unfavorable $\Delta S^{\ddagger}$. For the slower reaction $\Delta H^{\ddagger}$ is less favorable because overlap with the π system cannot readily occur. Restrictions must also be relaxed on the angle of approach of the base in the slow reaction because $\Delta S^{\ddagger}$ is not so unfavorable as in the rapid reaction.

For enzymes, the potential significance of the activation parameters for the fast reaction is substantial and the following speculation is therefore warranted. Correct positioning of an auxiliary base at the active site of the enzyme could make $\Delta S^{\ddagger}$ much less negative. For the low value of $\Delta H^{\ddagger}$ observed by us and $\Delta S^{\ddagger} = 0$, the reaction would occur at a rate more rapid than is generally observed for reactions catalyzed by vitamin B_6 enzymes. It appears that the Dunathan hypothesis not only can explain the selectivity of vitamin B_6 enzymes but also may explain the magnitude of the rate enhancements observed with these enzymes.

Acknowledgment. The authors gratefully acknowledge support of this research by Grant AM 21568 from the National Institutes of Health.

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(4) Evidence for different environments of the two protons comes from NMR studies. The glycine moiety's CH_2 proton resonance appears as an AB pattern, consistent with different environments for the two protons. For each, the pseudo-allylic 4-bond coupling could be measured to the azomethine C–H proton. These couplings were $J = 1.85$ and 0.95 Hz. The larger coupling constant is consistent with the greatest angle to the plane of the π system (M. Barfield et al., *J. Am. Chem. Soc.*, **97**, 1482 (1975)) and it is this proton which exchanges most rapidly. NMR spectra showing these changes were supplied to the referees.
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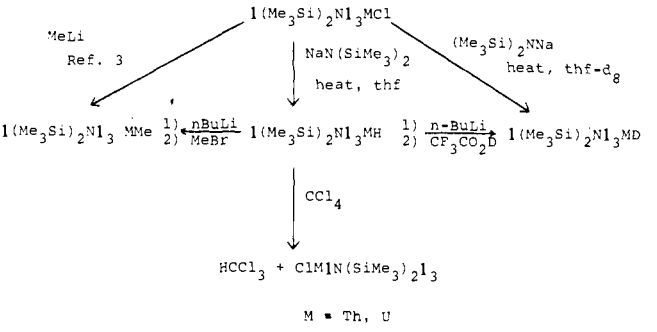
Hydrido[tris(hexamethyldisilylamido)]thorium(IV) and -uranium(IV)

Sir:

Metal hydrides are known for most of the metals. The 4f- and 5f-block metals, except those of the man-made ones, form rather stable metallic, binary hydrides of the type MH_2 and MH_3.[1] In contrast, only one molecular hydride of the f-block metals has been described, viz., $(Me_5C_5)_4M_2H_4$ where M is thorium or uranium.[2] We describe here the first monomeric, monohydride derivatives of these metals, viz., $HTh[N(SiMe_3)_2]_3$ and $HU[N(SiMe_3)_2]_3$.

Reaction of chloro[tris(hexamethyldisilylamido)]thorium(IV)[3] with 1 molar equiv of sodium hexamethyldisilylamide in refluxing tetrahydrofuran yields hydrido[tris(hexamethyldisilylamido)]thorium as white needles from pentane:[4] mp 145–147 °C; IR ν_{ThH} 1480 cm^{-1}; ^1H NMR (PhH) δ 0.90 and 0.40 due to the hydride and trimethylsilyl resonances, respectively. The deuteride, $DTh[N(SiMe_3)_2]$, ν_{ThD} 1060 cm^{-1}, can be prepared by refluxing $ClTh[N(SiMe_3)_2]_3$ and $NaN(SiMe_3)_2$ in perdeuteriotetrahydrofuran. The uranium hydride and deuteride were prepared similarly. Hydrido-

Scheme I



[tris(hexamethyldisilylamido)]uranium was crystallized from pentane as brown-yellow needles:[4] mp 97–98 °C; IR ν_{UH} 1430 cm^{-1}, ν_{UD} 1020 cm^{-1}. We have been unable to locate the hydride signal in the ^1H NMR spectrum of this paramagnetic ($\mu_B = 2.6$ BM in benzene solution) substance, though the trimethylsilyl groups resonate at δ −19.5. The hydrides can also be prepared from $ClM[N(SiMe_3)_2]_3$ and *tert*-butyllithium or lithium triethylhydridoborate in pentane.

The metal-bound hydrides were further characterized by their reaction chemistry; see Scheme I. The hydrides react with carbon tetrachloride yielding chloroform (identified by its NMR spectrum) and $ClM[N(SiMe_3)_2]_3$ (M is thorium or uranium). The latter were identified by melting point, mixture melting point, and IR and NMR spectra. Further, addition of *n*-butyllithium to a pentane solution of the hydrides, followed by methyl bromide, yields $MeM[N(SiMe_3)]_3$[3] (M = Th or U quantitatively). The product from reaction of *n*-butyllithium with the hydride derivatives affords $HM[(N(SiMe_3)_2]_3$ or $DM[N(SiMe_3)_2]_3$ (M = Th or U) upon addition of trifluoroacetic acid or deuteriotrifluoroacetic acid, respectively.

The uranium and thorium hydrides have also been characterized by a single-crystal X-ray analysis, though the hydrogen atom was not located.[5]

Acknowledgment. This work was supported by the Division of Nuclear Sciences, Office of Basic Energy Sciences, U.S. Department of Energy.

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A New Approach toward the Synthesis and Chemistry of Fluoroxy Compounds

Sir:

Since the pioneering investigations of Barton and Hesse[1] in which electrophilic fluorination was developed, work in this new area has been restricted to the use of fluoroxytrifluoromethane (CF_3OF).[2,3] Recently reactions have been developed in which a fluorine molecule acts as an electrophile, replacing tertiary hydrogens in organic substrates.[4]

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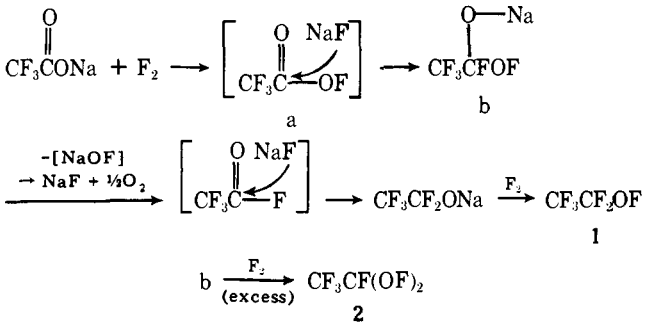
Scheme I



There are many cases, however, in which the readily available elemental fluorine can not substitute a fluoroxy reagent. For example, the reaction of fluorine with electron-rich olefins, as enol acetates, gives a very complicated mixture from which no definite compounds can be isolated. Besides, there is no substitution for fluoroxy reagents whenever an adduct containing the important perfluoroether group is desired.

We report here a novel use of elemental fluorine. By manipulating the reaction conditions, we were able to synthesize in situ for the first time some hypofluorite and fluoroxy compounds and use them conveniently.

Fluoroxypentafluoroethane (CF_3CF_2OF, **1**) was first synthetized, together with several other fluoroxy compounds, more than 10 years ago.[5] However the difficult synthesis and the low yield completely mitigated against its use as a synthetic tool.[6] Still, if readily available, **1** should be capable of serving as an excellent source of electrophilic fluorine and provide a way to the preparation of new perfluoro ethers.

When sodium trifluoroacetate, as a suspension in Freon, is reacted with nitrogen diluted fluorine at −75 °C, a stable oxidizing solution is obtained,[7] which contains **1** as a major component.

A number of observations lead us to propose Scheme I for the formation of **1**.

It is necessary to use a salt of trifluoroacetic acid since using the acid alone produces only trifluoroacetyl hypofluorite (CF_3COOF) in low yield.[8] Nucleophilic fluorine acts similarly on a carbonyl group in the synthesis of CF_3OF from COF_2, F_2, and anhydrous CsF under drastic conditions. We have observed that no **1** was formed when fluorine was passed at −75 °C through a suspension of trifluoroacetic acid and sodium fluoride in Freon, so that the formation of the cage pair of molecules a is vital to the reaction. It is worth noting that, if the CF_3COONa is not completely dried, the F^- is immediately almost completely hydrated and CF_3COOF is the main reaction product (see later). The intermediate b can split off the elements of the unstable NaOF, followed by the formation of **1**. On the other hand, when an excess of fluorine is present various oxyfluoro compounds like **2** can be produced.[5] Indeed, we can mention now that the presence of **2** and similar materials, in synthetic work when both parts of the fluoroxy molecule are needed, leads to the formation of undefined unstable compounds, resulting in significantly reduced yields of the desired products.

When a little less than an equivalent of *cis*-stilbene (**3a**) is reacted at −75 °C with the oxidizing solution containing **1** formed in situ, the cis adduct, DL-*erythro*-2-fluoro-3-pentafluoroethoxybibenzyl (**4a**), is obtained (38% yield, mp 59 °C)[9] together with ~7% more of the threo isomer **4b**.

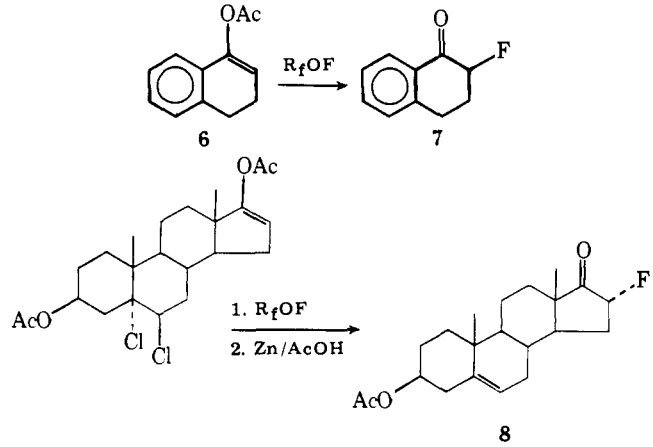
PhCH=CHPh — **3a**, cis; **3b**, trans

PhCHFCH(OCF$_2$CF$_3$)Ph — **4a**, DL-erythro; **4b**, DL-threo

PCHFCHFPh

5

Scheme II



Cis addition also took place when *trans*-stilbene (**3b**) was reacted with the oxidizing solution producing the threo isomer **4b** (28%, mp 87 °C) accompanied by <5% **4a**.[10] It is worth noting that the cis addition described here is quite similar to the addition of CF_3OF to some olefins. Apart from **4a** and **4b**, a number of very-low-yield (2–5%) byproducts were isolated. These are of type **4**, with extra fluorine(s) on the aromatic ring, and difluorides of type **5**.[11]

This reaction opens a new route toward the synthesis of perfluoro ethers which in many cases have enhanced pharmacological activity relative to the unsubstituted analogues, probably because of their lipophilic properties.

All of our results, including the examples mentioned above, show that, under the reaction conditions, **1** constitutes ~50% of the reactants in the oxidizing solution. However it is reasonable to assume that most of the other oxidizing products formed also possess a fluoroxy moiety. There is thus an excellent opportunity for synthesizing α-fluoro ketones in a most efficient way, since the deciding factor is that the electrophilic fluorine of the fluoroxy group be attacked by an electron-rich olefin. Thus, when the enol acetate of α-tetralone (**6**) was prepared and reacted with the oxidizing solution, the expected 2-fluoro-α-tetralone (**7**) was formed in >85% yield (mp 38 °C). The synthesis of the biologically interesting 16α-fluoro-3β-hydroxy-5-androsten-17-one acetate **8** (mp 205 °C, 85% yield)[12] serves as another useful example of the indirect use of elemental fluorine in the synthesis of α-fluoro ketones (Scheme II)

Scheme I suggested that it may be possible to use fluorine not only for producing fluoroxy compounds but for hypofluorites as well. Indeed, when damp CF_3COONa is used, the sodium fluoride in the intermediate a is immediately hydrated. A nucleophilic attack on the carbonyl by the fluorine anion is no longer favored and trifluoroacetyl hypofluorite (**9**)[13] is the main oxidant in the resulting oxidative solution. Thus, when *trans*-stilbene (**3b**) was reacted with this solution, the cis adduct, DL-*threo*-α-fluoro-β-trifluoroacetylbibenzyl (**10**),[14] was isolated in >60% yield. Mild basic hydrolysis of **10** gave practically quantitatively the fluorohydrin DL-*threo*-α-fluoro-β-hydroxybibenzyl (**11**).[15] A very high stereoselectivity was obtained by reacting *cis*-stilbene (**3a**) in this manner. After basic hydrolysis the fluorohydrin DL-*erythro*-α-fluoro-β-hydroxybibenzyl (**12**)[15] was obtained in >65% yield.

This new synthesis of the important fluorohydrin group seems to be shorter and more efficient than the method usually used.[15]

3a or **3b** + CF_3COOF → PhCHFC(OR)Ph

9

10, R = $COCF_3$ (DL-threo from **3b**)
11, R = H (DL-threo)
12, R = H (DL-erythro from **3a**)

The above-described method for in situ preparation of oxyfluoro reagents from elemental fluorine promises great versatility and possesses a broad potential in organofluoro chemistry.[16]

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(6) The use of CF_3CF_2OF is mentioned in three patents. When irradiated by UV, it served as a fluorine radical source for the following reactions; $C_6H_{12} \rightarrow C_6H_{11}F$; $C_6H_6 \rightarrow C_6H_5F$. See, for example, J. Kollonitsch (to Merck and Co., Inc.), U.S. Patent 4 030 994 (1977).
(7) The oxidation power of the reaction mixture can be determined by titration of the iodine liberated from acidic solution of KI.
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(9) This product was also synthetized by one of the authors (S. Rozen) during his work with D. H. R. Barton, R. Hesse, and M. Pechet in the Research Institute for Medicine and Chemistry, Cambridge, Mass. He is very grateful for the opportunity to work in their laboratories.
(10) The stereochemistry of the isomers **4** is evident from their NMR (^1H and ^{19}F) spectra. The erythro isomers possess coupling constants J_{H-H} smaller than those of the threo isomers. See also D. H. R. Barton, R. H. Hesse, G. P. Jackmann, L. Ogunkoya, and M. M. Pechet, *J. Chem. Soc., Perkin Trans. 1*, 739 (1974). In addition in the erythro isomers the fluorine nuclei resonates at higher field than in the threo ones.
(11) While CF_3OF, when reacting with olefins, yields considerable amounts of the undesired difluorides (**5**) (see ref 3, 10), we found that **1** gives only very small amounts of them.
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(16) All new compounds had the correct composition established by microanalysis. Their spectral data (IR, UV, ^{19}F and ^1H NMR, and mass spectra) are in excellent agreement with the assigned structures and stereochemisty.

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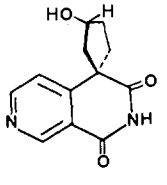
Sesbanine, a Novel Cytotoxic Alkaloid from *Sesbania drummondii*

Sir:

An earlier report from our laboratory disclosed the potent antileukemic activity associated with extracts from seeds of *Sesbania drummondii* (Leguminosae), a native plant with a history of toxicity to livestock.[1] We now report the isolation and structural elucidation of sesbanine (**1**), a cytotoxic compound in the extract. Sesbanine has a previously unreported and highly unusual spirocyclic structure based on the 2,7-naphthyridine nucleus.



1

Sesbanine (~50 mg) was isolated from the ethanol extract of *S. drummondii* seed (450 kg) through a multistage fractionation procedure that included a series of solvent partitioning steps,[2] a 10-stage countercurrent distribution, chromatography on silica, removal of polyphenolics by extraction with aqueous sodium carbonate, chromatography on Sephadex G-10, and finally high-performance liquid chromatography in two stages on reversed-phase columns. This sequence provided crystalline **1**, $C_{12}H_{12}N_2O_3$ (M + 1, *m/e* 233.0907; $C_{12}H_{13}N_2O_3$ requires *m/e* 233.0888):[3] mp 240–243 °C (MeOH); $[\alpha]^{23}_D$ +14.6° (*c* 0.56, MeOH); IR 3510, 3490, 1710, 1690, 1600 cm^{-1} (KBr);[4] UV λ_{max}^{MeOH} 228 nm (ϵ 10 500). The ^1H NMR spectrum in $CDCl_3$–CD_3OD (1:1) showed aromatic protons at δ 9.26 (d, J = 1 Hz, H-8), 8.88 (dd, $J_{6,8}$ = 1, $J_{5,6}$ = 6 Hz, H-6), and 7.94 (d, $J_{5,6}$ = 6 Hz, H-5);[5] the H-10 proton was apparent (δ 4.74, m), but remaining protons appeared in poorly resolved upfield multiplets (1.8–2.5). In Me_2SO-d_6, the ^1H NMR spectrum showed δ 8.5–9.4 (br m, H-8 and H-6), 7.85 (d, $J_{5,6}$ = 6 Hz, H-5), 4.50 (m, H-10), 2.65 (dd, J = 7.14 Hz, B portion of ABM system, one H-9 proton),[6] 1.7–2.8 (br m, remaining H-9, H-11, H-12 protons). ^{13}C NMR spectra of **1** are summarized in Table I. Since the available spectral data did not specify a structure for sesbanine and the limited amount precluded an extensive chemical study, a single-crystal X-ray crystallographic study was undertaken.

Table I. ^{13}C NMR Chemical Shift Assignments for Sesbanine[a]

position	in Me_2SO-d_6	in pyridine-d_5
1	177.2	178.5 (s)
3	163.8	165.0 (s)
4	52.1	53.2 (s)
4a	155.8	156.6 (s)
5	121.7[b]	*c*
6	148.3	*c*
8	153.9	154.5 (d)
8a	121.7[b]	*c*
9	48.5	49.7 (t)
10	72.7	73.9 (d)
11	36.1	37.8 (t)
12	42.4	43.9 (t)

[a] Chemical shifts (δ) are in parts per million from tetramethylsilane. For pyridine-d_5 spectrum, multiplicities of signals were determined by partial decoupling. [b] Overlapping signals. [c] Signal obscured by solvent peaks.

Sesbanine (**1**) crystallized as flat plates in the monoclinic crystal system. Accurate lattice constants, obtained by carefully centering 15 high angle reflections, were a = 8.00 (3), b = 14.665 (5), c = 9.549 (4) Å; β = 70.69 (3)°. The systematic absences and known chirality indicated space group $P2_1$, and the cell volume required *two* molecules of $C_{12}H_{12}N_2O_3$ in the asymmetric unit for a physically reasonable density. The extremely limited amount of sesbanine precluded a density measurement. All available crystals of sesbanine had considerable mosaic spread in their diffraction maxima. Intensity data were collected on a fully automated four-circle diffractometer using graphite monochromated Mo Kα radiation (0.71069 Å) and a variable-speed, 2.5° ω scan. A total of 2306 unique diffraction maxima with $2\theta \leq 50.0°$ were collected in this fashion, and, after correction for Lorentz, polarization, and background effects, 2116 (92%) were judged observed ($F_o \geq 3\sigma(F_o)$).[7] During data collection, it became apparent that, while the crystal must belong to space group $P2_1$ and have two independent molecules, it could be approximately described as being $P2_1/a$ ($h0l$, h = $2n$ + 1, very weak) with only one independent molecule. In view of the limited data at high 2θ values and the size of the structure, we elected to determine an approximate phasing model in the centrosymmetric space group $P2_1/a$. Most of the molecule was revealed by this procedure except for the C(10), C(11), and O(15) fragment. After lowering the symmetry to $P2_1$ and carrying out full-matrix least-squares refinements with anisotropic nonhydrogen atoms and fixed isotropic hydrogens, the conventional crystallographic discrepancy index was 0.059 for the observed data.

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