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Fluorine-containing Aminoacids

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CONTENTS

I. Introduction 290
II. The scope of the synthesis of fluorine-containing aminoacids 290
III. Preparation of fluorine-containing aminoacids by classical methods for aminoacid synthesis 290
IV. Syntheses of fluorine-containing aminoacids by the introduction of fluorine into aminoacids or their derivatives 295
V. Special methods for the synthesis of fluorine-containing aminoacids 296

I. INTRODUCTION

Organofluorine compounds are important not only because they have unusual chemical properties and applications in engineering but also because some of them prove to be physiologically active. The fluorides of dialkylphosphoric acids and derivatives of monofluoroacetic acid are highly toxic, 5-fluorouracil and fluoro-orotic acid are tumour inhibitors, and the replacement of hydrogen by fluorine in certain steroid hormones greatly increases their biological activity.

The reason for the physiological activity of fluorine compounds probably consists in the fact that the cell cannot distinguish fluorinated and non-fluorinated compounds and makes use of them equally because the dimensions of the hydrogen and fluorine atoms are similar (covalent radii: H 0.35 Å, F 0.64 Å; van der Waals radii: H 1.20 Å, F 1.55 Å). However, the replacement of hydrogen by very electronegative fluorine creates a centre with an enhanced electron density and the powerful hydrogen bonds formed by this component of the molecule with enzymes can prevent the formation of normal enzyme–substrate complexes[1,2].

Since aminoacids play an important role in metabolism, the effects of fluorinated aminoacids on the organism is particularly interesting. This review deals with the synthesis and properties of fluorinated aminoacids and also their biological activity (in those cases where it is has been investigated). The review is restricted mainly to carboxylic 2-aminoacids (apart from fluorinated 3-aminopropionic acids).

II. THE SCOPE OF THE SYNTHESIS OF FLUORINE-CONTAINING AMINOACIDS

The syntheses of fluorinated aminoacids achieved hitherto can be divided into three general groups.

1. It is possible to use the classical syntheses for aminoacids from fluorinated starting materials, for example Erlenmeyer's azlactone synthesis, syntheses with acylmalonic esters, ammonolysis of carboxylic 2-halogenoacids, and Strecker's cyanohydrin synthesis. However, the replacement of hydrogen by fluorine in the starting compound can lead to complications. Because of the powerful *I*-effects of the fluoroalkyl and fluoroaryl groups, the substitution and addition reactions in the course of the synthesis may be hindered, facilitated, or take place in a different way. Finally, decomposition reactions, in particular the elimination of fluorine, may occur.

2. Another possibility is to introduce fluorine into existing aminoacids, their derivatives, or intermediate products by exchanging hydrogen, another halogen, or a hydroxyl for fluorine.

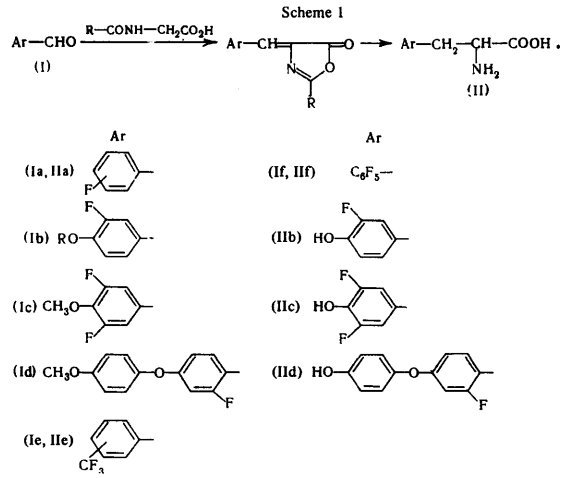
3. Special methods have also been developed (particularly for the synthesis of polyfluorinated aminoacids), which have no analogy in the chemistry of non-fluorinated aminoacids.

III. PREPARATION OF FLUORINE-CONTAINING AMINOACIDS BY CLASSICAL METHODS FOR AMINOACID SYNTHESIS

1. Fluorinated Aromatic Aminoacids

Fluorine-substituted aromatic compounds are readily obtained by the decomposition of aromatic diazonium fluoroborates and can be used for the synthesis of fluorinated aromatic aminoacids. Thus as early as 1932 Schiemann and Roselius succeeded in obtaining three isomeric fluorinated derivatives of phenylalanine (IIa) by the condensation of *o*-, *m*-, or *p*-fluorobenzaldehyde (Ia) with hippuric acid and subsequent hydrolysis and reduction[3] (see Scheme 1).

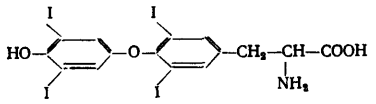
Scheme 1



It proved possible to obtain 3-fluorotyrosine (IIb) by this method using as starting materials 3-fluoro-4-methoxy- or 4-ethoxy-3-fluoro-benzaldehyde (Ib, R = CH_3 or C_2H_5) as starting materials. This compound can be also synthesised

from *m*-fluorophenylalanine by nitration, reduction, and decomposition of the corresponding diazo-compounds on refluxing[4,5]. 3,5-Difluorotyrosine (IIc) was obtained similarly[6].

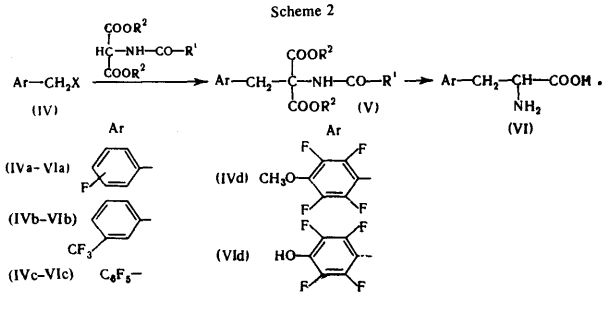
Thyronine, a compound related to tyrosine, is the non-iodinated analogue of the thyroid hormone—thyroxine (III):



Schiemann and coworkers succeeded in synthesising 2-fluorothyronine (IId) using a fluoroaldehyde (Id)[4,5]. In connection with their possible application in therapy, subsequently a series of similar fluoro-derivatives of thyronine were obtained: 3′-fluorothyronine, 3′-fluoro-3,5-di-iodothyronine, 3′-fluoro-3,5,5′-tri-iodothyronine, 3′,5′-difluorothyronine, and 3′,5′-difluoro-3,5-di-iodothyronine[7,8].

Three isomeric fluorophenylalanines were obtained in high yields by the condensation of the corresponding fluorine-substituted benzyl chlorides (IVa, X = Cl) with acetamidomalonic ester and subsequent hydrolysis of the acylamino esters formed (V, $R^1 = CH_3$, $R^2 = C_2H_5$) (see Scheme 2).

Scheme 2



The racemate produced can be separated into optical isomers by synthesising enzymically in the presence of papain the phenylhydrazides of the *N*-acylaminoacids, only the L-aminoacids reacting[9]. Similar resolution of racemates is possible also for 3-fluorotyrosine[10].

All the above aminoacids proved to be biologically active. Thus a number of studies have been published on the biological activity of fluorotyrosine and *p*-fluorophenylalanine. Only a few examples illustrating the importance of these antimetabolites were selected arbitrarily and are described below.

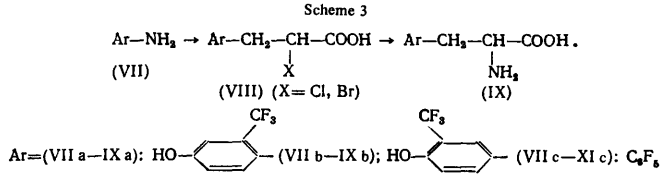
3-Fluorotyrosine is much more toxic than sodium fluoride: the lethal dose is about 12 mg kg^{-1} (for white mice)[11]. The lethal dose is independent of whether the D-isomer, the L-isomer, or the racemate is employed (experiments on rats)[10]. The Gudernatsch test on tadpoles (their growth is greatly accelerated by the addition of thyroxine) showed that fluorotyrosine may counteract the effect of thyroxine[12]. For this reason, fluorotyrosine is used in medicine in the treatment of goitre ("Pardinon") produced by the Bayer Company)[13]. It also inhibits the growth of tumours in rats and mice[14].

Fluorophenylalanines also inhibit the growth of *Neurospora crassa*[15] and are toxic to rats[16]. The addition of *p*-fluorophenylalanine to cultures of *E. coli* retards their growth, but at a certain phase in the development of *p*-fluorophenylalanine is incorporated in the proteins[17-19]. It is also possible to grow strains which are stable in relation to *p*-fluorophenylalanine[20]. These stable strains contain a phenylalanine-RNA synthetase, which no longer activates *p*-fluorophenylalanine[21,22].

A number of trifluoromethylphenylalanines and trifluoromethyltyrosines were obtained by Filler and coworkers. While *m*-trifluoromethylphenylalanine (VIb) is readily obtained from *m*-trifluoromethylbenzyl bromide (VIb, X = Br) and dibenzyl *N*-benzylyxycarbonylaminomalonate ($R^1 = C_6H_5CH_2O$, $R^2 = C_6H_5CH_2$; Scheme 2), the synthesis is unsuitable for the *o*- and *p*-isomers. However, all three isomers of trifluoromethylphenylalanine (IIe) can be readily obtained by azlactone synthesis (Scheme 1) from trifluoromethyl-substituted benzaldehydes (Ie) and aceturic acid ($R = CH_3$) (the benzamido-group is eliminated only with difficulty after the synthesis)[23].

Meerwein arylation was chosen for the synthesis of 2- and 3-trifluoromethyltyrosines (IXa, b):

Scheme 3



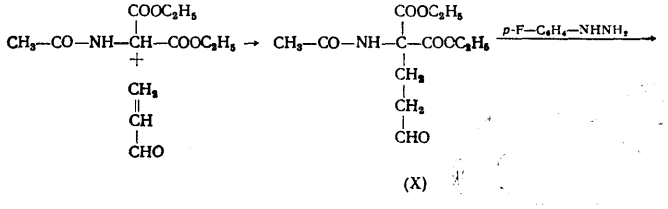
The diazonium chloride obtained from the aromatic amine (VII) is converted under the action of copper(I) chloride and acrylic acid into 3-aryl-2-chloropropionic acid (VIII), which yields the aminoacid after ammonolysis[24,25].

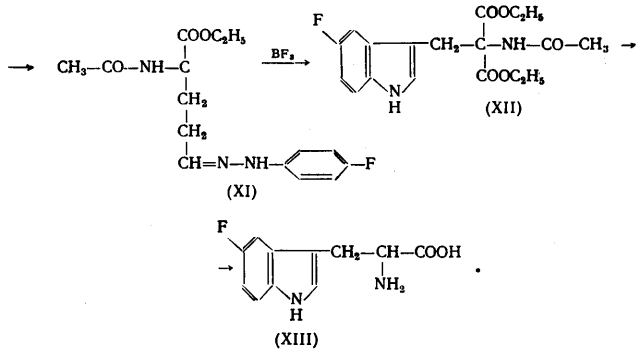
The corresponding aminoacids were obtained from the available polyfluorinated aromatic compounds. Pentafluorophenylalanine was synthesised by all three methods: azlactone synthesis (Scheme 1) with pentafluorobenzaldehyde (If)[26,27,30], synthesis with acetamidomalonic ester (Scheme 2) using pentafluorobenzyl bromide (IVc, X = Br)[28,30], and finally Meerwein arylation (Scheme 3) starting with pentafluoroaniline (VIIc) via 3-aryl-2-halogenopropionic acid (VIIIc)[28,30]. In this case it is impossible to obtain the aminoacid (IXc) by treating the chloride or bromide (VIIIc) with ammonia, since elimination and substitution reactions result in the formation of *trans*-4-amino-2,3,5,6-tetrafluorocinnamic acid. It is necessary to employ the azide and hydrogenate it catalytically. Pentafluorophenylalanine proved to be biologically inactive[28,30].

Finally, tetrafluorotyrosine (VId) was also obtained according to Scheme 2.[29,30]

The next aromatic acid for which fluoro-derivatives are known is tryptophan. Rinderkneche and Niemann[31] synthesised a fluoro-derivative using the method for the synthesis of tryptophan developed by Warner and Moe[32,33].

The addition of acetamidomalonic ester to acrolein by the Michael reaction gives 4-acetamido-4,4-diethoxycarbonylbutyraldehyde (X), the *p*-fluorophenylhydrazone (XI) of which can be cyclised by the Fischer method to an indole derivative (XII) and 5-fluorotryptophan (XIII) may be obtained by subsequent hydrolysis:





(XI) (XII) (XIII)

Hoffmann et al. prepared the same compound by the usual method of synthesis via gramine starting with 5-fluoroindole[34]. 5- and 6-Fluorotryptophans proved to be just as interesting key compounds for biochemical studies as fluorophenylalanine and fluorotyrosine. Only a few examples will be quoted: fluorotryptophan is toxic to mice[35], inhibits the tryptophan hydroxylase of rat brain[36], and inhibits the growth of a wild strain of *E. coli*. However, a mutant of *E. coli* incapable of synthesising tryptophan incorporates fluorotryptophan in its proteins[37].

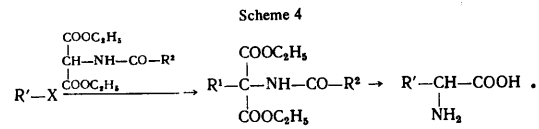
2. Fluorinated Aliphatic Monoaminoacids

After the reason for the toxicity of monofluoroacetic acid became known, the attention of biochemists was drawn to other aliphatic monofluoro-compounds. Monofluoroacetic acid takes part in the citric acid cycle, like acetic acid. The condensation of fluoroacetate with oxalylacetate is irreversible and aconitase cannot propagate the cycle in the usual way.

It was found that unbranched carboxylic ω-fluoroacids with an even number of carbon atoms are just as toxic as monofluoroacetic acid, since on β-oxidation in the living organisms they are converted into monofluoroacetic acid.

Aliphatic monofluoro-substituted aminoacids were synthesised for further investigation. Using an acylaminomalonic ester, Raasch and Lontz obtained 2-amino-4-fluorobutyric acid (XVIa), 5-fluoronorvaline (XVIb), and 6-fluoronorleucine (XVIc).

Scheme 4



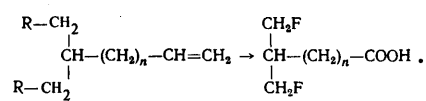
(XV) (XVI)

	R′		R′
(XIV a — XVI a)	$F(CH_2)_2$—	(XIV d — XVI d)	CH_3—CHF—$(CH_2)_2$—
(XIV b — XVI b)	$F(CH_2)_3$—	(XIV e — XVI e)	CF_3—$(CH_2)_3$—
(XIV c — XVI c)	$F(CH_2)_4$—	(XIV f — XVI f)	CF_3—CH(CH$_3$)—$(CH_2)_2$—

The fluorine atom in the ω-position is very sensitive to hydrolysis; for example, the hydrolysis of the derivative (XVa) of acetamidomalonic ester with dilute sulphuric acid yields, together with the fluorine-containing aminoacid, an equal amount of 2-amino-4-hydroxybutyric acid. Therefore compounds (XVb) and (XVc) were hydrolysed with 48% hydrofluoric acid to prevent this exchange reaction[38,39]. Hudlický obtained by the same method 5-fluoronorleucine (XVId) from 4-bromo-2-fluorobutane (XIVd). In this case too the fluorine atom is readily substituted; more prolonged heating with dilute inorganic acids yields almost exclusively 5-hydroxynorleucine[40,41].

As was to be expected from the above, 5-fluoronorvaline proved to be very toxic (actually 10 times more toxic than sodium monofluoroacetate), while 6-fluoronorleucine is almost non-toxic. In this connection it is interesting to note that 3-fluoropyruvic acid (the product of the transamination of 3-fluoroalanine, the synthesis of which will be discussed below) is non-toxic and is not converted into monofluoroacetic acid in the rat organism[39].

Lettré and Wolcke[42] obtained a number of mono- and di-fluoro-substituted aminoacids starting with carboxylic fluoroacids[42]. When the latter were not known, the authors developed a new method of synthesis. Toluene-*p*-sulphonates (XVIII) obtained from the unsaturated diols (XVII) were converted by the action of potassium fluoride in diethylene glycol into fluoro-olefins (XIX), the ozonolysis and oxidation of which gave the carboxylic acids (XX):

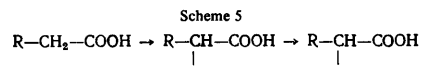


(XX)

(XVII) R=OH
(XVIII) R = OTs
(XIX) R=F
(n = 1 and 2)

The bromides of the fluoroacids (XXI) were brominated in the α-position and subsequently converted into aminoacids by the action of ammonia:

Scheme 5



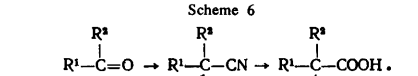
(XXI) (XXII) (XXIII)

(XXI a — XXIII a)	FCH_2—	(XXI d — XXIII d)	FH_2C(FH$_2$C)CH—CH_2—
(XXI b — XXIII b)	$F(CH_2)_2$—	(XXI e — XXIII e)	CF_3—CF_2—CF_2—$(CH_2)_2$—
(XXI c — XXIII c)	FH_2C(FH$_2$C)CH—	(XXI f — XXIII f)	CF_3—CF_2—CF_2—$(CH_2)_3$—

This method improved the synthesis of 3-fluoroalanine (XXIIIa) and 2-amino-4-fluorobutyric acid (XXIIIb) and made it possible to obtain for the first time 4,4′-difluorovaline (XXIIIc) and 5,5′-difluoroleucine (XXIIId). Attempts to prepare 4-fluoroleucine by this method had to be abandoned, because even the intermediate 3-fluoro-5-methylhex-1-ene splits off hydrogen fluoride at room temperature. The dipeptide DL-3-fluoroalanyl-L-leucine can be obtained from *N*-benzyloxycarbonyl-3-fluoroalanine and the trimethylsilyl ester of *N*-trimethylsilyl-L-leucine.

The Strecker method for the synthesis of aminoacids was also successfully employed to prepare mono- and di-fluoro-substituted aminoacids:

Scheme 6

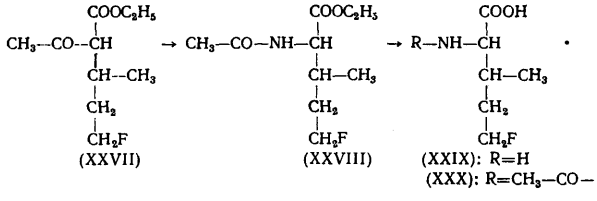


(XXIV) (XXV) (XXVI)

(XXIV a — XXVI a)	R^1=CH_2F—; R^2=CH_3—
(XXIV b — XXVI b)	R^1=R^2=CH_2F—
(XXIV c — XXVI c)	R^1=CF_3—CH_2—CH_2—; R^2=H—
(XXIV d — XXVI d)	R^1=CF_3—; R^2=CH_3—

However, here too side reactions play an appreciable role. Thus a mixture of 3-fluoro-2-hydroxyisobutyronitrile and 2-amino-3-fluoroisobutyronitrile (XXVa) was obtained by the reaction of fluoroacetone (XXIVa) with sodium cyanide and ammonium chloride; similarly, hydrolysis gives a mixture of 3-fluoro-2-hydroxyisobutyric acid and 2-amino-3-fluoroisobutyric acid (XXVIa)[43,44]. In the reaction of 1,6-difluoroacetone (XXIVb) 3,3'-difluoro-2-hydroxyisobutyronitrile formed as an intermediate is converted by the action of gaseous ammonia into 2-amino-3,3'-difluoroisobutyronitrile (XXVb), the hydrolysis of which gives 2-amino-3,3'-difluoroisobutyric acid (XXVIb)[43].

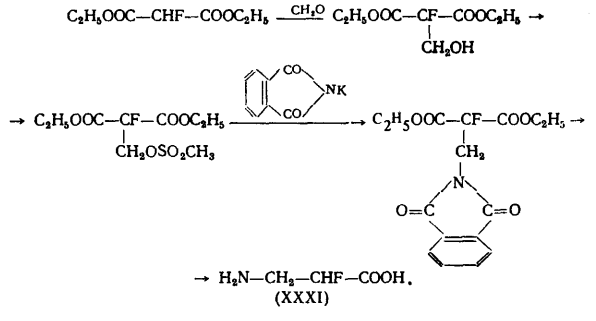
Hudlický chose a completely new method for the synthesis of monofluoro-derivatives of isoleucine[45]. Alkylation of acetoacetic ester with 3-bromo-1-fluorobutane gives the ethyl ester of 2-acetyl-5-fluoro-3-methylvaleric acid (XXVII). This acetyl derivative is converted by the Schmidt rearrangement into ethyl 2-acetamido-5-fluoro-3-methylvalerate (XXVIII):



(XXVII) (XXVIII) (XXIX): R=H (XXX): R=CH$_3$—CO—

While acid hydrolysis gives DL-2-amino-5-fluoro-3-methylvaleric acid (XXIX), alkaline hydrolysis under mild conditions gives an *N*-acetyl derivative (XXX). To separate it into its optical isomers, this compound was acted upon by pig kidney acylase. However, instead of the expected L-aminoacid, its cyclisation product—*cis*-3-methyl-L-proline—was obtained together with D-2-acetamido-5-fluoro-3-methylvaleric acid. These results provide a key to the solution of the problem of the stereochemistry of the compounds. Since the *cis*-compound is obtained by the cyclisation of *threo*-2-amino-5-fluoro-3-methylvaleric acid, the product of the synthesis is evidently DL-5-fluoroalloisoleucine (XXIX). The *N*-acetyl derivative obtained by enzymic hydrolysis is thus (2S : 3R)-2-acetamido-5-fluoro-3-methylvaleric acid (XXX).

Here we should also mention the fluoro-derivative of 3-aminopropionic acid (β-alanine), although this is not an α-aminoacid. β-Alanine is one of the few β-aminoacids occurring in nature; it is a component of pantothenic acid. 3-Amino-2-fluoropropionic acid (XXXI) may be isolated as a decomposition product of 5-fluorouracil from the urine of mice, cats, or man after internal administration of 5-fluorouracil[46]. Bergmann and Cohen obtained α-fluoro-β-alanine (XXXI) in the following way[47]:



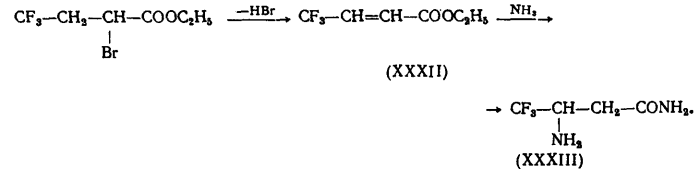
(XXXI)

A similar synthesis was developed by Tolman and Vereš on the basis of 2-fluoro-3-hydroxypropionic acid[48].

Bearing in mind the ease with which mono- and di-fluoro-substituted aminoacids lose fluorine, it is evident that the problem of whether the observed cytotoxic effect of the compound is determined by its properties as an antimetabolic or whether it is caused by the formation of fluoride ions remains open[42].

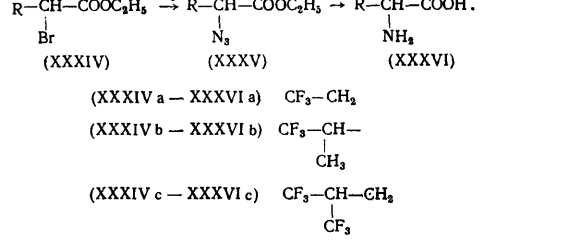
The stability of fluorine-containing aminoacids should increase following the introduction of a complete trifluoromethyl group or other perfluoroalkyl group at once instead of replacing one or two hydrogen atoms by fluorine.

Walborsky et al. synthesised 2-amino-4,4,4-trifluorobutyric acid (XXXVIa) from 4,4,4-trifluorobutyric acid. It is readily brominated in the α-position and is converted into ethyl 2-bromo-4,4,4-trifluorobutyrate. However, instead of the expected 2-amino-4,4,4-trifluorobutyramide ammonolysis yields the isomeric 3-amino-4,4,4-trifluorobutyramide (XXXIII)[49]:



(XXXII) (XXXIII)

As a result of the elimination of hydrogen bromide, ethyl trifluorocrotonate (XXXII) is formed initially, since the inductive effect of the trifluoromethyl group facilitates the elimination of a proton from the β-position. Subsequently ammonia adds in the usual way to the β-carbon atom. A less basic but more nucleophilic reagent (for example the azide ion) should drive the reaction towards normal substitution. Indeed, when the α-bromoester (XXXIVa) was treated with an azide with subsequent catalytic hydrogenation, 2-amino-4,4,4-trifluorobutyric acid (XXXVIa) was obtained[50]; 4,4,4-trifluorovaline (XXXVIb)[51] and 5,5,5,5',5',5'-hexafluoroleucine (XXXVIc)[52] were obtained similarly:

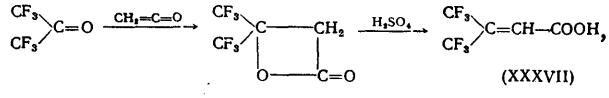


(XXXIV a — XXXVI a) CF$_3$—CH$_2$

(XXXIV b — XXXVI b) CF$_3$—CH(CH$_3$)—

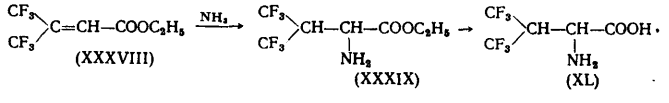
(XXXIV c — XXXVI c) CF$_3$—CH(CF$_3$)—CH$_2$—

Knunyants and Cheburkov showed that 3,3-bis(trifluoromethyl)acrylic acid (XXXVII), obtained from hexafluoroacetone and keten via a β-lactone[53],



(XXXVII)

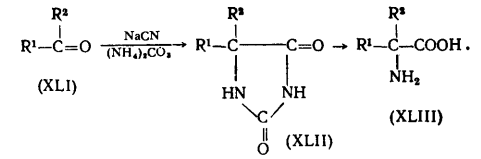
and also the ethyl ester of this acid (XXXVIII) do not behave like ethyl 4,4,4-trifluorocrotonate (XXXII). In the case of the ester (XXXII) the attack by ammonia is directed to the β-carbon atom and 3-amino-4,4,4-trifluorobutyramide (XXXIII) is formed; on the other hand, the ester (XXXVIII) combines with ammonia at the α-position. Free 4,4,4,4',4',4'-hexafluorovaline (XL) is then obtained from the aminoacid ester thus produced[54]:



(XXXVIII) (XXXIX) (XL)

A number of trifluoromethyl-substituted aminoacids have also been obtained in other ways. 6,6,6-Trifluoronorleucine (XVIe) and 6,6,6-trifluoro-5-methylnorleucine (XVIf) were synthesised with the aid of formamidomalonic ester (Scheme 4, $R^2 = H$)[49]; the starting materials were respectively 4,4,4-trifluorobutyl iodide (XIVe) or 4,4,4-trifluoro-2-methylbutyl iodide (XIVf), which may be obtained in several stages from 1,1,1-trifluoroacetone.

The Strecker synthesis (Scheme 6) was used successfully to prepare 5,5,5-trifluoronorvaline (XXVIc)[49] and 2-amino-3,3,3-trifluoroisobutyric acid (XXVId)[44]. However, while the yield of 5,5,5-trifluoronorvaline [(XXVIc) or (XLIIIa)] synthesised by the Strecker method is only 4.6%, synthesis via the hydantoin makes it possible to increase the yield to 30%:[49]

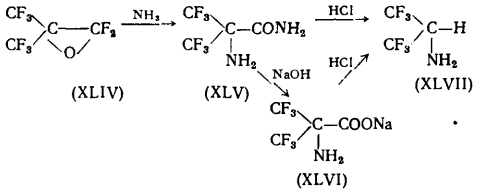


(XLI a — XLIII a) $R^1 = CF_3—CH_2—CH_2—$; $R^2 = H$

(XLI b — XLIII b) $R^1 = CF_3—$; $R^2 = CH_3—$

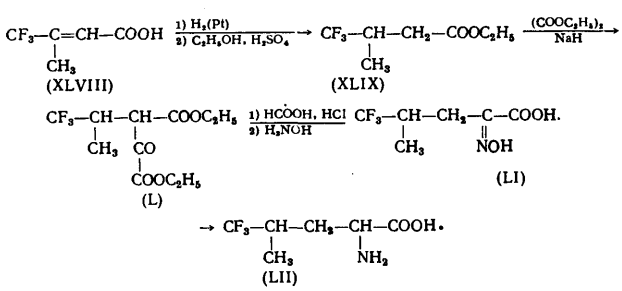
2-Amino-3,3,3-trifluorobutyric acid (XLIIIb) was also obtained via hydantoin[38].

In this connection it is interesting to note an observation by Knunyants and coworkers: it was found that the corresponding aminoacid derivative of hexafluoroacetone—2-amino-3,3,3,3′,3′,3′-hexafluoroisobutyric acid—is unstable. The interaction of epoxyperfluoroisobutane (XLIV) with ammonia at −10°C yields the amide of 2-amino-3,3,3,3′,3′,3′-hexafluoroisobutyric acid (XLV)[55]. Hydrolysis of this amide with dilute hydrochloric acid is accompanied by decarboxylation and gives hexafluoroisopropylamine (XLVII); although the sodium salt of the aminoacid (XLVI) can be obtained by alkaline hydrolysis, on acidification it too decarboxylates spontaneously[56]:



Yet another synthesis of 5,5,5-trifluoronorvaline and 4,4,4-trifluorovaline has so far been mentioned only in conference abstracts[57].

The synthesis of 5,5,5-trifluoroleucine (LII) should also be described. Rennert and Anker employed 4,4,4-trifluoro-3-methylcrotonic acid (XLVIII) as the starting material. Catalytic hydrogenation, esterification, and condensation with oxalate ester leads to compound (L). After hydrolysis and decarboxylation, the resulting 2-ketoacid is converted into the oxime (LI). Its catalytic hydrogenation yields the aminoacid (LII)[58]:



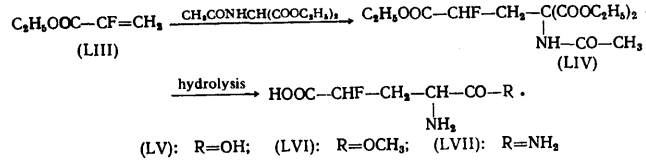
In view of their possible biochemical importance, Walborsky and Lang determined the pK's of a number of trifluoromethyl-substituted aminoacids and compared them with those of the corresponding non-fluorinated compounds[59]. As expected, pK_{COOH} and pK_{NH_2} decrease under the influence of electronegative trifluoromethyl groups and to a greater extent the closer the latter are to the dissociating groups. However, in biological tests the aminoacids obtained did not fulfil the expectations. 6,6,6-Trifluoronorleucine, 6,6,6-trifluoro-5-methylnorleucine, 4,4,4,4′,4′,4′-hexafluorovaline, 4,4,4-trifluorovaline, and 5,5,5,5′,5′,5′-hexafluoroleucine proved to be inactive in relation to *Saccharomyces cerevisiae* and *E. coli*; only 5,5,5-trifluoronorvaline inhibits the growth of *E. coli*[49,51,52]. On the other hand, the growth of HeLa cells ceases almost completely at a hexafluorovaline concentration as low as 7.2×10^{-4} M.[60]

An interesting effect was observed with 5,5,5-trifluoroleucine. Leucine dependent *E. coli* mutants continue to grow exponentially when trifluoroleucine is added to the nutrient medium. Inhibition is not observed until the concentration of trifluoroleucine exceeds by severalfold the concentration of leucine. When the trifluoroleucine : leucine ratio is 2, at least half of the leucine in the bacterial protein is replaced by trifluoroleucine. *E. coli* can actually become adapted to grow in a nutrient medium containing solely trifluoroleucine and the leucine in the protein is entirely replaced by trifluoroleucine. On the other hand, a wild strain of *E. coli* does not incorporate trifluoroleucine added to the nutrient medium[58].

Two perfluoroalkyl-substituted long-chain aminoacids, obtained by Brace[61] according to Scheme 4 from fluoroacids (XXIe) and (XXIf), namely 2-amino-5,5,6,6,7,7,7-heptafluoroheptanoic acid (XXIIIe) and 2-amino-6,6,7,7,8,8,8-heptafluorocaprylic acids (XXIIIf)[61], are not analogues of natural aminoacids.

3. Fluorinated Monofunctional Aliphatic Aminoacids

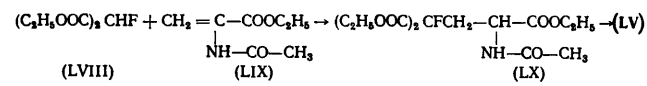
A monofluoro-derivative of glutamic acid has been obtained by several methods. 4-Fluoroglutamic acid (LV) was obtained for the first time by Hudlický[62,63] from ethyl α-fluoroacrylate (LIII). The Michael condensation of acetamidomalonic ester and subsequent hydrolysis of the addition product led to the aminoacid (LV):



(LV): R=OH; (LVI): R=OCH_3; (LVII): R=NH_2

Tolman and Vereš[64] obtained 5-fluoroglutamine (LVII) by treating the γ-methyl ester of 4-fluoroglutamic acid (LVI) with ammonia; the amino-group was protected with carbon disulphide as the dithiocarbamate.

Independently of Hudlický, Buchanan et al. obtained 4-fluoroglutamic acid by this method. However, they described a second method as well, which is also based on the Michael addition but is otherwise the converse of the Hudlický method. They added diethyl fluoromalonate (LVIII) to ethyl 2-acetamidoacrylate (LIX) and hydrolysed the addition product (LX):

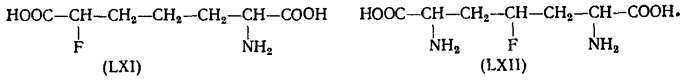


The yield was almost twice as high as in the previous synthesis. Biological tests showed that fluoroglutamic acid has virtually no activity.

Attempts to synthesise 3-fluoroaspartic acid proved to be unsuccessful[42,63].

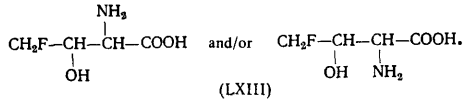
2,6-Diaminopimelic acid is present in bacterial cell walls. Together with other aminoacids, it gives rise to the formation of cross-links between polysaccharide chains thereby imparting stability to the cell walls.

Cavalleri et al. synthesised as possible antimetabolites 2-amino-6-fluoropimelic acid (LXI) and 2,6-diamino-4-fluoropimelic acid (LXII) from the fluoropimelic acids by bromination in the α-position and replacement of bromine by the action of ammonia or potassium phthalimide[66]:



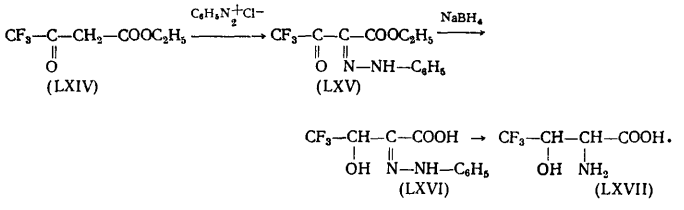
(LXI) (LXII)

Furthermore, mention should also be made of 4-fluorothreonine (LXIII), a monofluorinated polyfunctional aminoacid. It was obtained by the addition of hypobromite to 4-fluorocrotonic acid with subsequent ammonolysis in liquid ammonia. So far it has not been determined whether this leads to the formation of DL-4-fluorothreonine or DL-4-fluoroallothreonine[42]:



(LXIII)

Walborsky and Baum[67] proposed a synthesis of 4,4,4-trifluorothreonine (LXVII):

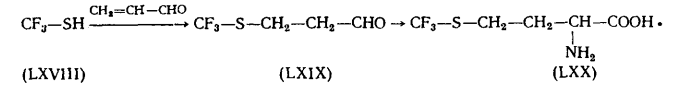


(LXIV) (LXV)

(LXVI) (LXVII)

For this purpose, 4,4,4-trifluoroacetoacetic ester (LXIV) is treated with phenyldiazonium chloride (the Japp–Klingemann reaction), the keto-group is reduced to an alcoholic group with sodium borohydride, and the ester is hydrolysed. Finally, the phenylhydrazone (LXVI) is hydrogenated catalytically with formation of the aminoacid. Here too a mixture of trifluorothreonine and trifluoroallothreonine is probably formed. The attempts by the same authors to achieve the asymmetric synthesis of 4,4,4-trifluorothreonine will be described in Section V (subsection 1).

S-Adenosylmethionine is a transferring agent for the methyl group in biological methylation. Interesting results might have been expected on replacement of the methyl group by a trifluoromethyl group. Trifluoromethionine (or *S*-trifluoromethylhomocysteine) (LXX) was synthesised by Dannley and Taborsky[68] starting with trifluoromethanethiol (LXVIII), obtained by the fluorination of carbon disulphide with mercury fluoride. The mercaptan was added to acrolein and 3-trifluoromethylthiopropionaldehyde (LXIX) obtained in this way was converted into trifluoromethionine (LXX) by hydantoin synthesis:



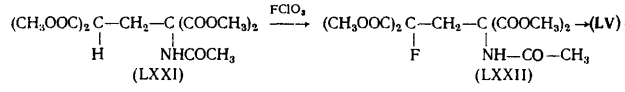
(LXVIII) (LXIX) (LXX)

The hopes concerning trifluoromethionine were indeed realised. It inhibits the growth of many micro-organisms[69] and forms an *S*-adenosyl derivative both *in vitro* and *in vivo*, competing thereby with methionine and preventing the demethylation of *S*-adenosylmethionine[70].

IV. SYNTHESES OF FLUORINE-CONTAINING AMINOACIDS BY THE INTRODUCTION OF FLUORINE INTO AMINOACIDS OR THEIR DERIVATIVES

1. Replacement of Hydrogen by Fluorine

4-Fluoroglutamic acid (LV) is not obtained solely by the two methods mentioned above. It is also possible to replace the hydrogen atom in the γ-position of the tetramethylester of 2-acetamido-2,4-dicarboxyglutaric acid (LXXI) by fluorine with the aid of perchloryl fluoride and then hydrolyse the fluorinated ester (LXXII)[71–73]:

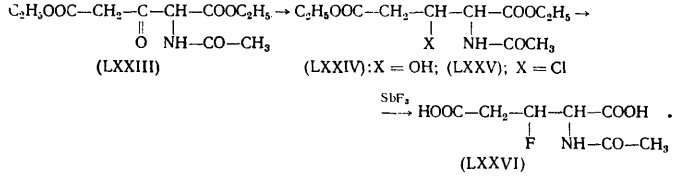


(LXXI) (LXXII)

The diastereoisomers obtained could be separated[74].

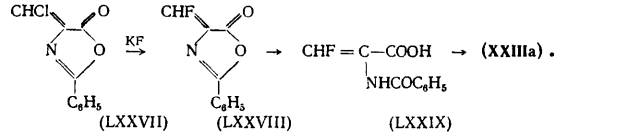
2. Replacement of a Halogen by Fluorine

3-Fluoroglutamic acid, isomeric with 4-fluoroglutamic acid can be synthesised [as the *N*-acyl derivative of compound (LXXVI)] from the diethyl ester of 2-acetamidoacetonedicarboxylic acid (LXXIII)[75]. This ester is hydrogenated catalytically and the hydroxy-group in compound (LXXIV) thus formed is replaced by chlorine. The chlorine in the resulting chloro-derivative (LXXV) is replaced by fluorine by the action of antimony trifluoride and the ethoxycarbonyl group is then hydrolysed, which yields the *N*-acyl derivative of (LXXVI):



(LXXIII) (LXXIV): X = OH; (LXXV); X = Cl (LXXVI)

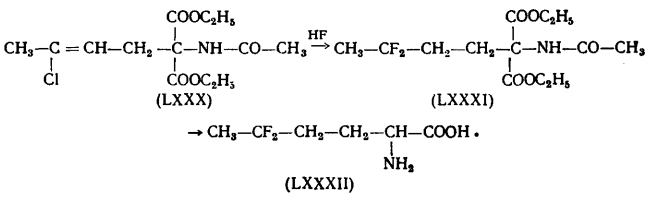
3-Fluoroalanine (XXIIIa) was obtained for the first time by a similar replacement of a halogen. 4-Chloromethylene-2-phenyl-5-oxazolone (LXXVII) is converted into the fluoro-derivative (LXXVIII) by the action of potassium fluoride in acetylacetone; the unsaturated *N*-benzamidoacid (LXXIX) obtained by hydrolysis is hydrogenated catalytically and finally the benzoyl group is eliminated[76]:



(LXXVII) (LXXVIII) (LXXIX)

In an attempt to replace chlorine by fluorine in a derivative of acetamidomalonic ester (LXXX) Hudlický[77] obtained immediately a difluoro-product (LXXXI), since hydrofluoric

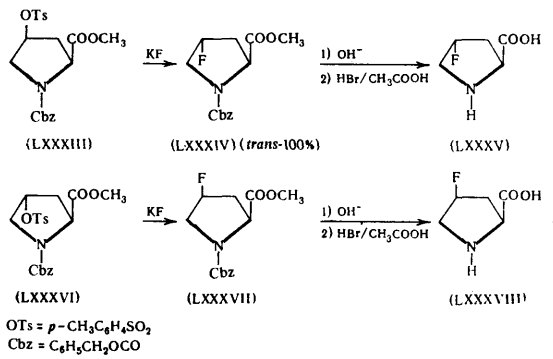
acid added simultaneously to the double bond. Hydrolysis gave 5,5-difluoronorleucine (LXXXII):



(LXXX) (LXXXI) (LXXXII)

3. Replacement of a Hydroxy-group by Fluorine

Aminoacids containing hydroxy-groups are used in such syntheses. Witkop and coworkers achieved the stereospecific synthesis of *cis*- and *trans*-4-fluoro-L-proline (LXXXVIII) and (LXXXV) from L-hydroxyproline and L-hydroxyalloproline[78]:

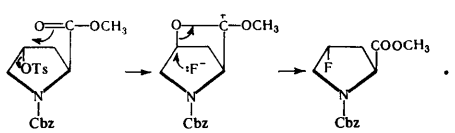


(LXXXIII) (LXXXIV) (*trans*-100%) (LXXXV)

(LXXXVI) (LXXXVII) (LXXXVIII)

OTs = *p*-$CH_3C_6H_4SO_2$
Cbz = $C_6H_5CH_2OCO$

When the methyl ester of *N*-benzyloxycarbonyl-*O*-tosyloxy-L-alloproline (LXXXIII) is heated with potassium fluoride in diethylene glycol, the *trans*-compound (LXXXIV) is obtained as a result of a stereospecific S_N2 reaction. Hydrolysis and elimination of the benzyloxycarbonyl group give *trans*-4-fluoro-L-proline (LXXXV). However, the fluorination of the methyl ester of *N*-benzyloxycarbonyl-*O*-tosyloxy-L-proline (LXXXVI) gives rise to a mixture of 83% of the *cis*-compound and 17% of the *trans*-compound. This can be explained by the intramolecular involvement of the ester carbonyl group in the substitution reaction:

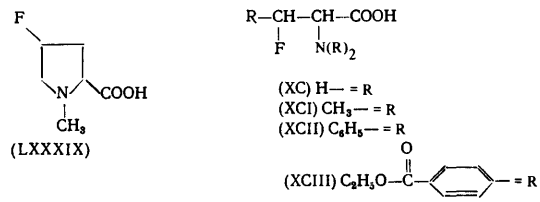


Ts = *p* $CH_3C_6H_4SO_2$, Cbz = $C_6H_5CH_2OCO$

A somewhat modified synthesis was described by another group of investigators[79].

In tests on *E. coli* it was found that both isomers are incorporated in the protein but the *trans*-isomer is incorporated to a much greater extent. In contrast to the *cis*-isomer, *trans*-fluoroproline does not inhibit the growth of mice. On the other hand, in the presence of *cis*-fluoroproline the weight of mice is smaller approximately by one-quarter compared with the control experiment. When the animals were cut open, pathological changes were found, particularly in the liver. Therefore it is suggested that in the experiments with *E. coli* too *cis*-fluoroproline inhibits the biosynthesis of proteins[78,79]. In the case of collagens, which contain particularly large amounts of proline and hydroxyproline, the latter is obtained as a result of the replacement in the finished protein of a *trans*-hydrogen atom in the 4-position of proline by a hydroxy-group; hydroxyproline is not incorporated in proteins. Experiments with *trans*-fluoroproline labelled with tritium showed that fluorine can also be replaced enzymically by a hydroxy-group[78].

Cohen and Bergmann[80] attempted to use 2-chloro-1,1,2-trifluoroethyldiethylamine as a fluorinating agent for the replacement of a hydroxy-group by fluorine in the synthesis of monofluoro-substituted aminoacids from hydroxyaminoacids. However, this method proved to be suitable only for aminoacids with alkylated amino- and carboxy-groups. 4-Fluoro-*N*-methylproline (LXXXIX) (from hydroxyproline), 3-fluoro-*NN*-dimethylalanine (XC) (from serine), 2-amino-3-fluoro-*NN*-dimethylbutyric acid (XCI) (from threonine), 3-fluoro-*NN*-dimethylphenylalanine (XCII) (from phenylserine), and *O*-ethoxycarbonyl-3-fluoro-*NN*-dimethyltyrosine (XCIII) (from hydroxyphenylserine) were obtained in this way; the last two compounds were prepared only as the methyl esters:



(LXXXIX)

(XC) H— = R
(XCI) CH_3— = R
(XCII) C_6H_5— = R
(XCIII) C_6H_5O—C(=O)— = R

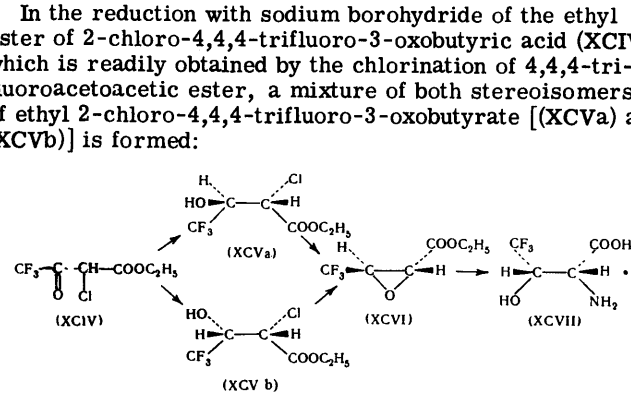
V. SPECIAL METHODS FOR THE SYNTHESIS OF FLUORINE-CONTAINING AMINOACIDS

This section deals mainly with the syntheses of highly fluorinated aminoacids, which are possible only due to the electronic influence of perfluoroalkyl groups. These syntheses are unsuitable for non-fluorinated compounds or they give rise to different products.

1. Opening of the Ring in Glycidic Esters

Apart from the synthesis of 4,4,4-trifluorothreonine already described, Walborsky and Baum attempted an asymmetric synthesis, which would not result in a mixture of 4,4,4-trifluorothreonine and 4,4,4-trifluoroallothreonine[67].

In the reduction with sodium borohydride of the ethyl ester of 2-chloro-4,4,4-trifluoro-3-oxobutyric acid (XCIV), which is readily obtained by the chlorination of 4,4,4-trifluoroacetoacetic ester, a mixture of both stereoisomers of ethyl 2-chloro-4,4,4-trifluoro-3-oxobutyrate [(XCVa) and (XCVb)] is formed:



(XCIV) (XCVa) (XCVI) (XCVII)

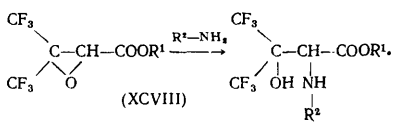
(XCV b)

The isomers may be separated by distillation; they are obtained in proportions of 7 : 4. According to Cram's rule, more of the *erythro*-compound (XCVb) than of the threo-isomer (XCVa) should be formed, so that the ester formed

in a greater amount should be the *erythro*-isomer. However, ring closure in both isomers gave the same epoxy-compound (XCVI), to which Walborsky and Baum attributed the *trans*-configuration.

It was of interest to elucidate how the glycidic ester (XCVI) behaves when its ring is cleaved with ammonia; whether the attack is directed to the α-carbon atom with formation of a 2-amino-3-hydroxyacid or whether a 3-amino-2-hydroxy acid is formed as a result of attack on the β-carbon atom. Experiments showed that the ring is opened exclusively at the α-carbon atom, i.e. 4,4,4-trifluorothreonine or its amide is formed, depending on the conditions. Since ring opening is also a *trans*-reaction, the *erythro*-compound, i.e. 4,4,4-trifluoroallothreonine (XCVII), should be produced.

Knunyants and coworkers showed that diazoacetic ester reacts with hexafluoroacetone in an unusual manner with formation of bis(trifluoromethyl)glycidic ester (XCVIII)[81]. In this case too reaction with amines, for example, benzylamine or aniline, gives 2-amino-3-hydroxy-compounds (XCIX) or (C)[82]. When the amine employed is 2,4-dimethoxybenzylamine, the 2,4-dimethoxybenzyl group can be very readily eliminated from the resulting ethyl ester of 4,4,4,4′,4′,4′-hexafluoro-2-[*N*-(2,4-dimethoxybenzyl)-amino]-3-hydroxyisovaleric acid (CI) by means of a mixture of trifluoroacetic acid and its anhydride[83]. After hydrolysis, 2-amino-4,4,4,4′,4′,4′-hexafluoro-3-hydroxyisovaleric acid (CII) is obtained[84]:



(XCVIII)

(XCIX) $R^1 = C_2H_5-$; $R^2 = C_6H_5-CH_2-$

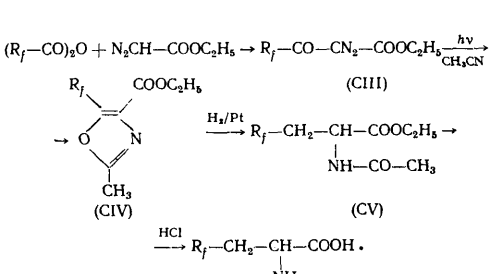
(C) $R^1 = C_2H_5-$; $R^2 = C_6H_5-$

(CI) $R^1 = C_2H_5-$; $R^2 = CH_3O-C_6H_3(OCH_3)-CH_2-$

(CII) R^1, $R^2 = H$

2. Opening of the Ring in Esters of 5-Perfluoroalkyl-2-methyloxazole-4-carboxylic Acids

Steglich et al.[85] developed a general method for the synthesis of alanines with perfluoroalkyl substituents in the β-position. The starting materials were perfluoroacyldiazoacetic esters (CIII), which are readily obtained from the anhydrides of perfluoroacids and diazoacetic ester:



(CIII)

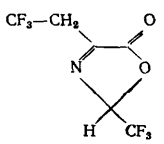
(CIV)

(CV)

(CVI): $R_f = CF_3-$; (CVII): $R_f = CF_3-CF_2-$; (CVIII): $R_f = CF_3-CF_2-CF_2-$

When compounds CIII) are irradiated in acetonitrile, esters of 5-perfluoroalkyl-2-methyloxazole-4-carboxylic acids (CIV) are formed. Catalytic hydrogenation of the latter is accompanied by hydrogenolysis, which leads to the ethyl esters of *N*-acetyl-3-perfluoroalkylalanines (CV). Hydrolysis with concentrated hydrochloric acid gives, depending on the perfluoroalkyl group, 2-amino-4,4,4-trifluorobutyric acid (CVI), 4,4,5,5,5-pentafluoronorvaline (CVII), or 4,4,5,5,6,6,6-heptafluoronorleucine (CVIII). Measurements of the pK's showed that, as expected, they are again lower compared with the non-fluorinated aminoacids[86].

DL-2-Amino-4,4,4-trifluorobutyric acid (CVI) can be converted into the L-form. The aminoacid is trifluoroacetylated and then cyclised by reaction with dicyclohexylcarbodi-imide to 4-(2,2,2-trifluoroethyl)-2-trifluoromethyl-Δ^3-5-oxazolinone (CIX):



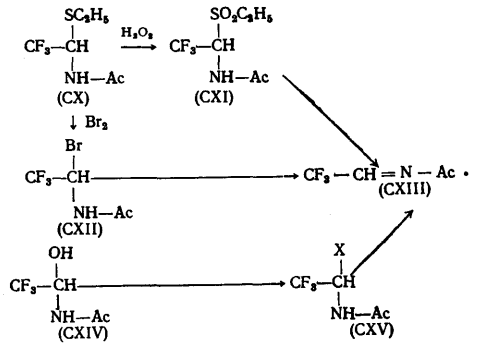
(CIX).

When the ring of this optically inactive Δ^3-oxazoline derivative is opened by the action of the dimethyl ester of L-glutamic acid, the product is the dimethyl ester of *N*-trifluoroacetyl-(2-amino-4,4,4-trifluorobutyryl)-L-glutamic acid, which, as a result of optical induction, consists of 83% of the LL- and 17% of the DL-diastereoisomer (determined by gas–liquid chromatography). Repeated recrystallisation, hydrolysis, and elimination of L-glutamic acid gave pure L-2-amino-4,4,4-trifluorobutyric acid (CVI)[85]. L-4,4,5,5,5-pentafluoronorvaline (CVII) was obtained similarly[86].

3. Reactions involving Addition to *N*-Acylimines of Perfluoroaldehydes and Perfluoroketones

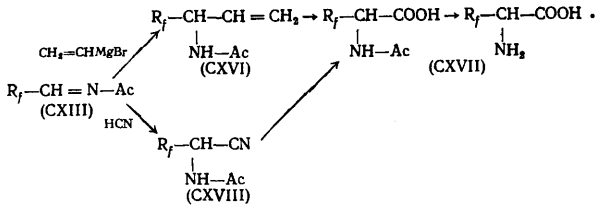
Weygand, Steglich, and coworkers observed that the *N*-acylimines of trifluoroacetaldehyde (CXIII) are extremely reactive. *N*-Acyl-1-ethylthio-2,2,2-trifluoroethylamines (CX, Ac = CH_3CO, CF_3CO, C_6H_5CO, or $C_6H_5CH_2OCO$) are readily oxidised to sulphones (CXI) with hydrogen peroxide in glacial acetic acid[87]. It has been shown that the mechanism of reactions of the sulphones (CXI) with nucleophilic reagents involves elimination and addition; initially the sulphones are converted by bases into *N*-acyltrifluoroacetaldimines (CXIII), to which the nucleophilic agents were then added[87]. The bromination of the thioesters (CX) yields *N*-acyl-1-bromo-2,2,2-trifluoroethylamines (CXII) from which highly moisture-sensitive aldimines (CXIII) can be isolated in a pure form[88]. A simpler pathway to the aldimines (CXIII) involves the condensation of trifluoroacetaldehyde, trifluoroacetaldehyde hydrate, or hemiacetals of trifluoroacetaldehyde with acid amides; this results in the formation of *N*-acyl-2,2,2-trifluoro-1-hydroxyethylamines (CXIV), which can be readily converted into the chloro-derivatives (CXV, X = Cl) by the action of phosphorus pentachloride[88]; in the presence of acid-sensitive acyl groups such as the p-methoxybenzyloxycarbonyl or t-butoxycarbonyl groups, the hemiaminals (CXIV) can be

converted into acyloxy-compounds (CXV, X = CR_3COO or CH_3COO)[89,90]:



As already stated, *N*-acyltrifluoroacetaldimines (CXIII) react with many nucleophilic reagents; there is then no necessity to isolate them in a pure form—one can start with their precursors[87-91].

The possibility of using these aldimines in the synthesis of fluorinated aminoacids is self-evident. For this purpose vinylmagnesium bromide was added to them initially[87]. The resulting 3-acylamino-4,4,4-trifluorobut-1-ene (CXVI) was oxidised with potassium permangate to 2-acylamino-3,3,3-trifluoropropionic acid (CXVII), Ac = C_6H_5CO or $C_6H_5CH_2OCO$)[87,92] and then the acyl residue was eliminated. 3,3,3-Trifluoroalanine (CXIX) was obtained in this way[92]:



(CXIX): R_f = CF_3—; (CXX) CF_3—CF_2—; (CXXI) CF_3—CF_2—CF_2—

This sequence of reactions is also applicable to other perfluoroalkyl residues and has led to the synthesis of 2-amino-3,3,4,4,4-pentafluorobutyric acid (CXX) and 3,3,4,4,5,5,5-heptafluoronorvaline (CXXI)[93].

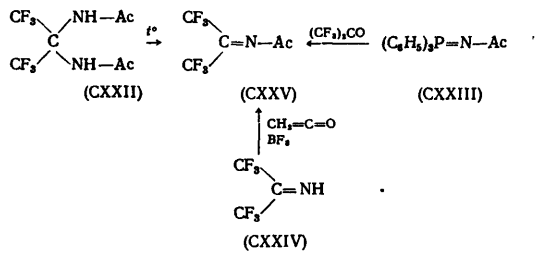
An attempt to use another method for the preparation of fluorinated aminoacids—by the interaction of the sulphone (CXI) with a cyanide—led only to the ethylene derivative as a result of the elimination of the fluoride ion[87].

However, the addition of anhydrous hydrocyanic acid to aldimines (CXIII) made it possible to develop yet another method for the synthesis of 3,3,3-trifluoroalanine. The resulting nitrile (CXVIII) is readily hydrolysed and the subsequent elimination of the acyl group gives the aminoacid (CXIX)[94].

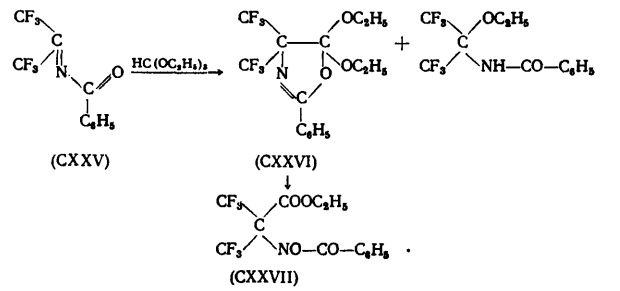
However, this synthesis is not suitable for higher α-perfluoroalkylglycines.

α-Perfluoroalkylglycines (CXIX–CXXI) have pronounced acid properties. pK_{NH_2} for trifluoroalanine (5.61) is much lower than for alanine itself (9.69). In contrast to the usual monocarboxylic 2-monoaminoacids, trifluoroalanine forms a crystalline dicyclohexylammonium salt. It may be acylated at the nitrogen atom and converted to the methyl ester with diazomethane[92,93].

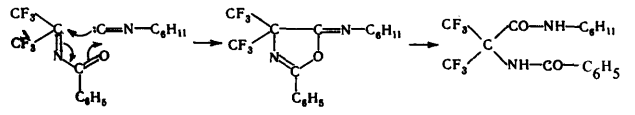
N-Acyl-1,1,1,3,3,3-hexafluoroisopropylideneimines (CXXV) are also very reactive in relation to nucleophilic agents. The acylimino-derivatives of hexafluoroacetone (CXXV) are obtained by the pyrolysis of bisbenzamido-compounds (CXXII, Ac = C_6H_5CO), oy the reaction of hexafluoroacetone with triphenylphosphine-*N*-benzoylimine (CXXIII, Ac = C_6H_5CO)[95], and also by the acylation of the imino-derivative of hexafluoroacetone by the action of keten in the presence of boron trifluoride[96]:



The benzoylimino-derivative of hexafluoroacetone (CXXV, Ac = C_6H_5CO) enters into a 1,4-addition reaction with orthoformic ester, yielding 5,5-diethoxy-4,4,-di(trifluoromethyl)-2-phenyl-Δ²-oxazoline (CXXVI), the hydrolysis of which gives the ethyl ester of 2-benzamido-3,3,3,3′,3′,3′-hexafluoroisobutyric acid (CXXVII)[97]. However, as stated above, the free acid is unstable[56]:

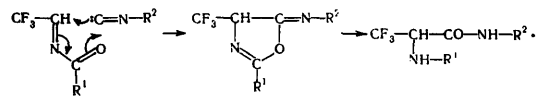


The addition of isonitriles to *N*-acylketimines (CXXV) is of great importance:



The resulting 5-cyclohexyl-4,4,-di(trifluoromethyl)-2-phenyl-Δ²-oxazoline(CXXVIII) may be hydrolysed to the cyclohexylamide of 2-benzamido-3,3,3,3′,3′,3′-hexafluoroisobutyric acid (CXXIX)[98].

The application of this reaction to *N*-acyltrifluoroacetaldimines (CXIII) makes it possible to synthesise the cyclohexylamide of *N*-benzyloxycarbonyl-3,3,3-trifluoroalanine (CXXXI):



(CXXXI) R^1=C_6H_5—CH_2—OCO—; R^2=C_6H_{11}—

(CXXXII) R^1=C_6H_5—CH_2—OCO—; R^2=CH_3OOC—CH(—CH_2—CH(CH_3)$_2$)—

(CXXXIII) R^1=C_6H_5—CH_2—OCO—NH—CH_2—CO—; R^2=CH_3OOC—CH(—CH_2—CH(CH_3)$_2$)—

Trifluoroalanyl peptides can be obtained directly in this way by introducing into the reaction the isonitriles obtained from esters of *N*-formylaminoacids. The methyl ester of *N*-benzyloxycarbonyl-3,3,3-trifluoroalanyl-L-leucine (CXXXII) was obtained by this procedure. Additional possibilities are provided by the application of *N*-(*N*-benzyloxycarbonylaminoacyl)trifluoroacetaldimines. This results in the ester of the *N*-benzyloxycarbonyltripeptide with trifluoroalanine in the centre of the chain, for example the methyl ester of *N*-benzyloxycarbonylglycyl-3,3,3-trifluoroalanyl-L-leucine (CXXXIII)[92].

Peptides containing trifluoroalanine may be obtained also from *N*-benzyloxycarbonyl-3,3,3-trifluoroalanine by allowing it to react in the usual way with aminoacid esters in the presence of dicyclohexylcarbodi-imide. Trifluoroalanine can also be used in the form of the methyl or t-butyl ester as the ester component in peptide synthesis. However, while the benzyloxycarbonyl group is readily eliminated, it is impossible to hydrolyse the ester group by alkalis. It has been shown for the methyl ester of *N*-benzyloxycarbonyl-3,3,3-trifluoroalanine that the trifluoromethyl group is first hydrolysed to a carboxy-group[93]. Another possibility of synthesising peptides is provided by the sequence of reactions of compounds (CXIII)–(CXVII) using as the acyl residue an aminoacid residue with a protected amino-group[93].

According to the data on the biological activity obtained hitherto, the addition of trifluoroalanine inhibits many micro-organisms, albeit at relatively high concentrations[93]. L-Aminoacid oxidase does not act upon trifluoroalanine, but the addition of trifluoroalanine can prevent it from acting on other L-aminoacids[93].

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