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

FLUOROURETHAN AND DERIVATIVES[1]

EUGENE SAWICKI AND FRANCIS E. RAY

Received May 5, 1953

The remarkable effects of urethan and its derivatives on biological systems have been pointed out by many workers. In 1943 it was found that urethan could induce pulmonary tumors in mice (1) and later work on tumor induction in both mice (2–4) and rats (5, 6) has confirmed the carcinogenicity of this compound. Urethan is the most potent carbamate in lung tumorigenesis (3) and leukopenic activity (7) although methylene and ethylidene diurethans are also strong carcinogens (8). On the other hand, a change of the ester group from ethyl to methyl renders the urethan inactive (3).

In 1946 it was found that urethan inhibited the growth of some animal tumors (9) and was of value in the treatment of human leukemia (10). Of the many carbamates tested the carbamate most active against leukemia (11) and carcinoma (9) was found to be urethan. Thus, urethan appears to be a highly specific molecule with regard to carcinogenic and anti-leukemic action.

Because of this specificity it is probable that the molecular dimensions of the molecule are of some importance. In this case the Van der Waals radii of the common atoms and groups are of interest. These radii are reported to be: H, 1.2 Å.; F, 1.35 Å.; Cl, 1.80 Å,; Br, 1.95 Å.; CH_3, 2.0 Å. and I, 2.15 Å. (12). It is apparent that the two smallest substituents (with the same order of size) are —H and —F. On this basis the fluorourethans are worthy of extensive biological study.

EXPERIMENTAL

β-Fluorourethan or β-fluoroethyl carbamate. Excess dry ammonia was passed through an ice-cold solution of 12.7 g. of β-fluoroethyl chlorocarbonate (13) in 100 ml. of dry ether. Filtration gave 5.2 g. (96%) of ammonium chloride. Evaporation of the ether followed by crystallization from benzene-pentane or vacuum distillation at 128–130° and 40 mm. gave 9.7–10.2 g. (91–95%) of colorless crystals, m.p. 23–24°.

Anal. Calc'd for $C_3H_6FNO_2$: C, 33.64; H, 5.61; N, 13.1.
Found: C, 33.87; H, 5.62; N, 13.0.

β-Fluoroethyl N-ethylcarbamate. The same procedure was used for the preparation of this compound as for fluorourethan except that dry ethylamine[2] was used. Vacuum distillation at 116–117° and 30 mm. gave an 85–90% yield of colorless liquid.

Anal. Calc'd for $C_5H_{10}FNO_2$: N, 10.4. Found: N, 10.3.

Di-β-fluoroethyl N,N'-methylenedicarbamate. To a solution of 0.55 g. of fluorourethan in 3 ml. of water and 0.40 ml. of 40% formaldehyde was added 0.01 ml. of concentrated hydrochloric acid. The clear solution was allowed to stand for 48 hours. Crystals formed slowly in the reaction flask. Crystallization from benzene gave 0.35 g. (60%) of colorless crystals, m.p. 152–153°.

Anal. Calc'd for $C_7H_{12}F_2N_2O_4$: N, 12.4. Found: N, 12.4.

[1] The work described in this paper was supported by a grant from the Sloan-Kettering Institute for Cancer Research.

[2] Kindly supplied by Carbide and Carbon Chemicals Corp.

Di-β-fluorethyl N,N'-ethylidenedicarbamate. A drop of concentrated hydrochloric acid was added to a solution of 1.8 g. of fluorourethan in 2 ml. of water and 1.9 ml. of acetaldehyde. Within a few minutes the solution had solidified. The mixture was allowed to stand for two hours. Crystallization from water gave 1.82 g. (90%) of colorless needles, m.p. 158.5–159.5°.

Anal. Calc'd for $C_8H_{14}F_2N_2O_4$: C, 40.00; H, 5.83.
Found: C, 40.27; H, 5.61.

Di-β-fluoroethyl N,N'-propylidenedicarbamate. This compound was prepared by the same procedure used for the acetaldehyde derivative except that propionaldehyde was used. Crystallization from benzene gave a 90% yield of colorless crystals, m.p. 153–154°.

Anal. Calc'd for $C_9H_{16}F_2N_2O_4$: C, 42.52; H, 6.30.
Found: C, 42.60; H, 6.45.

Di-β-fluoroethyl N,N'-(β-chloroethylidene)dicarbamate. A drop of concentrated hydrochloric acid was added to a solution of 2.14 g. of fluorourethan in 2 ml. of 40% chloroacetaldehyde. Within several hours an oil had formed which gradually changed into crystals after 24 hours standing. Crystallization from alcohol gave 2.3 g. (84%) of colorless crystals, m.p. 156–157°.

Anal. Calc'd for $C_8H_{13}ClF_2N_2O_4$: N, 10.2. Found: N, 10.4.

Di-β-fluorethyl N,N'-benzylidenedicarbamate. One drop of concentrated hydrochloric acid was added to a solution of 2.14 g. of fluorourethan in 4 ml. of alcohol and 1 ml. of benzaldehyde. The clear solution was allowed to stand overnight. Excess water was added. Crystallization from alcohol gave 2.86 g. (95%) of colorless crystals, m.p. 205–206°.

Anal. Calc'd for $C_{13}H_{16}F_2N_2O_4$: C, 51.66; H, 5.30.
Found: C, 51.88; H, 5.37.

β-Fluoroethyl N-acetylcarbamate. A mixture of 2.14 g. of fluorourethan and 1.58 ml. of acetylchloride was gently refluxed for one hour. The crude brown product was crystallized twice from hexane to give 1.04 g. (35%) of colorless crystals, m.p. 79–80.5°.

Anal. Calc'd for $C_5H_8FNO_3$: C, 40.27; H, 5.37; N, 9.40.
Found: C, 40.21; H, 5.44; N, 9.49.

β-Fluoroethyl carbanilate. (*a*). To a stirred solution of 9.3 g. of aniline in 40 ml. of pyridine at 0–10° was added dropwise 9 ml. of fluoroethyl chlorocarbonate. The mixture was stirred an additional hour at the same temperature. It was added to 200 ml. of ice-cold 25% sulfuric acid. The oil was extracted with ether. Distillation of the ether followed by vacuum distillation at 136–140° and approximately 2–4 mm. gave colorless crystals. Crystallization from hexane gave 16.5 g. (90%) of colorless crystals, m.p. 53.5–55°.

(*b*). Equimolar amounts of phenyl isocyanate and 2-fluoroethanol were refluxed for several hours. Vacuum distillation and crystallization from hexane gave an 85–90% yield of colorless crystals, m.p. 54–55°.

Anal. Calc'd for $C_9H_{10}FNO_2$; C, 59.02; H, 5.46.
Found: C, 59.09; H, 5.35.

β-Fluoroethyl N-2-naphthylcarbamate. This compound was prepared from 2-naphthylamine by the same procedure used for the benzene analog except that ether extraction and vacuum distillation were not necessary. Crystallization from hexane gave a 95% yield of colorless crystals, m.p. 108–109°.

Anal. Calc'd for $C_{13}H_{12}FNO_2$: N, 6.01. Found: N, 6.00.

Di-β-fluoroethyl 1,2-di(carboxyamino)benzene was prepared by a procedure similar to that used for the preceding compound except that *o*-phenylenediamine and two equivalents of fluoroethyl chlorocarbonate were used. Crystallization from benzene-heptane and then from water gave a 75–85% yield of colorless needles, m.p. 118.5–119.5°.

Anal. Calc'd for $C_{12}H_{14}F_2N_2O_4$: C, 50.00; H, 4.86.
Found: C, 49.99; H, 4.70.

Di-β-fluoroethyl 1,4-di(carboxyamino)benzene. The same procedure used as for the 1,2-isomer. Crystallization from hexane gave a 90–95% yield of colorless crystals, m.p. 192–193°.

Anal. Calc'd for $C_{12}H_{14}F_2N_2O_4$: C, 50.00; H, 4.86.
Found: C, 50.18; H, 4.74.

SUMMARY

β-Fluorourethan and some N-substituted aliphatic and aromatic derivatives have been prepared.

GAINESVILLE, FLORIDA

REFERENCES

(1) NETTLESHIP AND HENSHAW, *J. Natl. Cancer Inst.*, **4**, 309 (1943).
(2) ORR, *Brit. J. Cancer*, **1**, 311 (1947).
(3) LARSEN, *J. Natl. Cancer Inst.*, **8**, 99 (1947).
(4) ROGERS, *J. Exptl. Med.*, **93**, 427 (1951).
(5) JAFFÉ, *Cancer Research*, **7**, 107 (1947).
(6) GUYER AND CLAUS, *Cancer Research*, **7**, 342 (1947).
(7) SKIPPER, BRYAN, RISER, WELTY, AND STELZENMULLER, *J. Natl. Cancer Inst.*, **9**, 77 (1948).
(8) LARSEN, *J. Natl. Cancer Inst.*, **9**, 35 (1948).
(9) HADDOW AND SEXTON, *Nature*, **157**, 500 (1946).
(10) PATERSON, APTHOMAS, HADDOW, AND WATKINSON, *Lancet*, **1**, 677 (1946).
(11) SKIPPER AND BRYAN, *J. Natl. Cancer Inst.*, **9**, 391 (1949).
(12) PAULING, *Nature of the Chemical Bond*, Cornell University Press, Ithaca, N. Y., 1948, p. 189.
(13) KNUNYANTS, KIL'DISHEVA, AND PETROV, *J. Gen. Chem.* (*U.S.S.R.*), **19**, 95 (1949); *Chem. Abstr.*, **43**, 6163 (1949).