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β-Fluoro-substituted aminoacids

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ABSTRACT. The review gives a systematic account of data concerning the methods of synthesis of α-, β-, and γ-aminoacids containing fluorine atoms in the β-position relative to the amino-group. The interest in these compounds is in many respects due to the fact that most of them have proved to be highly selective irreversible inhibitors of pyridoxal-5-phosphate-dependent enzymes acting via the "suicide-substrate" mechanism. Attention is concentrated on β-fluoro-derivatives of natural α-aminoacids.

The bibliography includes 114 references.

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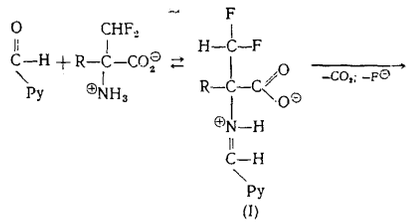
I. Introduction

Even if one disregards the unique importance of aminoacids in the initiation of life on Earth, compounds of this class possess a sufficient number of biological functions to be placed in the forefront of substances without which living organisms could not exist. The synthesis of aminoacids and their organoelement analogues therefore constitutes a most important aspect of modern bioorganic chemistry concerned with the creation of new medicinal preparations and fine biochemicals.

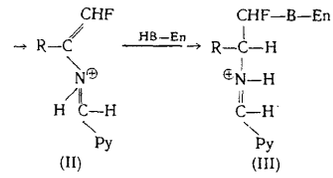
The vigorous development of organofluorine compounds after the 1940s and certain advances in the use of fluorinated analogues of natural products have created objective grounds for the initiation of vigorous research into fluorine-containing aminoacids. At the present time these compounds are one of the most promising types of low-molecular-weight bioregulators.[1]

Analysis of a considerable amount of data on the biological activity of fluoro-substituted aminoacids made it possible to differentiate in the first place compounds which are highly selective irreversible inhibitors of enzymes with the pyridoxal phosphate group, such as aminoacid racemases, transaminases, and decarboxylases. A common structural feature of substances exhibiting the properties of inhibitors of this type was found to be the presence of fluorine atoms in the β-position relative to the amino-group.

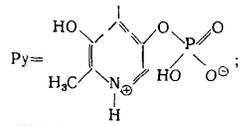
On the basis of numerous studies undertaken to explain the biochemical activity of β-fluoro-substituted aminoacids, a mechanism has been proposed[2–4] whose idea is that the enzyme itself synthesises the substance inhibiting it—the "suicide-substrate". Thus in the case where the substrate of decarboxylase is a β-fluoro-α-aminoacid, the reversible formation reaction of the Schiff base (I) is followed by the irreversible decarboxylation stage with elimination of the fluorine atom from the β-position and the formation of the Michael acceptor (II). The latter reacts with the nucleophilic groups of the enzyme located near the active centre. This reaction is irreversible; the enzyme, bound covalently to the aminoacid residue (III), loses its ability to interact further with the substrate and is deactivated.



(I)



(II) (III)



HB = HO, H_2N, En = enzyme.

The deactivation of transaminases or racemases by β-fluoro-substituted aminoacids also proceeds via an elimination stage or a stage involving activation with respect to the nucleophilic substitution of the fluorine atom with the subsequent chemical binding of the aminoacid residue to the nucleophilic centre of the enzyme. The suppression of the enzymic reaction via the mechanism described above leads to the appearance of bactericidal and other types of biological activity in β-fluoro-substituted aminoacids.[5,6]

The determination of the biochemical mechanism of the inhibition of enzymes by β-fluoro-derivatives of aminoacids has greatly stimulated studies on these compounds.

The syntheses of β-fluoro-substituted aminoacids achieved hitherto are various from the standpoint of both the methods and the initial compounds employed. However, certain types of aminoacids have been obtained using mainly the methods of organic or organofluorine chemistry. This made it possible to differentiate in this review two main sections: the classical and special methods of synthesising β-fluoro-derivatives of aminoacids.

The reviews available in the literature[7,8] deal with the methods of synthesis of all types of fluorine-containing aminoacids, including β-fluoro-derivatives, published up to 1968. Later publications[9–11] deal with the methods of synthesis and biological activity of only

individual types of β-fluoro-substituted aminoacids, for example, such as α-polyfluoromethyl-substituted aminoacids. The present review surveys studies on the synthesis of α-, β-, and γ-aminoacids containing fluorine atoms in the β-position relative to the amino-group, carried out mainly during the last twenty years, earlier sources being referred to when necessary.

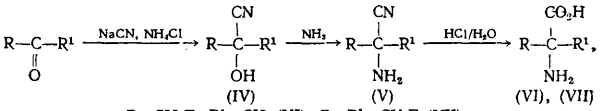
Data on the biological activity of the compounds examined are quoted only in those cases where in the sources referred to the biological activity of the aminoacids is reported together with their synthesis. A number of reviews have been devoted to the biological properties of β-fluoro-substituted aminoacids.[3,4,9–12]

II. Classical methods of synthesis of β-fluoro-substituted aminoacids

Almost all the known methods of synthesis of non-fluorinated aminoacids have been used to obtain their fluorinated analogues. However, only a few of these methods proved to be preparatively valuable and remained of current interest up to the present time. The applicability of the classical methods of synthesis of aminoacids to the series of fluorine-containing compounds is limited by the specific influence of fluorine or perfluoralkyl groups as a result of which many reactions may alter their character during the synthesis. The influence of fluorine atoms next to reaction centres is especially marked. The classical methods have therefore found only limited applications in the synthesis of β-fluoro-derivatives of aminoacids.,

1. Synthesis of β-fluoro-derivatives of aminoacids from fluorine-containing carbonyl compounds

The Strecker synthesis of aminoacids was one of the first used to obtain mono- and di-fluoroaminoacids. However, in contrast to the non-fluorinated ketones, the reactions mainly stop in the first stage—the formation of the corresponding cyanohydrins (IV). Thus a mixture of nitriles of 3-fluoro-2-hydroxyisobutyric and 3-fluoro-2-aminoisobutyric acids in proportions of 13:87 has been obtained from monofluoroacetone, while 3,3′-difluoro-2-hydroxyisobutyric acid has been obtained as the only reaction product from 1,3-difluoroacetone.[13,14]

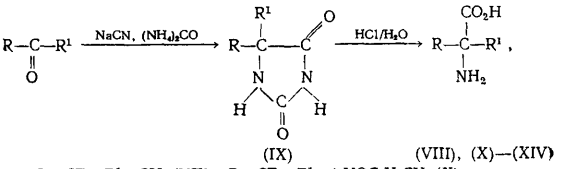


R=CH_2F, $R^1=CH_3$ (VI); $R=R^1=CH_2F$ (VII).

In order to obtain aminoacids, the cyanohydrins (IV) were converted by treatment with ammonia into the aminonitriles (V), from which mono- and di-fluoro-derivatives of α-aminoisobutyric acid (VI) and (VII) were obtained by acid hydrolysis.

3,3,3-Trifluoro-α-aminoisobutyric acid (VIII) was obtained from 3,3,3-trifluoroacetone via a stage involving the formation of 5-methyl-5-trifluoromethylhydantoin (IX), whose yield was 23%.[15]

A series of α-trifluoromethylphenylalanines (X)–(XII) have been obtained by the same methods from the corresponding fluorinated ketones. The yield of the hydantoins (IX) formed initially did not exceed 50%.[16] Compounds (X)–(XII) can be used to regulate the level of noradrenalin.

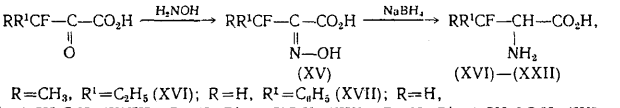


(IX) (VIII), (X)–(XIV)

R=CF_3, $R^1=CH_3$ (VIII); R=CF_3, R^1=4-$HOC_6H_4CH_2$ (X);
R=CF_3, R^1=3, 4-$(OH)_2C_6H_3CH_2$ (XI); R=CF_3,
R^1=3, 4, 5-$(OH)_3C_6H_2CH_2$ (XII);
R=CHF_2, R^1=4-$HOC_6H_4CH_2$ (XIII); R=CH_2F,
$R^1=HO_2C(CH_2)_2$ (XIV).

The introduction of ketones containing less electron-accepting mono- and di-fluoromethyl groups into the Bucherer reaction affords the hydantoins (IX) in higher yields. α-Difluoromethyltyrosine (XIII)—an effective hypotensive preparation[17]—and α-fluoromethyl-glutamic acid (XIV)—an irreversible inhibitor of glutamate decarboxylase[18]—were also obtained by this method.

A widely used method of synthesis of aminoacides and amines, based on the reduction of compounds with a C=N bond, has also been employed to synthesise β-fluoro-derivatives of aminoacids. A disadvantage of this method is the low availability of β-fluoro-α-keto-acids. Fluorine-containing ketoacids were introduced into the reaction with hydroxylamine and the corresponding aminoacids were obtained by the subsequent reduction of the oximes (XV) formed. β-Fluoroisoleucine (XVI),[19] a series of β-fluorophenylalanines (XVII)–(XXI), exhibiting antimicrobial and anticancer activities,[20,21] as well as ββ-difluoroaspartic acids (XXII), which is an irreversible inhibitor of aspartate aminotransferase,[22] were obtained by this procedure.

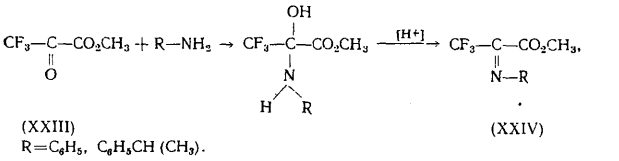


(XV) (XVI)–(XXII)

R=CH_3, $R^1=C_2H_5$ (XVI); R=H, $R^1=C_6H_5$ (XVII); R=H,
R^1=4-$CH_3C_2H_4$ (XVIII); R=H, R^1=4-ClC_6H_4 (XIX); R=H, R^1=4-$CH_3OC_6H_4$ (XX);
R=H, R^1=4-$O_2NC_6H_4$ (XXI); R=F, $R^1=HO_2C$ (XXII).

The stereochemical aspects of the formation of *erythro*- and *threo*-β-fluorophenylalanines (XVII)–(XXI) during the reduction of the oximes (XV) have also been investigated in a series of studies[21,23,24] and it has been shown that mainly the *erythro*-isomers of β-fluoro-substituted aminoacids are obtained.

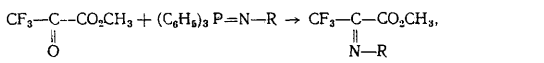
A method of synthesis of trifluoroalanine and of a series of its *N*-alkyl- and *N*-aryl-derivatives from the readily available methyl trifluoropyruvate (XXIII) have been developed recently.[25] The corresponding imines cannot be obtained by the direct interaction of the ketoester (XXIII) with ammonia or amines. An exception is provided by α-phenylethylamine and aniline, whose adducts with the ketoester (XXIII) are dehydrated in the presence of acid catalysts to the corresponding imines (XXIV).



(XXIII) (XXIV)

R=C_6H_5, $C_6H_5CH(CH_3)$.

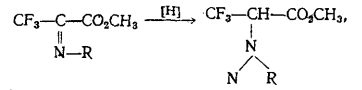
The most general method of synthesis of imines of methyl trifluoropyruvate is the Staudinger reaction, which makes it possible to obtain the imines (XXV)–(XXVIII) in 60–95% yields.



(XXII) (XXV)—(XXVIII)

R = C_6H_5 (XXV), n-C_4H_9 (XXVI); $C_2H_5CH(CH_3)$ (XXVII), CH_3O_2C (XXVIII)

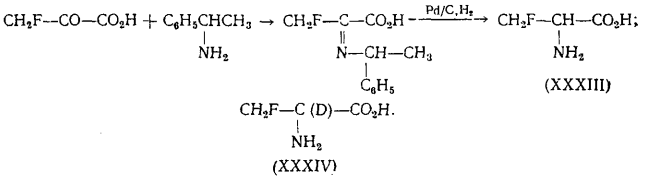
Sodium tetrahydroborate and hydrogen on palladium black have been used to reduce compounds (XXIV), (XXV), (XXVII), and (XXVIII) to the corresponding alanines (XXIX)–(XXXII), but reduction with zinc in acetic or formic acid proved to be the most convenient.



(XXIV), (XXV), (XXVII), (XXVIII) (XXIX)—(XXXII)

R = $C_6H_5CH(CH_3)$ (XXIX); C_6H_5 (XXX), $C_2H_5CH(CH_3)$ (XXXI), CH_3O_2C (XXXII).

The reduction of the optically active *N*-phenylethylimine (XXIV) with various reducing agents proceeds with a slight asymmetric induction (the ratio of the diastereoisomers is 5 : 4). However, in the case of monofluoropyruvic acid the use of the optically active L-α-phenylethylamine makes it possible to achieve the asymmetric synthesis of a highly effective antibacterial agent—3-fluoro-D-alanine (XXXIII)[26]—in accordance with the following scheme:



(XXXIII)

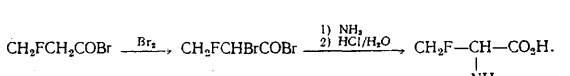
(XXXIV)

A deuteriated analogue of fluoroalanine (XXXIII)—"fludalanine" (XXXIV)—has been obtained by a similar procedure from monofluoropyruvic acid using $NaBD_4$ as the reducing agent.[27]

2. The substitution of the α-halogen atom or the α-hydroxy-group by the amino-group

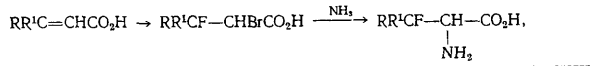
The method of synthesis of aminoacids by the introduction of an amino-group into carboxylic α-halogeno- or α-hydroxy-acids has been used successfully to synthesise a wide variety of fluorine-containing aminoacids.[7,8] However, this method proved to be applicable to the synthesis of β-fluoro-substituted aminoacids only in the case of the monofluoro-derivatives. This is associated with the fact that fluoroalkyl and especially perfluoroalkyl groups hinder nucleophilic substitution in the neighbouring carbon atom.

Thus monofluoroalanine (XXXIII) has been obtained in a low yield from the bromide of 3-fluoropropionic acid by the successive bromination and treatment with ammonia of the bromide of α-bromo-β-fluoropropionic acid formed.[28]



(XXXIII)

Subsequently the method was improved by employing acrylic acid derivatives as the starting compounds.[29] The coupled addition of fluorine and bromine to 3-alkylacrylic acids was carried out by treatment with *N*-bromosuccinimide in liquid hydrogen fluoride with formation of carboxylic α-bromo-β-fluoroacids. The latter were converted into the corresponding aminoacids (XXXIII), and (XXXV)–(XXXIX) in 10–63% yields by treatment with ammonia.

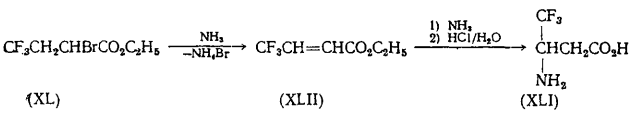


(XXXIII), (XXXV)—(XXXIX)

R = R^1 = H (XXXIII); R = R^1 = CH_3 (XXXV); R = H, R^1 = CH_3 (XXXVI); R = H, R^1 = C_2H_5 (XXXVII); R = H, R^1 = n-C_3H_7 (XXXVIII); R = H, R^1 = n-C_4H_9 (XXXIX).

This method made it possible to increase the yield of fluoroalanine (XXXIII) and to obtain a series of new aliphatic β-fluoro-α-aminoacids with antifungal or antimicrobial activity.[29]

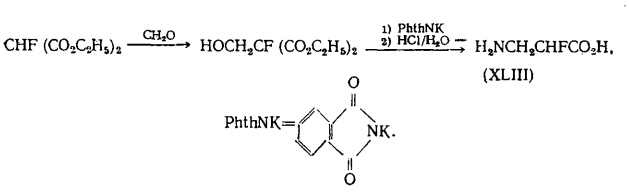
Instead of the expected derivative of 4,4,4-trifluoro-2-aminobutyric acid, the ammonolysis of ethyl 2-bromo-4,4,4-trifluorobutyrate (XL) afforded the β-alanine ester—4,4,4-trifluoro-3-aminobutyric acid (XLI).[30,31]



(XL) (XLII) (XLI)

It was found that, on treatment of the bromo-derivative (XL) with ammonia, hydrogen bromide is split off and ethyl trifluorocrotonate (XLII) is formed, which can be explained by the inductive effect of the trifluoromethyl group, facilitating the elimination of the proton in the β-position. In the next stage of the reaction, ammonia adds in the usual way to the β-carbon atom. The above mechanism of the formation of the β-alanine (XLI) has been confirmed by its synthesis from trifluorocrotonic acid (XLII).[32] Biological tests have shown that β-trifluoromethyl-β-alanine (XLI) possesses antibacterial activity.[32]

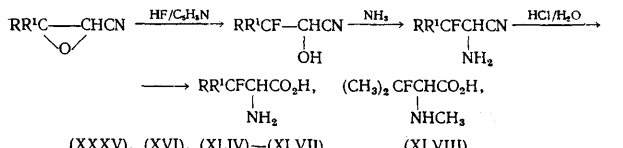
The synthesis of β-fluoro-derivatives of aminoacids with the replacement of the hydroxyl by the amino-group proved successful only in the synthesis of monofluoro-derivatives. α-Fluoro-β-alanine (XLIII), first isolated as a 5-fluorouracil metabolite,[33–35] has been synthesised from diethyl fluoromalonate in accordance with the following scheme:[36]



(XLIII)

α-Fluoro-β-alanine (XLIII) has been synthesised similarly from α-fluoro-β-hydroxypropionic acid.[37]

A general method of synthesis using 2-cyanoepoxides has been developed recently to obtain β-fluoro-α-aminoacids.[38]



(XXXV), (XVI), (XLIV)—(XLVII), (XVII), (XXXVI) (XLVIII)

R = R^1 = CH_3 (XXXV); R = CH_3, R^1 = C_2H_5 (XVI); R = R^1 = C_2H_5 (XLIV); R = H, R^1 = C_6H_5 (XVII); R = CH_3, R^1 = C_6H_5 (XLV); R = H, R^1 = CH_3 (XXXVI); R + R^1 = $(CH_2)_4$ (XLVI); R + R^1 = $(CH_2)_5$ (XLVII).

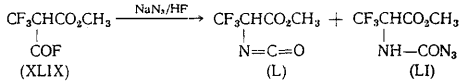
The opening of the epoxide ring with the aid of the Olah reagent (a solution of hydrogen fluoride in pyridine) leads to a high yield of β-fluoro-α-hydroxynitriles, from which the corresponding amino-derivatives were obtained in 13–85% yield by treatment with ammonia in the presence of $MgSO_4$. Hydrolysis of these compounds afforded the free β-fluoro-α-aminoacids (XVI), (XVII), (XXXV), (XXXVI), and (XLIV)–(XLVII).

The use of methylamine in this reaction instead of ammonia made it possible to synthesise the corresponding *N*-methyl derivatives of β-fluoroaminoacids (XLVIII).[38]

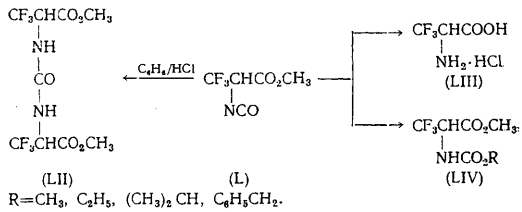
3. Other methods of synthesis of β-fluoro-derivatives of aminoacids

The conversion of the carboxy-group into the amino-group by the Curtius method has been used to obtain α-trifluoromethyl- and α-difluoromethyl-substituted aminoacids.

A method[39] based on the conversion of the fluoride of 2-methoxycarbonyl-3,3,3-trifluoropropionic acid (XLIX) has been proposed for the synthesis of trifluoroalanine. The acid fluoride (XLIX) was converted by treatment with sodium azide or trimethylsilyl azide into the corresponding isocyanate (L). When the initial acid fluoride (XLIX) contains an admixture of hydrogen fluoride, the reaction is complicated by the formation of the carbamoyl azide (LI).

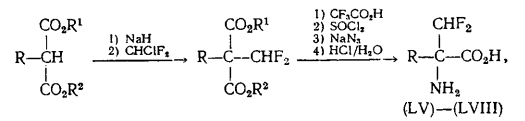


The interaction of the isocyanate (L) with water proceeds in different ways depending on the reaction conditions. Thus hydrolysis of a benzene solution of compound (L) with concentrated hydrochloric acid proceeds with formation of the symmetrical urea (LII). The hydrochloride of trifluoroalanine (LIII) has been obtained by treating the isocyanate (L) with hydrochloric acid in the absence of a solvent.



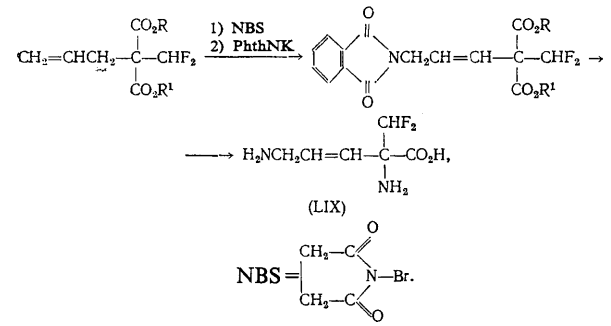
The introduction of the isocyanate (L) into a reaction with alcohols made it possible to obtain the methyl esters of trifluoroalanine (LIV) containing *N*-alkoxycarbonyl groups.

The Curtius reaction has also been used as the key stage in the synthesis of α-difluoromethyl-substituted aminoacids. Treatment of substituted malonates, having two different substituents in the ester groups, with Freon subsequently made it possible to eliminate selectively one of these substituents (OBu^t) by treatment with trifluoroacetic acid. The subsequent treatment of the intermediate acid ethyl malonates with thionyl chloride and sodium azide yielded the corresponding isocyanates, which were hydrolysed to the aminoacids without isolation.[40–42]

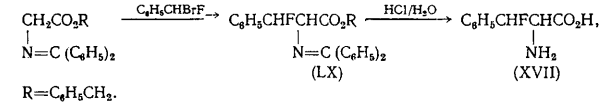


The difluoromethyl derivatives of aspartic acid (LV), alanine (LVI), and phenylalanine (LVII) have been obtained by this method.

By bromination and subsequent replacement of the bromine atom by the phthalamide group, 2-allylmalonic ester has been converted into the protected δ-amino-derivative from which δ-difluoromethyldehydroornithinine (LIX)—an irreversible inhibitor or ornithinine decarboxylase—was obtained in accordance with the scheme presented above.[40]



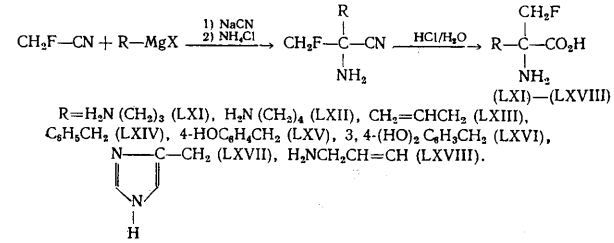
Yet another example of the use of classical methods of synthesis of aminoacids for the preparation of their β-fluorinated analogues is the alkylation of the benzyl ester of *N*-(α-phenylbenzylidene)glycine by bromofluorophenylmethane.[43]



The Schiff base was alkylated in methylene chloride in the presence of $(C_4H_9)_4N^{\oplus}HSO_4^{\ominus}$ and the alkylated product (LX) was obtained in 71% yield. It was hydrolysed to β-fluorophenylalanine (XVII).

The involvement of carboxylic acid nitriles in reactions with organometallic reagents has been rarely used to synthesise non-fluorinated aminoacids. However, in the synthesis of α-monofluoromethyl derivatives of aminoacids, this approach proved to be a successful alternative method of the direct fluoromethylation of the C-anions of protected aminoacids, which will be examined in the next section.

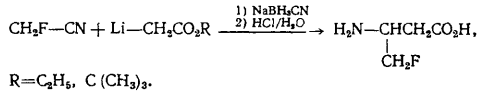
The reactions of monofluoroacetonitrile with organomagnesium reagents have been carried out at −40 °C in solution in tetrahydrofuran. The imines formed under these conditions were treated, without isolation, with sodium cyanide and then ammonium chloride was added.[44,45]



α-Monofluoromethyl-substituted derivatives of ornithine (LXI), lysine (LXII), 2-allylglycine (LXIII), phenylalanine (LXIV), tyrosine (LXV), dihydroxyphenylalanine (LXVI), and histidine (LXVII) were obtained by this method. A patent[45] states that monofluoroornithine (LXI) can be used as an effective antifertility agent.

α-Monofluoromethyldehydroornithine (LXVIII) has been obtained by introducing a functional group into 2-allyl-3-fluoroalanine (LXIII) similarly to the scheme employed for the synthesis of α-difluoromethyldihydroornithine (LX).

The application of lithium derivatives of acetate esters in the reaction of monofluoroacetonitrile made it possible to achieve the synthesis of 3-amino-4-fluorobutyric acid (LXIX)—an inhibitor of γ-aminobutyric acid transaminase.[46]



$R=C_2H_5$, $C(CH_3)_3$.

III. Special methods of synthesis of β-fluoro-substituted aminoacids

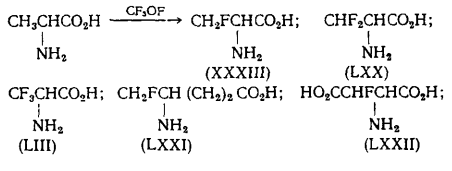
The methods of organofluorine chemistry have been recently used extensively for the synthesis of fluorine-containing aminoacids. The procedures for the introduction of fluorine into the molecules of organic compounds with the aid of elemental fluorine transferring agents, such as trifluoromethyl hypofluorite and perchloryl fluoride and fluorinating agents—antimony trifluoride, sulphur tetrafluoride and its derivatives, as well as metal fluorides (KF, AgF)—proved especially useful.

1. The replacement of hydrogen and halogen atoms and of hydroxy-, mercapto-, and amino-groups by fluorine atoms in the molecules of aminoacids of their derivatives

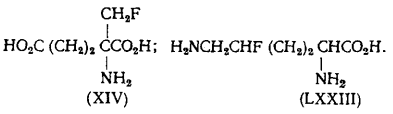
One of the most promising but little used methods of synthesis of fluorine-containing aminoacids involves the direct fluorination of aminoacid molecules. An important disadvantage of this method still remains its low selectivity, as a result of which mixtures of reaction products are formed, which hinders the isolation of the target product.

A synthesis of this type was first achieved in the preparation of 4-fluoroglutamic acid using perchloryl fluoride.[47–49]

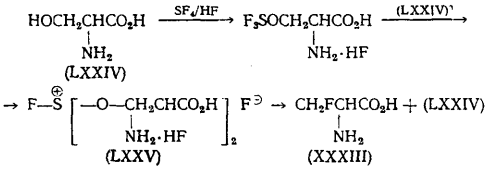
The most effective fluorinating agent for the synthesis of β-fluoro-derivatives of aminoacids is trifluoromethyl hypofluorite.



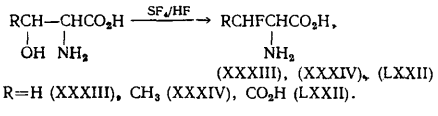
The reactions were carried out under UV irradiation in hydrogen fluoride. Monofluoroalanine (XXXIII),[50–52] difluoroalanine (LXX), trifluoroalanine (LIII),[53] γ-fluoromethyl-γ-aminobutyric acid (LXXI),[54] β-fluoroaspartic acid (LXXVII),[53] and α-fluoromethylglutamic acid (XIV)[55,56] were synthesised in this way from non-fluorinated aminoacids. In the fluorination of lysine with CF_3OF, one of the reaction products was 5-fluorolysine (LXXIII).[57] The lack of selectivity is the main disadvantage of the method.



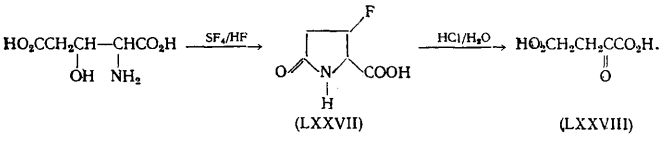
The method involving the replacement of the hydroxy-group by fluorine with the aid of sulphur tetrafluoride or its derivatives, widely used in organofluorine chemistry, has been applied successfully in the synthesis of β-monofluoro-derivatives of aminoacids. Since sulphur tetrafluoride reacts with amino- and carboxy-groups, liquid hydrogen fluoride, which converts the amino-group into the ammonium group $NH_3^{\oplus}$ which is inert to the action of sulphur tetrafluoride, was used as the solvent in this reaction. In order to prevent the fluorination of the carboxy-group to the trifluoromethyl group, the reaction was performed at low temperatures. In the case of β-hydroxy-α-aminoacids, the fluorination must be carried out also at low reactant concentrations in addition to the conditions indicated above. It has been shown for the interaction of sulphur tetrafluoride with serine (LXXIV) that the reaction is complicated by the formation of the sulphenium salt (LXXV). Further reaction of compound (LXXV) leads to the formation of the initial aminoacid and monofluoroalanine (XXXIII) in proportions of 1 : 1.[58] When the reaction is carried out at high dilution, the formation of the product (LXXV) is prevented, which makes it possible to obtain monofluoroalanine (XXXIII) with a very low serine content (the ratio is 99 : 1).



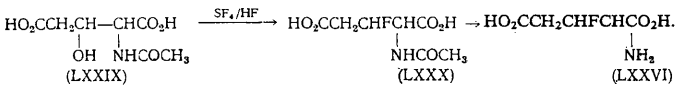
This method, which has been called fluorodehydroxylation, made it possible to obtain 3-fluoro-2-aminobutyric acid (XXXIV)[59] and 3-fluoroaspartic acid (LXXII)[59,60] in moderate yields, apart from monofluoroalanine (XXXIII),[58,59] from the corresponding hydroxy-derivatives.



3-Fluoroglutamic acid (LXXVI) could not be obtained by the fluorodehydroxylation of 3-hydroxyglutamic acid because the lactam (LXXVII) is formed in the fluorination reaction. It was found that acid hydrolysis of compound (LXXVII) takes place only under severe conditions and is accompanied by the elimination of hydrogen fluoride, as a result of which ketoacid (LXXVIII) was isolated as the main reaction product.[61]



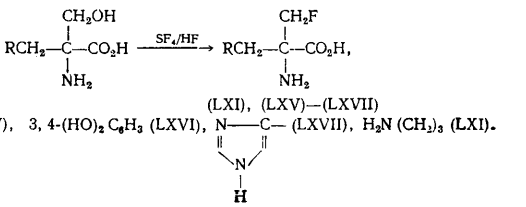
The formation of the lactam (LXXVII) can be prevented by using β-hydroxyglutamic acid with a protected amino-group (LXXIX) in the fluorodehydroxylation reaction.



When the acetyl protecting group in compound (LXXX) was removed with the aid of acylase, L-*threo*- and L-*erythro*-isomers of 3-fluoroglutamic acid (LXXVI) were obained in a pure state.[61]

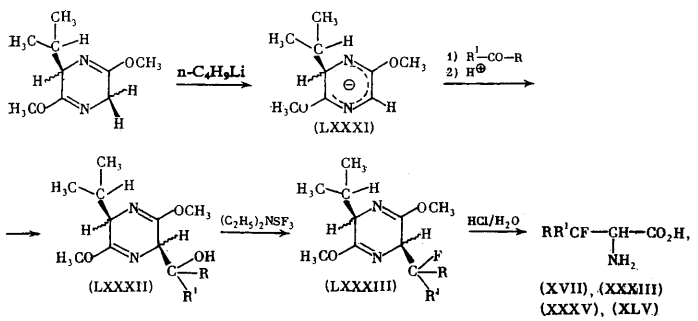
The advantage of the fluorodehydroxylation method is that it is based on readily available initial compounds. Furthermore, optical activity is not lost in the fluorination of pure enantiomers of β-hydroxy-α-aminoacids, since the chiral carbon atom is not involved in the reaction. A disadvantage of the method is the incomplete conversion of the initial aminoacids in many cases, which complicates the isolation of the final products, as well as the formation of fluoro-substituted aminoacids as the hydrofluorides.

The replacement of the hydroxy-group by fluorine in α-hydroxy-derivatives of natural aminoacids with the aid of sulphur tetrafluoride is one of the convenient methods of synthesis of α-(fluoromethyl)-substituted aminoacids, which are irreversible inhibitors of decarboxylases. The initial α-hydroxymethyl derivatives are formed readily on treatment of copper complexes of the corresponding aminoacids with formaldehyde.

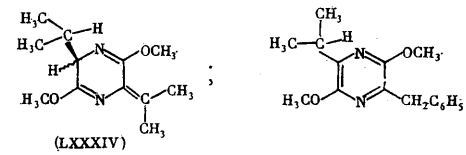


This method makes it possible to obtain α-fluoromethyl derivatives of aliphatic, aromatic, and heterocyclic aminoacids.[62]

The asymmetric synthesis of certain β-fluoro-substituted aminoacids has been achieved by fluorinating optically active derivatives of dihydropyrazine with diethylaminotrifluorosulphurane $(C_2H_5)_2NSF_3$.[63]

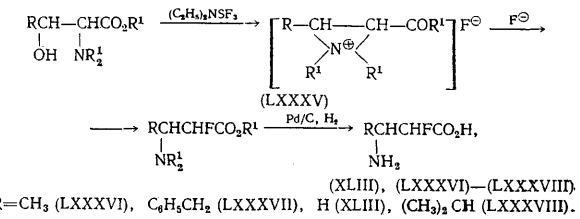


Alkylation of the anion (LXXXI) with carbonyl compounds (acetone, benzaldehyde, acetophenone, formaldehyde) takes place with different optical yields, which are not, however, below 85%. In the case of compound (LXXXII) with R = H and $R^1 = C_6H_5$ or R = CH_3 and $R^1 = C_6H_5$, the ratios of the *erythro*- and *threo*-isomers are 6:1 and 12:1 respectively. Further conversion of the hyroxy-derivatives (LXXXII) into the fluoro-substituted products (LXXXIII) proceeds with moderate yields (~45%) owing to the formation of side products—3-isopropylidenedihydropyrazine (LXXXIV) or a pyrazine derivative.



In compound (LXXXII, R = R^1 = H), the hydroxy-group could not be substituted by the fluoro-group with the aid of diethylamino-trifluorosulphurane (diethylaminosulphur trifluoride, DAST. Ed. of translation). In order to obtain monofluoroalanine, the anion (LXXXI) was therefore made to react with fluoroiodomethane, as a result of which the corresponding monofluoromethyl derivative (LXXXIII, R = R^1 = H) was obtained in 80% yield. The optical yield did not then exceed 45%.

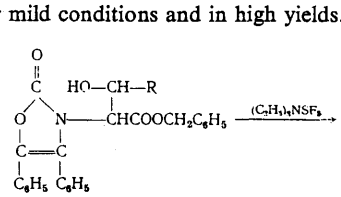
The use of DAST for the fluorination of *NN*-dibenzyl derivatives of β-hydroxy-α-aminoacid esters leads to α-fluoro-β-amino-derivatives.[64]

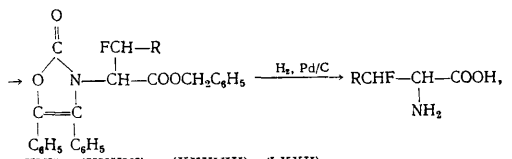


The formation of β-aminoacids from their α-amino-derivatives is believed[64] to be explained by the intermediate formation of the aziridinium ion (LXXXV), which is attacked by the fluoride anion at the α-carbon atom, affording substituted β-aminoacids in 90% yield. An advantage of this method is its high stereospecificity. Thus the double inversion of the configuration of the α-carbon atom (the formation of the aziridinium ion and the opening of its ring by the fluoride anion) results in the formation from the optically active L- or D-aminoacids of the corresponding optically active α-fluoro-derivatives. Furthermore, in the case of β-hydroxy-α-aminoacids having two asymmetric centres (α- and β-carbon atoms), the initial *erythro*- or *threo*-configuration is retained during their conversion into α-fluoro-β-amino-derivatives.[64]

Free α-fluoro-β-aminoacids (XLIII) and (LXXXVI)—(LXXXVIII) have been obtained by the hydrogenolysis of *NN*-dibenzyl derivatives in the presence of a palladium catalyst.

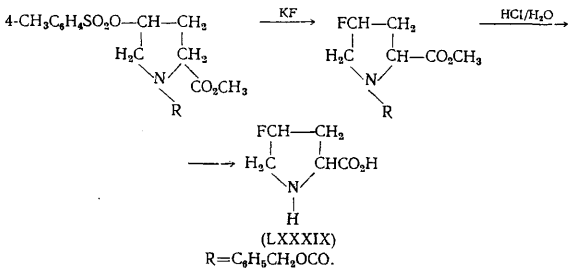
The decrease in the nucleophilicity of the nitrogen atom when the amino-group is protected by employing 4,5-diphenyl-4-oxazolin-2-one rules out the possibility of the isomerisation of α-amino-β-hydroxy-derivatives of carboxylic acid via the aziridinium ion (LXXXV). The employment of DAST in this instance makes it possible to obtain β-fluoro-derivatives of various natural aminoacids under mild conditions and in high yields.[65]





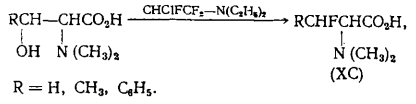
(XVII), (XXXVI) — (XXXVIII), (LXXII)
R=C_6H_5 (XVII), CH_3 (XXXVI), C_2H_5 (XXXVII),
n-C_3H_7 (XXXVIII), COOH (LXXII).

Another method for the substitution of the hydroxy-group by a fluorine atom consists in treatment of *O*-tosyl derivatives of β-hydroxyaminoacid with anhydrous potassium fluoride. This procedure led to the formation of *cis*- and *trans*-4-fluoroprolines (LXXXIX) from hydroxyproline and hydroxyalloproline.[66,67]

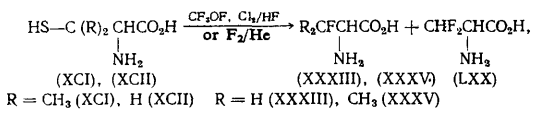


The experiments with *E. coli* have shown that *cis*-4-fluoroproline inhibits protein biosynthesis.

It is noteworthy that the use of 2-chloro-1,1,2-trifluoroethyl-(diethyl)amine (the Yarovenko reagent) as the fluorinating agent for the replacement of the hydroxy-group by fluorine proved to be possible only for aminoacids with a tertiary amino-group. A series of β-fluoro-derivatives of *NN*-dimethylaminoacids (XC) have been obtained by this procedure.[68]



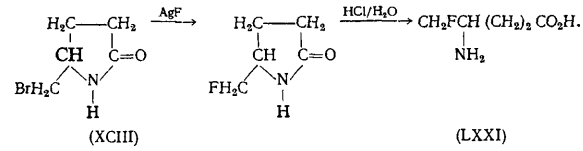
The synthesis of β-fluoro-substituted aminoacids by the replacement of the mercapto-group by fluorine has been demonstrated in relation to the conversion of D-penicillamine (XCI) into 3-fluoro-D-valine and also by the synthesis of mono- and di-fluoroalanines from 3-mercaptoalanine (XCII).[69]



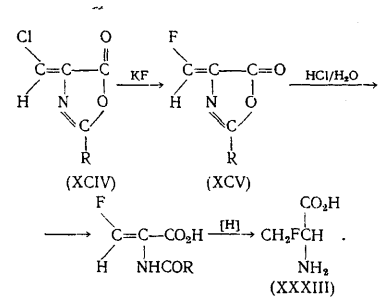
This method, which has been called fluorodesulphurisation,[69] is apparently relatively unsuitable for laboratory practice, since the yields of the final products are low and it requires the employment of trifluoromethyl hypofluorite or elemental fluorine.

The method of synthesis of fluorinated aminoacids involving the replacement of a halogen atom by fluorine has not found a wide scale application, which is apparently due to the low availability of the initial compounds.

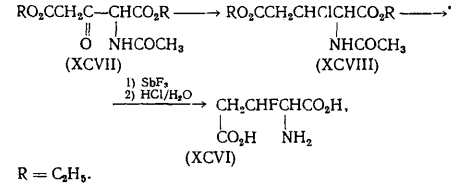
The replacement of a bromine atom in 5-bromomethyl-2-pyrrolidinone (XCIII) by fluorine on treatment with AgF in anhydrous acetonitrile and subsequent acid hydrolysis afforded γ-fluoromethyl-γ-aminobutyric acid (LXXI), which proved to be an effective inactivator of γ-aminobutyric acid transaminase.[70,71]



3-Fluoroalanine (XXXIII) was first obtained by the replacement of the chlorine atom by a fluorine atom on treatment of 4-chloromethylene-2-phenyloxazolinone (XCIV) with potassium fluoride and subsequent hydrolysis and reduction of the fluoro-derivative (XCV).[72]

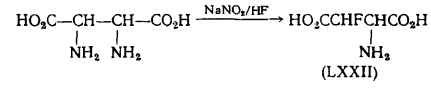


The employment of antimony trifluoride as the fluorinating agent made it possible to achieve the synthesis of β-fluoroglutamic acid (XCVI) from diethyl 2-acetamidoacetonedicarboxylate (XCVII).[73] The diethyl ester of the ketoacid (XCVII) was reduced and converted by subsequent chlorination into the chloro-derivative (XCVIII), from which the aminoacid (XCVI) was obtained by treatment with antimony trifluoride and subsequent hydrolysis.



R = C_2H_5.

A single example of the replacement of the amino-group by a fluorine atom in the synthesis of β-fluoroaspartic acid (LXXII) by the diazotisation of diaminosuccinic acid by treatment with sodium nitrite in liquid hydrogen fluoride is known.[74] By carrying out the reaction at a reduced temperature, it is possible to replace selectively only one amino-group by fluorine.

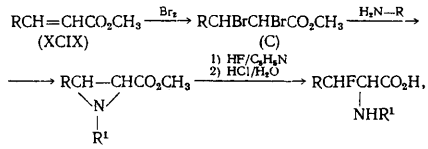


2. Syntheses based on the opening of the rings of fluorine-containing heterocyclic compounds

The majority of methods considered in this section are feasible because of the specific effect of fluorine atoms or perfluoroalkyl groups. In the case of non-fluorinated compounds, these reactions are inapplicable or lead to other products. Syntheses of this type give rise to the possibility of obtaining individual β-fluoro-derivatives of aminoacids, but in many instances the approaches are general and can be used to synthesise a series of fluorinated aminoacids.

The procedure based on the opening of the aziridine[75–79] or azirine[80] ring by the Olah reagent ($HF.C_5H_5N$) can be regarded as one of the most modern and general methods of synthesis of β-fluoro-derivatives of aminoacids (mono- and difluorinated).

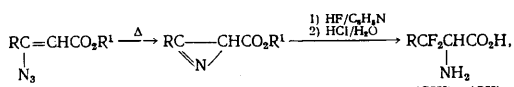
The starting materials for the synthesis of monofluoro-compounds were substituted acrylic esters (XCIX), which were converted by bromination into the dibromo-derivatives (C) and the aziridines (CI) were obtained by subsequent treatment with ammonia. The aziridines afford the corresponding aminoacids in high yields on treatment with the Olah reagent. The use of alkylamines instead of ammonia in this reaction permits the synthesis of *N*-substituted derivatives of fluorinated aminoacids.



(XCIX) (C) (CI) (XVII), (CII)—(CVI)

R = H, $R^1 = (CH_3)_3C$ (CII); R = $R^1 = CH_3$ (CIII); R = C_6H_5, R^1 = H (XVII); R = C_6H_5, $R^1 = CH_3$ (CIV); R = 4-ClC_6H_4, R^1 = H (CV); R = 4-ClC_6H_4, $R^1 = CH_3$ (CVI).

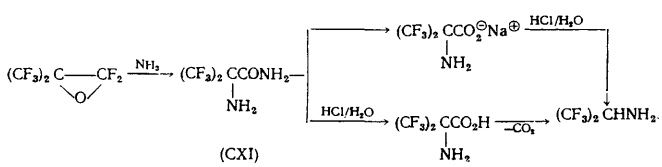
Treatment with the Olah reagent of the azirinecarboxylates (CVII), formed on thermal decomposition of the azides (CVIII), is a convenient method of synthesis of ββ-difluoro-derivatives of aminoacids (yield 37–42%).



(CVIII) (CVII) (CIX), (CX)

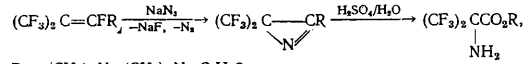
R = CH_3 (CIX), C_6H_5 (CX); $R^1 = CH_3$, C_2H_5.

The opening of the three-membered oxiran and azirine rings containing perfluoroalkyl groups has also been used to synthesise β-fluoro-derivatives of aminoacids. Thus interaction of perfluoroisobutene oxide with ammonia[81] affords the amide of 3,3,3,3′,3′,3′-hexafluoro-2-aminoisobutyric acid (CXI). The attempt to hydrolyse the amide (CXI) with dilute hydrochloric acid causes the decarboxylation of the aminoacid with formation of hexafluoroisopropylamine. Nevertheless, by means of alkaline hydrolysis it has been possible to isolate the sodium salt of hexafluoro-2-aminoisobutyric acid, which, however, also decarboxylates on acidification.[82]



(CXI)

Other derivatives of hexafluoro-α-aminoisobutyric acid—dialkylamides and the ethyl ester—were obtained by the hydrolysis of the corresponding azirines, which are formed readily on treatment of dialkylamino- or ethoxy-derivatives of perfluoroisobutene with sodium azide.[83,84]

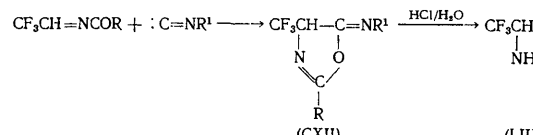


R = $(CH_3)_2N$, $(CH_2)_5N$, C_2H_5O.

It is noteworthy that derivatives of hexafluoro-α-aminoisobutyric acid do not form stable salts even with H_2SO_4, which has been explained by the electron-accepting influence of the two trifluoromethyl groups in the α-position relative to the amino-group.

A series of methods based on the formation and opening of the oxazole ring have been proposed for the synthesis of 3,3,3-trifluoroalanine. A disadvantage of these methods is their multistage nature, which reduces appreciably the yield of the product.

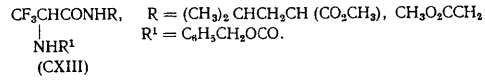
Trifluoroalanine (LIII) was first obtained by the acid hydrolysis of the oxazolines (CXII) formed on [1 + 4]cycloaddition of *N*-acyltrifluoroacetaldimines to isonitriles.[85]



(CXII) (LIII)

R = $C_6H_5CH_2O$; $R^1 = n\text{-}C_6H_{11}$.

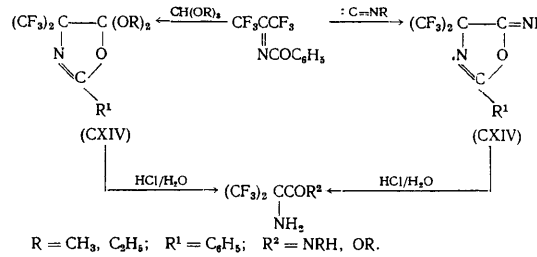
The use in this reaction of isonitriles synthesised from *N*-formylaminoacid esters made it possible to obtain trifluoroalanyl peptides (CXIII).[85]



(CXIII)

It is noteworthy that alkaline hydrolysis of alanine derivatives (LIII) takes place with conversion of the trifluoromethyl group into the carboxy-group.

Like *N*-acyltrifluoroacetaldimines, hexafluoroacetone *N*-benzoylimine readily enters into the [1 + 4]cycloaddition reaction with isonitriles and orthoformic ester. Hydrolysis of the oxazolines (CXIV) formed affords derivatives of the unstable 3,3,3,3′3′,3′-hexafluoro-2-aminoisobutyric acid.[86,87]

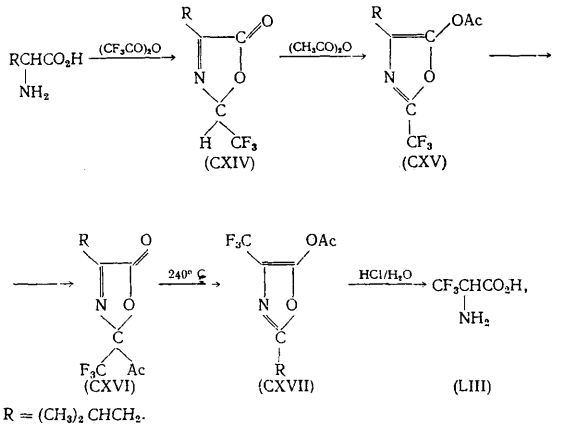


(CXIV) (CXIV)

R = CH_3, C_2H_5; $R^1 = C_6H_5$; R^2 = NRH, OR.

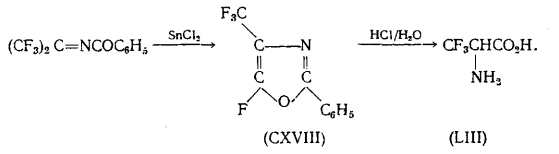
Another approach to the synthesis of trifluoroalanine (LIII) involves the cyclisation of *N*-trifluoroacetyl derivatives of aminoacids to the oxazolines (CXIV), their subsequent conversion into the oxazoles (CXV), and the isomerisation of the latter by treatment with γ-(*NN*-dimethylamino)pyridine to the oxazolines (CXVI), whose

brief heating at 240 °C affords the oxazoles (CXVII). Acid hydrolysis of the latter yields trifluoroalanine (LIII).[88,89]

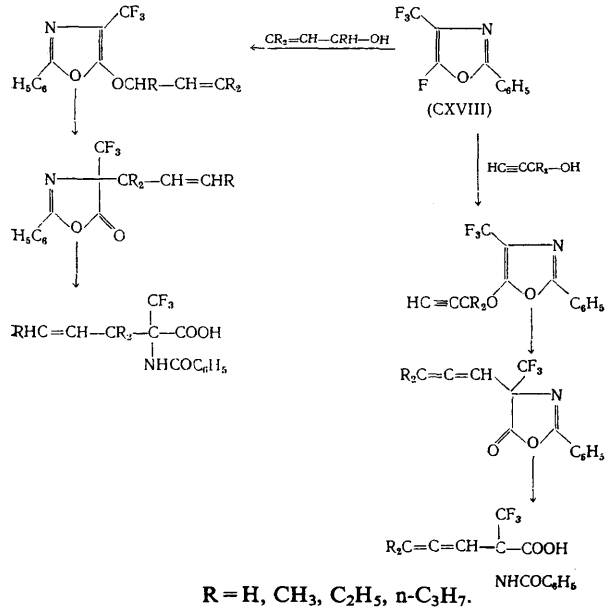


R = $(CH_3)_2CHCH_2$.

An interesting method of synthesis of trifluoroalanines (LIII) from hexafluoroacetone benzoylamine has been proposed.[90] It was found that hexafluoroacetone *N*-benzoylamine cyclises on treatment with tin dichloride to the oxazole (CXVIII) whose hydrolysis affords trifluoroalanine (LIII) in a overall 20% yield.

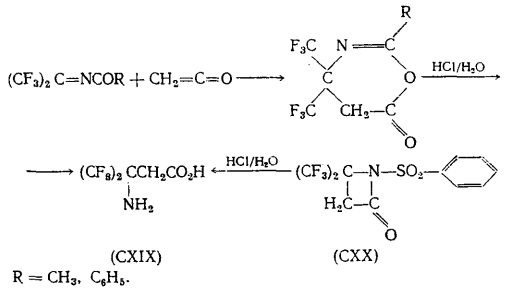


The possibility of substituting the fluorine atom in the 5-position of the oxazole ring of compound (CXVIII) in reactions with alcohols has been used successfully in devising a general method of synthesis of novel compounds—2-allyl- and 2-allenyl-3,3,3-trifluoroalanines.[91]



R = H, CH_3, C_2H_5, n-C_3H_7.

The introduction of hexafluoroacetone N-acylimines into the [4+2]cycloaddition reaction with the keten and subsequent hydrolysis of the resulting oxazinones leads to β-amino-ββ-bis-(trifluoromethyl)propionic acid (CXIX).[87]

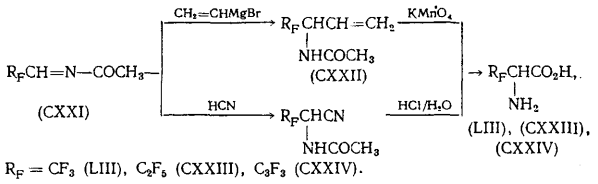


R = CH_3, C_6H_5.

The β-alanine derivative (CXIX) has also been obtained by the reaction of keten with hexafluoroacetone *N*-toluene-*p*-sulphonylimine and subsequent hydrolysis of the propiolactam (CXX).[92]

3. Synthesis of α-perfluoroalkylaminoacids from the *N*-acylimines of fluorinated aldehydes and ketoacids

A general method of synthesis of α-perfluoroalkylglycines from the *N*-acylimines of perfluorinated aldehydes (CXXI) has been developed.[85,93–96] Vinylmagnesium bromide adds readily to the C=N bond of the azomethines (CXXI) with formation of the derivatives (CXXII). Oxidation of the C=C bond in compounds (CXXII) with potassium permanganate and subsequent hydrolysis leads to the α-perfluoroalkyl-substituted aminoacids (LIII), CXXIII), and (CXXIV). The possibility of synthesising such aminoacids by adding hydrocyanic acid to the acylimines (CXXI) and the hydrolysis of the resulting nitriles has been demonstrated.



R_F = CF_3 (LIII), C_2F_5 (CXXIII), C_3F_3 (CXXIV).

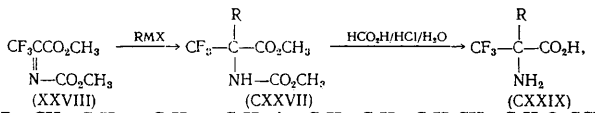
The sulphone (CXXV) or the halogeno-derivatives (CXXVI) can be used as species equivalent to the imines (CXXI) in the above reaction, but the presence of a base (triethylamine) is then essential.



X = Cl, Br.

Trifluoroalanine (LIII) has also been obtained by substituting the chlorine atom by the CN group on treatment of the chloro-derivative (CXXVI) with CuCN[97] and subsequent hydrolysis of the corresponding cyanamide.

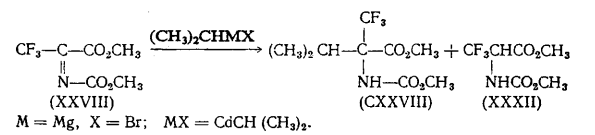
A method based on the alkylation of the *N*-methoxycarbonylimine of methyl trifluoropyruvate (XXVIII) for the synthesis of β-fluoro-substituted aminoacids which are most difficult to obtain, namely α-trifluoromethylaminoacids, has been proposed recently.[98,99]



R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, iso-C_4H_9, C_6H_5, $C_6H_5CH_2$, $C_2H_5O_2CCH_2$;
M = Mg, Zn, Cd; X = Cl, Br, I.

The regioselective alkylation of the *N*-methylcarbonylimine (XXVIII) with organomagnesium compounds can be achieved only by mixing the reactants at the liquid nitrogen temperature with subsequent heating of the reaction mixture at 20 °C because of the high electrophilicity of the imine (XXVIII). The use of less reactive organocadmium compounds permits the alkylation of the imine (XXVIII) at 4 °C. The yields of the aminoesters (CXXVII) are almost independent of the metal employed and amount to 60–90%.

In the synthesis of α-trifluoromethylvaline by alkylating the *N*-methoxycarbonylimine (XXVIII) with diisopropylcadmium or isopropylmagnesium bromide, the reaction is complicated by the reduction of the imine (XXVIII) to the methyl ester of *N*-methoxycarbonyl-3,3,3-trifluoroalanine (XXVII).[100]

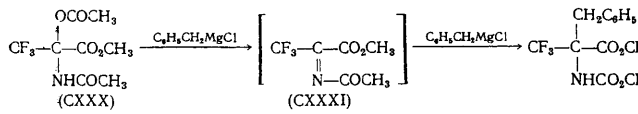


M = Mg, X = Br; MX = CdCH $(CH_3)_2$.

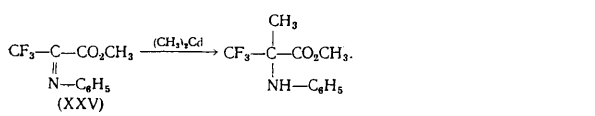
In the case of isopropylmagnesium bromide, the ratio of compounds (CXXVIII) and (XXXII) is 1.5:1, while the use of diisopropylcadmium makes it possible to obtain predominantly the valine derivative (CXXVIII).

The amidoesters (CXXVII) and (CXXVIII) proved to be resistant to acid hydrolysis. In order to obtain the hydrochlorides of α-trifluoromethylaminoacids (CXXIX), it is essential to heat compounds (CXXVII) and (CXXVIII) in a mixture of concentrated hydrochloric and formic acids at 100 °C for 40 h.

The possibility of synthesising α-trifluoromethylaminoacids by treating with two moles of an organomagnesium reagent the diacetyl derivative (CXXX), which can be regarded as a species equivalent to the *N*-acetylimine (CXXXI), has been demonstrated.[99]

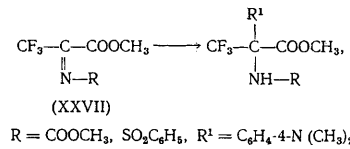


The use of the *N*-alkylimines of methyl trifluoropyruvate in reactions with organometallic reagents in order to synthesise *N*-alkyl-substituted α-trifluoromethylaminoacids proved unsuccessful. However, the *N*-phenylimine (XXV) was alkylated with dimethylcadmium to form the methyl ester of *N*-phenyl-α-trifluoromethylalanine.[99]

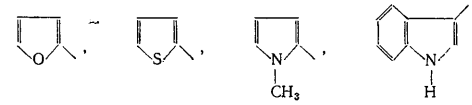


An advantage of the method considered is the availability of the reagents employed and also the high yields of α-trifluoromethylaminoacids. However, its disadvantage is that its application in the synthesis of heterocyclic or polyfunctional natural aminoacids is problematical.

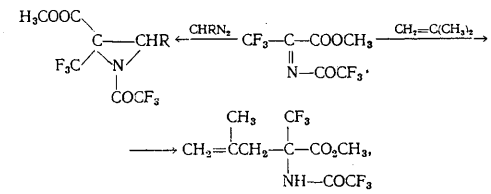
One of the prospects for the further application of imines of methyl trifluoropyruvate in the synthesis of α-trifluoromethyl-substituted aminoacids apparently involves the use of these compounds in *C*-alkylation and cycloaddition reactions. Thus the high electrophilicity of the *N*-acylimines (XXVII) makes it possible to synthesise derivatives of 2-aryl- and 2-heteroaryl-3,3,3-trifluoroalanines by the regioselective alkylation of *NN*-dimethylalanine and a series of heterocycles.[101,102]



R = $COOCH_3$, $SO_2C_6H_5$, R^1 = C_6H_4-4-N $(CH_3)_2$,



Furthermore, the introduction of the *N*-trifluoroacetylimine of methyl trifluoropyruvate into the reaction with diazo-compounds and alkenes made it possible to obtain derivatives of α-trifluoromethylcoronamic acid and α-trifluoromethyl-γδ-dehydroleucine.[103]



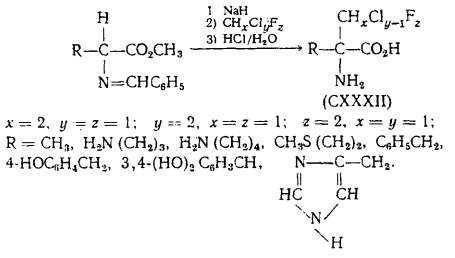
R = H, $COOC_2H_5$.

4. Halogenoalkylation of the α-C-anions of protected aminoacids

A method involving the fluoromethylation of the α-C-anions of protected aminoacids has been developed comparatively recently for the synthesis of α-monofluoromethyl- and α-difluoromethyl-substituted aminoacids.

The carboxy-group in the initial aminoacids was protected by conversion into the methyl ester and the amino-group was protected by conversion into a Schiff base by treatment with benzaldehyde. In those cases where the aminoacid molecules contained OH and SH groups, the latter were converted into ether and sulphide groups; in order to protect the NH groups, for example, in histidine, the *N*-trityl derivative was obtained. The α-C-anions of aminoacids protected in this way were obtained by employing strong bases such as lithium diisopropylamide, sodium hydride, and potassium t-butoxide. The aminoacid C-anions proved to be most stable in tetrahydrofuran (for 24 h), which was used as the solvent. The subsequent alkylation of the C-anions with chlorofluoro- or chlorodifluoro-methane leads to the formation of the α-monofluoroethyl or α-difloromethyl derivatives of aminoacids (CXXXII) after the removal of the protecting group.[45,104,105] The use of the Freon

$CHCl_2F$ makes it possible to obtain the corresponding α-chlorofluoromethyl derivatives. The latter proved to be less stable than the difluoromethyl-substituted aminoacid.



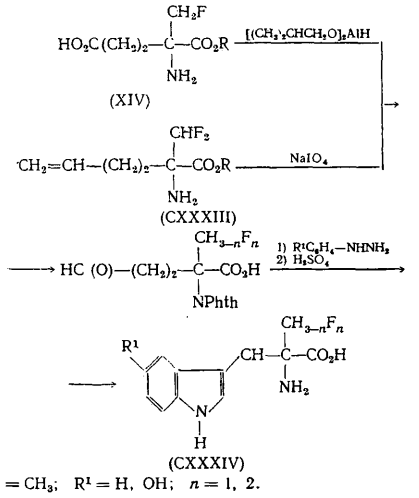
(CXXXII)

$x = 2,\ y = z = 1;\ y = 2,\ x = z = 1;\ z = 2,\ x = y = 1;$
$R = CH_3,\ H_2N(CH_2)_3,\ H_2N(CH_2)_4,\ CH_3S(CH_2)_2,\ C_6H_5CH_2,$
4-$HOC_6H_4CH_2$, 3,4-$(HO)_2C_6H_3CH$,

This method proved to be applicable to both aliphatic and aromatic and to heterocyclic and polyfunctional aminoacids. The yields of the fluorinated aminoacids are 20–50%.

The formation of a dihalogenocarbene on halogenoalkylation[104] of aminoacid Schiff bases precludes the formation of α-trifluoromethyl derivatives of aminoacids by this reaction using chlorotrifluoromethane or bromotrifluoromethane.

The possibility of the introduction of further functional groups into fluorine-containing aminoacids greatly extends the limits of the applicability of known methods. Thus α-fluoromethylglutamic acid (XIV) and 2-butenyl-3,3-difluoroalanine (CXXXIII), obtained by the halogenoalkylation of the corresponding Schiff bases of the methyl esters of the aminoacids, were used as the starting compounds in the synthesis of α-monofluoromethyl- and α-difluoromethyl-tryptophans and their 5-hydroxy-derivatives (CXXXIV) in accordance with the following scheme:[106]



(XIV)

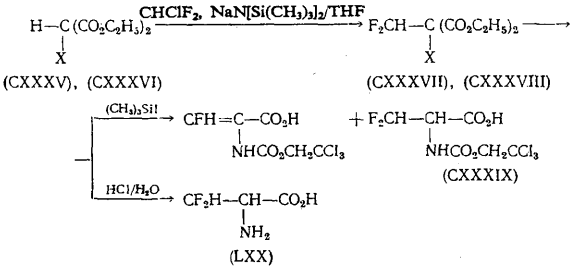
(CXXXIII)

(CXXXIV)

$R = CH_3$; $R^1 = H$, OH; $n = 1$, 2.

α-Monofluoromethyl- and α-difluoromethyl-tryptophans (CXXXIV) proved to be inhibitors of aromatic aminoacid decarboxylases.[106]

It is noteworthy that monofluoro- or difluoro-alanine could not be obtained directly from protected glycine. Therefore, *N*-substituted derivatives of aminomalonic ester (CXXXV) were used as the initial compounds for the synthesis of difluoroalanine (LXX).[107,108] The C-anions were obtained from compounds (CXXXV) in tetrahydrofuran using sodium hexamethyldisilazanide as the base. Subsequent alkylation of the C-anions obtained in this way with chlorodifluoromethane leads to the formation of the difluoromethyl derivatives (CXXXVII) in a yield which is high for reactions of this type (50%).



(CXXXV), (CXXXVI) (CXXXVII), (CXXXVIII)

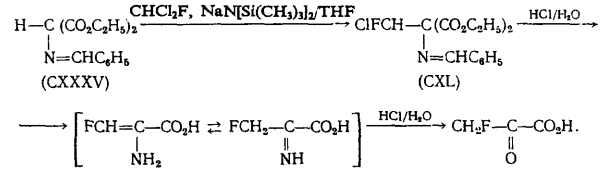
(CXXXIX)

(LXX)

$X = N{=}CHC_6H_5$ (CXXXV), (CXXXVII); $NHCO_2CH_2CCl_3$ (CXXXVI), (CXXXVIII).

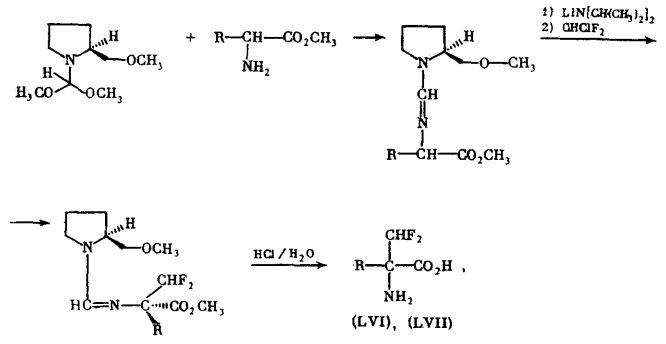
The hydrolysis and decarboxylation of the Schiff base (CXXXVII) take place readily with formation of difluoroalanine (LXX), while the carbamate (CXXXVIII) proved to be extremely resistant to acid hydrolysis. Alkaline hydrolysis proved to be inapplicable in the given instance in view of dehydrofluorination. The employment of trimethylsilyl iodide made it possible to remove only the ester group with formation of the acid (CXXXIX). Together with compound (CXXXIX), the product of the dehydrofluorination of the urethane (CXXXVIII), namely *N*-acyl-β-fluorodehydroalanine, was detected in this reaction.

The use of dichlorofluoromethane for the alkylation of the C-anion obtained from the Schiff base (CXXXV) permitted the synthesis of the chlorofluoromethyl derivative (CXL). However, the corresponding β-chloro-β-fluoroalanine could not be isolated because of the lack of resistance of compound (CXL) even to acid hydrolysis. The main reaction product proved to be monofluoropyruvic acid formed in accordance with the scheme[107]



(CXXXV) (CXL)

The employment of (*S*)-(−)-1-dimethoxymethyl-2-methoxymethylpyrrolidine to protect the amino-group made it possible to achieve the asymmetric synthesis of α-difluoromethyl-substituted alanine (LXI) and phenylalanine (LVII).[109,110]



(LVI), (LVII)

$R = CH_3$ (LVI), $C_6H_5CH_2$ (LVII).

IV. Conclusion

The literature data examined show that the methods of synthesis of β-fluoro-substituted aminoacids available at present permit the preparation of almost all possible types of these compounds containing between one and three fluorine atoms in the β-position relative to the amino-group. Nevertheless, the impressive results of studies on the biological properties of fluorine-containing aminoacids have stimulated the search for new more convenient methods of synthesis of these compounds.

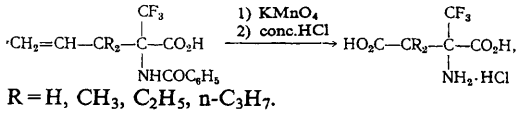
Together with advances in the synthesis of β-fluoro-substituted aminoacids, there still exist problems for which optimum solutions have not been found. This applies particularly to polyfunctional and optically active compounds.

It is to be expected that further studies on the synthesis of β-fluoro-substituted aminoacids will be directed in the first place mainly towards the creation of new simpler and more convenient methods of synthesis of known as well as still unknown representatives of the series of β-fluoro-derivatives of aminoacids and secondly, they will be directed towards the development of an asymmetric synthesis of these compounds, which will permit a more detailed investigation of the biological activity of β-fluoro-substituted aminoacids and also their use in the synthesis of peptides.

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During the preparation of the review for the press, several new studies illustrating further utilisation of the synthetic possibilities of the methods described above for the preparation of α-trifluoromethyl-α-aminoacids were published.

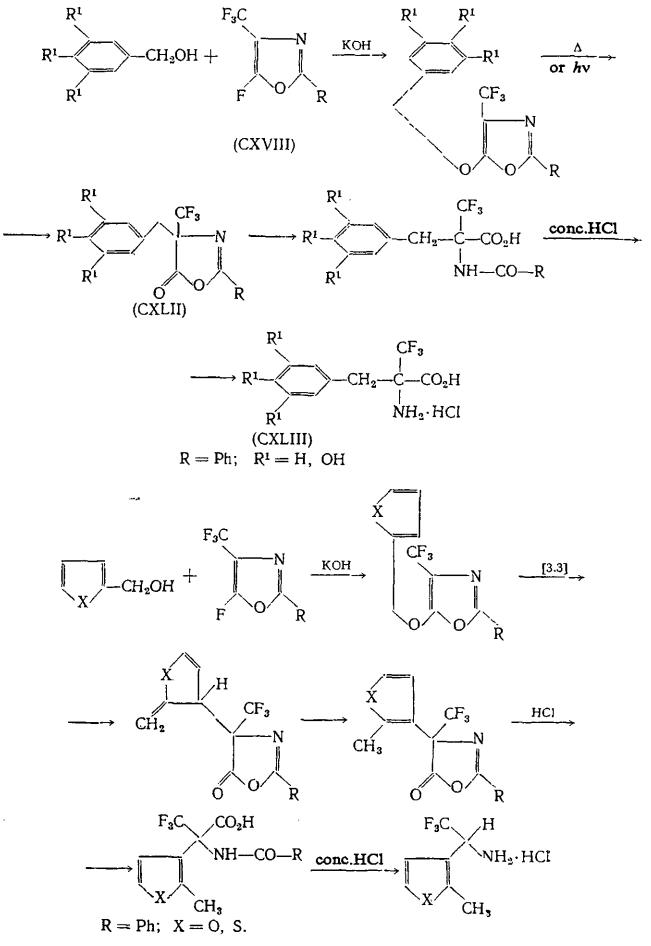
α-Trifluoromethylaspartic acid as well as its previously unknown 3-alkyl- and 3,3-dialkyl-derivatives were obtained by oxidising the C=C double bond in 2-allyltrifluoroalanines (CXLI), synthesised from 5-fluoro-4-trifluoromethyloxazole (CXVIII) and the corresponding allyl alcohols.[111]



R = H, CH_3, C_2H_5, n-C_3H_7.

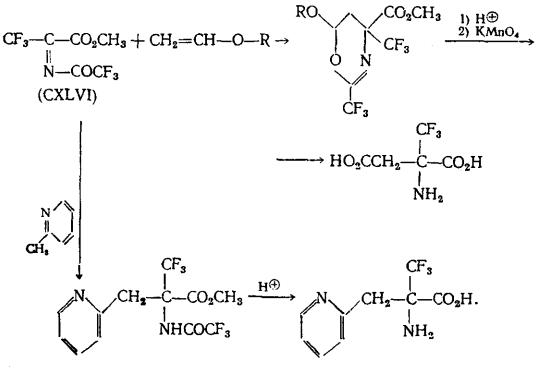
A series of 4-benzyl-4-trifluoromethyl-5(4*H*)-oxazolones (CXLII) were synthesised by the reaction of benzyl alcohols (the allyl double bond is a purely aromatic system) with 5-fluoro-4-fluoromethyloxazole (CXVIII) and subsequent rearrangement of the resulting products. The hydrolysis of the oxazolones affords α-trifluoromethylphenylalanines (CXLIII).[112]

The use of 2-hydroxymethyl-substituted furan and thiophene in the analogous reactions with oxazole (CXVIII) is limited to the formation of only *N*-acyl derivatives of 3-heteroaryltrifluoroalanines (CXLIV). This is associated with the fact that under the conditions corresponding to the removal of the *N*-protecting group (refluxing in concentrated HCl), decarboxylation takes place readily with formation of the corresponding amines (CXLV).[112]



Yet another general approach to the synthesis of α-trifluoromethyl-α-aminoacids, based on the reactions of the *N*-acylimines of methyl trifluoropyruvate has also been developed further.

The introduction of *N*-trifluoroacetylimine (CXLVI) into the [4+2]cycloaddition reaction with vinyl ethers and the subsequent hydrolysis and oxidation reactions of the product constitute yet another convenient method of synthesis of α-trifluoromethylaspartic acid.[113]



The regioselective *C*-alkylation of 2-methylpyridine with the *N*-trifluoroacetylimine (CXLVI) is of special interest.[114] This reaction opens a pathway to the synthesis of the virtually uninvestigated β-heteroaryl-α-trifluoromethylalanines.

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