The Synthesis of 5-Fluorodibenz[*a*,*h*]anthracene

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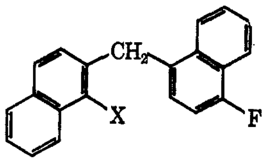
5-Fluorodibenz[*a*,*h*]anthracene (V) has been prepared from 1-bromo-2-[(4-fluoro-1-naphthyl)methyl]naphthalene (I) *via* the corresponding anthrone (IV). The electronic spectrum of V is practically identical with that of the parent hydrocarbon.

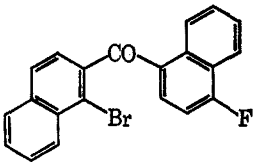
For reasons stated previously,[1] it seemed of interest to prepare fluoro derivatives of the carcinogenic hydrocarbon, dibenz[*a*,*h*]anthracene, in particular the 5-fluoro compound (V) which contains the fluorine atom in the so-called K region. 4-Fluoro-1-naphthylmagnesium bromide condensed smoothly with the reactive (benzylic)bromine atom in 1-bromo-2-bromomethylnaphthalene to give 1-bromo-2-[(4-fluoro-1-naphthyl)-methyl]naphthalene (I). We expected to obtain the same compound by reduction of 1-bromo-2-naphthyl 4-fluoro-1-naphthyl ketone (II), which was prepared in the usual manner from 4-fluoro-1-naphthylmagnesium bromide and 1-bromo-2-naphthonitrile. However, the reduction of the carbonyl group in II was extremely difficult, and the results were erratic.

The magnesium derivative of I was carbonated, yielding III, and the latter was smoothly cyclized to the fluorinated anthrone (IV). As often in the benzologs of anthrone,[2] IV appears to be a tautomeric mixture of the anthrone and the corresponding anthrol; the absorptions corresponding to both appear in the infrared spectrum. Reduction of IV gave the desired fluoro compound V. Its structure follows—apart from the unambiguity of the synthesis—from the identity of its spectrum with that of the parent hydrocarbon, dibenz[*a*,*h*]anthracene:[3] dibenz[*a*,*h*]anthracene, 280 mμ (log ε 4.63), 289 (4.96), 299 (5.20), 322 (4.28), 335 (4.23), 350 (4.16), 374 (3.00), 384 (2.61), 394 (3.01); V, 274 s mμ (log ε 4.58), 290 (4.92), 300 (5.20), 322 (4.34), 334 (4.20), 350 (4.16), 367 (2.78), 377 (3.19), 388 (2.75), 399 (3.30). We expected in the same manner to prepare the 5,12-difluoro derivative VI of dibenz[*a*,*h*]anthracene by coupling 4-fluoro-1-naphthylmagnesium bromide with 1-bromo-2-bromomethyl-4-fluoronaphthalene (VII) which was prepared by the sequence VIII → IX → X. However, the product formed proved to be 1,2-di(1-bromo-4-fluoro-2-naphthyl)ethane (XII); the Grignard compound was demetalated by VII to the known 4,4'-difluoro-1,1'-binaphthyl.[4]

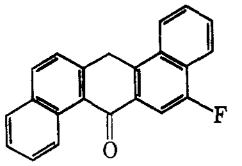
This refractory behavior of VII in the condensation with arylmagnesium halides was equally evident when VII was treated with phenylmagnesium bromide. Part of VII was recovered unchanged, and a 2% yield of XII was obtained. In any event, the failure of the condensation cannot be ascribed to the 4-fluoro-1-naphthylmagnesium bromide, as it condensed normally with 1-bromo-2-bromomethylnaphthalene (see above) and with 2-bromobenzyl bromide. In the latter case, 1-(*o*-bromobenzyl)-4-fluoronaphthalene (XIII) was obtained in 76% yield. Its structure was proved by successive treatment with magnesium and carbon dioxide, yielding the known[4] *o*-(4-fluoro-1-naphthylmethyl)benzoic acid (XIV).



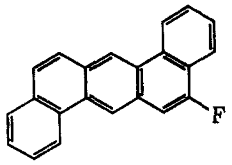
I, X = Br
III, X = COOH



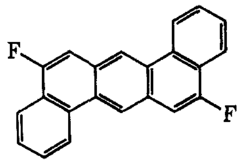
II



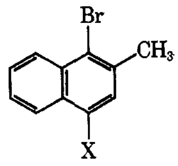
IV



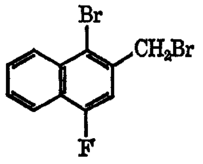
V



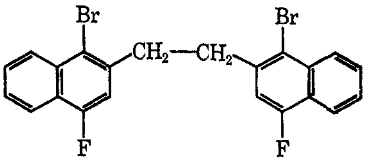
VI



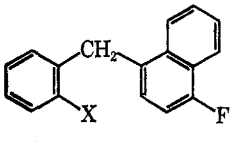
VIII, X = NO_2
IX, X = NH_2
X, X = F
XI, X = $NH\cdot COCH_3$



VII



XII



XIII, X = Br
XIV, X = COOH

Experimental Section

1-Bromo-2-[(4'-fluoro-1'-naphthyl)methyl]naphthalene (I).—The Grignard reagent was prepared from 56 g of 1-bromo-4-fluoronaphthalene,[4,5] 6 g of magnesium, and 150 ml of ether. Then 150 ml of benzene was added and most of the ether was distilled off. A solution of 37.5 g of 1-bromo-2-bromomethyl-

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(1) E. D. Bergmann and J. Blum, *J. Org. Chem.*, **27**, 527 (1962).

(2) *Cf.* E. Clar, "Polycyclic Hydrocarbons," Vol. I, Academic Press Inc., New York, N. Y., 1964, p 108.

(3) Reference 2, p 331.

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

(5) G. Schiemann, W. Gueffroy, and W. Winkelmüller, *Ann.*, **487**, 270 (1931).

naphthalene[6] in 150 ml of benzene was now added gradually during 90 min. After 6 hr of refluxing with stirring, the mixture was decomposed with cold 5% hydrochloric acid. The organic layer was washed with 5% sodium hydrogen carbonate solution and water and concentrated, and the residual liquid was distilled to yield 40 g of a viscous, yellow oil, bp 180–230° (0.2 mm), which solidified on trituration with hexane. Recrystallization from the same solvent (active carbon) yielded 28 g (61%) of pure I as thick, colorless prisms, mp 107.5–108.5°.

Anal. Calcd for $C_{21}H_{14}BrF$: C, 69.1; H, 3.8; F, 5.2. Found: C, 69.2; H, 3.9; F, 5.6.

1-Bromo-2-naphthyl 4-Fluoro-1-naphthyl Ketone (II).—A solution of 44.5 g of 1-bromo-2-cyanonaphthalene[7] in 100 ml of benzene was added to a solution of 4-fluoro-1-naphthylmagnesium bromide, prepared from 45 g of 1-bromo-4-fluoronaphthalene, 4.8 g of magnesim, 100 ml of ether, and 100 ml of benzene. Most of the ether was distilled off and the mixture was refluxed for 12 hr. Then 200 g of ice and 100 ml of concentrated hydrochloric acid were added. The organic solvents were steam-distilled and the resulting tan ketimine hydrochloride refluxed for 3 hr with 100 ml of concentrated hydrochloric acid, 200 ml of water, 100 ml of acetic acid, and 120 ml of toluene. The aqueous layer was extracted with toluene, and the combined organic solutions were washed with alkali and water and concentrated. The residue was taken up with 200 ml of benzene and chromatographed on alumina (benzene as eluent). The first pale yellow fraction yielded 35 g (48%) of II, mp 157°, from benzene and petroleum ether (bp 40–60°).

Anal. Calcd for $C_{21}H_{12}BrFO$: C, 66.5; H, 3.2; F, 5.0. Found: C, 66.6; H, 3.4; F, 5.1.

All attempts to reduce II to I failed. In the only experiment, in which a 5% yield of I was obtained, a mixture of 5 g of II, 50 g of zinc powder, and 500 ml of 80% aqueous formic acid was refluxed for 24 hr. Separation of I from the oily by-products was effected by chromatography on alumina. Melting point and infrared spectrum of the compound were the same as those of that obtained in the foregoing experiment.

2-[(4-Fluoro-1-naphthyl)methyl]-1-naphthoic Acid (III).—A stirred mixture of 15.0 g of I, 6 g of magnesium, 0.5 ml of methyl iodide, and 150 ml of absolute ether (freshly distilled over lithium aluminum hydride) was refluxed for 4 hr. The solution was decanted from the excess magnesium and poured onto 200 g of crushed solid carbon dioxide in 250 ml of ether. The mixture was allowed to stand overnight and then acidified with 18% hydrochloric acid. The ethereal layer was concentrated and 10% potassium carbonate solution was added. The brown, oily potassium salt of III was dissolved in hot warm water and freed from a small quantity of neutral material by extraction with ether and benzene. Acidification with dilute hydrochloric acid and recrystallization of the precipitate from ethanol (decolorizing carbon) and toluene afforded 12.8 g (94%) of III as a white powder, mp 218–219°.

Anal. Calcd for $C_{22}H_{15}FO_2$: C, 80.0; H, 4.5; F, 5.8. Found: C, 80.3; H, 4.5; F, 5.9.

5-Fluorodibenz[*a,h*]anthr-7(14H)-one (IV).—The foregoing acid (III) (3.5 g) was treated with 100 ml of anhydrous hydrofluoric acid. When the hydrofluoric acid had evaporated (15 hr), the residue was washed with 10% potassium carbonate solution and recrystallized from toluene. Thus was obtained 3.17 g (96%) of IV as dark olive-green needles which turned brown above 200° and decomposed at about 240°. The product is a mixture of the anthrone and the isomeric anthrol, as indicated by the infrared absorption spectrum: $\nu_{\max}^{\mathrm{KBr}}$ 3410 (OH), 1645 (C=O), 1060 cm^{-1} (CF).

Anal. Calcd for $C_{22}H_{13}FO$: C, 84.6; H, 4.2; F, 6.1. Found: 84.7; H, 4.4; F, 6.4.

5-Fluorodibenz[*a,h*]anthracene (V).—A mixture of 2.8 g of the foregoing compound, 5 g of zinc dust (activated with copper sulfate), 250 ml of 8% sodium hydroxide solution, and 30 ml of toluene was refluxed for 24 hr with agitation. The toluene layer was separated and the aqueous solution and the undissolved zinc was extracted four times with 50 ml of hot benzene. The combined organic solutions were shaken for 3 min with 10% hydrochloric acid and washed successively with water, sodium hydrogen carbonate solution, and water. The concentrated solution was chromatographed on alumina, benzene–hexane (5:1) serving as eluent. Recrystallization of the first fraction from ethanol and benzene gave 2.18 g (82%) of V as very pale yellow, oblong crystals, mp 213–214° (sublimation occurs close to the melting point).

Anal. Calcd for $C_{22}H_{13}F$: C, 89.2; H, 4.4; F, 6.4. Found: C, 89.4; H, 4.5; F, 6.8.

The 2,4,7-trinitrofluorenone complex was prepared in, and recrystallized from, benzene as orange needles, mp 254–256° (with some sintering above 250°).

Anal. Calcd for $C_{35}H_{18}FN_3O_7$: C, 68.8; H, 2.9; F, 3.1; N, 6.9. Found: C, 68.9; H, 3.2; F, 3.2; N, 6.4.

1-Bromo-2-methyl-4-nitronaphthalene (VIII).—The following procedure gave a better yield than the methods described by Veselý and Kapp.[8]

A mixture of 166 g of 2-methyl-4-nitro-1-naphthylamine hydrobromide,[9] 250 ml of concentrated hydrobromic acid and 150 ml of water was diazotized with 41 g of sodium nitrite in 100 ml of water. The mixture was stirred for 2 hr at 0–5°, and urea was added, in order to destroy the excess nitrous acid. The suspension of the diazonium salt was then added gradually to a solution of 80 g of cuprous bromide in 200 ml of concentrated hydrobromic acid. The mixture was heated slowly to 100° and held at this temperature for 10 min. Two liters of water was then added and the precipitate was taken up in 1.5 l. of hot benzene. After concentration of the benzene solution, the dark residue was distilled. The yellow distillate, bp 176–178° (2 mm), was recrystallized from ethanol. Thus was obtained 128 g (82%) of yellow needles, mp 100–101° (lit.[8] mp 100–101°).

1-Bromo-2-methyl-4-naphthylamine (IX).—The reduction of VIII was effected by stirring 50 g of VIII with 100 g of iron dust, 10 g of ferrous sulfate, and 1 l. of water for 2 hr at reflux temperature. To the hot solution, 500 ml of benzene was added and stirring was continued for 10 min. The mixture was filtered, the benzene layer was removed, and the unreacted iron was washed several times with boiling benzene. Concentration of the combined organic solutions resulted in a dark oil which was taken up with cyclohexane, leaving a red by-product undissolved. Upon cooling, 36.5 g (82%) of IX separated as thick colorless crystals, mp 78–78.5°. The amine turns light tan when exposed to air and light; it cannot be distilled under reduced pressure (0.2 mm) without decomposition.

Anal. Calcd for $C_{11}H_{10}BrN$: C, 55.9; H, 4.2; N, 5.9. Found: C, 55 9; H, 4.1; N, 6.0.

N-(4-Bromo-3-methyl-1-naphthyl)acetamide (XI) was obtained in quantitative yield from the amine and acetic anhydride in benzene as colorless needles, mp 227–228° (from large quantities of benzene). Rapid sublimation was observed above 200°.

Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.1; H, 4.3; Br, 28.8; N, 5.0. Found: C, 56.2; H, 4.5; Br, 28.4; N, 5.2.

1-Bromo-4-fluoro-2-methylnaphthalene (X).—The amine hydrochloride prepared from IX (71 g) was diazotized in 600 ml of aqueous hydrochloric acid with 22 g of sodium nitrite at 0°. The mixture was stirred at 3–5° for 2 hr and a small quantity of solid was removed by filtration. Excess of nitrous acid was decomposed with urea and 100 ml of 50% fluoroboric acid was added. The mixture was stirred at 0° for 30 min and filtered, and the precipitate was washed with 1% fluoroboric acid, absolute ethanol, and dry ether. The crude dry diazonium fluoroborate (90 g, 97%) yellow-tan crystals, melted at 112° dec. After decomposition was completed, the residue was taken up in benzene and washed with 10% sodium hydroxide solution and water. Distillation at 103–104° (1.5 mm) and recrystallization of the distillate from methanol afforded 46 g (64%, based on IX, or 66%, based on the diazonium fluoroborate) of long, colorless needles, mp 72–72.5°. The compound sublimes below the melting point.

Anal. Calcd for $C_{11}H_8BrF$: C, 55.2; H, 3.3; F, 7.9. Found: C, 55.1; H, 3.4; F, 8.2.

The 2,4,7-trinitrofluorenone complex was recrystallized from benzene and formed orange clusters, mp 149–152°.

Anal. Calcd for $C_{24}H_{13}BrFN_3O_7$: C, 52.1; H, 2.3; Br, 14.5; F, 3.4; N, 7.6. Found: C, 51.9; H, 2.2; Br, 14.1; F, 3.4; N, 7.5.

1-Bromo-2-bromomethyl-4-fluoronaphthalene (VII).—A mixture of 38.0 g of X, 28.5 g of N-bromosuccinimide, 200 ml of carbon tetrachloride, and 0.1 g of benzoyl peroxide was refluxed for 90 min. The succinimide was filtered off from the hot solution

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(6) M. S. Newman and A. I. Kosak, *J. Org. Chem.*, **14**, 375 (1949).

(7) W. H. D. Boyes, J. L. Grieve, and H. G. Rule, *J. Chem. Soc.*, 1833 (1938).

(8) V. Veselý and J. Kapp, *Rec. Trav. Chim.*, **44**, 360 (1925).

(9) R. Lesser, *Ann.*, **402**, 1 (1914).

and the filtrate was concentrated. The product was recrystallized from cyclohexane, affording 40 g (79%) of thick, colorless prisms, mp 120–121°.

Anal. Calcd for $C_{11}H_7Br_2F$: C, 41.5; H, 2.2; F, 6.0. Found: C, 41.7; H, 2.3; F, 6.4.

1,2-Di(1-bromo-4-fluoro-2-naphthyl)ethane (XII).—To the Grignard reagent prepared from 1.59 g of 1-bromo-4-fluoronaphthalene, 0.122 g of magnesium and 50 ml of ether, 1.59 g of VII in 100 ml of benzene was added. The ether was removed by distillation and the solution was refluxed for 20 hr. Dilute hydrochloric acid was added and the organic layer was concentrated. The sparingly soluble solid that separated was triturated with cold benzene and recrystallized from xylene, yielding 0.219 g (9%) of XII as shiny, colorless needles, mp 221.5–222.5°.

Anal. Calcd for $C_{22}H_{14}Br_2F_2$: C, 55.5; H, 2.9; F, 8.0. Found: C, 55.5; H, 3.1; F, 8.0.

The remaining material, *i.e.*, that which dissolved in cold benzene during the trituration, was separated by fractional crystallization from cyclohexane into 1.21 g of starting material VII and 0.83 g of X.

Attempted Coupling of 4-Fluoro-1-naphthylmagnesium Bromide and VII.—In analogy with the previous experiment, 28 g of 1-bromo-4-fluoronaphthalene in 75 ml of ether was treated with 3 g of magnesium. Benzene (75 ml) was added and the ether was distilled off. Powdered VII (17.5 g) was then added and the mixture was refluxed for 6 hr. Decomposition of excess Grignard reagent with 10% hydrochloric acid, followed by removal of half of the organic solvents, caused fluffy, white needles to separate. Upon recrystallization from xylene 9.0 g (69%) of XII was obtained, mp and mmp 221.5–222.5°. The benzene-soluble material was fractionated at 0.5 mm. The fraction boiling at 180–230° was triturated with hexane and recrystallized from toluene (carbon), yielding 6.5 g of 4,4′-difluoro-1,1′-binaphthyl, mp 177–177.5° (lit.[4] mp 176–177°). Under analogous conditions, phenylmagnesium bromide failed equally to couple with VII. Together with much starting material, a 2% yield of XII was obtained.

1-(*o*-Bromobenzyl)-4-fluoronaphthalene (XIII).—A quantity of 22.5 g of 1-bromo-4-fluoronaphthalene was treated with 2.43 g of magnesium in 150 ml of ether. After addition of 150 ml of benzene the ether was distilled off and 12.5 g of *o*-bromobenzyl bromide in 100 ml of benzene was added. The mixture was refluxed for 6 hr with agitation, decomposed with ice and dilute hydrochloric acid, and worked up in the usual manner. The residue was fractionated at 0.5 mm and the oil boiling at 182–200° was chromatographed on alumina (hexane serving as eluent). Recrystallization of the first fraction from ethanol and then from hexane afforded 11.9 g (76%) of XIII as colorless cubes, mp 44.0–44.5°.

Anal. Calcd for $C_{17}H_{12}BrF$: C, 64.8; H, 3.8; Br, 25.4; F, 6.0. Found: C, 64.5; H, 3.7; Br, 25.4; F, 6.3.

Its structure was proved by carbonation of the corresponding magnesium compound, giving a 84% yield of *o*-(4-fluoro-1-naphthylmethyl)benzoic acid (XIV), mp 180–181° (from nitromethane) (lit.[4] mp 176–177°). The product did not depress the melting point of an authentic sample.

4-Fluorobenzo[*a*]pyrene and 8-Fluorobenz[*l*]aceanthrylene

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Starting from 12-cyanomethyl-5-fluorobenz[*a*]anthracene (I), (5-fluoro-12-benz[*a*]anthryl)acetaldehyde (V) has been prepared. Its cyclodehydration gave 4-fluorobenzo[*a*]pyrene (VI) and 8-fluorobenz[*l*]aceanthrylene (VII).

Several fluorine derivatives of carcinogenic polycyclic hydrocarbons have been described.[1]

In the present paper the 4-fluoro derivative of the powerful carcinogen benzo[*a*[pyrene has been added to this list. A suitable starting point appeared to be the 12-cyanomethyl-5-fluorobenz[*a*]anthracene (I), which has been prepared before in this laboratory.[1] At that time it had already been pointed out that alkaline hydrolysis of nitrile I was practically impossible—probably for steric reasons. In repeated experiments traces (less than 1%) of an acidic material have been obtained, mp 274–275°, which is not the desired acid (II), although it has the same elementary analysis. Its structure has not been elucidated.

The hydrolysis of I to acid II has been accomplished in 88% yield by prolonged (150 hr) heating with boiling saturated alcoholic hydrogen chloride solution and saponification of the crude ester. The acid gave, with diazomethane, the methyl ester III in quantitative yield.

This ester was reduced with lithium aluminum hydride to the corresponding primary alcohol (IV) and the latter oxidized to the aldehyde V by the chromic acid anhydride–pyridine complex. No other method gave us V; the Stephen reduction of I and the reduction of the chloride of II with lithium tri(*t*-butoxy)-aluminum hydride[2] failed.

From the aldehyde V, a very simple reaction led directly to the desired 4-fluorobenzo[*a*]pyrene (VI), *viz.* the treatment of the (crude) aldehyde with polyphosphoric acid. This is a novel application of Bradsher's synthesis of 9-alkylphenanthrenes from (2-biphenylyl)alkylacetaldehydes[3] to the transformation of the benz[*a*]anthracene into the benzo[*a*]pyrene system and opens many interesting possibilities.

In fact, two isomeric fluorinated hydrocarbons have been formed in this reaction: 4-fluorobenzo[*a*]pyrene (VI) in 25% yield and 8-fluorobenz[*l*]aceanthrylene (VII); both gave well-defined trinitrofluorenone complexes.

The structure of VI was easily established by comparison of its electronic spectrum with that of benzo-[*a*]pyrene:[4] the two are practically identical (Table I).

As to the isomeric fluoro compound VII, the orange color already led us to assume that by a very obvious reaction a derivative of acenaphthylene had been formed. Here again, proof was obtained by comparison of the spectrum of VII with that of benz[*l*]-aceanthrylene (VIII) (Table I). The hydrocarbon VIII which had not been described before, was obtained by dehydrogenation, with chloranil, of its dihydro derivative (IX).[5]

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[1] See, for further references, E. D. Bergmann and J. Blum, *J. Org. Chem.*, **27**, 527 (1962); and M. S. Newman and S. Blum, *ibid.*, **29**, 1414 (1964).

[2] H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **80**, 5372 (1958); H. C. Brown and B. C. Subba Rao, *ibid.*, **80**, 5377 (1958).

[3] C. K. Bradsher and W. J. Jackson, *ibid.*, **76**, 734 (1954).

[4] E. Clar, "Polycyclic Hydrocarbons," Vol. 2, Academic Press Inc., New York, N. Y., 1964, p 135.

[5] L. F. Fieser and A. M. Seligman, *J. Am. Chem. Soc.*, **57**, 2174 (1935).