[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY OF THE DEPARTMENT OF SURGERY, UNIVERSITY OF WASHINGTON, SCHOOL OF MEDICINE]

Derivatives of Fluorene. XV. Fluorofluorenes. IV[1]

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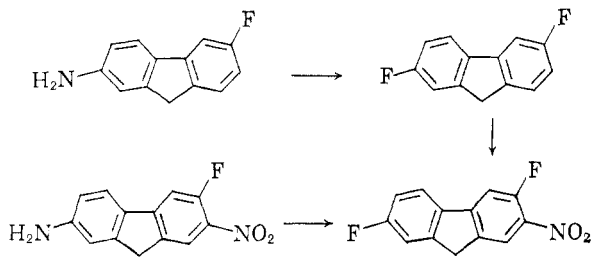
New difluorinated derivatives of fluorene are described, particularly 1,7- and 3,7-difluoro-2-acetamidofluorene, for cancer research. These are of interest because blocking metabolic hydroxylation sites may lead to more potent carcinogens and to metabolic products pertinent to the origin of cancer.

Previously[3] we discussed the importance of fluorinated *N*-2-(fluorenyl)acetamides in carcinogenicity studies being done by Drs. J. A. and E. C. Miller,[4] and described preparation of six new monofluoro-2-acetamidofluorenes[3,5,6] We felt that difluoro-2-acetamidofluorenes, with one fluorine atom in the 7-position,[7] the major hydroxylation site, might have enhanced carcinogenicity. Additionally, if the positions *ortho* to the acetamido group were to be blocked, thus preventing N—OH[8] to ring —OH migration, the metabolic picture as related to carcinogenicity might be clarified.

We synthesized 2-nitro-3,7-difluorofluorene in two ways:



By an improved procedure using tetrahydrofuran[9] 6-fluoro-2-fluorenamine[6] was diazotized in fluoboric acid. Decomposition of the salt in boiling xylene gave 2,6-difluorofluorene. Nitration of the latter gave a good yield of 2-nitro-3,6-difluorofluorene which was also obtained from 3-fluoro-2-nitro-7-fluorenamine.[6] Reduction[10] and acetylation gave *N*-2-(3,7-difluorofluorenyl)acetamide.

2-Nitro-1,7-difluorofluorene was prepared by Schiemann decomposition of the diazonium salt[9] of 1-fluoro-2-nitro-7-fluorenamine.[5] Nitration of 1,7-difluorofluorene (from 8-fluoro-2-fluorenamine[5]) gave a mixture which seemed difficult to separate by crystallization and chromatography. Its infrared spectrum, however, showed that the mixture was chiefly 2-nitro-1,7-difluorofluorene.

EXPERIMENTAL[11]

2,6-Difluorofluorene. 6-Fluoro-2-fluorenamine[6] (11 g., 0.055 mole) was dissolved in 100 ml. of tetrahydrofuran[9] (warm) and 200 ml. of 48–50% fluoboric acid was added. A white precipitate came out upon cooling. To the cooled mixture (0°), an aqueous solution of 4 g. (0.059 mole) of sodium nitrite was added dropwise with stirring. After 15 min. (0°), the salt was filtered and washed with cold 5% fluoboric acid, methanol, and ether and dried, giving 15 g., dec. 120°. The diazonium salt was decomposed in boiling xylene. After filtration from a small amount of residue, the solvent was evaporated and the product was recrystallized from petroleum ether (b.p. 30–60°), giving 7.1 g. (63% based on the amine), m.p. 46–48°. One more recrystallization from petroleum ether gave an analytical sample, m.p. 48–49°; λ_{max} 255 mμ (ϵ 1.48 × 10^4), 260 (1.49 × 10^4), 264 (1.47 × 10^4), 281 (6.05 × 10^3), 287 (5.37 × 10^3), 293 (8.2 × 10^3), 298 (7.70 × 10^3), 305 (1.12 × 10^4); C—F stretching: 8.23 μ, 8.51 μ.

Anal. Calcd. for $C_{13}H_8F_2$: C, 77.22; H, 3.99; F, 18.79. Found: C, 77.22; H, 4.05; F, 18.60.

2-Nitro-3,7-difluorofluorene. (a) To a cooled (0°) mixture of 1.5 g. (0.061 mole) of 3-fluoro-2-nitro-7-fluorenamine[6] and 30 ml. of fluoboric acid (50%) and 60 ml. of 85% phosphoric acid, a saturated aqueous solution of 0.5 g. (0.072 mole) of sodium nitrite was added dropwise with stirring. After stirring for 10 min., the diazonium salt was treated as above, giving 1.5 g. (73%) of salt, dec. 135–140°. Decomposition of the salt in boiling xylene, evaporation of the solvent and recrystallization from alcohol (Darco) gave 0.75 g. (50%, based on the amine) of 2-nitro-3,7-difluorofluorene, m.p.

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(11) Melting points were taken on a Fisher-Johns block and are corrected to standards. Analyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Alfred Bernhardt, Mülheim (Ruhr), Germany. Miss Barbara Bigley gave us valuable assistance in preparation and purification of starting compounds. Ultraviolet spectra were obtained on a DK-1 recording spectrophotometer ($3 \times 10^{-5}M$ in absolute ethanol for all except acetamido-compounds which were $2 \times 10^{-5}M$). Infrared spectra were taken on a Beckman IR-5.

182–187°. Recrystallization from benzene raised the m.p. to 186–187°. An analytical sample was prepared by sublimation at 180° (1 mm.), m.p. 187–187.5°; λ_{max} 288 mμ (ϵ 8.20 × 10^3), 327 (1.38 × 10^4); C–F stretching: 8.17 μ, 8.32 μ.

Anal. Calcd. for $C_{13}H_7F_2NO_2$: C, 63.16; H, 2.85; N, 5.67. Found: C, 63.39; H, 3.29; N, 5.92.

(b) To a solution of 2.02 g. (0.01 mole) of 2,6-difluorofluorene in 8 ml. of glacial acetic acid at 50°, 2 ml. of nitric acid (d. 1.42) was added, the mixture was heated to 70° and 4 drops of concd. sulfuric acid were added with stirring. An exothermic reaction occurred with formation of a yellow precipitate. The temperature of the mixture was kept 85° for 5 min., then allowed to drop to 25°. The precipitate was filtered, washed with cold acetic acid and water, and dried, giving 2.2 g. (89%) of crude product, m.p. 182–186°. One recrystallization from benzene (Darco) gave 1.8 g. (73.5%) of the pure compound, m.p. 186–187°. A mixture melting point with the Schiemann decomposition product of 3-fluoro-2-nitro-7-fluorenamine was undepressed, and the infrared spectra of the two compounds were identical.

2-Amino-3,7-difluorofluorene. An alcoholic solution (50 ml.) of 0.46 g. (0.002 mole) of 2-nitro-3,7-difluorofluorene was reduced with 0.5 ml. of 100% hydrazine hydrate and Raney nickel[10] giving 0.38 g. (95%) of the amine, m.p. 124–124.5°. One recrystallization from alcohol gave an analytical sample, m.p. 124–124.5°; λ_{max} 279 mμ (ϵ 1.97 × 10^4), 326 (8.75 × 10^3), C—F stretching: 8.01 μ, 8.56 μ.

Anal. Calcd. for $C_{13}H_9F_2N$: N, 6.45. Found: N, 6.28.

N-2-(3,7-Difluorofluorenyl)acetamide. The foregoing compound was acetylated quantitatively with acetic anhydride on the steam bath for 10 min. The product was recrystallized from alcohol (Darco), m.p. 240–240.5°; λ_{max} 274 m μ (ϵ 2.03 × 10^4), 308 (1.49 × 10^4), $\lambda_{shoulder}$ 280 mμ, 286 μ; C–F stretching: 8.08 μ, 8.57 μ.

Anal. Calcd. for $C_{15}H_{11}F_2NO$: C, 69.49; H, 4.28; F, 14.66; N, 5.40. Found: C, 69.68; H, 4.28; F, 14.47; N, 5.40.

1,7-Difluorofluorene. A solution of 4.3 g. (0.0216 mole) of 1-fluoro-7-fluorenamine[5] in 25 ml. of tetrahydrofuran[9] and 25 ml. of 48–50% fluoboric acid (0°) was diazotized. After 30 min., the salt was filtered and washed giving 5.9 g. (91%), dec. 170°. This was suspended in *o*-dichlorobenzene and heated gradually to the boiling point. Upon evaporating the solvent and recrystallizing the residue from petroleum ether (b.p 30–60°), 2.7 g. (62%, based on the amine) of product was obtained, m.p. 64–66°. Two recrystallizations from cyclohexane followed by sublimation (75°, 1 mm.) gave an analytical sample, m.p. 73.5–74.5°; λ_{max} 261 mμ (ϵ 1.84 × 10^4), 278 (7.60 × 10^3), 287 (3.67 × 10^3), 299 (3.27 × 10^3), $\lambda_{shoulder}$ 216 mμ, 255, 271, 292; C—F stretching : 8.03 μ, 8.13 μ.

Anal. Calcd. for $C_{13}H_8F_2$: C, 77.22; H, 3.99; F, 18.79. Found: C, 77.35; H, 4.08; F, 18.67.

Nitration of 1,7-difluorofluorene. The foregoing compound (2 g., 0.001 mole) was nitrated in the same manner as above, giving 2.2 g. of crude product, m.p. 125–128°, three recrystallizations from alcohol raised the m.p. to 127–130°. A benzene solution of this was percolated through alumina and upon evaporating the solvent, 1.72 g. was recovered with melting point unchanged. The infrared spectrum of this material was almost the same as that of 2-nitro-1,7-difluorofluorene, described in the following section, with a few additional bands.

2-Nitro-1,7-difluorofluorene. To a solution of 3.85 g. (0.017 mole) of 1-fluoro-2-nitro-7-fluorenamine[6] in 30 ml. of tetrahydrofuran[9] 50 ml. of 50% fluoboric acid was added to form a thick white salt. This was cooled to 0° and a saturated aqueous solution of 2 g. (0.029 mole) of sodium nitrite was added dropwise with stirring. The resulting diazonium salt was filtered, washed as above, and dried, giving 4.5 g. (90%), dec. 140°. Upon decomposition in boiling xylene, evaporation of the liquid and recrystallization from alcohol (Darco) 2.8 g. (71% based on the amine) of the 2-nitro-1,7-difluorofluorene was obtained, m.p. 164–165°. An analytical sample was prepared by sublimation at 150° (1 mm.), m.p. 165.5–166°; λ_{max} 230 mμ (ϵ 1.27 × 10^4), 319 (1.77 × 10^4); C—F stretching: 8.05 μ, 8.18 μ.

Anal. Calcd. for $C_{13}H_7F_2NO_2$: C, 63.16; H, 2.85; N, 5.67. Found: C, 63.44; H, 3.24; N, 5.63.

1,7-Difluoro-2-fluorenamine. The foregoing compound was reduced[10] in quantitative yield, m.p. 124–125°. One recrystallization from alcohol gave an analytical sample, m.p. 125–125.5°; λ_{max} 287 mμ (ϵ 2.58 × 10^4); C–F stretching: 8.1 μ, 8.21 μ.

Anal. Calcd. for $C_{13}H_9F_2N$: N, 6.45. Found: N, 6.48.

N-2-(1,7-Difluorofluorenyl)acetamide. Acetylation in benzene with acetic anhydride gave a quantitative yield, m.p. 198–199°. One recrystallization from alcohol (Darco) gave an analytical sample, m.p. 199–199.5°; λ_{max} 275 mμ (ϵ 3.17 × 10^4), 285 (3.00 × 10^4), $\lambda_{shoulder}$ 298 mμ; C—F stretching: 8.08 μ, 8.29 μ.

Anal. Calcd. for $C_{15}H_{11}F_2NO$: C, 69.49; H, 4.28; F, 14.66; N, 5.40. Found: C, 69.59; H, 4.32; F, 14.63; N, 5.50.

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[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY OF THE DEPARTMENT OF SURGERY, UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE]

Derivatives of Fluorene. XVI. *N*-9-Fluorenylmaleamic Acids and Maleimides[1]

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Several *N*-9-fluorenylmaleamic acids, maleimides, and some new intermediates are described. Cyclization of three *N*-9-fluorenylmaleamic acids is effected in boiling glacial acetic acid. Acetic anhydride with fused sodium acetate, in the usual cyclization procedure, gives highly colored mixtures.

In a recent paper we described the preparation of a number of *N*-(ring)-fluorenylmaleamic acids and maleimides.[3] The end- products described below are *N*-aralkylmaleimides. Various substituents on the rings might be expected, among other effects,

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(3) T. L. Fletcher and H. L. Pan, "Derivatives of Fluorene. XIV," submitted for publication.