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Fluorodehydroxylation, a Novel Method for Synthesis of Fluoroamines and Fluoroamino Acids

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The alcoholic hydroxyl groups in hydroxyamines and hydroxyamino acids are selectively replaced by fluorine by reaction with sulfur tetrafluoride (SF_4) in liquid hydrogen fluoride solution. In contrast to the traditional methodology of fluorination with SF_4 (50–250 °C, in a high pressure reactor) this method, called fluorodehydroxylation, can usually be run at −78 °C and atmospheric pressure. This indicates a large increase in the reactivity of SF_4. The mechanism of fluorodehydroxylation involves carbocation intermediates in some instances and S_N2 mechanism in others, probably always proceeding via a $ROSF_3$ intermediate.

This paper amplifies and extends our earlier communication[1] on a novel method of organofluorine synthesis which we call *fluorodehydroxylation*. The term denotes a general method for the transformation of hydroxyamines and hydroxyamino acids into fluoroamines and fluoroamino acids, respectively. The method involves reacting sulfur tetrafluoride, SF_4, with the above substrates in liquid hydrogen fluoride solvent at low temperatures, usually at −78 °C, and at atmospheric pressure. A wide variety of alcohols containing basic nitrogen can serve as substrates. An important area of application is the synthesis of antimetabolites by employment of a particular principle in design of antimetabolites and drugs, namely, the principle of isogeometric modification of metabolites with maximal shift of electron distribution.[2]

The development of fluorodehydroxylation was motivated mainly by the lack of methods for the synthesis of fluoroamines and fluoroamino acids via fluorination of the corresponding hydroxy precursors. A large number of such hydroxy compounds are easily accessible, many of them in optically active form and with established stereochemistry. Whereas there are excellent methods available for the ROH–RF transformation for a large variety of alcohols, these methods invariably fail with substrates containing unprotected primary and secondary amines.[3] Moreover, even in cases where protection of the amine function (e.g., by phthaloylation) allows fluorination of the hydroxyl group, deprotection is rarely feasible.[4] In our search for alternative methods, sulfur tetrafluoride, SF_4, was considered, although its known limitations in transforming alcohols into RF compounds[5] suggested that a new approach would be required. The first problem was to find an appropriate solvent which satisfied several requirements: namely, it had to be (a) a solvent for SF_4; (b) nonreactive with SF_4; (c) protective against the reaction[6] between SF_4 and $-NH_2$; and (d) readily removable. Since the failure of fluorination of serine with SF_4 in liquid HF at 150 °C was already reported,[7] our first attempt in the fluorination of this compound utilized −78 °C as the reaction temperature. It is to be noted that fluorinations of organic compounds with SF_4 are usually done between 50 and 150 °C in a sealed reactor, under pressure. We obtained rapid and clean fluorination of serine in the first experiment which furnished 3-fluoroalanine (**1**). This result suggested not only that the reactivity of SF_4 is substantially increased in liquid HF solvent, but also that there was an increase in the desired selectivity favoring the fluorination of the alcoholic hydroxyl group. DL-β-Fluorophenylalanine (**2**) was also readily prepared in this way.

Results and Discussion

Encouraged by the clean fluorination of serine, we decided to study the reactivity of this system on a variety of structural types. As results in Table I illustrate, liquid HF at −78 °C not only fulfills all of the requirements stated above, but also renders the carboxyl and carbonyl functions impervious to the transformations usually observed in "traditional" SF_4 chemistry. The inertness of these functionalities provides essential selectivity.

In Table II we illustrate the variety of hydroxyamino compounds which were successfully fluorodehydroxylated.

The thiamine analogue, deoxyfluorothiamine chloride (**4**), was readily prepared as was the deoxyfluoro derivative of quinine (**5**). It appears that the latter is a single diastereoisomer from an analysis of its ^1H NMR spectrum.

Although a 6-fluoro derivative of pyridoxol has been reported,[8] no fluorodeoxy derivatives have been mentioned. We have synthesized a number of these as outlined in Scheme I. It was not possible to fluorodehydroxylate pyridoxal itself directly to the 5-deoxy-5-fluoro derivative **6**, presumably because it exists as a hemiacetal involving the 5-hydroxymethyl group. **6** was readily obtained by MnO_2 oxidation of the 5-deoxy-5-fluoropyridoxol (**7**), which in turn was syn-

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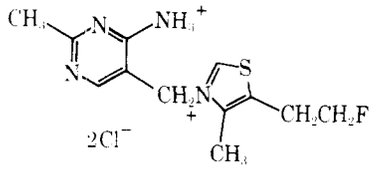

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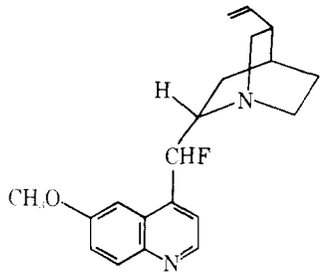

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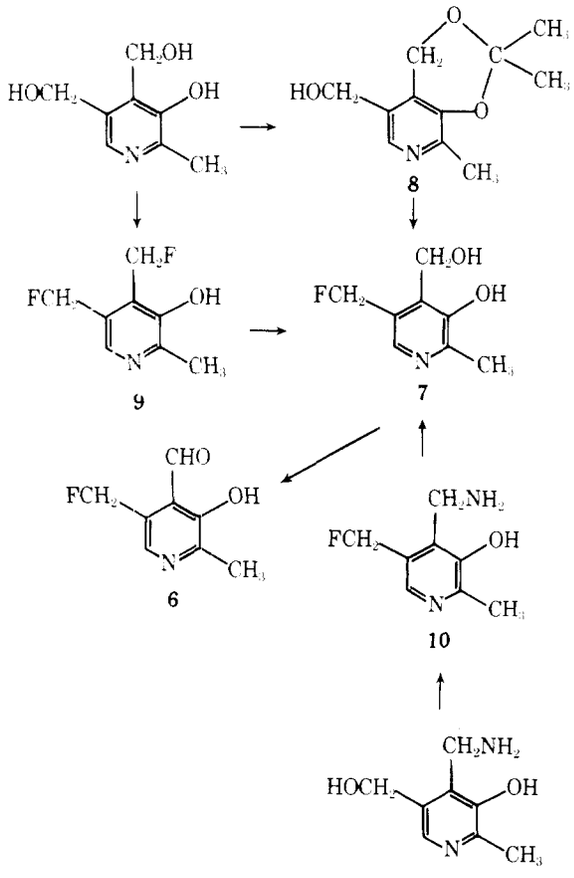
thesized in the following ways: (a) directly from the 3-*O*,4α-isopropylidenepyridoxol (**8**); (b) from 4,5-bis(deoxyfluoro)-pyridoxol (**9**) by hydrolysis; and (c) by diazotization of the 5-deoxy-5-fluoropyridoxamine (**10**). The latter was carried out in trifluoroacetic acid medium because a substantial amount of 4α-chloride is formed when the reaction is carried out in HCl. Thus, three 5-fluorodeoxy derivatives (**6**, **7**, and **10**) of the vitamin B_6 cofactors have been synthesized. The enhanced reactivity of the 4α vis-a-vis the 5α position (e.g., the conversion of **9** to **7**) proved to be a problem in the synthesis of the 4-deoxy-4-fluoropyridoxol series. An analogous set of transformations from isopyridoxamine to 4-deoxy-4-fluoropyridoxol was accomplished in very low yield presumably due to the instability of the intermediate 4-fluoro-4-deoxyisopyridoxamine.

Mechanism. The mechanism of the reaction appears to

Scheme I



Scheme II

1. $SF_4 + HF \rightarrow SF_3^+ + HF_2^-$ (ref 9)
2. $ROH + SF_3^+ \rightarrow ROSF_3 + H^+$ (ref 10)
3. $ROSF_3 + HF \rightarrow ROSF_2^+ + HF_2^-$ (ref 11)

A

4. $ROSF_2^+ + F^- \rightarrow RF + SOF_2$

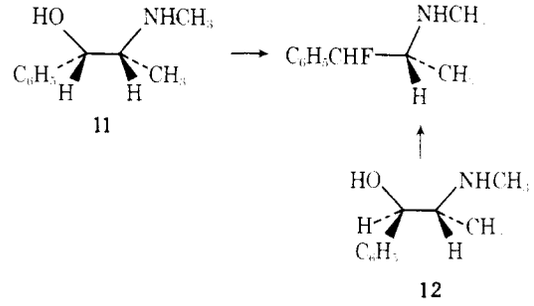
involve initial generation of a powerful leaving group at the alcoholic carbon. This is followed by fluorine substitution which is mechanistically dependent on the structural type: S_N1 reactions in those types which are good carbonium ion formers and S_N2 reactions in those primary and secondary alkyl systems which usually require direct displacements.

A. The Role of HF. Besides being a solvent and a protective agent (vide supra), liquid HF appears to play an integral role in the chemistry. Choline (a "protected" amine) is readily transformed into the (2-fluoroethyl)trimethylammonium ion in liquid HF with SF_4, but the reaction does *not* occur in diglyme or trifluoroacetic acid. In addition, 2-(*tert*-butylamino)ethanol is not transformed with SF_4 in trifluoroacetic acid.

$$(CH_3)_3N^+CH_2CH_2OH \rightarrow (CH_3)_3N^+CH_2CH_2F$$

We interpret this as an activation of both SF_4 and the putative alkoxysulfur trifluoride intermediate by HF. It also points to HF as the source of the fluorine in the displacement reaction (Scheme II).

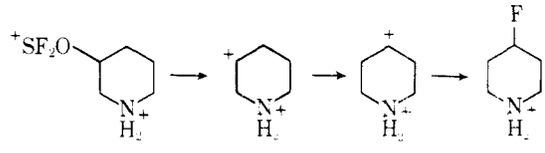
B. Good Carbonium Ion Formers. Fluorodehydroxylation of the diastereomeric benzylic alcohols *d*-ephedrine (**11**) and pseudoephedrine (**12**) afforded, in 100% yield, the same



11 12

roughly 2:1 mixture (by NMR analysis) of 1-phenyl-1-fluoro-2-(methylamino)propane. This implies that bond breaking precedes bond making in these good carbonium ion precursors.

C. Further Evidence for Considerable Bond Breaking in the Transition State. Both 3- and 4-hydroxypiperidine exclusively form 4-fluoropiperidine (**13**) when fluorodehy-



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droxylated. A positive charge at position 3 of the protonated piperidine ring would be destabilized relative to one in the 4 position because the charge in the 4 position would be one additional bond away from the positively charged nitrogen, and hence a migration to this position is expected. In addition, the fluorodehydroxylation of 2-methylserine afforded not only the expected 2-(fluoromethyl)alanine (18%), but also a 28% yield of 1-aminocyclopropanecarboxylic acid (**14**). The latter product may best be explained by the insertion of a high energy primary carbonium ion into the C–H bond of the neighboring methyl group.[12]

Table I. Conventional Fluorination with SF_4 vs. Fluorodehydroxylation

substrate	reaction product under conventional conditions[a]	reaction product in fluorodehydroxylation[b]
C_6H_5CHO	$C_6H_5CHF_2$	no reaction
$C_6H_5COCH_2NH_2$		no reaction
NH_2CH_2COOH	$NH_2CH_2CF_3$	no reaction
$HOCH_2CH(NH_2)COOH$	no useful reaction[c]	$FCH_2CH(NH_2)COOH$

[a] At 50–200 °C in sealed system. [b] Reaction in liquid HF solution at −78 °C, at atmospheric pressure. [c] See ref 7.

Table II.[a] Products of Fluorodehydroxylation of Various Hydroxyamino Compounds

product[b]	registry no.	mp, °C dec (uncor)	yield, %[c]
fluorodeoxythiamine chloride hydrochloride (**4**)	68813-10-5	233–234	44
fluorodeoxyquinine dihydrochloride (**5**)	68781-11-3	210–211	84
5-fluoro-5-deoxypyridoxol hydrochloride (**7**)	64068-26-4	173–174	29
4,5-bis(fluorodeoxy)pyridoxol hydrochloride (**9**)	64068-28-6	142–143	52
5-fluoro-5-deoxypyridoxamine dihydrochloride (**10**)	64068-25-3	>260	49
β-fluorohistamine dihydrochloride (**15**)	64068-30-0	130	71
DL-3-fluoroaspartic acid hydrochloride[d] (**16**)		144–145	42
DL-3-fluoroaspartic acid hydrochloride[e] (**17**)		157–158	71
DL-4-amino-3-fluorobutyric acid hydrochloride (**3**)	68781-12-4	159.5–160.5	50
1-aminocyclopropanecarboxylic acid hydrochloride[f] (**14**)	68781-13-5	228–229	28
(2*R*,3*S*)-2-amino-3-fluorobutyric acid[g] (**21**)	68781-14-6	197–198	48
(2*R*,3*R*)-2-amino-3-fluorobutyric acid[h] (**20**)	58960-35-3	193–194	57
(2*S*,3*R*)-2-amino-3-fluorobutyric acid[i] (**22**)	68781-15-7	197–198	
(2*S*,3*S*)-2-amino-3-fluorobutyric acid[j] (**23**)	68781-16-8	194–195	60

[a] This table is an extension of Table I, ref. 1. [b] Elemental analyses and NMR spectra were in accord with product structures. The substrates were the hydroxy congeners except where otherwise noted. [c] Yields are those of pure isolated products except where otherwise noted. [d] Erythro or threo isomer prepared by fluorodehydroxylation of dimethyl ester of erythro-3-hydroxyaspartic acid. Yield is of the hydrochloride; melting point is of the free amino acid. [e] Threo or erythro isomer prepared by fluorodehydroxylation of dimethyl ester of threo-3-hydroxyaspartic acid. Yield is of the hydrochloride; melting point is of the free amino acid. [f] The substrate was 2-methylserine. An 18% yield (NMR) of α-(fluoromethyl)alanine was also formed. [g] The substrate was L-threonine. [h] The substrate was L-allothreonine. [i] The substrate was D-threonine. [j] The substrate was D-allothreonine.

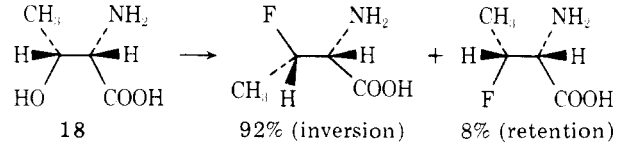
Finally, the reaction requires more stringent conditions (i.e., 0 °C) when the alcohol function is flanked by an additional positive charge. This occurs in the case of β-hydroxyhistamine, which is undoubtedly diprotonated in the HF system and which affords β-fluorohistamine (**15**) in good yield. Secondly, both diastereomeric 3-hydroxyaspartic acids are refractory to fluorodehydroxylation presumably because the 4-carboxy group is transformed into the positively charged acylonium ion or the electron-withdrawing acyl fluoride. However, when the carboxyl groups are esterified, reaction occurs at 0 °C and both diastereomeric 3-fluoroaspartic acids (**16** and **17**) may be isolated after hydrolysis. It is noted that both **16** and **17** proved to be perfectly stable, notwithstanding the suggestion that 3-fluoroaspartate should be extremely unstable, thus preventing both its synthesis "by all methods tested so far" as well as its isolation from the enzymatic transamination product of fluorooxaloacetate.[13]

D. Evidence for Bimolecular Reaction. It seemed likely that α-(fluoromethyl)alanine (vide supra) was formed in a bimolecular reaction, and therefore we felt it would be informative to know the stereochemistry in a system where a bimolecular reaction was likely. We have done this by examining the fluorodehydroxylation of both L-threonine [(2*S*,3*R*)-2-amino-3-hydroxybutyric acid, **18**] and its C-3 epimer, L-allothreonine [**19**, (2*S*,3*S*)-2-amino-3-hydroxybutyric acid]. In both cases, a mixture was formed with the major product being the one with an inverted configuration at C-3, threonine affording 92% and allothreonine 78% inverted products. Analogous results were obtained in the D series. The configuration of the major product from L-allothreonine was determined to be (2*R*,3*R*)-2-amino-3-fluorobutyric acid (**20**) by a single-crystal X-ray diffraction study.[14] These results seem to indicate that in the threonine–allothreonine system, the lowest

Table III

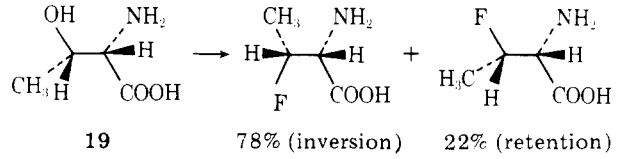
fraction	ret. time, min	relative peak area
A	1.75	8
	1.90	92
B	1.75	95
	1.90	5
C	1.90	100
D	1.75	78
	1.90	22

energy pathway is a bimolecular (S_N2) one (75 ± 10%) with some pure unimolecular (S_N1) pathway (25 ± 10%). These stereochemical results are consistent with those of other sec-



18 92% (inversion) 8% (retention)

21



19 78% (inversion) 22% (retention)

20

ondary alkyl systems undergoing solvolysis.[15] It is recognized that heterolysis to a tight ion pair[16] followed by asymmetric discharge by fluoride ion might also be proposed to explain these results. However, in our opinion, the intermediate A

(Scheme II) would not afford a tight ion pair and therefore we favor the former explanation.

Our view is that there is a relatively large amount of positive charge on the carbon atom in the transition state and that the pathway (i.e., uni- or bimolecular) depends upon the system's ability to stabilize a full positive charge.

Experimental Section

Caution. The herein described technique for handling liquid hydrogen fluoride is relatively safe as it does *not* involve transfer of *liquid* HF. A well-ventilated hood is a necessity for this type of work, and the operator should wear a face shield as well as rubber gloves. With these precautions, handling of HF and SF_4 proved to be routine in our laboratory. Instructions of the suppliers for the safe handling of these reagents should be observed. First-aid treatment of HF burns has been described.[17]

Fluorodehydroxylation. General Procedure. The flow diagram of the apparatus has been described[18] but has been modified so that the CF_3OF or F_2 cylinder is replaced by an SF_4 cylinder. Substrates were generally sealed in the reactor except when circumstances (e.g., β-fluorophenylalanine) required the addition of the substrate to a solution of SF_4 in HF. The reactor was then immersed in a −78 °C bath and HF was introduced into the reactor by condensation.[18] SF_4 (ca. 17.5 mmol/mL of liquid at −78 °C) was condensed out in the graduated tube and then introduced, subsurface, into the HF solution.

After completion of the reaction, N_2 was introduced into the reactor until all HF was evaporated from the reactor, and with the aid of a water aspirator the HF was continuously flushed down the drain. The residue was then dissolved in HCl (2.5 N) and the solution concentrated in vacuo. At this point, analytical measurements (e.g., NMR, amino acid analyses) were made followed by chromatography on Dowex 50 cation exchange resin (200–400 mesh, H^+ form). The column was washed with water until no fluoride ion could be detected in the effluent (fluoride ion test paper, Macherey, Nagel & Co.). Elution was continued with a stepwise increasing gradient of HCl. A Teflon bellows pump was used, and 15–20 mL fractions were collected. Concentration of positive fractions (as detected by the LKB UVICORD II or ninhydrin) was effected in vacuo at temperatures <40 °C. Amino acid analyses were run on a Beckman 121M analyzer using a Durrum DC-6A resin and buffer system.

3-Fluoro-L-alanine (1). A 1.05-g amount of L-serine (10 mmol) was dissolved at −78 °C in 20 mL of anhydrous liquid HF. SF_4 (1.2 mL, 21 mmol) was condensed into this solution, which was allowed to remain at −78 °C overnight. The HF was then removed, and the residue was taken up in concentrated HCl and evaporated to dryness in vacuo. This procedure of dissolution in HCl and evaporation was repeated three times. The resultant hydrochloride was dissolved in 2 mL of H_2O and 5 mL of 2-propanol, cooled to 0 °C, and treated with 0.81 mL of pyridine. Crystallization afforded, in two crops, 543 mg (51%) of 3-fluoro-L-alanine. A small sample was recrystallized from H_2O: mp 167–168 °C dec; 60-MHz NMR (D_2O–DCl) δ 4.08 (apparent d of t, 1 H, J = 29.5, 3.5 or 4.5 Hz), 4.83 and 4.85 (m, 2 H, J = 46 or 47 Hz, J = 3.5 or 4.5 Hz); $[\alpha]_D$ + 11.2° (c 3.3, 1 N HCl). Anal. Calcd for $C_3H_6NO_2F$: C, 33.65; H, 5.65; N, 13.08; F, 17.74. Found: C, 33.44; H, 5.91; N, 12.73; F, 18.08.

β-Fluorophenylalanine (2). *threo*-DL-β-Hydroxyphenylalanine monohydrate (1.99 g, 10 mmol) was added to a cooled (−78 °C) solution of 2.5 mL of SF_4 (42 mmol) in 40 mL of anhydrous liquid HF. After allowing the solution to remain at −78 °C for 45 min, the cooling bath was removed and the HF was evaporated in a stream of dry N_2 as rapidly as possible. The residue was taken up in concentrated HCl and then concentrated in vacuo to 1.86 g (85%) of a material whose NMR spectrum indicated that it was 100% β-fluorophenylalanine. A 1.1-g amount of this material was dissolved in 3.0 mL of H_2O, cooled to 0 °C, and treated with 0.325 mL of pyridine. The precipitate was collected and washed with 9:1 2-propanol–H_2O to yield 700 mg (76% recovery, 65% overall yield) of β-fluorophenylalanine. An analytical sample was prepared by recrystallization from 1:1 acetonitrile–H_2O: mp 173–174 °C dec (inserted at 160 °C); 60-MHz NMR (D_2O–DCl) δ 4.75 (dd of d, 1 H, J = 26, 4 Hz), 6.33 (d of d, 1 H, J = 45, 4 Hz), 7.53 (s, 5 H). Anal. Calcd for $C_9H_{10}NO_2F$: C, 59.10; H, 5.46; N, 7.56; F, 10.37. Found: C, 57.81; H, 5.64; N, 7.33; F, 10.90. The amino acid analysis showed a single symmetrical peak at 68′ (Phe 89′) color constant: 0.925 Phe.

DL-4-Amino-3-fluorobutyric Acid Hydrochloride (3). A 960-mg amount of DL-4-amino-3-hydroxybutyric acid (8.06 mmol) was dissolved in 30 mL of anhydrous liquid HF and treated with 1 mL of SF_4 (17.5 mmol) at −78 °C. The turbid solution was stirred at −78 °C for 3 h, and then the HF was evaporated. The residue was taken up in 2.5 N HCl and concentrated, affording a material whose NMR showed it to be a 100% deoxyfluoro compound. This material was applied to a 35-mL Dowex 50X2 column (H^+ form) which was washed with 240 mL of H_2O (until no further fluoride ion could be detected in the effluent) and then eluted with 4 N HCl. The combined ninhydrin positive fractions were concentrated and transferred to a filter with 2-propanol, affording 920 mg. A 576-mg amount of this material was recrystallized from 3 mL of ethanol, yielding 400 mg (50%): mp 159.5–160.5 °C; 60-MHz NMR (D_2O–DCl) three overlapping multiplets centered at δ 3.13 (4 H), 5.28 (doublet of multiplets, 1 H, J_{HF} = 50 Hz). Anal. Calcd for $C_4H_9NO_2FCl$: C, 30.48; H, 5.71; N, 8.89; F, 12.06. Found: C, 30.30; H, 5.70; N, 8.80; F, 11.83. Spinco amino acid analysis showed one peak at 80′ (Leu 84′) color constant: 0.677 Leu.

Deoxyfluorothiamine Chloride Hydrochloride (4). Thiamine chloride hydrochloride (3.5 g, 10.4 mmol) was dissolved in anhydrous liquid HF. The HF was blown off in a stream of dry N_2 (to remove chloride ions), and the residue was dissolved in 65 mL of liquid HF at −78 °C. SF_4 (6 mL, 105 mmol) was added and the resultant solution remained at this temperature overnight. After blowing off the HF and concentrating the residue with concentrated HCl, there was obtained 3 g of crude deoxyfluorothiamine salt. A 1-g amount of this material was applied to a 30-mL Dowex 50X2 column, washed free of fluoride ion with ca. 100 mL of H_2O, and eluted with concentrated HCl. The UV positive fractions were concentrated in vacuo to 800 mg. This was crystallized from methanol, affording 515 mg (44%) of deoxyfluorothiamine chloride hydrochloride hemihydrate: mp 233.5–234.5 °C dec; 60-MHz NMR (D_2O–DCl) δ 2.63 (s, 3 H), 2.73 (s, 3 H), 3.52 (doublet of triplets, 2 H, J = 26 Hz, J = 5 Hz), 4.80 (doublet of triplets, 2 H, J = 48 Hz, J = 5 Hz), 5.60 (s, 2 H), 8.16 (s, 1 H), 9.83 (s, 1 H). Anal. Calcd for $C_{24}H_{36}N_8OS_2F_2Cl_4$: C, 41.37; H, 5.17; N, 16.09; S, 9.20; F, 5.46; Cl, 20.40. Found: C, 41.68; H, 5.69; N, 16.19; S, 9.04; F, 5.62; Cl, 20.45.

Heating this material at 100 °C for 2 h afforded the anhydro compound (very hygroscopic). Anal. Calcd for $C_{12}H_{17}N_4FSCl_2$: C, 42.48; H, 5.01; N, 16.52; S, 9.49; F, 5.60. Found: C, 42.22; H, 4.95; N, 16.33; S, 9.65; F, 5.30.

Deoxyfluoroquinine Dihydrochloride (5). Quinine (6.5 g, 20 mmol) was dissolved in 35 mL of anhydrous liquid HF at −78 °C. SF_4 (4.8 mL, 85 mmol) was added and the resultant solution remained at −78 °C overnight. The HF was evaporated and the residue dissolved in concentrated HCl. This solution was evaporated to dryness in vacuo. This procedure was repeated twice, affording 8.0 g of crude dihydrochloride. The solid was dissolved in 200 mL of 2-propanol containing 5 mL of H_2O, treated with activated charcoal (Darco G-60), and filtered through Celite, and the filtrate was treated with 8.85 g of 1,5-naphthalenedisulfonic acid. There resulted a precipitate of 11.49 g (93%) of deoxyfluoroquinine naphthalene-1,5-disulfonate, mp 293–294 °C. Anal. Calcd for $C_{30}H_{31}N_2O_7S_2F$: C, 58.63; H, 5.05; N, 4.56; S, 10.42; F, 3.09. Found: C, 58.03; H, 4.97; N, 4.46; S, 10.55; F, 3.20.

To 6.15 g of the naphthalenedisulfonate salt (10 mmol) suspended in 25 mL of H_2O was added 25 mL of 2.5 N NaOH, and the mixture was extracted with 4 × 25 mL of methylene chloride. The organic solution was dried over $MgSO_4$, filtered, and concentrated to a yellow oil. This was dissolved in 20 mL of concentrated HCl and concentrated to dryness in vacuo. The residue was crystallized from acetonitrile, affording 3.61 g (90%) of deoxyfluoroquinine dihydrochloride: mp 210–211 °C dec; 100-MHz NMR ($CDCl_3$) δ 4.0 (s, 3 H, CH_3O), 5.83 (double doublet, 1 H, J_{HF} = 58 Hz, J_{HH} = 10 Hz). Anal. Calcd for $C_{20}H_{25}N_2OFCl_2$: C, 60.15; H, 6.31; N, 7.01; F, 4.76; Cl, 17.76. Found: C, 59.87; H, 6.49; N, 6.90; F, 4.42; Cl, 17.50.

5-Deoxy-5-fluoropyridoxal (6). 5-Deoxy-5-fluoropyridoxol hydrochloride (4.37 g, 21 mmol) was dissolved in 25 mL of H_2O, filtered, and treated with 1 g of Na_3PO_4 and 7 mL of 2.5 N NaOH. The solution (pH 6.2) was extracted with 5 × 25 mL of ethyl acetate, which was combined and washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated to 2.39 g (67% recovery) of the free base. A 2.30-g amount of the free base (13.4 mmol) was suspended in 75 mL of $CHCl_3$ and stirred for 22 h with 20 g of activated MnO_2. The resultant mixture was filtered through Celite, and the filter cake was washed with 5 × 40 mL of warm $CHCl_3$. The combined $CHCl_3$ extracts were concentrated and the residue was sublimed in vacuo, affording 920 mg of 5-deoxy-5-fluoropyridoxal (41%): mp 73–75 °C; IR ($CHCl_3$) 6.0 μm; 60-MHz NMR ($CDCl_3$) δ 2.60 (d, 3 H, J = 2 Hz), 5.7 (d, 2 H, J = 48 Hz), 8.13 (d, 1 H, J = 3 Hz), 10.50 (d, 1 H, J = 2 Hz), 11.5 (broad, 1 H). Anal. Calcd for $C_8H_8NO_2F$: C, 56.80; H, 4.77; N, 8.28; F, 11.23. Found: C, 56.95; H, 4.91; N, 8.18; F, 11.11.

5-Deoxy-5-fluoropyridoxol Hydrochloride (7). A. From 3-*O*,4α-Isopropylidenepyridoxol (8). To a −78 °C solution of 11.3

mL of SF_4 (198 mmol) in 300 mL of anhydrous liquid HF was added 20.9 g of 3-*O*-4α-isopropylidenepyridoxol (100 mmol). The HF was slowly evaporated overnight in a stream of N_2, allowing the −78 °C bath to warm up to ambient temperature. Completion of the HF removal was accomplished at room temperature. The residue was dissolved in concentrated HCl, evaporated to dryness, redissolved in diluted HCl, and treated with Darco G-60 decolorizing charcoal for 15 min on the steam bath. The solution was filtered through Celite and concentrated to 19.7 g. This material was purified by applying it to a 400-mL Dowex 50X2 column (H^+ form), washing with H_2O until the eluate was neutral and then eluting with 4 N HCl. The UV positive fractions collected between 500 and 1100 mL of column effluent were concentrated to 15.8 g of product, whose NMR indicated 85% purity. An 11.2-g amount of this material was dissolved in 200 mL of H_2O, the pH was adjusted to 7.9 with aqueous NaOH, and the solution was then extracted with 5 × 100 mL of ethyl acetate. The combined organic layers were backwashed with H_2O, dried, and concentrated to 5.1 g of 5-deoxy-5-fluoropyridoxol. This material was dissolved in concentrated HCl, concentrated to dryness, and crystallized from ethanol, affording 4.29 g (29%) of 5-deoxy-5-fluoropyridoxol hydrochloride: mp 173–174 °C dec; 60-MHz NMR (D_2O–DCl) δ 2.80 (s, 3 H), 5.13 (s, 2 H), 5.73 (d, 2 H, J = 44 Hz), 8.26 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_8H_{11}NO_2FCl$: C, 46.27; H, 5.34; N, 6.75; F, 9.15; Cl, 17.08. Found: C, 46.24; H, 5.33; N, 6.64; F, 9.08; Cl, 17.14.

B. From 5-Deoxy-5-fluoropyridoxamine (10). Crude 5-deoxy-5-fluoropyridoxamine hydrofluoride (1.1 g) (direct reaction product) was applied to 25 mL of Dowex 50X2 and eluted with 20% aqueous trifluoroacetic acid (TFA). The ninhydrin positive eluate was concentrated in vacuo and then redissolved in 15 mL of 2.5 N TFA. To this solution, heated at 90 °C, was added 390 mg of $NaNO_2$, and after stirring for 15 min an additional 200 mg of $NaNO_2$ was added. At this point the ninhydrin test was negative. The solution was stirred for a total of 45 min at 90 °C and then concentrated to dryness in vacuo. The residue was extracted with hot ethanol, filtered, and concentrated twice with concentrated HCl. By extracting with ethanol and adding ether, 500 mg of 5-deoxy-5-fluoropyridoxol hydrochloride, mp 167–168 °C, was obtained. One recrystallization afforded material, mp 171–172 °C dec, whose NMR was identical with material prepared in A.

C. By Hydrolysis of 4,5-Bis(deoxyfluoro)pyridoxol (9). 4,5-Bis(deoxyfluoro)pyridoxol hydrochloride (3.0 g) was dissolved in 30 mL of H_2O and heated at 90 °C for 1.75 h. The solution was then concentrated to dryness and applied to a 50-mL Dowex 50X8 column (H^+ form) which was washed with H_2O until the effluent was free of fluoride ion and then eluted with HCl. The UV positive material was concentrated to 3 g of crude product which was recrystallized from 100 mL of 2-propanol, affording 1.9 g of 5-deoxy-5-fluoropyridoxol hydrochloride, mp 169–170 °C dec. The NMR was identical with that of material prepared in A.

4,5-Bis(deoxyfluoro)pyridoxol Hydrochloride (9). Pyridoxol hydrochloride (1.025 g, 5 mmol) was dissolved in 30 mL of anhydrous liquid HF at −78 °C. The HF was evaporated to remove HCl and the residue redissolved in 30 mL of liquid HF. SF_4 (2 mL, 35 mmol) was added, and the solution was allowed to remain at −78 °C overnight. The HF was then evaporated, and the residue, which appeared by NMR to be 100% product, was applied to a 100-mL column of Dowex 50X4 (H^+ form). The column was washed free of fluoride ion with H_2O and eluted with 2.5 N HCl, and the UV positive fractions were concentrated to 550 mg of crude 4,5-bis(deoxyfluoro)pyridoxol hydrochloride (52%). Recrystallization from ethanol afforded material having mp 142–143 °C: 60-MHz NMR (D_2O) δ 2.80 (s, 3 H), 5.78 (double doublet, 2 H, J = 46 Hz, J = 2 Hz), 5.83 (d, 2 H, J = 45 Hz), 8.4 (s, 1 H). Anal. Calcd for $C_8H_{10}NOF_2Cl$: C, 45.82; H, 4.78; N, 6.68; F, 18.14; Cl, 16.95. Found: C, 45.98; H, 4.71; N, 6.60; F, 18.09; Cl, 17.31.

5-Deoxy-5-fluoropyridoxamine Dihydrochloride (10). Pyridoxamine dihydrochloride (2.56 g) was dissolved in 30 mL of anhydrous liquid HF. The solution was treated with 1.3 mL of SF_4 (23 mmol) and allowed to remain at −78 °C overnight. The HF was then removed, the residue was taken up in 30 mL of concentrated HCl, and the solution was concentrated in vacuo to 2.5 g of crude 5-deoxy-5-fluoropyridoxamine salts. This material was applied to a 100-mL Dowex 50X2 column (H^+ form) which was eluted with H_2O until the eluate was free of fluoride ion. Elution with 4 N HCl and concentration of the UV positive fractions afforded 2.33 g of a white glass which was crystallized by dissolving it in a minimal amount of methanol and adding hot ethanol (100 mL total volume). There was obtained 1.26 g (49%) of 5-deoxy-5-fluoropyridoxamine dihydrochloride: mp >260 °C; 60-MHz NMR (D_2O) δ 2.80 (s, 3 H), 4.47 (s, 2 H), 5.77 (d, 2 H, J = 46 Hz), 8.34 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_8H_{13}N_2OFCl_2$: C, 39.51; H, 5.39; N, 11.53; F, 7.82; Cl, 29.17. Found: C, 39.11; H, 5.32; N, 11.57; F, 7.96; Cl, 29.29.

Fluorodehydroxylation of the Diastereomeric 2-(Methylamino)-1-phenylpropanols. A. *d*-Ephedrine (11) (D-*erythro*-2-(Methylamino)-1-phenylpropanol). *d*-Ephedrine (19.8 g, 120 mmol) was dissolved in 180 mL of anhydrous HF at −78 °C, and to this solution was added 14.4 mL of SF_4 (255 mmol). The resultant mixture was allowed to warm to room temperature overnight under a stream of dry N_2. HF was removed by a stream of N_2. The residue was dissolved in concentrated HCl and concentrated to 24.8 g of crude fluoro products: 60-MHz NMR (D_2O) δ 1.3 (2 doublets, 3 H, J = 8 Hz), 8.06 (s, 3 H), 3.9 (m, 1 H), 7.6 (s, 5 H), and two sets of double doublets (CHF) [A, δ 5.73 (d of d, 0.67 H, J = 49 Hz, J = 9 Hz); and B, δ 6.22 (d of d, 0.33 H, J = 46 Hz, J = 3 Hz], corresponding to a 2:1 ratio of the diastereomeric fluoro compounds.

The crude mixture was applied to a 300-mL Dowex 50X8 (200–400 mesh) column and eluted with H_2O until the effluent was free of fluoride ion and then with 6 N HCl. The UV absorbing effluent (as detected by an LKB UVICORD II) was concentrated to 24.8 g of diastereomeric hydrochlorides. The solid was slurried with 100 mL of acetonitrile overnight and filtered. The insoluble portion was extracted with 50 mL of boiling acetonitrile, affording 13.3 g of the major isomer as the insoluble solid, mp 213–218 °C. This was twice recrystallized from 2-propanol, yielding 8.6 g (35%) of a 2-(methylamino)-1-phenylpropyl fluoride: mp 223–225 °C; 60-MHz NMR (D_2O) δ 1.7 (d, 3 H, J = 7 Hz), 2.92 (s, 3 H), 3.9 (m, 1 H), 5.68 (d of d, 1 H, J = 49 Hz, J = 9 Hz), 7.6 (s, 5 H); $[\alpha]_D$ −56.4° (*c* 3, 1 N HCl). Anal. Calcd for $C_{10}H_{15}NFCl$: C, 58.96; H, 7.44; N, 6.90; F, 9.35; Cl, 17.41. Found: C, 59.03; H, 7.60; N, 6.75; F, 8.54; Cl, 18.00.

The combined concentrated acetonitrile and 2-propanol mother liquors were extensively chromatographed on Dowex 50X8, but it was not possible to isolate the minor isomer in the pure state.

B. Pseudoephedrine (12) (D-*threo*-2-(Methylamino)-1-phenylpropanol). The fluorodehydroxylation of pseudoephedrine was effected in the same way as ephedrine. The NMR of the crude product showed it to contain approximately the same mixture as in the ephedrine case: 60-MHz NMR (D_2O) δ 1.3 (2 doublets, 3 H, J = 7.5 Hz), 3.05 (s, 3 H), 3.9 (m, 1 H), 7.53 (s, 5 H), and two sets of double doublets (CHF) [A, δ 5.83 (d of d, 0.74 H, J = 48 Hz, J = 9 Hz); and B, δ 6.20 (d of d, 0.26 H, J = 46 Hz, J = 3 Hz)].

4-Fluoropiperidine Hydrochloride (13). 4-Hydroxypiperidine (2.0 g, 19.8 mmol) was cooled to −78 °C and dissolved in 20 mL of anhydrous liquid HF. SF_4 (2 mL, 35 mmol) was added to the solution at −78 °C, which was then allowed to warm to room temperature overnight. The HF was removed, and the residue, whose NMR spectrum showed 100% fluoro product, was applied to a 40-mL Dowex 50X2 column (H^+ form). This column was eluted with H_2O to remove fluoride ion and then with 4 N HCl. The ninhydrin positive eluate was concentrated to 1.8 g (64%) of 4-fluoropiperidine hydrochloride. An analytical sample was prepared with 90% recovery by recrystallization from acetonitrile: mp 163–164 °C; 60-MHz NMR (D_2O–DCl) δ 2.20 (m, 4 H), 3.40 (m, 4 H), 5.06 (d of m, 1 H, J = 46 Hz). Anal. Calcd for $C_5H_{11}NFCl$: C, 43.05; H, 7.89; N, 10.05; F, 13.62; Cl, 25.45. Found: C, 42.95; H, 7.88; N, 9.88; F, 13.84; Cl, 24.72.

1-Aminocyclopropanecarboxylic Acid Hydrochloride (14). DL-α-Methylserine (1.2 g, 10 mmol) was dissolved at −78 °C in 20 mL of anhydrous liquid HF and then treated at this temperature with 2 mL of SF_4 (35.4 mmol). The solution was stirred at −78 °C for 3 h and then allowed to come to room temperature overnight. The HF was removed, and the residue was taken up in concentrated HCl. The resultant solution was concentrated to dryness in vacuo (ca. 40 °C). The resulting material was combined with a similar 8-mmol run, and the total (18 mmol) was applied to a 450-mL Dowex 50X8 (200–400 mesh, H^+ form) column which was then eluted, collecting 20-mL fractions, with H_2O (0.28 L) and HCl [0.2 N (0.54 L), 0.5 N (1 L), 1.0 N (3.9 L)]. After the first liter of 1.0 N HCl had been collected, the fraction size was reduced to 10 mL. Fractions 121–132 were found to contain α-methylserine, fractions 133–145 α-(fluoromethyl)serine, and fractions 182–225 the 1-aminocyclopropanecarboxylic acid. The latter fractions were combined and concentrated to 700 mg of 1-aminocyclopropanecarboxylic acid hydrochloride (28%). A small sample was recrystallized from ethanol–ether, affording an analytical sample; mp 228–229 °C. Anal. Calcd for $C_4H_8NO_2Cl$: C, 34.92; H, 5.86; N, 10.18; Cl, 25.78. Found: C, 35.48; H, 5.78; N, 10.10; Cl, 25.97. The mass spectrum of the bis(trimethylsilyl) derivative (*m/e* 245, 230, 202, 147, 128, 73) was identical with the same derivative of a commercial sample (Calbiochem, La Jolla, Calif. 92037). The NMR spectrum of the crude product showed a mixture of 52.2% 1-aminocyclopropanecarboxylic acid, 17.9% α-(fluoromethyl)alanine, and 29.9% α-methylserine.

β-Fluorohistamine Dihydrochloride (15). β-Hydroxyhistamine dihydrochloride (700 mg, 3.5 mmol) was dissolved in 25 mL of anhydrous liquid HF, and the solution was evaporated in a stream of dry nitrogen to remove HCl. The residue was redissolved in 40 mL of HF at −78 °C, treated with 2.3 mL of SF_4 (40.3 mmol), and warmed to 0 °C for 2.5 h. After recooling to −78 °C, an additional 2 mL of SF_4 was condensed into the solution. The reactor was then immersed in an ice bath (ca. 1 L) which was allowed to warm to room temperature overnight. The HF was then removed in a stream of N_2, the residue was dissolved in 25 mL of 2.5 N HCl, and the solution was concentrated in vacuo to a gummy residue. This was applied to 150 mL of Dowex 50X8 and eluted with 200 mL of H_2O, 400 mL of 1 N HCl, and ca. 1 L of 2.5 N HCl. The ninhydrin positive fractions (2.5 N HCl) were concentrated to 500 mg of crystalline β-fluorohistamine dihydrochloride (71%): decomposition at 130 °C when inserted at this temperature; 60-MHz NMR (D_2O–DCl) δ 3.3–4.2 (broad multiplet, 2 H), 6.27 (doublet of four-line multiplets, 1 H, J_{HF} = 47 Hz), 7.83 (m, 1 H, J_{HF} = 2 Hz), 9.0 (s, 1 H). Anal. Calcd for $C_5H_{10}N_3FCl_2$: C, 29.70; H, 4.95; N, 20.80; F, 9.40. Found: C, 29.69; H, 4.94; N, 20.51; F, 9.72.

DL-3-Fluoroaspartic Acids. A. From DL-*erythro*-3-Hydroxyaspartic Acid. DL-*erythro*-3-Hydroxyaspartic acid dimethyl ester hydrochloride (1.0 g, 4.68 mmol) was dissolved in 10 mL of anhydrous liquid HF at −78 °C, and the resultant solution was concentrated in a stream of dry N_2 to remove HCl. The residue was redissolved in 30 mL of liquid HF, and the solution was treated with 2 mL of SF_4 (35 mmol) at −78 °C. The cooling bath was then replaced with an ice bath, and after 1.5 h at 0 °C an additional 2.2 mL of SF_4 was passed into the reactor at 0 °C. After an additional 3.5 h at 0 °C, the HF was removed. The residue was dissolved in 2.5 N HCl and concentrated to 1 g of mixed salts whose NMR indicates a quantitative yield of fluoroaspartate.

A 1.0-g amount of this diester was hydrolyzed by heating at 80 °C for 16 h in 45 mL of 4 N HCl, affording on concentration 800 mg of the free acid salt. This was applied to a 150-mL Dowex 50X8 column (H^+ form) and eluted with H_2O until the effluent was free of fluoride ion and then with 0.1 N HCl, collecting 10-mL fractions. After 700 mL of effluent, there appeared a ninhydrin positive fraction which was concentrated to 370 mg (42%) of 3-fluoroaspartic acid hydrochloride: 60-MHz NMR (D_2O–DCl) δ 5.07 (double doublet, 1 H, J = 29 Hz, J = 2 Hz), 5.85 (double doublet, 1 H, J = 47 Hz, J = 2 Hz). Anal. Calcd for $C_4H_7NO_4FCl$: C, 25.60; H, 3.76; N, 7.47; F, 10.13. Found: C, 24.85; H, 3.77; N, 7.30; F, 10.40.

Liberation of the Free Amino Acid. A 300-mg amount of the above salt was applied to a 50-mL Dowex 1X8 column (formate form) and eluted with three column volumes of H_2O and then with aqueous formic acid. Concentration of the ninhydrin positive fractions yielded 261 mg, which was recrystallized from H_2O to yield 148 mg of a DL-3-fluoroaspartic acid (**16**): mp 144–145 °C dec (inserted at 135 °C): ^{19}F NMR (D_2O–trifluoroacetic acid) φ 202.5 (double doublet, J = 47 Hz, J = 29 Hz). Anal. Calcd for $C_4H_6NO_4F$: C, 31.79; H, 4.00; N, 9.27; F, 12.57. Found: C, 31.47; H, 4.24; N, 9.19; F, 12.38. Spinco amino acid analysis showed a single symmetrical peak, 16′ (Asp 31′) color constant: 1.03 Asp.

B. From DL-*threo*-3-Hydroxyaspartic Acid. This compound was transformed to its fluoro congener using a procedure identical with the one employed in A. DL-*threo*-3-Hydroxyaspartic acid dimethyl ester hydrochloride (1 g) afforded 800 mg of crude fluorinated dimethyl ester, which was then hydrolyzed to give 629 mg (71%) of the chromatographed 3-fluoroaspartic acid hydrochloride: 60-MHz NMR (D_2O–DCl) δ 4.95 (double doublet, 1 H, J = 26 Hz, J = 2 Hz), 5.92 (double doublet, 1 H, J = 44 Hz, J = 2 Hz).

Liberation of the free amino acid as in A (288 mg) afforded 128 mg (67% recovery) (recrystallized from H_2O) of a DL-3-fluoroaspartic acid (**17**): mp 157–158 °C dec. Anal. Calcd for $C_4H_6NO_4F$: C, 31.79; H, 4.00; N, 9.27; F, 12.57. Found: C, 31.60; H, 4.05; N, 9.15; F, 12.59. Spinco amino acid analysis showed a single symmetrical peak, 15′ (Asp 31′) color constant: 1.11 Asp.

2-Amino-3-fluorobutyric Acids. A. From L-Threonine. L-Threonine (2.4 g, 20.1 mmol) was cooled to −78 °C and dissolved in 30 mL of anhydrous liquid HF. SF_4 (2.3 mL, 40 mmol) was added to the solution, which was then allowed to stir at −78 °C for 3 h. The HF was then removed, the residue was dissolved in concentrated HCl, and the solution was evaporated to dryness. The residue was dissolved in H_2O, and an aliquot was found, by amino acid analysis, to contain 93% of the theoretical amount of 2-amino-3-fluorobutyric acids. This aqueous solution was applied to a 100-mL Dowex 1X8 (200–400 mesh, formate form) column and eluted with H_2O. All ninhydrin positive fractions were combined and concentrated in vacuo to 2.4 g of free amino acids. A small amount (fraction A) was removed for GLC analysis, and 2.0 g was chromatographed on 1.9 L of Dowex 50X8 (200–400 mesh, H^+ form). Fractions (19-mL) were collected, and the column was eluted with H_2O (0.95 L), 0.1 N HCl (1.9 L), 0.2 N HCl (1.9 L), 0.4 N HCl (4 L), and 0.5 N HCl (7.4 L). Ninhydrin positive material appeared after 3.8 L of 0.5 N HCl and ended after 5.7 L. Two cuts of the ninhydrin positive material were concentrated to dryness: the second 200 mL and the last 200 mL, affording 120 mg (fraction B) and 114 mg (fraction C), respectively. These solids were analyzed by GLC. The tailing 1 L of ninhydrin positive eluate was concentrated to 1.67 g of (2*R*,3*S*)-2-amino-3-fluorobutyric acid hydrochloride (**21**). This was then dissolved in 7 mL of H_2O and treated with 0.9 mL of pyridine and 28 mL of 2-propanol. After aging overnight at 5 °C, there was obtained 1.18 g (48%) of free amino acid: mp 197–198 °C dec; $[\alpha]_D$ +25.6° (*c* 1, 1 N HCl), +12.5° (*c* 1, H_2O): 60-MHz NMR (D_2O–DCl) δ 1.53 (d of d, J = 25 Hz, J = 6 Hz), 4.54 (d of d, J = 22 Hz, J = 2 Hz), 5.37 (d of m, J = 46 Hz). Anal. Calcd for $C_4H_8FNO_2$: C, 39.67; H, 6.66; N, 11.57; F, 15.69. Found: C, 39.94; H, 6.79; N, 11.28; F, 15.98.

B. From L-Allothreonine. Using the same conditions as in A, 2.0 g of L-allothreonine (16.8 mmol) in 30 mL of anhydrous liquid HF was reacted with 2.0 mL of SF_4 (35 mmol). After removal of the HF and concentration of the HCl solution, the residue was applied to 125 mL of Dowex 1X8 (200–400 mesh, formate form) and eluted with H_2O. The total ninhydrin positive fraction was evaporated to dryness to give 1.9 g of free amino acids. A small amount (fraction D) was subjected to GLC analysis, and 1.80 g was applied to a 2-L Dowex 50X8 (200–400 mesh, H^+ form) column. The column was eluted with H_2O (1 L) and HCl [0.1 N (2 L), 0.2 N (2 L), 0.4 N (5 L)]. Beginning with the 0.4 N HCl, 20-mL fractions were collected. The initial 1400 mL of eluate was combined and concentrated to afford 1.6 g of pure (GLC) (2*R*,3*R*)-2-amino-3-fluorobutyric acid hydrochloride (**20**). This 1.6 g was dissolved in 6 mL of H_2O, cooled in an ice bath, and treated with 0.87 mL pyridine followed by the addition of 30 mL of 2-propanol. After aging for 2 h at 5 °C, there was collected 1.16 g (57%) of the free amino acid: mp 193–194 °C dec; $[\alpha]_D$ −16.2° (*c* 1, 1 N HCl), −28.4° (*c* 1, H_2O); 60-MHz NMR (D_2O–DCl) δ 1.59 (d of d, J = 26 Hz, J = 6 Hz), 4.38 (d of d, J = 24 Hz, J = 3 Hz), 5.43 (d of m, J = 46 Hz). Anal. Calcd for $C_4H_8FNO_2$: C, 39.67; H, 6.66; N, 11.57; F, 15.69. Found: C, 39.65; H, 6.71; N, 11.43; F, 15.60.

From the 2- to 2.4-L cut of the 0.4 N HCl eluate, there was isolated 0.2 g of pure (GLC) (2*R*,3*S*)-2-amino-3-fluorobutyric acid hydrochloride, which corresponds to the major component of experiment A.

C. From the fluorodehydroxylation of D-threonine there was isolated (2*S*,3*R*)-2-amino-3-fluorobutyric acid (**22**) ($[\alpha]_D$ −26° (*c* 1, 1 N HCl)), and from the fluorodehydroxylation of D-allothreonine there was isolated (2*S*,3*S*)-2-amino-3-fluorobutyric acid (**23**) ($[\alpha]_D$ +18° (*c* 1, 1 N HCl)). Spinco amino acid analyses for both threo and erythro acids were the same, 27′ (Thr 38′) color constant: 0.82 Thr.

D. Analysis by Gas Chromatography (GLC).[19] A 10-mg amount of the appropriate solid was dissolved in 5 mL of methanol which had been saturated with HCl (gas), 1 mL of dimethyl sulfite was added, and the solution was refluxed for 30 min. The solution was then evaporated to dryness and the residue dissolved in 1 mL trifluoroacetic anhydride and refluxed for 10 min. After evaporation to dryness, the residue was dissolved in chloroform and aliquots were gas chromatographed on a 10 ft × ¼ in. UCON-50-HB2000 column at 165 °C (see Table III).

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Registry No.—**1**, 35455-21-1; **2**, 57362-93-3; **6**, 68781-17-9; **8**, 1136-52-3; **11**, 321-98-2; **12**, 321-97-1; **13**, 57395-89-8; **16**, 68832-48-4; **16** hydrochloride, 68832-49-5; **17**, 68832-50-8; **17** hydrochloride, 68832-51-9; **20** hydrochloride, 68781-18-0; **21** hydrochloride, 68781-19-1; L-serine, 56-45-1; *threo*-DL-β-hydroxyphenylalanine, 2584-75-0; DL-4-amino-3-hydroxybutyric acid, 924-49-2; thiamine chloride hydrochloride, 67-03-8; quinine, 130-95-0; deoxyfluoroquinine naphthalene-1,5-disulfonate, 68781-21-5; 5-deoxy-5-fluoropyridoxol, 68781-22-6; 5-deoxy-5-fluoropyridoxamine hydrofluoride, 68781-23-7; pyridoxol hydrochloride, 58-56-0; pyridoxamine dihydrochloride, 524-36-7; [*R*-(*R**,*R**)]-2-(methylamino)-1-phenylpropyl fluoride, 68781-24-8; [*S*-(*R**,*S**)]-2-(methylamino)-1-phenylpropyl fluoride, 68781-25-9; [*R*-(*R**,*R**)]-2-(methylamino)-1-phenylpropyl fluoride hydrochloride, 68781-26-0; [*S*-(*R**,*S**)]-2-(methylamino)-1-phenylpropyl fluoride hydrochloride, 68781-27-1; 4-hydroxypiperidine, 5382-16-1; DL-α-methylserine, 5424-29-3; α-(fluoromethyl)serine, 68781-28-2; β-hydroxyhistamine dihydrochloride, 64068-29-7; DL-*erythro*-3-hydroxyaspartic acid dimethyl ester hydrochloride, 18598-50-0; DL-*erythro*-3-fluoroaspartic acid

dimethyl ester hydrochloride, 68781-29-3; DL-*threo*-3-fluoroaspartic acid dimethyl ester hydrochloride, 68781-30-6; L-threonine, 72-19-5; L-allothreonine, 28954-12-3; D-threonine, 632-20-2; D-allothreonine, 24830-94-2; DL-*threo*-3-hydroxyaspartic acid dimethyl ester hydrochloride, 13515-98-5.

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Thermolysis of 1-*n*-Butoxy-1-(*tert*-butylperoxy)ethane[1]

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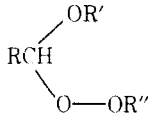
The monoperoxy acetal 1-*n*-butoxy-1-(*tert*-butylperoxy)ethane (1), prepared by the acid-catalyzed addition of *tert*-butyl hydroperoxide to *n*-butyl vinyl ether, undergoes pyrolysis at temperatures above 120 °C. The major pyrolysis products of 1 are methane, *tert*-butyl alcohol, *n*-butyl formate, and *n*-butyl acetate. The formate/acetate ratio depends on the reaction temperature, the concentration of the peroxy acetal, and the solvent in which the thermolysis is performed. Decomposition of 1 in *tert*-butylbenzene, a solvent in which the acetate/formate ratio is greater than unity, is faster than in cumene, a solvent in which the acetate/formate ratio is less than unity. The effects of solvent on the thermolysis rates and the product distributions are explained in terms of two modes of decomposition of 1, a unimolecular homolysis of the peroxide function that yields the formate ester and a free-radical chain reaction that accounts for the formation of the acetate ester.

Monoperoxy acetals have been prepared by the addition of an alkyl hydroperoxide to a vinyl ether,[1] by the transacetalation of acetals with an alkyl hydroperoxide,[2] by displacement reactions of alkyl hydroperoxides on α-halo ethers,[3] by alkylation of either peroxy hemiacetals or α-hydroperoxy ethers,[4] and by Cu_2Cl_2-catalyzed oxidation of ethers with an alkyl hydroperoxide. The predominant reaction products of the pyrolysis of these compounds have been reported to be the alcohol R″OH, the carboxylate ester RCO_2R', the formate ester HCO_2R', and the hydrocarbons derived from the alkyl moiety R.[6] The present work describes the kinetics and products of the thermolysis reactions in *tert*-butylbenzene and in cumene of 1-*n*-butoxy-1-(*tert*-butylperoxy)ethane (1),



1, R = CH_3; R′ = *n*-C_4H_9; R″ = *t*-C_4H_9

the addition product of *tert*-butyl hydroperoxide and *n*-butyl vinyl ether. *tert*-Butylbenzene and cumene were chosen as solvents for these reactions because they differ in their capabilities of reacting with chain-carrying peroxide-derived radicals, the latter having a benzylic hydrogen reactive toward abstraction by free radicals, whereas the *tert*-butylbenzene, having only primary alkyl hydrogens, is less reactive toward reaction with peroxide-derived radicals.

Results

Gas chromatographic examination of the reaction products obtained in the thermolysis of 1 in both cumene and *tert*-butylbenzene showed that the only nongaseous compounds formed in measurable amounts are *tert*-butyl alcohol, *n*-butyl acetate, and *n*-butyl formate. Methane, identified gas chromatographically, was the only gaseous product observed. Gas chromatographic analyses of the reaction mixtures of the decomposition of 1 in cumene and in *tert*-butylbenzene at different temperatures and solvent/peroxide ratios are shown in Table I. The reliability of these data is evident from the agreement between the amount of 1 that has reacted and the amount of *tert*-butyl alcohol and the sum of the amounts of the esters formed. Examination of the kinetic data and the product distributions shows the following facts that require explanation in terms of the mechanism for the thermolysis of this monoperoxy acetal. (1) The decomposition rate is faster at a given concentration ratio and temperature in *tert*-butylbenzene than in cumene. (2) The acetate/formate ratio is greater than unity in *tert*-butylbenzene but less than unity in cumene. (3) The acetate/formate ratio is dependent on the concentration of the peroxy acetal, the effect being more pronounced in *tert*-butylbenzene than in cumene.

Discussion

A mechanism for the thermal decomposition of 1 in a solvent RH capable of hydrogen abstraction by peroxide-derived radicals consistent with the observed experimental data is shown in eq 1–6. The amount of *n*-butyl formate formed in the fragmentation of 2 serves as a measure of the amount of 1 that decomposes in the unimolecular homolysis. If radical 2 participated in a hydrogen atom abstraction, the hemiacetal $CH_3CH(OH)OC_4H_9$-*n* would have been formed. Since no detectable amounts of either acetaldehyde or *n*-butyl alcohol were observed, it is reasonable to conclude that the formation

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