Direct Fluorination of Substituted Carbamates[1]

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The fluorination of N-substituted carbamates was shown to be a general method for the synthesis of difluoramino compounds and substituted fluorocarbamates. Substituents included alkyl and cycloalkyl groups as well as alkyl groups containing ester, nitro, or nitramino groups. The fluorination of carboalkoxyguanidines gave carboalkoxytetrafluoroguanidines, and the fluorination of 1,3-dicarboalkoxyguanidines gave carboalkoxytetrafluoroguanidines as well as 1,3-dicarboalkoxytrifluoroguanidines. 1-Carbethoxy-3-cyanoguanidine gave carbethoxytetrafluoroguanidine, ethyl N-(difluoraminodifluoromethyl)-N-fluorocarbamate, and ethyl N-(fluoriminofluoromethyl)-N-fluorocarbamate.

We have previously reported the synthesis of alkyl fluorocarbamates and alkyl difluorocarbamates by the direct liquid phase fluorination of alkyl carbamates.[2] Only one example of the fluorination of an N-substituted carbamate, ethyl methylcarbamate, has been reported, and the only product isolated was difluoraminomethane.[3]

The present paper describes the fluorination of a variety of N-substituted carbamates to give fluorocarbamates as well as difluoramino compounds. The products obtained by the fluorination of alkylcarbamates, cycloalkylcarbamates, and alkylidenedicarbamates are shown in Table I. These reactions represent successive fluorination of NH and fluorinolysis of carboalkoxy groups. The rates of the two reactions are of the same order of magnitude; the use of less than a stoichiometric amount of fluorine resulted in the isolation of a considerable amount of the difluoramino compound as well as the fluorocarbamate and starting material.

$$\mathrm{RNHCOR'} \xrightarrow{F_2} \mathrm{RNFCOR'} \xrightarrow{F_2} \mathrm{RNF_2}$$

Fluorinations were conducted using solutions or suspensions of the substrates in water or acetonitrile. One example, methyl butylcarbamate, was fluorinated as a neat liquid. The presence of the substrate as a separate base required a reduced rate of fluorine input to avoid localized ignition at the inlet.

The products were characterized by elemental analysis and spectral data or by comparison with authentic samples. Ethyl N-fluoro-N-methylcarbamate, ethyl N-cyclopentyl-N-fluorocarbamate, and ethyl N-cyclohexyl-N-fluorocarbamate were prepared previously by the alkylation of ethyl fluorocarbamate.[2] Difluoraminocyclohexane was prepared previously by the addition of difluoramine to cyclohexene[4] as well as by the direct fluorination of buffered aqueous cyclohexylamine.[5] Methyl β-difluoraminopropionate has been synthesized from difluoramine and methyl acrylate.[6] Difluoraminobutane and 2-difluoraminobutane were prepared previously by the reaction of butane with tetrafluorohydrazine.[7] The infrared spectrum of difluoraminocyclopentane, which was fully characterized in the present work, did not correspond to that of the tentatively assigned compound in the literature.[5]

The only product which was not sufficiently stable for isolation was ethyl difluoraminoacetate, which underwent partial dehydrofluorination under the conditions of synthesis. Attempts to separate ethyl difluoraminoacetate from ethyl cyanoacetate by gas chromatography resulted in further dehydrofluorination. On the other hand, no problems were encountered in the isolation of methyl α-difluoraminobutyrate.

This method for the synthesis of difluoramino compounds has advantages of generality and convenience compared with other reported methods. The alkylation of difluoramine[4,6,8] does not yield simple primary derivatives, and remote manipulation is required because of the high sensitivity of difluoramine. Reactions of tetrafluorohydrazine are somewhat less hazardous but are also limited in scope[9-11] or selectivity[7,12] depending on the class of substrate. The fluorination of buffered amines was reported to give impure products.[5]

The technique of using a carboalkoxy group as a leaving group in fluorinolysis was also applied to the synthesis fluorinated guanidines, a class of compounds that has recently been investigated by several groups.[13-18]

Products of the fluorination of carboalkoxyguanidines, 1,3-dicarboalkoxyguanidines, and 1-carboethoxy-3-cyanoguanidine are shown in Table II. Carboalkoxyguanidines gave carboalkoxytetrafluoroguanidines, whereas 1,3-dicarboalkoxyguanidines gave both dicarboalkoxytrifluoroguanidines and carboalkoxytetrafluoroguanidines. The carboalkoxytetrafluoroguanidines were obtained as mixtures of *syn* and *anti* isomers which could be distinguished on the basis of fluorine nmr spectra. For one set of isomers, $-NF_2$, $=NF$, and $-NF-$ signals appeared at close to ϕ^* -42.5, -32, and 44.5, while, for the other set, the signals appeared at -45.5, -25, and 52, respectively. The doublet coupling constants between $-N=F$ and $-NF-$, resolvable only for the $-NF-$ signals, were 6 cps for the former set of isomers and 9 cps for the latter set. Since *trans* coupling constants to fluorines

(1) This work was supported by the Office of Naval Research and the Advanced Research Projects Agency.

(2) V. Grakauskas and K. Baum, *J. Amer. Chem. Soc.*, in press.

(3) R. E. Banks, R. N. Haszeldine, and L. P. Lalu, *J. Chem. Soc., C*, 1514 (1966).

(4) K. Baum, *J. Org. Chem.*, **32**, 3648 (1967).

(5) C. M. Sharts, *ibid.*, **33**, 1008 (1968).

(6) K. Baum, *J. Amer. Chem. Soc.*, **90**, 7083 (1968).

(7) S. F. Reed, Jr., and R. C. Petry, *Tetrahedron*, **24**, 5089 (1968).

(8) W. H. Graham and J. P. Freeman, *J. Amer. Chem. Soc.*, **89**, 716 (1967).

(9) J. W. Frazer, *J. Inorg. Nucl. Chem.*, **16**, 63 (1960).

(10) R. C. Petry and J. P. Freeman, *J. Amer. Chem. Soc.*, **83**, 3912 (1961).

(11) R. C. Petry and J. P. Freeman, *J. Org. Chem.*, **32**, 4034 (1967).

(12) C. L. Bumgardner, *Tetrahedron Lett.*, 3683 (1964).

(13) D. A. Rausch and J. J. Hoekstra, *J. Org. Chem.*, **33**, 2522 (1968).

(14) R. A. Davis, J. L. Kroon, and D. A. Rausch, *ibid.*, **32**, 1662 (1967).

(15) R. L. Rebertus and B. W. Nippoldt, *ibid.*, **32**, 4044 (1967).

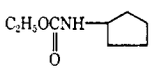
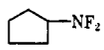
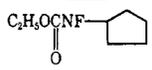
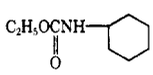
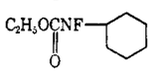
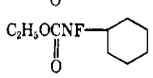
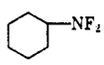
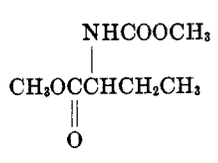
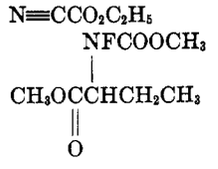
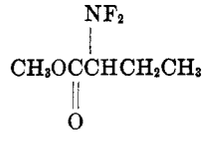
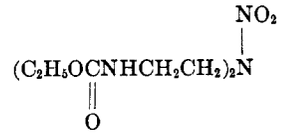
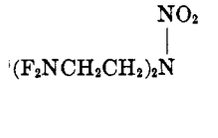
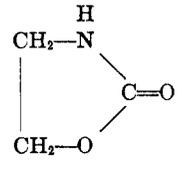
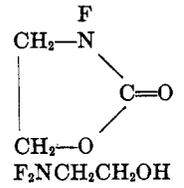
(16) R. L. Rebertus and P. E. Toren, *ibid.*, **32**, 4045 (1967).

(17) R. J. Koshar, D. R. Husted, and C. D. Wright, *ibid.*, **32**, 3859 (1967).

(18) W. C. Firth, Jr., *ibid.*, **33**, 3489 (1968).

TABLE I

FLUORINATION OF CARBAMATES

Starting material	Registry no. of product	Products	Bp, °C (mm)
$C_2H_5OCNHCH_3$ (O)	21298-14-6	$C_2H_5OCNFCH_3$ (O)	50 (25)
$CH_3OCNH(CH_2)_3CH_3$ (O)	17832-42-7	$CH_3OCNF(CH_2)_3CH_3$ (O)	68–69 (25)
	10524-16-0	$F_2CNH_2CH_2CH_2CH_3$	74
$CH_3OCNHCH(CH_3)CH_2CH_3$ (O)	10524-17-1	$CH_3CH(NF_2)CH_2CH_3$	64–65
	14182-80-0		24–25 (25)
	21298-19-1		39 (0.2)
	21298-20-4		50–51 (0.1)
	14182-78-6		34 (12)
$C_2H_5OCNH(CH_2)_2NHCOC_2H_5$ (O, O)	21298-22-6	$F_2NCH_2CH_2CH_2NF_2$	25–32 (25)[a]
	21298-23-7	$C_2H_5OCNF(CH_2)_2NFCOC_2H_5$ (O, O)	95–96 (0.2)
$C_2H_5OCNHCH_2CH_2NHCOC_2H_5$ (O, O)	17832-43-8	$C_2H_5OCNFCH_2CH_2NFCOC_2H_5$ (O, O)	78–79 (0.2)
	21298-25-9	$C_2H_5OCNFCH_2CH_2NF_2$ (O)	60 (0.1)[a]
$CH_3OCNHCH_2COC_2H_5$ (O, O)	21298-26-0	$F_2NCH_2CO_2C_2H_5$	33–42 (25)[b]
	21298-27-1		48–49 (0.3)
	21298-28-2		52–53 (4)
$CH_3OCCH_2CH_2NFCOC_2H_5$ (O, O)	20955-65-1	$CH_3OCCH_2CH_2NF_2$ (O)	47 (20)
	21298-30-6		70–71 (0.1)
$CH_3OCNHCH_2C(NO_2)_2F$ (O)	21297-31-7	$CH_3OCNFCH_2C(NO_2)_2F$ (O)	59–61 (0.1)
	21298-32-8		47–48 (0.1)
	21298-33-9	$F_2NCH_2CH_2OH$	40–42 (25)

[a] Impure distillate; analytical sample was isolated by gas chromatography. [b] Dehydrofluorinated during attempted purification. Spectral identification

TABLE II

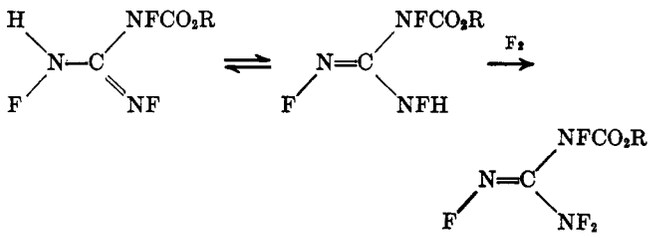
FLUORINATION OF CARBOALKOXYGUANIDINES

Starting material	Registry no. of product	Products	Bp, °C (mm)
$C_4H_9OCNHCNH_2$ (O, NH)	21298-01-1	$C_4H_9OCNFCNF_2$ (O, NF)	70 (40)[a]
	21298-02-2	$C_4H_9OCNFCNF_2$ (O, FN)	
$(CH_3)_2CHOCNHCNH_2$ (O, NH)	21298-03-3	$(CH_3)_2CHOCNFCNF_2$ (O, NF)	20–23 (0.3)[a]
	21298-04-4	$(CH_3)_2CHOCNFCNF_2$ (O, FN)	
$C_2H_5OCNHCNHCOC_2H_5$ (O, NH, O)	21298-34-0	$C_2H_5OCNFCNFCOC_2H_5$ (O, NF, O)	72 (0.1)
	21298-05-5	$C_2H_5OCNFCNF_2$ (O, NF)	25–28 (0.1)[a]
	21298-06-6	$C_2H_5OCNFCNF_2$ (O, FN)	
$[(CH_3)_2CHOCNH]_2C{=}NH$ (O)	21298-35-1	$[(CH_3)_2CHOCNF]_2C{=}NF$ (O)	80 (0.1)
$C_2H_5OCNHCNHCN$ (O, NH)	21298-36-2	$C_2H_5OCNFCF_2NF_2$ (O)	40–60 (25)[a]
	21298-37-3	$C_2H_5OCNFC{=}N$ (O, F, F)	
		$C_2H_5OCNFCNF_2$ (O, NF)	
		$C_2H_5OCNFCNF_2$ (O, FN)	

[a] Impure distillate; analytical sample was isolated by gas chromatography.

in olefins[19] as well as fluorimonium ions[4] are larger than *cis* coupling constants, the configurations can be assigned.[18]

The predominant isomer of the carboalkoxyguanidines depended upon whether a carboalkoxyguanidine or a dicarboalkoxyguanidine was used as the starting material. The ratio of NF_2CNFCO_2R (NF) / NF_2CNFCO_2R (FN) was 1:2 and 1:5 for the butyl and isopropyl derivatives prepared from carboalkoxyguanidines and 1.8:1 for the ethyl derivative prepared from the dicarboalkoxyguanidine. These results are qualitatively in accord with the expected stepwise fluorination path. The last step for the carboalkoxyguanidine reactions involves fluorination of a mobile tautomeric system in which the sterically favored position of the fluorimino fluorine is *anti* to the carboalkoxy group. Replacement of the last NH by fluorine would then prevent further equilibration. On the other hand, the last step for the dicarboalkoxyguanidine reactions most likely is fluorinolysis of acarboalkoxy group of the dicarboalkoxytrifluoroguanidine. The least hindered such group is *anti* to the fluorimine fluorine.



The fluorination of 1-carbethoxy-2-cyanoguanidine gave carbethoxytetrafluoroguanidine, ethyl N-(difluoraminodifluoromethyl)-N-fluorocarbamate, and ethyl N-(fluoriminofluoromethyl)-N-fluorocarbamate. The carbethoxytetrafluoroguanidine is a product of the fluorinolysis of the cyano group, and the other products represent elimination of the –NHCN group. The nmr spectrum of the last product showed that only one isomer was present. The magnitude of the –CF=NF coupling constant indicated that these fluorine atoms

(19) J. A. Pople, W. O. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 335.

were in the *syn* configuration.[20] The same configuration was reported for tetrafluoroformamidine obtained in the fluorination of guanylurea sulfate.[17] The reaction of fluorine with cyanoguanidine[13] has been reported to give products of fluorinolysis of the cyano or amino groups as well as products of fluorine addition to the cyano group.

Infrared and nmr spectra of the products are detailed in the Experimental Section.

Experimental Section

General.—Fluorinations were conducted as described previously[2,21] using fluorine diluted fourfold to tenfold with nitrogen. Safety shielding should be used in handling neat NF compounds. *The guanidine derivatives are extremely sensitive explosives and must be handled remotely.*

Method A. Ethyl N-Fluoro-N-methylcarbamate.—A solution of 26 g (0.25 mol) of ethyl methylcarbamate in 350 ml of water was fluorinated at 0–5° with 0.4 mol of fluorine. The product was extracted with four 150-ml portions of methylene chloride, dried over sodium sulfate, and distilled to give 16 g (53% yield) of ethyl N-fluoro-N-methylcarbamate with physical properties identical with reported values.[2]

Method B. 2-Difluoraminobutane.—Fluorine (1 mol) diluted with nitrogen was passed into a solution of 66.5 g (0.50 mol) of methyl 2-butylcarbamate in 350 ml of acetonitrile at −20° over a 3-hr period. The solution was diluted with 1 l. of ice–water, and the insoluble material was washed with three 70-ml portions of ice–water. The product was dried over sodium sulfate and distilled to give 25 g (46% yield) of 2-difluoraminobutane, bp 64–65°.

Anal. Calcd for $C_4H_9NF_2$: C, 44.03; H, 8.31; N, 12.83; F, 34.82. Found: C, 43.62; H, 8.60; N, 13.0; F, 33.8.

The proton nmr spectrum of 2-difluoraminobutane consisted of a triplet (J = 8 cps) at δ 1.01 for CH_3CH_2–, a doublet (J = 8 cps) of triplets (J = 1 cps) at δ 1.26 for $CH(NF_2)CH_3$, a multiplet with maximum intensity at δ 3.33 for the methine, and a multiplet at δ 1.61 for the methylene. The fluorine spectrum consisted of a broadened AB pattern centered at ϕ^* −39.1, with J_{FF} = 569 cps, and inner members separated 116 cps. Infrared peaks in the NF region were 10.23 (m), 10.5 (s), 11.5 (s), 11.8 (s), and 12.37 μ (m).

Fluorination of Methyl Butylcarbamate.—Fluorine (0.71 mol) diluted fourfold with nitrogen was passed into 131 g (1.0 mol) of neat methyl butylcarbamate with stirring at 0 to −10° over a 3.5-hr period. More rapid fluorination resulted in localized firing at the inlet. The product was washed with three 200-ml portions of ice–water, dried over sodium sulfate, and distilled to give 21.2 g (0.195 mol) of 1-difluoraminobutane, bp 74°; 26.0 g (0.175 mol) of methyl butyl-N-fluorocarbamate, bp 68–69° (25 mm), $n^{25}D$ 1.4010; and 34 g (0.26 mol) of starting material, bp 45° (0.1 mm).

Anal. Calcd for $C_4H_9NF_2$: C, 44.03; H, 8.31; N, 12.83; F, 34.82. Found: C, 44.30; H, 8.21; N, 12.8; F, 35.0.

The proton nmr spectrum of 1-difluoroaminobutane consisted of an irregular triplet at δ 0.99 for the methyl, a triplet of triplets (J_{HH} = 7 cps, J_{HF} = 28.9 cps) at δ 3.43 for CH_2NF_2, and a multiplet with maximum intensity at δ 1.57 for the other methylenes. The fluorine spectrum consisted of a broad signal at ϕ^* −55.58. Infrared peaks in the NF region were 9.87 (m), 10.12 (m), 10.40 (m), 10.91 (s), 11.47 (m), 12.0 (s), and 12.6 μ (s).

Anal. Calcd for $C_6H_{12}NO_2F$: C, 48.31; H, 8.11; N, 9.39; F, 12.74. Found: C, 48.40; H, 8.47; N, 9.4; F, 12.6.

The proton nmr spectrum of methyl butyl-N-fluorocarbamate in CCl_4 consisted of a singlet at δ 3.79 for the methoxy, an irregular triplet at δ 0.96 for the other methyl, a doublet (J_{HF} = 34.7 cps) of triplets at δ 3.63 for $-CH_2-NF-$, and a multiplet at δ 1.55 for the other methylenes. The fluorine spectrum consisted of a triplet (J = 33.8 cps) at ϕ^* 70.92.

Fluorination of Ethyl Cyclopentylcarbamate.—Fluorination of 64 g (0.50 mol) of ethyl cyclopentylcarbamate by method B (350 ml of acetonitrile, 1 mol of fluorine, 0 to −10°, 3 hr) and distillation through a 25-cm Holzmann column gave 30 g (50% yield) of difluoraminocyclopentane, bp 24–25° (25 mm).

Anal. Calcd for $C_5H_9NF_2$: C, 49.58; H, 7.49; N, 11.56; F, 31.37. Found: C, 49.22; H, 7.80; N, 11.4; F, 31.0.

The proton nmr spectrum (CCl_4 solution) showed a triplet of multiplets (J_{HF} = 24 cps) at δ 3.90 for the methine and a multiplet at δ 1.81 for the methylenes. The fluorine spectrum showed a signal at ϕ^* −52.3. Infrared peaks in the NF region were 10.04 (w), 10.60 (w), 10.83 (m), 11.0 (sh), and 11.75 μ (s).

Method A (42.6 g, 0.3 mol, of ethyl cyclopentylcarbamate in 650 ml of water, 0.6 mol of fluorine, 3 hr) gave 7.5 g of somewhat impure difluoraminocyclopentane, 11.5 g (22% conversion) of ethyl N-cyclopentyl-N-fluorocarbamate,[2] and 8 g of starting material.

Ethyl N-Cyclohexyl-N-fluorocarbamate.—The fluorination of 100 g (0.585 mol) of ethyl cyclohexylcarbamate by method A (1200 ml of water, 1.0 mol of fluorine, 5–10°) gave 35 g of impure difluoraminocyclohexane, bp 36–42° (25 mm); 7.0 g (6.3% conversion) of ethyl N-cyclohexyl-N-fluorocarbamate,[2] and 20 g of starting material.

Difluoraminocyclohexane.—Fluorination of 5.2 g (0.030 mol) of ethyl N-cyclohexyl-N-fluorocarbamate by method A (200 ml of water, 0.030 mol of fluorine) gave 1.0 g (25% conversion, 54% yield) of difluoraminocyclohexane, bp 34° (12 mm), identical with an authentic sample,[4] and 2.8 g (54% recovery) of starting material.

Fluorination of Diethyl Trimethylenedicarbamate.—Fluorination of 34.7 g (0.16 mol) of diethyl trimethylenedicarbamate by method A (650 ml of water, 0.6 mol of fluorine) gave 0.80 g of 75% pure 1,3-bis(difluoramino)propane, bp 25–32° (26 mm), containing five other compounds (2.6% yield). An analytical sample was isolated by gas chromatography (15 ft × $^3/_{16}$ in. column of 10% dioctyl phthalate on Chromosorb P, 80°, 60 ml/min helium flow).

Anal. Calcd for $C_3H_6N_2F_4$: C, 24.66; H, 4.14; N, 19.18. Found: C, 25.10; H, 5.10; N, 18.9.

The proton nmr spectrum (CCl_4 solution) consisted of a triplet of triplets (J_{HF} = 28 cps, J_{HH} = 6.5 cps) at δ 3.64 for the α-methylenes and a quintet (J = 7 cps) at δ 2.18 for the central methylene. The fluorine spectrum consisted of a triplet (J = 25 cps) at ϕ^* −53.9. The infrared spectrum showed bands in the NF region at 9.8 (m), 10.2 (m), 10.9 (s), 11.23 (s), and 12.0 μ (s).

Distillation of the above residue gave 5.0 g of colorless liquid, bp 43–45° (0.2 mm); 2.5 g, bp 45–80° (0.2 mm); and 4.5 g, bp 95–105° (0.2 mm). The first of these fractions appeared to consist mainly of ethyl (3-difluoraminopropyl)fluorocarbamate on the basis of infrared and nmr spectra (NF_2 triplet at ϕ^* −54.8, J = 29 cps; –NFC=O triplet at ϕ^* 69.5, J = 34 cps), but a pure sample was not obtained on redistillation. The second fraction was indicated likewise to be impure ethyl (3-difluoraminopropyl)carbamate (NF_2 triplet at ϕ^* −54.19, J = 29.0 cps). Redistillation of the 95–105° fraction gave 3.8 g (9.4% yield) of diethyl N,N′-difluorotrimethylenedicarbamate, bp 95–96° (0.2 mm), $n^{25}D$ 1.4265.

Anal. Calcd for $C_9H_{16}N_2F_2O_4$: C, 42.52; H, 6.34; N, 11.12. Found: C, 42.02; H, 6.11; N, 11.2.

The proton nmr spectrum (CCl_4 solution) consisted of a triplet at δ 1.34 and a quartet at δ 4.27 for the ethoxy groups, a quintet at δ 2.08 for the internal methylene, and a doublet of triplets (J_{HF} = 35 cps) at δ 3.79 for the α-methylenes. The fluorine spectrum consisted of a triplet (J = 35 cps) at ϕ^* 69.5. The infrared spectrum showed a carbonyl band at 5.8 μ.

Fluorination of Diethyl Ethylenedicarbamate.—Fluorination of 40.5 g (0.20 mol) of diethyl ethylenedicarbamate by method A (650 ml of water, 0.7 mol of fluorine, 15–20°) gave 12 g of liquid, bp 20–65° (0.1 mm); and 2.0 g (4.2% yield) of diethyl N,N′-difluoroethylenedicarbamate, bp 78–79° (0.2 mm). The infrared spectrum showed carbonyl bands at 5.69 and 5.79 μ (s) and no NH.

Anal. Calcd for $C_8H_{14}N_2F_2O_4$: C, 40.00; H, 5.87; N, 11.66; F, 15.82. Found: C, 39.8; H, 5.76; N, 11.80; F, 15.4.

Gas chromatography ($^3/_8$ in. × 6 ft column of 5% ethylene glycol succinate on Chromosorb W, 90°, 200 ml/min helium flow) of the low-boiling fraction showed seven components. The major component (85% of the total, 7-min retention time) was identified as ethyl (2-difluoraminoethyl)fluorocarbamate (27% yield). The infrared spectrum showed carbonyl bands at 5.69 and 5.79 μ (s) and no NH.

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Anal. Calcd for $C_5H_9N_2F_3O_2$: C, 32.66; H, 4.87; N, 15.05; F, 30.62. Found: C, 32.49; H, 4.82; N, 14.8; F, 30.8.

Fluorination of Ethyl N-Carbomethoxyglycine.—Fluorination of 48.3 g (0.30 mol) of ethyl N-carbomethoxyglycine by method A (650 ml of water, 0.6 mol of fluorine, 75 min) gave 11 g of colorless liquid, bp 33–42° (25 mm), each fraction of which was found by nmr spectroscopy to be a mixture of ethyl difluoraminoacetate and ethyl cyanoformate. Attempts to isolate ethyl difluoraminoacetate by gas chromatography resulted in further dehydrofluorination. Proton nmr signals assigned to ethyl difluoraminoacetate follow: a triplet at δ 1.32 and a quartet at δ 4.24 for the ethoxy, and a triplet (J = 28 cps) at δ 4.24 for NF_2CH_2–. The fluorine spectrum of the mixture consisted of a broad triplet at ϕ^* −56.4 (J = 26 cps).

Methyl N-Carbomethoxy-α-aminobutyrate.—Methyl chloroformate (190 g, 2.0 mol) was added over 1 hr to a solution of 205 g (2.0 mol) of DL-α-aminobutyric acid and 160 g (4.0 mol) of sodium hydroxide in 500 ml of water at 15–20°. The product was extracted with 300 ml of methylene chloride, dried over sodium sulfate, stripped of solvent, and refluxed for 4 hr in 500 ml of methanol containing 2 drops of concentrated sulfuric acid. Dilution with 1 l. of ice–water, extraction with three 100-ml portions of methylene chloride, and distillation gave 297 g (85% yield) of methyl N-carbomethoxy-α-aminobutyrate, bp 75–76° (0.1 mm).

Anal. Calcd for $C_7H_{13}NO_4$: C, 48.00; H, 7.44; N, 8.00. Found: C, 47.82; H, 7.78; N, 8.40.

Fluorination of Methyl N-Carbomethoxy-α-aminobutyrate.—Fluorination of 70 g (0.40 mol) of methyl N-carbomethoxy-α-aminobutyrate by method B (300 ml of acetonitrile, 0.7 mol of fluorine, 0–5°) gave 22 g (36% conversion) of methyl α-difluoraminobutyrate, bp 52–53° (40 mm), and 34 g (44% conversion) of methyl N-carbomethoxy-N-fluoro-α-aminobutyrate, bp 48–49° (0.3 mm).

The proton nmr spectrum ($CDCl_3$ solution) of methyl α-difluoraminobutyrate consisted of a singlet at δ 3.81 for the methoxy, a triplet at δ 1.03 for CH_3CH_2 a quintet at δ 1.95 for the methylene, and a doublet (J_{HF_A} = 25.7 cps) of doublets (J_{HF_B} = 24.4 cps) of triplets (J_{HH} = 6.5 cps) for the methine at δ 4.10. The fluorine spectrum consisted of an AB quartet (ϕ^*_B = 43.10, ϕ^*_A = −50.66, J_{FF} = 592.4 cps) with additional doublet splitting (J_{HF_A} = 25.5 cps, J_{HF_B} = 24.0 cps). The infrared spectrum showed a carbonyl band at 5.73 μ and bands in the NF region at 9.84 (m), 10.61 (s), 10.53 (s), 10.7 (m), 11.0 (w), 11.15 (m), 11.6 (v, s), and 12.42 μ (s).

Anal. Calcd for $C_5H_9NF_2O_2$: C, 39.20; H, 5.92; 9.15. Found: C, 39.49; H, 6.10; N, 9.5.

The proton nmr spectrum of methyl N-carbethoxy-N-fluoro-α-aminobutyrate ($CDCl_3$ solution) consisted of a triplet at δ 1.10 for CH_3CH_2, a multiplet at δ 2.67 for the methylene, singlets at δ 3.79 and 3.92 for the methoxy groups, and a doublet of doublets of doublets at δ 4.59 for the methine with unequal coupling constants to the adjacent methylene hydrogens (J_{HF} = 40.5 cps, J_{HH} = 6.8, 9.8 cps). The infrared spectrum showed carbonyl bands at 5.63 (s) and 5.77 μ (s) and bands in the NF region at 9.95 (m), 10.45 (w), 11.40 (w), 11.98 (m), 12.5 (m), and 12.9 μ (m).

Anal. Calcd for $C_7H_{12}NFO_4$: C, 43.52; H, 6.22; N, 7.27. Found: C, 43.49; H, 6.20; N, 7.4.

Methyl β-(Difluoramino)propionate.—Fluorination of 3.2 g (0.0166 mol) of methyl N-carbethoxy-N-fluoro-β-aminopropionate[2] by method A (200 ml of water, 0.022 mol of fluorine) gave 0.7 g (30% yield) of methyl β-(difluoramino)propionate identical with an authentic sample.[6]

1,5-Bis(difluoramino)-3-nitrazapentane.—Fluorination of 45 g (0.15 mol) of diethyl 3-nitraza-1,5-pentanedicarbamate[22] by method A (650 ml of water, 0.6 mol of fluorine) gave, after removal of methylene chloride, a viscous oil. Extraction with five 50-ml portions of carbon tetrachloride gave an insoluble solid (25 g), which was found to be impure starting material. Distillation of the carbon tetrachloride solution gave 4.4 g (13% conversion) of 1,5-bis(difluoramino)-3-nitrazapentane, bp 70–71° (0.1 mm). The infrared spectrum showed peaks at 6.58 (s), 6.9 (m), 7.08 (m), 7.6 (m), 7.83 (s), 8.3 (w), 8.8 (w), 9.7 (m), 10.4–10.5 (m), 10.8 (w), 11.12 (w), and 11.8 μ (s).

Anal. Calcd for $C_4H_8N_4F_4O_2$: C, 21.82; H, 3.66; N, 25.45; F, 34.52. Found: C, 21.50; H, 3.71; N, 24.9; F, 35.0.

Methyl N-Fluoro-N-(2-fluoro-2,2-dinitroethyl)carbamate.—Fluorination of 2.8 g (0.0133 mol) of methyl(2-fluoro-2,2-dinitroethyl)carbamate[23] by method A (350 ml of water, 0.04 mol of fluorine) gave 1.0 g (33% conversion, 52% yield) of methyl N-fluoro-N-(2-fluoro-2,2-dinitroethyl)carbamate, bp 59–61° (0.1 mm), and 1.0 g of starting material.

Anal. Calcd for $C_4H_5N_3F_2O_6$: C, 20.97; H, 2.20; N, 18.34; F, 16.59. Found: C, 21.21; H, 2.32; N, 18.0; F, 16.8.

The proton nmr spectrum (CCl_4 solution) consisted of a singlet at δ 3.94 for the methoxy and a doublet of doublets (J_{H-NF} = 30.0 cps, J_{H-CF} = 15.5 cps) at δ 5.05 for the methylene. The fluorine spectrum consisted of a triplet (J_{HF} = 30.2 cps) of doublets (J_{FF} = 10.2 cps) at ϕ^* 58.14 for the NF and a broad band at ϕ^* 108.5 for the CF. The infrared spectrum showed carbonyl at 5.75 μ (s), nitro at 6.30 μ (s), and the following bands in the 10–13-μ region: 10.11 (w), 10.5 (w), 11.22 (w), 11.79 (m), 12.03 (m), 12.5 (m), and 13.0 (m).

Fluorination of 2-Oxazolidone.—Fluorination of 42 g (0.50 mol) of 2-oxazolidone by method A (250 ml of water, 0.5 mol of fluorine, extraction with methylene chloride and of ether) gave, after distillation through a 25-cm Holzmann column, 4.1 g (8.5% yield) of 2-difluoraminoethanol, bp 40–42° (25 mm); and 18 g (41% yield) of N-fluoro-2-oxazolidone, bp 47–48° (0.1 mm).

The fluorine nmr spectrum of 2-difluoraminoethanol ($CDCl_3$ solution) consisted of a triplet (J = 26 cps) at ϕ^* −54.88. Infrared bands in the NF region were 10.42 (s), 11.10 (m), 11.90 (s), and 12.60 μ (s).

Anal. Calcd for $C_2H_5NF_2O$: C, 24.74; H, 5.16; N, 14.44; F, 39.15. Found: C, 24.61; H, 5.30; N, 14.3; F, 38.5.

The fluorine nmr spectrum of N-fluoro-2-oxazolidone ($CDCl_3$ solution) consisted of a triplet (J = 15.4 cps) at ϕ^* 69.48. The infrared spectrum showed peaks at 5.5–5.6 (s), 6.8 (m), 7.27 (m), 8.4 (s), 9.0 (m), 9.2 (m), 9.53 (s), 9.88 (s), 10.4 (m), and 12.8 μ (s).

Anal. Calcd for $C_3H_4NFO_2$: C, 34.28; H, 3.84; N, 13.33; F, 18.08. Found: C, 34.59; H, 4.11; N, 13.2; F, 18.2.

Carboalkoxyguanidines and Dicarboalkoxyguanidines.—1,3-Dicarbethoxyguanidine hemihydrate was prepared by the method of Nencki.[24] 1-Carboisopropoxyguanidine and 1,3-dicarboisopropoxyguanidine were prepared by adding 491 g (4.0 mol) of isopropyl chloroformate at 20° to a solution of 360 g (2.0 mol) of guanidine carbonate and 8 mol of potassium hydroxide in 1500 ml of water. After 45 min, the product was filtered at 5° and recrystallized from water to give 180 g (62% conversion) of carboisopropoxyguanidine, mp 143–145°, and 60 g of crude 1,3-dicarboisopropoxyguanidine which was insoluble in hot water. Recrystallization of the latter from methanol gave 45 g (10% conversion), mp 170°.

Anal. Calcd for $C_5H_{11}N_3O_2$: C, 41.38; H, 7.59; N, 29.0. Found: C, 41.51; H, 7.73; N, 28.3.

Anal. Calcd for $C_9H_{17}N_3O_4$: C, 46.74; H, 7.41; N, 18.17. Found: C, 46.60; H, 7.51; N, 18.2.

Carbobutoxyguanidine, mp 130°, was prepared in 70% yield using an equimolar amount of butyl chloroformate.

Anal. Calcd for $C_6H_{13}N_3O_2$: C, 45.38; H, 8.18; N, 26.40. Found: C, 45.42; H, 8.09; N, 26.7.

1-Carbobutoxytetrafluoroguanidine.—Fluorination of 63.6 g (0.40 mol) of carbobutoxyguanidine by method B (750 ml of acetonitrile, 1.6 mol of fluorine, 0–5°) gave 6.0 g of 70% pure (gc analysis) 1-carbobutoxytetrafluoroguanidine, bp 70° (40 mm). Careful control of the rate of fluorine input was required to avoid localized firing. An analytical sample was isolated by gas chromatography (8 ft × 0.25 in. column of 15% diethylene glycol adipate on Fluoropak 80).

Anal. Calcd for $C_7H_9N_3F_4O_2$: C, 31.17; H, 3.99; N, 18.18; F, 32.88. Found: C, 31.20; H, 4.12; N, 17.8; F, 31.2.

The proton nmr spectrum ($CDCl_3$ solution) consisted of a triplet at δ 4.42 for the α-methylene, a multiplet at δ 1.57 for the β-methylene, and a triplet at δ 0.97 for the methyl. The fluorine spectrum indicated a 1:2 mixture of NF_2CNFCO_2R and $NF_2CNF-CO_2R$, with NF_2 signals at ϕ^* −42.4 and −25.4, –NF– doublets at 44.1 (J = 6 cps) and 51.5 (J = 9 cps), and =NF signals at ϕ^* −32.8 and −25.0, respectively. The infrared spectrum showed carbonyl bands at 5.53 (s) and 5.64 μ (s), a fluorimine

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band at 6.13 μ (w), and bands in the NF region at 10.2 (m), 10.72 (m), and 11.40 μ (m).

1-Carboisopropoxytetrafluoroguanidine.—Fluorination of 46 g (0.30 mol) of carboisopropoxyguanidine by method B (350 ml of acetonitrile, 0.7 mol of fluorine, 0–5°, 2.5 hr) gave 5.5 g (7.6% yield) of 1-carboisopropoxytetrafluoroguanidine, $NF_2C(=NF)NFCO_2C_3H_7$, bp 20–23° (0.3 mm), 90% pure by gc analysis. An analytical sample was obtained by gas chromatography (8 ft × 0.25 in. column of 15% diethylene glycol adipate on Fluoropak 80).

Anal. Calcd for $C_5H_7N_3F_4O_2$: C, 27.66; H, 3.24; N, 19.35; F, 35.0. Found: C, 27.41; H, 3.12; N, 19.1; F, 35.0.

The proton nmr spectrum (CH_2Cl_2 solution) consisted of a doublet for the methyl at δ 1.39 and a septet for the methine at δ 5.21. The fluorine spectrum indicated a 1:5 mixture of *syn–anti* isomers, NF_2CNFCO_2R and NF_2CNFCO_2R, with NF_2 signals at ϕ^* −42.68 and −45.52, –NF– doublets at ϕ 44.69 (J = 6 cps) and 52.26 (J = 9 cps), and =NF signals at ϕ^* −31.6 and −24.24, respectively. The infrared spectrum showed carbonyl bands at 5.53 (s) and 5.69 μ (m), a fluorimine band at 6.2 μ (w), and bands in the NF region at 9.9 (w), 10.21 (w), 10.81 (m), 11.11 (m), 11.41 (m), 12.0 (m), and 12.83 μ (m).

1-Carbethoxytetrafluoroguanidine and 1,3-Dicarbethoxytrifluoroguanidine.—Fluorination of 20.3 g (0.10 mol) of 1,3-dicarbethoxyguanidine by method B (300 ml of acetonitrile, 0.35 mol of fluorine, 0°, 2 hr gave 2.5 g (11.7% yield) of 95% pure (gc analysis) 1-carbethoxytetrafluoroguanidine, bp 25–28° (0.1 mm); and 4.5 g (17.5% yield) of 1,3-dicarbethoxytrifluoroguanidine, bp 72° (0.1 mm). Analytical sample of 1-carbethoxytetrafluoroguanidine was prepared by gas chromatography (8 ft × 0.25 in. column of 15% diethylene glycol adipate on Fluoropak 80).

The proton nmr spectrum ($CDCl_3$ solution) showed a quartet at δ 4.48 and a triplet at δ 1.41. The fluorine spectrum indicated a 1.8:1 mixture of *syn–anti* isomers, NF_2CNFCO_2R and NF_2CNFCO_2R, with NF_2 signals at ϕ^* −42.4 and −45.4, –NF– doublets at ϕ^* 44.1 (J = 6 cps) and 51.4 (J = 9 cps), and =NF signals at ϕ^* −32.8 and −25.0, respectively. The infrared spectrum showed carbonyl bands at 5.57 (s) and 5.69 μ (s), a fluorimino band at 6.2 μ (w), and bands in the NF region at 10.0 (w), 10.28 (m), 10.88 (m), 11.4 (m), and 11.7 μ (m).

Anal. Calcd for $C_4H_5N_3F_4O_2$: C, 23.65; H, 2.50; N, 20.69. Found: C, 24.02; H, 2.80; N, 21.09.

The proton nmr spectrum ($CDCl_3$ solution) of 1,3-dicarbethoxytrifluoroguanidine showed a quartet at δ 4.45 and a triplet at δ 1.40. The fluorine spectrum showed a broadened band at ϕ^* −18.6 for the fluorimino and a triplet at 54.05 (J = 7 cps) and a doublet of doublets at 59.58 (J = 8.0, 12.1) for the geometrically nonequivalent –NF– groups.

Anal. Calcd for $C_7H_{10}N_3F_3O_4$: C, 32.69; H, 3.92; N, 16.34; F, 22.17. Found: C, 32.60; H, 4.11; N, 16.4; F, 21.9.

1,3-Dicarboisopropoxytrifluoroguanidine.—Fluorination of 23 g (0.10 mol) of 1,3-diisopropoxyguanidine by method B (350 ml of acetonitrile, 0.3 mol of fluorine, 1 hr, 0 to −10°) gave 12 g (42% yield) of 1,3-dicarboisopropoxytrifluoroguanidine, bp 80° (0.1 mm).

Anal. Calcd for $C_9H_{14}N_3F_3O_4$: C, 37.90; H, 4.95; N, 14.73; F, 19.19. Found: C, 37.90; H, 4.71; N, 15.0; F, 20.0.

The proton nmr spectrum ($CDCl_3$ solution) showed a doublet at δ 1.40 and a septet at δ 5.17. The fluorine spectrum consisted of a broadened band at ϕ^* −18.54 for =NF, and a doublet of doublets (J = 5.9, 7.9 cps) at ϕ^* 53.65 and a doublet of doublets (J = 8.8, 11.0 cps) at ϕ^* 60.25 for the *syn* and *anti* –NFCO groups.

Redistillation of the forecuts gave 2.6 g of 1-carboisopropoxytetrafluoroguanidine, identified by its infrared spectrum.

Fluorination of 1-Carbethoxy-3-cyanoguanidine.—Fluorination of 31.2 g (0.20 mol) of 1-carbethoxy-3-cyanoguanidine by method B (350 ml of acetonitrile, 1.2 mol of fluorine, 0 to −10°) gave 18 g of slightly yellow liquid, by 40–60° (25 mm). Gas chromatography (8 ft × 0.25 in. column of 15% diethylene glycol adipate on Fluoropak 80) showed that the distillate was a 26:50:24 mixture of ethyl N-(difluoraminodifluoromethyl)-N-fluorocarbamate, ethyl N-(fluoriminofluoromethyl)-N-fluorocarbamate, and 1-carbethoxytetrafluoroguanidine, respectively, in the order of their retention times.

The fluorine nmr spectrum of ethyl N-(difluoraminodifluoromethyl)-N-fluorocarbamate (CCl_4 solution) consisted of a broadened signal at ϕ^* −19.8 for NF_2, a broadened signal at ϕ^* 77.4 for –NF–, and a doublet (J = 12 cps) at ϕ^* 97.9 for CF_2. Irradiation at −19.8 resolved the 77.4 signal to a triplet (J = 12 cps). The infrared spectrum showed carbonyl bands at 5.55 and 5.62 μ (s) and bands in the NF region at 10.0 (m), 10.70 (m), 10.88 (s), and 11.68 μ (w).

Anal. Calcd for $C_4H_5N_2F_5O_2$: C, 23.08; H, 2.42; N, 13.46. Found: C, 23.39; H, 2.70; N, 13.6.

The fluorine nmr spectrum of ethyl N-(fluoriminofluoromethyl)-N-fluorocarbamate (CCl_4 solution) consisted of a broad signal at ϕ^* 15.0 for =NF, a doublet (J = 26 cps) at 53.2 for –NF—C=O, and a doublet of doublets (J = 26, 13 cps) at 63.4 for CF. Irradiation at 15.0 simplified the 63.4 signal to a doublet (J = 13 cps). The infrared spectrum showed carbonyl bands at 5.54 (s) and 5.64 μ (s), a fluorimino band at 5.98 μ (s), and bands in the NF region at 10.0 (m), 10.70 (s), 11.49 (m), and 11.70 μ (m).

Anal. Calcd for $C_4H_5N_2F_3O_2$: C, 28.24; H, 2.96; N, 16.47; F, 33.51. Found: C, 28.40; H, 3.02; N, 16.9; F, 33.6.

Registry No.—Ethyl (3-difluoraminopropyl)fluorocarbamate, 21298-38-4; ethyl (3-difluoraminopropyl)-carbamate, 21298-39-5; methyl N-carbomethoxy-α-aminobutyrate, 21298-40-8; carboisopropoxyguanidine, 21298-42-0; 1,3-dicarboisopropoxyguanidine, 21298-43-1; carbobutoxyguanidine, 21298-44-2; 1-carbobutoxytetrafluoroguanidine, 21298-45-3; 1-carboisopropoxytetrafluoroguanidine, 21298-46-4; 1-carbethoxytetrafluoroguanidine, 21298-47-5.

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