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# STEREOSPECIFIC SYNTHESIS OF 2-AMINO-3-FLUORONITRILES. PREPARATION OF β-FLUORO-α-AMINO ACIDS AND ESTERS

A.I. AYI * and R. GUEDJ
Laboratoire de Chimie Structurale Organique
UER-IMSP - Parc Valrose - 06034 NICE CEDEX

SUMMARY

The synthesis of some 2-amino-3-fluoro-nitriles and 2-amino-3-fluoro-acids and their esters have been achieved by means of a Strecker-type reaction. The method involved the action of amines with 3-fluoro-2-hydroxy-nitriles followed by acid solvolysis. The first step has been found to be stereospecific leading to the 2-amino-3-fluoronitriles with inversion of configuration at the carbon atom carrying hydroxyl.

## INTRODUCTION

Fluorinated aminoacids have been recently studied as possible antimetabolites and/or irreversible enzyme inactivators [1,2,3]. Some of these compounds have been prepared by direct fluorination of aminoacids [4], or hydroxyaminoacids [5,6] and reductive amination of 3-fluoro-2-ketoacids [7]. Often these methods lack generality and the yields of isolated products are sometimes low.
Our research team have described a route to alkyl 2-amino-3-fluoro acid esters which involved ring-opening reactions of some alkyl 2-aziridine-carboxylates by Olah's reagent, but any attempted ester cleavage by chemical means failed [8, 9,10].
Recently, we described briefly facile routes to these important compounds starting from 2-cyanoaziridines or 3-fluoro-2-hydroxynitriles [11,12]. This paper amplifies and extends the lastnamed method which enabled us to obtain a number of 2-amino-3-fluoro acids and esters in good yields (scheme 1).

The stereochemistry of the reaction, together with a plausible mechanism of hydroxyl group substitution in such cyanofluorohydrins, is disscussed.

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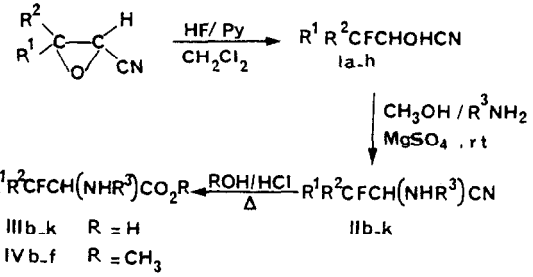



Scheme 1

RESULTS

The starting 3-fluoro-2-hydroxynitriles (Ia-Ih), have been prepared by the reaction of 2-cyanoepoxides with HF in pyridine solution (70:30, w:w) as previously described [13].

When (Ia-Ih) were treated with dry ammonia gas or amines (e.g. methylamine, α-methylbenzylamine) in methanol solution and in presence of anhydrous magnesium sulfate,* slow but complete conversion to 2-amino-3-fluoronitriles (IIb-k) was observed as showed by thin layer chromatography except for Ia and Ig. In these cases, the residual syrup obtained after evaporation of the solvent was complex (Table 1).

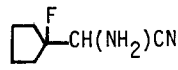
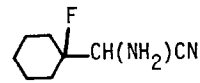
These aminonitriles were used in the next step for amino acid syntheses. Thus, treatment of (IIb), (IIc), (IId), (IIe), (IIf), (IIh) and (IIi) with hydrogen chloride (6N in water) at 0°C for 24h followed by heating under reflux for 2-5h led to 2-amino-3-fluoro-acids (IIIb-h) in about 60% yields. Analogously, the acid methanolysis provided a good method to methyl 2-amino-3-fluoro-acid esters (IVb-f) (Table 2).

We have also examined the stereochemistry of the reaction in order to obtain some interesting information on the mechanism of the Strecker reaction. Thus, when the mixtures of threo - and erythro- 3-fluoro-2-hydroxy-3-methylbutanonitrile (53/47) and threo- and erythro-3-fluoro-2-hydroxy-3-phenylbutanonitrile (55/45), derived from ring-opening of 2,3-epoxy-3-methylbutanonitrile 2,3-epoxy-3-phenylbutanonitrile, respectively, with Olah's reagent were treated with dry ammonia gas in methanol for ten days, the products obtained sisted of two diastereoisomeric fluorinated aminonitriles of the inverse ratios as shown by $^{19}F$ NMR of the crude mixtures : $\delta_F$ and $^3J_{FH}$ [14,15].

* When the reaction was carried without magnesium sulfate, a low yield (10-15%) of 2-amino-3-fluoro acid amide derived from the hydration of the aminonitrile was obtained.

Table 1

Action of amines with 3-fluoro-2-hydroxynitriles in methanol.

| Starting cyanofluorohydrine $R^1$ $R^2$ | N° | Amines | Product | N° | Yield (%) [a] |
|---|---|---|---|---|---|
| $CH_3$ H (T 56 / E 44) | Ia | $NH_3$ | complex mixture | | |
| $CH_3$ $CH_3$ | Ib | $NH_3$ | $(CH_3)_2CFCH(NH_2)CN$ | IIb | 85 |
| $C_2H_5$ $CH_3$ (T 57 / E 43) | Ic | $NH_3$ | $C_2H_5-\underset{CH_3}{C}FCH(NH_2)CN$ (T 42 / E 58) | IIc | 85 |
| $C_2H_5$ $C_2H_5$ | Id | $NH_3$ | $(C_2H_5)_2CFCH(NH_2)CN$ | IId | 85 |
| $-(CH_2)_4-$ | Ie | $NH_3$ |  | IIe | 85 |
| $-(C_2H)_5-$ | If | $NH_3$ |  | IIf | 85 |
| $C_6H_5$ H | Ig | $NH_3$ | $C_6H_5-C\equiv C-CN$ | IIg | 13 |
| $C_6H_5$ $CH_3$ (T 55 / E 45) | Ih | $NH_3$ | $C_6H_5-\underset{CH_3}{C}FCH(NH_2)CN$ (T 41 / E 59) | IIh | 80 |
| $CH_3$ $CH_3$ | Ib | $CH_3NH_2$ | $(CH_3)_2CFCH(NHCH_3)CN$ | IIi | 95 |
| $CH_3$ $CH_3$ | Ib | $C_6H_5\underset{CH_3}{C}HNH_2$ | $(CH_3)_2CFCH(NH\underset{CH_3}{C}HC_6H_5)CN$ | IIj | 90 |
| $C_2H_5$ $CH_3$ T | Ic | $NH_3$ | $C_2H_5-\underset{CH_3}{C}FCH(NH_2)CN$ (T 25 / E 75) | IIk | 85 |
| $C_2H_5$ $CH_3$ E | Ic | $NH_3$ | $C_2H_5-\underset{CH_3}{C}FCH(NH_2)CN$ (T 80 / E 20) | IIk | 82 |

[a] Yield of the crude aminonitrile obtained after evaporation of the methanol and excess ammonia.

Table 2

Acid hydrolysis and methanalysis of α-amino-β-fluoronitriles

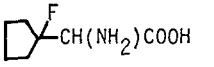
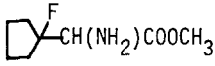
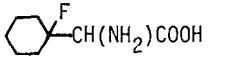
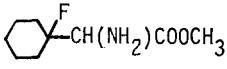
| N° | ROH /HCl | Product | N° | Yield (%) |
|---|---|---|---|---|
| IIb | R = H | $(CH_3)_2CFCH(NH_2)COOH$ | IIIb | 65 |
| | R = $CH_3$ | $(CH_3)_2CFCH(NH_2)CO_2CH_3$ | IVb | 80 |
| IIc | R = H | $C_2H_5\overset{CH_3}{\underset{|}{C}}FCH(NH_2)COOH$ | VIIc | 60 |
| | R = $CH_3$ | $C_2H_5\overset{CH_3}{\underset{|}{C}}FCH(NH_2)CO_2CH_3$ | IVc | 72 |
| IId | R = H | $(C_2H_5)_2CFCH(NH_2)COOH$ | IIId | 65 |
| | R = $CH_3$ | $(C_2H_5)_2CFCH(NH_2)CO_2CH_3$ | IVd | 85 |
| IIe | R = H |  | IIIe | 50 |
| | R = $CH_3$ |  | IVe | 65 |
| IIf | R = H |  | IIIf | 55 |
| | R = $CH_3$ |  | IVf | 65 |
| IIh | R = H | $C_6H_5\overset{CH_3}{\underset{|}{C}}FCH(NH_2)COOH$ | IIIh | 50 |
| IIi | R = H | $(CH_3)_2CFCH(NHCH_3)COOH$ | IIIi | 60 |
| IIj | R = H | $(CH_3)_2CFCH(NH\underset{CH_3}{\underset{|}{C}}HC_6H_5)COOH$ | IIIj | 21 |
| IIk | R = H | $(CH_3)_2CFCH(NH\underset{CH_3}{\underset{|}{C}}HC_6H_5)COOH$ | IIIk | 17 |

Table 3 :

Asymmetric synthesis of aminonitriles and aminoacids.

| $R^1R^2CFCHOHCN$ | Amine [a] | 2-amino-3-fluoronitriles | | | N-(2-methylbenzyl) aminoacids | |
|---|---|---|---|---|---|---|
| | | overall yield (%) [b] | $[\alpha]_{589}^{20°}$ [c] | de (±5%) [d] | overall yield (%) | $[\alpha]_{589}^{20°}$ [e] |
| $(CH_3)_2CFCHOHCN$ | (S)-(-)-Me | 41 | -69.2° | 70 | 21 | -11.57° |
| $(CH_3)_2CFCHOHCN$ | (R)-(+)-Me | 38 | +77.5° | 80 | 17 | +10.6° |

[a] (S)-(-)-Me, (S)-(-)-2-methylbebzylamine $[\alpha]_D^{20}$ -39° (neat),
(R)-(+)-Me, (R)-(+)-2-methylbenzylamine $[\alpha]_D^{23}$ +38°(neat).

[b] Yield of aminonitrile isolated by silica gel column chromatography.

[c] Spectroscopic grade methanol was used.

[d] The diastereoisomeric excess (de) is defined as follows:

$$de = \left| \frac{[threo] - [erythro]}{[threo] + [erythro]} \right| \times 100$$

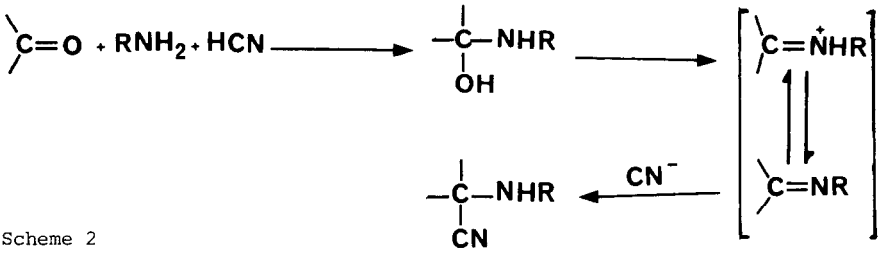
. Values were determined by $^{19}F$ NMR analysis.

[e] 6N HCl solution in distilled water.

When pure threo-IIc and erythro-IIc were reacted with ammonia, in methanol, mixtures of both threo-and erythro-aminonitriles were formed, the major product being the one with an inverted configuration at C-2 (Table 1). Moreover, when IIb was reacted with (S)-(-)- and (R)-(+)-2-methylbenzylamine at room temperature for a week, the aminonitriles which were isolated were optically active. Further acid hydrolysis of these aminonitriles yielded N-(2-methyl benzyl)-3-fluorovaline. The diastereoisomeric excess ranged from 65-80% after one recrystallization (Table 3).

DISCUSSION

The mechanism of the synthesis of 2-aminonitriles by the Strecker method has been widely discussed in the literature [16]. The formation of the aminonitriles is generally explained through a process which involves an enamine (or an enamonium ion) derived from the amino alcohol formed in situ (Scheme 2).




Scheme 2

In our case, the stereospecificity, the inversion of the configuration that occurs at the hydroxylic carbon atom can be clearly explained by a $S_N2$-type mechanism as suggested in Fig. 1.

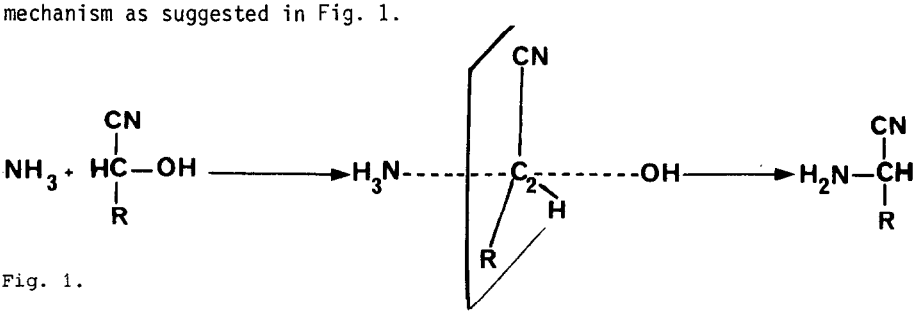



Fig. 1.

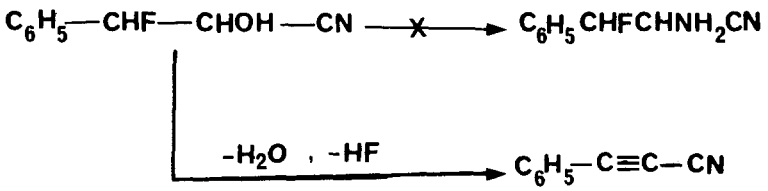
The substitution of the alcoholic group seems to proceed through an initial attack of the unshared electron-pair of the nitrogen at the carbon atom C-2 simultaneously with the departure of the hydroxyl.
Depending on the structure of the starting fluorocyanohydrins, this major process can be accompanied by elimination of hydrogen fluoride and water.

## Influence of the fluorine at position 3

The introduction of a fluorine atom at the position 3 of the cyanhydrins seems to cause a decreasing of the rate of the reaction since several days (7-10) were required to convert 3-fluoro-2-hydroxynitriles to the corresponding aminonitriles, while only 48h or less are generally quite enough for nonfluorinated cyanohydrins [17].
This fact can be explained by the electron withdrawing effect of the fluorine atom which strengthens the C-OH bond.

Influence of the starting cyanofluorohydrins

The observation that when 3-fluoro-2-hydroxynitriles of the type $R^1CHFCHOHCN$ were reacted with ammonia in methanol, no aminonitriles were obtained, but only a low yield of an unsaturated nitrile (i.e. for $R^1 = C_6H_5$) can be interpreted by the formation of an intermediate which eliminated water and hydrogen fluoride (Scheme 3).




Scheme 3

Evidence for $S_N2$ reaction

The substitution of the alcoholic function in 3-fluoro-2-hydroxynitriles of the $R^1R^2CFCHOHCN$ type by the amino group can be compared with the intramolecular displacement of the same function in 2-amino alcohols, reaction which is a well-known route for the preparation of aziridines [18].
This cyclisation of 2-amino alcohols was firmly established and demonstrated to proceed through a Walden inversion at the alcoholic carbon atom [18,19]. This result and our own described above, clearly indicated that the reaction proceeded probably through a bimolecular process. We think that there is a partial positive charge on the carbon C-2 and that the pathway (i.e. substitution or elimination) depends upon the ability of the system to stabilize a full positive charge. Even though, the formation of 2-aminonitriles by the Strecker method has been accounted by an enamine derived from the aminoalcohol formed in situ, we think that the 2-amino-3-fluoro-alcohols which may be formed in our cases, may not be stable. Actually, no amino alcohol was detected by the spectrometric analysis as shown by IR, $^1H$ and $^{19}F$ NMR of the crude product from (Ib-h).
We therefore favor the $S_N2$ mechanism.

EXPERIMENTAL

All melting points were determined on a Kofler block apparatus and are uncorrected. IR spectra were recorded on a Leitz Model IIIG or on a Perkin Elmer 577 spectrometers. $^1H$ NMR were measured on a Varian EM360 or a Jeol A60 (60 MHz)

and on a Bruker Spectrospin W80 (80 MHz). $^{19}F$ NMR spectra were obtained with a Bruker Spectrospin WH 90 DS (84,67 MHz). Mass spectra were determined on a Ribber Mag 10-10 (electronic impact 70 eV) instrument connected to a Girdel S-30 gas chromatograph (Carbowax, capillary, glass, 20m). Optical rotations were performed with a Roussel-Jouan automatic polarimeter.

General procedure for the formation of 2-amino-3-fluoronitriles

The 3-fluoro-2-hydroxynitrile (10-20 mmol) was dissolved in 15 ml of distilled methanol. 0.5 g of anhydrous magnesium sulfate was added. The mixture was cooled and dry ammonia gas, methylamine or 2-methylbenzylamine was introduced. The mixture was allowed to warm to room temperature and kept under this temperature for the time required for each product. The reaction was followed by thin layer chromatography and/or gas chromatography. At the end, the magnesium sulfate was filtered off, the methanol was evaporated in vacuo and the residual oil was applied to chromatography on a silica gel column.

General procedure for the acid hydrolysis

The crude 2-amino-3-fluoronitrile was used in this case without further purification. Water (10 ml) was added to the oily product from the experiment above and the mixture was cooled to 0°C. Concentrated HCl (sp.gr.1.19) (15-20 ml) was carefully added at this temperature. The mixture was maintained in a refrigerator overnight and then heated under reflux on a oil bath with gentle stirring for 2-6h. The excess hydrochloric acid and the water were evaporated under reduced pressure. Water (3x10 ml) was added to the residual solid and the solution again evaporated to dryness. The resulting aminoacid hydrochloride was dissolved in distilled water and treated at 0°C with pyridine until pH 6.5 was reached. The crude fluorinated aminoacid which was obtained after evaporation of the water can be purified by recristallization (Ethanol:water 90:10 v:v) or by chromatography on Dowex 50 cation exchange resin (200-400 mesh, $H^+$ form). The column was eluated with distilled water until neutral and with aqueous HCl solutions increasing the gradient of HCl (0.1N-2N). The ninhydrin positive eluates were collected and evaporated to dryness under vacuo at water bath temperature (≃ 40°C). The IR spectrum (KBr) of the product showed an absorption band at 1600-1620 $cm^{-1}$ due to C=O stretching and 3300-3450 $cm^{-1}$ attributed to $\overset{+}{N}H_3$ or $\overset{+}{N}H_2R$.

General procedure of the acidic methanolysis

The crude 2-amino-3-fluoronitrile was dissolved in methanol (25 ml) and the solution was cooled to 0°C. Dry hydrogen chloride gas was passed through the solution with continuous cooling for 0.5h. The mixture was stirred at 0°C for 10h warmed at reflux for 10-12h, allowed to cool to 0°C and treated with pyridine until neutral. The mixture was extracted with ether (4 x 15 ml). The organic layers were dried ($MgSO_4$) and the solvent was evaporated under vacuo. The IR spectrum ($CHCl_3$) of the product showed a strong absorption band at 1680-1730 $cm^{-1}$ due to C=O striching and at 3300-3400 $cm^{-1}$ attributed to $NH_2$ or NHR. The mass spectrum was obtained from G.C.-M.S. coupling. The $^1H$ NMR showed a singlet at 3.85 ppm due to $OCH_3$.

2-Amino-3-fluoro-3-methylbutanonitrile (nc) (II b)

From 10 mmol of Ib, IIb was obtained after 7 days of reaction time. Chromatography on a silical gel column (eluant hexane:ether 85:15).
Yield : 80% ; IR 3330 $cm^{-1}$($NH_2$) ; 2220 $cm^{-1}$ (CN) ; $\delta_H$ ($CDCl_3$/TMS) 1.48 and 1.81 (2d,6H, $^3J_{FH}$ = 22 Hz and 13 Hz respectively, $C(CH_3)_2$), 3.0 (s, 2H, $NH_2$), 3.73 (d, 1H, $^3J_{FH}$ = 14.5 Hz, $CH(NH_2)$ ; $\delta_F$($CDCl_3$/$CCl_3F$) 149.15 (m, $^3J_{FH}$ = 14 Hz, $^3J_{FH}$ = 22 Hz) ; m/e 116 ($M^+$, 1.2), 117 ($M^+$ + H, 5.3), 61 ($(CH_3)_2$ + CF, 35).

2-Amino-3-fluoro-3-methylpentanonitrile (nc)(IIc)

Threo- and erythro-IIc were obtained in a similar manner as the above starting from the fluorhydrin (Ic) derived from ring-opening of 2-3 epoxy-3-methylbutanonitrile with HF/pyridine (70/30, w/w). Evaporation of the solvent afforded a yellowish liquid. Chromatography as above gave the pure compound.
In a similar experiment, the two 2-amino-3-fluoronitriles (threo and erythro), were separated by chromatography over a silica gel column (Woelm, activity grade I). The column was eluted with hexane/ether (95/5, 20 ml).
IR ($CHCl_3$) 3335 $cm^{-1}$ ($NH_2$), 2220 $cm^{-1}$ (CN) ; threo-(IIc) $\delta_H$ ($CDCl_3$/TMS) 0.98 (t, 3H, $^3J_{HH}$ = 6.5 Hz, $CH_3CH_2$), 1.45 (d, 3H, $^3J_{FH}$ = 22 Hz, $CH_3CF$), 1.6-2.4 (m, 2H, $CH_2$), 3 (s broad, 2H, $NH_2$), 3.7 (d, 1H, $^3J_{FH}$ = 16 Hz, $CH(NH_2)$ ; $\delta_F$($CDCl_3$/$CCl_3F$) 159.2 (unresolved multiplet) ; erythro-(IIc) $\delta_H$ 1 (d, 3H, $^3J_{HH}$= 6.5 Hz, $CH_3CH_2$) ; 1.48 (d, 3H, $^3J_{FH}$ = 22 Hz, $CH_3CF$), 1.6-2.4 (m, 2H, $CH_2$), 3.0 (s broad, 2H, $NH_2$), 3.72 (d, 1H, $^3J_{FH}$ = 15 Hz, $CH(NH_2)$) ; $\delta_F$($CDCl_3$/$CCl_3F$) 158.1 (unresolved multiplet) ; m/e (of the mixture) 130 ($M^+$, 2.5), 75 ($C_2H_5CFCH_3$).

2-Amino-3-fluoro-3-ethylpentanonitrile (nc)(IId)

This product was prepared as described for (IIb) after 7 days of reaction starting from 10 mmol of (Id). Yield 78%. IR ($CHCl_3$) 3330 $cm^{-1}$ ($NH_2$), 2225 $cm^{-1}$ (CN); $\delta_H$($CDCl_3$/TMS) 1.0, 1.2 (2t, 6H, $^3J_{HH}$ = 6.5 Hz, $2CH_3$), 1.5-2.3 (m, 4H, $2CH_2$), 3.0 (s broad, 2H, $NH_2$), 3.71 (d, 1H, $^3J_{FH}$ = 20 Hz, C<u>H</u>($NH_2$)), $\delta_F$($CDCl_3$/$CCl_3F$), 164.57 (apparent sextuplet, $^3J_{FH}$ = 20 Hz) ; m/e 144 ($M^+$, 2), 89 (($C_2H_5)_2CF^+$, 39.5).

2-Amino-2-(1-fluorocyclopentyl)ethanonitrile (nc)(IIe)

The title compound was obtained as above (7 days, room temperature). Yield 75%. IR ($CHCl_3$) 3335 $cm^{-1}$ ($NH_2$), 2220 $cm^{-1}$ (CN) ; $\delta_H$ ($CDCl_3$/TMS) ; 1.5-2.5 (m, 8H, $CH_2)_4$), 2.8 (s, broad, 2H, $NH_2$), 3.78 (d, 1H, $^3J_{FH}$ = 20 Hz, C<u>H</u>$NH_2$) ; $\delta_F$($CDCl_3$/$CCl_3F$) 155.8 (unresolved multiplet ; m/e 142 ($M^+$, 5.5) ; 122 ($M^+$-HF, 3), 115 ($M^+$-HCN, 15).

2-Amino-2-(1-fluorocyclohexyl) ethanonitrile (nc)(IIf)

IIf was obtained in the same manner as IIe. Yield 78% IR($CHCl_3$) 3335 $cm^{-1}$ ($NH_2$), 2220 $cm^{-1}$ (CN) ; $\delta_H$ ($CDCl_3$/TMS) 1.25-2.3 (m, 10H, $(CH_2)_5$), 3 (s, broad, 2H, $NH_2$) 3.78 (d, 1H, $^3J_{FH}$ = 18.5 Hz, C<u>H</u>$NH_2$) ; $\delta_F$($CDCl_3$/$CCl_3F$), 164.1 (unresolved multiplet) ; m/e 156 ($M^+$, 2), 136 ($M^+$-HF, 6.3), 129 ($M^+$-HCN, 1).

2-Amino-3-fluoro-3-phenylbutanonitrile (nc)(IIh)

When (Ih) was reacted with ammonia in anhydrous methanol for 7 days, (IIh) was obtained. The crystalline solid,which was isolated after chromatography, melted at 106-108°C. IR ($CHCl_3$) 3330 $cm^{-1}$ ($NH_2$), 2220 $cm^{-1}$ (CN).
Although the threo and erythro isomers could be separated by column chromatography, the stereochemistry was deduced from the vicinal F-H coupling constants and $^{19}F$ chemical shifts.
$\delta_H$ ($CDCl_3$/TMS) 1.73, 1.76 (2d, 3H, $^3J_{FH}$ = 22 Hz, $CH_3CF$), 3.5 (s, broad, 2H, $NH_2$), 4.58, 4.50 (2d, 1H, $^3J_{FH}$ = 16.5 Hz, 13.8 Hz C<u>H</u>$NH_2$, threo and erythro respectively), 7.44 (s, $C_6H_5$) ; $\delta_F$ ($CDCl_3$/$CCl_3F$) 154.0 (dq, $^3J_{FH}$ = 16.5 Hz, $^3J'_{FH}$ = 22 Hz, threo), 150.2 (dq, $^3J_{FH}$ = 13.8 Hz, $^3J'_{FH}$ = 22 Hz, erythro) ; m/e (of the mixture) 178 ($M^+$, 2.5) 179 ($M^+$+H, 35).

2-N-Methylamino-3-fluoro-3-methylbutanonitrile (nc)(IIi)

To a solution of 10 mmol of (Ia) in 15 ml of methanol containing 0.50 g of ($MgSO_4$) was added 20 mmol of condensed methylamine. The mixture was kept at room temperature for 5 days. The solvent and excess methylamine were evaporated under reduced pressure. The yellow liquid which was obtained was applied to a column chromatography (Hexane:ether 90/10). Yield 85%.
IR ($CHCl_3$) 3310 $cm^{-1}$ (NH), 2220 $cm^{-1}$ (CN) ; $\delta_H$ ($CDCl_3$/TMS) 1.45, 1.80 (2d, 6H, $^3J_{FH}$ = 21.5 Hz, $(CH_3)_2CF$), 2.5 (s, 3H, $CH_3N$), 3.67 (d, 1H, $^3J_{FH}$ = 15 Hz, $C\underline{H}NH(CH_3)$) ; $\delta_F(CDCl_3/CCl_3F)$ 148.3 (doublet of sextets) ; m/e 130 ($M^+$, 5.5), 61 ($(CH_3)_2CF^+$, 15).

(-)-2-[N-α-Methylbenzylamino]-3-fluoro-3-methylbutanonitrile (nc)(IIj)

To a solution of 10 mmol of (Ia) in 15 ml of anhydrous methanol, containing 0.50 g of $MgSO_4$, was added at 0°C 10 mmol of (S)-(-)-α-methylbenzylamine. The mixture was kept at room temperature for 10 days. The methanol was evaporated and the slight yellow oil which was obtained was applied to chromatography on a silica gel column (benzene:ethylacetate 95:5). Yield 41% (liq).
IR ($CHCl_3$) 3330 $cm^{-1}$ (NH), 2220 $cm^{-1}$ (CN) ; $\delta_H$ 1.23 (d, 3H, $^3J_{HH}$ = 6 Hz, $C\underline{H}_3CH$), 1.4 (2d, 6H, $^3J_{FH}$ = 20 Hz, $(CH_3)_2CF$), 3.3 (d, 1H, $^3J_{FH}$ = 13 Hz, $C\underline{H}NH$), 4.1(q, 1H, $^3J_{FH}$ = 6 Hz, $C\underline{H}CH_3$), 7.3 (s, 5H, $C_6H_5$) ; m/e 220 ($M^+$ 6.5), $[\alpha]_{589}^{20}$ = -69° (c = 1.1, MeOH).
The product was dissolved in anhydrous ether (10 ml), cooled at 0°C and treated with an ether:hydrochloric acid solution until no further precipitation was observed. The ether and excess HCl were evaporated and the solid residue was recrystallized from ethanol:ether.m.p. 112-113°C ; $[\alpha]_{589}^{20}$ = -71.5° (c = 1.5, 6N, HCl).
$\delta_F(CDCl_3/CCl_3F)$
(2S, 2'S)-2-[N-2'-methylbenzylamino]-3-fluoro-3-methylbutanonitrile :
118.34 (heptet) 15% of overall yield.
(2R, 2'S)-2-[N-2'-methylbenzylamino]-3-fluoro-3-methylbutanonitrile :
147.37 (heptet) 85% of overall yield.
The yiels and optical rotations of (IIj) prepared under differents reaction times are as follow : 3 days, 11%, $[\alpha]_{589}^{20}$ = -105° ; 5 days, 17%, $[\alpha]_{589}^{20}$ = -89°7; 7 days, 26.5%, $[\alpha]_{589}^{20}$ = - 78°.

(+)-2-[N-α-Methylbenzylamino]-3-fluoro-3-methylbutanonitrile (nc)(IIh)

This product was obtained in the same manner as described above starting from 10 mmol of (Ia) and 10 mmol of (+)-2-methylbenzylamine (7 days). Yield 38% (liq) $[\alpha]_{589}^{20}$ = +77.5° (c = 2.67, MeOH).

$\delta_H$($CDCl_3$/TMS) 1.23 (d, 3H, $^3J_{HH}$ = 6 Hz, $C\underline{H}_3$-CH), 1.1 and 1.5 (2d, 6H, $^3J_{FH}$ = 22 Hz, $(CH_3)_2CF$), 3.35 (d, 1H, $^3J_{FH}$ = 13 Hz, C<u>H</u>NH), 4.1 (q, 1H, $^3J_{HH}$ = 6 Hz, C<u>H</u>$CH_3$), 7.3 (s, 5H, $C_6H_5$).

$\delta_F$($CDCl_3$/$CCl_3F$) (2R, 2'R)-2-[N-2'-methylbenzylamino]-3-fluoro-3-methylbutanonitrile : 147.46 (heptet) 10% of overall yield ; (2S, 2'R)-2-[N-2'-methylbenzylamino]-3-fluoro-3-methylbutanonitrile : 148.58 (heptet) 90% of overall yield.

3-Fluorovaline (IIIb)

A solution of 3-fluoro-2-hydroxy-3-methylbutanonitrile (10 mmol) in methanol was saturated at -78°C with dry ammonia gas. The mixture was kept at room temperature for 10 days. The methanol and excess ammonia were evaporated in vacuo. The residual syrup was mixed with 10 ml of water, cooled to 0°C and 15 ml of concentrated hydrochloric acid was carefully added at this temperature. The mixture was kept at 0°C for 24 h and refluxed for 4 h. The water and excess HCl were removed under reduced pressure ; the solid residue was dissolved in distilled water and again concentrated in vacuo. The resultant 3-fluorovaline hydrochloride was dissolved in about 15 ml of ethanol, cooled to 0°C and treated with pyridine to precipitate crude IIIb. Pure 3-fluorovaline was obtained by recrystallization from ethanol:water (90:10) m.p. 193-194°C, lit. 204°C [6].

3-Fluoroisoleucine (IIIc) and 2-amino-3-ethyl-3-fluoro-pentanoïc acid (IIId) were obtained and purified in the same manner.

3-Fluoroisoleucine m.p. 170-172°C, yield 60%.

2-Amino-3-ethyl-3-fluoropentanoïc acid (nc) m.p. 201-203 (IIId)
Yield 65%, $\delta_H$ ($D_2O$ : DCl/DSS) 1.0 (poorly resolved triplet, 6H, $^3J_{HH}$ = 6.5 Hz, $2CH_3$, 1.5-2.4 (m, 4H, $2CH_2$), 4.50 (d, 1H, $^3J_{FH}$ = 18 Hz, $CHNH_2$)
$\delta_F$ ($D_2O$ : DCl/$CCl_3F_{ext}$), 153.8 (poorly resolved quintet).

(1-Fluorocyclopentyl) glycine (IIIe)

After acid hydrolysis, the titled product was isolated by the use of a Dowex 50 column as described in the general procedure. m.p. 194-195°C, yield 50%.

(1-Fluorocyclohexyl) glycine (IIIf)

Was obtained and purified in the same manner as above. m.p. 185-186°C, yield 55%.

3-Fluoro-3-methylphenylalanine (IIIh)

The 2-amino-3-fluoro-3-methylphenylpropionitrile (IIh) was mixed with 20 ml of 6N HCl at 0°C, kept at this temperature for 24 h and then heated under reflux for 6 h. The water and the hydrochloric acid was evaporated to dryness under reduced pressure. Ethanol was added to the residue and the solution was filtred to remove insoluble impurities. The clear solution was cooled to 0°C and pyridine was added until pH 6.5. On standing in a refrigerator for 24 h, (IIIh) precipitated. This sample containing ammonium chloride was purified by recrystallization from alcohol:water (90:10), m.p. 158-160°C, yield 50%.

N-Methyl-3-fluorovaline (nc)(IIIi)

The aminonitrile (IIi) (10 mmol) was treated as described for (IIb). The crude N-methyl-3-fluorovaline hydrochloride was dissolved in a small amount of water and the solution was applied to a Dowex 50 column as described earlier.
m.p. 178-179°C, yield 60%
$\delta_H$ ($D_2O$ : DCl/DSS), 1.45, 1.9 (2d, 6H, $^3J_{FH}$ = 22 Hz, $(CH_3)_2CF$), 3.15 (s, 3H, $CH_3N$), 4.4 (d, 1H, $^3J_{FH}$ = 14.5 Hz, C<u>H</u>(NH )) ;
$\delta_F$ ($D_2O$ : DCl/$CCl_3F_{ext}$) - 152.2 (doublet of heptets)

(-)-[N-α-Methylbenzyl]-3-fluorovaline (nc)(IIIj)

(-)-2-[N-( α -methylbenzylamino)]-3-fluoro-3-methylbutanonitrile (10 mmol) was dissolved in 15 ml of 6N hydrochloric acid at 0°C. The solution was kept at this temperature for 24 h and heated under reflux for 4 h. The water and the excess of hydrochloric acid were evaporated to dryness as described in the general procedure. The solid residue was dissolved in ethanol, filtered and treated at 0°C with pyridine until pH 6.5. The fluorinated aminoacid precipated. Recrystallization from ethanol:water (90:10) afforded (IIIj).
m.p. 189-190°C, yield 21%
$\delta_H$ ($D_2O$ : DCl/DSS) 1.9 (d, $^3J_{HH}$ = 6.5 Hz, C<u>H</u>$_3$CH), 1.45, 1.8 (2d, $^3J_{FH}$ = 16 Hz, $(CH_3)_2CF$), 4.25 (q, 1H, $^3J_{HH}$ = 6.5 Hz), 4.5 (d, 1H, $^3J_{FH}$ = 13 Hz, C<u>H</u>NH), 7.45 (s, 5H, $C_6H_5$).
$[\alpha]_{580}^{20}$ = -11.47° (c = 1.7, 6NHCl).

(+)-N-(α-methylbenzyl)-3-fluorovaline (nc)

The titled product was obtained as above starting with (+)-2-[N-(α-methylbenzylamino)]-3-fluoro-3-methylbutanonitrile. m.p. 188-190°C, yield 17%. $[\alpha]_{589}^{20}$ = +10,5° (c = 2, 6NHCl).

## CONCLUSION

The reaction of ammonia or other amines with 3-fluoro-2-hydroxynitriles provides a good method to 2-amino-3-fluoro-nitriles. The reaction has been found to be stereospecific. Our results can be explained by a bimolecular ($S_N2$) mechanism.

The fluorinated aminonitriles which were obtained by this route allowed us to prepare some β-fluoro-α-aminoacids and esters. They also are versatile intermediates to fluorinated diamines, the synthesis of which is under current investigation and will be reported in due course.

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