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AN IMPROVED SYNTHESIS OF 1-AMINOFLUORENE

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Recently Bergmann and Orchin (1) described a synthesis of 1-aminofluorene, which is currently of interest because of the carcinogenic activity of the isomeric 2-aminofluorene (2). However, when sizeable amounts of 1-aminofluorene or its derivatives are required for animal feeding experiments, the procedure of Bergmann and Orchin is not very convenient as it involves a sealed tube hydrolysis of 1-fluorenylurethan.

Our own experiments indicated that 1-aminofluorene could not be readily prepared by hydrolysis of 1-fluorenyl isocyanate. The Lossen rearrangement, involving reaction of 1-fluorenecarboxylic acid and hydroxylamine in polyphosphoric acid (3), also gave a poor yield of the desired amine. Since the isocyanate is one of the intermediates or products in the Lossen rearrangement (4, 5), the low conversion to the amine may, in this case, be ascribed to the difficulty of hydrolyzing the isocyanate.

However, treatment of 1-fluorenecarbonyl azide with excess acetic anhydride gave a good yield of 1-diacetylaminofluorene which was easily hydrolyzed to 1-aminofluorene. This variation (6, 7) of the Curtius reaction seems to be useful in those cases where the normal procedure leads to poor yields of the desired amine because of difficulty in hydrolyzing the intermediates.

1-Hydroxyfluorene and several derivatives were prepared from 1-aminofluorene. The ultraviolet absorption spectrum of 1-hydroxyfluorene has been described by Friedel and Orchin (8) but no synthesis of this compound has been published. The procedure used for preparation of 2-hydroxyfluorene from 2-aminofluorene (9), gave a very poor yield of 1-hydroxyfluorene and much tarry material, owing to self-coupling of the diazonium compound with formation of a dark red material. This was prevented, with a subsequent improvement in the yield of 1-hydroxyfluorene, by diazotizing 1-aminofluorene in a higher concentration of acid.

The spectra of 1-amino-, 1-acetylamino-, and 1-diacetylamino-fluorene are reproduced in Figure 1. The curves of the first two compounds are remarkable because they do not exhibit the generally pronounced minimum of 2-substituted fluorene derivatives around 230 mμ. They also do not have the customary maximum around 260–270 mμ, but instead present a rather long plateau, with one maximum at 250 and a slightly lower one at 265 mμ. The diacetylamino derivative on the other hand gives a curve quite similar to that of fluorene itself (10).

Both 1-acetylamino- and 1-diacetylamino-fluorene are being tested for carcinogenic activity in this laboratory.

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EXPERIMENTAL

1-Fluorenecarbonyl chloride. 1-Fluorenecarboxylic acid, prepared according to Bergmann and Orchin (1), was treated with thionyl chloride, giving a 95% yield of 1-fluorenecarbonyl chloride, m.p. 110–113°. A sample crystallized from petroleum ether melted at 112–113°.

Anal. Calc'd for $C_{14}H_9ClO$: C, 73.50; H, 3.97; Cl, 15.50.
Found: C, 73.82; H, 4.43; Cl, 15.00.

1-Fluorenecarbonyl azide. A solution of 53 g. of 1-fluorenecarbonyl chloride in 1 l. of dry acetone was cooled with stirring in an ice bath. A solution of 17 g. of sodium azide in 50 ml. of water was added and stirring was continued for 1½ hours. The mixture was diluted with water to a volume of approximately 2 l. The precipitated cream-colored azide was filtered off, washed with water, and dried *in vacuo* at room temperature. It weighed 52 g. and began decomposing at 85° (1).

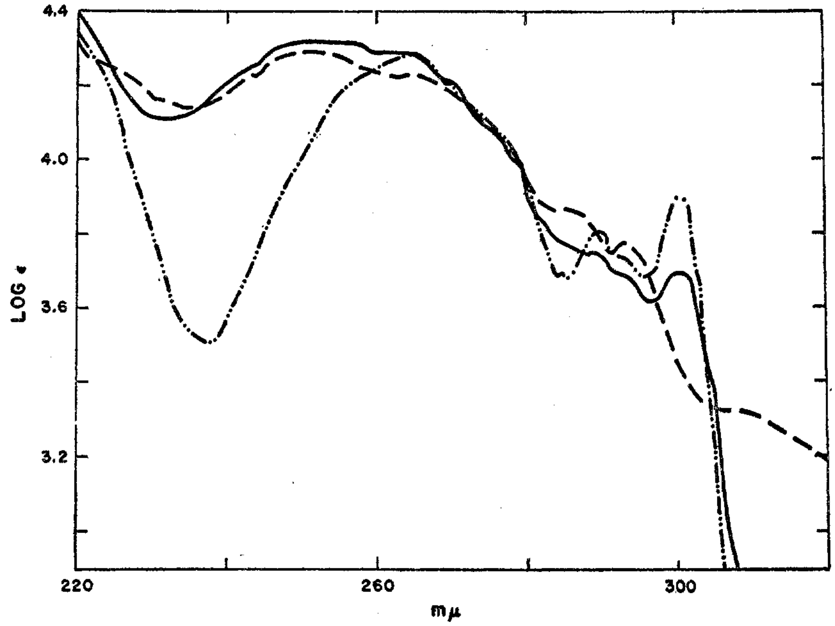

FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRA IN 95% ETHANOL (Beckman DU Spectrophotometer): ——— 1-Acetylaminofluorene; – – 1-Aminofluorene; – •• – 1-Diacetylaminofluorene.

1-Diacetylaminofluorene. The azide (51 g.) was dissolved in 600 ml. of acetic anhydride, warmed gently until the evolution of gas had slowed down, and then refluxed for four hours. The solution was poured into 2 l. of ice-water; upon decomposition of the excess anhydride a cream-colored precipitate (weight 56 g., m.p. 132–134°) formed. Recrystallization of 10 g. from 35 ml. of benzene yielded 7.4 g. of product, m.p. 135–136°. Further recrystallization of a sample from benzene-petroleum ether gave shiny white crystals melting at 137–138°.

Anal. Calc'd for $C_{17}H_{15}NO_2$: C, 77.00; H, 5.70.
Found: C, 76.97; H, 5.80.

1-Aminofluorene. A. A solution of 10 g. of 1-diacetylaminofluorene in 100 ml. of ethanol and 100 ml. of concentrated hydrochloric acid was refluxed for one hour. The mixture was poured into 500 ml. of water and made alkaline with ammonium hydroxide. After stirring for one hour the precipitate was filtered off. It weighed 6.8 g., m.p. 120–121° with a little sintering at 116°. Recrystallization from 30 ml. of ethanol and 10 ml. of water gave 6 g. of product, m.p. 122–123°. Further recrystallization of a sample from water (1 mg./2 ml.) or from petroleum ether yielded white crystals, m.p. 124–125°. The melting point was not depressed on mixing with samples prepared by hydrolysis of 1-fluorenylurethan (1) or by hydrolysis of 1-fluorenyl isocyanate (see below).

B. A mixture of 731 mg. of 1-fluorenecarboxylic acid, 1.7 g. of hydroxylamine hydrochloride, and 25 g. of polyphosphoric acid was heated slowly with manual stirring. At 70–100° gas was evolved. At 130° a slight yellow coloration appeared at the bottom of the white suspension and as the temperature continued rising a dark yellow-brown solution formed. After 10–15 minutes a temperature of 165° was reached, whereupon the mixture was cooled and 100 ml. of water was added.

A brown precipitate was filtered off and extracted with hot sodium bicarbonate solution. After treatment with Norit and acidification 28 mg. of the starting acid was recovered.

The orange-colored filtrate was made basic by the slow addition of concentrated ammonium hydroxide with external ice cooling. A brown precipitate weighing 370 mg. was obtained. After air-drying the solid was extracted with 150 ml. of boiling benzene. The benzene solution was percolated through an alumina column (1 × 8 cm.). After washing the column with 50 ml. of benzene and taking the yellow eluate to dryness 160 mg. of a yellow solid, m.p. 80–90°, was obtained. Crystallization from 350 ml. of water gave 154 mg. of white 1-aminofluorene, m.p. 116–120°, mixture m.p. with an authentic sample, 116–121°.

Acetylation and recrystallization from benzene-petroleum ether gave the 1-acetylaminofluorene, m.p. 188–189°, mixture m.p. with an authentic sample, 188–191°.

1-Acetylaminofluorene. A solution of 1.1 g. of 1-aminofluorene in 25 ml. of benzene and 2 ml. of acetic anhydride was refluxed for 15 minutes. Upon cooling 1 g. of white, needle-shaped crystals, m.p. 189–190°, separated, which after recrystallization from ethanol or benzene melted at 190–191°.

Anal. Calc'd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87.
Found: C, 80.44; H, 5.70.

1-Fluorenyl isocyanate. A solution of 2.1 g. of 1-fluorenecarbonyl azide in 75 ml. of benzene was refluxed for four hours. The benzene was evaporated, leaving 1.5 g. of a waxy white solid, m.p. 74–76°. Recrystallization from benzene-petroleum ether gave creamy-white needles of 1-fluorenyl isocyanate, m.p. 77°.

Anal. Calc'd for $C_{14}H_9NO$: C, 81.14; H, 4.35; N, 6.76.
Found: C, 80.65; H, 4.64; N, 6.71.

Hydrolysis of the isocyanate. A mixture of 0.8 g. of the isocyanate, 15 g. of potassium hydroxide, 30 ml. of water, and 20 ml. of ethanol, when refluxed for 8 hours yielded some white, insoluble material which precipitated gradually during refluxing and 0.42 g. of benzene-extractable material which sintered at 100–105°, melted at 109–112°. Recrystallization from benzene-petroleum ether yielded 0.15 g. of 1-aminofluorene, m.p. 122–124°. Further crystallizations from ethanol-water yielded the amine melting at 124–125°.

The benzene-insoluble material which melted over 230° was not hydrolyzed to an appreciable extent by refluxing in acetic acid which was 5 *N* in hydrochloric acid for 16 hours.

1-Hydroxyfluorene. 1-Aminofluorene (5 g.) was dissolved in a mixture of 100 ml. of concentrated sulfuric acid, 200 ml. of water, and 100 ml. of glacial acetic acid. The mixture was heated almost to boiling and filtered through a sintered glass funnel if necessary. Upon cooling the filtrate to 15°, a shiny silky precipitate formed.

A solution of 2.3 g. of sodium nitrite in 50 ml. of water was dropped in with stirring yielding a yellow-orange solution which was kept in an ice-bath for one-half hour. Urea (5 g.) was added and the mixture, after keeping cold for one-half hour more, was added to 250 ml. of boiling water containing 25 ml. of concentrated sulfuric acid over a period of 20 minutes. The mixture was refluxed for one hour, cooled, and the precipitate filtered off. The filtrate was partially neutralized with sodium bicarbonate and extracted with ether. The residue from the evaporation of the ether was combined with the main product. This was dissolved in 200 ml. of 7.5% potassium hydroxide solution, boiled with Norit, filtered and neutralized with hydrochloric acid, yielding a pink precipitate, m.p. 118–120°, weighing 2.8–3.5 g. (on various runs). The compound was best crystallized from water; when 0.50 g. was crystallized twice from 300 ml. of water, 0.41 g. of almost white fluffy needles, m.p. 119.0–120.5° was obtained.

Anal. Calc'd for $C_{13}H_{10}O$: C, 85.69; H, 5.46.
Found: C, 85.58; H, 5.66.

1-Methoxyfluorene, prepared in the usual manner with dimethyl sulfate, melted at 77°. It was extremely soluble in organic solvents. When crystallized from a mixture of 25 ml. of ethanol and 50 ml. of water, 60 mg. afforded 31 mg. of long white needles, m.p. 85–86°.

Anal. Calc'd for $C_{14}H_{12}O$: C, 85.68; H, 6.17.
Found: C, 85.60; H, 6.13.

1-Acetoxyfluorene, prepared from 1-hydroxyfluorene and acetic anhydride, melted at 90–92°. Crystallization from petroleum ether yielded shiny short white needles, m.p. 90–91.5°.

Anal. Calc'd for $C_{15}H_{12}O_2$: C, 80.33; H, 5.40.
Found: C, 80.25; H, 5.42.

SUMMARY

A modified Curtius reaction — 1-fluorenecarboxylic acid → 1-fluorenecarbonyl azide → 1-diacetylaminofluorene → 1-aminofluorene — gives good yields of the last compound. The procedure given is valuable in such cases where the intermediate isocyanates or urethans are hydrolyzed to the amine with difficulty. The direct Lossen rearrangement 1-fluorenecarboxylic acid → 1-aminofluorene is not as satisfactory. A number of compounds derived from 1-aminofluorene, including 1-hydroxyfluorene, are reported.

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