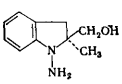
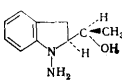
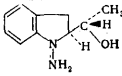
The catalytic hydrogenation of various prochiral substrates with C=O, C=C, or C=N bonds in the presence of optically active bases in various solvents leads to very low optical yields[344]. The reduction of the C=N double bond in the Schiff bases of ketoacids with the aid of $NaBH_4$ and subsequent hydrogenolysis give better results in terms of both chemical and asymmetric yield than catalytic reduction[345]. In almost all the known cases the optical purity of the aminoacids (without additional purification) is low. The inadequate stereospecificity of the non-enzymatic reductive transamination reaction in these examples is apparently due to the inadequate rigidity of the intermediates undergoing hydrogenation. Their conformation is such that the alternative approach of hydrogen to the prochiral centre is not fully excluded and this leads to partial formation of the aminoacid with the opposite configuration. Moreover, the irreversible loss of the chiral agent lowers the practical value of this method.

An asymmetric synthesis of α-aminoacids with high chemical yields and high optical purities was achieved by Corey and coworkers[346-348]. *N*-Amino-2-hydroxymethyl- and *N*-amino-2-(α-hydroxyethyl)-indolines were used as chiral aminating agents. The 2-hydroxymethylindoline formed in the reaction was reconverted by nitrosation and reduction into the initial *N*-amino-derivative with only slight losses. All the *N*-aminoindoline derivatives had the (*S*)(-)-configuration and induced the formation of the D(*R*)-configuration at the new asymmetric centre. The explanation is that the rigid conformation of the seven-membered ring in the intermediate hydrazonolactone ensures the approach of hydrogen, with formation of a new asymmetric centre, in the *cis*-position relative to the substituent (hydrogen or the methyl group) in the α-position with respect to the indoline nitrogen. The results are in Table 4.



When recrystallised hydrazinolactone is used, the optical purity of the resulting aminoacid is 99 ± 1% for alanine and 98 ± 2% for α-aminobutyric acid[347].

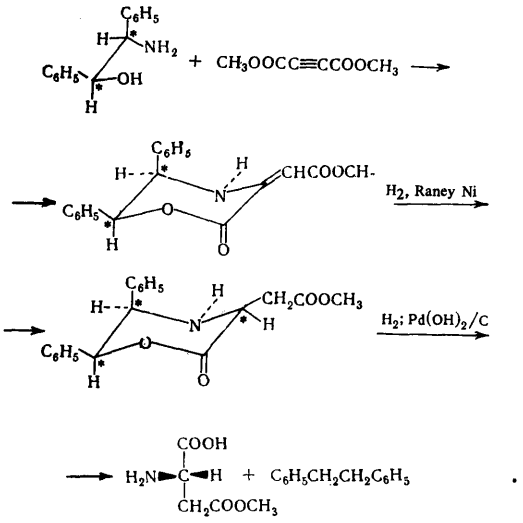
Table 4 (Corey et al.[347,348]).

D(*R*)-Aminoacid obtained	Chiral aminating (*S*)(-)-agent							
								
	yield, %		yield, %		yield, %		yield, %	
	total	optical	total	optical	total	optical	total	optical
Alanine	67	78—82	50	75	52	96	41	92
α-Aminobutyric acid	47	85—90	—	—	55	97	41	96
Valine	—	—	—	—	15	97	—	—
Leucine	—	—	—	—	54	99	—	—

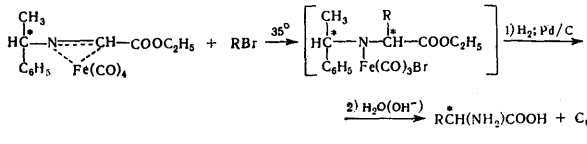
D-Alanine was obtained with an optical purity of 40% and a chemical yield of 10% by the transamination of ethyl pyruvate with chiral *N*-aminoanabasine, which can be regenerated[349,350].

† A new type of asymmetric induction—the synthesis of chiral α-aminoacids with the aid of dissymmetric cobalt(III) complexes—is examined in the section dealing with syntheses based on glycine bound in complexes.

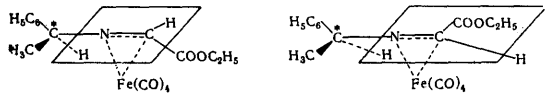
Almost complete stereoselectivity was achieved in the hydrogenation of the cyclic compound obtained by the condensation of *erythro*(+)-1,2-diphenylethanolamine and dimethyl acetylenedicarboxylate:



The stereospecificity of the hydrogenation of the exocyclic double bond is determined by the nature of the intermediate ring in which there is a difference between the degrees of steric hindrance of its two surfaces, namely the axial phenyl group prevents the approach of hydrogen from the axial side. In the hydrogenolysis of the reduced product, methyl L(S)-aspartate was obtained with an optical purity of 98% and in almost quantitative chemical yield[352,353]. High stereospecificity, owing to the rigid fixation of the reaction centre, is achieved in the alkylation by alkyl halides of the π-complexes of the α-methylbenzylimino-derivative of ethyl glyoxylate in the presence of iron nonacarbonyl:



The groups R used, the chemical yields, and the optical purities obtained (expressed as percentages) were as follows: $C_6H_5CH_2$, 53, 77; o-$CH_3OC_6H_4CH_2$, 28, 95; $C_2H_5OOCCH_2$, 24, 78. Alanine is not obtained when the complexes are alkylated with methyl iodide. The optical yield decreases with increase of temperature; the racemate of phenylalanine was obtained at 80°C with a chemical yield of 100%. A pair of diastereoisomeric complexes in proportions of 1:9 is obtained for each of the enantiomeric imines:

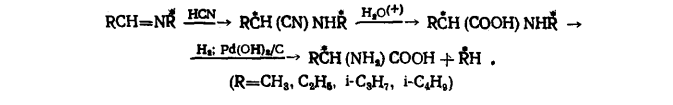


complexes obtained from the D-imine

When the diastereoisomer formed in excess is employed in the reaction, the L-amino-acid is obtained from the D-imine and conversely[354].

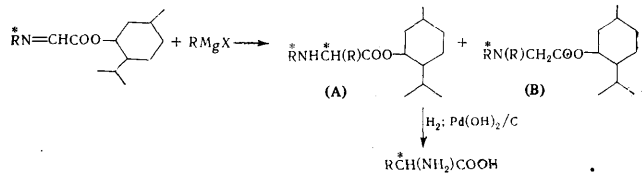
Chiral alkylarylamines have been used as aminating agents in yet another series of reactions but the optical purities of the resulting aminoacids are as a rule low.

Thus optically active aminoacids have been obtained by the addition of hydrogen cyanide[355] or benzyl cyanide[356] to the azomethines obtained from aldehydes and chiral amines:



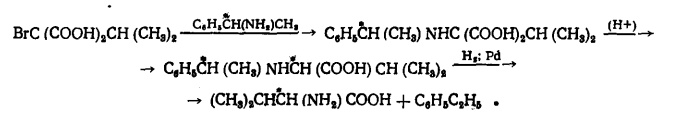
The chemical yields of the aminoacids are 9–58% [355] and 15–57% [356] and the optical purities are 22–58% [355] and 17–37%.[356] However, according to other data, a number of aminoacids with chemical yields of 40–60% and optical purities of 98–99% have been obtained by the addition of hydrogen cyanide to Schiff bases. The configuration of the resulting centre corresponds to that of the chiral amine[357].

The chiral imines of (-)-methyl glyoxylate combine with organomagnesium compounds by the following mechanism:

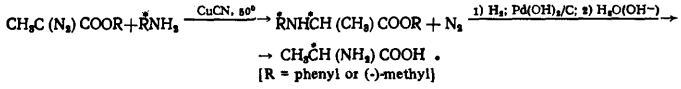


The overall chemical yield of A + B is 45–55%.[358,359] The mode of reaction depends on the structure of the group R in the organomagnesium compound. When R = CH_3, CH_2 = $CHCH_2$, or t-C_4H_9, A is the main addition product, which leads to an aminoacid. When R = C_2H_5, n-C_3H_7, s-C_4H_9, or $C_6H_5CH_2$, the main product is B, which yields *N*-alkylglycines. Optically active alanine was obtained in this way in a chemical yield of 41–45%. The configuration of the resulting aminoacid is determined by (-)-menthol and the optical purity depends on the configuration of the chiral amine: both (*S*)- and (*R*)-amines lead to L(*S*)-alanine with optical purities of 47.5 and 65%.[358] Organocadmium adds selectively to imines with formation of A exclusively. Alanine, norvaline, valine, and phenylalanine have been obtained with their aid in chemical yields of 55–70% and with optical purities of 38–46%.[359]

Valine has been obtained at 20°C in almost quantitative yield with an optical purity of 23% by the selective decarboxylation of (benzylmethylamino)isopropylmalonic acid and its configuration was the opposite of that of the amine employed[360]:



Optically active alanine was obtained by the insertion of the carbene formed in the decomposition of α-diazopropionic acid ester in the N–H bonds of a chiral amine:



The optical purity of the alanine was 12–26% and the configuration was the opposite of that of the inducing amine; the chirality of the ester group [(-)-menthyl] plays a secondary role[361].

Aspartic acid with an optical purity between 21 and 67% has been obtained from chloroacetonitrile and monochloroacetic acid anhydride by a series of reactions involving chiral amines:

$$\overset{*}{R}NH_2 + ClCH_2CN \rightarrow \overset{*}{R}NHCH_2CN \xrightarrow{(ClCH_2CO)_2O} \overset{*}{R}N(COCH_2Cl)CH_2CN \xrightarrow{B:}$$
$$\rightarrow \overset{*}{R}N{-}\overset{*}{C}HCN \xrightarrow{H_2O(H^+)} HOOC\overset{*}{C}HN(\overset{*}{R})CH_2COOH \xrightarrow{H_2;\ Pd(OH)_2/C}$$
$$\rightarrow HOOCCH_2\overset{*}{C}H(NH_2)COOH .$$

The configuration of the resulting aminoacid is the opposite of that of the inducing amine. The optical purity depends on its structure: α-methylbenzylamine, α-ethylbenzylamine, and α-methylnaphthylamine give 41–49, 19–29, and 54–67% respectively[362]. The same dependence of the configuration of the resulting aminoacid on that of the inducing amine is observed in the synthesis of alanine from α-bromopropionamide. The optical yield of D(R)-alanine is between 11 and 36%.[363] The Baumgarten reaction[364] has been used for the asymmetric synthesis of aminoacids. Thus L(S)-phenylalanine, L(S)-alanine, L(S)-phenylglycine, and L(S)-leucine with optical purities of 62, 33, 27, and 75% respectively have been obtained by the rearrangement of (-)-menthyl N-chloroimidates. When (-)-2-methyl-1-butanol is used instead of (-)-menthol, better results are obtained[365].

The possibility of employing chiral alkylboranes[366] and aminoboranes[367] for the asymmetric synthesis of aminoacids has been demonstrated.

The following aminoacids have been obtained by the cyanohydrin synthesis using chiral amines [the aminoacids, their chemical yields (%) (in brackets), and optical purities (%) are listed]: alanine (42–47), 41–50; α-aminobutyric acid (27–32), 36–51; valine (17–26), 31–45; leucine (28–32), 22–39. The configuration of the resulting aminoacid is the same as that of the initial chiral amine. After additional purification, alanine can be obtained with an optical purity of 90%.[297,368] Aromatic S(L)-α-methylaminoacids (α-methyl-DOPA, tyrosine, and phenylalanine) have been synthesised from the corresponding methyl ketones by the cyanohydrin method. Virtually complete stereospecificity has been achieved with the aid of (4S, 5S)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane as the chiral amine[369].

V. ENZYMATIC METHODS FOR THE SYNTHESIS OF AMINOACIDS

The employment of enzymes makes it possible to achieve under extremely mild conditions transformations which normally require cumbersome multistage synthesis. Moreover, enzymatic reactions are stereospecific and lead to the formation of only one enantiomer (usually the natural enantiomer). The culture liquids of various strains of micro-organisms and purified and immobilised enzymes are used for such reactions.

The widely employed selective enzymatic hydrolysis of acyl derivatives of L-aminoacids with the aid of acylases of various origins[370,371] is more correctly regarded as resolution of racemates and will not be considered here.

Enzymatic syntheses proper include, for example, the formation of L-tryptophan from indole, pyruvic acid and ammonia, which is carried out in a single stage in the presence of pyridoxal phosphate under the influence of the tryptophanase present in the culture liquid of *Escherichia coli*. For an initial concentration of 6.5%, 72% of tryptophan is obtained after 48 h (34°C and pH 8.8).[372] This synthesis was based on a study of the mechanism of the cleavage of tryptophan by the above enzyme. The reaction was reversed by increasing the concentration of the decomposition products. A complex of the enzyme with α-aminoacrylic acid served as an intermediate in this synthesis[373]. The exchange of the p-hydroxyphenyl group for the 3,4-dihydroxyphenyl group in the formation of L-DOPA by the interaction of L-tyrosine and catechol in the presence of crystalline β-tyrosinase and pyridoxal proceeds via the same complex. The replacement of catechol by other substrates leads to the possibility, in principle, of the formation of numerous aminoacids[374].

The synthesis of tryptophan from indole, pyruvic acid, and ammonia is catalysed by tryptophanase immobilised on Sepharose bound covalently to pyridoxal 5'-phosphate[375].

L-DOPA can be obtained by the enzymatic hydroxylation of L-tyrosine derivatives under the influence of enzymes from different strains of fungi[376–378]. The reaction occurs when L-tyrosine protected by acylation is incubated with the culture of the fungus in an appropriate nutrient medium. The protection of the amino-group prevents deamination and racemisation. The fermentation gives a mixture of 57% L-tyrosine and 25–30% of L-DOPA. Microorganisms can also convert D-tyrosine into D-DOPA. The authors of the method believe it to be one of the most economical[376]. Polyphenol oxidase with tyrosinase activity, bound covalently to DEAE-cellulose subjected to preliminary treatment with 6-amino-2,6-dichloro-s-thiazine, was used to synthesise L-DOPA by this method. A disadvantage is 75% loss of activity of the immobilised enzyme in 24 h.[379] A recently developed method for the continuous conversion of ammonium fumarate into L-aspartic acid has already been considered (see Section II, 6).

Data for the enzymatic synthesis of certain aminoacids are summarised in Table 5.

Table 5.

Enzymic transformation	Yield, %	References
L-Aspartic acid formed from fumaric acid and NH_3	90	90, 380
L-Alanine formed from L-aspartic acid	90	380
L-Tyrosine formed from phenol, pyruvic acid, and NH_3	90	380
L-DOPA formed from catechol, pyruvic acid, and NH_3	70	380
L-DOPA formed from L-tyrosine	65–70	377
L-Tryptophan formed from indole, pyruvic acid, and NH_3	72	372

The *meso*-form of diaminopimelic acid is known to be converted into L-lysine under the influence of decarboxylase in the presence of pyridoxal phosphate. It was obtained from synthetic diaminopimelic acid with the aid of partially purified microbial decarboxylase[381]. The racemic diaminopimelic acid remaining after the decarboxylation of the *meso*-form can be converted into the *meso*-form by epimerisation[382–384].

The esters of racemic acylaminoacids undergo selective hydrolysis under the influence of chymotrypsin or subtilisin, which results in a high yield of the L-acylaminoacid. The D-form remains as the non-hydrolysed ester. In particular, benzoyloxycarbonyl-L-phenylalanine was obtained by this procedure[385].

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Derivatives of the Elements,
USSR Academy of Sciences,
Moscow