Synthesis of Fluorinated 1,2-Benzanthracenes[1]

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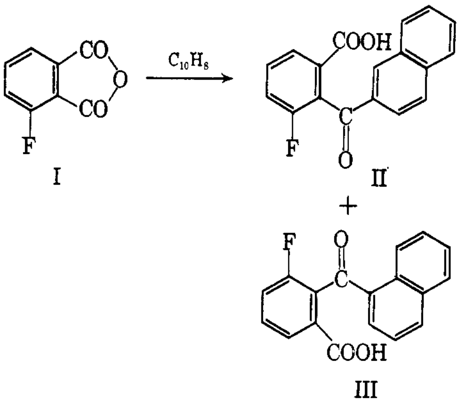
A compound previously believed to be 8-fluoro-10-methyl-1,2-benzanthracene[3] has been shown to be 5-fluoro-9-methyl-1,2-benzanthracene. The syntheses of 5-fluoro-10-methyl-1,2-benzanthracene, 5-fluoro-9,10-dimethyl-1,2-benzanthracene, and 8-fluoro-9,10-dimethyl-1,2-benzanthracene are described.

In a previous publication[3] the synthesis of 8-fluoro-10-methyl-1,2-benzanthracene was described. We now show that an error was made and that the compound believed to be 8-fluoro-10-methyl-1,2-benzanthracene was really 5-fluoro-9-methyl-1,2-benzanthracene.[4] In this paper we also describe the synthesis of 5-fluoro-10-methyl-1,2-benzanthracene, 5-fluoro-9,10-dimethyl-1,2-benzanthracene, and 8-fluoro-9,10-dimethyl-1,2-benzanthracene. This synthetic work continues the program outlined previously.[5]

The error can be traced to a mistake in identification of the ketone formed by decarboxylation of a keto acid formed by the condensation of 3-fluorophthalic anhydride (I) with naphthalene. In the previous paper,[3] it was stated that 3-fluoro-2-(1-naphthoyl)benzoic acid (III) was the sole product whereas we have shown in the accompanying paper[6] that a mixture of II and III in the ratio 3:1 is formed. We cannot account for the differing results described in the two papers other than to say that, in the hands of two subsequent workers, the results reported in the earlier paper[3] could not be duplicated. In addition, the error in proof of structure of the supposed acid III stems from the fact that the Friedel–Crafts condensation of *o*-fluorobenzoyl chloride with naphthalene at about 90° in *o*-dichlorobenzene gives mainly 2-fluorophenyl 2-naphthyl ketone, whereas it was assumed[3] that this condensation gave 2-fluorophenyl 1-naphthyl ketone. Hence the decarboxylation product was said to be the latter ketone whereas it was the former.[6] Accordingly, the keto acid used previously[3] was mainly II and not III.



The structure of other compounds described[3] must accordingly be revised. Compound III[3] was 4-fluoro-3-(2-naphthyl)phthalide, compound IV[6] was 3-fluoro-2-(2-naphthylmethyl)benzoic acid, and compound V[3] was 5-fluoro-9-methyl-1,2-benzanthracene.[4,7]

The syntheses of 5-fluoro-10-methyl-1,2-benzanthracene (VIII) and 5-fluoro-9,10-dimethyl-1,2-benzanthracene (IX) from II and 8-fluoro-9,10-dimethyl-1,2-benzanthracene (XIII) from III were carried out as shown in Chart I. A point of interest is the high yield (96%) and stability of anthrone VI, formed from V on cyclization with anhydrous hydrogen fluoride. In our experience anthrones in the 1,2-benzanthracene series have never been obtained pure in such a yield.[8] Unfortunately, the yield of IX from treatment of VI with methyllithium was low (12%) so that the alternate route to IX (V to VII to IX) was preferable.

Previously, the pyrolysis of 1-(2-methyl-3-fluorobenzoyl)naphthalene at 400° to give 1,2-benzanthracene was reported.[3] Repetition of this work at about 365–385° afforded 5-fluoro-1,2-benzanthracene, although the product was contaminated with an isomeric compound which proved difficult to separate. Professor Bergmann supplied us with a sample of pure 5-fluoro-1,2-benzanthracene, the synthesis of which is described in the paper referred to in ref. 4 of this paper.

Experimental[9]

4-Fluoro-3-methyl-3-(2-naphthyl)phthalide (IV) and 4-Fluoro-3-methyl-3-(1-naphthyl)phthalide (X).—Treatment of a solution of 10.5 g. of II in 300 ml. of benzene with a solution of the Grignard reagent prepared from 1.8 g. of magnesium and excess

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[2] Postdoctoral Fellow, 1963.

[3] M. S. Newman and E. H. Wiseman, *J. Org. Chem.*, **26**, 3208 (1961).

[4] After our error was discovered (by S. Blum) we received a letter from Professor E. D. Bergmann, Hebrew University, Jerusalem, stating that he had synthesized 5-fluoro-9-methyl-1,2-benzanthracene and had submitted an article to the *Bulletin de la societe chimique de France* describing its synthesis [see E. D. Bergmann and M. Bentov, *Bull. soc. chim. France*, 963 (1963)]. We then obtained a sample of this compound from Dr. Bergmann and showed that it was identical with our compound, supposedly the 8-fluoro-10-methyl derivative. We were then certain that the compound we had previously described as 8-fluoro-10-methyl-1,2-benzanthracene was actually 5-fluoro-9-methyl-1,2-benzanthracene. During this correspondence we learned that the synthesis of 8-fluoro-10-methyl-1,2-benzanthracene was being carried out by Professor Bergmann. We discontinued our efforts to prepare this compound as he very kindly consented to supply us with our needs.

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

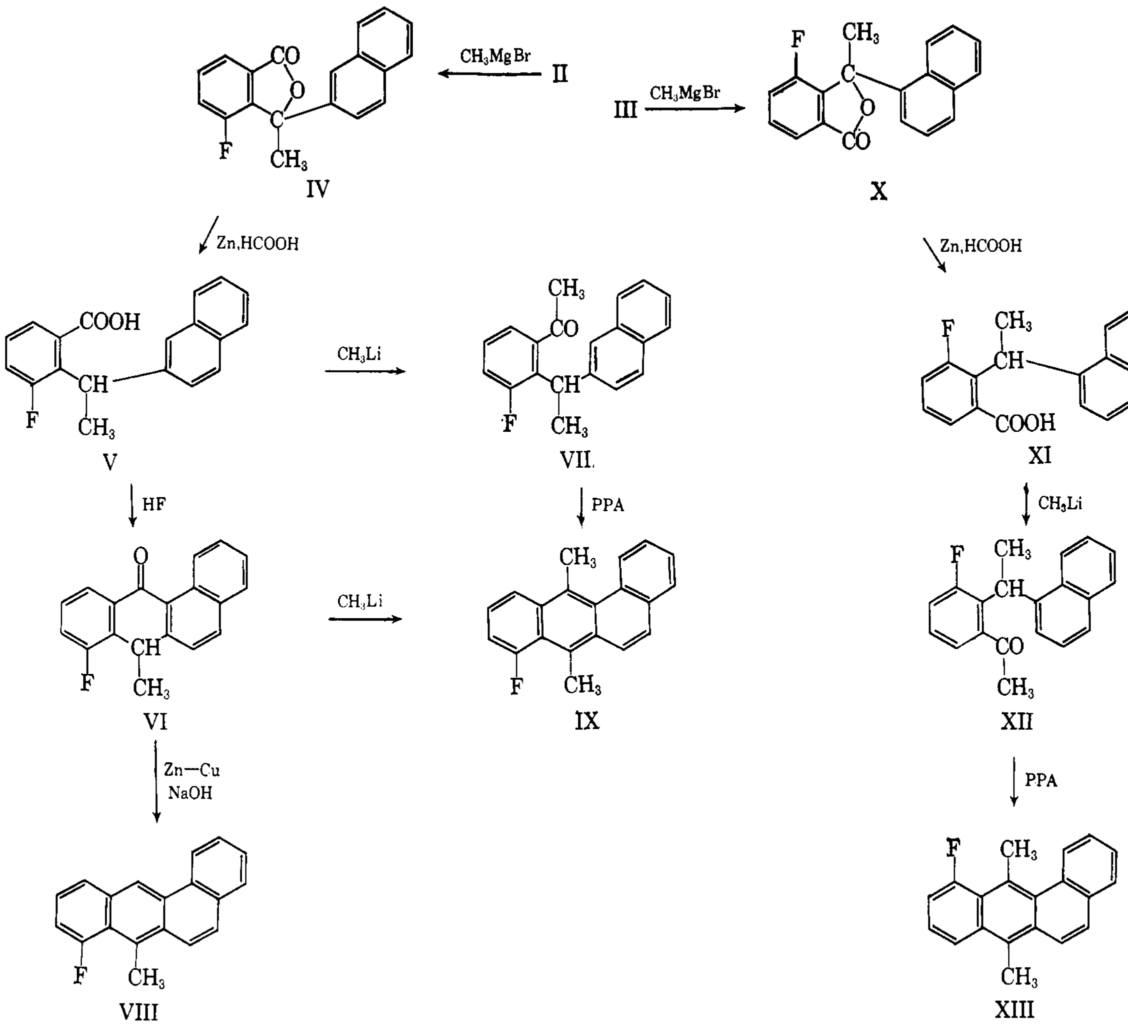
[6] M. S. Newman and S. Blum, *ibid.*, **29**, 1416 (1964).

[7] In a recent letter, Dr. James A. Miller, McArdle Memorial Laboratory for Cancer Research, University of Wisconsin, states that 5-fluoro-9-methyl-1,2-benzanthracene is rather active as a carcinogen.

[8] See, for example, M. S. Newman and S. Seshadri, *J. Org. Chem.*, **27**, 76 (1962), and ref. 3 and 10 therein; see also L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **61**, 1272 (1939), and references therein for a discussion of earlier results.

[9] All melting points are uncorrected. The term "worked up in the usual manner" means that a solution of the products in an organic solvent, usually ether–benzene, was washed with acid and/or alkali as required and saturated sodium chloride solution, and then was dried by shaking with, or filtration through, anhydrous magnesium sulfate. The solvents then were removed and the residue was purified by crystallization, distillation, or chromatography.

CHART I



methyl bromide in 80 ml. of ether essentially as described[10] afforded 7.9 g. (76%) of crude IV, m.p. 110–115°, suitable for the next step. The analytical sample of IV, obtained with little loss by crystallization from methanol, melted at 128–129°. Similarly 11.3 g. (71%) of crude X, m.p. 175–178°, was obtained from 16.0 g. of III. The analytical sample, obtained with little loss by crystallization from methanol, melted at 183–184°.

Anal. Calcd. for $C_{19}H_{13}FO_2$: C, 78.0; H, 4.4; F, 6.5. Found[11] for IV: C, 77.9; H, 4.5; F, 6.7. Found for X: C, 77.9; H, 4.6; F, 6.6.

3-Fluoro-2-(α-2-naphthylethyl)benzoic Acid (V) and 3-Fluoro-2-(α-1-naphthylethyl)benzoic Acid (XI).—A mixture of 7.0 g. of crude IV, 50 g. of zinc dust, 500 ml. of formic acid (98%), and 50 ml. of water was stirred at reflux for 20 hr.[12] After appropriate work-up there was obtained 6.7 g. (94%) of V, m.p. 157–159°, as colorless crystals. Similarly XI, m.p. 172–173° (analytical sample), was obtained in 95% yield after crystallization from toluene. The analytical sample of V, m.p. 160–161°, was obtained by crystallization from toluene–cyclohexane.

Anal. Calcd. for $C_{19}H_{15}FO_2$: C, 77.5; H, 5.1; F, 6.5. Found for V: C, 77.4; H, 5.1; F, 6.6. Found for XI: C, 77.8; H, 5.3; F, 6.8.

5-Fluoro-9,10-dihydro-9-keto-10-methyl-1,2-benzanthracene (VI).—To 7.0 g. of powdered V in a polyethylene bottle was added 200 ml. of anhydrous hydrogen fluoride. After the hydrogen fluoride had evaporated, a conventional work-up, including extraction with benzene and recrystallization from cyclohexane, afforded 6.3 g. (96%) of VI as pale yellow elongated crystals, m.p. 108.5–109.5° (infrared band at 6.05 μ, no band in the OH region).

Anal. Calcd. for $C_{19}H_{13}FO$: C, 82.6; H, 4.7; F, 6.9. Found: C, 82.4; H, 4.7; F, 7.0.

5-Fluoro-10-methyl-1,2-benzanthracene (VIII).—A mixture of 1.5 g. of VI, 3 g. of zinc dust activated with copper sulfate, 12 g. of sodium hydroxide, 15 ml. of toluene, and 150 ml. of water was held at reflux for 24 hr. A conventional work-up, including careful extraction of the zinc with boiling benzene followed by treatment of the benzene extracts with hydrochloric acid yielded a crude product which was purified by chromatography over alumina [using benzene-petroleum ether, b.p. 65–70° (Skellysolve B), in a 1:1 ratio as eluent] to yield 1.03 g. (73%) of pure VIII, m.p. 140–141°, on crystallization from benzene–ethanol.

Anal. Calcd. for $C_{19}H_{13}F$: C, 87.7; H, 5.0; F, 7.3. Found[b]: C, 87.8; H, 5.1; F, 7.5.

The 2,4,7-trinitrofluorenone (TNF) derivative, m.p. 212–213°, was prepared in, and recrystallized from, benzene.

Anal. Calcd. for $C_{32}H_{18}FN_3O_7$: C, 66.8; H, 3.1; F, 3.3; N, 7.3. Found[a]: C, 67.0; H, 3.3; F, 3.5; N, 7.1.

3-Fluoro-2-(α-2-naphthylethyl)acetophenone (VII) and 3-Fluoro-2-(α-1-naphthylethyl)acetophenone (XII).—A solution of methyllithium prepared from 6.5 g. of methyl iodide and 0.7 g. of lithium in 100 ml. of ether was added rapidly under nitrogen to a stirred solution of 3.6 g. of V in 50 ml. of ether. After stirring at room temperature for 30 min. a conventional work-up yielded 2.3 g. (64%) of pure VII, after crystallization from ethanol, as colorless crystals, m.p. 89–90° (infrared band at 5.9

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[10] L. F. Fieser and M. S. Newman, *J. Am. Chem. Soc.*, **58**, 2376 (1936).

[11] Analyses were by Galbraith Analytical Laboratories, Knoxville, Tenn., except a few marked [b], by A. Bernhardt, Max Planck Institute, Mulheim, Germany, and [a], by Spang Laboratory, Ann Arbor, Mich.

[12] Compare R. L. Letsinger, J. D. Jamison, and A. L. Hussey, *J. Org. Chem.*, **26**, 97 (1961); see also M. S. Newman and S. Seshadri, *ibid.*, **27**, 76 (1962), and M. S. Newman and K. Naiki, *ibid.*, **27**, 863 (1962).

μ). Similarly XII, m.p. 114–116°, was obtained in 80% yield. Recrystallization of XII from methanol afforded the analytical sample, m.p. 117–118° (infrared band at 5.92 μ). Small amounts of the acids, V and XI, were received from alkaline extracts of the reaction mixtures.

Anal. Calcd. for $C_{20}H_{17}FO$: C, 82.2; H, 5.9; F, 6.5. Found for VII: C, 81.9; H, 6.0; F, 6.5. Found for XII: C, 82.2; H, 5.9; F, 6.4.

5-Fluoro-9,10-dimethyl-1,2-benzanthracene (IX) and 8-Fluoro-9,10-dimethyl-1,2-benzanthracene (XIII).—A solution of 1.5 g. of VI in 50 ml. of benzene was treated with a solution of methyllithium made from 1.0 g. of lithium and 10 g. of methyl iodide in 150 ml. of ether. After refluxing overnight the mixture was worked up to yield crude IX which purified by chromatography over alumina (as above) to yield 174 mg. (12%) of IX, m.p. 130–131°. Alternately, in the best of several runs, 2.2 g. of VII was stirred into 50 g. of polyphosphoric acid[13] (PPA) at 85°. After 40 min. the mixture was poured on ice and left until the dark color disappeared (2–3 hr.). The yellow solid was purified by chromatography over alumina and recrystallization from ethanol to yield 0.86 g. (41%) of pure IX, m.p. 130–131°, as pale yellow plates.

In a similar way (at 80° for 40 min.), 4.2, g. of XII afforded 1.95 g. (50%) of pure XIII, m.p. 61.5–62.5, as pale yellow crystals, b.p. 35–40° on recrystallization from petroleum ether.

Anal. Calcd. for $C_{20}H_{15}F$: C, 87.6; H, 5.5; F, 6.9. Found[8] for IX: C, 87.4; H, 5.5; F, 7.1. Found for XIII: C, 87.5; H, 5.6; F, 6.8.

The TNF derivative of IX was prepared in benzene and was recrystallized from acetic acid to yield brown crystals, m.p. 177–178°. The TNF derivative of XIII was prepared in, and recrystallized from, benzene. It formed brown elongated crystals, m.p. 175–176°.

Anal. Calcd. for $C_{33}H_{20}FN_3O_7$: C, 67.3; H, 3.4; F, 3.2; N, 7.1. Found[8] for IX-TNF: C, 67.1; H, 3.3; F, 3.1; N, 7.4. Found for XIII-TNF: C, 67.3; H, 3.5; F, 3.2; N, 7.2.

5-Fluoro-1,2-benzanthracene.—In a typical experiment (repeated several times) 2.0 g. of 1-(2-methyl-3-fluorobenzoyl)-naphthalene, m.p. 49–50° (obtained from the sample of ketone previously reported[3] as a liquid), was heated in a bath from 365 to 385° during 3 hr. Distillation at 3 mm. afforded a crude product which was purified by chromatography over alumina. Colorless needles, m.p. 105–106°, were obtained in about 32% yield. This material, which vapor phase chromatography on a 9 ft. × 0.125 in. Carbowax 20M column showed to be a mixture of two compounds in a ratio of 88:12, gave satisfactory analysis for a fluorobenzanthracene.

Anal. Calcd. for $C_{18}H_{11}F$: C, 87.8; H, 4.5; F, 7.7. Found: C, 87.6; H, 4.7; F, 7.4.

The red TNF derivative, m.p. 223–224°, was obtained by crystallization from benzene.

Anal. Calcd. for $C_{31}H_{16}FN_3O_7$: C, 66.4; H, 2.9; F, 3.4; N, 7.5. Found: C, 66.7; H, 3.2; F, 3.6; N, 7.3.

The melting point of pure 5-fluoro-1,2-benzanthracene[4] is 150°. Our crude material (about 88% pure) could be converted into the pure substance by careful purification. However, because of the difficulties involved, this route is not a good one. Our pure compound was identical with the sample supplied by Professor Bergmann as determined by comparison of the infrared spectra and X-ray powder photographs.

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[13] Compare C. K. Bradsher and S. T. Webster, *J. Am. Chem. Soc.*, **79**, 343 (1957). We thank the Victor Chemical Co., Chicago, Ill., for a generous gift of polyphosphoric acid.

The Behavior of 3-Fluorophthalic Anhydride in Friedel–Crafts and Grignard Reactions[1]

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Condensation of 3-fluorophthalic anhydride (I) with naphthalene in *o*-dichlorobenzene at 95° took place only on the 2-carbonyl group to yield a mixture of 53% of 3-fluoro-2-(2-naphthoyl)benzoic acid (II) and 18% of 3-fluoro-2-(1-naphthoyl)benzoic acid (III). In Grignard reactions with 1-naphthyl- and 2-naphthylmagnesium bromides, both possible keto acids were formed. In the case of 2-naphthylmagnesium bromide, condensation occurred at the 1-carbonyl in preference to the 2-carbonyl group of I in the ratio of about 1.4:1, whereas with 1-naphthylmagnesium bromide condensation at each carbonyl was about the same.

In previous studies from this laboratory, the reaction of 3-substituted phthalic anhydrides in Grignard and Friedel–Crafts condensations have been described.[3,4] In summary,[4] Grignard condensations take place preferentially on the 1-carbonyl group in both 3-methyl- and 3-chlorophthalic anhydride. In the Friedel–Crafts reaction, condensation occurs on both carbonyl groups in 3-methylphthalic anhydride, but with 3-chlorophthalic anhydride, condensation is almost entirely at the 2-carbonyl group.

In this paper we report on the reactions of 3-fluorophthalic anhydride with naphthalene and with 1- and 2-naphthylmagnesium bromides. This work was undertaken not only to obtain more information about the behavior of unsymmetrical anhydrides but also to ascertain the source of an error in a previous publication.[5] The consequences of this error is discussed in the accompanying article.[6]

The Friedel–Crafts condensation of 3-fluorophthalic anhydride (I) with naphthalene in *o*-dichlorobenzene at 95° gave a mixture of about 53% of 3-fluoro-2-(2-naphthoyl)benzoic acid (II) and 18% of 3-fluoro-2-(1-naphthoyl)benzoic acid (III) as determined by fractional recrystallization of the methyl esters (compare ref. 5). In a run at 45°, II and III were produced in about 22 and 45% yields, respectively. At 125° the proportion of II increased over that in the run at 95°, but yield of acids was lower owing to tar formation. Thus in the Friedel–Crafts condensation with naphthalene, 3-fluorophthalic anhydride behaves like 3-chlorophthalic anhydride in that condensation occurs

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[1] This work was supported by a grant from The National Institutes of Health, Bethesda, Md.

[2] Postdoctoral Fellow, 1963.

[3] (a) M. S. Newman and C. D. McCleary, *J. Am. Chem. Soc.*, **63**, 1542 (1941); (b) M. S. Newman and C. W. Muth, *ibid.*, **72**, 5191 (1950).

[4] M. S. Newman and P. G. Scheurer, *ibid.*, **78**, 5004 (1956).

[5] M. S. Newman and E. H. Wiseman, *J. Org. Chem.*, **26**, 3208 (1961).

[6] M. S. Newman and S. Blum, *ibid.*, **29**, 1414 (1964).