[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Syntheses of 3′-Fluoro- and 4-Fluoro-10-methyl-1,2-benzanthracenes[1]

MELVIN S. NEWMAN AND RONALD H. B. GALT

Received October 9, 1959

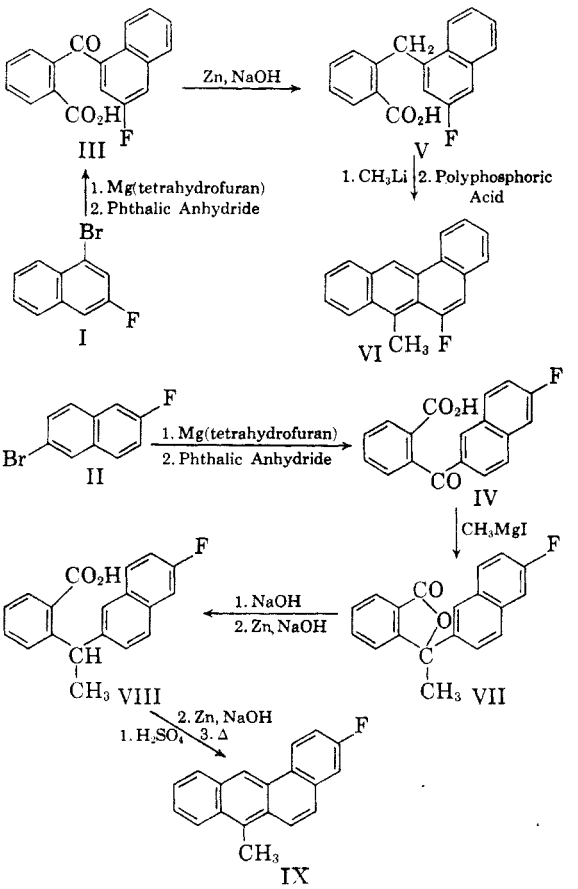
The syntheses of 3′-fluoro- and 4-fluoro-10-methyl-1,2-benzanthracenes are described.

A previous paper[2] presented reasons for synthesizing all the monofluoro-10-methyl-1,2-benzanthracenes in an attempt to locate the position or positions in the nucleus of 10-methyl-1,2-benzanthracene directly responsible for the carcinogenic activity. This sequel describes the syntheses of 4-fluoro- and 3′-fluoro-10-methyl-1,2-benzanthracenes, the routes to which involved, as before,[2] initial preparation of suitable bromofluoronaphthalenes.

1-Amino-2-nitro-4-bromonaphthalene[3] was the precursor of 1-bromo-3-fluoronaphthalene(I). Reduction of the nitro group[4] and deamination gave 1-bromo-3-naphthylamine. Best yields (60–65%) for replacement of the amino group by fluorine were obtained by decomposition of the diazonium hexafluorophosphate.[5] The normal Schiemann reaction using fluoboric acid afforded yields of 50–55%. The purity of the insoluble intermediate diazonium salt was of prime importance since the best yields on decomposition were obtained when thorough washing and drying of this salt were effected.

6-Bromo-2-fluoronaphthalene(II) was prepared similarly from 6-bromo-2-naphthylamine, the hexafluorophosphoric acid modification[5] once again giving slightly higher yields than the normal Schiemann. A 95% conversion of 6-bromo-2-naphthol to 6-bromo-2-naphthylamine by heating at 190° with ammonium sulphite under pressure for twenty-four hours has been reported.[6] In our hands, these conditions proved capricious and good yields (*ca.* 80%) could only be obtained consistently by lowering the temperature to 150°.

Condensation of the Grignard reagents of I and II with phthalic anhydride afforded the keto-acids, III and IV, respectively. Clemmensen reduction of III produced the acid IV which with excess methyllithium was converted to the methyl ketone. The



latter, without characterization, was cyclodehydrated[7] with polyphosphoric acid to give 4-fluoro-10-methyl-1,2-benzanthracene VI.

On treatment with methylmagnesium iodide, IV was converted to the lactone VII, which, by cleavage with alkali followed by zinc dust reduction, afforded the acid VIII. Cyclization was effected with concentrated sulfuric acid and the anthrone obtained was reduced and dehydrated to yield 3′-fluoro-10-methyl-1,2-benzanthracene (IX). The structure of IX was verified by comparison of its ultraviolet absorption spectrum with that of 10-methyl-1,2-benzanthracene, since the precursor

(1) This work was supported by a grant from the National Institutes of Health.

(2) M. S. Newman, D. MacDowell, and S. Swaminathan, *J. Org. Chem.*, **24**, 509 (1959).

(3) H. H. Hodgson and S. Birtwell, *J. Chem. Soc.*, 321 (1943).

(4) M. P. Cava and J. F. Stucker, *J. Am. Chem. Soc.*, **79**, 1706 (1957).

(5) We are greatly indebted to Dr. K. Rutherford, Chemistry Department, Essex College, Windsor, Canada, for information about this new method soon to be published.

(6) L. C. Anderson and D. Johnston, *J. Am. Chem. Soc.*, **65**, 241 (1943).

(7) Cyclodehydrations of this sort have previously been carried out by Bradsher and his co-workers, *e.g.*, C. K. Bradsher and F. A. Vingiello, *J. Am. Chem. Soc.*, **71**, 1434 (1949), C. K. B. and S. T. Webster, *J. Am. Chem. Soc.*, **79**, 393 (1957) who used hydrobromic acid in acetic acid. To our knowledge, the first use of polyphosphoric acid for such cyclodehydrations was by M. S. Newman, D. MacDowell, and S. Swaminathan, *J. Org. Chem.*, **24**, 509 (1959).

acid VIII could conceivably give rise to an isomeric tetracene derivative.

EXPERIMENTAL[8]

6-Bromo-2-naphthylamine. 6-bromo-2-naphthol[9] (30 g.), ammonium hydroxide (60 ml., 28%) saturated with sulfur dioxide, and ammonium hydroxide (60 ml., 28%) were heated together at 150° for 27 hr. in a steel bomb. The bomb was washed out with boiling ethyl acetate and its contents extracted with the same solvent. Distillation of the residue from concentration of the organic extract afforded a distillate, b.p. 155–160° at 1 mm., which yielded 24.0 g. (80%) of colorless 6-bromo-2-naphthylamine, m.p. 126–127° (lit.[6] 128°) on crystallization from alcohol.

6-Bromo-2-fluoronaphthalene (II). The above bromoamine (49 g.) was heated for 15 min. with excess concentrated hydrochloric acid. To the cooled solution (0°) was added, dropwise, a solution of sodium nitrite (15.5 g.) in water (30 ml.). When diazotisation was complete, hexafluorophosphoric acid[10] (50 ml., *ca.* 65%, polyethylene measuring cylinder) was added rapidly in portions. Immediately a heavy yellow-brown precipitate separated and mixing was best effected by manual shaking. The diazonium hexafluorophosphate was filtered, washed thoroughly with water, methanol, and ether. After drying over phosphorus pentoxide the salt (68 g.) melted with decomposition at 107–110°. This salt was added in portions through a Gooch rubber tube from a flask fitted to a three-necked flask held at 120–130°. After decomposition was complete the decomposition residue was extracted with ether-benzene and worked up in the usual way. Distillation of the product followed by crystallization from aqueous methanol gave 27 g. (55% from bromoamine) of colorless 6-bromo-2-fluoronaphthalene, m.p. 66.0–67.0°. A second run gave a 58% yield.

Anal. Calcd. for $C_{10}H_6BrF$: C, 53.3; H, 2.7. Found:[s] C, 53.2; H, 2.9.

The normal Schiemann reaction using fluoboric acid afforded yields of 49 and 53%.

1-Bromo-3-fluoronaphthalene (I). I was prepared similarly from 1-bromo-3-naphthylamine by the hexafluorophosphoric acid modification; the yields were 58 and 64%, by the normal Schiemann, 50 and 55%. Decomposition of the diazonium hexafluorophosphate, m.p. 120–125° (dec.), at 140° gave 1-bromo-3-fluoronaphthalene (I), b.p. 84–88° at 1 mm. Since this compound was a liquid, it was characterized as the *trinitrobenzene complex*, m.p. 92.0–93.0° (from aqueous methanol).

Anal. Calcd. for $C_{16}H_9BrFN_3O_6$: C, 43.8; H, 2.1. Found:[s] C, 43.7; H, 2.1.

ortho-(6-Fluoro-2-naphthoyl)benzoic acid (IV). The Grignard reagent formed from 6-bromo-2-fluoronaphthalene (II) was treated with phthalic anhydride as in a similar case.[2] The ketoacid IV proved difficult to purify. Crystallization from benzene–ethyl acetate gave a 65% yield of crude acid, m.p. 185–195°. Further crystallizations afforded IV, m.p. 193–197°, in 50% yield. This material was used directly in the next step without further purification.

3-Methyl-3-(6-fluoro-2-naphthyl)phthalide (VII). Treatment of 8.0 g. of IV in 200 ml. of benzene-tetrahydrofuran (1:1) with two equivalents of methylmagnesium iodide as described[11] afforded 4.5 g. (56%) of VII as colorless plates, m.p. 129–130°. The analytical sample melted at 130.0–131.0°.

Anal. Calcd. for $C_{19}H_{13}FO_2$: C, 78.1; H, 4.5. Found:[s] C, 77.8; H, 4.7.

2-[1-(6-Fluoro-2-naphthyl)ethyl]benzoic acid (VIII). The lactone VII was reduced in 85% yield as described for a similar lactone[12] to VIII, m.p. 185.0–187.0°. The analytical sample was crystallized from a mixture of benzene and Skellysolve B (petroleum ether, b.p. 60–70°).

Anal. Calcd. for $C_{19}H_{15}FO_2$: C, 77.6; H, 5.1. Found:[s] C, 77.3; H, 5.2.

3′-Fluoro-10-methyl-1,2-benzanthracene (IX). The acid VIII (6 g.) was dissolved in concentrated sulfuric acid (75 ml.). After standing 2 hr. the solution was poured on ice. The organic product was treated at reflux for 7 hr. with zinc dust (24 g.), water (350 ml.), and 55% aqueous sodium hydroxide (90 ml.). From the neutral portion of this reaction mixture was isolated 1.75 g. (33%) of crude IX, m.p. 148–150°. Purification by means of formation of the 1,3,5-trinitrobenzene derivative, recrystallization of this, and chromatography over alumina gave 1.5 g. (28%) of pure IX, m.p. 146.0–147.0°.

Anal. Calcd. for $C_{19}H_{13}F$: C, 87.7; 5.0; F, 7.3. Found:[s] C, 87.4; H, 5.3; F, 7.8.

The 1,3,5-trinitrobenzene complex, m.p. 185.5–186.5°, formed red-orange prisms when crystallized from benzene.

Anal. Calcd. for $C_{25}H_{16}N_3O_6F$: N, 8.9. Found: N, 8.8.

ortho-(3-Fluoro-1-naphthoyl)benzoic acid (III). 1-Bromo-3-fluoronaphthalene (I) (20 g.) in tetrahydrofuran (150 ml.) was added to magnesium (2.3 g.) under dry nitrogen. In the best run the halide was added over 45 min. at the rate of about 2 drops per sec. After 30 min. the Grignard solution was transferred under nitrogen to a dropping funnel then added, dropwise, to a flask containing phthalic anhydride (13.5 g.) dissolved in tetrahydrofuran (150 ml.). After 2 hr. reflux the tetrahydrofuran was replaced by benzene. Work up of the reaction mixture as described for IV yielded by 12.6 g. (48%) of III, m.p. 183–188°. Recrystallization from aqueous methanol yielded 10.4 g. (40%) of pure III, m.p. 187–189°.

Anal Calcd. for $C_{18}H_{11}FO_3$: C, 73.5; H, 3.7. Found:[s] C, 73.3; H, 4.0.

Distillation of the neutral fraction obtained in the Grignard reaction yielded small amounts of 3,3′-difluoro-1,1′-dinaphthyl, m.p. 58–59°, on crystallization from aqueous methanol.

Anal. Calcd. for $C_{20}H_{12}F_2$: C, 83.3; H, 4.2. Found:[s] C, 83.0; H, 3.8.

ortho-(3-Fluoro-1-naphthylmethyl)benzoic acid (V). III was reduced to yield crude V which, on crystallization from aqueous methanol yields pure V, m.p. 165–166°, in 75% yield.

Anal. Calcd. for $C_{18}H_{13}FO_2$: C, 77.2; H, 4.6. Found:[s] C, 77.1; H, 4.8.

4-Fluoro-10-methyl-1,2-benzanthracene (VI). A solution of 13.5 g. of V in 200 ml. of ether was added to a methyllithium solution prepared from 30 g. of methyl iodide and 2.8 g. of lithium in 100 ml. of ether. After the resulting purple solution had been stirred at room temperature for 30 min., the organic product, isolated in the usual way, was stirred into 150 g. of polyphosphoric acid. The resulting mixture was stirred at 100° for 15 min., overnight at room temperature, and was then poured on ice. The solid was taken up in benzene, and filtered through alumina. Chromatography over alumina in Skellysolve B afforded 5.4 g. (44%) of crude VI, m.p. 105–109°, in two crops. A further crystallization gave 37% yield of pure fluorohydrocarbon, VI, m.p. 109–110°.

Anal. Calcd. for $C_{19}H_{13}F$: C, 87.7; H, 5.0; F, 7.3. Found:[s] C, 87.7; H, 4.9; F, 7.1.

COLUMBUS 10, OHIO

(8) All melting points are uncorrected. Analyses marked[g] and[s] were done by the Galbraith and Schwarzkopf Laboratories respectively. The term "worked up in the usual way" means that an ether-benzene extract of the organic products was washed with acid and/or alkali as required, saturated sodium chloride solution, and filtered through a layer of anhydrous magnesium sulphate; the solvents were removed and the residue treated as described.

(9) C. F. Koelsch, *Org. Syntheses*, **Coll. Vol. III** (1955) p. 132.

(10) Obtained from the Ozark Mahoning Company, Tulsa, Okla.

(11) M. S. Newman and M. Orchin, *J. Am. Chem. Soc.*, **60**, 586 (1938).

(12) M. S. Newman, *J. Am. Chem. Soc.*, **60**, 1369 (1938).