Specific Synthesis of *N*-Fluoro-compounds using Perfluorofluoroxy-reagents

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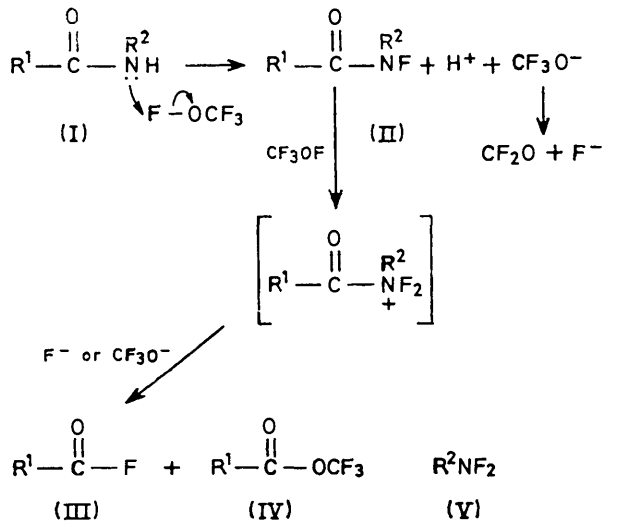
Secondary sulphonamides react with perfluorofluoroxy-compounds to give *N*-fluoro-derivatives in high yields. With secondary carboxamides the initially formed *N*-fluoroamides react further with cleavage of the amide bond and formation of *NN*-difluoroamines. An aromatic ring that is not deactivated towards electrophilic attack reacts in preference to an amide. Conversion of amides into the more reactive imino-ethers overcomes this problem. This is illustrated by the synthesis of the *NN*-difluoro-derivatives of amphetamine and tyramine. Evidence is presented for the mechanism of these reactions.

GENERAL methods for the synthesis of organic *N*-fluoro-ompounds involve either introduction of an intact NF_2 group from difluoramine [1] or tetrafluorohydrazine,[2] or modification of an existing NH function using fluorine

[1] E. A. Lawton and J. Q. Weber, *J. Amer. Chem. Soc.*, 1963, **85**, 3595; W. H. Graham and J. P. Freeman, *ibid.*, 1967, **89**, 716.

[2] R. C. Petry and J. P. Freeman, *J. Org. Chem.*, 1967, **32**, 4034.

and/or a metal fluoride.[3a-f] Apart from their frequent lack of specificity the appeal of these methods is greatly reduced by the hazardous nature of the reagents. We have recently shown that perfluorofluoroxy-compounds are safe and efficient electrophilic reagents for the preparation of various *C*-fluorinated compounds.[4] We now report some further reactions of these reagents leading to



the specific synthesis of various *N*-fluoro-compounds. Notable, but not identical, studies on *N*-fluoro-compounds were reported[3g] after the completion of this manuscript.

In an initial experiment *N*-methylstearamide (I; $R^1 = CH_3[CH_2]_{16}$, $R^2 = CH_3$) was treated with fluoroxytrifluoromethane (CF_3OF). The products were identified as *N*-fluoro-*N*-methylstearamide (II; $R^1 = CH_3[CH_2]_{16}$, $R^2 = CH_3$), stearoyl fluoride (III; $R^1 = CH_3[CH_2]_{16}$) (isolated as stearic acid), and trifluoromethyl stearate (IV; $R^1 = CH_3[CH_2]_{16}$). Results obtained by varying the ratio of reactants (see Table 1) suggested that the last two products were being formed by further reaction of *N*-fluoro-*N*-methylstearamide. This was confirmed in a separate experiment. The increased reactivity of the initial product has analogies in the reactions of sulphonamide[5] and urea[3a] with fluorine to yield *NN*-difluoro-derivatives. To determine the nature of the nitrogen fragment of the amide a similar reaction was performed on *N*-(1-adamantyl)acetamide (I; $R^1 = CH_3$, R^2 = 1-adamantyl). The non-volatile products were *N*-(1-adamantyl)-*N*-fluoroacetamide (II; $R^1 = CH_3$, R^2 = 1-adamantyl) (4%) and the product of its further reaction, 1-difluoroaminoadamantane (V; R^2 = 1-adamantyl) (60%). The reaction of secondary carboxamides with fluoroxytrifluoromethane thus parallels their reaction with fluorine, where rapid fluorinolysis of an initially formed *N*-fluoroamide leads to an *NN*-difluoroamine and an acid fluoride.[3a,d] We consider the reaction to involve attack of electrophilic fluorine at the amide nitrogen (see Scheme 1).

We have previously shown that perfluorofluoroxy-compounds can effect electrophilic fluorination of a range of aromatic compounds.[4b] We therefore examined the mode of reaction of some compounds containing both benzenoid and secondary amide functions. Treatment of *p*-fluoro-*N*-methylbenzamide (I; $R^1 = p\text{-}FC_6H_4$, $R^2 = CH_3$) with fluoroxytrifluoromethane afforded *N*,*p*-difluoro-*N*-methylbenzamide (II; $R^1 = p\text{-}FC_6H_4$, $R^2 = CH_3$) and the further derived *p*-fluorobenzoyl fluoride (III; $R^1 = p\text{-}FC_6H_4$) and trifluoromethyl *p*-fluorobenzoate (IV; $R^1 = p\text{-}FC_6H_4$), indicating preferential reaction at the amide group. However, this situation was reversed for the substrates (VI; R = H or Ac) and (VII; $R^1R^2 = O$) which contain a benzene ring activated

TABLE 1

Reactions of amides with perfluorofluoroxy-compounds

Amide	Reagent	(mol. equiv.)	Product	Yield (%) *
(I; $R^1 = CH_3[CH_2]_{16}$, $R^2 = CH_3$)	CF_3OF	(1·2)	(II; $R^1 = CH_3[CH_2]_{16}$, $R^2 = CH_3$)	30 (81)
(I; $R^1 = CH_3[CH_2]_{16}$, $R^2 = CH_3$)	CF_3OF	(3·0)	(II; $R^1 = CH_3[CH_2]_{16}$, $R^2 = CH_3$)	20 (40)
(I; $R^1 = CH_3[CH_2]_{16}$, $R^2 = CH_3$)	CF_3OF	(4·0)	(II; $R^1 = CH_3[CH_2]_{16}$, $R^2 = CH_3$)	12 (24)
(I; $R^1 = CH_3$, R^2 = 1-adamantyl)	CF_3OF	(excess)	(V; R^2 = 1-adamantyl)	60 (75)
(I; $R^1 = CH_3$, R^2 = 1-adamantyl)	SF_5OF	(excess)	(V; R^2 = 1-adamantyl)	29 (77)
(I; $R^1 = CH_3$, R^2 = 1-adamantyl)	$CF_2(OF)_2$	(1·0)	(V; R^2 = 1-adamantyl)	27 (96)
(I; $R^1 = CH_3$, R^2 = 1-adamantyl)	CF_3OF	(0·25)	(II; $R^1 = CH_3$, R^2 = 1-adamantyl)	8 (35)
(I; $R^1 = p\text{-}FC_6H_4$, $R^2 = CH_3$)	CF_3OF	(excess)	(II; $R^1 = p\text{-}FC_6H_4$, $R^2 = CH_3$)	13 (45)
(I; $R^1 = p\text{-}FC_6H_4$, $R^2 = CH_3$)	SF_5OF	(1·0)	(II; $R^1 = p\text{-}FC_6H_4$, $R^2 = CH_3$)	14 (41)
(X; R^1 = H, $R^2 = CH_3$)	CF_3OF	(excess)	(X; R^1 = F, $R^2 = CH_3$)	85 (90)
(X; R^1 = H, $R^2 = CH_3$)	SF_5OF	(1·0)	(X; R^1 = F, $R^2 = CH_3$)	68 (84)
(X; R^1 = H, $R^2 = CH_3$)	$CF_2(OF)_2$	(0·5)	(X; R^1 = F, $R^2 = CH_3$)	67 (85)
(X; R^1 = H, R^2 = *endo*-norbornyl)	CF_3OF	(excess)	(X; R^1 = F, R^2 = *endo*-norbornyl)	71
(X; R^1 = H, R^2 = *endo*-norbornyl)	SF_5OF	(1·0)	(X; R^1 = F, R^2 = *endo*-norbornyl)	70 (80)

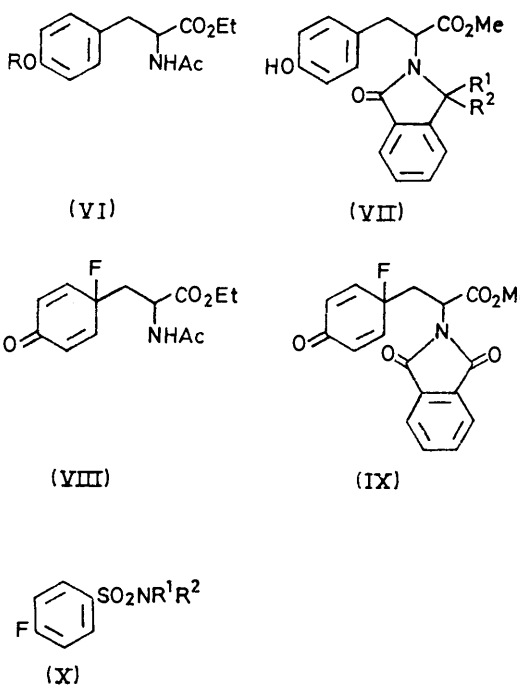
* Values based on recovered starting material in parentheses.

[3] (*a*) R. E. Banks, R. N. Haszeldine, and J. P. Lalu, *J. Chem. Soc.* (*C*), 1966, 1514; (*b*) V. Grakauskas and K. Baum, *J. Amer. Chem. Soc.*, 1969, **91**, 1679; (*c*) *J. Org. Chem.*, 1969, **34**, 2840; (*d*) 1970, **35**, 1545; (*e*) C. M. Sharts, *ibid.*, 1968, **33**, 1008; (*f*) C. L. Coon, M. E. Hill, and D. L. Ross, *ibid.*, p. 1387; (*g*) J. Leroy, F. Dudragne, J. C. Adenis, and C. Michaud, *Tetrahedron Letters*, 1973, 2771.

[4] (*a*) D. H. R. Barton, L. S. Godinho, R. H. Hesse, and M. M. Pechet, *Chem. Comm.*, 1968, 804; (*b*) D. H. R. Barton, A. K. Ganguly, R. H. Hesse, S. N. Loo, and M. M. Pechet, *ibid.*, p. 806; (*c*) D. H. R. Barton, L. J. Danks, A. K. Ganguly, R. H. Hesse, G. Tarzia, and M. M. Pechet, *ibid.*, 1969, 227; (*d*) D. H. R. Barton, R. H. Hesse, M. M. Pechet, G. Tarzia, H. T. Toh, and N. D. Westcott, *J.C.S. Chem. Comm.*, 1972, 122.

[5] R. A. Wiesboeck and J. K. Ruff, *Inorg. Chem.*, 1965, **4**, 123.

towards electrophilic attack. Here the products of reaction with fluoroxytrifluoromethane were the 4-fluorodienones (VIII) and (IX) respectively. The structure of these products followed from spectroscopic data (see Experimental section) and their reduction with zinc in acetic acid to yield (VI; R = H) and (VII; R^1 = H, R^2 = OH) respectively. The latter product was identical with material prepared by the reduction of (VII; R^1R^2 = O) with zinc in acetic acid.[6] In *N*-acetyl-β-naphthylamine also, reaction is confined to the ring.[4b] The reaction of carboxamides with fluoroxy-reagents is thus restricted by the presence of a benzenoid system that is not deactivated towards electrophilic attack.



SCHEME I

The sulphonamide group occurs in a number of important drugs. We have found that the secondary sulphonamides (X; R^1 = H, R^2 = CH_3) and (X; R^1 = H, R^2 = *endo*-norbornyl) react with perfluorofluoroxy-compounds to give high yields of the *N*-fluorosulphonamides (X; R^1 = F, R^2 = CH_3) and (X; R^1 = F, R^2 = *endo*-norbornyl). Unlike the corresponding reactions with carboxamides, further reaction of the initially formed *N*-fluoroamide is not a problem, and this method therefore constitutes an excellent route to *N*-alkyl-*N*-fluorosulphonamides. With the primary sulphonamide (X; R^1 = R^2 = H) two products were observed, the *N*-fluorosulphonamide (X; R^1 = F, R^2 = H) and the bis-(*p*-fluorophenylsulphonyl) derivative (X; R^1 = F, R^2 = $SO_2C_6H_4F$-*p*). The usefulness of this reaction was marred by the extreme difficulty encountered in recovering appreciable amounts of material from attempted chromatographic separations.

In addition to providing convenient syntheses of *N*-fluoroamides and *NN*-difluoroamines, the above reactions also constitute a novel and mild method for the cleavage of a carboxamide bond. Although most experiments have been performed using fluoroxytrifluoromethane, we consider these reactions to be typical of perfluorofluoroxy-compounds in general since, when tried, the alternative reagents fluoroxysulphur pentafluoride and bis(fluoroxy)-difluoromethane (two available fluorines) have given analogous results (see Table 1).[4d]

The synthesis of *NN*-difluoroamines from reactants containing other potentially reactive functional groups required use of a nitrogen function more nucleophilic than amide. The direct reaction of amines with perfluorofluoroxy-compounds was unsatisfactory in that side-reactions (formation of isocyanates, insoluble hydrofluorides, *etc.*) predominated. Thus, treatment of 1-aminoadamantane with fluoroxytrifluoromethane gave 1-adamantylisocyanate (55%). It was, however, possible to isolate low yields of *NN*-difluoroamines by this method (see Table 2). Imino-ethers, which are readily available by the reaction of amides with trialkyloxonium salts,[7] proved to be superior substrates.

TABLE 2

Reactions of amines and imino-ethers with perfluorofluoroxy-compounds

Substrate	Reagent	Product	Yield (%)
$PhCH_2CH(CH_3)NH_2$	CF_3OF	$PhCH_2CH(CH_3)NF_2$	10 (75) *
$PhCH_2CH(CH_3)NH_2$	SF_5OF	$PhCH_2CH(CH_3)NF_2$	20 (33) *
$PhCH_2CH(CH_3)NH_2$	$CF_2(OF)_2$	$PhCH_2CH(CH_3)NF_2$	15 (15) *
n-$C_{18}H_{37}NH_2$	CF_3OF	n-$C_{18}H_{37}NF_2$	5 (35) *
(XI; R^1 = F, R^2 = 1-adamantyl)	CF_3OF	(V; R^2 = 1-adamantyl)	70
(XI; R^1 = F, R^2 = 1-adamantyl)	SF_5OF	(V; R^2 = 1-adamantyl)	54
(XI; R^1 = F, R^2 = 1-adamantyl)	$CF_2(OF)_2$	(V; R^2 = 1-adamantyl)	57
(+)-[(XI; R^1 = F, R^2 = $PhCH_2CHCH_3$)]	CF_3OF	(−)-$PhCH_2CH(CH_3)NF_2$	75
(−)-[(XI; R^1 = H, R^2 = $PhCH_2CHCH_3$)]	CF_3OF	(+)-$PhCH_2CH(CH_3)NF_2$	84
(XI; R^1 = H, R^2 = n-$C_{18}H_{37}$)	CF_3OF	n-$C_{18}H_{37}NF_2$	52
(XI; R^1 = H, R^2 = 4-$BzOC_6H_4CH_2CH_2$)	CF_3OF	4-$BzOC_6H_4(CH_2)_2NF_2$	50 †

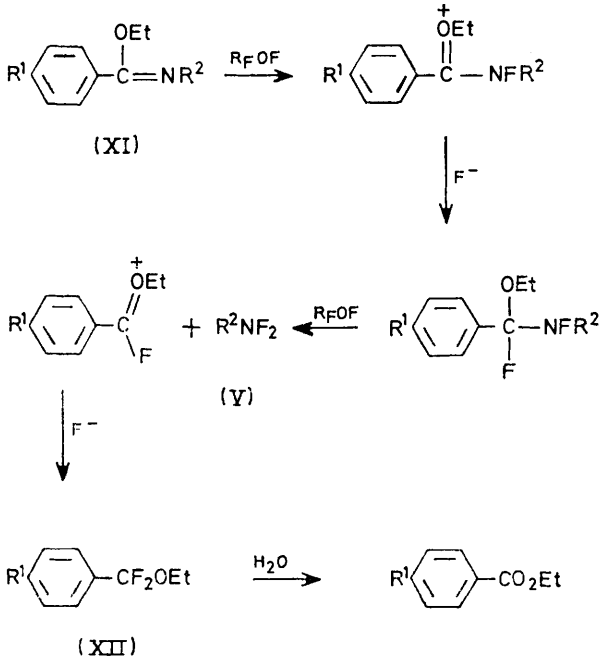
* Yields in parentheses based on fluoroxy-reagent. † Based on amide and allowing for recovered amide.

The imino-ether (XI; R^1 = F, R^2 = 1-adamantyl) behaved typically. At −78°, two mol. equiv. of fluoroxytrifluoromethane, were consumed, the first within 15 min, and the second over *ca.* 3 h. After a normal aqueous work-up 1-difluoroaminoadamantane

[6] J. H. Brewster, A. M. Fusco, L. E. Carosino, and B. G. Corman, *J. Org. Chem.*, 1963, **28**, 498.

[7] M. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, and J. Spille, *Chem. Ber.*, 1956, **89**, 2060; R. F. Borch, *Tetrahedron Letters*, 1968, 61.

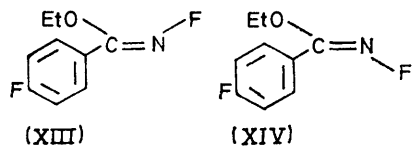
(V; R^2 = 1-adamantyl) and ethyl *p*-fluorobenzoate were isolated in approximately equimolar amounts (*ca.* 70% yield). G.l.c., however, indicated that the latter product was not present prior to work-up. To gain insight into the intermediate stages of this reaction the imino-ether (XI; R^1 = F, R^2 = CH_3) was employed. This substrate has the advantage that one of the final products, *NN*-difluoromethylamine, is relatively volatile and hence easily removed from the reaction mixture. With up to one equiv. of fluoroxytrifluoromethane the ^{19}F n.m.r. spectrum of the reaction mixture showed the appearance of signals at ϕ^* + 59·8br (q, *J* 34 Hz, $NFCH_3$) and +117·4br p.p.m. (s, $CFNFCH_3$) in addition to the characteristic multiplet for the aromatic fluorine at ϕ^* +11·0 p.p.m. On continued addition of fluoroxytrifluoromethane the aliphatic signals were replaced by one at ϕ^* +68·8 p.p.m. (s, $ArCF_2OEt$) which ultimately had twice the intensity of the signal for the aromatic fluorine at +110·4 p.p.m. These facts suggested that the reaction proceeds as shown in Scheme 2. In confirmation, we have been able to isolate the intermediate (XII; R^1 = F) in a state of 90% purity by careful vacuum distillation. This material showed strong absorptions in the region 1020—1200 cm^{-1} (C–F and C–O stretching). The ^1H n.m.r. spectrum had signals at δ 1·3 and 4·0 (3H and 2H respectively, t and q, *J* 7 Hz, OCH_2CH_3) and 6·9 and 7·4 (each 2H, m, aromatic H) only. Attempts to obtain a mass spectrum did not give the expected molecular ion, but gave an intense peak at *m/e* 142·0226

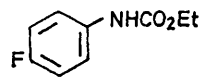


SCHEME 2 R_F = Perfluoro-group.

(Calc. for $C_7H_4F_2O$: 142·0230) (*p*-fluorobenzoyl fluoride?) The n.m.r. data, however, leave no doubt as to the true structure of (XII; R^1 = F). It is transformed into ethyl *p*-fluorobenzoate on exposure to air or on contact with moist glassware.

The reaction of imino-ethers with perfluorofluoroxy-compounds makes possible the synthesis of *NN*-difluoro-derivatives of primary amines that contain other electrophilically sensitive groups. Thus, treatment of the imino-ethers (XI; R^1 = H, R^2 = $PhCH_2CHCH_3$) and (XI; R^1 = F, R^2 = $PhCH_2CH_3$), derived from (−)- and (+)-amphetamine respectively, with two mol. equiv. of fluoroxytrifluoromethane at −78° gave ethyl benzoate and ethyl *p*-fluorobenzoate respectively as well as (+)- and (−)-*NN*-difluoroamphetamine (V; R^2 = $PhCH_2CHCH_3$) (84 and 75%) respectively. The ^{19}F





n.m.r. spectra of the latter products were characteristic. The two fluorines are non-equivalent by virtue of the adjacent asymmetric centre,[8] and thereby appear as the AB portion of an ABX system, J_{AB} 565 and $J_{AX} \approx J_{BX} \approx 25$ Hz. Similarly, the imino-ether (XI; R^1 = H, R^2 = 4-$BzOC_6H_4CH_2CH_2$) afforded *O*-benzoyl-*NN*-difluorotyramine, which with hydrogen chloride in methanol was converted into *NN*-difluorotyramine. Further data are summarised in Table 2.

Finally, we describe the reaction of the imino-ether (XI; R^1 = F, R^2 = H) with fluoroxytrifluoromethane. Two products were formed in a ratio of 10 : 1 and were separated by chromatography on neutral alumina. Physical data indicated that these compounds were the isomers (XIII) and (XIV). Whereas the minor product was recovered unchanged from a silica gel column, the major product rearranged to a compound identified as ethyl *N*-(*p*-fluorophenyl)carbamate (XV).[9] By analogy to the known mechanism of the Beckmann rearrangement, we therefore assign structure (XIII) to the major product.

EXPERIMENTAL

^1H and ^{19}F n.m.r. spectra were recorded at 60 and 56·4 MHz respectively. Unless otherwise stated they refer to solutions in deuteriochloroform with tetramethylsilane (^1H) or trichlorofluoromethane (Freon) (^{19}F) as internal standards. I.r. data are for potassium bromide discs except for liquids, which were run as neat films. Except as indicated, rotations and u.v. data are for solutions in chloroform and methanol respectively. M.p.s were determined with a Kofler hot-stage apparatus. Silica refers to silica gel GF_{254} and alumina to that of neutral grade III. Solutions were dried with anhydrous $MgSO_4$.

General Methods of Fluorination.—(1) The required volume of fluoroxytrifluoromethane was measured by

[8] F. A. Johnson, C. Haney, and T. E. Stevens, *J. Org. Chem.*, 1967, **32**, 466.

[9] V. T. Oliverio and E. Sawicki, *J. Org. Chem.*, 1955, **20**, 363.

means of a gas burette, and then diluted with an equal volume of nitrogen, before being slowly bubbled through a solution of the substrate. The effluent from the reaction vessel was passed into aqueous potassium iodide where unchanged reagent was destroyed, and could be estimated titrimetrically. This method was used for relatively reactive substrates.

(2) A solution of the fluoroxy-reagent in Freon at −78° was prepared. Its concentration was determined by iodometric titration. This solution was then added to the substrate in a pressure bottle at −78° and the temperature adjusted to the required level. This method was used for substrates which reacted slowly.

Fluorination of N-*Methylstearamide*.—*N*-Methylstearamide (1 g, 3·4 mmol) in chloroform at room temperature was treated with fluoroxytrifluoromethane (4 mmol) by method (1). The solution was washed with cold, saturated sodium hydrogen carbonate solution (50 ml), cold water (2 × 50 ml), dried, and evaporated. The residual oil was chromatographed on silica. Elution with benzene afforded a mixture of stearoyl fluoride and trifluoromethyl stearate, $\nu_{max.}$ 1850 (COF) and 1815 (CO_2CF_3) cm^{-1}, ϕ^* −44·4 (s, COF) and +58·2 (s, CF_3) p.p.m., followed by N-*fluoro*-N-*methylstearamide*, m.p. (from hexane) 53—54°, $\nu_{max.}$ 1700 cm^{-1}, δ 5·3 (3H, d, *J* 27 Hz, $NFCH_3$), ϕ^* +56·4 p.p.m. (tq, *J* 27 and 4·5 Hz, $CH_2CONFCH_3$) (Found: C, 72·35; H, 11·95; N, 4·5; F, 6·15. $C_{19}H_{38}FNO$ requires C, 72·3; H, 12·1; N, 4·4; F, 6·0%). The effect of varying the ratio of reactants is shown in Table 1. Rechromatography of the mixed fraction on silica eluting with hexane gave pure *trifluoromethyl stearate*, m.p. (from hexane) 49·5—50°, *m/e* 352 (M^+) (Found: C, 65·0; H, 9·9; F, 16·1. $C_{19}H_{35}F_3O_2$ requires C, 64·7; H, 10·0; F, 16·2%). Further elution with 5% methanol in chloroform gave stearic acid.

Fluorination of N-*Fluoro*-N-*methylstearamide*.—The *N*-fluoroamide (II; $R^1 = CH_3[CH_2]_{16}$, $R^2 = CH_3$) was treated with fluoroxytrifluoromethane by method (1). The reaction was followed by i.r. spectroscopy (replacement of band at 1700 by bands at 1850 and 1815 cm^{-1}). Work-up as in the previous experiment and chromatography on silica gave trifluoromethyl stearate (IV; $R^1 = CH_2[CH_2]_{16}$) and stearic acid.

Reduction of N-*Fluoro*-N-*methylstearamide*.—The *N*-fluoroamide (II; $R^1 = CH_3[CH_2]_{16}$, $R^2 = CH_3$) (50 mg) and zinc dust (150 mg) in glacial acetic acid (2 ml) were stirred at room temperature for 15 h. The mixture was filtered and the residual zinc washed thoroughly. The filtrate was neutralised with sodium hydrogen carbonate solution and extracted with chloroform to give *N*-methylstearamide (40 mg), identical with an authentic sample.

Fluorination of N-(1-*Adamantyl*)*acetamide* (I; $R^1 = CH_3$, R^2 = 1-adamantyl).—The amide [10] (5 g, 25 mmol) in chloroform (30 ml) at room temperature was treated with fluoroxytrifluoromethane (60 mmol) by method (1). During the addition a precipitate formed. This was redissolved by the addition of water (20 ml). The chloroform layer was separated and the aqueous layer extracted with chloroform twice. The combined extracts were dried and evaporated. The residual oil was triturated with hexane until the precipitation of starting material was complete (630 mg). The mother liquors were chromatographed on alumina when elution with hexane gave 1-*difluoroaminoadamantane* (V; R^2 = 1-adamantyl) (2·91 g). An analytical sample was prepared by sublimation at 100° and 20 mmHg, m.p. 113—115° (sealed tube), $\nu_{max.}$ 944, 930, 850, and 805 cm^{-1}, ϕ^* −20·3br p.p.m. (s, NF_2), *m/e* 187 (M^+) (Found: C, 64·4; H, 7·9; N, 7·4; F, 20·3. $C_{10}H_{15}F_2N$ requires C, 64·15; H, 8·1; N, 7·5; F, 20·3%). Further elution with benzene gave N-*fluoro*-N-(1-*adamantyl*)*acetamide* (II; $R^1 = CH_3$, R^2 = 1-adamantyl) (190 mg, 4%), liquid at room temperature, purified for analysis by vacuum distillation (0·5 mmHg; pot temperature 85°), $\nu_{max.}$ 1700 cm^{-1}, ϕ^* (CCl_4) +81·3 p.p.m. (q, *J* 10 Hz, CH_3CONF), *m/e* 211 (M^+) (Found: C, 68·4; H, 8·7; N, 6·8; F, 8·8. $C_{12}H_{18}FNO$ requires C, 68·2; H, 8·6; N, 6·6; F, 9·0%). Finally, elution with 5% methanol in chloroform gave starting material (350 mg). Fluorination of the *N*-fluoroamide (II; $R^1 = CH_3$, R^2 = 1-adamantyl) under the same conditions gave the *NN*-difluoroamine (V; R^2 = 1-adamantyl) (83%).

Fluorination of N-*Methyl*-p-*fluorobenzamide* (I; $R^1 = p$-FC_6H_4, $R^2 = CH_3$).—The amide (2·5 g, 16 mmol) in chloroform (25 ml) at room temperature was treated with fluoroxytrifluoromethane (23 mmol) by method (1). After the usual aqueous work-up the residual oil was chromatographed on silica. Elution with hexane gave *trifluoromethyl* p-*fluorobenzoate* (IV; $R^1 = p$-FC_6H_4) (120 mg), purified for analysis by vacuum distillation (200 mmHg; pot temperature 90°), $\nu_{max.}$ 1795, 1615, 1250—1180, and 1150 cm^{-1}, ϕ^* +57·8 (3F, s, CF_3) and +104 p.p.m. (1F, m, aromatic F), *m/e* 208 (M^+) (Found: C, 46·4; H, 2·1; F, 36·3. $C_8H_4F_4O_2$ requires C, 46·2; H, 1·9; F, 36·5%). Further elution gave a mixture of (IV; $R^1 = p$-FC_6H_4) and *p*-fluorobenzoyl fluoride (III; $R^1 = p$-FC_6H_4) (150 mg), $\nu_{max.}$ 1810 (COF) and 1795 (CO_2CF_3) cm^{-1}, ϕ^* (CCl_4) −16·6 (s, COF), +57·8 (s, CF_3), and +104 p.p.m. (m, aromatic F). Elution with hexane–methylene dichloride (1 : 1) gave N,p-*difluoro*-N-*methylbenzamide* (II; $R^1 = p$-FC_6H_4, $R^2 = CH_3$), purified for analysis by vacuum distillation (0·5 mmHg; pot temperature 75°), $\nu_{max.}$ 1675, 1600, 1230, 1160, and 1100 cm^{-1}, δ 3·5 (3H, d, *J* 27 Hz, $NFCH_3$), ϕ^* (CCl_4) +46·4 (1F, q, *J* 27 Hz, $NFCH_3$) and +106·1 p.p.m. (1F, m, aromatic F), *m/e* 171 (M^+) (Found: C, 55·8; H, 4·0; N, 8·0; F, 22·5. $C_8H_7F_2NO$ requires C, 56·1; H, 4·1; N, 8·2; F, 22·2%). Finally elution with methylene dichloride gave starting material (1·8 g, 72%).

Fluorination of Ethyl N-*Acetyl*-L-*tyrosinate* (VI; R = H).—The amide [11] (400 mg, 1·6 mmol) in chloroform (20 ml) at −22° was treated with fluoroxytrifluoromethane (1·5 mmol) by method (2). When no reagent remained the solution was warmed to room temperature and then evaporated. P.l.c. of the oily residue gave starting material and the fluorodienone (VIII), $\nu_{max.}$ 1730, 1670, and 1630 cm^{-1}, δ 1·3 (3H, t, *J* 8 Hz, CH_2CH_3), 2·0 (3H, s, $COCH_3$), 4·2 (2H, q, *J* 8 Hz, CH_2CH_3), 6·3 (2H, d, *J* 11 Hz), 6·4 (NH), and 6·9 (2H, m), ϕ^* +149 p.p.m. (m), $[\alpha]_D$ +28° (*c* 0·7), $\lambda_{max.}$ 220 nm (ε 6500), *m/e* 269 (M^+).

Similar fluorination of ethyl *NO*-diacetyl-L-tyrosinate also gave the fluorodienone (VIII), but the reaction proceeded approximately five times more slowly.

Fluorination of Methyl N-*Phthaloyl*-L-*tyrosinate* (VII; $R^1R^2 = O$).—The amide,[12] m.p. 103—105°, $[\alpha]_D$ −133° (*c* 2·54 in acetone) (150 mg, 0·44 mmol), in acetone at −78°

[10] P. E. Aldrich, E. C. Hermann, W. E. Meier, M. Paulshock, W. W. Prichard, J. A. Snyder, and J. C. Watts, *J. Medicin. Chem.*, 1971, **14**, 535.

[11] J. H. Barnes, R. C. Cookson, G. T. Dickson, J. Elks, and V. D. Poole, *J. Chem. Soc.*, 1953, 1448.

[12] Prepared from L-tyrosine according to G. H. L. Nefkins, G. I. Tesser, and R. J. F. Nivard, *Rec. Trav. chim.*, 1960, **79**, 688, followed by methylation with diazomethane.

was treated with fluoroxytrifluoromethane by method (2). Work-up as in the previous experiment including p.l.c. afforded *methyl 3-fluoro-3-(4-oxocyclohexa-2,5-dienyl)-2-phthalimidopropionate*, m.p. (from chloroform–hexane) 136—138°, $[\alpha]_D$ −58° (*c* 1·43; acetone), $\nu_{max.}$ 1780, 1750, 1720, and 1680 cm^{-1}, δ 3·0 (2H, m), 3·8 (3H, s), 5·1 (1H, m), 6·2 (2H, m), 7·0 (2H, m), and 7·9 (4H, m), ϕ^* +151 p.p.m. (m), *m/e* 343 (M^+) (Found: C, 63·15; H, 3·8; N, 4·15; F, 5·5. $C_{18}H_{14}FNO_5$ requires C, 63·0; H, 4·1; N, 4·1; F, 5·5%).

Reduction of the Fluorodienones (VIII) *and* (IX).—The fluorodienone (VIII) (10 mg) in acetic acid (0·5 ml) was stirred at room temperature with zinc dust (30 mg) for 30 min. Work-up as in the reduction of *N*-fluoro-*N*-methylstearamide gave ethyl *N*-acetyl-L-tyrosinate, identical with an authentic sample.

Similar reduction of the fluorodienone (IX) gave *methyl 2-(1-hydroxy-3-oxoisoindolin-2-yl)-3-(4-hydroxyphenyl)propionate* (VII; R^1 = H, R^2 = OH), m.p. (from chloroform–hexane) 173—175°, $[\alpha]_D$ −158° (*c* 2·14; acetone), $\nu_{max.}$ 3500, 1740, 1720, 1675, 1655, 1620, and 1600 cm^{-1}, δ ([$^2H_6$]-acetone) 3·4 (2H), 3·7 (3H), 5·1 (1H, m), 5·5 (1H, s), 6·0 (1H), 6·7—7·2 (4H, m), 7·6 (4H, m), and 8·2 (1H, s), *m/e* 327 (M^+) (Found: C, 65·85; H, 5·4; N, 4·2; O, 24·2. $C_{18}H_{17}NO_5$ requires C, 66·05; H, 5·25; N, 4·3; O, 24·4%). The same product was also obtained by similar reduction of (VII; R^1R^2 = O).

Fluorination of N-*Methyl*-p-*fluorobenzenesulphonamide* (X; R^1 = H, R^2 = CH_3).—The sulphonamide (100 mg, 0·53 mmol) in methylene chloride (5 ml) and Freon (20 ml) at 0° was treated with fluoroxytrifluoromethane (1·3 mmol) by method (1). The effluent gases were passed into aqueous potassium iodide solution. Titration indicated that *ca.* 0·5 mmol of reagent was consumed during the reaction. After an aqueous work-up p.l.c. gave N,p-*difluoro*-N-*methylbenzenesulphonamide* (92 mg, 85%), m.p. (from hexane) 40·5—41°, δ (CCl_4) 3·2 (3H, d, *J* 32 Hz, $NFCH_3$) and 7·1 and 8·0 (each 2H, m, aromatic H), ϕ^* +37·6 (1F, q, *J* 32 Hz, $NFCH_3$) and +101·2 p.p.m. (1F, m, aromatic F) (Found: C, 40·7; H, 3·3; N, 6·8; F, 18·4; S, 15·5. $C_7H_7F_2NO_2S$ requires C, 40·6; H, 3·4; N, 6·8; F, 18·3; S, 15·5%).

Similarly, *N*-(2-*endo*-norbornyl)-*p*-fluorobenzenesulphonamide (X; R^1 = H, R^2 = 2-*endo*-norbornyl) afforded N,p-*difluoro*-N-(2-endo-*norbornyl*)*benzenesulphonamide* (X; R^1 = F, R^2 = 2-*endo*-norbornyl), m.p. (from chloroform–hexane) 96—97°, ϕ^* +36·9br (1F, dd, *J* 16 and 6 Hz, SO_2NF) and +101·6 p.p.m. (1F, m, aromatic F) (Found: C, 54·5; H, 5·1; N, 4·9; F, 13·5; S, 11·3. $C_{13}H_{15}F_2NO_2S$ requires C, 54·3; H, 5·3; N, 4·9; F, 13·2; S, 11·2%).

Fluorination of p-*Fluorobenzenesulphonamide* (X; R^1 = R^2 = H).—The amide (175 mg, 1 mmol) in acetone (10 ml) was treated with fluoroxytrifluoromethane (2 mmol) in Freon (45 ml) in a pressure bottle at 0°. After 15 h the solution was flushed thoroughly with nitrogen and then evaporated to give a dark oil. T.l.c. indicated the presence of two products less polar than starting material. Attempts to separate these products by p.l.c. on silica were unsuccessful, but low yields of each component could be recovered from p.l.c. on ChromAR sheet 1000. N,p-*Difluorobenzenesulphonamide* (X; R^1 = F, R^2 = H) (20 mg) had m.p. (from carbon tetrachloride) 63—65°, $\nu_{max.}$ 3240, 1600, 1500, 1180, 855, and 745 cm^{-1}, δ 7·3 and 8·1 (each 2H, m, aromatic H) and 8·9 (1H, d, *J* 52 Hz, exchanged with deuterium oxide, NHF), ϕ^* +91·2 (1F, d, *J* 52 Hz, s in the presence of deuterium oxide, NHF) and +110·8 p.p.m. (1F, m, aromatic F), *m/e* 193 (M^+) (Found: C, 37·6; H, 2·7; N, 7·0; F, 19·9; S, 16·3. $C_6H_5F_2NO_2S$ requires C, 37·3; H, 2·6; N, 7·25; F, 19·7; S, 16·6%).

Fluorobis-(p-*fluorophenylsulphonyl*)*amine* (X; R^1 = F, R^2 = $SO_2C_6H_4F$-*p*) (5 mg) had m.p. (from carbon tetrachloride) 115—116°, $\nu_{max.}$ 1600, 1500, 1190, 845, and 785 cm^{-1}, δ 7·3 and 7·9 (each of same intensity, m, aromatic H), ϕ^* +37·1 (1F, s, NF) and +99·0 p.p.m. (2F, m, aromatic F), *m/e* 351 (M^+) (Found: C, 40·75; H, 2·7; N, 4·1; F, 16·1. $C_{12}H_8F_3NS_2O_4$ requires C, 41·0; H, 2·3; N, 4·0; F, 16·2%).

Preparation of Amides.—*p*-Fluorobenzoyl chloride (or benzoyl chloride) (1 equiv.) was added slowly to the amine (1 equiv.) in dry pyridine. The solution was left at room temperature overnight and then poured into ice–water. The solid was collected and recrystallised from chloroform–hexane. N-(1-*Adamantyl*)-p-*fluorobenzamide* had m.p. 163—164° (Found: C, 74·55; H, 7·3; N, 4·9; F, 7·0. $C_{17}H_{20}FNO$ requires C, 74·7; H, 7·4; N, 5·1; F, 6·95%). (−)-p-*fluoro*-N-(1-*methyl*-2-*phenylethyl*)*benzamide* had m.p. 129—130°, $[\alpha]_D$ −13·8° (*c* 1·95) (Found: C, 74·6; H, 6·4; N, 5·3; F, 7·4. $C_{16}H_{16}FNO$ requires C, 74·7; H, 6·3; N, 5·4; F, 7·4%). ON-*Dibenzoyltyramine* had m.p. 172° (Found: C, 76·5; H, 5·65; N, 4·1. $C_{22}H_{19}NO_3$ requires C, 76·5; H, 5·55; N, 4·1%). *p*-Fluoro-*N*-methylbenzamide [13] and (+)-*N*-(1-methyl-2-phenylethyl)benzamide [14] had physical data identical with those in the literature.

Preparation of Imino-ethers.—The amide (1 equiv.) and triethyloxonium fluoroborate (1·1 equiv.) in dry methylene chloride were left at room temperature overnight. The solution was washed with ice-cold, aqueous sodium carbonate and water, dried, and evaporated. The residue was treated with hexane and any unchanged starting material filtered off. Evaporation of the filtrate gave the imino-ether. *Ethyl* N-(1-*adamantyl*)-p-*fluorobenzimidate* (XI; R^2 = F, R^3 = 1-adamantyl) had m.p. 70—71° (Found: C, 75·7; H, 8·0; N, 4·65; F, 6·3. $C_{19}H_{24}FNO$ requires C, 75·7; H, 8·1; N, 4·85; F, 6·5%). The N-*methyl analogue* (XI; R^1 = F, R^2 = CH_3) had b.p. 65—66° (at 0·2 mmHg), n_D^{22} 1·4950, $\nu_{max.}$ 1675, 1610, 1270, 1240, 1100, and 845 cm^{-1}, δ (CCl_4) 1·3 (3H, t, *J* 7 Hz, OCH_2CH_3), 3·0 (3H, s, NCH_3), 4·1 (2H, q, *J* 7 Hz, OCH_2CH_3), and 7·2 (4H, m, aromatic H). *Ethyl* N-(1-*methyl*-2-*phenylethyl*)*benzimidate* (XI; R^1 = H, R^2 = $PhCH_2CHCH_3$), had b.p. 128—129° at 0·2 mmHg, n_D^{25} 1·5380, $[\alpha]_D$ −48·1° (*c* 9·9) (Found: C, 80·8; H, 7·8; N, 5·3. $C_{18}H_{21}NO$ requires C, 80·9; H, 7·9; N, 5·2%). The p-*fluoro-analogue* (XI; R^1 = F, R^2 = $PhCH_2CHCH_3$) had b.p. 128° at 0·2 mmHg, n_D^{25} 1·5254, $[\alpha]_D$ +47·4° (*c* 6·9) (Found: C, 75·6; H, 7·2; N, 5·0; F, 6·8. $C_{18}H_{20}FNO$ requires C, 75·8; H, 7·1; N, 4·9; F, 6·7%). The N-*stearyl analogue* (XI; R^1 = H, R^2 = n-$C_{18}H_{37}$) had $\nu_{max.}$ 1660, 1450, 1260, 1110, 775, and 700 cm^{-1}, δ 0·9—1·3 (38H), 3·4 (2H, CH_2N), 4·3 (2H, q, *J* 7 Hz, $-OCH_2CH_3$), and 7·4 (5H, m, aromatic H). The N-2-(4-*benzoyloxyphenyl*)*ethyl analogue* (XI; R^1 = H, R^2 = 4-$BzOC_6H_4CH_2CH_2$) had $\nu_{max.}$ ($CHCl_3$) 1730, 1660, 1270, 1220, 1080, 1060, 880, and 700 cm^{-1}, δ 1·3 (3H, t, *J* 7 Hz, OCH_2CH_3), 2·9 (2H), 3·6 (2H), 4·2 (2H, q, *J* 7 Hz, OCH_2CH_3), and 7·3—8·1 (14H). The N-*unsubstituted analogue* (XI; R^1 = F, R^2 = H) had b.p. 59—60° at 0·2 mmHg, n_D^{23} 1·5070, $\lambda_{max.}$ 229 nm (ε 7140) (Found: C, 64·6; H, 6·1; N, 8·35; F, 11·6. $C_9H_{10}FNO$ requires C, 64·7; H, 6·0; N, 8·35; F, 11·4%).

Fluorination of Imino-ethers.—The imino-ether (XI; R^1

[13] R. Campbell and C. J. Peterson, *J. Org. Chem.*, 1963, **28**, 2294.

[14] J. Bernstein, K. A. Losee, C. I. Smith, and B. Rubin, *J. Amer. Chem. Soc.*, 1959, **81**, 4433.

= F, R^2 = 1-adamantyl) (300 mg, 1 mmol) in chloroform (6 ml) and Freon (2 ml) at −78° was treated with fluoroxytrifluoromethane (2 mmol) by method (2). After 3 h at −78° the solution was warmed to room temperature, diluted with chloroform (20 ml), washed with ice-cold, aqueous sodium hydrogen carbonate and water, dried, and evaporated. Chromatography on alumina eluting with hexane gave 1-difluoroaminoadamantane (130 mg, 70%) and then ethyl *p*-fluorobenzoate (120 mg, 70%), both identical with authentic samples. Similar results were obtained from analogous experiments using fluoroxysulphur pentafluoride or bis(fluoroxy)difluoromethane.

The imino-ether (XI; R^1 = H, R^2 = $PhCH_2CHCH_3$) (2·6 g, 10 mmol) in Freon (50 ml) containing calcium oxide (2·6 g) at −78° was treated with fluoroxytrifluoromethane (20 mmol) by method (1). After addition of the reagent (*ca.* 30 min) the solution was stirred for another 3 h. The calcium oxide was filtered off and the solvent evaporated. Chromatography on alumina eluting with hexane gave (+)-NN-*difluoroamphetamine* (1·44 g, 84%), b.p. 91—92° at 20 mmHg, n_D^{22} 1·4745, $[\alpha]_D$ +5° (*c* 11·1), $\nu_{max.}$ 1610, 1500, 960, 850, 750, and 705 cm^{-1}, δ (CCl_4) 1·2 (3H, d, *J* 6 Hz, $CHCH_3$), 2·4—3·4 (2H, m), 3·6 (1H, m), and 7·2 (5H), ϕ^* −40·0 p.p.m. (dq, J_{AB} 565, $J_{AX} \approx J_{BX} \approx$ 25 Hz), (Found: *m/e* 171·0853. $C_9H_{11}F_2N$ requires: *M*, 171·0859) (Found: C, 63·2; H, 6·3; N, 8·0; F, 22·3. $C_9H_{11}F_2N$ requires: C, 63·1; H, 6·5; N, 8·2; F, 22·2%).

Similarly, the imino-ether (XI; R^1 = F, R^2 = $PhCH_2CHCH_3$) afforded (−)-NN-*difluoroamphetamine*, n_D^{22} 1·4745, $[\alpha]_D$ −5° (*c* 2·01).

The imino-ether (XI; R^1 = H, R^2 = n-$C_{18}H_{37}$) afforded NN-*difluorostearamine*, $\nu_{max.}$ 1030, 900, 825, and 730 cm^{-1}, δ 0·8—1·3 (35H) and 3·4 (2H, tt, *J* 29 and 7 Hz, CH_2NF_2), ϕ^* −55·6 p.p.m. (t, *J* 29 Hz) (Found: C, 70·6; H, 12·05; N, 4·5. $C_{18}H_{37}F_2N$ requires C, 70·8; H, 12·2; N, 4·6%).

O-*Benzoyl*-NN-*difluorotyramine*.—*ON*-Dibenzoyltyramine (2 g, 5·8 mmol) and triethyloxonium fluoroborate in dry methylene chloride (55 ml) were left at room temperature overnight. The solution was washed as before, dried, and evaporated. The residue, without purification, in chloroform at −50° was treated with fluoroxytrifluoromethane (12 mmol) by method (1). After 3 h the mixture was worked-up as before and chromatographed on silica. Elution with hexane gave O-*benzoyl*-NN-*difluorotyramine* (500 mg), m.p. (from hexane) 67—67·5°, $\nu_{max.}$ 1725, 1600, 1270, 1200, 1080, 1063, 1020, 935, 830, and 710 cm^{-1}, δ 3·0 (2H, t, *J* 7 Hz, $ArCH_2$), 3·6 (2H, tt, *J* 7 and 28 Hz, $CH_2CH_2NF_2$), and 7·0—8·1 (9H, aromatic H), ϕ^* −54·8 p.p.m. (t, *J* 28 Hz, CH_2NF_2) (Found: *m/e*, 277·0918. $C_{15}H_{13}NO_2$ requires *M*, 277·0914) (Found: C, 64·9; H, 4·8; N, 5·1; F, 13·7. $C_{15}H_{13}F_2NO_2$ requires C, 65·0; H, 4·7; N, 5·05; F, 13·7%). Elution with 5% methanol in chloroform afforded starting amide (0·8 g).

NN-*Difluorotyramine*.— *O*-Benzoyl-*NN*-difluorotyramine (130 mg) in methanol saturated with hydrogen chloride was heated at 60° for 3 h. P.l.c. gave NN-*difluorotyramine* (40 mg, 40%), liquid, $\nu_{max.}$ 3350, 1620, 1520, 1220, 1020, and 845 cm^{-1}, δ 3·0 (2H, t, *J* 8 Hz, $ArCH_2$), 3·6 (2H, tt, *J* 8 and 27 Hz, $CH_2CH_2NF_2$), 4·9br (1H, s, exchanged with deuterium oxide, OH), and 6·8 (4H, m, aromatic H), ϕ^* −55·3 p.p.m. (t, *J* 27 Hz, CH_2NF_2) (Found: *m/e*, 173·0653. $C_8H_9F_2NO$ requires *M*, 173·0652).

Fluorination of the Imino-ether (XI; R^1 = H, R^2 = F).— The imino-ether (335 mg, 2 mmol) in methylene chloride (5 ml) and Freon (10 ml) containing calcium oxide (1 g) at −22° was treated with fluoroxytrifluoromethane (2·2 mmol) by method (1). Work-up as before and chromatography on alumina eluting with hexane gave (Z)-*ethyl* N,p-*difluorobenzimidate* (XIII) (70%), liquid, $\nu_{max.}$ 1610, 1600, 1305, 1225, 1075, 1050, 1000, 870, and 835 cm^{-1}, δ (CCl_4) 1·4 (3H, dt, *J* 7 and 1 Hz), 4·6 (2H, dq, *J* 7 and 3 Hz), and 7·0 and 7·7 (each 2H, m, aromatic H), ϕ^* +43·7 (1F, s, =NF) and +108·4 p.p.m. (1F, m, aromatic F), $\lambda_{max.}$ 232 nm (ε 8700), *m/e* 185 (M^+) (Found: C, 58·5; H, 5·0; N, 7·5; F, 20·7. $C_9H_9F_2NO$ requires C, 58·6; H, 4·9; N, 7·5; F, 20·4%). Further elution with hexane gave the (E)-*isomer* (XIV), $\nu_{max.}$ 1610, 1510, 1320, 1280, 1240, 1020, 940, 850, and 785 cm^{-1}, δ (CCl_4) 1·4 (3H, t, *J* 7 Hz), 4·3 (2H, q, *J* 7 Hz), and 7·1 and 7·8 (each 2H, m, aromatic H), ϕ^* +51·7 (1F, s, =NF) and +107·8 p.p.m. (1F, m, aromatic F), $\lambda_{max.}$ 227 nm (ε 7910) (Found: *m/e* 185·0651. $C_9H_9F_2NO$ requires *M*, 185·0652). Whereas (XIV) was recovered unchanged from chromatography on silica, (XIII) gave the carbamate (XV), m.p. 55° (lit.,[9] 55—56°) (Found: C, 58·9; H, 5·6; N, 7·8; F, 10·5. Calc. for $C_9H_{10}FNO_2$: C, 59·0; H, 5·5; N, 7·6; F, 10·4%).

1-*Adamantyl Isocyanate*.—1-Aminoadamantane (2 g) was suspended in methylene chloride (200 ml) at room temperature and treated with fluoroxytrifluoromethane (15 mmol). Titration of the trap indicated that only 6 mmol of reagent were consumed. Unchanged starting material was filtered off (0·7 g) and the filtrate washed with 5N-sulphuric acid and water and dried. Evaporation gave 1-adamantyl isocyanate (0·86 g), purified by chromatography and sublimation, m.p. 144—145° (lit.,[15] 144—145°).

Fluorination of (+)-*Amphetamine*.—(+)-Amphetamine (7 mmol) in Freon was treated with fluoroxytrifluoromethane (2 mmol) by method (2). After all the reagent was consumed, amine hydrofluoride and unchanged amine were dissolved by the addition of dilute hydrochloric acid. The organic layer was separated, washed as before, and dried. Evaporation and chromatography on silica gave *NN*-difluoroamphetamine (0·73 mmol), identical with an authentic sample, and *NN'*-bis-(1-methyl-2-phenylethyl)urea (0·5 mmol), identical to material prepared from (+)-amphetamine and phosgene. Normal processing of the aqueous acid layer afforded (+)-amphetamine (3·7 mmol). Analogous experiments were performed using fluoroxysulphur pentafluoride and bis(fluoroxy)difluoromethane. The results are summarised in Table 2. Use of higher ratios of fluoroxy-reagents did not lead to increased yields of *NN*-difluoroamine.

[15] H. Stetter and C. Wulff, *Chem. Ber.*, 1962, **95**, 2302.

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