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The Oxidation of Fluorene Derivatives by Potassium Persulfate[1]

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The possibility of hydroxylating fluorene, 2-acetylaminofluorene, and 2-nitrofluorene with potassium persulfate was investigated under conditions which yield the *ortho*-hydroxy derivatives of 1- and 2-naphthylamine and of dimethylaniline with this reagent. Fluorene and 2-acetylaminofluorene were not oxidized by potassium persulfate. 2-Nitrofluorene yielded 2-nitrofluorenone and 2,2′-dinitro-9,9′-bifluorylidene. Evidence is presented to indicate that 2,2′-dinitro-9,9′-bifluorylidene arises by a base-catalyzed condensation of 2-nitrofluorene and 2-nitrofluorenone.

One of the common reactions of the *in vivo* metabolism of aromatic amines is nuclear oxidation with formation of hydroxylated derivatives. In the case of carcinogenic amines such as the naphthylamines and benzidine these oxidations may be highly significant, since, in some cases, the hydroxylated derivatives proved to be very carcinogenic[2,3] and are regarded by some as responsible for initiation of neoplastic growth.[4] Efforts to throw light on the mechanism of biological nuclear oxidations have recently led to attempts to accomplish hydroxylation of aromatic compounds by model experiments. Brodie, *et al.* reported that aromatic compounds may be oxidized with ascorbic acid.[5] Boyland and co-workers have used alkaline persulfate to produce *ortho*-aminophenols of the benzene and naphthalene series at room temperature.[6] In these experiments, sulfuric acid esters were formed as intermediates presumably through attack by the persulfate ion-radical,[7] the free phenolamine being obtained by acid hydrolysis.

An investigation of the action of potassium persulfate on fluorene derivatives under the conditions used by Boyland, *et al.*[6] was undertaken to determine whether this reagent might be available for hydroxylation of the fluorene nucleus. If the fluorene nucleus were attacked in similar manner to naphthalene,[6] the 1- and 3-hydroxy derivatives of the carcinogen 2-acetylaminofluorene might be obtained conveniently. These compounds as well as 7-hydroxy-2-acetylaminofluorene have been reported as metabolites of 2-acetylaminofluorene in rat urine.[8,9] In the present investigation, persulfate oxidations were attempted on 2-nitrofluorene, 2-acetylaminofluorene, and fluorene. The latter two compounds were resistant to oxidation, while the former was attacked at the methylene carbon atom to yield 2-nitrofluorenone and 2,2′-dinitro-9,9′-bifluorylidene. This indicates that potassium persulfate attacks the fluorene nucleus at the same position which is sensitive to oxidation by the customary oxidizing agents.[10,11] Since of the three fluorene derivatives investigated only 2-nitrofluorene which has a strongly electron-attracting substituent on the nucleus was attacked, it appears that successful oxidation of fluorene compounds by persulfate depends upon the formation of an anion. In all cases investigated, oxidation was observed only when the solution of the starting material had an intense dark-red or purple color. It was further noted that 2-nitrofluorene dissolved in several neutral solvents such as dioxane, dimethylformamide or nitrobenzene without change of the color of the solution. On addition of solid potassium hydroxide the solution became highly colored. This supports the view that 2-nitrofluorene in alkaline medium forms a colored anion which is susceptible to attack by persulfate. Colored solutions have been reported by Sawicki[12] when 2-nitrofluorene is dissolved in alkaline acetone. This investigator has proposed that interaction between the solute and the solvent accounts for the color. It would appear doubtful that the color observed in the present experiments was due to such an interaction since colors of high intensity could readily be produced in relatively inert solvents, such as dioxane. Moreover, none of the isolated oxidation products contained solvent residues.

The reactions which take place when 2-nitrofluorene is treated with potassium persulfate are represented by the equations which follow.

Oxidation of 2-nitrofluorene, presumably by the persulfate ion-radical formulated by Baker and Brown,[7] resulted in the formation of 2-nitrofluorenone which is considered to be the primary oxida-

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[2] Bonser, Clayson, Jull, and Pyrah, *Brit. J. Cancer*, **6**, 412 (1952).

[3] Baker, *Cancer Research*, **13**, 137 (1953).

[4] Clayson, *Brit. J. Cancer*, **7**, 460 (1953).

[5] Brodie, Axelrod, Shore, and Udenfriend, *J. Biol. Chem.*, **208**, 741 (1954).

[6] Boyland, Manson, and Simms, *J. Chem. Soc.*, 3623 (1953).

[7] Baker and Brown, *J. Chem. Soc.*, 2303 (1948).

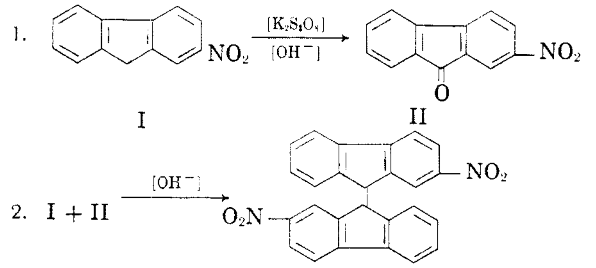
[8] Weisburger and Weisburger, *J. Org. Chem.*, **19**, 964 (1954).

[9] Bielschowsky, *Biochem. J.*, **39**, 287 (1945).

[10] Courtot, *Ann. chim.*, **14**, 5 (1930).

[11] Huntress, Hershberg, and Cliff, *J. Am. Chem. Soc.*, **53**, 2720 (1931).

[12] Sawicki, *Anal. Chem.*, **24**, 1204 (1952)



tion product. A small quantity of the ketone then condensed with 2-nitrofluorene to yield 2,2′-dinitro-9,9′-bifluorylidene. Some of the isolated 2-nitrofluorenone very probably arose from the 2,2′-dinitro-9,9′-bifluorylidene since treatment of the latter compound with alkaline pyridine and potassium persulfate yielded a small amount of the ketone. This reaction may be a reversal of the above mentioned aldol condensation the equilibrium being displaced by oxidation of the 2-nitrofluorene. An analogous situation may obtain in the conversion of dibiphenylene ethylene to fluorenone.[13,14] The possibility of direct oxidation of the ethylenic bond should be considered as an alternative explanation.

The synthesis of 2,2′-dinitro-9,9′-bifluorylidene requires 9-bromo-2-nitrofluorene as starting material.[15] During the preparation of this compound from 2-nitrofluorene by the method of Korczynaki, *et al.*[16] it was observed that only about 45 per cent of 2-nitrofluorene was brominated. The modification of the original procedure which is described here raised the yield of pure 9-bromo-2-nitrofluorene by approximately 20 per cent.

EXPERIMENTAL

Oxidation of 2-nitrofluorene in pyridine. 2-Nitrofluorene, m.p. 157–158°,[17] (3 g., 0.0142 mole) was dissolved in a mixture of 300 ml. of pyridine and 25 ml. of distilled water. Aqueous potassium hydroxide (22 ml., 2.4*N*) was added which caused the appearance of an intense purple color. A solution of 3.9 g. (0.0144 mole) of potassium persulfate in 150 ml. of distilled water was added dropwise over a period of 7 hours to the stirred pyridine solution. Upon addition of a small amount of the persulfate solution a precipitate was noted in the reaction mixture; this precipitate increased progressively during the addition. After the addition of persulfate was complete, the mixture was allowed to stand at room temperature for 10 hours. The precipitate was collected, washed with hot water, and dried at 105°. There was obtained 1.9 g. of a tan product which did not melt below 300°,[18] (Fraction I).

The filtrate from the oxidation mixture was concentrated under reduced pressure to one-half of its original volume. The precipitate was filtered, washed with hot water, and dried at 105° to give 0.69 g. of a yellow, crystalline material, m.p. 222–224°, 22% yield (Fraction II). Fraction II was recrystallized from glacial acetic acid (Norit A added) yielding 0.37 g. of yellow crystals, m.p. 223°. A second crop (28 mg.) was obtained from the mother liquor after standing at 4° overnight. The infrared spectrum of the recrystallized material was identical with that of an authentic sample of 2-nitrofluorenone.[19] A sample of the recrystallized material was further purified by sublimation at 145–150° (<1 micron). The purified product, m.p. 225–226°, did not depress the melting point of authentic 2-nitrofluorenone, m.p. 223–224°. Complete evaporation under reduced pressure of the concentrated mother liquor from which Fraction II had been separated gave a tar from which no crystalline material could be isolated. To purify Fraction I, the isolated product was heated under reflux with 50 ml. of benzene for $^1/_2$ hour and the boiling mixture was filtered. The residue was treated again in the same manner. There was obtained 1.2 g. of brown material which decomposed above 320°. One gram of this material was boiled for $^1/_2$ hour in 55 ml. of N,N-dimethylformamide. After cooling, the mixture was filtered and the precipitate washed with boiling ethanol. After drying at 105° there was obtained 0.19 g. of a red compound. Recrystallization of the material from N,N-dimethylformamide yielded red needles which decomposed above 390°.

Anal. Calc'd for $C_{26}H_{14}N_2O_4$: C, 74.7; H, 3.35; N, 6.69. Found: C, 74.4; H, 3.49; N, 6.52.

The infrared spectrum was identical with that of a sample of 2,2′-dinitro-9,9′-bifluorylidene prepared by dehydrohalogenation of 9-bromo-2-nitrofluorene.[15]

Anal. Calc'd for $C_{26}H_{14}N_2O_4$: C, 74.7; H, 3.35; N, 6.69. Found: C, 74.7; H, 3.45; N, 6.52.

The absorption spectrum of the isolated product in the visible region was identical with that of the authentic sample of 2,2′-dinitro-9,9′-bifluorylidene which has an absorption maximum at 470 mμ and an absorption minimum at 392 mμ (Fig. 1).

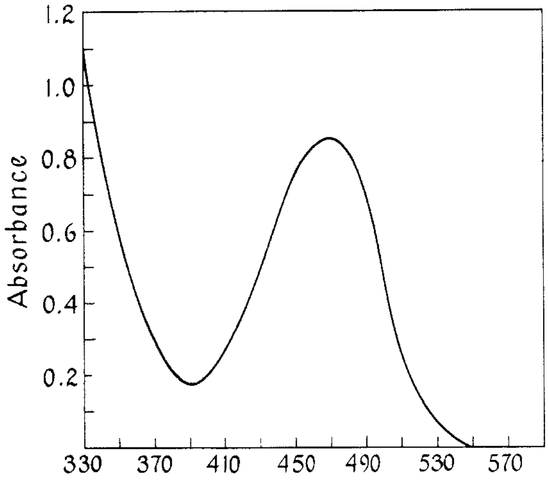


FIG. 1. ABSORPTION SPECTRUM OF 0.028 *M* 2,2′-DINITRO-9,9′-BIFLUORYLIDENE IN N,N-DIMETHYLFORMAMIDE

The filtrate from which the crude 2,2′-dinitro-9,9′-bifluorylidene had been separated was concentrated under reduced pressure to approximately 5 ml. and diluted with distilled water. The brown material which precipitated was collected and washed with distilled water. After drying at

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(13) Graebe, *Ber.*, **25**, 3146 (1892).

(14) Hantzsch and Glover, *Ber.*, **39**, 4156 (1906).

(15) Weisburger, Weisburger, and Ray, *J. Org. Chem.*, **14**, 488 (1949).

(16) Korczynaki, Karlowska, and Kierczk, *Bull. soc. chim.*, **41**, 65 (1927).

(17) Melting points up to 300° were taken on a Fisher-Johns melting point block and are corrected to reference standards.

(18) Melting points above 300° were determined on the block described by L. F. Fieser, *Experiments in Organic Chemistry*, 2nd edition, D. C. Heath and Company, New York, 1941, p. 329, and are uncorrected.

(19) Diels, *Ber.*, **34**, 1758 (1901).

105° it weighed 0.51 g. and decomposed at 170–180°. A portion of this material (100 mg.) was dissolved in 10 ml. of warm benzene and chromatographed on an alumina column (1 × 19 cm.). Elution of the column with 37 ml. of benzene and evaporation of the yellow eluate gave 13 mg. of 2-nitrofluorenone, m.p. 223–224°. The mixture melting point of this material with an authentic sample of 2-nitrofluorenone m.p. 223–224°, was 223–224°.

Oxidation of 2-nitrofluorene in dioxane. 2-Nitrofluorene, m.p. 158–159°, (3 g., 0.014 mole) was dissolved in 300 ml. of purified dioxane, b.p. 101.5°. To the solution was added 25 ml. of distilled water and 21 ml. of 2.4 N potassium hydroxide. The mixture turned red on the addition of potassium hydroxide and the intensity of the color was increased by warming and agitation. The solution was cooled to room temperature and 3.9 g. (0.014 mole) of potassium persulfate in 130 ml. of distilled water was added dropwise to the stirred mixture during 7 hours. The red precipitate which formed during the addition was removed by filtration (Fraction I). The filtrate was kept at 4° for 12 hours and the material which had precipitated on standing was collected, washed with hot water, and dried in air (Fraction II). It weighed 1.2 g., m.p. 217–220°. Recrystallization from dilute acetic acid (Norit A added) yielded 2-nitrofluorenone, m.p. 222–224°, 39% yield. A mixture melting point with authentic 2-nitrofluorenone, m.p. 223–224°, was not depressed. The mother liquor from which Fraction II had been separated was extracted 4 times with 100 ml. of benzene. After evaporation of the benzene there was obtained 1.1 g. of brown material which decomposed at 179–199° (Fraction III). Sublimation of 85 mg. of the material at 135–170° (0.01 mm.) yielded 23 mg. of 2-nitrofluorenone, m.p. 221–224°, and 21 mg. of a yellow product which melted from 209–218° and was presumably impure 2-nitrofluorenone. Further attempts to purify Fraction III were unsuccessful. Fraction I was washed with hot distilled water and, after drying at 105°, weighed 80 mg. which decomposed above 300°. It was combined with 0.34 g. which had been obtained in two other reactions carried out under similar conditions. The material was suspended in 50 ml. of glacial acetic acid and was heated under reflux for one hour. The boiling suspension was filtered and the precipitate was washed with glacial acetic acid and distilled water. After drying at 105° there was obtained 0.14 g. of a red product which decomposed above 380°. Recrystallization from N,N-dimethylformamide yielded red needles which decomposed above 390°.

Anal. Calc'd for $C_{26}H_{14}N_2O_4$: N, 6.69. Found: N, 6.71.

The absorption spectra of the isolated product in the infrared and visible region were identical with those of authentic 2,2′-dinitro-9,9′-bifluorylidene.[15]

Condensation of 2-nitrofluorene and 2-nitrofluorenone. One gram (0.0047 mole) of 2-nitrofluorene and 1.07 g. (0.0046 mole) of 2-nitrofluorenone were dissolved, with slight warming, in 60 ml. of pyridine. Aqueous potassium hydroxide (7 ml., 2.4 N) was added and the purple solution was allowed to stand at room temperature for 4 days. The reaction mixture was filtered and the red precipitate was washed with water. The material then was extracted for 12 hours in a Soxhlet apparatus with benzene. After drying at 105° it weighed 0.25 g. and decomposed above 380°. Recrystallization of the material from N,N-dimethylformamide yielded red needles which decomposed above 390°.

Anal. Calc'd for $C_{26}H_{14}N_2O_4$: N, 6.69. Found: N, 6.52.

The absorption spectra of the isolated product in the infrared and visible region were identical with those of authentic 2,2′-dinitro-9,9′-bifluorylidene.[15]

Reaction of 2,2′-dinitro-9,9′-bifluorylidene with potassium persulfate. To a stirred suspension of 0.50 g. (0.0012 mole) of 2,2′-dinitro-9,-9′-bifluorylidene in 50 ml. of pyridine and 4 ml. of 2.4 N potassium hydroxide was added dropwise 0.33 g. (0.0012 mole) of potassium persulfate in 25 ml. of distilled water during 4 hours. As addition proceeded, the color of the mixture became green and gradually turned red. After addition was completed, the remaining solid was removed by filtration. The filtrate was diluted with an equal volume of distilled water and acidified with concentrated hydrochloric acid. The precipitate was collected and dried at 105° yielding 0.086 g. of a brown crystalline product. Sublimation of the material at 145–150° (< 1 micron) gave 0.060 g. of yellow crystals, m.p. 218–219°. A mixture melting point did not depress the melting point of authentic 2-nitrofluorenone,[19] m.p. 223–224°, and the infrared spectrum of the material was identical with that of authentic 2-nitrofluorenone.[19] A second sublimation under the same conditions gave a product melting at 221–222°.

Oxidation of fluorene. Alkaline oxidation of 1.0 g. of fluorene (0.006 mole), m.p. 114–116°, in pyridine solution was attempted using one molecular equivalent of potassium persulfate and the standard procedure. Unchanged fluorene, 0.83 g., m.p. 113–115°, was recovered when the reaction mixture was diluted with 4 times its volume of distilled water, filtered, and dried over calcium chloride at atmospheric pressure. No oxidation products of fluorene were found.

Oxidation of 2-acetylaminofluorene. Oxidation of 3.0 g. (0.0135 mole) of 2-acetylaminofluorene, m.p. 196–198°, was attempted in 300 ml. of pyridine under standard conditions. Unchanged starting material (2.4 g., m.p. 196°) was isolated by diluting the reaction mixture with 3 l. of distilled water, filtering, and drying the precipitate at 105°. No oxidation products of 2-acetylaminofluorene were found.

9-Bromo-2-nitrofluorene. 2-Nitrofluorene (11 g., 0.052 mole) was heated under reflux in 300 ml. of glacial acetic acid with 2.9 ml. (0.055 mole) of bromine for 3 hours. The reaction mixture was allowed to stand at room temperature for 10 hours. The precipitate was collected, washed with distilled water, and dried at atmospheric pressure over calcium chloride. There was obtained 4.8 g. of 9-bromo-2-nitrofluorene, m.p. 141–142°. Recrystallization from 95% ethanol gave a product melting at 142–143°. The mother liquor was concentrated under reduced pressure to 150 ml. The precipitate was collected and washed with distilled water. After drying over calcium chloride it weighed 8.3 g., m.p. 110–115°. The material was dissolved, with heating, in 150 ml. of glacial acetic acid and 1.0 ml. of bromine was added. The mixture was heated under reflux for 10 hours. After cooling to room temperature the precipitate was collected, washed with distilled water, and dried at atmospheric pressure over calcium chloride. It weighed 3.5 g., m.p. 140–142°. An additional 1.8 g., m.p. 140–141°, was obtained by diluting the mother liquor with distilled water; 67% yield.

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