silica gel. It gave 0.52 g (49%) of the product **9**. Recrystallization in hexane furnished the pure sample with the following: mp 119–120 °C; mass spectrum (CI), *m/e* (relative intensity) 351 (M + 1, 10), 295 (17), 268 (34), 241 (52), 239 (100), 212 (36), 198 (15), 196 (11), 185 (74), 171 (22), 156 (14), 140 (20), 84 (23).

Anal. Calcd for $C_{18}H_{27}ClN_4O$: C, 61.63; H, 7.70. Found: C, 61.79; H, 8.03.

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# Ring Opening of Aziridines by Different Fluorinating Reagents: Three Synthetic Routes to α,β-Fluoro Amines with Different Stereochemical Pathways

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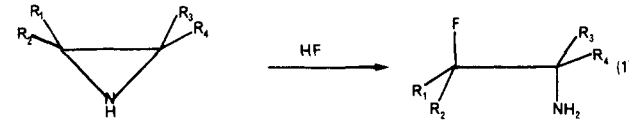
The syntheses of α,β-fluoro amines from the reaction of secondary aziridines with either Olah's reagent (HF, pyridine) or anhydrous hydrogen fluoride and of N-activated aziridines with partially neutralized Olah's reagent ($NR_3$–$n$HF) are reported. The stereochemistry of these reactions is highly dependent on the structure of the starting compound and on the fluorinating agent. From the same aziridine it is thus possible to synthesize selectively each diastereoisomeric fluoro amine by proper choice of fluorination conditions.

Fluorine compounds are widely used as drugs in pharmacology and chemotherapy.[1-4] However, a convenient synthetic route to α,β-fluoro amines, particularly those with a primary amine function, does not exist. These compounds exhibit biological activity on the central nervous system.[5] A new synthetic route to fluoro amines has recently been reported by Kollonitsch and co-workers.[6] This method, however, needs special handling of sulfur tetrafluoride, a very toxic reagent. More frequently used fluorinating reagents are fluoroalkylamines,[7] metallic and nonmetallic fluorides,[8] and trifluoromethyl hypofluorite.[9] Fluorodesulfurization[10] and diazotization[11] reactions have also been carried out in this connection. Finally, the possible replacement of the chlorine atom by an amine function in α,β-chlorofluoro compounds should be mentioned.[12]

The fact that the hydrogen fluoride addition to epoxides is a very clean and good method for preparing α,β-fluoro alcohols[13] led us to investigate the same type of reaction sequence (eq 1) with secondary aziridines. This reaction




(1)

has been performed in the mytomycine series.[14] Numerous synthetic methods leading to secondary aziridines have been developed during the past 15 years, and these compounds in monocyclic, steroid, and acyclic series are now easily available.

Prompted by a recent paper of Wade[15] concerning the synthesis of fluoro amines via aziridine ring opening by HF–pyridine (Olah's reagent), which appeared while this work was in progress, we present results obtained in our laboratory. In preliminary notes[16] we have reported the synthesis of α,β-fluoro amines by ring-opening of secondary or N-activated aziridines with anhydrous hydrogen fluoride, Olah's reagent, or modified Olah's reagent. We present here a comparative study of the fluorinating ability of these three reagents toward aziridines. The stereoselectivity of the reaction appears to be very different in each case, and the synthetic advantages of each reagent are discussed.

## Results

Two fluorinating agents were previously used with secondary aziridines (R = H), i.e., anhydrous hydrogen fluoride and Olah's reagent.[16] Fluoro amines are generally obtained in fair yields (Table I). However, in some cases we could not get satisfactory results (i.e., **10aT** and **10aC**,

(1) E. D. Bergmann, *Bull. Soc. Chim. Fr.*, 2676 (1965).
(2) T. B. Patrick, *J. Chem. Educ.*, **56**, 228 (1979).
(3) M. Schlosser, *Tetrahedron*, **34**, 3 (1978).
(4) J. Kollonitsch, *Isr. J. Chem.*, **17**, 53 (1978).
(5) B. B. Molloy, R. W. Fuller, and K. L. Hauser, U.S. Patent *Appl.* 162621; *Chem. Abstr.*, **78**, 110850 (1973).
(6) J. Kollonitsch, S. Marburg, and L. M. Perkins, *J. Org. Chem.*, **44**, 771 (1979).
(7) A. Cohen and E. D. Bergmann, *Tetrahedron*, **22**, 3545 (1966); B. Cavalleri and E. D. Bellasio, *Farmaco, Ed. Sci.*, **25**, 901 (1970); *Chem. Abstr.*, **73**, 53188 (1971).
(8) R. Mengel and W. Gulschbauer, *Angew. Chem., Int. Ed. Engl.*, **17**, 525 (1978); N. B. Chapmann, R. M. Scrowston, and R. Westwood, *J. Chem. Soc. C*, 528 (1967).
(9) D. H. R. Barton, *Pure Appl. Chem.*, **49**, 1241 (1977), and references cited therein.
(10) J. Kollonitsch, S. Marburg, and L. M. Perkins, *J. Org. Chem.*, **41**, 3107 (1976).
(11) K. Matsumoto, Y. Ozaki, T. Iwasaki, M. Horikawa, and M. Miyoshi, *Experientia*, **35**, 850 (1979).
(12) R. Guedj, R. Nabet, and T. Wade, *Tetrahedron Lett.*, 907 (1973) and *C.R. Hebd. Seances Acad. Sci.*, **274**, 1317 (1972).
(13) W. G. Dauben, *Org. React.*, **21**, 201–205, (1974).
(14) W. E. Meyer and J. H. Mowat, U.S. Patent Appl., 3230233; *Chem. Abstr.*, **64**, 8147 (1966).
(15) T. N. Wade, *J. Org. Chem.*, **45**, 5328 (1980).
(16) G. Alvernhe, E. Kozlowska-Gramsz, S. Lacombe-Bar, and A. Laurent, *Tetrahedron Lett.*, 5203 (1978); G. Alvernhe, S. Lacombe, and A. Laurent, *ibid.*, 289, 1437 (1980).

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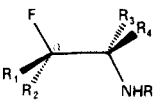
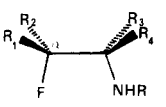
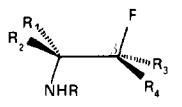
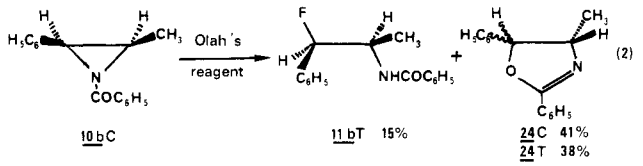
Table I. Reaction of Fluorinating Reagents with Aziridines[a]

| aziridine | reagent | product (yield, %) | | | conditions | |
|---|---|---|---|---|---|---|
| | |  |  |  | time | temp, °C |
| 1, $R_1 = C_6H_5$; $R_2 = R_3 = CH_3$; $R_4 = H$; R = H | anh HF | 2T (41) | 2E (29) | 3 (13) | 18 h | 20 |
| | Olah's | 2T (61) | 2E (39) | 3 (0) | 70 h | 50 |
| 4, $R_1 = C_6H_5$; $R_2 = H$; $R_3 = CH_3$; $R_4 = C_2H_5$; R = H | Olah's | 5E (12) | 5T (48) | 6E (23), 6T (2) | 70 h | 50 |
| 7aC, $R_1 = R_3 = C_6H_5$; $R_2 = R_4 = R = H$ | anh HF | 8aT (95) | 8aE (5) | | 15 min | 20 |
| | Olah's | 8aT (92) | 8aE (8) | | 3 h | 20 |
| 7bC, $R_1 = R_3 = C_6H_5$; $R_2 = R_4 = H$; $R = COC_6H_5$ | $NR_3$, 2.5 HF | 8bT (69) | 8bE (17) | | 4 h | 50 |
| 7aT, $R_1 = R_4 = C_6H_5$; $R_2 = R_3 = R = H$ | anh HF | 8aE (100) | 8aT (0) | | 15 min | 20 |
| | Olah's | 8aE (8) | 8aT (92) | | 3 h | 20 |
| 7bT, $R_1 = R_4 = C_6H_5$; $R_2 = R_3 = H$; $R = COC_6H_5$ | $NR_3$, 2.5 HF | 8bT (5) | 8bE (25) | | 3 h | 20 |
| 10aC, $R_1 = C_6H_5$; $R_3 = CH_3$; $R_2 = R_4 = R = H$ | anh HF | the experiment is not reproducible and affords a mixture of isomers in very poor yield | | | | |
| | Olah's | 11aE + 11aT (15) | | | 5 h | 20 |
| 10dC, $R_1 = C_6H_5$; $R_3 = CH_3$; $R_2 = R_4 = H$; $R = CO_2$-*t*-Bu | $NR_3$, 2.5 HF | 11dT (63) | 11dE (traces) | | 6 h | 20 |
| 10aT, $R_1 = C_6H_5$; $R_4 = CH_3$; $R_2 = R_3 = R = H$ | anh HF | 11aE (20) | 11aT (5) | | 15 min | 20 |
| 12a, $R_1 = CH_3$; $R_2 = R_3 = R_4 = R = H$ | Olah's | 13a (54) | | 14a (29) | 20 h | 70 |
| 12b, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$; $R = COC_6H_5$ | $NR_3$, 3 HF | 13b (85) | | 14b (0) | 5 h | 50 |

[a] The letters T, E, and C refer respectively to threo (or occasionally trans), erythro, and cis compounds. Yields based on aziridine.

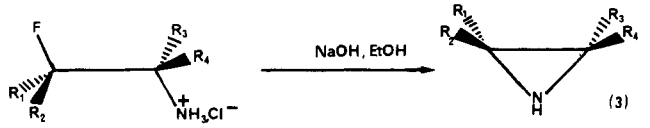
Table I). In order to improve the fluoro amine yields, we have been led, first, to facilitate the aziridine ring opening by activation of the ring nitrogen and, second, to increase the fluorinating ability of the reagents used. When *N*-benzoylaziridines react with Olah's reagent, the main isolated products are not the desired *N*-benzoylfluoro amines but rather the 2-phenyl-$\Delta^2$-oxazolines (eq 2). From




these results it is obvious that Olah's reagent is either too strongly acidic or insufficiently nucleophilic to be effective in the desired fluorination reaction. Thus, we looked for a less acidic and more nucleophilic agent than Olah's in order to decrease the oxazoline yields. Amine hydrofluoride derivatives, already synthesized by Jullien[17] and Rozhkov,[18] are reported to be good fluorinating reagents. We investigated the reactivity of a similar reagent: triethylamine was carefully added to commercial Olah's reagent in order to obtain different mixtures of $NR_3$–*n*HF (*n* = 3, 2.5, 2). We have also used anhydrous hydrogen fluoride or Olah's reagent with secondary aziridines and only this reagent ($NR_3$–*n*HF) with activated aziridines.

*N*-Benzoylaziridines when treated with $NR_3$–*n*HF give predominantly *N*-benzoylfluoro amines along with much smaller amounts of oxazolines. The yields of fluorinated products are greatly improved with the same time and temperature used with secondary aziridines. Hydrolysis of *N*-benzoyl amines to free amines usually requires vigorous conditions. In contrast, *N*-*tert* butoxycarbonyl amines are readily converted into amines in a few minutes by acidic treatment.[19] We therefore thought it interesting to prepare the corresponding fluorocarbamates which could then be easily hydrolyzed to give fluoro amines. Thus, when *N*-(*tert*-butoxycarbonyl)-2-phenyl-3-methylaziridine (**10dC**, Table I) is reacted with $NR_3$–2.5HF, only one fluorocarbamate diastereoisomer, **11dT**, is obtained in 63% yield. No oxazolidones are detected. Hydrolysis of the *N*-(*tert*-butoxycarbonyl)fluoro amine is effected by Olah's reagent and may occur directly in the fluorination mixture without an intermediate workup. Having at hand this mild and efficient fluorination method, we extended it to other aziridines as indicated in Scheme I and Table VI.

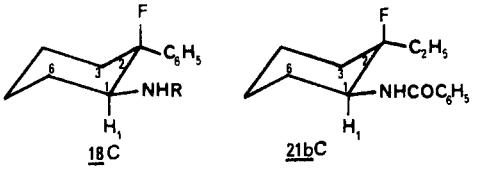
**Structure and Relative Configuration.** The structures of fluoro amines were established by IR, $^1H$ and $^{19}F$ NMR, and mass spectroscopy. However, spectroscopic data were inadequate for the assignment of relative configurations, which were determined in most of the cases by cyclization of the fluoro amine hydrochlorides into aziridines (eq 3) in the presence of alcoholic sodium or




potassium hydroxide. Hassner has applied this ring-clo-

(17) G. Aranda, J. Jullien, and J. A. Martin, *Bull. Soc. Chim. Fr.* 1890 (1965).
(18) I. N. Rozhkov and Y. Alyev, *Tetrahedron*, 31, 977 (1975).
(19) R. A. Boissonas and G. Preitner, *Helv. Chim. Acta*, 110, 875 (1953); R. A. Boissonas, *Adv. Org. Chem.*, 3, 159 (1963).

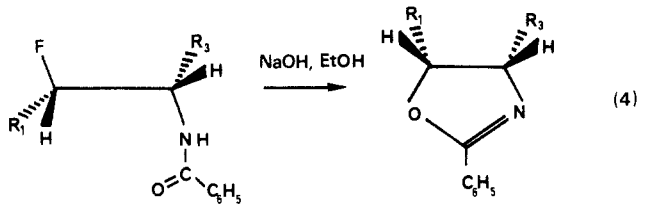
Table II. NMR Characteristics of *cis*-2-Substituted-2-fluorocyclohexylamines[a]




| | $^1$H NMR | | | | | | | $^{19}$F NMR | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $H_1$ signal | | | | | | | | | |
| | $\delta$ | multiplicity | $W$ | $^3J_{H_1F}$ | $^3J_{H_1H_{a_6}}$ | $^3J_{H_1H_{e_6}}$ | $R_2$, $\delta$ | $\phi$ | $W$ | $J$ |
| **18aC**, R = H | 2.9 | 2 4-line m | 43 | 27 | 11.6 | 4.3 | 7.4 | 184.7 | 90 | $^3J_{FH_{a3}}$ = 42, $^3J_{FH_{e3}}$ = 12, $^3J_{H_1F}$ = 28 |
| **18bC**,[b] R = $COC_6H_5$ | 4.6 | 2 m | 56 | 30 | | | 7.54 | 178 | 84 | $^3J_{FH_{a3}}$ = 42, $^3J_{FH_{e3}}$ = 12, $^3J_{H_1F}$ = 30 |
| **21bC** | 4.16 | 2 8-line m[c,e] | 54 | 28 | 11 | 5 | 0.94[d,f] | 174.5 | 112 | not attributable |

[a] Instrumental conditions: $CDCl_3$ solvent; proton chemical shifts ($\delta$) measured from $Me_4Si$ as an internal standard; fluorine chemical shifts ($\phi$) measured from $CFCl_3$ as an internal standard; $J$ and line-width ($W$) values are given in hertz. All spectra were recorded at 350 MHz unless otherwise stated and are described as follows: s, singlet, t, triplet, m, multiplet. [b] Recorded at 60 MHz. [c] On irradiation of the NH group, the signal becomes two four-line multiplets. [d] $CH_2$ signal overlapping the multiplet arising from the cyclohexyl group. [e] $J_{H\text{-}NH}$ = 11 Hz. [f] Triplet, 3 H, $J$ = 7 Hz.

sure method to determine the configuration of chloro amines,[20] the reaction taking place with inversion of configuration.[21] The aziridines were then compared with authentic samples, except the one produced from **5T**. In this case, the aziridine configuration was determined from NMR investigations. The more volatile fluoro amines **13a**, **14a**, **21aT,C** and **23aT,C** were converted into their *N*-benzoyl derivatives for identification studies; the crude product obtained after fluorination was benzoylated in situ according to Schotten–Baumann's method. The configuration of the *N*-benzoylfluoro amine was determined either by comparison with an authentic sample or by cyclization into an oxazoline in basic medium[22] (eq 4).

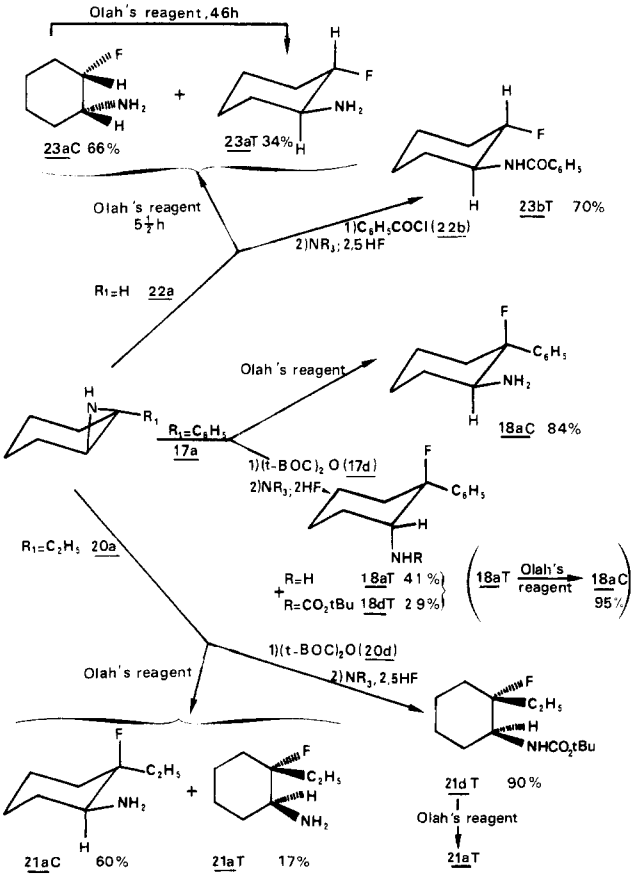



(4)

**Cyclic Series (Scheme I).** The $^1$H NMR spectra of 2-fluorocyclohexylamines (or of their *N*-benzoyl derivatives) **18aC**, **18aT**, **21bC**, and **23bT** were recorded at 350 MHz (Tables II and III). The $H_1$ proton (linked to the carbon bearing the NHR group) is deshielded and gives rise to a multiplet which is completely resolved at 350 MHz. (The high resolution of the multiplet and the symmetry of the observed signals suggest that the conformation of each compound is rigid). The knowledge of the different vicinal coupling constants enabled us to determine the configuration of the fluoro amine or of its derivative, since vicinal coupling constants $^3J_{HH}$ and $^3J_{HF}$ are known to be very dependent on the dihedral angle and the electronegativity of the substituents.[23]

**2-Fluoro-2-phenylcyclohexylamines 18aC and 18aT.** The high values of vicinal coupling constants $^3J_{HF}$ and $^3J_{H_1H_{a6}}$ for **18aC** suggest that the $H_1$ proton and fluorine

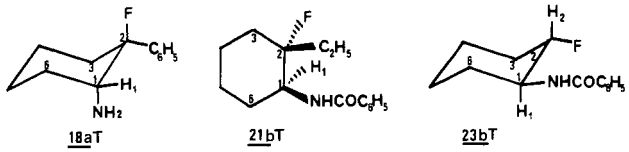
Scheme I




are diaxial. Hence the configuration of the fluoro amine **18aC** can only be cis.[24] For **18aT**, the smaller line width and the multiplicity of the signal of the $H_1$ proton are in agreement with an equatorial position. Moreover, proton $H_{a3}$, vicinal to the fluorine, appears as a double eight-line multiplet with $^3J_{FH_{a3}}$ = 39 Hz, indicating that $H_{a3}$ and fluorine are diaxial. Thus for isomer **18aT**, a trans con-

(20) A. Hassner and S. S. Burke, *Tetrahedron*, **30**, 2613 (1974).
(21) O. C. Dermer and G. E. Ham, "Ethylenimine and other Aziridines", Academic Press, New York and London, 1969, pp 26–27.
(22) R. A. Wohl, *J. Org. Chem.*, **38**, 3099 (1973); R. A. Wohl and J. Cannie, *ibid.* **38**, 1787 (1973).
(23) J. Cantacuzene and R. Jantzen, *Tetrahedron*, **26**, 2429 (1970).
(24) Thus the presence of electronegative groups such as $NH_2$ (**18aC**) or $NHCOC_6H_5$ (**18bC** prepared by benzoylation of **18aC**) decreases the theoretical coupling constant ($^3J_{HF}$ = 45 Hz) to about 30 Hz.

Table III. NMR Characteristics of *trans*-2-Substituted-2-fluorocyclohexylamines[a]




| | $^1$H NMR | | | | | | $^{19}$F NMR | | |
|---|---|---|---|---|---|---|---|---|---|
| | $H_1$ signal | | | | | | | | |
| | $\delta$ | multiplicity | $W$ | $^3J_{H_1F}$ | $^3J_{H_1H_{a6}}$ | $^3J_{H_1H_{e6}}$ | $R_2$ | $\phi$ | $W$ | $J$ |
| **18aT** | 3.18 | poorly resolved t | 22 | <10 | <10 | <10 | 7.4[b] | 152 | 70 | $^3J_{FH_{a3}}$ = 39 |
| **21bT**[c] | 4.5 | unresolved m | 36[d] | <10 | | | 0.95[e,i] | 160.6 | 96 | not attributable |
| **23bT** | 4.12 | 8-line m[f] | 33 | 10 | 9.5[h] | 4.3 | 4.40[g] | 179.6 | 80 | $^1J_{HF}$ = 50 |

[a] See footnote *a* of Table II. [b] $H_{a3}$ appears as a double eight-line multiplet ($\delta$ 2.38, $^3J_{FH_{a3}}$ = 39 Hz). [c] Recorded at 80 MHz. [d] On irradiation of the NH group, $W$ falls to 29 Hz. [e] See footnote *d* of Table II. [f] By irradiating the NH group. [g] Double six-line multiplet: $^2J_{H_2F}$ = 50 Hz, $^3J_{H_2H_{a3}}$ = 9.5 Hz, $^3J_{H_2H_1}$ = 9.5 Hz, $^3J_{H_3H_{e3}}$ = 4.3 Hz. [h] $^3H_{H_1H_2}$ = 9.5 Hz. [i] Triplet, 3 H, $J$ = 7 Hz.

figuration, with the fluorine and the amine group occupying diaxial positions, may be assigned.

***N*-Benzoyl-2-fluoro-2-ethylcyclohexylamines 21bC and 21bT.** The relatively high values of coupling constants $^3J_{H_1F}$ and $^3J_{H_1H_{a6}}$ exhibited by **21bC** indicate that $H_1$ and fluorine are in axial positions. Therefore, fluorine is in a cis relation to the amine group, and the molecule **21bC** exists in the cis configuration. The mass spectrum of the isomer **21bT** is similar to that of **21bC**, but the $^1$H NMR line width ($W$ = 36 Hz) observed in this case is fairly low in magnitude compared to that of **21bC** ($W$ = 54 Hz), suggesting that $^3J_{H_1F}$ is very small. This result is in agreement with a trans configuration (i.e., the $H_1$ or the fluorine is equatorial).

***N*-Benzoyl-2-fluorocyclohexylamines 23bT and 23bC.** The trans configuration of **23bT** was determined by a cyclization reaction. The low value of the line width ($W$ = 33 Hz) of the signal from the $H_1$ proton is in agreement with this trans configuration. This is confirmed by calculation of the coupling constants from the related NMR spectra at 350 MHz. The fact that $^3J_{H_1F}$ is small whereas the other two vicinal coupling constants ($^3J_{H_1H_2}$, $^3J_{H_1H_6}$) both amount to 10 Hz indicates that the two protons $H_1$ and $H_2$ occupy diaxial positions, the fluorine being equatorial. Thus the trans configuration may be confined to the fluoro amine **23bT**. The cis isomer **23bC** was not isolated, but $^{19}$F NMR spectra taken on the crude product resulting after 7 h of reaction was confirmative ($\phi$ 177.4).

Structures of *N*-butoxycarbonyl derivatives were assigned by hydrolyzing them to the known fluoro amines. Their relative configurations were determined by NMR. This method was especially helpful in the case of **18dT**.

***N*-(*tert*-Butoxycarbonyl)-2-fluoro-2-phenylcyclohexylamine (18dT).** The $^{19}$F NMR spectrum of the crude product obtained by fluorination of **17d** (Scheme I) consisted of two signals ($\phi$ 152.4 and 155.6), indicating that it was a mixture in a 41/29 ratio. Neither of these signals corresponded to the cis derivative **18dC** ($\phi$ 178.6), independently prepared by reacting di-*tert*-butyl dicarbonate ($(Boc)_2O$) with **18aC**. Hydrolysis of this fluorinated mixture with Olah's reagent provided the two fluoro amines **18aC** and **18aT** as shown in Table IV. . To confirm the structure of the product exhibiting a chemical shift at 155.6 ppm, the fluorocarbamate **18dT** was independently prepared. A fluorine chemical shift at $\phi$ 155.6 was observed for the product, confirming the presence of **18dT** in the crude mixture.

**Isomerization.** From Table IV it can be seen that the *trans*-fluoro amine **18aT** was isomerized into the cis compound **18aC** in 95% yield within 1 h by Olah's reagent. It

Table IV. Relative Distribution of Fluoro Amines Obtained by Fluorination by $NR_3$-*n*HF of *N*-(*tert*-Butoxycarbonyl)-2-phenyl-7-azabicyclo[4.1.0]heptane (17d) and Subsequent Hydrolysis with Olah's Reagent

**17d** $\xrightarrow{NR_3\text{-}nHF}$ **18aT + 18dT** $\xrightarrow{\text{Olah's Reagent}}$ **18aT,C**

| | fluorination | | | hydrolysis | | |
|---|---|---|---|---|---|---|
| | | product distribution after fluorination | | | product distribution after hydrolysis | |
| $NR_3$/HF ratio | reaction time[b] | **18aT** | **18dT** | reaction time[b,c] | **18aT** | **18aC** |
| 1/3 | 15 min | 60 | 40 | 15 min | 17 | 83 |
| 1/2 | 30 min | 58 | 42 | 30 min | 70 | 30[a] |
| 1/2 | 16 h | 70 | 30 | | | |
| | | 100 | | 1 h | 5 | 95 |

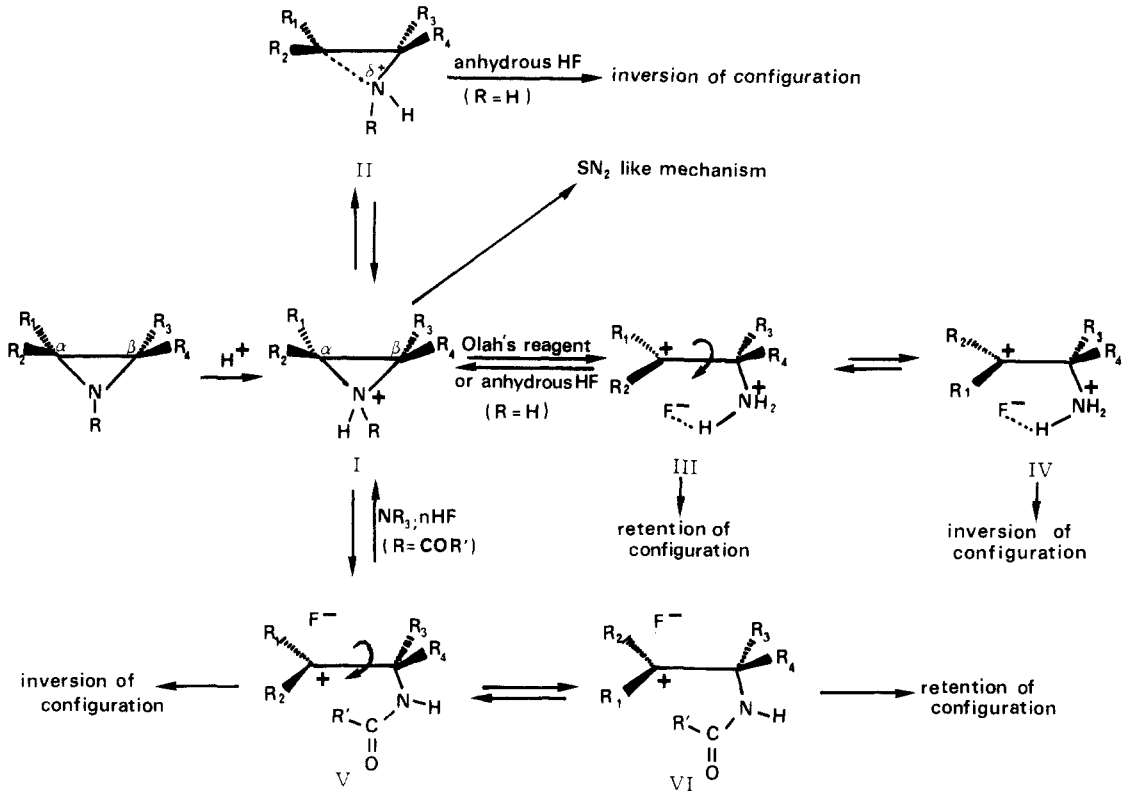
[a] Hydrolyses of the mixture of **18aT** and **18dT** (entries 1 and 2) were performed with two different samples of Olah's reagent: this may explain the different **18aT**/**18aC** ratios obtained in each case. [b] The temperature was 20 °C in all cases. [c] For mixtures of **18aT** and **18dT** with Olah's reagent.

Table V. Reaction Time Dependence of the Isomer Distribution of 23aC and 23aT Produced by the Reaction of 22 with Olah's Reagent

| reaction time, h | rel isomer ratio of **23aC**/**23aT** | % unreacted aziridine | % total yield (**22** + **23**) |
|---|---|---|---|
| 5.5 | 66/34 | 51 | 74 |
| 7.5 | 40/60 | 20 | 77 |
| 46 | 0/100 | 0 | 70 |

is important to note that in the reaction of **17a** with Olah's reagent the trans isomer **18aT** was never detected, even when the reaction was run for a shorter time (7 min). 1-Ethyl-7-azabicyclo[4.1.0]heptane (**20a**) gave rise, in Olah's reagent, to a mixture of *cis*- and *trans*-fluoro amino compounds **21aC** (60%) and **21aT** (17%). No isomerization of **21aT** to **21aC** or vice versa was observed when the reaction time was varied from 2 to 72 h. On the other hand, only the *trans*-fluoro amine **23aT** was obtained when 7-azabicyclo[4.1.0]heptane (**22a**) reacted for 46 h with Olah's reagent. However, at the beginning of the reaction, the two isomers **23aC** and **23aT** were present, the cis compound being formed predominantly (Table V). Therefore, the formation of the *trans*-fluoro amine **23aT** resulted, at least to some extent from the isomerization of **23aC**.

Scheme II




In the case of acyclic fluoro amines **8a** we determined that the erythro compound **8aE** did not undergo any isomerization in Olah's reagent (Scheme III); no isomerization was apparent after 15 h of contact with Olah's reagent at room temperature, whereas the threo fluoro amine **8aT** was partially isomerized to the erythro compound **8aE**. Thus the 8% yield of erythro isomer **8aE** isolated from **7aC** or **7aT** may result from the isomerization of **8aT** to **8aE**.

## Discussion

The regio and stereochemical courses of these reactions are determined by the relative stabilities of the aziridinium ion and the open carbonium ion. These relative stabilities are determined largely by the structure of the aziridine and the nature of the fluorinating reagent.[25] All the results can be explained by the concept of "borderline mechanisms", as summarized in Scheme II.

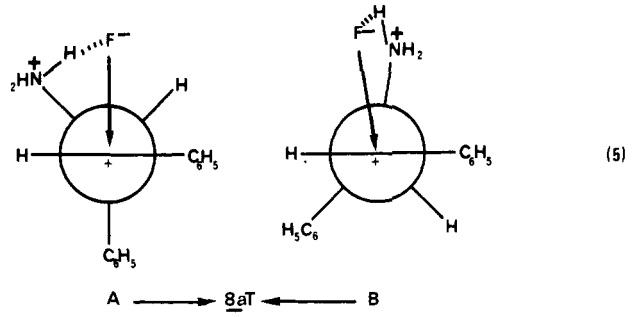
**Regioselectivity.** Fluoride attack is generally directed to the carbon most capable of stabilizing a positive charge. Only two exceptions were observed: the 13% and 29% yields of fluoro amines **3** and **14a**, resulting from fluoride attack at the less substituted carbon of the aziridines **1** and **12a**, may be accounted for by a $S_N2$-like mechanism on the aliphatic secondary or primary $\beta$-carbon of the ring. A regioselectivity enhancement was observed in the reaction of N-activated aziridines with $NR_3$–$n$HF. For instance, starting from the *N*-benzoylaziridine **12b**, we observed no fluoride attack at the $\beta$-carbon, in contrast with the production of a mixture of regioisomers **13a** and **14a** with the secondary aziridine **12a**. The reaction is thus regiospecific in this case. It is interesting to note that ring-opening of aziridine **12** by different nucleophiles in acidic media usually proceeds regioselectively at the less substituted carbon of the ring.[26] The regioselectivity of this reaction with $(H_nF_n)F^-$ is in the opposite direction to that observed with other nucleophiles such as $Br^-$, $Cl^-$, and $OH^-$.

**Stereoselectivity.** The results shown in Table I clearly indicate that the stereochemistry of the reaction is highly dependent on the substrate and the reagent used.

**Reaction of Secondary Aziridines.** A fundamental difference in behavior between anhydrous hydrogen fluoride and Olah's reagent is observed with secondary aziridines that have secondary benzylic carbon atoms (Scheme III). Hydrogen fluoride adds to the cis compounds **7aC**, giving almost exclusively the threo fluoro amine **8aT**, and its trans isomer **7aT** affords only the erythro compound **8aE**. In contrast, these two aziridines give similar results in the presence of Olah's reagent, yielding exclusively the threo fluoro amine **8aT** (>92%). (The low yield of erythro isomer **8aE**, detected in the reaction mixtures, results from an isomerization of **8aT**.) Thus the reaction of aziridines **7aC** and **7aT** with anhydrous hydrogen fluoride always occurs with inversion of configuration at the concerned carbon center. In this case the partially ring-opened aziridinium ion **II** is the reactive intermediate (Scheme II), and it undergoes a backside attack by the fluoride ion. Hassner has observed the same inversion of configuration when hydrochloric acid is added to the *cis*- or *trans*-aziridines **7a**.[20] In contrast, the obtention of the threo fluoro amine **8aT** from both aziridines **7aC** and **7aT** is best accounted for by the formation of a cation which rotates to its most stable conformation A or B before reacting with fluoride ion delivered by the ammonium group (eq 5). Complex formation resulting from hydrogen fluoride addition to an amine function is supported by the fact that many amine hydrofluorides are well-known from literature reports, and a few of these compounds are stable enough to be distilled.[27a] Moreover,

(25) W. R. Dolbier, *J. Chem. Educ.*, 46, 342, (1969).

(26) M. Blanc, Doctorat Thesis, Montpellier University, Montepellier, France, 1976; J. E. Earley, C. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lawes, *J. Am. Chem. Soc.*, 80, 3458 (1958); ref 3, p 248.




(5)

Rozen and co-workers have reported the existence of such interactions between iodine and fluorine when reacting iodine fluoride with *cis*- and *trans*-stilbenes.[27b] This mechanism, already advanced by one of us,[28] is supported by the recent paper of Wade[15] as well as the work of Kamernitskii and co-workers is the steroid series.[29] In summary, this result is in agreement with the formation of carbocation intermediates III or IV during the reaction course (Scheme II).

For other secondary acylic aziridines exhibiting a tertiary carbon center, reactions with either Olah's reagent or anhydrous hydrogen fluoride proceed via a carbocation intermediate.[16] Thus the reaction of aziridine 1 with either of these reagents follows the same stereochemical course and leads to about the same diastereoisomeric ratio, as a consequence of the relative stabilities of the two conformations III and IV of the cation (Scheme II).

Further differences between anhydrous HF and Olah's reagent were evidenced when we investigated the reactivity of 7-azabicyclo[4.1.0]heptanes **17a** and **20a** (Scheme I). These compounds are inert to hydrogen fluoride and are recovered quantitatively. In contrast, they react with Olah's reagent. Aziridine **17a** produces only the *cis*-fluoro amine **18aC** in 84% yield. This may be explained by the greater ionizing power of Olah's reagent (compared to that of hydrogen fluoride) which readily leads to a carbocation. Because of the steric interactions between the phenyl group borne by the $sp_2$ carbon and the amine function, the latter assumes the axial position (i.e., the conformation D is preferred; Scheme IV).[30] The complexation of nitrogen with hydrogen fluoride is again followed by cis addition of the fluoride ion in relationship with the amine group. Similarly, the compound 1-ethyl-7-azabicyclo[4.1.0]heptane (**20a**) is opened to a carbocation in Olah's reagent. The conformational equilibrium of this carbocation is shifted to a high extent in the direction of the conformer D, but, presumably, a small part of the conformer C must also be present. The latter conformer, in which the dihedral angle $R_1CCN$ falls to zero, provides the two *cis*- and *trans*-fluoro amines. One thus obtains, in preponderant amounts, the cis isomer **21aC** (78%) and only 22% of the trans isomer **21aT**. Finally, 7-azabicyclo[4.1.0]heptane (**22a**) yields, in Olah's reagent, a mixture of *cis*- and *trans*-fluoro amines, the former being totally isomerized into the trans compound at the end of the reaction (Table V). In opposition to Wade's formulations,[15] the *cis*-fluoro amine can only result from carbocation formation. However, in this case, a backside attack of the fluoride ion on the partially ring-opened aziridinium ion II (scheme II) may also explain the initial obtention of the trans isomer in 34% yield. In this case, species II and III are probably in competition.

Table VI. Diastereoisomeric Fluoro Amine Distribution from Treatment of Derivatives of Aziridine 10C with $NR_3$-*n*HF

| aziridine deriv | reagent | threo/erythro ratio | % yield |
|---|---|---|---|
| **10bC**, R = $COC_6H_5$ | $NR_3$-3HF | 68/32 | 60 |
| **10eC**, R = $CO_2C_2H_5$ | $NR_3$-2.5HF | 92/8 | 67 |
| **10dC**, R = $CO_2$-*t*-Bu | $NR_3$-2.5HF | 100 | 63 |

Under the same reaction conditions, we observed the isomerizations of **18aT** to **18aC** and of **23aC** to **23aT**. The fluoro amines **18aC** and **23aT** result in each case from thermodynamic control, the bulkiest substituents assuming diequatorial positions. Presumably, the fluoro amines **18aT** and **23aC** give rise in Olah's reagent, through C–F bond cleavage, to the carbocation. In the case of aziridine **20a** an equilibrium between the two conformers C and D of the carbocation is rapidly reached and leads to a mixture of **21aC** and **21aT** in an 80/20 ratio.

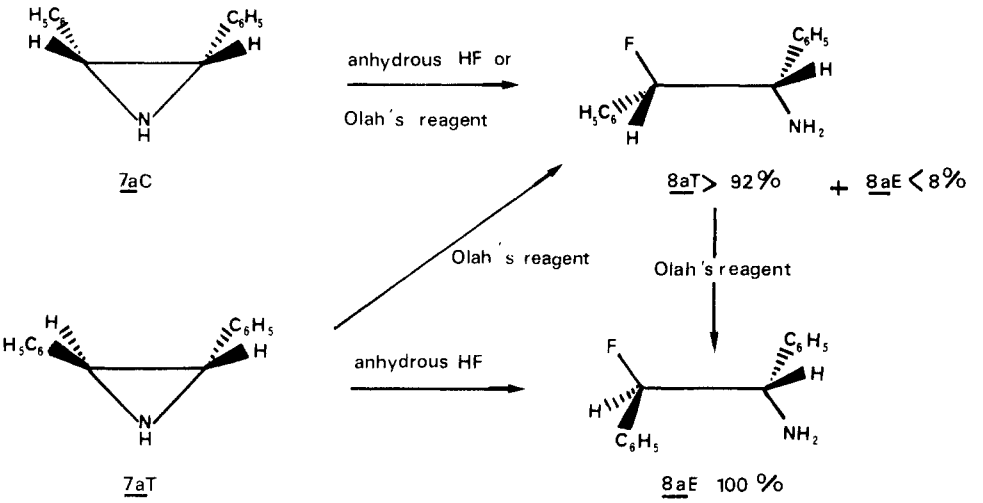
**Reaction of N-Activated Aziridines.** The results obtained with N-activated 7-azabicyclo[4.1.0]heptanes and $NR_3$-*n*HF indicate that only trans isomers are formed under such conditions (Scheme I: **18dT**, **21dT**, and **23bT**). Thus, with these three N-activated aziridines, the reaction is stereospecific. This is confirmed by the formation of only one fluoro amine derivative in the sugar series when an *N*-benzoylaziridine is treated with tetrabutylammonium fluoride.[31]

These results rule out the intervention of species III and IV (Scheme II) during the reaction; no complexation between the substituted amino group and hydrogen fluoride is observed. Two mechanistic pathways can explain the stereochemical results: either the formation of an aziridinium ion II (R = COR', Scheme II) which undergoes a backside attack by fluoride or the formation of the cation intermediate V which is quenched by the nucleophile in the trans position relative to the N-activated group. In this latter case, the bulky NHCOR' group would prevent fluoride attack on the same side of the carbocation.

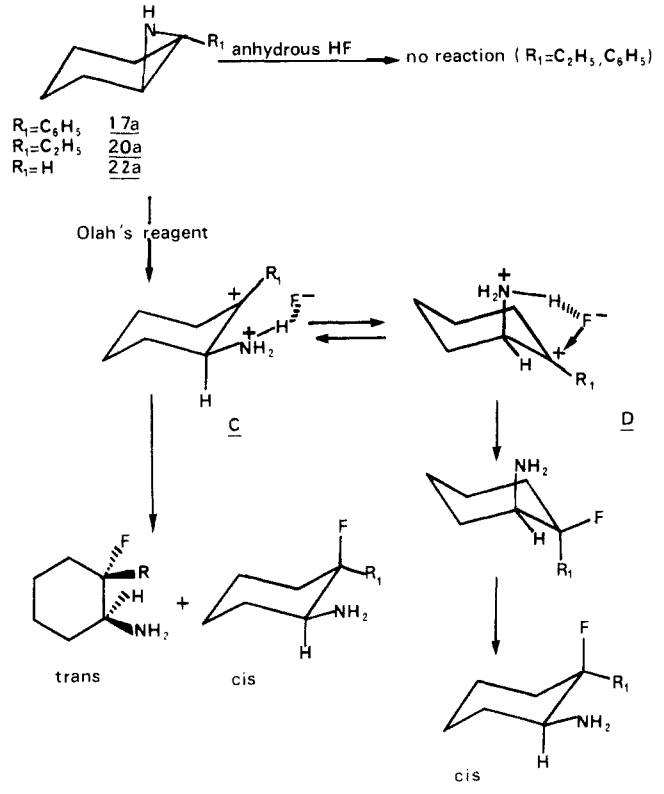
In order to choose between these two mechanisms, we submitted the diastereoisomeric aziridines **7bC** and **7bT** to the same reaction conditions (Scheme V). In both cases fluorination proceeded with predominant but not exclusive inversion of configuration. However, each isomer gave rise to oxazolines **9** in variable yields,[32] these oxazolines being formed in both cases with retention of configuration. The carbocation mechanism, i.e., formation of intermediates V and VI (Scheme II), best accounts for the results obtained with **7bC** and **7bT**[33] and can probably also be applied to the case of 7-azabicyclo[4.1.0]heptanes **17d** and **20d** (Scheme I). With these two bicyclic aziridines, the more stable conformation of the carbocation intermediate is the one exhibiting an axial, substituted amino group (i.e., with less steric interaction). The steric hindrance due to the N-activated group thus explains the exclusive formation of the trans compounds. In the case of the aliphatic

(27) (a) R. Franz, *J. Fluorine Chem.*, **15**, 423, (1980). (b) S. Rozen and M. Brand, *Tetrahedron Lett.*, **21**, 4543 (1980).
(28) S. Lacombe, Engineer Doctor Thesis, No. 386, Lyon University, May 12, 1980.
(29) A. V. Kamernitskii, A. M. Turuta, and T. M. Fadeeva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1637 (1980); *Chem. Abstr.* **94**, 4162 (1981).
(30) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).
(31) L. Hough, A. A. E. Penglis, and A. C. Richardson, *Carbohydr. Res.*, **83**, 142 (1980).
(32) The different yields of oxazoline **9** from each isomeric aziridine, **7bC** and **7bT** can be explained as follows: from the cis ring oxazoline formation increases the steric hindrance whereas fluoro amide formation results in steric decompression, and this pathway is thus preferred (oxazoline/fluoroamide, 9/91). With the trans isomer intramolecular cyclization is predominant (oxazoline/fluoroamide, 70/30).
(33) The absence of any trace of diastereoisomeric oxazoline in each case and the great stereoselectivity of the fluorination reaction indicate that the rate of nucleophilic attack at the carbocation center is much higher than the conformational equilibrium of this carbocation.

Scheme III




Scheme IV[a]




[a] Relative percentages of fluoro amines obtained after running the reaction for 5.5 h.

aziridine **22b** the reaction more probably proceeds via an intermediate of type II (Scheme II), as the most stable carbocation conformation (with an equatorial NHCOR' group) should lead to a mixture of *cis*- and *trans*-fluoro amines.

In the acyclic series the fluorination reaction is stereoselective but not stereospecific (i.e., *N*-benzoylaziridines **7bC** and **7bT**). In order to determine the influence of the steric hindrance due to the N-activating group on the stereochemical results, different **10C** aziridine derivatives were treated with $NR_3$–*n*HF (Table VI). The selectivity of the reaction increases from *N*-benzoyl compound **10bC** to *N*-ethoxycarbonyl derivative **10eC**, whereas the reaction affords only one diastereoisomer in the case of *N*-*tert*-butoxycarbonyl compound **10dC**. Thus by choice of a suitable N substituent, the fluorination reaction with $NR_3$–*n*HF can be made stereospecific in all the cases: only one fluoro amine diastereoisomer is obtained whatever the structure of the starting compound (acyclic or bicyclic).

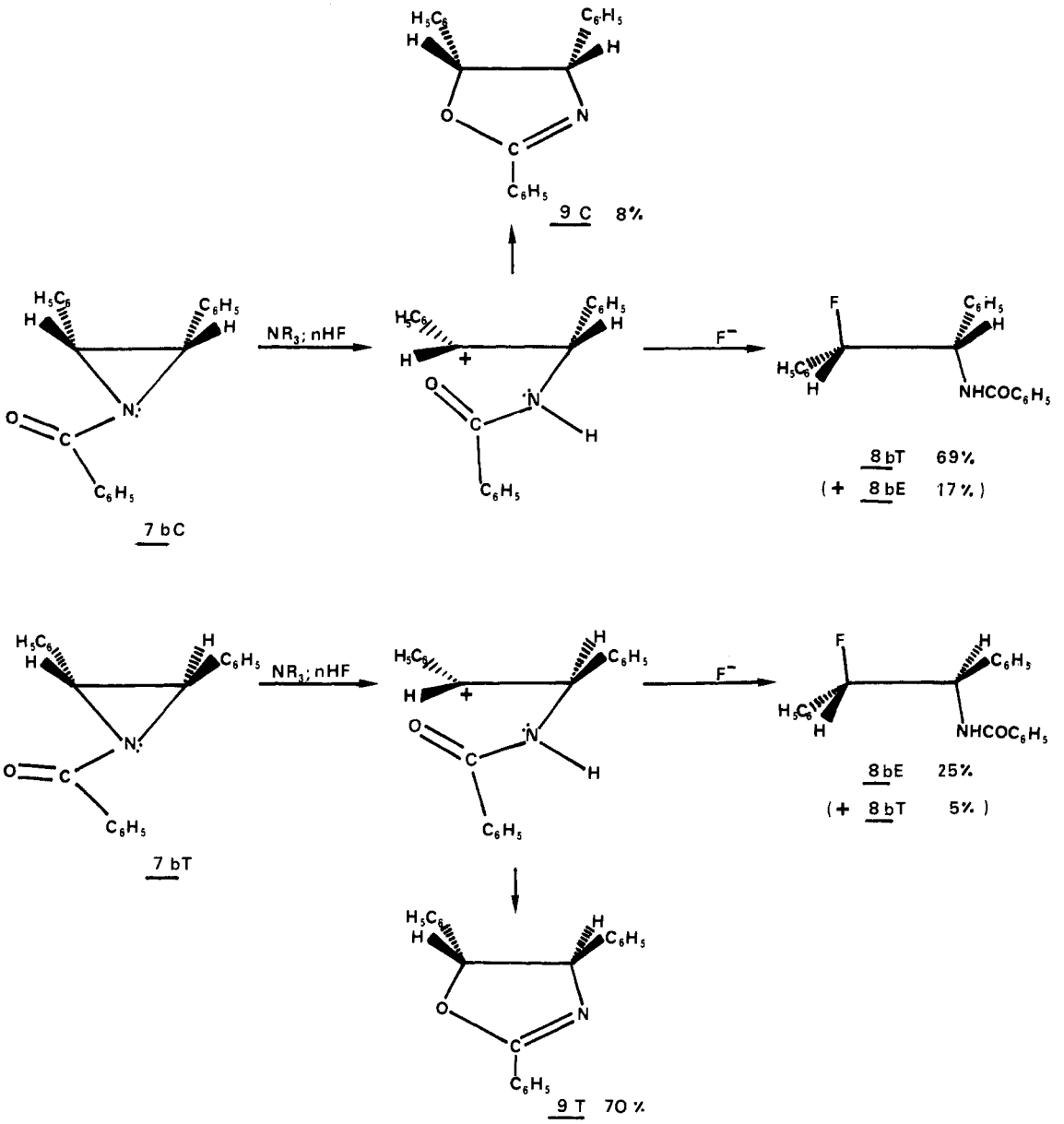
## Conclusion

Ring-opening of aziridines by different fluorinating agents provides a convenient route to $\alpha,\beta$-fluoro amines. The choice of the proper reagent (anhydrous HF or Olah's reagent for secondary aziridines and $NR_3$–*n*HF for N-activated aziridines) directs the stereochemistry of the final fluoro amine. With acyclic secondary aziridines, when the formation of a cation species is not favored, exclusive trans addition of fluorine is generally possible by using anhydrous HF. However, this reaction is ineffective with bicyclic aziridines. Exclusive trans addition is still obtained when *N*-(*tert*-butoxycarbonyl)aziridines are treated with $NR_3$–*n*HF whatever the structure of the starting compound (the *N*-*tert*-butoxycarbonyl group is easily removed by acid hydrolysis). In contrast, with Olah's reagent cis addition of fluorine relative to the ammonium group always occurs on the most stable carbocationic intermediate. Thus, in the cyclic series *trans*-fluoro amines are obtained from the reaction of N-activated aziridines with $NR_3$–*n*HF, whereas the cis compounds are available by treatment of the corresponding secondary aziridines with Olah's reagent. Ultimately, as it is possible to prepare a wide range of *cis*- and *trans*-aziridines, the choice of the proper fluorinating agent affords a versatile method for the preparation of various specific fluoro amines.

## Experimental Section

All melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 337 grating spectrophotometer and values are given in reciprocal centimeters (solvent $CHCl_3$). $^1H$ NMR spectra [$\delta$ ($Me_4Si$) 0)] were taken either on a Varian EM-360 (60 MHz) or on a Cameca 350 (350 MHz) and are described as follows: coupling constants $J$ are given in hertz; s, d, t, q, and m indicate singlet, doublet, triplet, quartet, and multiplet, respectively. $^{19}F$ NMR spectra were obtained on a Varian XL-100: $\phi$ values upfield compared to the signal for the standard ($CFCl_3$) are considered positive. Mass spectra were obtained on a Varian MAT CH5 (ionizing voltage 70 ev). All new fluoro amines were fully characterized by spectrometric analyses (including mass spectrometry) and/or satisfactory elemental analyses (±0.4% of theory) for C, H, N, and F of their hydrochlorides or *N*-benzoyl derivatives.

Scheme V




All starting aziridines are known in the literature and were prepared according to the following methods: action of Grignard reagents on oximes (**1**, **4**, **17a**, **20a**);[34] action of reducing organometallics on oximes (**7aC** and **10aC**);[35] iodoazide reduction (**7aT**, **10aT**, **22a**).[36] Compound **12a** was purchased from Eastman Kodak Co.

**General Procedure for Fluorination Reactions with Anhydrous Hydrogen Fluoride.** The reactions were performed under a $N_2$ atmosphere. Anhydrous hydrogen fluoride (approximately 10 mL) was introduced into a polyethylene flask cooled in liquid air, and 0.02 mol of aziridine was then added portionwise with stirring. The reaction mixture was then brought to room temperature, stirred for 1–12 h, and then subjected to a water pump vacuum for 10 min to evaporate the remaining HF. The residue was treated cautiously with 200 mL of a saturated $NaHCO_3$ solution and extracted with either ether or methylene chloride. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Crude products were separated by silica gel column chromatography.

**General Procedure for Fluorination Reactions with Olah's Reagent (Method A).** The reactions were performed under a $N_2$ atmosphere. The aziridine (0.005–0.01 mol, either pure or diluted in a solvent) was added portionwise to about 15 mL of Olah's reagent[15] in a polyethylene flask cooled to −78 °C. The reaction mixture was then warmed to the desired temperature and stirred under a nitrogen atmosphere for 1–70 h. The mixture was then hydrolyzed with either a saturated $NaHCO_3$ or $NH_4OH$ solution and extracted with ether or methylene chloride. The workup was as described above.

**General Procedure for Schotten–Baumann Benzoylation of Crude Fluorination Products (Method B).** After fluorination with Olah's reagent (method A), the reaction mixture was poured into a three-necked flask containing 80 mL of water and cooled in an ice bath. The solution was slowly neutralized by a 40% NaOH solution to pH 7–8. Benzoyl chloride (2 mL) was then added slowly and under cooling with a syringe, with the pH carefully controlled (pH 7–8) by dropwise addition of a 10% NaOH solution. At the end of this addition, the mixture was stirred for 2 h and then extracted with ether. The organic layer was dried over $MgSO_4$ and rotoevaporated. The fluoro-*N*-benzoyl derivatives were separated by column chromatography.

**General Procedure for Preparation of *N*-Benzoylaziridines.** Benzoyl chloride (0.07 mol) dissolved in 150 mL of

(34) G. Alvernhe and A. Laurent, *Bull. Soc. Chim. Fr.*, 3003 (1970); G. Alvernhe, Doctorat es-Sciences Thesis, No. 238, Lyon University, Lyon, France, 1974.

(35) Y. Diab, A. Laurent, and P. Mison, *Bull. Soc. Chim. Fr.*, 2202 (1974); Y. Diab, Doctorat d'Etat Thesis, No. 7644, Lyon University, Lyon, France, 1976.

(36) A. Hassner, G. M. Matthews, and F. W. Fowler, *J. Am. Chem. Soc.*, **91**, 5046 (1969).

benzene was added to a stirred and cooled solution of 0.07 mol of aziridine and 0.07 mol of triethylamine in 200 mL of benzene. The mixture was stirred 4–12 h, filtered, washed with water, dried, and rotoevaporated. The crude *N*-benzoylaziridine was purified either by column chromatography or by recrystallization.

**General Procedure for Preparation of *N*-(Ethoxycarbonyl)aziridines.**[37] To a solution of 0.05 mol of aziridine and 0.05 mol of $NEt_3$ in 70 mL of ether was added 0.048 mol of ethyl chloroformate dropwise with cooling in an ice bath. The reaction mixture was stirred for 2 h and filtered, and the organic layer was distilled under reduced pressure. The crude *N*-(ethoxycarbonyl)aziridine was used without further purification.

**General Procedure for Preparation of *N*-(*tert*-Butoxycarbonyl)aziridines.** To a solution of 0.01 mol of aziridine and 0.01 mol of NaOH in 3 mL of water and 6 mL of *tert*-butyl alcohol, was added 0.011 mol of di-*tert*-butyl-dicarbonate with cooling in an ice bath. After the mixture was stirred for 10 min, 10 mL of *t*-BuOH was added and the reaction mixture stirred for 20 h at room temperature. The mixture was then poured into 100 mL of water and extracted with ether. The extract was dried and evaporated under reduced pressure. The crude aziridine derivative was purified by column chromatography.

**General Procedure for Fluorination Reactions with $NR_3$–*n*HF.** To 4.6 mL of Olah's reagent in 10 mL of methylene chloride in a polyethylene flask cooled at −78 °C was cautiously added the required amount of triethylamine in 10 mL of methylene chloride in addition to 6 mL of $NEt_3$ for the reagent $NR_3$–3HF, 8 mL of $NEt_3$ for the reagent $NR_3$–2.5HF, and 11.5 mL of $NEt_3$ for the reagent $NR_3$–2HF.

After the mixture was stirred for 15 min, the aziridine derivative dissolved in 10 mL of methylene chloride was added dropwise. The mixture was then allowed to reach room temperature and stirred for various times. The workup was performed in the following ways. (a) Without hydrolysis with Olah's reagent: the mixture was slowly poured into a mixture of ice and $NH_4OH$ extracted with ether, dried, and rotoevaporated. (b) With intermediate hydrolysis with Olah's reagent: 20 mL of Olah's reagent was added directly and the mixture stirred for 0.5–1 h. The workup was as in part a.

**General Procedure for Cyclization of Fluoroamines into Aziridines.** The fluoro amine hydrochloride (0.10 mol) was slowly added to a stirred solution of 6 g of KOH in 50 mL of 95% ethanol. The resulting mixture was refluxed for 24 h, diluted with 100 mL of water, and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The aziridine was chromatographed on a silica gel column.

**General Procedure for Cyclization of Fluoro-*N*-benzoyl Derivatives to Oxazolines.** The *N*-benzoyl derivative (1 mmol) was added to a stirred solution of 3 g of KOH in 50 mL of ethanol. The mixture was refluxed for 47 h. The ethanol was removed by evaporation under vacuum. The resulting product was dissolved in water and extracted with ether. The organic layer was dried and distilled under reduced pressure.

**(1) Reaction of Anhydrous Hydrogen Fluoride with Aziridine 1.** The aziridine (4.4 g, 30 mmol) with a reaction time of 18 h at 20 °C gave the following.

2-Amino-2-phenyl-3-fluorobutane (**3**): eluant ether–petroleum ether, 10/90; 650 mg (13%); IR $\nu_{NH_2}$ 3320, 3220; $^1$H NMR $\delta$ 1.02 (2 d, 3 H, $^3J_{HH}$ = 6, $^3J_{HF}$ = 24), 1.42 (s, 5 H), 4,53 (2 q, 1 H, $^3J_{HH}$ = 6, $^2J_{HF}$ = 48), 7.01–7.69 (m, 5 H) $^{19}$F NMR $\phi$ 180.8 (6 lines, $^2J_{HF}$ = 48, $^3J_{HF}$ = 24). Cyclization of the hydrochloride (mp 199 °C) gave the aziridine **1**.

*threo*-2-Amino-3-fluoro-3-phenylbutane (**2T**): eluant ether/petroleum ether, 20/80; 2.06 g (41%); IR $\nu_{NH_2}$ 3380, 3320; $^1$H NMR $\delta$ 0.87 (d, 3 H, $^3J_{HH}$ = 6.5), 1.1 (s, $NH_2$), 1.6 (d, 3 H, $^3J_{HF}$ = 23), 2,97 (2 q, 1 H, $^3J_{HH}$ = 6.5, $^3J_{HF}$ = 16), 7.26 (s, 5 H); $^{19}$F NMR $\phi$ 159.1 (8 lines, $^3J_{HF}$ = 16, $^3J_{HF}$ = 23). Cyclization of the hydrochloride (mp 185–186 °C) gave the aziridine **1**.

*erythro*-2-Amino-3-fluoro-3-phenylbutane (**2E**): obtained in mixture with **2T** with the same eluant; yield 29% (determined by $^{19}$F NMR); $^1$H NMR $\delta$ ($CCl_4$) 0.84 (d, 3 H, $^3J_{HH}$ = 6.5), 1.36 (s, $NH_2$), 2.93 (2 q, 1 H, $^3J_{HH}$ = 6.5, $^3J_{HF}$ = 23), 7.35 (s, 5 H); $^{19}$F NMR $\phi$ 158.3 (8 lines, $^3J_{HF}$ = 16, $^3J_{HF}$ = 23).

**With Aziridine 7aC.** A 3.9-g (20 mmol) sample of the aziridine was used. Excess HF was removed by evaporation just at the end of the addition.

*threo*-2-Fluoro-1,2-diphenylethylamine (**8aT**): eluant ether–petroleum ether, 40/60; 4 g (95%); IR $\nu_{NH_2}$ 3380, 3300; $^1$H NMR $\delta$ 1.62 (s, $NH_2$), 4.12 (2 d, 1 H, M of an AMX multiplet, $^3J_{HH}$ = 7, $^3J_{HF}$ = 14), 5,32 (2 d, 1 H, A of an AMX multiplet, $^3J_{HH}$ = 7, $^2J_{HF}$ = 47), 7,12 (s, 10 H); $^{19}$F NMR $\phi$ 182.6 (q, $^2J_{HF}$ = 47, $^3J_{HF}$ = 14). Cyclization of the hydrochloride (mp 240 °C) gave the aziridine **7aC**.

*erythro*-2-Fluoro-1,2-diphenylethylamine (**8aE**): eluted after **8aT** with the same eluant; 227 mg (5%); IR $\nu_{NH_2}$ 3380, 3310; $^1$H NMR $\delta$ 1.47 (s, $NH_2$), 4.30 (2 d, 1 H, M of an AMX m, $^3J_{HH}$ = 7, $^3J_{HF}$ = 14), 5.5 (2 d, 1 H, A of an AMX m, $^3J_{HH}$ = 7, $^2J_{HF}$ = 47), 7.38 (s, 10 H); $^{19}$F NMR $\phi$ 181.3 (q, $^2J_{HF}$ = 47, $^3J_{HF}$ = 14). Cyclization of the hydrochloride (mp 252 °C) gave the aziridine **7aT**.

**With Aziridine 7aT.** The experiments were carried out according to the general procedure to give fluoro amine **8aE**; 2 g (97% from 10 mmol of **7aT**).

**With Aziridine 10aT.** A 2.7-g (20 mmol) sample of the aziridine was used. Excess HF was evaporated off at the end of the addition. The mixture of **11aT** and **11aE** was eluted with ether–petroleum ether to give 750 mg of product. Product determination was done by $^{19}$F NMR.

*threo*-1-Fluoro-1-phenyl-2-aminopropane (**11aT**): IR $\nu_{NH_2}$ 3380; $^1$H NMR $\delta$ 0.95 (d, 3 H, $^3J_{HH}$ = 6), 1.65 (s, $NH_2$), 3.20 (2 m, 1 H, $^3J_{HF}$ = 15, $^3J_{HH}$ = 6), 5.07 (2 d, 1 H, $^2J_{HF}$ = 48, $^3J_{HH}$ = 6), 7,4 (s, 5 H); $^{19}$F NMR $\phi$ 183.3 (q, $^2J_{HF}$ = 48, $^3J_{HF}$ = 15); mass spectrum, *m/e* (relative intensity), 152 (7.5), 132 (16), 118 (31), 117 (31), 109 (100), 91 (29), 83 (42), 81 (22), 44 (100); *N*-benzoyl derivative, mp 100–102 °C.

*erythro*-1-Fluoro-1-phenyl-2-aminopropane (**11aE**): same $^1$H NMR spectrum as **11aT**. $^{19}$F NMR $\phi$ 185.9 (q, $^2J_{HF}$ = 48, $^3J_{HF}$ = 15); *N*-benzoyl derivative, mp 129–135 °C.

**(2) Reaction of Olah's Reagent (by method A unless otherwise specified) with Aziridine 4.** A 4.3-g (27 mmol) sample of the aziridine was used. The $^1$H NMR of the crude product mixture indicated the presence of fluoroamines **5** (60%) and **6** (25%) together with 10% of unreacted aziridine **4**. The diastereoisomers were separated by two successive column chromatographs. Fluoro amine **5** was eluted with ether–petroleum ether (10/90). The ratio of the diastereoisomers **5T** and **5E** was determined by $^{19}$F NMR. The major isomer **5T**, was cyclized with NaOH to the other diastereoisomer, **25** of the aziridine **4** (65%). Fluoroamine **6** was eluted with ether–petroleum ether (20/80). The ratio of **6T** to **6E** was determined by $^{19}$F NMR. The major isomer, **6E**, was cyclized with NaOH to the aziridine **4** (yield 49%).

*threo*-1-Fluoro-1-phenyl-2-amino-2-methylbutane (**5T**): IR $\nu_{NH_2}$ 3380, 3310; $^1$H NMR $\delta$ 0.89 (s, 3 H), 0.90 (t, 3 H, *J* = 7), 1.31 (s, $NH_2$), 1.38 (m, 2 H), 5.20 (d, 1 H, $^2J_{HF}$ = 46), 7.40 (s, 5 H); $^{19}$F NMR $\phi$ 188.3 (d, $^2J_{HF}$ = 46).

*erythro*-1-Fluoro-1-phenyl-2-amino-2-methylbutane (**5E**): IR $\nu_{NH_2}$ 3380, 3310; $^1$H NMR $\delta$ 0.89 (s, 3 H), 0,90 (t, 3 H, *J* = 7), 1.31 (s, $NH_2$), 1,38 (m, 2 H), 5.18 (d, 1 H, $^2J_{HF}$ = 46), 7.40 (s, 5 H); $^{19}$F NMR $\phi$ 186.98 (d, $^2J_{HF}$ = 46).

*erythro*-1-Amino-1-phenyl-2-fluoro-2-methylbutane (**6E**): IR $\nu_{NH_2}$ 3380, 3310; $^1$H NMR $\delta$ 0.90 (t, 3 H, *J* = 7), 1.17 (d, 3 H, $^3J_{HF}$ = 22), 1.52 (dm, 2 H, $^3J_{HF}$ = 24), 1.69 (s, $NH_2$), 4.01 (d, 1 H, $^3J_{HF}$ = 15), 7.4 (s, 5 H); $^{19}$F NMR $\phi$ 158.13 (m).

*threo*-1-Amino-1-phenyl-2-fluoro-2-methylbutane (**6T**): same $^1$H NMR spectrum as **6E**; $^{19}$F NMR $\phi$ 159.3 (m).

**Aziridine 25**: IR $\nu_{NH_2}$ 3300; $^1$H NMR $\delta$ 0.75 (t, 3 H, *J* = 7), 1 (s, NH), 1.20 (m, 2 H), 1,35 (s, 3 H), 3 (s, 1 H), 7,37 (s, 5 H); mass spectrum, *m/e* (relative intensity) 161 (100, $M^{+\cdot}$), 146 (67), 132 (17), 105 (70), 91 (73), 77 (20).

**With Aziridine 12a.** Method B was used with 1 mL (16 mmol) of the aziridine. The mixture of *N*-benzoylfluoro amines **13b** and **14b** was eluted with ether–petroleum ether. Their relative ratio was determined by $^{19}$F NMR. Identification was accomplished by comparison with an authentic sample of **13b**.

*N*-Benzoyl-2-fluoropropylamine (**13b**): mp 47–49 °C (ether); IR $\nu_{NH}$ 3470, 3350, $\nu_{CO}$ 1680–1650; $^1$H NMR $\delta$ 1.3 (2 d, 3 H, $^3J_{HH}$ = 6, $^3J_{HF}$ = 24), 3.2–4.2 (m, 2 H), 4,83 (dm, 1 H, $^2J_{HF}$ = 50), 7.1 (s, NH), 7.4–8 (2 m, 5 H); $^{19}$F NMR $\phi$ 181.4 (8 multiple lines);

(37) Y. Iwakura and A. Nabeya, *J. Org. Chem.*, **25**, 1118 (1960).

mass spectrum, *m/e* (relative intensity) 181 (73, $M^{+\cdot}$), 161 (14), 131 (17), 105 (100), 77 (78).

*N*-Benzoyl-2-amino-1-fluoropropane (**14b**): IR $\nu_{NH}$ 3450, 3310, $\nu_{CO}$ 1680–1650; $^1H$ NMR $\delta$ 1.25 (d, $^3J_{HH}$ = 7), 4.45 (d, $^2J_{HF}$ = 48); $^{19}F$ NMR $\phi$ 233,7 (6 lines, $^2J_{HF}$ = 48, $^3J_{HF}$ = 24).

**With Aziridine 17a.** A 2-g (11.5 mmol) sample of the aziridine was used and gave *cis*-2-fluoro-2-phenylcyclohexylamine (**18aC**): eluant ether–petroleum ether 5/95; 1.80 g (80%); IR $\nu_{NH_2}$ 3370; NMR spectrum, see Table II; *N*-benzoyl derivative, mp 119–121 °C ($CH_3CN$).

**With Aziridine 20a.** Method B was used with 1.2 g (9.6 mmol) of the aziridine. The relative ratio of **21aT** and **21aC** was determined by $^{19}F$ NMR.

*cis*-*N*-Benzoyl-2-fluoro-2-ethylcyclohexylamine (**21bC**): eluant ether–petroleum ether, 10/90; 1200 mg (50%); mp 96–98 °C ($CH_3CN$); IR $\nu_{NH}$ 3440, 3320, $\nu_{CO}$ 1650; for NMR spectra, see Table II; mass spectrum, *m/e* (relative intensity); 249 (9, $M^{+\cdot}$), 229 (29), 200 (15), 173 (4), 160 (10), 124 (17), 122 (27), 108 (14),105 (100), 79 (7), 77 (37). The mixture of **21bT** and **21bC** was eluted (300 mg, 12%) followed by pure **21bT** (same eluant).

*trans*-*N*-Benzoyl-2-fluoro-2-ethylcyclohexylamine (**21bT**): 320 mg (13%); mp 102–105 °C ($CH_3CN$); IR $\nu_{NH}$ 3440, 3320, $\nu_{CO}$ 1660; for NMR spectra, see Table III; mass spectrum, *m/e* (relative intensity) 249 (9), 229 (31), 200 (16), 173 (4), 160 (10), 124 (23), 122 (20), 108 (12), 106 (10), 105 (100).

**With Aziridine 22a.** Method B was used with 500 mg (5 mmol) of the aziridine and a reaction time of 46 h. The $^1H$ NMR spectrum of the crude product indicated the sole presence of pure *trans*-*N*-benzoyl-2-fluorocyclohexylamine (**23bT**): 782 mg (70%, recrystallization from acetone); mp 160–161 °C; IR $\nu_{NH}$ 3440, 3340, $\nu_{cO}$ 1655; for NMR spectra, see Table III mass spectrum *m/e* (relative intensity) 221 (11, $M^{+\cdot}$), 201 (27), 183 (*), 173 (3), 160 (5), 122 (31), 105 (100), 77 (40), 51 (9).

For a reaction time 5.5 h with 1 g (10.3 mmol) of the aziridine, the $^1H$ NMR spectrum of the crude product (2.4 g) indicated the presence of unreacted starting material **22b** (51%) together with a mixture of fluorobenzamides **23bT** and **23bC** (total yield 23%). The $^{19}F$ NMR spectrum of the crude product gave two signals corresponding respectively to **23bT** ($\phi$ 179.6, 34%) and to *cis*-*N*-benzoyl-2-fluorocyclohexylamine (**23bC**; $\phi$ 177.4, 66%).

For a reaction time of 7.5 h with the same procedure and quantity as before, the $^1H$ NMR spectrum of the crude reaction mixture indicated unreacted aziridine **22b** (20%), *trans*-*N*-benzoylfluoro amine **23bT** (60%), and *cis*-*N*-benzoylfluoro amine **23bC** (40%).

**Cyclization of 23bT into Oxazoline 26.** A 277-mg (1.2 mmol) sample of fluoro amide **23bT** was used. Purification of the crude product by TLC gave pure oxazoline **26**: 114 mg (47%); eluted at $R_f$ 0.2; mp 43–48 °C (petroleum ether) (lit.[38] mp 45–46 °C; IR (film) $\nu_{CN}$ 1640; $^1H$ NMR $\delta$ 1.1–2 (m, 8 H), 4.1 (m, 1 H, $W_{1/2}$ = 20), 4,7 (m, 1 H, $W_{1/2}$ = 18 Hz), 7.6 and 8.1 (2 m, 5 H); mass spectrum (*m/e* (relative intensity) 201 (94, $M^{+\cdot}$), 172 (9), 160 (28), 159 (20), 158 (100), 145 (8), 131 (10), 130 (27), 122 (15), 117 (22), 105 (50), 104 (36), 77 (36), 51 (12).

***N*-Benzoylaziridine (10bC):** mp 63–64 °C (ether); IR $\nu_{CO}$ 1680; $^1H$ NMR $\delta$ 1.12 (d, 3 H, *J* = 6), 2.9 (m, 1 H, *J* = 6), 3.72 (d, 1 H, *J* = 6), 7.5–8.15 (2 m, 10 H). After reaction of **10bC** (1 g, 4,2 mmol) with Olah's reagent the products were separated by column chromatography. The oxazoline **24C** (410 mg, 41%) followed by **24T** (380 mg, 38%) were first eluted with ether–petroleum ether (5/95). Then the *N*-benzoyl amine *threo*-*N*-benzoyl-1-fluoro-1-phenyl-2-aminopropane (**11bT**) was isolated (ether–petroleum ether, 20/80): 160 mg (15%); mp 100–102 °C (ether); IR $\nu_{NH}$ 3450, 3320, $\nu_{CO}$ 1660; $^1H$ NMR $\delta$ 1.2 (d, 3 H, *J* = 7), 4.7 (m, 1 H), 5.55 (2 d, *J* = 6, $^2J_{HF}$ = 48, 1 H), 6.6 (s, NH), 7.4–7.9 (2 m, 10 H); $^{19}F$ NMR $\phi$ 186.9 (q, $^2J_{HF}$ = 48, $^3J_{HF}$ = 18); mass spectrum *m/e* (relative intensity) 257 (4, $M^{+\cdot}$), 149 (8), 148 (63), 105 (100), 77 (31). Cyclization of **11bT** in basic medium led to the oxazoline **24C**.

**(3) Reaction of $NR_3$–*n*HF with N-Activated Aziridines. With *cis*-*N*-Benzoyl-2,3-diphenylaziridine (7bC):** mp 138–141 °C; IR $\nu_{CO}$ 1660; $^1H$ NMR $\delta$ 4.1 (s, 2 H), 7.3 and 8.1 (2 m, 10 H). After treatment of **7bC** (3.2 mmol) with $NR_3$–2.5HF there was obtained 960 mg of crude product. After column chromatography, 75 mg of **9C** (8%) was isolated[39] (ether–petroleum ether, 90/10) followed by 885 mg (86%) of a mixture of **8bT** and **8bE** (determination by $^{19}F$ NMR). The $^{19}F$ chemical shifts of the diastereoisomeric fluoro amine derivatives were identical with those of authentic samples of **8bT** and **8bE**, prepared by benzoylation of each pure fluoro amine.

*threo*-*N*-Benzoyl-2-fluoro-1,2-diphenylethylamine (**8bT**): mp 196–198 °C ($Et_2O$); $^1H$ NMR $\delta$ (warm $CDCl_3$, very weakly soluble, bad resolution) 6 (2 d, $^2J_{HF} \simeq 50$, $^3J_{HH}$ = 4), 6 (q, 2 H), 7 (m, 1 H), 7.6 and 7.9 (2 m, 15 H); $^{19}F$ NMR $\phi$ 192.1 (q, $^2J_{HF}$ = 45, $^3J_{HF}$ = 22). For **8bE**: $^{19}F$ NMR $\phi$ 194.6 (q, $^2J_{HF}$ = 48, $^3J_{HF}$ = 27).

**With *trans*-*N*-Benzoyl-2,3-diphenylaziridine (7bT):** IR $\nu_{CO}$ 1660; $^1H$ NMR $\delta$ 4 (s, 2 H), 7.4 and 8 (2 m, 15 H). After reaction of **7bT** with $NR_3$–2.5HF the products were determined by NMR.

**With *N*-(*tert*-Butoxycarbonyl)aziridine (10dC):** purified by column chromatography (eluant ether–petroleum ether, 2/98); IR $\nu_{CO}$ 1720; $^1H$ NMR $\delta$ 0.9 (d, 3 H, *J* = 6), 1.45 (s, 9 H), 2.7 (m, 1 H, *J* = 6), 3.55 (d, 1 H, *J* = 6), 7.4 (s, 5 H). Reaction of 1.5 g (6.4 mmol) of **10dC** with $NR_3$–2.5HF gave 1020 mg (63%) of **11dT** containing traces of **11dE**, isolated by column chromatography (eluant ether–petroleum ether, 5/95).

*threo*-*N*-(*tert*-Butoxycarbonyl)-1-fluoro-1-phenyl-2-aminopropane (**11dT**): IR $\nu_{NH}$ 3440, $\nu_{CO}$ 1690–1720; $^1H$ NMR $\delta$ 1, 1 (d, 3 H, *J* = 6), 1.25 (s, 9 H), 4.15 (m, 1 H), 4.85 (d, NH), 5.40 (2 d, 1 H, $^2J_{HF}$ = 48, $^3J_{HH}$ = 4), 7.4 (s, 5 H); $^{19}F$ NMR $\phi$ ($CD_3COCD_3$) 185.7 (q, $^2J_{HF}$ = 48, $^3J_{HF}$ = 15); mass spectrum, *m/e* (relative intensity) 253 (1, $M^{+\cdot}$), 160 (12), 144 (37), 109 (18), 88 (30), 83 (33), 57 (100). For **11dE**: $^{19}F$ NMR $\phi$ ($CD_3COCD_3$) 196.7 (q, $^2J_{HF}$ = 47, $^3J_{HF}$ = 23).

**With *N*-Benzoyl-2-methylaziridine (12b):** IR $\nu_{CO}$ 1675; $^1H$ NMR $\delta$ 1.2 (m, 3 H), 1.95 (m, 1 H), 2.4 (m, 2 H), 7.35–8.3 (2 m, 5 H). Treatment of 1 g (6.2 mmol) of **12b** with $NR_3$–3HF gave the regioisomeric oxazolines **15** and **16**, (130 mg, 13%) which were eluted first by column chromatography followed by 950 mg (85%) of **13b**. 2-Phenyl-5-methyl-$\Delta^2$-oxazoline (**15**): IR $\nu_{CN}$ 1645; $^1H$ NMR ($CCl_4$) $\delta$ 1.32 (d, 3 H, *J* = 6), 3.28–4.25 (8 lines, AB part of an ABX system, 2 H, $J_{AB}$ = 14), 4.75 (m, 1 H, X part of an ABX system), 7.30–8.10 (2 m, 5 H); mass spectrum, *m/e* (relative intensity) 161 (76, $M^{+\cdot}$) 146, (21), 117 (100), 105 (24), 91 (15), 77 (58). 2-Phenyl-4-methyl-$\Delta^2$-oxazoline (**16**): IR $\nu_{CN}$ 1650; $^1H$ NMR $\delta$ ($CCl_4$) 1.28 (d, 3 H, *J* = 6), 3.8–4.45 (m, 3 H), 7.35–7.85 (2 m, 5 H); mass spectrum, *m/e* (relative intensity) 161 (50, $M^{+\cdot}$), 146 (100), 131 (38), 118 (19), 105 (12), 103 (28), 77 (30), 51 (10).

***N*-(*tert*-Butoxycarbonyl)-1-phenyl-7-azabicyclo[4.1.0]heptane (17d).** The general procedure was slightly modified for the preparation of this compound because of its instability. In a three-necked flask containing 800 mg of NaOH, 10 mL of water, and 10 mL of *t*-BuOH and cooled at 0 °C was slowly added 2.26 g (13.1 mmol) of secondary aziridine in 10 mL of *t*-BuOH, and 3.92 g (18 mmol) of $(t\text{-BOC})_2O$ was then added. The mixture was stirred under nitrogen for 1 h, and the temperature was allowed to rise to 25 °C. The hydrolysis was as described in the general procedure. The crude product was used without further purification: IR $\nu_{CO}$ 1700; $^1H$ NMR $\delta$ 1.2–2.4 (m) (17 H), 3.1 (t, *J* = 2, 1 H), 7.4 (s, 5 H). Reaction of **17d** (1.1 g, 4 mmol) with $NR_3$–2HF followed by column chromatography gave first a mixture of **18aT** and **18dT** (660 mg, eluant ether–petroleum ether, 20/80), the relative ratio of which was determined by $^{19}F$ NMR, and then 200 mg (23%) of oxazolidone **19** (eluant ether).

For confirmation of the structure of **18dT**, the *N*-*tert*-butoxycarbonyl derivatives of the *cis*-fluoro amine and of the mixture of **18aT** and **18dT** isolated above were prepared by following the general procedure.

*cis*-*N*-(*tert*-butoxycarbonyl)-2-fluoro-2-phenylcyclohexylamine (**18dC**): mp 96 °C (petroleum ether); IR $\nu_{NH}$ 3450, $\nu_{CO}$ 1710; $^1H$ NMR $\delta$ 1.2 (s, 9 H), 1.3–2.3 (m, 8 H), 4 (2 br m), 4.65 (d) (2 H), 7.4 (s, 5 H); $^{19}F$ NMR $\phi$ 178.57 (7-line m, $^3J_{FH_1}$ = 30, $^3J_{FH_{a3}}$ = 40, $^3J_{FH_{e3}}$ = 12).

*trans*-*N*-(*tert*-butoxycarbonyl)-2-fluoro-2-phenylcyclohexylamine (**18dT**): mp 143–145 °C (petroleum ether); IR $\nu_{NH}$ 3450,

(38) W. S. Johnson and E. N. Schubert, *J. Am. Chem. Soc.*, **72**, 2187 (1950); R. A. B. Bannard, N. C. C. Gibson, and J. H. Parkari, *Can. J. Chem.*, **49**, 2064 (1971).

(39) K. Bunge and R. Huisgen, *Chem. Ber.*, **105**, 1272 (1972).

$\nu_{CO}$ 1710; $^1$H NMR $\delta$ 1.15 (s, 9 H), 1.3–2.4 (m, 8 H), 4.05 (br m, 1 H), 4.8 (br m, NH); $^{19}$F NMR $\phi$ 155.5 (not resolved m).

4,5-Tetramethylene-2-oxazolidone (**19**): IR: $\nu_{NH}$ 3450 (sharp), 3250 (br), $\nu_{CO}$ 1750; $^1$H NMR $\delta$ 1.3–2.2 (m, 8 H), 4 (t, $J$ = 4, 1 H), 6.45 (s, 1 H), 7.46 (s, 5 H).

***N*-(*tert*-Butoxycarbonyl)-1-ethyl-7-azabicyclo[4.1.0]heptane (20d)**: crude product, IR $\nu_{CO}$ 1710; $^1$H NMR $\delta$ 0.8-1.9 (m exhibiting a sharp s at 1.4, 22 H), 2,3 (m, 1 H). A 1-g (4.4 mmol) sample of **20d** was allowed to react with $NR_3$–2.5HF. The crude solid isolated (970 mg) exhibited only one signal in the $^{19}$F NMR spectrum; its $^1$H NMR spectrum was consistent with pure **21dT**. The structure of **21dT** was confirmed by its hydrolysis to the amine **21aT** in Olah's reagent, followed by Schotten–Baumann benzoylation to **24bT**.

***N*-(*tert*-Butoxycarbonyl)-2-fluoro-2-ethylcyclohexylamine (21dT)**: yield 90; mp 107–109 °C ($CH_3CN$); IR $\nu_{NH}$ 3440, $\nu_{CO}$ 1710; $^1$H NMR $\delta$ 0.9 (2 overlapping t, $J$ = 7), 1.4 (s) and 1.2-2,2 (m, total 22 H), 3,85 (br m, 1 H), 4,7 (br m, 1 H); mass spectrum, $m/e$ (relative intensity) $\phi$ 161.6; 245 (10, $M^{+\cdot}$), 225 (2), 189 (34), 169 (4), 152 (7), 145 (7), 140 (3), 113 (10), 109 (9), 108 (16), 100 (10), 96 (4), 82 (6), 67 (5), 57 (100).

***N*-Benzoyl-7-azabicyclo[4.1.0]heptane (22b)** was purified by recrystallization from petroleum ether: mp 69–71 °C; IR $\nu_{CO}$ 1660; $^1$H NMR $\delta$ 1.1–2.4 (m, 8 H), 2.7 (br s, 2 H), 7.6 and 8.1 (2 m, 5 H). Reaction of **22b** (1.136 g, 5.7 mmol) with $NR_3$–2.5HF gave 1.060 g of crude product containing primarily *trans*-*N*-benzoyl-2-fluorocyclohexylamine (**23bT**; yield 70%, as determined by integration of the $^1$H NMR spectrum).

**Registry No.** 1, 25865-52-5; **2E**, 71057-05-1; **2T**, 71057-06-2; **2T**·HCl, 79121-05-4; **3**, 71057-07-3; **3**·HCl, 79102-18-4; **4**, 30031-86-8; **5E**, 79102-19-5; **5T**, 79102-20-8; **6E**, 79102-21-9; **6T**, 79102-22-0; **7aC**, 1605-06-7; **7bC**, 13866-14-3; **7aT**, 25125-72-8; **7bT**, 79102-23-1; **8aE**, 71057-09-5; **8aT**, 71057-08-4; **8bT**, 79102-24-2; **8bE**, 79102-25-3; **9C**, 58821-35-5; **9T**, 71027-98-0; **10aC**, 1485-13-8; **10aT**, 20993-60-6; **10aT** *N*-benzoyl derivative, 79102-26-4; **10dC**, 74275-05-1; **10bC**, 79102-27-5; **10eC**, 20993-62-8; **11aE**, 74275-07-3; **11dE**, 74275-06-2; **11dT**, 79102-28-6; **11bT**, 79102-29-7; **11aT**, 75197-98-7; **12a**, 75-55-8; **12b**, 21384-41-8; **13a**, 66679-40-1; **13b**, 74275-02-8; **14a**, 66679-45-6; **14b**, 74275-01-7; **15**, 23437-02-7; **16**, 25393-66-2; **17a**, 25022-23-5; **17a** *N*-benzoyl derivative, 79102-30-0; **17d**, 79102-31-1; **18aC**, 79102-32-2; **18aT**, 75213-92-2; **18bC**, 79102-33-3; **18dT**, 79102-34-4; **18dC**, 79102-35-5; **19**, 17539-96-7; **20a**, 51617-08-4; **20d**, 79102-36-6; **21bC**, 79102-37-7; **21bT**, 79102-38-8; **21dT**, 79102-39-9; **21aC**, 79102-40-2; **21aT**, 79102-41-3; **22a**, 286-18-0; **22b**, 4714-50-5; **23aC**, 79102-42-4; **23bT**, 79102-43-5; **23aT**, 75198-04-8; **23bC**, 79102-44-6; **24C**, 51650-18-1; **24T**, 38222-77-4; **25**, 79121-06-5; **26**, 57437-13-5.

# Anomeric Effect in 2-Alkoxytetrahydropyrans Studied by $^{13}$C and $^{17}$O NMR Chemical Shifts[1]

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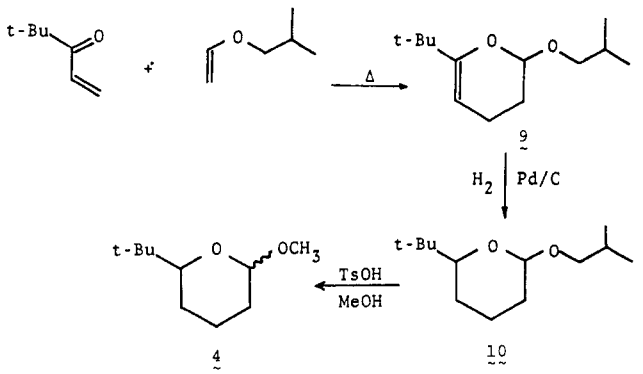
A series of 13 2-alkoxytetrahydropyrans has been prepared and studied by $^{13}$C and $^{17}$O NMR spectroscopy. Ten of these were in the form of cis and trans isomeric pairs, where the chemical shifts of isomers containing axial and equatorial alkoxy groups could be compared directly. A consistent pattern was observed, where the chemical shifts of not only the two oxygens but also the three carbons attached to oxygens were shifted "upfield" for the axial isomers. The results are interpreted in terms of three factors: a stereochemical $\gamma$-effect, back-bonding of a nonbonding orbital on the ring oxygen with the $\sigma^*$ orbital of the exocyclic C–O bond, and local paramagnetic screening.

The anomeric effect is a general phenomenon of 1,3-diheteroatomic systems. In 2-alkoxytetrahydropyrans and related systems, it manifests itself primarily in a preference for axial over equatorial stereochemistry. This difference can be either configurational or conformational depending on the system under study. In systems where cis and trans isomers are possible, configurational equilibration can be used to establish free-energy differences. In simpler systems, spectral techniques such as NMR can be used to at least establish preferred geometry.

A variety of experimental techniques and theoretical calculations have been used to explain the origin of the anomeric effect.[3] The nonbonding electron pairs on oxygen are of paramount importance. Interactions between pairs on different oxygens (dipole–dipole) and also overlap of nonbonding orbitals with C–X bonds have been shown to be important. One manifestation of the latter is the conformational preference known as the exo-anomeric effect.[4]

Scheme I. Preparation of *cis*- and *trans*-6-*tert*-Butyl-2-methoxytetrahydropyrans (4)




(1) Part 7 of "$^{17}$O Nuclear Magnetic Resonance Studies". Part 6: Kobayashi, K.; Sugawara, T.; Iwamura, H. *J. Chem. Soc., Chem. Comm.* **1981**, 479.

(2) IMS Invited Foreign Scholar, 1980.

(3) For pertinent reviews, see: (a) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Wiley: New York, 1965; Chapter 6. (b) Szarek, W. A.; Horton, D., Eds. "Anomeric Effect. Origin and Consequences"; American Chemical Society: Washington, DC, 1979; ACS Symp. Ser No. 87.

(4) Lemieux, R. U.; Koto, S. *ACS Symp. Ser.* **1979**, *No. 87*, 17.

0022-3263/81/1946-4948$01.25/0 