[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY,
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SOME FLUORINE DERIVATIVES OF URETHAN[1]

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Since so many chemicals are known to cause tumors (1), it is conceivable that the solution to the problem of cancer may be found in further intensive investigations at the chemical or molecular level. Urethan (ethyl carbamate) seems rather specific for the induction of lung tumors, as methyl, isoamyl, and *n*-butyl carbamate are inactive (2) while ethyl N-isopropylcarbamate, methylene, and ethylidene diurethan show some carcinogenic activity (3). Inhibition of the growth of Walker rat carcinoma (4) and temporary palliative therapy of human leukemia (5) have been effected with urethan.

The highly specific nature of urethan with regard to carcinogenic and antileukemic action may be linked to the molecular dimensions of urethan. On this basis, a number of fluorourethan derivatives have been prepared (6) primarily because fluorine and hydrogen atoms are of approximately the same order of size. While some of the fluorourethans tested thus far have received a ± rating for slight inhibition of Sarcoma 180 in mice, all of them have been quite toxic (7). The toxicity may be linked to the formation of fluoroethanol in the body which is oxidized to fluoroacetic acid and is condensed to fluorocitric acid which interferes with the Krebs cycle. The toxicity might be expected to vary considerably with changes in the rest of the molecule.

In connection with studies on urethan derivatives of possible cancer therapeutic properties, we have extended the synthesis of monofluorourethans and have prepared derivatives of di- and tri-fluorourethan.

EXPERIMENTAL[3]

Benzyl trifluoroacetate. To 146 g. (0.695 mole) of trifluoroacetic anhydride was added 150 g. (1.39 moles) of benzyl alcohol in the cold. The mixture was gently refluxed for one hour. Fractional distillation gave 250 g. (88%) of a colorless liquid, b.p. 178–179°.

Anal. Calc'd for $C_9H_7F_3O_2$: C, 52.9; H, 3.4.

Found: C, 52.9; H, 3.4.

β,β,β-Trifluoroethanol. This compound was prepared from benzyl trifluoroacetate by a modification of the method of Campbell, *et al.* (8). Benzyl trifluoroacetate was more conveniently used than butyl trifluoroacetate because (a) the benzyl ester is prepared in one hour while the butyl ester is reported to require 24 hours for preparation; (b) the final products, benzyl alcohol (b.p. 205°) and trifluoroethanol (b.p. 74–75°) are readily separated, and (c) the recovered benzyl alcohol may be reused.

To a three liter three-neck flask fitted with a reflux condenser, stirrer, dropping-funnel, and inlet for nitrogen gas was added 600 ml. of anhydrous ether. To this was added 33.6 g.

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[3] All melting points and boiling points are uncorrected. Analyses are by Peninsular ChemResearch, Inc., Gainesville, Fla.

TABLE I

MONOFLUORINATED DERIVATIVES OF URETHAN

General Procedure	Compound	M.p., °C.	Yield, %	Formula	Analyses					
					Calc'd			Found		
					C	H	N	C	H	N
I	β-Fluoroethyl 2-nitrocarbanilate	65–66	64	$C_9H_9FN_2O_4$			12.3			12.2
	β-Fluoroethyl 3-nitrocarbanilate	88–89	51	$C_9H_9FN_2O_4$			12.3			12.1
	β-Fluoroethyl 4-nitrocarbanilate	137–139	14	$C_9H_9FN_2O_4$	47.4	3.9	12.3	47.4	3.9	12.3
	β-Fluoroethyl 4-ethoxycarbanilate	91.5–92.5	62	$C_{11}H_{14}FNO_3$	58.1	6.2		58.0	6.1	
	β-Fluoroethyl N-1-naphthylcarbamate	130–130.5	60	$C_{13}H_{12}FNO_2$			6.0			6.0
	β-Fluoroethyl N-4-xenylcarbamate	148	73	$C_{15}H_{14}FNO_2$	69.5	5.4	5.4	69.5	5.5	5.3
II	β-Chloroethyl 4-fluorocarbanilate	74.5	75	$C_9H_9ClFNO_2$			6.4			6.5
	β-Fluoroethyl 4-fluorocarbanilate	74–75	93	$C_9H_9F_2NO_2$	53.7	4.5	7.0	53.8	4.6	6.9
	Ethyl 3-fluorocarbanilate	38.5–39	86	$C_9H_{10}FNO_2$			7.7			7.6
	Ethyl 4-fluorocarbanilate[a]	55–56	92	$C_9H_{10}FNO_2$						
	Ethyl 3-fluorothiolcarbanilate[b]	41–42	85	$C_9H_{10}FNOS$						
	Ethyl 4-fluorothiolcarbanilate[c]	69–70	70	$C_9H_{10}FNOS$						
	Di-β-fluoroethyl N,N′-*m*-phenylenedicarbamate	114–115	77	$C_{12}H_{14}F_2N_2O_4$			9.7			9.9
III	β-Fluoroethyl N,N-dimethylcarbamate[d]	b.p. 75–80 (5 mm.)	76	$C_5H_{10}FNO_2$			10.3			10.4
	β-Fluoroethyl N,N-diethylcarbamate[d]	b.p. 96 (23 mm.)	69	$C_7H_{14}FNO_2$			8.6			8.5

[a] Compound analyzed for fluorine; Calc'd; F, 10.4. Found: F, 10.7.

[b] Compound analyzed for sulfur; Calc'd; S, 16.1. Found: S, 16.1.

[c] Compound analyzed for sulfur; Calc'd; S, 16.1. Found: S, 16.2.

[d] Prepared from β-fluoroethyl chlorocarbonate and the appropriate dialkylamine by Olah and Pavlath, *Acta Chim. Acad. Sci. Hung.*, **4**, 89 (1954).

TABLE II

DIFLUORO- AND TRIFLUORO-URETHANS

General Procedure	Compound	M.p., °C.	Yield, %	Formula	Analyses					
					Calc'd			Found		
					C	H	N	C	H	N
I	β,β,β-Trifluoroethyl N-ethylcarbamate	25–26[a]	71	$C_5H_8F_3NO_2$	35.1	4.7	8.2	34.9	4.6	8.2
	β,β,β-Trifluoroethyl 3-nitrocarbanilate	92–93	69	$C_9H_7F_3N_2O_4$			10.6			10.6
	β,β,β-Trifluoroethyl 4-nitrocarbanilate	131–131.5	48	$C_9H_7F_3N_2O_4$			10.6			10.7
	β,β-Difluoroethyl carbanilate[b]	41–42	38	$C_9H_9F_2NO_2$	53.7	4.4	6.9	53.6	4.5	6.8
	β,β,β-Trifluoroethyl carbanilate	70	92	$C_9H_8F_3NO_2$	49.3	3.7	6.4	49.6	3.8	6.3
	β,β-Difluoroethyl 4-ethoxycarbanilate	95–96	52	$C_{11}H_{13}F_2NO_3$	53.8	5.3	5.7	53.8	5.4	5.7
	β,β,β-Trifluoroethyl 4-ethoxycarbanilate	112	52	$C_{11}H_{12}F_3NO_3$			5.3			5.4
	β,β-Difluoroethyl N-1-naphthylcarbamate	103	17	$C_{13}H_{11}F_2NO_2$	62.1	4.4	5.5	62.3	4.2	5.5
	β,β-Difluoroethyl N-2-naphthylcarbamate	91–92	40	$C_{13}H_{11}F_2NO_2$	62.1	4.4	5.5	62.2	4.5	5.4
	β,β,β-Trifluoroethyl N-1-naphthylcarbamate	109	71	$C_{13}H_{10}F_3NO_2$	57.9	3.7	5.2	58.0	3.7	5.1
	β,β,β-Trifluoroethyl N-2-naphthylcarbamate	114.5	80	$C_{13}H_{10}F_3NO_2$			5.2			5.4
	β,β,β-Trifluoroethyl N-4-xenylcarbamate	168	44	$C_{15}H_{12}F_3NO_2$	61.0	4.1	4.8	61.0	4.1	4.8
II	4-(β,β,β-Trifluorocarbethoxyamino)-2′,3-dimethylazobenzene	143	80[c]	$C_{17}H_{16}F_3N_3O_2$			11.9			11.9
	β,β,β-Trifluoroethyl carbamate	b.p. 172–174	100	$C_3H_4F_3NO_2$	25.2	2.8	9.8	25.1	2.7	9.9
III	β,β,β-Trifluoroethyl N,N-dimethylcarbamate	b.p. 58 (20 mm.)	42	$C_5H_8F_3NO_2$			8.2			8.1
	β,β,β-Trifluoroethyl N,N-diethylcarbamate	b.p. 65–68 (66 mm.)	50	$C_7H_{12}F_3NO_2$	42.2	6.0	7.0	42.3	6.1	7.2
IV	Di-β,β,β-trifluoroethyl N,N′-ethylidenedicarbamate	168	83	$C_8H_{10}F_6N_2O_4$			8.9			9.1
	Di-β,β,β-trifluoroethyl N,N′-propylidenedicarbamate	156	86	$C_9H_{12}F_6N_2O_4$			8.5			8.5
	Di-β,β,β-trifluoroethyl N,N′-benzylidenedicarbamate	208	88	$C_{13}H_{12}F_6N_2O_4$	41.7	3.2	7.4	41.4	3.4	7.6

[a] b.p. 90–91° (37 mm.). [b] The starting product, β,β-difluoroethanol was prepared by the procedure of Sroog, Chih, Short, and Woodburn, *J. Am. Chem. Soc.*, **71**, 1710 (1949). [c] Yield based on aminoazobenzene recovered; yield 15% based on amount of starting aminoazobenzene.

(0.884 mole) of powdered lithium aluminum hydride and the mixture was stirred for 30 minutes. Then 150 g. (0.735 mole) of benzyl trifluoroacetate was added at a rate which would not cause flooding of the condenser. After the complete addition of the ester, stirring was continued for one hour.

Excess lithium aluminum hydride was decomposed by the dropwise addition of 200 ml. of water which resulted in considerable evolution of heat and a white curdy precipitate. The intermediate was hydrolyzed by the addition of 500 ml. of 20% sulfuric acid. Extraction of the mixture with ether and distillation gave a fraction boiling at 65–80°. Distillation of the latter fraction from concentrated sulfuric acid gave 47 g. (64%) of a colorless liquid, b.p. 74–75°. Reported b.p. 74.05° (9).

β,β,β-Trifluoroethyl carbamate. This compound was prepared in poor yield (approximately 7%) from trifluoroethanol by the procedure used for the synthesis of β-fluorourethan (6). Trifluoroethanol was reacted with 5 moles of phosgene at 0–5° and allowed to stand overnight at room temperature. The excess phosgene was distilled off and the crude residual liquid (consisting mainly of unreacted trifluoroethanol and a small amount of trifluoroethyl chlorocarbonate) then was dissolved in ether and reacted with dry ammonia. Based upon the amount of β,β,β-trifluoroethyl chlorocarbonate assumed present (calculated from the amount of ammonium chloride recovered), the yield was approximately quantitative. The product was obtained as a colorless liquid, b.p. 172–174°.

The following general procedures are examples of the methods used to prepare representative types of the four groups of compounds reported in Tables I and II.

General procedure (I). Reaction of an isocyanate and alcohol. β,β,β-Trifluoroethyl 4-ethoxycarbanilate. To 8.2 g. (0.05 mole) of *p*-ethoxyphenyl isocyanate was added 5 g. (0.05 mole) of trifluoroethanol and a drop of triethylamine as catalyst. The mixture was gently refluxed for a few minutes. Upon cooling, the material solidified. Recrystallization from hexane gave 6.8 g. (52%) of white glistening needles, m.p. 112°.

General procedure (II). Reaction of a chlorocarbonate with an amine. Ethyl 3-fluorocarbanilate. To 3 g. (0.027 mole) of 3-aminofluorobenzene in 20 ml. of cold pyridine was added dropwise 3 g. (0.028 mole) of ethyl chlorocarbonate. The mixture was poured into cold dilute sulfuric acid and the resulting precipitate was collected and washed well with water. The dried precipitate was recrystallized from hexane and gave 4.2 g. (86%) of colorless crystals, m.p. 38.5–39.0°.

The ethyl chlorothiolcarbonate, used in the preparation of the two thiolcarbamates listed in Table I, was prepared by the procedure of Salomon (10).

General procedure (III). Interaction of carbamyl chlorides and alcohols. β-Fluoroethyl N,N-dimethylcarbamate. A mixture of 5 g. (0.078 mole) of fluoroethanol (11) and 8.4 g. (0.078 mole) of dimethylcarbamyl chloride[4] was refluxed 45 minutes. Vacuum distillation at 75–80° and 5 mm. yielded 8 g. (76%) of a colorless liquid.

General procedure (IV). Reaction of aldehydes with urethan. Di-β,β,β-trifluoroethyl N,N'-ethylidenedicarbamate. To a solution of 0.1 g. (0.002 mole) of acetaldehyde and 0.6 g. (0.004 mole) of trifluorourethan was added a micro-drop of concentrated hydrochloric acid. The mixture was allowed to stand overnight. The solid material was recrystallized from aqueous ethanol and gave 0.5 g. (83%) of white needles, m.p. 168°.

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SUMMARY

Thirty-two new fluorine derivatives of urethan have been prepared for cancer therapeutic studies.

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