[Contribution from the Chemistry Research Laboratory, Department of Surgery, University of Washington]

DERIVATIVES OF FLUORENE. I. N-SUBSTITUTED 2-AMINOFLUORENE AND 2-AMINOFLUORENONE[1]

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Interest in 2-aminofluorene and some of its derivatives in cancer research, hope of finding biologically interesting new substances, and curiosity about certain new or little explored series of fluorene compounds, led us first to attempt a better preparation of some simple derivatives which, even when available commercially, are sometimes in a state of purity which is belied by their cost. We can report a significant increase in yield with improvements in efficiency and convenience for several known compounds as indicated in the experimental section.

The derivatives discussed below are either new or were prepared by a better or more convenient method than so far reported.

Since triethylphosphate[2] is an outstanding dialkylating (1) and good monoalkylating agent for certain primary aromatic amines, we tried its action on 2-aminofluorene. A ratio of 3 moles of amine to 2 of the phosphate gave a high yield of 2-N,N-diethylaminofluorene. Extraction of the reaction mixture and use of acetic anhydride were not required. A final fraction, representing a 2% yield, was found to be 2-N-ethylaminofluorene (2). Dialkyl alkylphosphonates apparently have not been used as alkylating agents for aromatic amines. Diethyl ethylphosphonate[3] was reacted with 2-aminofluorene (one mole of amine to two of the phosphonate), with a quantitative crude yield, giving 98% of pure product. No trace of monoalkylated compound was detected.

The yield of 2-N,N-dimethylaminofluorene has been reported from 22% (crude yield with dimethyl sulfate alone) (3) to about 92% by way of the trimethylammonium iodide compound (4). The highest yield obtained with use of dimethyl sulfate was 50–60% (5). Our results with triethyl phosphate suggested use of trimethyl phosphate in a similar reaction. Convenience and yield recommend this as the best preparative method.

N-2-Fluorenyl-*p*-toluenesulfonamide (6, 7) was methylated with dimethyl sulfate. Attempts to hydrolyze the tosyl group with concentrated sulfuric acid, successful with some other derivatives of aminofluorene (6) resulted in a product, apparently 2-N-methylaminofluorene-*x*-sulfonic acid, isolated as the methyl ester.

2-N-Methylaminofluorenone was made from 2-aminofluorenone in a 94% over-all yield, by way of the N-*p*-tosyl and N-methyl-N-*p*-tosyl derivatives.

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[2] Kindly supplied by the Tennessee Eastman Corporation, Kingsport, Tennessee.

[3] Kindly supplied by the Virginia-Carolina Chemical Corporation.

The latter was hydrolyzed smoothly in cold concentrated H_2SO_4 (6), and the resultant N-methyl amine was quantitatively acetylated in pyridine.

2-N,N-Dimethylaminofluorenone was reported by Gerhardt (8) to melt at 146–147° with a yield of 40%. His method did indeed give us a product melting in this range but it was demonstrably a mixture. Fusion of 2-aminofluorenone with an excess of methyl-*p*-toluenesulfonate gave the pure compound, reported as an unexpected by-product in an attempted condensation (9).

Alkylation of 2-aminofluorenone with triethyl phosphate gave 25% yields of 2-N-ethylaminofluorenone (1). In the presence of lithium bromide, however, yields of 50–60% were obtained.

Further new substances are described below.

EXPERIMENTAL

Melting points are corrected and up to 300° were taken on a Fischer-Johns block; over 300° they were taken in a capillary in an aluminum block. A few of the microanalyses were done by W. Manser, Zürich, Switzerland, and some of the others by the Schwarzkopf Microanalytical Laboratory, Woodside 77, New York. Mr. Moses Namkung gave us valuable assistance in preparation and purification of starting compounds.

The 2-aminofluorene used in the following work was in general obtained as reported in the literature (10), but we had no success using acetic acid in the reduction step. We were, however, able to lower the requirement of zinc to 40 g. and to raise the yield of pure 2-aminofluorene to 95–97% by avoiding acetic acid in the final recrystallization of the nitro compound, using toluene instead.

2-N,N-Diethylaminofluorene. A. Redistilled triethyl phosphate (12.1 g., 0.067 mole) was added to 18.1 g. (0.1 mole) of 2-aminofluorene and heated under reflux in a wax bath kept at 205° ± 2° for two hours. A solution of 10 g. of sodium hydroxide in 60 ml. of water was added and refluxing was continued for one hour. The reaction mixture was poured out and when the upper layer solidified it was removed, rinsed with water, and the dry cake was ground and digested in warm water. Upon filtering, washing, and drying 23.4 g. (98.6%) of crude yield was obtained; m.p. 81–83° with slight softening ∽ 75°. The purified yield was 92–95%; shining white leaflets from ethanol; m.p. 84.5–85°.

Anal. Calc'd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90.
Found: C, 85.89; H, 7.90; N, 6.06.

A final crop (about 2% crude yield) was recrystallized twice from ethanol; m.p. 78–80°; mixture m.p. with the diethyl compound, 70–74°; mixture m.p. with known 2-N-ethylaminofluorene (m.p. 89–89.5°, prepared from the N-tosyl, N-ethyl compound and hydrolysis), 85–88°. Vanags and Vanags (2) reported the m.p. as 79°. Their material appears to have been a mixture. The same crude yield, but 95–97% pure dialkylated amine was recovered when twice the above amount of triethyl phosphate was used.

B. A mixture of 3.6 g. (0.02 mole) of 2-aminofluorene and 6.6 g. (6.5 ml., 0.04 mole) of diethyl ethylphosphonate was heated one hour in a wax bath kept at 220° ± 3°. The mixture darkened considerably. A solution of 6 g. of sodium hydroxide in 50 ml. of water was added and the mixture was refluxed for one hour and poured out. When cool, the cake was rinsed, ground, and dried, and weighed 4.75 g. (100%). Upon crystallization from ethanol (Darco) a glistening first crop, weighing 4.5 g., was obtained; m.p. 84–84.5°. A second crop weighed 0.2 g.; m.p. 80–82° (softening at 78°), mixture m.p. with known 2-N,N-diethylaminofluorene, 81–84° (softening at 80°). A low-melting third crop, recrystallized, gave a mixture m.p. with the diethyl compound of 80–84°, and with known monoethyl compound of 70–76°.

2-N,N-Dimethylaminofluorene. A. A mixture of 2-aminofluorene (9.1 g.; 0.05 mole) and 9.4 g. (0.067 mole) of trimethyl phosphate was heated in a wax bath at 160° until the initial vigor of the reaction subsided. The temperature then was raised to 195° ± 2° and the reaction was continued for one hour. The mixture was refluxed with aqueous alkali and the solids were separated. The crude yield was 9.2 g.; m.p. 170–182°. After Darco treatment and two crystallizations from methanol the pure yield was 65%; m.p. 180–180.5° [lit. (5) m.p. 180°, after repeated recrystallization].

2-N-Methylaminofluorene-x-sulfonic acid (methyl ester). In an attempt to prepare 2-N-methylaminofluorene, N-methyl-N-2-fluorenyl-*p*-toluenesulfonamide (3.5 g., m.p. 135.5–136.5°, from N-2-fluorenyl-*p*-toluenesulfonamide and dimethyl sulfate (11)) was stirred into 12 ml. of cold concentrated sulfuric acid and allowed to stand with occasional stirring for six hours, warmed to 40° for five minutes, and stirred into 300 ml. of water. After standing overnight this was filtered and the precipitate was dried (2.5 g.). Two recrystallizations (Darco) from 50% methanol gave 1 g. of product as white needles which soon became slightly discolored. The substance left no ash, did not melt, and was not acid to wet litmus.

Anal. Calc'd for $C_{15}H_{15}NO_3S$: C, 62.28; H, 5.23; N, 4.84; S, 11.08.
Found: C, 62.58; H, 5.45; N, 4.67; S, 10.99.

N-Methyl-N-2-fluorenylacetamide. 2-N-Methylaminofluorene was prepared in 100% yield (0.05 mole) from a boiling glacial acetic acid solution of the N-methyl-N-*p*-tosyl derivative by the gradual addition of 200 ml. of concentrated hydrochloric acid, precipitation with alkali, crystallization from 18% hydrochloric acid and treatment with ammonium hydroxide [*cf.* (11)].

To 5.8 g. (0.03 mole) of 2-N-methylaminofluorene in 30 ml. of pyridine 4.2 ml. of acetic anhydride was gradually added with swirling. This was heated on the steam-bath for 45 minutes, cooled, poured into 200 ml. of 15% hydrochloric acid, filtered, and the product washed with water, and crystallized from aqueous ethanol (Darco) to give white granular crystals; m.p. 125.5–128.5°. Recrystallization from ether gave 5.8 g. (82%); m.p. 128.5–130°.

Anal. Calc'd for $C_{16}H_{15}NO$: N, 5.90. Found: N, 6.09.

N-(2-Fluorenyl)phthalamic acid. Phthalic anhydride (14.8 g., 0.10 mole) was added in portions to a solution of 9.1 g. (0.05 mole) of 2-aminofluorene in 240 ml. of glacial acetic acid with stirring. After standing for 0.5 hour, 200 ml. of water was added and the mixture was boiled a few minutes and filtered hot. The product was digested in 200 ml. of boiling water, filtered, washed, and dried to give 15 g. (91%) of a white compound, soluble in cold dilute sodium hydroxide; m.p. 239–240° (dec.). Neutralization equivalent. Calc'd: 329. Found: 323.

Anal. Calc'd for $C_{21}H_{15}NO_3$: N, 4.25. Found: N, 4.23.

For further characterization, recrystallization from glacial acetic acid yielded 96% of the imide; m.p. 293–294° (slight dec., sinters 288°). The reported m.p. is 288° (12).

Anal. Calc'd for $C_{21}H_{13}NO_2$: N, 4.50. Found: N, 4.57.

N-(2-Fluorenyl)succinamic acid. This was prepared in the same way as the 9-oxo analog below. The literature reports m.p. 225° (13) but our substance melts at 242–242.5°. Neutralization equivalent. Calc'd: 281. Found: 280.

Anal. Calc'd for $C_{17}H_{15}NO_3$: N, 4.98. Found: N, 5.04.

2-Aminofluorenone, used in the following preparations, was made according to Diels' method (14), but use of toluene-recrystallized (*acetic acid free!*) 2-nitrofluorenone and commercial ammonium sulfide raised the yield from 65% to 93% (0.1 mole).

N-(9-Oxo-2-fluorenyl)phthalamic acid. This substance was prepared in the same manner as the 2-fluorenyl analog, and was purified by dissolving the water-digested, filtered, and dried product in dilute sodium hydroxide, filtering and acidifying the filtrate with dilute hydrochloric acid. The powdery, light yellow precipitate (94%) melted at 305–310° (dec., uncor.). Neutralization equivalent. Calc'd: 343. Found: 337.

Anal. Calc'd for $C_{21}H_{13}NO_4$: N, 4.08. Found: N, 4.01.

N-(9-Oxo-2-fluorenyl)phthalimide. One crystallization of the foregoing substance from glacial acetic acid gave lemon-yellow needles; m.p. 326–327° (100%).

Anal. Calc'd for $C_{21}H_{11}NO_3$: N, 4.31. Found: N, 4.30.

N-(9-Oxo-2-fluorenyl)succinamic acid. A solution of 0.025 mole of succinic anhydride (kindly supplied by National Aniline Division, Allied Chemical and Dye Corporation) in 150 ml. of chloroform, at 50–55°, was poured rapidly into a solution of 0.025 mole of 2-

aminofluorenone in 50 ml. of chloroform at the same temperature. Orange crystals began to come out almost at once and the mixture was allowed to cool. After filtration the product was washed copiously with ethanol and dried; m.p. 260–261° (dec.). The yield was 99% of the theoretical. Recrystallization from glacial acetic acid did not result in imide formation. Neutralization equivalent. Calc'd: 295. Found: 297.

Anal. Calc'd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74.
Found: C, 69.26; H, 4.52; N, 4.79.

N-(9-Oxo-2-fluorenyl)trifluoroacetamide. A. A sealed tube reaction with 0.05 mole of 2-aminofluorenone and trifluoroacetic acid[4] (15) (7.5 g., 0.67 mole) at 120–125° for 1.5 hours and at 150° for 5 hours yielded 12.1 g. (83%) of pure product.

B. Simple modifications of the method of Sawicki and Ray (16) gave a high yield of this substance. 2-Aminofluorenone (9.75 g., 0.05 mole) was dissolved in boiling benzene, and the solution removed from the heat. While hot, 15.7 g. (0.075 mole) of trifluoroacetic anhydride[4] was added dropwise with vigorous agitation, and stirring was continued for five minutes. When cooled to room temperature, the mixture was filtered and the precipitate was washed with 50 ml. of benzene. Evaporation yielded a second crop. The combined crops were recrystallized from ethanol to give 13.5 g. (93%) of long, bright yellow needles; m.p. 245.5–246°. A slightly lower yield was obtained when the same reaction was carried out in pyridine (steam-bath, one hour).

Anal. Calc'd for $C_{15}H_8F_3NO_2$: N, 4.81. Found: N, 4.90.

N-(9-Oxo-2-fluorenyl)-p-toluenesulfonamide. This was prepared with a 1.5 hour reflux in pyridine in the same manner as the N-2-fluorenyl analog (6), (a five minute reflux in pyridine gave a 96% yield of the latter). The water-washed product was crystallized from a 5:1 ethanol-chlorobenzene mixture yielding 97% of the calculated amount of product (0.2 mole level); m.p. 192–194°. Three recrystallizations from acetone raised the m.p. to 193.5–194.5° for analysis.

Anal. Calc'd for $C_{20}H_{15}NO_3S$: C, 68.75; H, 4.33; N, 4.01; S, 9.18.
Found: C, 68.60; H,4.23; N, 3.88; S, 9.16.

N-Methyl-N-(9-oxo-2-fluorenyl)-p-toluenesulfonamide. The above crude sulfonamide (26.1 g., 0.075 mole) was dissolved in 135 ml. of 5% sodium hydroxide, and 20 ml. of dimethyl sulfate was added over a period of 5 minutes with agitation. The mixture then was heated on the steam-bath for 15 minutes, 3 g. of sodium hydroxide in 30 ml. of ethanol was added, and then this mixture was boiled a few minutes and filtered hot. For analysis, the dried precipitate (26.7 g., 98%) was crystallized from 1:3 toluene-ethanol mixture yielding a bright yellow product; m.p. 175.5–176.5°.

Anal. Calc'd for $C_{21}H_{17}NO_3S$: C, 69.40; H, 4.72; N, 3.86; S, 8.83.
Found: C, 69.48; H, 4.78; N, 3.78; S, 8.84.

2-N-Methylaminofluorenone. The foregoing crude product (18.2 g., 0.05 mole) was dissolved in 195 ml. of concentrated sulfuric acid and the mixture was allowed to stand at room temperature for 15 minutes. Water (1150 ml.) then was added, the mixture was brought to a boil, filtered hot, the filtrate made alkaline, and the precipitated N-methyl amine was separated by filtration and washed. Crystallization from carbon tetrachloride gave 10.3 g. (98%) of dark red needles; m.p. 159.5–160.5°.

Anal. Calc'd for $C_{14}H_{11}NO$: N, 6.70. Found: N, 6.73.

N-Methyl-N-(9-oxo-2-fluorenyl)acetamide. To the above product (3.1 g., 0.015 mole) in 30 ml. of pyridine was added 3 ml. of acetic anhydride and the mixture was heated on the steam-bath for 0.5 hour and poured into 150 ml. of 30% hydrochloric acid. The yellow precipitate, upon filtration, washing, and drying, weighed 3.7 g. (100%); m.p. 155.5–159.5°. Crystallization from a 1:4 ethanol-water solution gave an analytical sample; m.p. 157.5–159°.

Anal. Calc'd for $C_{16}H_{13}NO_2$: N, 5.58. Found: N, 5.56.

2-N,N-Dimethylaminofluorenone. A mixture of 9.8 g. (0.05 mole) of 2-aminofluorenone

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[4] Kindly supplied by the Minnesota Mining and Manufacturing Company, St. Paul, Minnesota.

and 27.9 g. (0.15 mole) of methyl-*p*-toluenesulfonate was fused at 165° ± 2° for one hour. The melt was cooled, partially digested in 20 ml. of methanol, and to it was added a solution of 4 g. of sodium in 70 ml. of methanol. The mixture then was heated on the steam-bath for five minutes and cooled, filtered, and the precipitate was washed with dilute alkali. Evaporation of the filtrate yielded a second crop. The combined precipitates were crystallized from carbon tetrachloride yielding 5.9 g. (53%) of glistening, deep purple plates; m.p. 166–166.5° (8, 9).

Anal. Calc'd for $C_{15}H_{13}NO$: N, 6.27. Found: N, 6.15.

2-N-Ethylaminofluorenone. A. A mixture of 9.8 g. (0.05 mole) of 2-aminofluorenone and 12.2 g. (0.067 mole) of triethyl phosphate (redistilled) was heated to 190° ± 2° for one hour, and refluxed in aqueous alkali as above. The aqueous layer was poured off and the remaining mass was washed, dried, taken up in carbon tetrachloride, and filtered. This was boiled down and 1.6 g. of product was obtained, which when recrystallized twice from methanol, in thin, shiny copper-red leaflets, melted at 153–154.5°. More was recovered from the mother liquor, the total crude yield being 3.2 g. (29%).

B. The above reaction, repeated in the presence of 8.8 g. of anhydrous lithium bromide (kindly supplied by the Lithium Corporation of America, Minneapolis, Minnesota), yielded 6.4 g. (57%) of the crude product.

Anal. Calc'd for $C_{15}H_{13}NO$: C, 80.68; H, 5.87; N, 6.27; O, 7.18.
Found: C, 80.69; H, 5.93; N, 6.20; O, 7.55 (direct determination).

SUMMARY

Preparation of new derivatives of 2-aminofluorene, including some with N-alkyl, N-acyl, and N-aroyl substitutions is reported. These, or substances derived from them, are of potential biological interest. High yield alkylations, using methods new to the fluorene series, and an observation concerning the effect of lithium bromide in an otherwise poor alkylation is described. Some significant and useful improvements in preparation of certain known fluorene derivatives are indicated.

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