Hydroxy *N*-Carbamoyl Chloride Syntheses. 3-(Hydroxymethyl)piperidine (2.0 g, 17.3 mmol) was added to an equimolar amount of triethylamine (2.5 mL) in 140 mL of dichloromethane. The round-bottomed flask was cooled to −65 °C by using dry ice–isopropyl alcohol. An equimolar amount of phosgene (1.26 mL) was condensed in a graduated finger in a dry ice–isopropyl alcohol bath and poured into the round-bottomed flask with the aid of 20 mL of cold dichloromethane with vigorous magnetic stirring. After 15 min, the flask was left to warm to room temperature, the solvent rotoevaporated, the product extracted with ether, and the triethylamine hydrochloride filtered out. If the reaction was run at a higher temperature than −65 °C or if the stirring was not vigorous, 3-[[(chloroformyl)oxy]methyl]-piperidine-*N*-carbamoyl chloride was formed. The yield as triethylamine hydrochloride was 95%. For **8d**: IR (neat) 1735 (C=O, br), 2850, 2925 (CH), 3400 cm^{-1} (br, OH); NMR ($CDCl_3$) δ 4.3 (m, 3), 4.3 (s, 1, exch), 3.5 (d, 2), 3.0 (m, 2), 1.8 (m, 5); mass spectrum, *m/e* 177 (calcd for $C_7H_{12}NO_2Cl$ *m/e* 177).

Analogous treatment of 3-hydroxypiperidine gave **9d** in 87% yield: IR (neat) 1745 (C=O, s), 2860, 2935 (CH), 3400 cm^{-1} (OH, br); NMR ($CDCl_3$) δ 3.7 (m, 5 H), 1.8 (m, 4 H), variable (s, 1 H, exch); mass spectrum, *m/e* 163 (calcd for $C_6H_{10}NO_2Cl$ *m/e* 163).

Analogous treatment of 2-(hydroxymethyl)piperidine gave **7d** in 91% yield.

These compounds could not be crystallized or molecularly distilled without decomposition.

Cyclization of an (Unisolated) Hydroxy *N*-Carbamoyl Chloride. To 1.00 g (8.6 mmol) of 2-(hydroxymethyl)piperidine was added 1.76 g (2. 41 mL, 17.2 mmol) of triethylamine in dichloromethane in a 250-mL round-bottomed flask. This was cooled in a dry ice–isopropyl alcohol bath to −60 °C, and 0.86 g (0.62 mL, 8.6 mmol) of phosgene was condensed in a graduated finger by using a dry ice–isopropyl alcohol bath and was transferred to the reaction vessel with the aid of 20 mL of cool dichloromethane with vigorous magnetic stirring. The flask was left to warm to room temperature, the dichloromethane was rotoevaporated, and the urethane **10** was extracted with anhydrous ether; yield 1.15 g (94%). The product, characterized by IR and NMR, was identical with a sample prepared from the cyclization of the chloroformate salt.

Cyclization of the Hydroxy *N*-Carbamoyl Chloride to 3-Oxa-1-azabicyclo[3.3.1]nonan-2-one (11). 3-(Hydroxymethyl)piperidine-*N*-carbamoyl chloride (**8d**) was prepared as usual and taken into 30 mL of ethyl ether, 60 mL (10 equiv) of triethylamine was added, and the mixture was stirred magnetically at room temperature for 24 h. Triethylamine hydrochloride started precipitating out directly. The white solid was filtered, the solvents were rotoevaporated, and the oily residue was dissolved in 20 mL of 1:1 pentane/ether mixture and cooled at −50 °C. The crystals that came out were separated by decanting the liquid above them. The crystals were dissolved in ether, rejecting the insoluble residue, and the solvent was decanted and cooled. This process was repeated five times until nice white crystals were obtained which were sublimed at 25–60 °C (0.1–0.2 mmHg). The overall yield was 15% (0.12 g). In another experiment, 3-(hydroxymethyl)piperidine-*N*-carbamoyl chloride (13.4 mmol) was dissolved in 150 mL of toluene, and then 0.5 g of tetra-*n*-butylammonium iodide was added together with 15 mL of triethylamine. The mixture was refluxed at 110 °C (oil bath at 120 °C) for 3 h, cooled to room temperature, filtered, and rotoevaporated at 50 °C. Ethyl ether (50 mL) was added to the orange-brown residue. The insoluble material was rejected. When the ether solution was cooled at −60 °C, it gave 0.80 g of crude yellowish crystals, crude yield 35%. This was distilled in a Kugelrohr apparatus at 25–85 °C (0.01 mmHg), giving 0.64 g (28% yield) of product: mp 146–147 °C; IR (KBr) 1710 (C=O), 2855, 2940 (CH); NMR ($CDCl_3$) δ 4.8 (d, 1), 4.2 (d, 1), 4.1–2.7 (m, 4), 2.2 (m, 1), 1.7 (m, 4); mass spectrum, *m/e* 141, 97 (M − CO_2), 83 (M − CH_2CO_2), 69 (M − $CH_2CH_2CO_2$).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.57; H, 7.80; N, 9.93. Found: C, 59.57; H, 8.32; N, 9.90.

6-Oxa-1-azabicyclo[3.2.1]octan-7-one. 3-Hydroxypiperidine-*N*-carbamoyl chloride was extracted into 180 mL of toluene. To the toluene solution was added 20 mL (4 equiv, 142.4 mmol) of triethylamine, and triethylamine hydrochloride started precipitating out immediately. The mixture was refluxed for 1 h at 90 °C (100 °C oil bath), the white triethylamine hydrochloride was filtered, the toluene was rotoevaporated at 50 °C, and the brown residue was distilled in a Kugelrohr apparatus at 98 °C (0.01 mmHg), giving 1.72 g (38%) of the [3.2.1] bicyclic urethane. The residue in the distillation flask was dissolved in dichloromethane and added dropwise to 400 mL of ethyl ether in a 400-mL beaker. Polymer precipitated out (1.40 g, 31% yield). The ether was evaporated to give an additional 1.05 g of the monomer. An analytical sample was purified by sublimation at 25° (0.01 mmHg): total overall yield of **12** 61.3%; mp 112–113 °C; IR (KBr) 1770 (C=O), 2940, 2860 (CH) cm^{-1}; NMR ($CDCl_3$) δ 4.8 (m, 1), 3.3 (m, 4), 1.95 (m, 4); mass spectrum, *m/e* 127, 83 (M − CO_2), 70 (M − $CHCO_2$), 55 (M − $CH_2CH_2CO_2$), 42 (M − $CHCH_2CH_2CO_2$).

Anal. Calcd for $C_6H_9NO_2$: C, 56.69; H, 7.09; N, 11.02. Found: C, 56.37; H, 7.20; N, 10.94.

For polymer: IR (KBr) 1700 (C=O), 2860, 2945 (CH) cm^{-1}; NMR ($CDCl_3$) δ 3.63 (1, br m), 3.4 (4, br m), 1.7 (4, br m).

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Registry No. 7a, 3433-37-2; **7b**, 75431-11-7; **7c**, 75431-13-9; **7d**, 75431-14-0; **8a**, 4606-65-9; **8b**, 75431-15-1; **8c**, 75431-17-3; **8d**, 75431-18-4; **9a**, 6859-99-0; **9b**, 75431-19-5; **9c**, 75431-17-3; **9b**, 75431-20-8; **10**, 42329-17-9; **11**, 75431-05-9; **12**, 75431-07-1; **13** polymer, 75431-06-0; **13** repeating unit, 75431-10-6; **14** polymer, 75431-08-2; **14** repeating unit, 75431-09-3; phosgene, 75-44-5.

Preparation of Fluoro Amines by the Reaction of Aziridines with Hydrogen Fluoride in Pyridine Solution[1]

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Hydrogen fluoride combines regiospecifically with aziridines (**1**) to give 2-fluoro amines (**6**) in good yields. Fluorine attack is in all cases completely directed to the most substituted ring carbon or to the benzylic carbon. The results, for benzylic aziridines, are consistent with an S_N1-type mechanism.

Interest in the synthesis of β-fluoro amines and β-fluoro-α-amino acid derivatives arises from their biological and pharmacological properties.[3] However, their direct preparation is difficult since most of the common fluori-

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nating reagents can also react with the amine function.[4]

A general method called "fluorodehydroxylation" leading to these types of compounds which involves reacting sulfur tetrafluoride, SF_4, with amino alcohols in liquid HF at low temperatures has been reported.[5] However, the use of SF_4 demands special handling conditions as a consequence of its high vapor pressure and its high toxicity (comparable to phosgene).[4]

Since aziridines, with a variety of functional groups have now become easily accessible,[6] their ring opening by hydrogen fluoride should be a convenient method of synthesizing β-fluoro amines and β-fluoro-α-amino ester derivatives.[7] Hydrogen fluoride is an industrially used fluorinating reagent and is easily handled at atmospheric pressure under simple laboratory conditions in the form of the readily available pyridine solution.[4,8] Although ring-opening reactions by hydrogen halides are among the oldest and most often reported reactions for aziridines, their reactivity with hydrogen fluoride has received little attention, the only reported example being the ring opening of mytomicins by liquid HF.[6] We therefore have undertaken testing of the reactivity of substituted aziridines with this reagent.

Results

Hydrogen fluoride combined, in most cases under mild conditions, with aziridines (**1**) to give the corresponding fluoro amines (**6**) in good yields as listed in Table I. The products were identified by IR, ^{19}F NMR, ^1H NMR, and mass spectrometry and also by their elemental analyses.

The presence of an alkyl group on the nitrogen of aziridine **1e** decreased the reaction rate, and heating the mixture to 70 °C for 1 h was required to obtain the corresponding fluoro amine **6e**. This result is in accordance with earlier reported works concerning the N-substitution effects on the reactivity of aziridines.[6] It is obvious that alkyl groups on the nitrogen attenuate the developing positive charge arising from the proton addition and, therefore, cause a decrease in rate, compared with that for the unsubstituted compounds.

Fluoride attack was in all cases completely directed to the most substituted ring carbon or to the benzylic carbon; competition between the two possible ring-opening pathways occurred for aziridine **1l** which possesses both a secondary benzylic and a tertiary aliphatic carbon center.

The isomers *cis*- and *trans*-2-phenyl-3-methylaziridine (**1f** and **1g**) as well as *cis*- and *trans*-2,3-diphenylaziridine (**1h** and **1i**) gave predominantly fluoroamines **6fT** and **6hT**, respectively, which were identified by cyclization[9] as being the threo isomers (i.e., *R*,R** and/or *S*,S**).

In accordance with earlier reported results on acidic ring opening of epoxides,[10] the *cis*-aziridines **1f** and **1h** were respectively less reactive than their corresponding trans isomers **1g** and **1i**. The discrepancy in behavior between these cis and trans isomers (for epoxides or aziridines) may be attributed to the fact that the presence of a "cis substituent" makes the phenyl group less effective in delocalizing the developing positive charge on the aziridinyl carbon (steric inhibition of resonance).

The same phenomenon is noted again for compounds **1o** and **1p** (decrease of the reaction rate relative to those of **1g** and **1i** in spite of the presence of a tertiary carbon), while the presence of a second phenyl group on the benzylic carbon of aziridines **1l** and **1m**, which can stabilize a positive charge being formed, causes an increase of the rate.

The ^1H NMR spectrum of 2-fluoro-2-phenylcyclohexylamine (**6k**) clearly showed for this product, by means of the high coupling constant between the hydrogen geminal to the amine group and the fluorine atom ($^3J_{FH}$ = 27 Hz), a structure where these nuclei were in trans positions. This indicates for this molecule a conformation in which the phenyl and the amine groups were in diequatorial positions while F and H ($CHNH_2$) were trans diaxial (Scheme II).

The ^{19}F NMR spectrum of 2-fluorocyclohexylamine (**6q**) showed a double multiplet at 179.7 ppm, whereas its ^1H NMR displayed a double six-signal multiplet at 4.1 ppm, corresponding to the hydrogen bound to the fluorinated carbon atom, and a multiplet centered at 2.75 ppm, corresponding to $CHNH_2$. Such a result is consistent with a structure where F and NH_2 are diequatorial, suggesting a trans ring opening of cyclohexenimine (**1q**) by HF, similar to the trans opening of this aziridine by hydrogen chloride.[11]

It is noteworthy that β-fluoro amines appeared to be very stable compared to their β-chloro amine analogues, which can undergo ring closure, yielding the starting aziridines; for example, Hassner and Burke reported the impossibility of isolating the chloro amine derived from 2,2-diphenyl-3-methylaziridine (**1m**).[12] Nevertheless, β-fluoro amines should be stored in their more stable hydrochloride forms.

Solvent, temperature, and fluoride ion concentration effects were evaluated on *cis*- and *trans*-aziridines **1f** and **1g**. Concentrating nucleophilic ions generally increases the reaction rates if the process is an S_N2-type mechanism.[13] From our experiments, neither the reaction rate nor the isomer distribution was much affected either by the polarity of the solvent or by introduction of sodium fluoride, the threo isomer always being preponderant (Table II).

Discussion

The mechanism of ring-opening reactions of aziridines and epoxides by hydrogen halide and water has been widely discussed from the standpoint of kinetics, regiochemistry, and stereochemistry in terms of an S_N1–S_N2 continuum depending on the extent of bond making and bond breaking in the transition state.[6,14] In spite of the sometimes observed stereochemical inversion, S_N1-type mechanisms were generally advanced for the addition of hydrogen halides to aziridines possessing tertiary or benzylic carbon centers. In our case, the regiochemistry (i.e.,

(1) Presented at the 9th International Symposium on Fluorine Chemistry, Avignon, France, Sept 1979, and at the 1st European Symposium on Organic Chemistry, Cologne, Federal Republic of Germany, Aug 1979.
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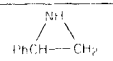
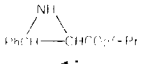
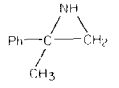
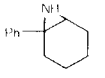
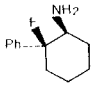
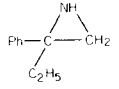
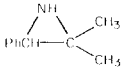
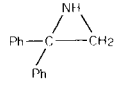
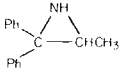
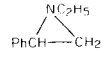
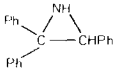
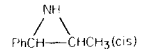
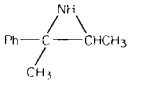
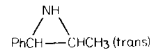
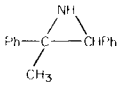
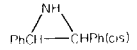
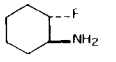
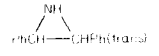
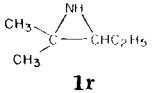
Table I. Conversion of Aziridines 1 to Fluoro Amines 6

aziridine	conditions (time/temp)[d]	fluoro amine[a]	yield,[b] %	aziridine	conditions (time/temp)[d]	fluoro amine[a]	yield,[b] %
 1a	1 h/rt	$PhCHFCH_2NH_2$ (6a)	78	 1j (36% cis + 64% trans)	2 h/rt 30 min/rt	$PhCHFCHNH_2CO_2$-*i*-Pr (6j "T" and 6J "E")	70 7
 1b	1 h/rt	$PhC(CH_3)FCH_2NH_2$ (6b)	60	 1k	1 h/rt	 6k	93
 1c	1 h/rt	$PhC(C_2H_5)FCH_2NH_2$ (6c)	70	 1l	5.5 h/50 °C	$PhCHFCNH_2(CH_3)_2$ (6l) $PhCHNH_2CF(CH_3)_2$ (8l)	88 7
 1d	1 h/rt	$Ph_2CFCH_2NH_2$ (6d)	98	 1m	1 h/rt	$Ph_2CFCHNH_2CH_3$ (6m)	70
 1e	1 h/70 °C	$PhCHFCH_2NHC_2H_5$·HCl (7e) (6fT)	47 69	 1n	1 h/rt	$Ph_2CFCHNH_2Ph$ (6n)	75
 1f	6 days/rt or 10 h/40 °C	$PhCHFCHNH_2CH_3$ (6fT) (6fE)	69 8	 1o (R^*,S^*)	48 h/rt	$PhC(CH_3)FCHNH_2CH_3$ (6o "T") (6o "E")	30 26
 1g	5 h/rt	$PhCHFCHNH_2CH_3$ (6fT) (6fE)	71 12	 1p (R^*,S^*)	5–8 h/rt	$PhC(CH_3)FCHNH_2Ph$ (6p "T") (6p "E")	52 21
 1h	12 h/rt	$PhCHFCHNH_2Ph$ (6hT) (6hE)	58 2	 1q	CH_3CN, 24 h/ 70 °C	 *trans*-6q	70[c]
 1i	1 h/rt	$PhCHFCHNH_2Ph$ (6hT) (6hE)	90 4	 1r	CH_3CN, 24 h/ 70 °C	$(CH_3)_2CFCHNH_2C_2H_5$·HCl (7r)	90[c]

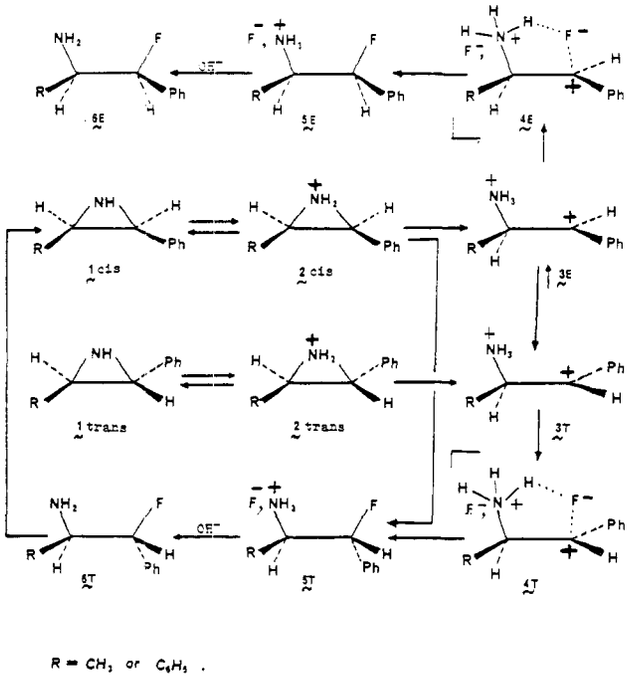
[a] Unless otherwise indicated. [b] Yield based on aziridine. [c] Yield of isolated hydrochloride. [d] rt = room temperature.

Table II. Solvent, Temperature, and Fluoride Ion Concentration Effects on the Reaction Rate of HF with Aziridines 1f and 1g and on the Isomer (Threo and Erythro) Distribution

	benzene		$CHCl_3$		$CHCl_3/FNa$[a]	
aziridine	condit[b]	distr, %	condit[b]	distr, %	condit[b]	distr, %
1f	6 days/rt or	89 T	72 h/rt	70 T	10 h/40 °C	77 T
	10 h/40 °C	11 E		30 E		23 E
1g	5 h/rt	86 T	3 h/rt	86 T	5 h/rt	90 T
		14 E		14 E		10 E
	1 h/70 °C	73 T				
		27 E				

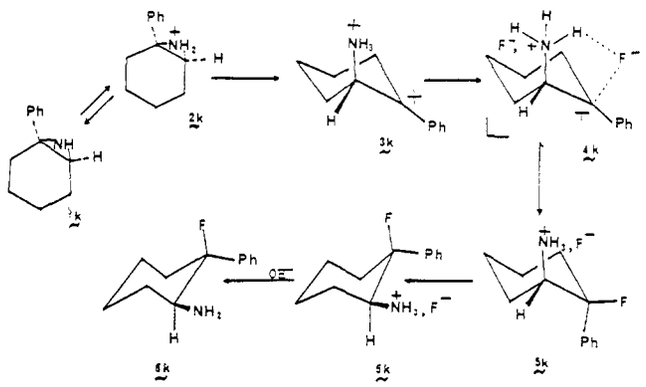
[a] Two equivalents of FNa. [b] rt = room temperature.

Scheme I[a]



[a] F^- is nothing but a representation of the reacting entities, which may be $(F_nH_{n-1})^-$.

Scheme II



fluoride attack exclusively directed to the benzylic or to the most substituted carbon center), the isomer distributions, the cis ring opening of phenylcyclohexenimine (**1k**), and the lack of influence of fluoride ion concentration can be clearly explained by an S_N1-type process as suggested in Schemes I and II. This type of mechanism has also been proposed by Berti et al.[15] for the ring-opening reaction of some benzylic epoxides by hydrogen chloride.

The observation that when the reaction was stopped before the time indicated in Table I only 2-fluoro amine **6** along with starting aziridine was obtained suggests that the slower step is the formation of **3T** or **3E**. It is, however, worth noting that the formation of threo isomers (**6fT** and **6hT**) from *cis*-2,3-disubstituted aziridines (**1f** and **1h**) is also consistent, as indicated in Scheme I, with a trans-opening process, which can be explained by a shielding effect of the leaving nitrogen atom,[6] the bond-breaking rate being slower for these *cis*-aziridines than for their trans isomers. The fact that *erythro*-fluoro amines were obtained in greater proportions from *trans*-aziridines **1g** and **1i** than from their cis isomers suggests a partial involvement of such a pathway.

Except for *cis*-aziridine **1j**, which probably reacts in a manner similar to that for **1f** and **1h**, all the other substrates possessing a phenyl substituent are likely to proceed via carbonium ions **3T** and **3E**. In such a pathway, taking into account the steric effects in the isomer distribution of intermediates **3E** and **3T**, it should be expected that the proportions of the *erythro*-fluoro amines (relative to the threo isomers) obtained from aziridines **1o** and **1p** (derivatives of compounds **1f** and **1h** by replacement of a benzylic hydrogen by a methyl group) will be higher than those of *erythro*-fluoro amines issued from **1f** and **1h**. For the same reasons, the proportion of the erythro isomer also should be higher in fluoro amines obtained from aziridines **1o** than that resulting from **1p**. The results obtained seem to be consistent with these qualitative considerations. Thus, even though the configurations of **6j"T"**, **6o"T"**, and **6p"T"** have not been fully established, we think that, account being taken of these results, it is not wrong to attribute to them the threo configuration arising from the more stable intermediate of type **3T** (Scheme I).[22]

Hydrogen fluoride solution in pyridine has been reported by Olah et al.[8] as being a pyridinium poly(hydrogen fluoride) containing a small amount of hydrogen fluoride in equilibrium. The difference in behavior of benzylic aziridines with this reagent on one hand and with HCl in ether solution on the other hand (which combines with aziridines following an anti-opening process)[12,14] is probably caused by the difference in the relative importance between the ionizing and the nucleophilic power of these reagents.

The advantage of this fluorination method is in the ease of handling of the HF–pyridine reagent (simple polyethylene or Teflon flasks can be used as the reaction vessels, under general laboratory conditions) and in the high regiospecificity of the reaction. Its limitation, however, is that both cis and trans isomers afford the same fluoro amines.

Experimental Section

All melting points were uncorrected. IR spectra were recorded on a Leitz Model IIIG spectrometer. ^1H NMR spectra were run on a Varian EM-360 instrument (60 MHz) using $CDCl_3$ as a solvent and Me_4SI as an internal standard, while ^{19}F NMR spectra

(15) G. Berti, F. Bottari, and B. Macchia, *Chim. Ind. (Milan)*, 45, 1527 (1963).

were recorded on a Bruker Spectrospin WH-90-DS (84.67 MHz) spectrometer with $CDCl_3$ as a solvent and $CFCl_3$ as an internal standard. Mass spectra were recorded on a VG Micromass 30F (electronic impact, 70 eV). Satisfactory elemental analyses (±0.4% of theory) were obtained for C, H, and F of all new fluoro amine hydrochlorides.

Aziridines **1a** and **1q** were prepared by cyclization of iodocarbamates;[16] compounds **1d,g,i,k,l,r** were obtained via LAH reduction of the iodine azide adduct of the olefin,[17] and compounds **1f** and **1h** were obtained by LAH reduction of the derived azirine.[18] Aziridines **1b,c,m–p** were prepared by addition of CH_3MgI, EtMgBr, and PhMgBr to the appropriate azirine.[19] Compound **1e** was produced by N-alkylation of **1a**[20] and aziridine **1j** by reacting NH_3 with the alkyl dibromocinnamate in Me_2SO as a solvent.[21]

General Procedure for the Ring Opening of Aziridines. Into a 70% solution of hydrogen fluoride in pyridine (10 mL) was added a solution of aziridine **1** (0.01 mol) in benzene (2 mL) dropwise at room temperature; the reaction mixture was maintained under the conditions indicated in Table I and then poured into 20 mL of water, washed with three portions of 15 mL of ether, neutralized with 30% ammonia solution, and extracted with three portions of 20 mL of ether. The ether extracts were then dried ($MgSO_4$) and evaporated in vacuo. Except for the relatively volatile compounds **6q** and **6r** (for which the pyridine and the fluoro amine were separated by column chromatography), pure fluoro amines **6** were obtained after the evaporation of the pyridine in vacuo, as indicated by their ^1H and ^{19}F NMR spectra and the single spots obtained in TLC.

Further purifications were made by crystallization of their hydrochlorides (solvent ether–alcohol). The physical characteristics of the obtained products are given here below: IR ($CHCl_3$), ν in cm^{-1}; ^1H (δ_H) and ^{19}F NMR (δ_F), s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; ^{19}F NMR, δ_F is taken positively with increasing fields; mp, °C; mass spectrum, *m/e* (relative intensity).

2-Fluoro-2-phenylethylamine (6a): $\nu(NH_2)$ 3305, 3385; δ_H 1.12 (s, 2 H, NH_2), 2.92 (m, AB part of ABMX pattern, 2 H, CH_2NH_2), 5.26 (ddd, 1 H, M of ABMX, ^2J = 48.7 Hz, ^3J = 6.2 Hz, ^3J = 4.7 Hz, CHF), 7.23 (s, 5 H, C_6H_5); δ_F 185.5 (ddd, ^2J = 47.5 Hz, ^3J = 22 Hz, ^3J = 25 Hz). **Hydrochloride 7a**: mp 169 °C;[11] *m/e* 140 [1.06, (M – Cl)$^+$], 109 (53.29, PhC^+HF).

2-Fluoro-2-phenylpropylamine (6b): $\nu(NH_2)$ 3330, 3390; δ_H 1.35 (s, 2 H, NH_2), 1.63 (d, 3 H, ^3J = 22.2 Hz, CH_3CF), 3.04 (d, 2 H, ^3J = 21.7 Hz, CH_2NH_2), 7.38 (s, 5 H, C_6H_5CF); δ_F 158.0 (sextet, ^3J = 22.1 Hz). **Hydrochloride 7b**: mp 144–146 °C; *m/e* 154 [3.62, (M – Cl)$^+$]; 123 [70.63, $PhCF^+(CH_3)$].

2-Fluoro-2-phenylbutylamine (6c): $\nu(NH_2)$ 3305, 3360; δ_H 0.80 (t, 3 H, ^3J = 7 Hz, CH_3CH_2), 1.50 (s, 2 H, NH_2), 1.89 (m, 2 H, CH_3CH_2CF), 3.04 and 3.06 (2 d, 2 H, AB of ABX pattern, ^3J = 21 Hz, ^3J = 24 Hz, $CFCH_2NH_2$), 7.40 (s, 5 H, C_6H_5); δ_F 171.1 [dddd, ^3J = 20, 24 Hz ($CFCH_2NH_2$), ^3J = 17.2, 28.5 Hz ($CFCH_2CH_3$)]. **Hydrochloride 7c**: mp 182–183 °C; *m/e* 168 [6.24, (M – Cl)$^+$], 137 [52.29, $PhC^+F(C_2H_5)$].

2-Fluoro-2,2-diphenylethylamine (6d): $\nu(NH_2)$ 3300, 3350; δ_H 1.02 (s, 2 H, NH_2), 3.27 (d, 2 H, ^3J = 22.4 Hz, CH_2NH_2), 7.20 (s, 10 H, $(C_6H_5)_2CF$); δ_F 156.8 (t, ^3J = 22.9 Hz). **Hydrochloride 7d**: mp 192–194 °C; *m/e* 195 [63.55, (M – HCl – HF)$^+$], 185 (100, Ph_2CF^+).

***N*-Ethyl-2-fluoro-2-phenylethylamine (6e)**: δ_H 1.12 (t, 3 H, ^3J = 7 Hz, CH_3CH_2), 1.65 (s, 1 H, NH), 2.4–3.5 (m, 4 H, $CHFCH_2NHCH_2CH_3$), 5.60 (ddd, 1 H, ^2J = 48.4 Hz, ^3J = 4 Hz, ^3J = 8.4 Hz, CHF), 7.35 (s, 5 H, C_6H_5). **Hydrochloride 7e**: mp 183–184 °C; δ_F (D_2O) 180.5 (ddd, ^2J = 48.5 Hz, ^3J = 18.5 Hz, ^3J = 29.4 Hz); *m/e* 168 [0.24, (M – Cl)$^+$], 58 [100, $(EtNHCH_2)^+$].

***threo*-2-Fluoro-2-phenyl-1-methylethylamine (6fT)**: $\nu(NH_2)$ 3280, 3350; δ_H 0.92 (d, 3 H, ^3J = 6.5 Hz, CH_3CHNH_2), 1.35 (s, 2 H, NH_2), 3.15 (quintet of d, 1 H, ^3J = 6.5 Hz, ^3J = 15.2 Hz, $CHNH_2$), 4.56 and 5.37 (dd, 1 H, ^2J = 47.2 Hz, ^3J = 6.5 Hz, CHF), 7.25 (s, 5 H, C_6H_5); δ_F 183.3 (dd, ^2J = 47.7 Hz, ^3J = 15.7 Hz). ***erythro*-6fE**, δ_F 184.2 (dd, ^2J = 47.1 Hz, ^3J = 13.9 Hz). **Hydrochloride 7fT**: mp 192 °C; *m/e* 154 [0.37, (M – Cl)$^+$], 44 [100, $(CH_3CHNH_2)^+$].

***threo*-2-Fluoro-1,2-diphenylethylamine (6hT)**: $\nu(NH_2)$ 3275, 3340; δ_H 1.87 (s, 2 H, NH_2), 4.2 (dd, 1 H, ^3J = 7 Hz, ^3J = 14.4 Hz, $CHNH_2$), 4.97 and 5.72 (dd, 1 H, ^2J = 47.2 Hz, ^3J = 7 Hz, CHF), 7.15 (s, 5 H, C_6H_5); δ_F 183.0 (dd, ^2J = 47.2 Hz, ^3J = 14.2 Hz). ***erythro*-6hE**, δ_F 181.0 (dd, ^2J = 46.7 Hz, ^3J = 13.2 Hz). **Hydrochloride 7hT**: mp 210–212 °C; *m/e* 195 [25.90, (M – HCl – HF)$^+$], 106 [98.32, $(PhCHNH_2)^+$].

3-Fluorophenylalanine isopropyl ester (6j"T"): $\nu(NH_2)$ 3300, 3350, ν(C=O) 1720; δ_H 1.17 (two overlapping doublets, 6 H, ^3J = 6.5 Hz, $(CH_3)_2CH$), 1.63 (s, 2 H, NH_2), 3.72 (dd, 1 H, ^3J = 24.8 Hz, ^3J = 4.2 Hz, $CHNH_2$), 5.00 [septet, 1 H, ^3J = 6.5 Hz, $CH(CH_3)_2$], 5.71 (dd, 1 H, ^2J = 46.8 Hz, ^3J = 4.2 Hz, CHF), 7.34 (s, 5 H, C_6H_5); δ_F 194.4 (dd, ^2J = 46.7 Hz, ^3J = 25.5 Hz. **6j"E"**, δ_F 184.1 (dd, ^2J = 45.5 Hz, ^3J = 13 Hz). **Hydrochloride 6j"T"**: mp 182–183 °C; *m/e* 226 [2.26 (M – Cl)$^+$], 116 [82.84, $(CH(NH_2)CO_2\text{-}i\text{-}Pr)^+$].

2-Fluoro-2-phenylcyclohexylamine (6k): $\nu(NH_2)$ 3290, 3335; δ_H 0.92 (s, 2 H, NH_2), 1.10–2.20 (br m, 8 H, $(CH_2)_4$), 2.73 (md, 1 H, $W_{1/2}$ = 18 Hz, ^3J = 27 Hz, $CHNH_2$), 7.26 (s, 5 H, C_6H_5); δ_F 183.6 [ddd, ^3J = 28 Hz ($CFCHNH_2$), ^3J = 38 Hz (CFCH, trans), ^3J = 13.5 Hz (CFCH, cis)]. **Hydrochloride 7k**: mp 220–221 °C; *m/e* 194 [3.00, (M – Cl)], 173 [19.22 (M – HCl – HF)$^+$].

2-Fluoro-2-phenyl-1,1-dimethylethylamine (6l): $\nu(NH_2)$ 3300, 3350; δ_H 1.02 (s, 3 H, CH_3), 1.1 (s, 3 H, CH_3), 1.37 (s, 2 H, NH_2), 5.12 (d, 1 H, ^2J = 45.4 Hz, CHF), 7.23 (s, 5 H, C_6H_5); δ_F 186.4 (d, ^2J = 45.8 Hz). **Hydrochloride 7l**: mp 214–215 °C; *m/e* 168 [0.68 (M – Cl)$^+$], 58 [100, $((CH_3)_2CHNH_2)^+$].

1-Fluoro-2-phenyl-1,1-dimethylethylamine (8l): δ_F 146.7 (septet of d, ^3J = 22 Hz, ^3J = 13.2 Hz).

2-Fluoro-2,2-diphenyl-1-methylethylamine (6m): $\nu(NH_2)$ 3300, 3350; δ 1.07 (d, 3 H, ^3J = 6.5, CH_3CHNH_2), 1.50 (s, 2 H, NH_2), 3.83 (qd, ^3J = 25.8 Hz, ^3J = 6.5 Hz, CH_3CHNH_2), 6.9–7.8 (br, 10 H, $(C_6H_5)_2$); δ_F 159.9 (d, ^3J = 22 Hz). **Hydrochloride 7m**: mp 228–230 °C; *m/e* 209 [14.52, (M – HCl – HF)$^+$], 44 [100, $(CH_3CHNH_2)^+$].

2-Fluoro-1,2,2-triphenylethylamine (6n): $\nu(NH_2)$ 3310, 3390; δ_H 1.94 (br s, 2 H, NH_2), 4.81 (d, 1 H, ^3J = 26.5 Hz, $CHNH_2$), 6.90–7.80 (br, 15 H, $(C_6H_5)_2$, C_6H_5); δ_F 154.4 (d, ^3J = 26.4 Hz). **Hydrochloride 7n**: mp 217.5 °C; *m/e* 271 [90.40, (M – HCl – HF)$^+$].

2-Fluoro-2-phenyl-1-methylpropylamines 6o"T" and 6o"E": $\nu(NH_2)$ 3290, 3365. For **6o"T"**: δ_H 1.01 (d, 3 H, ^3J = 6.5 Hz, CH_3CHNH_2), 1.60 (s, 2 H, NH_2), 1.62 (d, 3 H, ^3J = 23.4 Hz, CH_3CF), 3.22 (qd, 1 H, ^3J = 6.5 Hz, ^3J = 17.5 Hz, $CHNH_2CH_3$), 7.33 (s, 5 H, C_6H_5); δ_F 144 (qd, ^3J = 22.7 Hz, ^3J = 17.5 Hz). For **6o"E"**: δ_H 1.01 (d, 3 H, ^3J = 6.5 Hz, CH_3CHNH_2), 1.62 (s, 2 H, NH_2), 1.66 (d, 3 H, ^3J = 23.3 Hz, CH_3CF), 3.19 (qd, 1 H, ^3J = 6.5 Hz, ^3J = 15.5 Hz, $CHNH_2CH_3$), 7.33 (s, 5 H, C_6H_5); δ_F 146 (qd, ^3J = 22.7 Hz, ^3J = 15.4 Hz).

2-Fluoro-1,2-diphenylpropylamines 6p"T" and 6p"E": $\nu(NH_2)$ 3305, 3370. For **6p"T"**: δ_H 1.50 (d, 3 H, ^3J = 23 Hz, CH_3CF), 1.68 (s, 2 H, NH_2), 4.19 (d, 1 H, ^3J = 20 Hz, $CHNH_2$), 7.23 (s, 5 H, 2 C_6H_5); δ_F 139.3 (qd, ^3J = 22.2 Hz, ^3J = 22.1 Hz). For **6p"E"**: δ_H 1.65 (d, 3 H, ^3J = 23 Hz, CH_3CF), 1.68 (s, 2 H, NH_2), 4.23 (d, 1 H, ^3J = 14.4 Hz, $CHNH_2$), 7.30 [s, 5 H, 2 (C_6H_5)]; δ_F 146.6 (qd, ^3J = 23 Hz, ^3J = 15 Hz).

2-Fluorocyclohexylamine (6q): δ_H ($CDCl_3$–pyridine) 0.9–2.3 (br, 10 H, $(CH_2)_4$ and NH_2), 2.75 (m, 1 H, $CHNH_2$), 3.72 and 4.55 (a double six signals multiplet, 1 H, $^2J \simeq$ 49 Hz, CHF); δ_F 179.7 (md, $^2J \simeq$ 51 Hz). **Hyerochloride 7q**: mp 224–225 °C; *m/e* 118 [1.67, (M – Cl)$^+$], 56, (100).

2-Fluoro-2-methyl-1-ethylpropylamine (6r): δ_H ($CDCl_3$–pyridine) 1.03 (t, 3 H, CH_3CH_2), 1.29 [d, 6 H, ^3J = 22.5 Hz, $(CH_3)_2CF$], 1.3–2 (m, 4 H, CH_2CH_3 and NH_2), 2.68 (six signals, multiplet, 1 H, ^3J = 10.5 Hz, ^3J = 10.5 Hz, ^3J = 3 Hz, $CHNH_2$).

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(22) **Note Added in Proof.** The threo configuration of **6jT** has recently been confirmed by X-ray analysis [T. Tsushima, T. Sato, and T. Tsuji, *Tetrahedron Lett.*, 3591 (1980)]. The ester function has been hydrolyzed enzymatically by R. Azerad.

Hydrochloride 7r: mp 204–205 °C; δ_F (D_2O) 179.0 (septet of d, ^3J = 10.7 Hz, ^3J = 23 Hz); *m/e* 120 [3.39 $(M - Cl)^+$], 58 [100, $(EtCHNH_2)^+$].

Registry No. **1a**, 1499-00-9; **1b**, 22596-57-2; **1c**, 768-82-1; **1d**, 25564-63-0; **1e**, 4164-24-3; **1f**, 1485-13-8; **1g**, 20993-60-6; **1h**, 1605-06-7; **1i**, 25125-72-8; *cis*-**1j**, 51626-61-0; *trans*-**1j**, 75197-96-5; **1k**, 25022-23-5; **1l**, 23040-89-3; **1m**, 7764-13-8; **1n**, 26162-53-8; **1o**, 25865-52-5; **1p**, 25865-63-8; **1q**, 286-18-0; **1r**, 25022-28-0; **6a**, 55601-20-2; **6b**, 75197-97-6; **6c**, 69681-76-1; **6d**, 69681-77-2; **6e**, 69681-82-9; **6fT**, 74275-07-3; **6fE**, 75197-98-7; **6hT**, 71057-09-5; **6hE**, 71057-08-4; **6jT**, 75197-99-8; **6jE**, 75198-00-4; **6k**, 75213-92-2; **6l**, 69681-78-3; **6m**, 71057-03-9; **6n**, 75198-01-5; **6oT**, 71057-05-1; **6oE**, 71057-06-2; **6pT**, 75198-02-6; **6pE**, 75198-03-7; **6q**, 75198-04-8; **6r**, 75198-05-9; **7a**, 64068-24-2; **7b**, 75198-06-0; **7c**, 75198-07-1; **7d**, 75198-08-2; **7e**, 75198-09-3; **7fT**, 75198-10-6; **7hT**, 75198-11-7; **7jT**, 75198-12-8; **7k**, 75213-93-3; **7l**, 75198-13-9; **7m**, 75198-14-0; **7n**, 75198-15-1; **7q**, 75198-16-2; **7r**, 75198-17-3; **8l**, 69681-79-4; HF, 7664-39-3.

New Convenient Synthesis of β,β-Difluoro Amines and β,β-Difluoro-α-amino Acid Alkyl Esters by the Addition of Hydrogen Fluoride to 1-Azirines[1]

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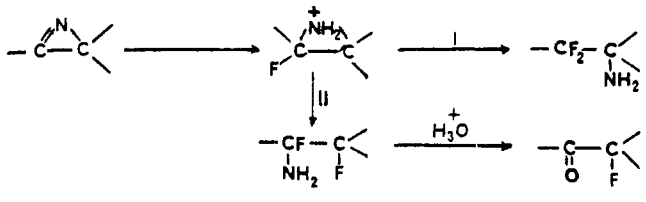
The reaction of hydrogen fluoride in pyridine solution with a series of substituted 1-azirines (**1**) was investigated. β,β-Difluoro amines (**4**) were obtained in good yields. The exceptions are the cases of 2-phenyl-3-methyl-1-azirine (**1b**) and 2,3-diphenyl-1-azirine (**1c**) for which the direct formation of a stabilized carbocation (**6**) from the azirinium ion **2** is probable. The former gave 54% of a pyrazine (**11b**) and 5% of α-fluoropropiophenone (**9b**) along with 20% of difluoro amine **4b**, while the latter afforded only the corresponding α-fluoro ketone (**9c**). A mechanism is suggested.

β-Fluorinated amines and amino acids are important targets in the search for new drugs by the application of the principle of isogeometric modification of metabolites with maximal shift of electron distribution in the design of antimetabolites and drugs.[3] The lack of general methods of synthesizing β,β-difluoro amines and β,β-difluoro-α-amino acids led us to examine the reactivity of the now easily accessible 1-azirines **1** with hydrogen fluoride.[4] This idea was supported by the fact that 1-azirines add smoothly 1 mol of such reagents as methanol, acyl chloride, and hydrogen to give aziridines, which can undergo ring opening if reacted with a second mole of reagent.[5,6]

Thus, it seemed to us of interest to evaluate whether or not the addition of hydrogen fluoride to these unsaturated rings will be a convenient synthetic route to β,β-difluoro amines.

Presumably, following the probable formation of fluoroaziridines in a first step, according to the above-mentioned reactions, two ring-opening pathways would be possible, yielding after hydrolysis either β,β-difluoro amines or α-fluoro ketones as described in Scheme I.

Scheme I



Results

The reactivity of hydrogen fluoride in pyridine solution with 1-azirines was tested on a series of substituted substrates, prepared by pyrolysis of the azidoalkene obtained from dehydrohalogenation of the corresponding iodo or bromo azide adducts of the olefin.[5,7]

1-Azirines **1g** and **1i** were reacted immediately after their preparation with hydrogen fluoride (in pyridine solution) to avoid any polymerization. For substrates **1e,f,i**, the reactions were run with a mixture containing, respectively, 44%, 65%, and 71% of 1-azirine. (The other components were minor nonseparated products such as iodo azide, azide, and iodoalkene arising from the preceding reactions.) The results are summarized in Table I.

All the products obtained were identified by their ^1H and ^{19}F NMR, IR, and mass spectra and also by elemental analyses for new compounds.

The 1-azirines **1** reacted under mild conditions (more easily than their aziridine homologues)[8] with hydrogen fluoride to give the corresponding β,β-difluoro amines **4** in convenient yields; exceptions, however, were 2-phenyl-3-methyl-1-azirine (**1b**), which gave 54% of 2,5-dimethyl-3,6-diphenylpyrazine (**11b**) and 5% of α-fluoro ketone **9b** along with a 20% yield of the difluoro amine **4b**, and 2,3-diphenyl-1-azirine (**1c**), which afforded only the corresponding α-fluoro ketone **9c**. From the azirine **1h**, only a trace amount of α-fluoro ketone **9h** was detected.

In order to avoid or diminish the dimerization observed on azirine **1b** in the HF–pyridine solution, hoping thus to improve the difluoro amine **4b** yield relative to that of

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