940. *An Improved Synthesis of Fluorene-1,2-quinone 2-Acetimide*

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The macro-scale preparation of fluorene-1,2-quinone 2-acetimide, thought to be a metabolite of the carcinogen *N*-(2-fluorenyl)acetamide,[1] is subject to two serious difficulties. First, it is solvent-sensitive at room temperature. The compound was first prepared [2] by lead tetra-acetate oxidation of *N*-(1-hydroxy-2-fluorenyl)acetamide; [2] 50 mg. batches were used to allow rapid desolvation at the end of the reaction. Secondly, the preparation of *N*-(1-hydroxy-2-fluorenyl)acetamide involves nine steps from indene [3] or ten from fluoranthrene,[2,4] both schemes requiring very large initial quantities of reactants. Some of the reactions in both sequences, easily workable in milligram amounts, were inoperable with 10—1000 grams.

The first problem was solved by lyophilisation. The 2-acetimide was solvent-stable at liquid-nitrogen temperature, and the oxidation could be run as prescribed,[2] the imide

[1] H. R. Gutmann, J. H. Peters, and J. G. Burtle, *J. Biol. Chem.*, 1956, **222**, 373; E. C. Miller and J. A. Miller, *J. Nat. Cancer Inst.*, 1955, **15**, 1571.
[2] H. R. Gutmann, J. G. Burtle, and H. T. Nagasawa, *J. Amer. Chem. Soc.*, 1958, **80**, 5551.
[3] M. A. Morgan and H. R. Gutmann, *J. Org. Chem.*, 1959, **24**, 1163.
[4] E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, 1953, **18**, 864; 1954, **19**, 964.

being isolated by lyophilisation. This technique increased the yields from the oxidation to *ca.* 90%. The batch size (1—1·25 g.) was limited by the size of the equipment.

Solution of the second problem required drastic revisions in procedure. Preliminary experiments indicated that the longer synthesis was better suited to the facilities of this laboratory. This sequence is described [2,4] as follows: oxidation of fluoranthene with chromium trioxide yielded 9-oxofluorene-1-carboxylic acid which was reduced (Wolff–Kishner) to fluorene-1-carboxylic acid. Thionyl chloride gave the acid chloride, which was treated with sodium azide to yield fluorene-1-carbonyl azide, and this, with acetic anhydride, gave 1-diacetylaminofluorene. Hydrolysis with hydrochloric acid, diazotisation, and hydrolysis produced fluoren-1-ol, and nitric acid gave 1-hydroxy-2-nitrofluorene which was reduced with zinc dust to the amino-compound. Acetic anhydride then yielded *N*-(1-hydroxy-2-fluorenyl)acetamide which was oxidised with lead tetra-acetate to fluorene-1,2-quinone 2-acetimide. The Wolff–Kishner reaction, excellent for 1—5 gram batches of 9-oxofluorene-1-carboxylic acid, had to be replaced by a modification of the phosphorus–hydriodic acid reduction [5] when applied to 200—500 g. batches because of excessive tar formation. Acid hydrolysis of 1-diacetylaminofluorene was inferior to basic hydrolysis in diethylene glycol in large runs (50—100 g.). In the seventh step the crude product (25—50 g.) was best purified by vacuum-sublimation (120°/0·1 mm.) yielding needles of almost pure fluoren-1-ol (50%), m. p. 121—123°.

The seventh and eighth stages were combined as a reductive acetylation [6] which shortened the sequence by one step and increased the overall yield of *N*-(1-hydroxy-2-fluorenyl)acetamide from 1-hydroxy-2-nitrofluorene by more than 30%.

The results of carcinogenicity tests on fluorene-1,2-quinone 2-acetimide will be reported elsewhere.

Experimental.—Preparations were by published methods,[2,4] with modifications.

Fluorene-1-carboxylic acid. 9-Oxofluorene-1-carboxylic acid (600 g.) was heated with glacial acetic acid (8 l.) and filtered while hot into a 12-l. flask. Red phosphorus (960 g.) and 47% hydriodic acid (1050 ml.) were added with more glacial acetic acid (1 l.). The mixture was heated under reflux for 72 hr., poured into water (30 l.), and the precipitate filtered off, washed with water, and extracted twice with a solution of potassium carbonate (480 g.) in water (6 l.). The combined extracts, when acidified with concentrated hydrochloric acid, gave fluorene-1-carboxylic acid (90%) usable in the subsequent step.

1-*Aminofluorene.* Potassium hydroxide (106 g.) was cautiously added to 1-diacetylaminofluorene (recrystallised from methanol) (50 g.) in hot diethylene glycol (500 ml.), and boiled (2·5 hr.). The pouring of the cooled mixture into water precipitated 1-aminofluorene (77%).

N-(1-*Hydroxy*-2-*fluorenyl*)*acetamide.* 1-Hydroxy-2-nitrofluorene (6·8 g.) was introduced into a low-pressure hydrogenator bottle with acetic anhydride (3 ml.), glacial acetic acid (200 ml.), and 10% palladium–charcoal catalyst (300 mg.). The mixture was reduced with hydrogen (30 p.s.i. initial pressure) until 90 mmoles of the gas had been consumed (*ca.* 1 hr.). The catalyst was filtered off and the product isolated by dilution of the filtrate with water and crystallisation of the precipitate from aqueous ethanol. The average yield (m. p. 207—209°) was 84%. Overall yield on the two steps reported by Weisburger and Weisburger [4] was 52%.

Fluorene-1,2-quinone 2-acetimide. The procedure described by Gutmann *et al.*[2] was used except that 1—1·25 g. batches were taken. The washed organic layer from the oxidation was quickly shell-frozen in a mixture of acetone and solid carbon dioxide, and then lyophilised at 1—5 μ pressure, with liquid nitrogen as the coolant. Yields as high as 90% of the dark red product were obtained. Purified samples showed $\lambda_{max.}$ (in $CHCl_3$) 456, 330 mμ (ε 2575, 8800).

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