[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

NEW FLUORINATED URETHANS[1]

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Fluorinated urethans were first synthesized in this laboratory (1, 2) with the object of enhancing the cancer therapeutic properties of urethan. It has been found (3) that, in general, monofluorourethans are more active and more toxic than trifluorourethans when tested against Sarcoma 180 in mice. Toxicity of the monofluorourethans has been attributed (2) to an interference by fluorocitric acid with the Krebs cycle.

In view of the slight but definite cancer therapeutic activity shown by some of the fluorinated urethans (3) previously prepared, over 30 new derivatives have been synthesized for biological testing and are described in this final paper of the series, Table I. Trifluorourethan was prepared from sodium trifluoroethoxide, phosgene, and ammonia in better yield than previously reported (2). Nobis (4) reports that all attempts to prepare dry sodium trifluoroethoxide have resulted in violent explosions. In our hands no difficulty was encountered with this compound but it is evident that precautions be exercised. Carbon^{14} studies (5) have shown that the carbon atoms of the urethan molecule are almost quantitatively eliminated in 24 hours. Bailey and Christian (6), who described an elaborate synthesis for urethan-N^{15}, have shown in preliminary animal work that the labeled nitrogen has been definitely taken up in the body. Consequently, we have prepared urethan-N^{15} and fluorourethan-N^{15} in excellent yield by a very simple procedure for eventual study of urethan and fluorourethan metabolism.

Fluorinated urethans may also find useful application in fields unrelated to cancer. George, *et al.* (7) compared the chemical structure and herbicidal activity of a number of esters of phenylcarbamic acid and showed that substitution of a vinyl group or a chlorine atom in the β-position of the ethyl portion of ethyl N-phenylcarbamate produced the most active herbicides. On this basis, trial of fluorinated N-phenylurethans, which are very easily prepared, is worthwhile. Olah and Pavlath (8) also pointed out that compounds containing the fluoroethoxy group possess strong insecticidal and rodenticidal properties.

EXPERIMENTAL[3]

2′,3-Dimethyl-4-isocyanatoazobenzene. This new compound, used as an intermediate in the preparation of 4-(β-fluorocarbethoxyamino)-2′,3-dimethylazobenzene, was prepared

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[3] All melting points and boiling points are uncorrected. Analyses are by Peninsular Chemical Research, Inc., Gainesville, Florida.

TABLE I

FLUORINATED AND OTHER URETHANS

General Procedure	Compound	M.p., °C.	Yield, %	Formula	Analyses					
					Calc'd			Found		
					C	H	N	C	H	N
I[a]	β-Fluoroethyl 3-chlorocarbanilate	36–38	40	$C_9H_9ClFNO_2$			6.4			6.3
	β-Fluoroethyl 4-chlorocarbanilate	69.5–71	60	$C_9H_9ClFNO_2$	49.7	4.1	6.4	49.9	4.3	6.5
	β-Fluoroethyl 4-methylcarbanilate	64–65	55	$C_{10}H_{12}FNO_2$			7.1			7.0
	β-Fluoroethyl 4-methoxycarbanilate	88–89	41	$C_{10}H_{12}FNO_3$			6.6			6.6
	4-(β-Fluorocarbethoxyamino)-2′,3-dimethylazobenzene	115–116	50	$C_{17}H_{18}FN_3O_2$	64.8	5.7	13.3	64.7	5.8	13.1
	β,β,β-Trifluoroethyl 3-chlorocarbanilate	37–38	53	$C_9H_7ClF_3NO_2$	42.6	2.8	5.5	42.5	2.8	5.4
	β,β,β-Trifluoroethyl 4-chlorocarbanilate	72–73	79	$C_9H_7ClF_3NO_2$			5.5			5.3
	β,β,β-Trifluoroethyl 4-methylcarbanilate	90.5–91.5	86	$C_{10}H_{10}F_3NO_2$			6.0			5.8
	β,β,β-Trifluoroethyl 4-methoxycarbanilate	84–85	83	$C_{10}H_{10}F_3NO_3$	48.2	4.0	5.6	48.3	4.1	5.4
IV[b]	Di-β-fluoroethyl N,N′-furfurylidenedicarbamate	191–192	51	$C_{11}H_{14}F_2N_2O_5$	45.2	4.8	9.6	45.1	4.7	9.9
	Di-β-fluoroethyl N,N′-2,4-dichlorobenzylidenedicarbamate	211	68	$C_{13}H_{14}Cl_2F_2N_2O_4$			7.5			7.6
	Di-β-fluoroethyl N,N′-3,4-dichlorobenzylidenedicarbamate	209–210	50	$C_{13}H_{14}Cl_2F_2N_2O_4$			7.5			7.4
	Di-β-fluoroethyl N,N′-4-chlorobenzylidenedicarbamate	214–215	38	$C_{13}H_{15}ClF_2N_2O_4$			8.3			8.2
	Diethyl N,N′-4-chlorobenzylidenedicarbamate	197–199	62	$C_{13}H_{17}ClN_2O_4$			9.3			9.3
	Di-β-fluoroethyl N,N′piperonylidenedicarbamate	180–181	38	$C_{14}H_{16}F_2N_2O_6$			8.1			7.9

[a] Prepared by reaction of an alcohol and isocyanate (2).

[b] Prepared by reaction of an aldehyde with a urethan (2).

TABLE I—*Continued*

General Procedure	Compound	M.p., °C.	Yield, %	Formula	Analyses					
					Calc'd			Found		
					C	H	N	C	H	N
	Di-β-fluoroethyl N,N′-4-methylbenzylidenedicarbamate	220	56	$C_{14}H_{18}F_2N_2O_4$	53.2	5.7	8.9	53.3	5.7	8.7
	Di-β-fluoroethyl N,N′-4-methoxybenzylidenedicarbamate	203	27	$C_{14}H_{18}F_2N_2O_5$			8.4			8.3
	Di-β-fluoroethyl N,N′-phenethylidenedicarbamate	177–178	60	$C_{14}H_{18}F_2N_2O_4$	53.2	5.7	8.9	53.3	5.7	8.7
	Diethyl N,N′-4-methylbenzylidenedicarbamate	198–199	77	$C_{14}H_{20}N_2O_4$			10.0			9.9
	Di-β-fluoroethyl N,N′-hydrocinnamylidenedicarbamate	163–164	44	$C_{15}H_{20}F_2N_2O_4$	54.5	6.1	8.5	54.5	6.1	8.3
	Diethyl N,N′-hydrocinnamylidenedicarbamate	131–132	48	$C_{15}H_{22}N_2O_4$			9.5			9.4
	Di-β-fluoroethyl N,N′-1-naphthylidenedicarbamate	208–210	48	$C_{17}H_{18}F_2N_2O_4$	58.0	5.1	8.0	58.1	5.2	7.8
	Diethyl N,N′-1-naphthylidenedicarbamate	207–208	73	$C_{17}H_{20}N_2O_4$			8.9			8.7
	Di-β,β,β-trifluoroethyl N,N′-4-methylbenzylidenedicarbamate	223–224	69	$C_{14}H_{14}F_6N_2O_4$	43.3	3.6	7.2	43.4	3.5	7.2
	Di-β,β,β-trifluoroethyl N,N′-1-naphthylidenedicarbamate	218–219	62	$C_{17}H_{14}F_6N_2O_4$	48.1	3.3	6.6	48.0	3.5	6.5
V	β-Chloroethyl N-fluoroacetylcarbamate	59–61	24	$C_5H_7ClFNO_3$	32.1	3.8		32.3	3.9	
	Ethyl N-fluoroacetylcarbamate	72–74	16	$C_5H_8FNO_3$	40.3	5.4		40.3	5.6	
	Ethyl N-propionylcarbamate	78.5–79.5	67	$C_6H_{11}NO_3$	49.7	7.6		50.0	7.8	
	Di-β-fluoroethyl N,N′-oxalyldicarbamate	187–188	13	$C_8H_{10}F_2N_2O_6$	35.8	3.7		35.7	3.8	
	β-Fluoroethyl N-phenacetylcarbamate	123.5–125.5	80	$C_{11}H_{12}FNO_3$	58.7	5.3		58.7	5.4	

from 4-amino-2′,3-dimethylazobenzene and phosgene according to the procedure of Raiford and Freyermuth (9). The isocyanate (54%) was obtained as dark-orange fluffy needles, m.p. 59–60°.

Anal. Calc'd for $C_{15}H_{13}N_3O$: C, 71.7; H, 5.2; N, 16.7.
Found: C, 71.9; H, 5.1; N, 16.5.

N,N′-Di-4-(2′,3-dimethylazobenzene)urea. This compound was obtained as a by-product of the reaction between 2′,3-dimethyl-4-isocyanatoazobenzene and fluoroethanol. Crystallization from nitrobenzene gave a 16% yield of dark-yellow platelets, m.p. 280–281°.

Anal. Calc'd for $C_{29}H_{28}N_6O$: C, 73.1; H, 5.9; N, 17.6.
Found: C, 73.2; H, 5.8; N, 17.5.

β,β,β-Trifluoroethyl carbamate. To a two-liter three-neck flask fitted with a reflux condenser, stirrer, dropping-funnel, and inlet for nitrogen gas was added 750 ml. of xylene which had been previously distilled from sodium hydride. To this was added 13.2 g. (0.550 mole) of powdered sodium hydride and the mixture was stirred 30 minutes in the cold. The system was purged with nitrogen gas and 50 g. (0.500 mole) of trifluoroethanol was added at a rate which would not cause flooding of the condenser. After complete addition of the alcohol, stirring was continued for one hour at room temperature. The resulting white curdy precipitate dissolved when the mixture was heated just below the boiling point for 30 minutes. Upon cooling, 60 g. (99%) of a white flocculent precipitate, sodium trifluoroethoxide was collected, washed well with pentane, and stored in a vacuum desiccator until the following day.

Sodium trifluoroethoxide (0.491 mole) was added in small portions to 5 moles of phosgene at 0–5°, stirred one hour at room temperature, and finally allowed to stand overnight in the cold. The mixture was filtered. The precipitate was extracted several times with ether and the combined ether extracts were added to the main filtrate. The unreacted phosgene was distilled and 500 ml. of ether was added to the mother liquor.

Excess dry ammonia was passed into an ice-cold ether solution of trifluoroethyl chlorocarbonate for one hour. Filtration of the ammonium chloride followed by vacuum distillation at 120°/0–10 mm. gave 20 g. (28%) of colorless crystals, m.p. 28.5–30°.

N^{15}-Urethan and N^{15}-β-fluorourethan. Five ml. of 50% aqueous sodium hydroxide was added to a cold solution of 1.6 g. (0.02 mole) of ammonium nitrate containing 64 atom-% N^{15} (as $N^{15}H_4NO_3$) in 2 ml. of water and 20 ml. of ether in a flask. The flask was stoppered and gently shaken with cooling. Three ml. (0.03 mole) of ethyl chlorocarbonate was added. The cooled, stoppered flask was shaken vigorously for 10–15 minutes and allowed to warm to room temperature during the next hour with occasional shaking. The mixture was saturated with powdered salt and extracted with ether. The ether solution was dried and evaporated. The residue was suspended in 15 ml. of pentane and cooled to 0° to give colorless needles (1.65 g.; 93%), m.p. 47–48°. β-Fluoroethyl carbamate-N^{15} was similarly prepared from β-fluoroethyl chlorocarbonate (1).

General procedure (V).[4] *Reaction of an acyl halide with a urethan. β-Chloroethyl N-fluoroacetylcarbamate.* To 3 g. (0.024 mole) of β-chloroethyl carbamate was added 2.4 g. (0.025 mole) of fluoroacetyl chloride. The mixture was heated on a steam-bath for two hours or until the rapid evolution of hydrogen chloride gas ceased. The mixture was cooled and washed well with pentane to remove any unreacted acyl halide. Recrystallization from pentane-hexane (1:1) gave 1 g. (24%) of colorless crystals, m.p. 59–61°.

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SUMMARY

Over 30 new derivatives of urethan were prepared for cancer therapeutic studies. An improved preparation of β,β,β-trifluoroethyl carbamate is described.

[4] See reference (2) for general procedures I, II, III, and IV.

Urethan-N^{15} and β-fluorourethan-N^{15} were prepared by a very simple procedure for eventual urethan metabolism studies.

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