# Reaction of Hydrogen Fluoride in Pyridine Solution with *cis*-Cyano-2- and *cis*-Amido-2-aziridines. Preparation of β-Fluoro-α-amino Acids and Esters by Means of Acidic Hydrolysis and Alcoholysis of β-Fluoro-α-Amino Nitriles and/or β-Fluoro-α-Amino Acid Amides

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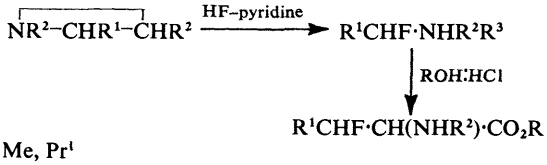
The addition of hydrogen fluoride generated from pyridinium poly(hydrogen fluoride) (*i.e.* Olah's reagent) to some *cis*-2-cyano- and *cis*-2-amido-aziridines has been examined.

The reaction led to fluoroamine derivatives which upon acidic hydrolysis and alcoholysis gave 3-fluoro-2-amino acids and esters in good yields.

The addition of hydrogen fluoride is highly regioselective for both substrates. It was found to be stereospecific for *cis*-2-amidoaziridines since *threo*-β-fluoro α-amino acid amides were exclusively obtained from the ring-opening with Olah's reagent. *cis*-2-Cyanoaziridines gave in all cases studied, mixtures (*i.e.* 57:43) of the *threo*- and *erythro*-2-amino-3-fluoronitriles.

Aziridine ring opening by hydrogen fluoride in pyridine solution has recently been developed in our laboratory, since the discovery that this route would be a convenient procedure for the preparation of fluoroamines in high yields.[1-4] Moreover, β-fluorinated α-amino acids are of great interest, because of their biological and pharmacological properties (*e.g.* irreversible enzyme inhibitors). Some synthetic methods have been reported but they lack generality and the yields of isolated fluoro amino acids are usually low.[2,4-7] We have recently shown that 3-fluoro-2-amino acids can be obtained by an acidic hydrolysis of 3-fluoro-2-amino nitriles derived from 3-fluoro-2-hydroxy nitriles and ammonia.[8] In a preliminary communication [9] we briefly reported the preparation of *cis*-2-cyano-3-phenylaziridine (4) and *cis*-3-phenylaziridinecarboxylic acid amide (8), by the Gabriel [10] type reaction, and their reaction with HF–pyridine, which enabled us to obtain 2-amino-3-fluoro-3-phenylpropiononitrile (15) (*threo*- and *erythro*) and 2-amino-3-fluoro-3-phenylpropionic acid amide (19), their acidic hydrolysis according to our previous study,[8] and their esterification for g.c./mass spectral analysis (Scheme 1).

Since 2-cyano- and 2-amido-aziridines have become easily accessible,[11] their ring-opening by HF–pyridine should be a convenient method of synthesizing β-fluoro-α-amino nitriles and converting β-fluoro-α-amino acid amide's versatile intermediates into β-fluoro-α-amino acids. Therefore, in our search for alternative routes to these important compounds, we directed our attention to these functionalized aziridines and have undertaken the testing of their reactivity.



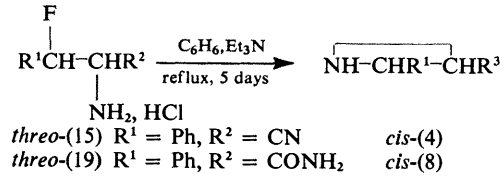

**Scheme 1.**

| | | | |
|---|---|---|---|
| | $NR^2–CHR^1–CHR^3$ | | |
| (1) | $R^1 = H$ | $R^2 = CMe_3$ | $R^3 = CN$ |
| (2) | $R^1 = H$ | $R^2 = PhCH_2$ | $R^3 = CN$ |
| (3) | $R^1 = Me$ | $R^2 = Me$ | $R^3 = CN$ |
| (4) | $R^1 = Ph$ | $R^2 = H$ | $R^3 = CN$ |
| (5) | $R^1 = Ph$ | $R^2 = Me$ | $R^3 = CN$ |
| (6) | $R^1 = p\text{-}ClC_6H_4$ | $R^2 = H$ | $R^3 = CN$ |
| (7) | $R^1 = p\text{-}ClC_6H_4$ | $R^2 = Me$ | $R^3 = CN$ |
| (8) | $R^1 = Ph$ | $R^2 = H$ | $R^3 = CONH_2$ |
| (9) | $R^1 = Ph$ | $R^2 = Me$ | $R^3 = CONH_2$ |
| (10) | $R^1 = p\text{-}ClC_6H_4$ | $R^2 = H$ | $R^3 = CONH_2$ |
| (11) | $R^1 = p\text{-}ClC_6H_4$ | $R^2 = Me$ | $R^3 = CONH_2$ |
| | $R^1CHF·CH·NHR^2R^3$ | | |
| (12) | $R^1 = H$ | $R^2 = Bu^t$ | $R^3 = CN$ |
| (13) | $R^2 = H$ | $R^2 = PhCH_2$ | $R^3 = CN$ |
| (14) | $R^1 = Me$ | $R^2 = Me$ | $R^3 = CN$ |
| (15) | $R^1 = Ph$ | $R^2 = H$ | $R^3 = CN$ |
| (16) | $R^1 = Ph$ | $R^2 = Me$ | $R^3 = CN$ |
| (17) | $R^1 = p\text{-}ClC_6H_4$ | $R^2 = H$ | $R^3 = CN$ |
| (18) | $R^1 = p\text{-}ClC_6H_4$ | $R^2 = Me$ | $R^3 = CN$ |
| (19) | $R^1 = Ph$ | $R^2 = H$ | $R^3 = CONH_2$ |
| (20) | $R^1 = Ph$ | $R^2 = Me$ | $R^3 = CONH_2$ |
| (21) | $R^1 = p\text{-}ClC_6H_4$ | $R^2 = H$ | $R^3 = CONH_2$ |
| (22) | $R^1 = p\text{-}ClC_6H_4$ | $R^2 = Me$ | $R^3 = CONH_2$ |
| (23) | $R^1 = H$ | $R^2 = Bu^t$ | $R^3 = CO_2H$ |
| (24) | $R^1 = Me$ | $R^2 = Me$ | $R^3 = CO_2H$ |
| (25) | $R^1 = Ph$ | $R^2 = H$ | $R^3 = CO_2H$ |
| (26) | $R^1 = Ph$ | $R^2 = Me$ | $R^3 = CO_2H$ |
| (27) | $R^1 = p\text{-}ClC_6H_4$ | $R^2 = H$ | $R^3 = CO_2H$ |
| (28) | $R^1 = p\text{-}ClC_6H_4$ | $R^2 = Me$ | $R^3 = CO_2H$ |
| (29) | $R^1 = Ph$ | $R^2 = H$ | $R^3 = CO_2Me$ |
| (30) | $R^1 = Ph$ | $R^2 = H$ | $R^3 = CO_2Pr^i$ |
| (31) | $R^1 = p\text{-}ClC_6H_4$ | $R^2 = H$ | $R^3 = CO_2Me$ |
| | $R^1CHNHR^2·CHFR^3$ | | |
| (32) | $R^1 = H$ | $R^2 = Bu^t$ | $R^3 = CN$ |
| (33) | $R^1 = H$ | $R^2 = PhCH_2$ | $R^3 = CN$ |

## Results

In all cases studied, hydrogen fluoride in pyridine solution combined under very mild conditions with the aziridines to give the corresponding fluoroamine derivatives in good yields (Experimental). The products were identified by i.r., $^{19}F$ n.m.r., $^1H$ n.m.r., and mass spectral elemental analyses. The stereochemistry of the β-fluoro-α-amino nitriles and β-fluoro-α-amino acid amides was assigned by $^{19}F$ n.m.r. and $^1H$ n.m.r. spectral analysis and confirmed by cyclization [10] of the hydrogen chloride salts of the *threo*-isomers of (15) and (19) with triethylamine (Scheme 2).

The configuration of the β-fluoro-α-amino acid (24) was deduced by the comparison of its properties with those of an authentic sample.[6] The structures of the 3-fluoro-2-amino




**Scheme 2.**

esters (28) and (29) were confirmed by synthesis *via* an alternative route.[2]

Fluoride ion attack was in all cases directed to the benzylic carbon for the aziridines (3)—(11) since the mass spectrometry of fluoroamino nitriles and fluoroamino acid amides (15)—(22) showed peaks at *m/z* 109 ($C_6H_5CHF^+$) or 143, 145 ($p$-$ClC_6H_4CHF^+$) which provides support for the regiochemical assignment.

Competition between the two possible ring-opening pathways occurred for aziridines in which $R^1$ is hydrogen [*i.e.* (1) and (2)]. Thus, the $^{19}F$ n.m.r. spectra showed for the crude mixtures from (1) and (2): (i)$\delta_F$ * 192.4 (m) [(31), 12%], 226.3 (dt), [(12), 45%]; and (ii) $\delta_F$ 191.9 (m) [(32), 15%], 226.4 (dt), [(13), 50%].

The presence of a phenyl group on C-3 of the aziridines, which can stabilize a partial positive charge being formed, caused an increase in the rate of the reaction, whereas the aliphatic aziridines were less reactive and needed more energetic conditions and longer times of contact (Experimental section). In accordance with earlier results [3] from our laboratory, neither the reaction rate nor the isomer distribution were altered by either the choice of solvent or the concentration of the fluoride ion introduced as potassium fluoride in the reaction mixture.

Treatment of the β-fluoro-α-amino nitriles or the β-fluoro-α-amino acid amides with aqueous or alcoholic hydrogen chloride solutions gave the β-fluoro-α-amino acids and esters in moderate to good yields depending on starting materials.

## Discussion

The mechanism of aziridine ring-opening reactions by nucleophiles has been widely discussed in the literature.[13] The regio- and stereo-chemistry of this reaction depend on the structure of the aziridine, the nature of the substituents, the nucleophile, and the reaction conditions in general.

When both *cis*- and *trans*-2,3-diphenylaziridines reacted with hydrogen fluoride in pyridine solution, Wade obtained a single fluoroamine which has been identified by cyclization as being the *threo*-isomer.[3] This result was explained by an $S_N1$-type mechanism involving the formation of a cation which rotates to its most stable conformation before the fluoride attack. Thus, taking into account the steric effects of the substituents, Wade thought that the isomer distribution could be explained.

Alvernhe *et al.* found that anhydrous hydrogen fluoride added to the *cis*- and *trans*-2,3-diphenylaziridines to give almost exclusively the *threo*- and *erythro*-fluoroamines respectively.[14] Here the reactive intermediate is the partially ring-opened aziridinium ion which undergoes a backside attack of the fluoride ion. Such a pathway implies that total invasion occurs at the carbon centre concerned.

In our experiments, the regiochemistry, the diastereoisomeric distribution, and the stereospecific ring-opening of the *cis*-2-aziridinecarboxylic acid amides (8)—(11) can be accounted for by an $S_N1/S_N2$ type mechanism as summarized in Scheme 3. Apart from the aziridines (1) and (2), fluorine attack was exclusively directed to C-3 indicating clearly the presence of a positive charge on this atom.

The fact that all the *cis*-2-cyanoaziridines exhibited the same isomer distribution (*i.e.* *threo*/*erythro* = 57/43) suggests an $S_N1$ type process for these compounds. Indeed, the inductive effect of the substituents (*i.e.* aryl groups are electron releasing, nitrile is electron attracting) favours the formation of a carbenium ion at the β position. This ion could rotate to its most stable conformation before the fluoride attack.†

The observation that when *cis*-2-amido-3-arylaziridines (8), (9), (10), and (11) were treated with hydrogen fluoride in pyridine solution, only the *threo*-β-fluoro-α-amino acid amides were obtained can be explained by the intervention of such a pathway, the steric interactions between the bulky $R^1$, $R^3$ (*i.e.* $CONH_2$) and $NHR^2$ groups hindering the formation of the rotamer B. This result could also be accounted for through an $S_N2$ mechanism, the aziridine ion undergoing a backside attack by the nucleophile (*i.e.* $F^-$) delivered by the pyridinium poly(hydrogen fluoride), because in the transition state the carbonium ion being formed is shielded by the departing nitrogen atom.[15]

The differences in the behaviour of aziridines with Olah's reagent and other halohydric acids (*i.e.* HCl, HBr, and HF), which combine with aziridines following a *trans*-opening process,[14,16] are probably caused by the differences in the ionizing and nucleophilic power of the former.

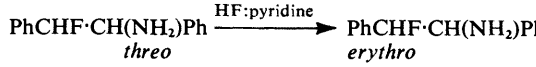
It is clear that the mechanism of the Olah's reagent ring-opening of aziridine is more complex than hitherto believed and requires further study. In any case, the advantages of this route toward β-fluorinated α-amino acids and their derivatives are: (i) the ease of handling the HF–pyridine reagent and the mild conditions of the reactions, (ii) the good yields of the products, and (iii) the high regiospecificity of the aziridine ring-opening. Moreover, the reaction is stereospecific for the *cis*-2-aziridine-carboxylic acid amides.

## Experimental

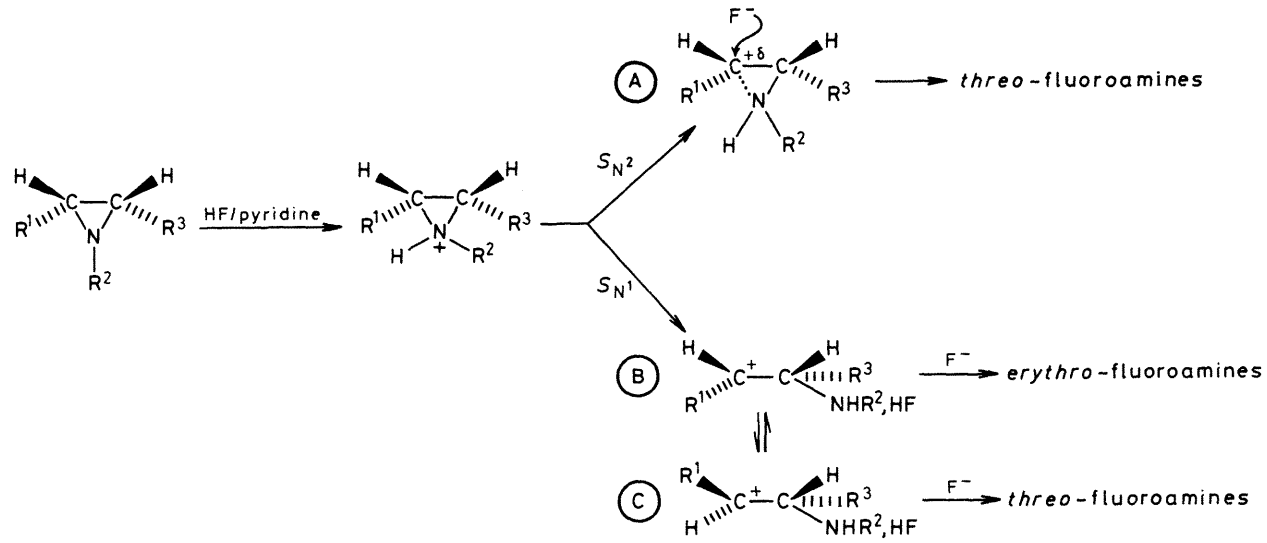
All m.p.s were determined on a Buchi 510 apparatus and are uncorrected: The i.r. spectra were recorded on a Leitz Model IIIG spectrometer. $^1H$ N.m.r. spectra were measured on a Varian EM 360 or A60 (60 MHz) and on a Bruker spectrospin W-80 (80 MHz). The spectra measured were of *ca.* 10—15% (w : v) solutions in $CDCl_3$, $(CD_3)_2SO$, or $D_2O$ using $SiMe_4$ or sodium 3-trimethylsilylpropanesulphonate as standards. $^{19}F$ N.m.r. spectra were recorded on a Bruker spectrospin WH-90-DS (84.67 MHz) spectrometer, in $CDCl_3$, $(CD_3)_2SO$, or DCl–$D_2O$ (1M), using $CFCl_3$ as a standard. Mass spectra were determined on a Ribler Mag 10-10 (electronic impact 70 eV) instrument.

* Primary fluorine atoms absorb [12] at 225 p.p.m. $< \delta <$ 210 p.p.m. from $CCl_3F$; Secondary fluorine absorbs [12] at 170 p.p.m. $< \delta <$ 200 p.p.m. and tertiary fluorine absorbs [12] at 140 p.p.m. $< \delta <$ 150 p.p.m.

† Alvernhe *et al.* reported the isomerization of the *threo*-1,2-diphenyl-2-fluoroethylamine by treatment with HF in pyridine solution (scheme 4).




We have never observed such an isomerization. When stirring was continued after the reaction of *cis*-2-cyanoaziridines with hydrogen fluoride in pyridine solution had ended, the diastereoisomeric distribution of the 2-amino-3-fluoro nitriles remained the same.




**Scheme 3.**

T.l.c. was carried out on Keiselgel $PF_{254}$ (Merck) (0.25 mm thickness). Silica gel used for column chromatography was Kieselgel 60 (Merck) (70—230 mesh ASTM). Dichloromethane and dimethyl sulphoxide were distilled from potassium hydroxide pellets and stored over activated molecular sieves. Acetonitrile was distilled from phosphorus pentaoxide before use. The 4-chlorocinnamonitrile was purchased from Aldrich (Belgium). All other solvents and reagents were of analytical grade and were purchased from Fluka AG (Switzerland).

*Procedures for the Preparation of 2-Cyanoaziridines.*—(*a*) The aziridines (1), (2), and (3) were prepared as indicated in ref. 18.

(*b*) The aziridines (4) and (6) were obtained as follows. A solution of α,β-dibromocinnamonitrile and 2,3-dibromo-3-(4-chlorophenyl)propionitrile (10 mmol) in dimethyl sulphoxide (150 ml) was saturated with dry ammonia gas (1h). The mixture was stirred for 8—12 h at room temperature, poured into aqueous sodium chloride, and extracted with benzene or dichloromethane. The organic layers were washed with water and dried over anhydrous magnesium sulphate. Removal of the solvent gave an oil which solidified on cooling. Recrystallization from benzene–diethyl ether (1 : 1) furnished white needles: compound (4) (2.52 g, 70%), m.p. 105—106 °C, $\nu_{max.}$ 3 330 (NH) and 2 220 $cm^{-1}$ (CN); $\delta_H(CDCl_3)$ 1.8 (s, NH), 3.14 and 3.25 (two AB quartets, $^3J$ 6.1 Hz, *cis*-aziridine ring protons),* 7.40 (s, $C_6H_5$); *m/z* 144 ($M^+$, 75.0) and 145 ($M^{+\cdot}$ + H, 100); compound (6) (3.35 g, 75%), m.p. 148—149 °C, $\nu_{max.}$ 3 335 (NH) and 2 220 $cm^{-1}$ (CN); $\delta_H(CDCl_3)$ 2,6 (s, NH), 3.08 and 3.45 (2 AB q, $^3J$ 6.5 Hz, *cis*-aziridine ring protons), and 7.3—7.45 (m, *p*-$ClC_6H_4$); *m/z* 178, 180 ($M^{+\cdot}$, 35.2, 23.7), 179, and 181 ($M^{+\cdot}$ + H, 100, 32.8).

(*c*) The aziridines (5) and (7) were prepared by treating methylamine (20 mmol) with 2,3-dibromocinnamonitrile and 2,3-dibromo-3-(4-chlorophenyl)propiononitrile (10 mmol) respectively, in dimethyl sulphoxide (150 ml). The mixture was stirred for 2 h and triethylamine (20 mmol) was added. The stirring was continued for an additional 24 h. Work-up was as above, and recrystallization from benzene yielded the products as white solids: compound (5) (2.92 g, 75%), m.p. 115—116 °C, $\nu_{max.}$ 2 225 $cm^{-1}$ (CN); $\delta_H(CDCl_3)$ 2.4 (s, $CH_3$), 2.75 (two overlapping AB q, $^3J$ 6.1 Hz, *cis*-aziridine ring protons), and 7.25—7.35 (m, $C_6H_5$); *m/z* 158 ($M^{+\cdot}$, 30.5), 159 ($M^{+\cdot}$ + H, 100); compound (7) (2.89 g, 70%), m.p. 123—124 °C; $\nu_{max.}$ 2 220 $cm^{-1}$ (CN); $\delta_H(CDCl_3)$ 2.4 (s, $CH_3$), 2.65 (two overlapping AB q, $^3J$ 6.1 Hz, *cis*-aziridine ring protons), 7.25 and 7.4 (m, *p*-$ClC_6H_4$); *m/z* 192, 194 ($M^{+\cdot}$, 30.5, 21.2), 193, 195 ($M^{+\cdot}$ + $H^+$, 100, 31.5).

(*d*) The aziridines (8)—(11) were obtained from the above 2-cyanoaziridines (4)—(7) (10 mmol), respectively, by treating them with potassium hydroxide (10 mmol) in water–alcohol (1 : 1, v : v) (15 ml), at room temperature for 7 days. After evaporation of solvents, the crude products were recrystallized from distilled water: compound (8) (0.88 g, 55%), m.p. 153—154 °C; $\nu_{max.}$ 3 380, 3 330 $cm^{-1}$ ($NH_2$, NH), 1 670 $cm^{-1}$ (CO); $\delta_H[(CD_3)_2SO]$ 2.85, 3.35 (two overlapping AB q, *J* 8 Hz, *cis*-aziridine ring protons), 3.5 (s, NH), 6.6—7.0 (m, $NH_2$), 7.15—7.5 (m, $C_6H_5$). Compound (9): (1.13 g, 65%), m.p. 184—185 °C, $\nu_{max.}$ 3 380 ($NH_2$) and 1 680 $cm^{-1}$ (CO); $\delta_H[(CD_3)_2SO]$ 2.35, 2.86 (AB q, *J* 7 Hz, *cis*-aziridine ring protons), 2.53 (s, $CH_3$), 6.9 (m, $NH_2$), 7.0—7.3 (m, $C_6H_5$); compound (10): (1.20 g, 60%), m.p. 178—180 °C; $\nu_{max.}$ 3 380, 3 330 $cm^{-1}$ ($NH_2$, NH), 1 675 $cm^{-1}$ (CO); $\delta_H[(CD_3)_2SO]$ 2.7, 3.4 (AB q, *J* 7.5 Hz, *cis*-aziridine ring protons), 3.38 (s, NH), 6.8 (s, $NH_2$), 7.3—7.5 (m, *p*-$ClC_6H_4$); compound (11): (1.23 g, 58%), m.p. 184—185 °C; $\nu_{max.}$ 3 385, 3 330 ($NH_2$), 1 670 $cm^{-1}$ (CO); $\delta_H[(CD_3)_2SO]$ 2.3, 2.85 (AB q, *J* 7.1 Hz, *cis*-aziridine ring protons), 2.55 (s, $CH_3$), 6.85 (m, $NH_2$), 7.35—7.40 (m, *p*-$ClC_6H_4$).

(*e*) *General Procedure for the Aziridine Ring-openings.*—All the fluorination reactions were carried out in Teflon flasks. The aziridine (10 mmol) in dichloromethane or dry benzene (10 ml) was added to a solution of hydrogen fluoride in pyridine (70 : 30, w/w) (10 ml) and the mixture was stirred at the conditions required for each starting material, and poured into water (10—15 ml). After neutralization at 0 °C with an ammonia solution (10%), the mixture was then carefully

* It has been shown that the pyramidal inversion around the trivalent nitrogen atom in azridine is relatively slow on the n.m.r. time scale at room temperature.[13,18,19] Since the *cis*-isomers in this series had consistently larger coupling constants and larger chemical shift differences than the *trans* ones,[18] if the aziridine (4) has the *trans*-configuration, the signals of the methine protons should be broad, while the *cis*-isomer should give two AB quartets. Thus the observation of the two AB quartets (*J* 6.1 Hz) indicates clearly that the aziridine (4) had the *cis*-configuration.

extracted with dichloromethane or ether (4 × 20 ml). The organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure on a water-bath (<40 °C). At this point n.m.r. measurements were made in order to determine the diastereoisomeric ratio (*i.e. threo* : *erythro*) or the regiochemistry of the adducts (*i.e.* relative abundance of β-fluoroamine to α-fluoroamine derivatives). Pure fluoroamines were obtained by column chromatography or by recrystallization.

*General Procedure for Acid Hydrolysis.*—The fluoroamino nitrile or amide (10 mmol) in a round-bottom flask was dissolved in aqueous HCl (12M) (15 ml) at 0 °C. The flask was stoppered and kept at 0 °C overnight. The mixture was then heated under reflux for 2—5 h, and allowed to cool to room temperature. The water was evaporated under reduced pressure. The resulting solid was dissolved in distilled water and again concentrated under reduced pressure. The 3-fluoro-2-amino acid hydrochlorides were obtained by chromatography on Dowex 50 cation exchange resin (200—400 mesh, $H^+$ form). The column was washed with distilled water until neutral. Elution was continued increasing the gradient of HCl (0.1M to 2M). The ninhydrin positive eluates were collected and evaporated to dryness under reduced pressure at water bath temperature (<40 °C). All β-fluoro-α-amino acids showed i.r. absorptions at $\nu_{max.}$ *ca.* 3 400—3 330 $cm^{-1}$ (OH, $NH_2$) and 1 670—1 700 $cm^{-1}$ (CO).

*General Acid Alcoholysis Procedure.*—The fluoroamino nitrile, amide or acid (10 mmol) was dissolved in HCl (approximately 3M in the alkyl alcohol) (30 ml), and the mixture was refluxed at oil-bath temperature with gentle stirring, for 10—12 h,* allowed to cool to 0 °C, and treated with pyridine until neutral (pH 6.5—7). The mixture was extracted with ether or methylene chloride (15 ml) in four portions. The organic layers were dried ($MgSO_4$) and the solvent was evaporated. I.r. and n.m.r. measurements could be made; mass spectra were also obtained from g.c.–m.s. couplings using a Ribbermag 10-10 mass spectrometer connected to Girdel S-30 gas chromatograph. (Carbowax capillary, glass, 20M.) The β-fluoro-α-amino acid esters have properties identical with those obtained by treating alkyl 3-phenylaziridinecarboxylates with HF–pyridine.

2-N-*t-Butylamino*-3-*fluoropropiononitrile* (12).—The aziridine (1) (2.48 g, 20 mmol) was treated with HF–pyridine (70 : 30, w/w) (10 ml) in anhydrous benzene (15 ml) at 40 °C for 5 days. Work-up gave an oil (2.7 g) containing starting material (30% by g.c.). Column chromatography (eluant hexane–ether, 9 : 1) yielded: (i) the starting aziridine (1) (0.60 g, 20%); (ii) 2-*N*-t-butylamino-3-fluoropropiononitrile (1.20 g, 45%) as an oil; hydrochloride, m.p. 163—164 °C, $\nu_{max.}$ 3 300 (NH) and 2 225 $cm^{-1}$ (CN); $\delta_H(CDCl_3)$ 0.85 [s, $C(CH_3)_3$], 1.8 (s, NH), 3.8 [dm, $^3J$ 4 Hz, $^3J'$ 25 Hz, CH(NHBu$^t$)], 4.35 (dm, $^3J$ 4 Hz, $^2J$ 46.5 Hz, $CH_2F$); $\delta_F$ 226.3 (dt, $^3J$ 25 Hz, $^2J$ 47.3 Hz); *m/z* 134 ($M^{+\cdot}$, 5.3, 135 ($M^{+\cdot}$ + H 35.6); (iii) 3-*N*-t-butylamino-2-fluoropropiononitrile (31) (0.35 g, 12%) as an oil; *hydrochloride*, m.p. 156—157 °C, $\nu_{max.}$ 3 330 $cm^{-1}$ (NH); $\delta_H$ 0.9 [s, $C(CH_3)_3$], 1.8 (s, NH), 4.07 [dm, $^3J$ 4 Hz, $^3J$ 24.5 Hz, $CH_2(NHBu^t)$], 4.4 (dt, $^3J$ 4 Hz, $^2J$ 47.5 Hz, CHF); $\delta_F$ 192.4 (m, $^3J$ 24.5 Hz, $^2J$ 47.5 Hz).

2-N-*Benzylamino*-3-*fluoropropiononitrile* (13). The aziridine (2) (3.16 g, 20 mmol) was treated with HF–pyridine (70 : 30, w/w) (20 ml) in benzene (15 ml) at 40 °C for 5 days. Work-up and column chromatography as above afforded: (i) the starting aziridine (2) (0.8 g, 25%); (ii) 2-*N*-benzylamino-3-fluoropropiononitrile (13) (1.78 g, 50%) as an oil; *hydrochloride* m.p. 147—148 °C, $\nu_{max.}$ 3 330 (NH) and 2 225 $cm^{-1}$ (CN); $\delta_H$ 1.85 (s, NH), 3.76 (c, $CH_2$), 3.8 (dm, $^3J$ 4.5 Hz, $^3J'$ 24 Hz, CHNH), 4.45 (dm, $^3J$ 4.5 Hz, $^2J$ 47.5 Hz, $CH_2F$), 7.3 (s, $C_6H_5$); $\delta_F$ 226.4 (dt, $^3J$ 24 Hz, $^2J$ 47.5 Hz); *m/z* 178 ($M^{+\cdot}$), 179 ($M^{+\cdot}$ + H); (iii) 3-*N*-benzylamino-2-fluoropropiononitrile (0.47 g, 15%); $\delta_H$ 2.0 (s, NH), 3.76 (s, $CH_2$), 4.1 (dm, $^3J$ 4.5 Hz, $^3J'$ 24.5 Hz, CHNH), 4.5 (dm, $^3$H 4.5 Hz, $^2J$ 45.5 Hz, CHF); $\delta_F$ 192.3 (m, $^3J$ 24.5 Hz, $^2J$ 45.5 Hz).

2-N-*Methylamino*-3-*fluorobutanonitrile* (14). The aziridine (3) (1.44 g, 15 mmol) was treated with HF–pyridine (15 ml) in dry benzene (10 ml) at 50 °C for 3 days. Work-up as described in general procedure (e) gave the adduct as a red oil (1.56 g), which consisted of the *threo*- and *erythro*-2-*N*-methylamino-3-fluorobutanonitriles in the ratio of 51 : 49. The product was obtained by column chromatography on silica gel; hydrochloride, m.p. 162—163 °C, $\delta_H$ 1.43, 1.55 (two overlapping doublets of doublets; $^3J$ 6.1 Hz, $^3J'$ 24 Hz, $CH_3$), 2.0 (s, NH), 2.5 (s, $CH_3N$), 3.65 [dd, $^3J$ 4 Hz, $^3J'$ 4 Hz, $^3J'$ 25.5 Hz, CHNH (threo)], 3.80 [dd, $^3J$ 5.1 Hz, $^3J'$ 12.5 Hz, CHNH (*erythro*)], 4.81 (dm, $^3J$ 4 Hz and 5.1 Hz, $^2J$ 47.5 Hz, CHF); $\delta_F$ 180.2 (m, $^3J$ 12.5 Hz, $^3J'$ 24 Hz, $^2J$ 46 Hz, *erythro*-(14)), 182.9 [m, $^3J$ 29.5 Hz, $^2J$ 46 Hz, *threo*-(14)]; *m/z* 116 ($M^{+\cdot}$, 15), 117 ($M^{+\cdot}$ + H, 100).

2-*Amino*-3-*fluoro*-3-*phenylpropiononitrile* (15).—The aziridine (4) (1.44 g, 10 mmol) was treated with HF–pyridine (70 : 30, w/w) (10 ml) in anhydrous dichloromethane (10 ml) at room temperature for 2 h. Work-up and evaporation of the solvent gave a mixture (57 : 43) of the *threo*- and *erythro*-β-*fluoro*-α-*amino nitriles* (15) (1.31 g, 80%). The isomers were separated by column chromatography [eluant, hexane–ethyl acetate (8 : 1)]. (i) *erythro*-(15), m.p. (benzene) 95—96 °C (Found: C, 65.75; N, 17.3; F, 11.4. $C_9H_9FN_2$ requires C, 65.85; N, 17.07; F, 11.58), $\nu_{max.}$ 3 390 and 3 330 ($NH_2$), and 2 230 $cm^{-1}$ (CN); $\delta_H(CDCl_3)$ 1.7 (s, $NH_2$), 4.30 (dd, $^3J$ 4.5 Hz, $^3J'$ 15 Hz, $CHNH_2$) 5.5 (dd, $^3J$ 4.1 Hz, $^2J$ 45.1 Hz, CHF), 7.3—7.4 (m, $C_6H_5$); $\delta_F$ 184.1 (dd, $^3J$ 15 Hz, $^2J$ 45.1 Hz); *m/z* 164 ($M^{+\cdot}$, 3.6), 137 ($M^{+\cdot}$ − HCN, 6.0), 109 ($C_7H_6F^+$, 100). (ii) *threo*-(15): δ-($CDCl_3$) 1.7 (s, $NH_2$), 4.12 (dd, $^3J$ 4.4 Hz, $^3J'$ 21 Hz, $CHNH_2$), 5.56 (dd, $^3J$ 4 Hz, $^2J$ 46.5 Hz, CHF), and 7.3—7.4 (m, $C_6H_5$); $\delta_F$ 188.7 (dd, $^3J$ 21 Hz, $^2J$ 46.5 Hz).

*Cyclisation of* threo-(15).—*threo*-2-Amino-3-fluoro-3-phenylpropiononitrile hydrochloride (2 g, 10 mmol), was dissolved in dry benzene (15 ml) and triethylamine (70 ml, 0.5 mol) and the mixture was heated under reflux for 5 days. Evaporation of the solvent and excess of triethylamine under reduced pressure on a water-bath yielded a residue which was dissolved in water (25 ml) and extracted with ether (4 × 15 ml). The organic layers were dried ($MgSO_4$) and the solvent was evaporated. The red oil which was obtained was chromatographed on a silica gel column [eluant, hexane–ether (85 : 15)]. *cis*-2-Cyano-3-phenylaziridine (4) was isolated in 45% yield.

2-N-*Methylamino*-3-*fluoro*-3-*phenylpropiononitrile* (16).—The aziridine (5) (1.58 g, 10 mmol) was treated with HF–pyridine (70 : 30, w/w) (10 ml) in anhydrous dichloromethane (10 ml) at room temperature for 2 h. Work-up gave a mixture (56.5 : 43.5) of the *threo*- and *erythro*-2-*N*-methylamino-3-fluorophenylpropiononitriles (16) (1.33 g, 75%), as a yellow solid. Although these isomers could be separated by column chromatography, the stereochemistry was readily deduced

* The yields could be improved when the mixture was allowed to stand in a refrigerator for 24 h before heating.

from the vicinal F–H coupling constants [20,21] ($^3J$ 22.5 and 12 Hz respectively) in the $^{19}F$ n.m.r. spectrum of the mixture. The pure compound (16) was obtained by crystallization from benzene; m.p. (of the mixture) 110—111 °C (Found: C, 67.3; N, 10.85; F, 10.35. $C_{10}H_{11}FN_2$ requires C, 67.41; F, 10.67; N, 15.73%) $\nu_{max.}$ 3 330 (NH) and 2 225 $cm^{-1}$ (CN). *erythro*-(16): $\delta_H(CDCl_3)$ 1.65 (s, NH), 2.63 (s, $CH_3$), 3.75 (dd, $^3J$ 6.1 Hz, $^3J'$ 12 Hz, $CHNHCH_3$), 5.46 (dd, $^3J$ 6.1 Hz, $^2J$ 45.5 Hz, CHF), 7.3—7.45 (m, $C_6H_5$); *m/z* 178 ($M^{+\cdot}$, 23.7) and 158 ($M^{+\cdot}$ – HF, 3.7). *threo*-(16): $\delta_H(CDCl_3)$ 1.65 (s, NH), 2.7 (s, $CH_3$), 3.75 (dd, $^3J$ 4 Hz, $^3J'$ 22.5 Hz, CHNH), 5.71 (dd, $^3J$ 4 Hz, $^2J$ 47.3 Hz, CHF), and 7.3—7.45 (m, $C_6H_5$); $\delta_F$ 189.3 (dd, $^3J$ 22.5 Hz, $^2J$ 47.3 Hz).

2-*Amino*-3-*fluoro*-3-(4-*chlorophenyl*)*propiononitrile* (17).—The aziridine (6) (1.78 g, 10 mmol) was treated with HF–pyridine (70 : 30, w/w) (10 ml) in anhydrous dichloromethane (10 ml) at room temperature for 2 h. Work-up gave a mixture (53 : 47) of the threo- and erythro-*fluoroamino nitriles* (17) (1.60 g, 80%). The isomers were separated by column chromatography. *erythro*-(17): m.p. 85—86 °C (Found: C, 54.35; H, 4.65; F, 9.40; N, 13.9. $C_9H_8ClFN_2$ requires C, 54.4; H, 4.03; N, 14.11; F, 9.57), $\nu_{max.}$ 3 380, 3 330 ($NH_2$), and 2 230 $cm^{-1}$ (CN); $\delta_H(CDCl_3)$ 1.8 (s, $NH_2$), 4.10 (dd, $^3J$ 5.0 Hz, $^3J'$ 14 Hz, $CHNH_2$), 5.50 (dd, $^3J$ 5.0 Hz, $^2J$ 44.5 Hz, CHF), and 7.35—7.5 (m, *p*-$ClC_6H_4$); $\delta_H$ 184.3 (dd, $^3J$ 14 Hz, $^2J$ 44.5 Hz); *m/z* 198, 200 [$M^{+\cdot}$ ($^{35}Cl$), $M^{+\cdot}$ ($^{37}Cl$) 16.6, 4.9], 178, 180 ($M^{+\cdot}$ – HF, 35.1, 12.5), 143, 145 ($C_7H_5ClF^+$, 100, 31.8); *threo*-(17), m.p. 88—90 °C, $\delta_H(CDCl_3)$ 2.0 (s, $NH_2$), 3.97 (dd, $^3J$ 4.0 Hz, $^3J'$ 21.0 Hz, $CHNH_2$), 5.52 (dd, $^3J$ 4.0 Hz, $^2J$ 46.1 Hz), and 7.3—7.5 (m, *p*-$ClC_6H_4$); $\delta_F$ 188.6 (dd, $^3J$ 21 Hz, $^2J$ 46.1 Hz).

2-N-*Methylamino*-3-*fluoro*-3-(4-*chlorophenyl*)*propiononitrile* (18).—The aziridine (7) (1.92 g, 10 mmol) was treated with NF–pyridine (70 : 30, w/w) (10 ml) as above. Work-up gave a mixture (56.3 : 43.7) of *threo*- and *erythro*-(18) as a crystalline solid (1.5 g, 78%), m.p. 123—124 °C. Although these isomers could be separated by column chromatography [eluant, hexane–ether (7 : 3, v/v)], the stereochemistry of each was readily deduced from the vicinal F–H coupling constants (*J* 22.5 Hz and 12 Hz respectively) in the $^{19}F$ n.m.r. spectrum of the mixture (Found: C, 56.55; H, 4.85; F, 8.75; N, 12.9. $C_{10}H_{10}ClFN_2$ requires C, 56.20; H, 4.83; F, 8.89; N, 13.11%, $\nu_{max.}$ 3 330 $cm^{-1}$ (NH) and 2 235 $cm^{-1}$ (CN); *erythro*-(18); $\delta_H(CDCl_3)$ 2.0 (s, NH), 2.5 (s, $CH_3$), 4.0 (dd, $^3J$ 5.5 Hz, $^3J'$ 12 Hz, CHNH), 5.57 (dd, $^3J$ 12 Hz, $^2J$ 45.7 Hz, CHF), 7.3—7.4 (m, *p*-$ClC_6H_4$); $\delta_F$ 181.9 (dd, $^3J$ 12 Hz, $^2J$ 45.7 Hz); *m/z* 212, 214 [$M^{+\cdot}$ ($^{35}Cl$), $M^{+\cdot}$ ($^{37}Cl$), 35.1, 12.7], 213, 215 ($M^{+\cdot}$ + H, 100, 37.6). *threo*-(18): $\delta_H(CDCl_3)$ 2.68 (s, $CH_3$), 3.75 (dd, $^3J$ 4.0 Hz, $^3J'$ 22.5 Hz,CHNH), and 5.75 (dd, $^3J$ 4.0 Hz, $^2J$ 47.2 Hz, CHF); $\delta_F$ 189.3 (dd, $^3J$ 22.5 Hz, $^2J$ 47.2 Hz).

threo-2-*Amino*-3-*fluoro*-3-*phenylpropionic Acid Amide* (19).—The aziridine (8) (1.62 g, 10 mmol) was treated with HF–pyridine (70 : 30, w/w) (10 ml) at room temperature for 2 h. Work-up gave a yellowish solid (1.85 g) which when recrystallized from water yielded threo-2-*amino*-3-*fluoro*-3-*phenylpropionic acid amide* (19) (1.45 g, 80%), m.p. 113—115 °C (Found: C, 59.25; H, 6.05, N, 15.30; F, 10.57. $C_9H_{11}N_2FO$ requires C, 59.34; H, 6.04; F, 10.43; N, 15.38%), $\nu_{max.}$ 3 500, 3 335 $cm^{-1}$ ($NH_2$), and 1 670 $cm^{-1}$ (CO); $\delta_H[(CD_3)_2SO]$ 4.15 (dd, $^3J$ 4.5 Hz, $^3J$ 26.0 Hz, $CHNH_2$), 5.65 (dd, $^3J$ 4.5 Hz, $^2J$ 45.7 Hz, CHF), 7.35—7.40 (m, $C_6H_5$); $\delta_H$ 192.3 (dd, $^3J$ 26.0 Hz, $^2J$ 45.7 Hz).

*Cyclization of* threo-(19).—The fluoroaminoamide (19) (hydrochloride) (2.18 g, 10 mmol) was dissolved in dry benzene (25 ml) and triethylamine (70 ml, 0.5 mol) and the mixture was refluxed for 5 days. The solvent and excess triethylamine were evaporated under reduced pressure on a water-bath (40—45 °C). The residue was dissolved with water and extracted with ether (4 × 15 ml). The organic layers were dried ($MgSO_4$) and the solvent was evaporated. The red oil which was obtained contained *cis*-2-amido-3-phenyl-aziridine (8) (40%) ($^1H$ n.m.r. and t.l.c. analysis). The aziridine (8) was isolated upon column chromatography (eluant hexane–ethyl acetate, 85 : 15).

erythro-2-*Amino*-3-*fluoro*-3-*phenylpropionic Acid Amide*.—*erythro*-Compound (19) was prepared by treating *erythro*-(15) (1.82 g, 10 mmol) with aqueous HCl (12M) (20 ml) at room temperature for 7 days. The water was evaporated and the solid residue dissolved in distilled water, which was again evaporated. The product was redissolved in water, cooled to 0 °C and treated with 10% ammonia solution until the pH was *ca.* 6.5. The mixture was extracted with dichloromethane (4 × 20 ml). The organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure on a water-bath. The solid residue, recrystallized from water, had m.p. 110—111 °C; $\delta_H(CDCl_3)$ 4.31 (dd, $^3J$ 5 Hz, $^3J'$ 16 Hz, $CHNH_2$), 5.85 (dd, $^3J$ 16 Hz, $^2J$ 45.2 Hz, CHF), 7.3—7.4 (m, $C_6H_5$); $\delta_F$ 188.2 (dd, $^3J$ 16.0 Hz, $^2J$ 45.2 Hz); *m/z* 182 ($M^{+\cdot}$, 24.7), 183 ($M^{+\cdot}$ +H, 100), and 109 ($C_7H_6F^+$, 13.5).

2-N-*Methylamino*-3-*fluoro*-3-*phenylpropionic Acid Amide* (20).—The aziridine (9) was treated with HF–pyridine (70 : 30, w/w) (10 ml) at room temperature for 2 h. Work-up gave a solid (1.80 g) which on recrystallization from water furnished threo-2-N-*methylamino*-3-*fluoro*-3-*phenylpropionic acid amide* (20) (1.5 g, 76%) as white needles, m.p. 123—124 °C; $\nu_{max.}$ 3 350, 3 330 ($NH_2$), and 1 675 $cm^{-1}$ (CO); $\delta_H(CDCl_3)$ 1.8 (s, NH), 2.51 (s, $CH_3$), 4.1 (dd, $^3J$ 4.1 Hz, $^3J'$ 25.5 Hz, CHNH), 5.63 (dd, $^3J$ 4.1 Hz, $^2J$ 46 Hz, CHF), 6.7 (m, $NH_2$), and 7.3—7.4 (m, $C_6H_5$); $\delta_F$ 193.1 (dd, $^3J$ 25.5 Hz, $^2J$ 46 Hz); *m/z* 196 ($M^{+\cdot}$, 23.5), 197 ($M^{+\cdot}$ + H, 75.1), and 109 ($C_6H_5$-$CHF^+$, 10.5).

2-*Amino*-3-*fluoro*-3-(4-*chlorophenyl*)*propionic Acid Amide* (21).—The aziridine (10) (1.96, 10 mmol) was treated with HF–pyridine (70 : 30, w/w) (10 ml) at room temperature for 2 h. Work-up yielded a yellow solid (2 g). Recrystallization from water afforded threo-2-*amino*-3-*fluoro*-3-(4-*chlorophenyl*)-*propionic acid amide* (21) (1.94 g, 85%), m.p. 134—135 °C (Found: C, 49.1; H, 4.65; F, 8.65; N, 12.95. $C_9H_{10}ClFNO$ requires C, 49.88; H, 4.61; F, 8.77; N, 12.93%), $\nu_{max.}$ 3 500, 3 330 ($NH_2$), and 1 670 $cm^{-1}$ (CO); $\delta_H$ [$(CD_3)_2SO$] 2.0 (s, $NH_2$), 3.52 (dd, $^3J$ 4.0 Hz, $^3J'$ 30.4 Hz, $CHNH_2$), 5.87 (dd, $^3J$ 4.0 Hz, $^2J$ 46.0 Hz, CHF), 7.1 (s, $NH_2$), 7.3—7.4 (m, *p*-$ClC_6H_4$); $\delta_F$ 192.8 (dd, $^3J$ 30.4 Hz, $^2J$ 46.0 Hz); *m/z* 216, 218 ($M^{+\cdot}$, 34.1, 24.7), 217, 219 ($M^{+\cdot}$ + H, 100, 34.5), and 143, 145 ($C_7H_5ClF^+$, 2.1, 0.9).

erythro-2-*Amino*-3-*fluoro*-3-(4-*chlorophenyl*)*propionic Acid Amide* (21).—This compound was obtained from *erythro*-(17) (1.98 g, 10 mmol) in the same manner as *erythro*-(19). After recrystallization from water, *erythro*-(21) (1.45 g, 65%) was isolated as a white solid, $\delta_H$[$(CD_3)_2SO$] 2.0 (s, $NH_2$), 3.7 (dd, $^3J$ 5.6 Hz, $^3J'$ 13.5 Hz, $CHNH_2$), 5.65 (dd, $^3J$ 5.6 Hz, $^2J$ 45.2 Hz, CHF), 7.10 (s, $NH_2$), and 7.3—7.4 (m, *p*-$ClC_6H_4$); $\delta_F$ 188.5 (dd, $^3J$ 13.5 Hz, $^2J$ 45.2 Hz).

2-N-*Methylamino*-3-*fluoro*-3-(4-*chlorophenyl*)*propionic Acid Amide* (22).—The aziridine (11) (2.1 g, 10 mmol) was treated with HF–pyridine (70 : 30, w/w) (10 ml) at room temperature for 2 h. Work-up and recrystallization from water afforded *threo*-2-*N*-methylamino-3-fluoro-3-(4-chlorophenyl)pro-

pionic acid amide (22) (1.85 g, 80%) as needles, m.p. 140—141 °C; $\nu_{max.}$ 3 500, 3 300 ($NH_2$), and 1 675 $cm^{-1}$ (CO); $\delta_H$-[$(CD_3)_2SO$] 2.0 (s, NH), 2.55 (s, $CH_2$), 3.5 (dd, $^3J$ 4.0 Hz, $^3J'$ 24.4 Hz, CHNH), 5.75 (dd, $^3J$ 4.0 Hz, $^2J$ 47.5 Hz, CHF), 6.9—7.0 (m, $NH_2$), 7.3—7.4 (m, *p*-$ClC_6H_4$); $\delta_H$ 187.2 (dd, $^3J$ 24.4 Hz, $^2J$ 47.5 Hz); *m/z* 230, 232 ($M^{+\cdot}$, 24.9, 8.2), 231, 233 ($M^{+\cdot}$ + H, 6.1, 1.7).

N-*t-Butyl*-3-*fluoroalanine* (23).—2-*N*-t-Butylamino-3-fluoropropiononitrile (12) (1.44g 10 mml) owas dissolved in aqueous HCl (12M; 15 ml) at 0 °C. The mixture was placed in a round-bottom flask, stoppered, kept in a refrigerator overnight, and then refluxed for 5 h. The water was evaporated and the resulting crude adduct was dissolved in distilled water (20 ml) and again reduced to dryness under reduced pressure. The solid obtained was dissolved in aqueous ethanol (20—25 ml), and the solution cooled to 0 °C and treated with pyridine until a pH of 6.5—7.0 was obtained. *N*-t-Butyl-3-fluoroalanine (23) (0.65 g, 40%) precipitated during 24 h at 0 °C and had m.p. 157—158 °C (decomp.); $\delta_H$($D_2O$ : DCl) 0.9 [s, $C(CH_3)_3$], 4.0 (dm, $^3J$ 4.5 Hz, $^3J'$ 29.5 Hz, CHNH), 4.6 (dm, $^3J$ 4.5 Hz, $^2J$ 47 Hz, $CH_2F$); $\delta_F$ 232.5 (d of t, $^3J$ 29.5 Hz, $^2J$ 47 Hz).

threo- *and* erythro-2-N-*Methylamino*-3-*fluorobutyric Acid* (24).—2-*N*-Methylamino-3-fluorobutyronitrile (14) (1.16 g, 10 mmol) was treated with aqueous HCl (12M; 15 ml) as above. The crude adduct (1.4 g) was dissolved in distilled water and applied to a Dowex 50 cation exchange resin column as described in the general procedure for acid hydrolysis. Evaporation of the water afforded 2-*N*-methylamino-3-fluorobutyric acid (24) (0.75 g, 55%), m.p. 202—203 °C; $\delta_H$($D_2O$–DCl) 1.51, 1.56 (2dd, $^3J$ 6 Hz, $^3J'$ 26.5 Hz, $CH_3$), 3.1 (s, $CH_3N$), 4.5, 4.37 (2dd, $^3J$ 2.5 Hz and 3 Hz, $^3J'$ 24 Hz and 14.2 Hz, CHN), 5.37, 5.42 (2 dm, $^2J$ 46 Hz, and 46.5 Hz); $\delta_F$ 183.4 [m, $^3J$ 24 Hz, $^3J'$ 14.2 Hz, $^2J$ 46.5 Hz, *erythro*-(24)], 201.3 [m, $^3J$ 24 Hz, $^3J'$ 26.5 Hz, $^2J$ 46 Hz, *threo*-(24)].

3-*Fluoro*-3-*phenylalanine* (25).—The 2-amino-3-fluoro-3-phenylpropiononitrile (15) (1.64 g, 10 mmol) was treated by aqueous HCl (12M; 15 ml) as above. The crude product was chromatographed on Dowex 50 cation exchange resin (200—400 mesh, $H^+$ form) as described in ref. 6. Evaporation of the eluant gave 3-fluoro-3-phenylalanine (25) (1.0 g, 60%), m.p. 172—173 °C (hydrochloride) (lit.,[6] 173—174 °C); (i) *threo*-(25) $\delta_H$($D_2O$–DCl) 4.73 (dd, $^3J$ 4.3 Hz, $^3J'$ 27 Hz, $CHNH_2$), 6.32 (dd, $^3J$ 4.3 Hz, $^2J$ 45.5 Hz, CHF), and 7.4—7.5 (m, $C_6H_5$); $\delta_F$ 198.5 (dd, $^3J$ 27 Hz, $^2J$ 45.5 Hz); (ii) *erythro*-(25) $\delta_H$($D_2O$–DCl) 4.95 (dd, $^3J$ 3.4 Hz, $^3J'$ 16 Hz, $CHNH_2$), 6.4, (dd, $^3J$ 3.4 Hz, $^2J$ 45 Hz, CHF), and 7.5 (m, $C_6H_5$); $\delta_F$ 194.2 (dd, $^3J$ 16 Hz, $^2J$ 45 Hz).

2-N-*Methyl*-3-*fluorophenylalanine* (26).—The α-amino-β-fluoronitrile (16) (1.78 g, 10 mmol) was dissolved in aqueous HCl (12M; 25 ml) at 0 °C, and kept at this temperature for 24 h. The mixture was refluxed on an oil-bath for 10 h. Work-up as above yielded 2-N-*methylamino*-3-*fluorophenylalanine* (26) (1.12 g, 57%). m.p. 178—180 °C. The stereochemistry of each isomer was deduced from the $^{19}F$ and $^1H$ n.m.r. spectra of the mixture. (i) *threo*-(26); $\delta_H$($D_2O$–DCl) 2.9 (s, $CH_3$), 4.7 (dd, $^3J$ 4.1 Hz, $^3J'$ 26.5 Hz, CHNH), 6.2 (dd, $^3J$ 26.5 Hz, $^2J$ 45 Hz, CHF), and 7.4—7.5 (m, $C_6H_5$); $\delta_H$ 196.3 (dd, $^3J$ 26.5 Hz, $^2J$ 45 Hz); (ii) *erythro*-(26), $\delta_H$($D_2O$–DCl) 2.85 (s, $CH_3$), 5.0 (dd, $^3J$ 4.0 Hz, $^3J'$ 15.5 Hz, CHNH), 6.5 (dd, $^3J$ 15.5 Hz, $^2J$ 44.5 Hz, CHF); $\delta_F$ 193.1 (dd, $^3J$ 15.5 Hz, $^2J$ 44.5 Hz).

3-*Fluoro*-(4-*chlorophenyl*)*alanine* (27).—The 2-amino-3-fluoro-3-(4-chlorophenyl)propiononitrile (17) (1.98 g, 10 mmol) was treated with aqueous HCl (12M) (25 ml) as above. Work-up and chromatography on Dowex 50 cation exchange resin (200—400 mesh, $H^+$ form) as described in ref. 6 gave a mixture (51 : 49) of the *threo*- and *erythro*-β-fluorinated α-amino acids (27) (1.2 g, 55%), m.p. 170—172 °C, which were identified by their signals in the $^{19}F$ and $^1H$ n.m.r. spectra: (i) *threo*-(27), $\delta_H$ ($D_2O$–DCl) 4.15 (dd, $^3J$ 4 Hz, $^3J'$ 30.5 Hz, $CHNH_2$), 6.35 (dd, $^3J$ 4 Hz, $^2J$ 45.5 Hz, CHF), and 7.3—7.45 (m, *p*-Cl-$C_6H_4$); $\delta_F$ 199.1 (dd, $^3J$ 30.5 Hz, $^2J$ 45.5 Hz). (ii) *erythro* (27) $\delta$($_H$$D_2O$–DCl) 4.3 (dd, $^3J$ 4.5 Hz, $^3J'$ Hz, $CHNH_2$) 6.43 (dd, $^3J$ 4.5 Hz, $^2J$ 45 Hz, CHF); $\delta_F$ 193.4 (dd, $^3J$ 14 Hz, $^2J$ 45 Hz).

threo-3-*Fluoro*-3-(4-*chlorophenyl*)*alanine*.—This was obtained when *threo*-2-amino-3-fluoro-3-(4-chlorophenyl)-propionic acid amide (21) (2.16 g, 10 mmol) was refluxed with aqueous HCl (12M; 15 ml) for 5 h. Work-up and chromatography as described in the general procedure for acid hydrolysis gave *threo*-(27) (1.35 g, 60%), m.p. 171—172 °C (decomp.)

2-N-*Methyl*-3-*fluoro*-3-(4-*chlorophenyl*)*alanine* (28).—The α-amino-β-fluoro nitrile (18) (2.12 g, 10 mmol) was treated with aqueous HCl (12M; 25 ml) as described for (17). 2-*N*-Methyl-3-fluoro-3-(4-chlorophenyl)alanine (28) (1.27 g, 55%) was obtained as a yellow solid, m.p. 170—173 °C (decomp) (i) *threo*-(28), $\delta_H$($D_2O$–DCl) 2.8 (s, $CH_3$), 4.15 (dd, $^3J$ 3.5 Hz, $^3J'$ 25.5 Hz, CHNH), 6.35 (dd, $^3J$ 3.5 Hz, $^2J$ 46.5 Hz, CHF), and 7.5 (m, *p*-Cl-$C_6H_4$); $\delta_F$ 197.8 (dd, $^3J$ 25.5 Hz, $^2J$ 46.5 Hz). (ii) *erythro*-(28) $\delta_H$($D_2O$–DCl) 2.75 (s, $CH_3$), 4.3 (dd, $^3J$ 4 Hz, $^3J'$ 13 Hz, CHNH), 6.4 (dd, $^3J$ 13 Hz, $^2J$ 45.5 Hz, CHF); $\delta_F$ 186.5 (dd, $^3J$ 13 Hz, $^2J$ 45.5 Hz).

threo-*Methyl*-3-*fluorophenylalanate* (29).—*threo*-2-Amino-3-fluoro-3-phenylpropionic acid amide (1.82 g, 10 mmol) was dissolved in methanolic HCl (3M; 30 ml) and the mixture was heated under reflux on an oil-bath. At intervals, samples of the solution were analysed by g.c. and t.l.c. [benzene–ethyl acetate (8 : 2 v/v]. After 10 h under reflux all the starting amide had been consumed. Work-up gave *threo*-methyl-3-fluorophenylalanate (29) (1.37 g, 70%) as a brown oil.

This product was dissolved in ether (15 ml), cooled to 0 °C, and treated with an ether–hydrochloric acid solution until no further precipitation was observed. The ether and the excess of HCl were evaporated under reduced pressure on a water-bath (<40 °C). Recrystallization from ethanol–ether afforded *threo*-(29)-hydrochloride, m.p. 165—167 °C; $\nu_{max.}$ 3 350, 3 330 ($NH_2$), and 1 715 $cm^{-1}$ (CO); $\delta_H$($CDCl_3$) 1.5 (s, $NH_2$), 3.7 (s, $OCH_3$), 3.74 (dd, $^3J$ 4 Hz, $^3J'$ 27.5 Hz, $CHNH_2$), 5.80 (dd, $^3J$ 4 Hz, $^2J$ 46.0 Hz, CHF), 7.2—7.4 (m, $C_6H_5$); $\delta_F$ 195.3 (dd, $^3J$ 27.5 Hz, $^2J$ 46 Hz); *m/z* 177 ($M^{+\cdot}$ − HF, 19.5), 88 ($CHNH_2COOCH_3$, 100), and 109 ($C_6H_5CHF^+$, 20.6).

erythro-*Methyl*-3-*Fluorophenylalanate* (29).—The *erythro*-2-amino-3-fluoro-3-phenylpropiononitrile (15) (1.64 g, 10 mmol) was dissolved in methanol in HCl (3M; 30 ml). Distilled water was added (0.1 ml) and the mixture was heated under reflux. G.c. and t.l.c. [benzene–ethyl acetate (8 : 2, v/v)] showed that after 12 h under reflux, the starting nitrile had been consumed. Work-up gave *erythro*-(29) (1.25 g, 65%) as an oil, $\delta_H$($CDCl_3$) 1.8 (s, $NH_2$), 3.8 (dd, $^3J$ 6 Hz, $^3J'$ 13.5 Hz, $CHNH_2$), 5.67 (dd, $^3J$ 6 Hz, $^2J'$ 44 Hz, CHF), and 7.2—7.4 (m, $C_6H_5$); $\delta_F$ 182.1 (dd, $^3J$ 13.5 Hz, $^2J$ 44 Hz).

*Isopropyl*-3-*Fluorophenylalanate* (30).—2-Amino-3-fluoro-3-phenylpropiononitrile (15) (1.64 g, 10 mmol) derived from the ring-opening of the aziridine (4) by HF–pyridine, was treated with HCl (3M in propan-2-ol) (30 ml) as described above. Work-up gave isopropyl 3-fluorophenylalanate (30) (1.73 g,

78%) as a brown oil, $\nu_{max.}$ 3 350, 3 330, ($NH_2$) and 1 720 $cm^{-1}$ (CO); (i) *threo*-(30) $\delta_H(CDCl_3)$ 1.17 [two overlapping doublets; $^3J$ 6.5 Hz, $(CH_3)_2CH$], 1.8 (s, $NH_2$), 3.7 (dd, $^3J$ 4.1 Hz, $^3J'$ 25.5 Hz, $CHNH_2$), 5.0 [septet, $^3J$ 6.5 Hz, $CH(CH_3)_2$], 5.73 (dd, $^3J$ 4.1 Hz, $^2J$ 46.7 Hz, CHF); $\delta_F$ 194.2 (dd, $^3J$ 25.5 Hz, $^2J$ 46.7 (Hz); *m/z* 225 ($M^{+\cdot}$, 0.2), 205 ($M^{+\cdot}$ − HF, 2.0), 138 ($C_8H_9NF^+$, 12.9), 116 ($\overset{+}{C}HNH_2CO_2Pr^i$, 27.9), 109 ($C_6H_5CHF$, 13.9); (ii) *erythro*-(30); $\delta_F$ 184.0 (dd, $^3J$ 13.5 Hz, $^2J$ 45.5 Hz).

This oil was dissolved in ahydrous ether (20 ml), cooled to 0 °C, and treated by an ether–hydrochloric acid solution until no further precipitation was observed. The solvent and excess HCl were evaporated and the solid residue was recrystallized from ethanol–ether to give isopropyl 3-fluorophenylalanate hydrochloride, m.p. 180—182 °C (lit.,[3] 182—183 °C).

threo-*Methyl* 3-*Fluoro*-3-(4-*chlorophenyl*)*alanate* (31).—This was prepared from *threo*-2-amino-3-fluoro-3-(4-chlorophenyl)propionic acid amide in the same manner as described for *threo*-(29). Work-up gave threo-*methyl* 3-*fluoro*-3-(4-*chlorophenyl*)*alanate* (1.85 g, 80%) as an oil which solidified on cooling and had m.p. 166—168 °C; $\nu_{max.}$ 3 350, 3 300 ($NH_2$), and 1 715 $cm^{-1}$ (CO); $\delta_H(CDCl_3)$ 1.8 (s, $NH_2$), 3.72 (dd, $^3J$ 3.5 Hz, $^3J'$ 26 Hz, $CHNH_2$), 3.81 (s, $OCH_3$), 5.8 (dd, $^3J$ 3.5 Hz, $^2J$ 46 Hz, CHF), 7.3—7.45 (m, *p*-$ClC_6H_4$); $\delta_F$ 192.5 (dd, $^3J$ 26 Hz, $^2J$ 46 Hz); *m/z* 231, 233 ($M^{+\cdot}$, 0.8), 211, 213 ($M^{+\cdot}$ − HF, 2.5), and 88 ($CHNH_2CO_2CH_3$, 100).

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