ane, and the mixture on dilution with 100 cc. of water was poured into 500 cc. of six *M* sulfuric acid. The product was filtered, washed with water, dried, and on crystallization from a mixture of benzene and heptane there was obtained 2.9 g. (47.5%) of the acid.

***p*-Acetophenyl sulfone, di-(*p*-acetophenyl) sulfone and *p*-(phenylsulfonyl)-phenylacetic acid** were prepared by the oxidation of 10 g. of I, II and *p*-(phenylmercapto)-phenylacetic acid, respectively, in 100 cc. of glacial acetic acid with excess of 30% hydrogen peroxide.

***p*-(Chloroaceto)-diphenyl Sulfide.**—This compound was prepared in the same manner as described for the preparation of I using 186 g. of diphenyl sulfide, 133 g. of aluminum chloride, and 125 g. of chloroacetyl chloride. The crude product was purified by crystallization from a mixture of benzene and petroleum ether to give a 60% yield of product melting 75–76°. The distillation of larger amounts of the product (b. p. (3 mm.) 188–190°) is accompanied by decomposition.

Summary

The Friedel–Crafts acetylation of diphenyl sulfide gives the mono- and diacetylated products. The mono-substitution product is obtained in 70–80% yields and the substitutions occur in the para positions. The *p*-(chloroaceto)-diphenyl sulfide is prepared by the Friedel–Crafts reaction, and the oxidation of the sulfides to the sulfoxides or sulfones is described. The Willgerodt reaction of *p*-(phenylmercapto)-acetophenone gives the expected substituted phenylacetic acid.

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[CONTRIBUTION FROM THE LABORATORY OF RADIOCHEMISTRY, UNIVERSITY OF CINCINNATI]

Derivatives of 2-Amino-7-iodofluorene[1]

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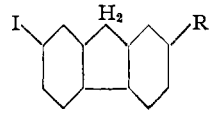
Since the discovery by Wilson, DeEds and Cox[3] of the carcinogenic activity of 2-acetylaminofluorene, there has been a good deal of experimentation with this compound. However, the synthesis and biological testing of derivatives of this carcinogen have been largely pretermitted.

Bielschowsky[4] has shown that during metabolism of 2-acetylaminofluorene the 7-position was hydroxylated and the resulting compound excreted. This pattern was previously established for carcinogenic aromatic hydrocarbons.[5] Hoch-Ligeti[6] found that 2-acetylamino-7-hydroxyfluorene was a weaker carcinogen than 2-acetylaminofluorene.

Possibly the 7-position in 2-acetylaminofluorene is of significance with respect to the carcinogenic effect of the compound. Resonance in the fluorene molecule[7] as well as the acetylamino group confers a high electron density on carbon number seven. Attack by an electrophilic compound[8] at this position might be the first in a series of reactions leading to formation of a tumor. There appears to be a correlation in some cases between high electron density in a molecule and its carcinogenic effect.[8,9]

In order to study the effect of blocking the important 7-position, it was decided to prepare 2-acetylamino-7-iodofluorene, III. In this compound the electron density at the 7-position is reduced so that the compound might not be carcinogenic in the light of the discussion mentioned previously. However, if biological testing would reveal the compound to be carcinogenic, the introduction of I^{131} in the 7-position would enable the use of tracer methods to study its action.



I, R = NO_2
II, R = NH_2
III, R = $NHCOCH_3$

2-Nitro-7-iodofluorene, I, had been prepared by Chanussot[10] by nitration of 2-iodofluorene. In the present investigation it was prepared from 2-amino-7-nitrofluorene[11] by a Sandmeyer reaction. Upon reduction with zinc dust and calcium chloride in dilute alcohol, 2-amino-7-iodofluorene, II, resulted. This showed a tendency to form a dark oil during attempted purification. Several recrystallizations, however, yielded a small pure sample. Acetylation afforded light tan needles of 2-acetylamino-7-iodofluorene, III.

Since this synthesis did not appear suitable for large scale preparations, 2-acetylaminofluorene was iodinated with a molar quantity of iodine monochloride which was dissolved in glacial acetic acid. The crystalline product was identical with the 2-acetylamino-7-iodofluorene previously obtained. However, when the synthesis was repeated on a larger scale, only a small amount of the desired product was isolated. The greater portion was a greenish-gray material of the theoretical iodine content. This decomposed when recrystallized to iodine and impure 2-acetylaminofluorene. Solution in acetone led to the formation of a lachrymatory substance. These facts indicated that the unstable material was an N-iodo compound.

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(3) Wilson, DeEds and Cox, *Cancer Research*, **1**, 596 (1941).

(4) Bielschowsky, *Biochem. J.*, **39**, 287 (1945).

(5) Chalmers and Peacock, *ibid.*, **35**, 1276 (1941).

(6) Hoch-Ligeti, *Brit. J. Cancer*, **1**, 391 (1947).

(7) Weisburger, Weisburger and Ray, in press.

(8) Pullman, *Compt. rend.*, **225**, 738 (1947).

(9) Badger, *Brit. J. Cancer*, **2**, 342 (1948).

(10) Chanussot, *Anales asoc. quim. Argentina*, **15**, 8 (1927).

(11) Cislak and Hamilton, THIS JOURNAL, **53**, 746 (1931).

Accordingly two moles of iodine monochloride were used per mole of 2-acetylaminofluorene in order that both the N- and 7-positions could be iodinated. The unstable intermediate was decomposed by heating in dilute acetic acid containing some sodium hydrogen sulfite, yielding 2-acetylamino-7-iodofluorene in satisfactory yield.

Radioactive iodine was introduced into the 7-position by iodinating 2-acetylaminofluorene in acetic acid with a mixture of NaI^{131}, iodine monochloride, glacial acetic acid, and sufficient acetic anhydride to react with the water in the NaI^{131} solution. The isotope yield was approximately 75%, based on theoretical yield of the iodination.

The carcinogenic activity of these compounds is being tested by Dr. Harold P. Morris of the National Cancer Institute.

Experimental

2-Nitro-7-iodofluorene.—To a suspension of 131 g. (0.5 mole) of 2-amino-7-nitrofluorene hydrochloride in 1 l. of water at 20° there was added 200 cc. of 6 *N* sulfuric acid. A solution of 37 g. of sodium nitrite in 50 cc. of water was dropped in over a period of one-half hour, the temperature being maintained at 20°. After excess nitrous acid had been decomposed by urea, a solution of 240 g. of potassium iodide in 250 cc. of water was added dropwise. The mixture was allowed to stand overnight and then heated. The brownish red product was filtered and washed. It weighed 130 g. and melted at 175°. Recrystallization from glacial acetic acid raised the m. p. to 234°.[10]

2-Amino-7-iodofluorene.—A mixture of 32 g. of 2-nitro-7-iodofluorene, 50 g. of zinc dust, 10 g. of calcium chloride, 760 cc. of ethanol, 150 cc. water and 10 cc. of glacial acetic acid was refluxed for four hours. After filtering off the excess zinc, the filtrate was poured into 4 l. of cold water, precipitating a cream colored material, weight 19 g., sintering at 90–95°, m. p. 109°. Four recrystallizations from 50% ethanol yielded cream colored needles, m. p. 158–160°.

Anal. Calcd. for $C_{13}H_{10}NI$: N, 4.56. Found: N, 4.61.

2-Acetylamino-7-iodofluorene. A. By Acetylation.—Three grams of 2-amino-7-iodofluorene was acetylated in 50 cc. of glacial acetic acid with 1.5 cc. of acetic anhydride. Dilution with water afforded the acetyl compound, sintering at 180°, melting at 209°. After two recrystallizations from ethanol there were obtained light tan needles, m. p. 224–225°.

B. **By Iodination.**—Thirty-three grams of 2-acetylaminofluorene was dissolved in 600 cc. of chloroform and the solution cooled to 24°. To the well-stirred solution 15.3 cc. of iodine monochloride was added dropwise. The temperature of the dark red solution rose to 36°. Next day the greenish-gray precipitate, weight 53 g., m. p. 165–175°, was filtered off. It was boiled with a mixture of 500 cc. glacial acetic acid, 50 cc. water and 12 g. of sodium hydrogen sulfite. After filtering and cooling 24 g. of tan needles of 2-acetylamino-7-iodofluorene, sintering at 205° and melting at 218–220°, crystallized out. Recrystallization from ethanol raised the m. p. to 225°, mixed m. p. with material by procedure A, 224–225°.

Anal. Calcd. for $C_{15}H_{12}ONI$: N, 4.01; I, 36.35. Found: N, 3.91; I, 36.49.

Hydrolysis by boiling overnight in alcoholic potassium hydroxide yielded 2-amino-7-iodofluorene, identical with that from reduction of 2-nitro-7-iodofluorene.

N-(7-Iodo-2-fluorenyl)-succinamic Acid.—To a solution of 0.6 g. of 2-amino-7-iodofluorene in 100 cc. of benzene there was added 0.25 g. of succinic anhydride. After refluxing for one-half hour, the solution was evaporated to a volume of 50 cc. Upon cooling 0.6 g. of light yellow crystals was collected. Two recrystallizations from ethanol yielded shiny yellow plates, m. p. 252°.

Anal. Calcd. for $C_{17}H_{14}O_3NI$: N, 3.44. Found: N, 3.64.

2-Acetylamino-7-iodo-I^{131}-fluorene.—A solution of 2.23 g. of 2-acetylaminofluorene in 50 cc. of glacial acetic acid was cooled to 22°. A mixture of 5 cc. of NaI^{131} solution (activity 16 microcuries), 5 cc. of acetic anhydride and 2 cc. of glacial acetic acid was allowed to stand for five minutes. To this there was added 0.75 cc. of iodine monochloride and the mixture allowed to stand one minute. It was then added dropwise with stirring to the acetylaminofluorene solution over a period of five minutes. A tan precipitate appeared after several minutes. Seven hours later 100 cc. of water containing 0.5 g. of sodium hydrogen sulfite was added slowly and the mixture centrifuged. The precipitate was washed three times with water. It was recrystallized from 70% acetic acid to give 2.0 g. of light tan needles having an activity of 3.6 microcuries/g.

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Summary

The synthesis of 2-amino-7-iodofluorene and several of its derivatives is described. These compounds may be of value in investigating the mechanism of the carcinogenic effect of 2-acetylaminofluorene.

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