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SYNTHESIS OF FLUORINATED DERIVATIVES OF DIBENZO[AH]PYRENE

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SUMMARY

Several fluoro derivatives of the potent carcinogenic hydrocarbon dibenzo[ah]pyrene (dibenzo[b,def]chrysene), hitherto unreported in the literature, were synthesized as a part of a project designated to investigate the mode of action of hexacyclic aromatic carcinogens. 3,10-Difluoro-DB[ah]P was synthesized from 1,5-dichloro- 4,8-bis(p-fluorobenzoyl) naphthalene by a base-catalyzed cyclization followed by reduction. 3-Fluoro-DB[ah]P was synthesized from 1,5-dichloro-4-benzoyl-8-(p-fluorobenzoyl)naphthalene; and 2-fluoro-DB[ah]P (together with a small amount of the 4-isomer) was formed by $AlCl_3$-catalyzed cyclization of 3-(m-fluorobenzoyl)benzanthrone. Cyclization of 1,5-dichloro-4,8-di(m-fluorobenzoyl)-naphthalene resulted in a mixture of three isomeric difluoro-DB[ah]P-diones and consequently of the related difluoro-DBP's. Reduction of 1,8-difluoro DB[ah]P- 7,14-dione, obtained from 1,5-dichloro-4,8-di(o-fluorobenzoyl)naphthalene, led to a mixture of 1,8-difluoro DB[ah]P, 1-fluoro-DB[ah]P and DB[ah]P.

INTRODUCTION

The hexacyclic hydrocarbon dibenzo[a,h]pyrene (dibenzo[b,def]chrysene, I), which occurs in coal tar [1a], polluted urban air [1b], exhaust fumes from internal combustion engines and in the neutral fraction of cigarette

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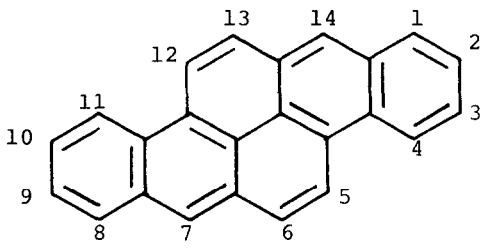
smoke [1c], is one of the most potent known carcinogens on skin [2].



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However, little is known about its metabolism. A study by Waterfall and Sims [3] of its *in vitro* metabolic activation by rat liver microsomes showed that metabolism did not occur in the symmetry-equivalent K-region double bonds (5,6 and 12,13), but the structure of the metabolite was not established. It was inferred that activation took place in the angular benzo ring [3]. This is consistent with the more recently proposed, and widely accepted, bay-region theory of polycyclic aromatic hydrocarbon (PAH) carcinogenicity [4], according to which dibenzo[a,h]pyrene (DB[a,h]P) would be anticipated to form, first, an arene oxide at the 1,2-bond, then a 1,2-dihydro-1,2-dihydroxy-DB[a,h]P, and ultimately a 1,2-dihydrodiol-3,4-epoxide. Our simple Hückel molecular orbital calculations designed to model progression of PAH through the presumed metabolic sequence, indicated that the predicted ease of epoxidation at the 1,2-bond, as well as the stabilities of the cations derived from the arene oxide and the 1,2-dihydrodiol-3,4-epoxide *via* oxirane ring-opening, placed DB[a,h]P in the range of expected strong carcinogens [5]. Subsequently, Lehr *et al.* [6] synthesized trans -1,2-dihydro-1,2-dihydroxy-DB[a,h]P and found it to be highly mutagenic in the Ames assay.

Despite the accumulation of circumstantial evidence favoring metabolic activation of DB[a,h]P in the bay-region benzo rings, it has been pointed out that, owing to its very low ionization potential (7.00 eV), activation may well occur

via a sequence involving one-electron oxidation of the hydrocarbon [7]. Reaction of a nucleophile with the radical cation derived from DB[a,h]P would be expected to take place at the 'peri' positions (7 and 14).

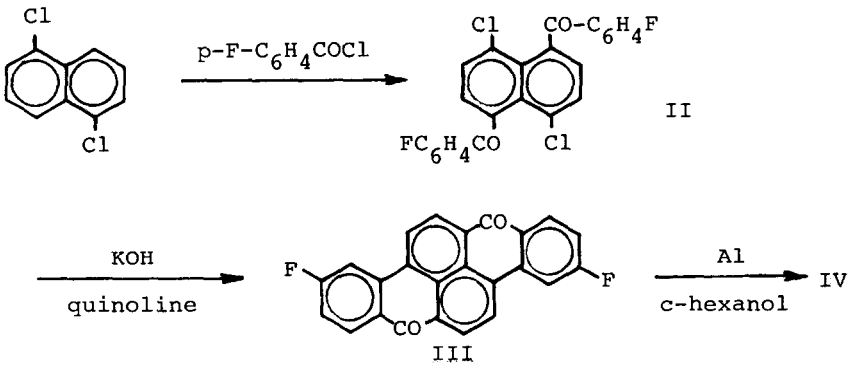
To distinguish between these two alternatives, we have applied the fluorine substitution methodology (FSM) [8] to the study of DB[a,h]P carcinogenesis, and report here syntheses of several derivatives of DB[a,h]P fluorinated in one or both angular benzo rings, some observations on their ionization potentials, and preliminary results of carcinogenicity tests [9].

RESULTS

Syntheses of Fluorinated Dibenzo[a,h]pyrenes

3,10-difluorodibenzo[a,h]pyrene

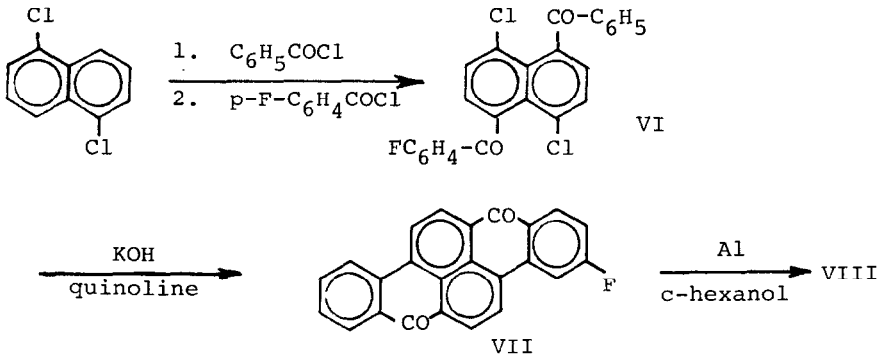
3,10-difluoro-DB[a,h]P (IV) was synthesized by the Friedel-Crafts reaction of p-fluorobenzoyl chloride with 1,5-dichloronaphthalene, yielding 1,5-dichloro-4,8-bis(p-fluorobenzoyl)naphthalene (II). Treatment of II with potassium hydroxide in quinoline under reflux [10] afforded the dione III, which was reduced to 3,10-difluoro-DB[a,h]P with aluminum and cyclohexanol.



3-Fluorodibenzo[a,h]pyrene

3-Fluoro-DB[a,h]P (VIII) was prepared in a similar manner. 1,5-Dichloronaphthalene was condensed successively with one molar equivalent each of benzoyl chloride and p-fluorobenzoyl

chloride to give, respectively, 1,5-dichloro-4-benzoylnaphthalene (V) and 1,5-dichloro-4-benzoyl-8-(p-fluorobenzoyl) naphthalene (VI). Cyclization with KOH in refluxing quinoline gave 3-fluoro-DB[a,h]P-7,14-dione (VII), which was in turn reduced (Al/cyclohexanol) to VIII.



An attempt to prepare VIII by introducing, first, the p-fluorobenzoyl group, then benzoyl, under a variety of experimental conditions failed to give produce.

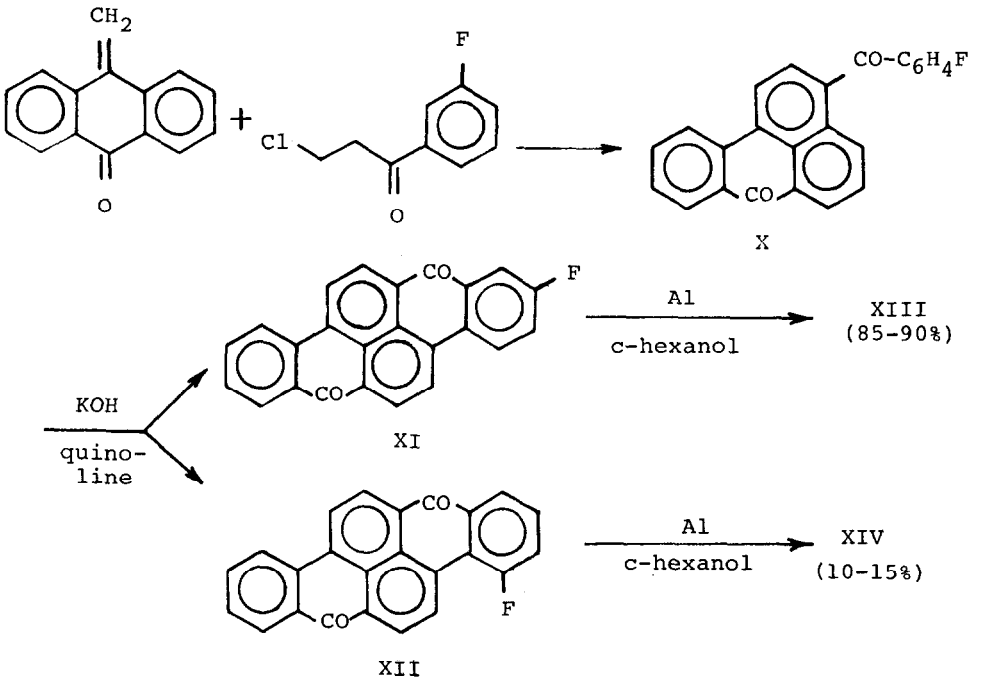
A prior attempt to prepare VIII involved condensation of 10-methyleneanthrone with β-chloro-p-fluoropropiophenone, affording 3-(p-fluorobenzoyl)benzanthrone (IX). However, in contrast to our experience with the isomeric 4-(p-fluorobenzoyl)benzanthrone, which cyclizes readily in a melt of $AlCl_3$, KCl and NaCl at 125° [11], IX failed to give the corresponding dione, even at high temperatures.

Attempted Preparation of 2-Fluoro-DB[a,h]P

Placement of the fluorine proved critical to the success of the cyclization. Thus, condensation of 10-methyleneanthrone with the hitherto unknown β-chloro-m-fluoropropiophenone (prepared from bis(m-fluorophenyl)cadmium and β-chloropropionyl chloride) yielded 3-(m-fluorobenzoyl)benzanthrone (X), which underwent cyclization in an $AlCl_3$-NaCl melt at 180-200° to afford a mixture* of 2-fluoro-DB[a,h]P-7,14-dione (XI,

*These proportions were inferred from HPLC and NMR analysis of the corresponding fluoro-DB[a,h]P product mixture (see below), the diones being too insoluble for spectral characterization.

85-90%) and 4-fluoro-DB[a,h]P-7,14-dione (XII, 10-15%). Reduction of the dione mixture (Al/cyclohexanol) gave a mixture of 2-fluoro-DB[a,h]P (XIII) and 4-fluoro-DB[a,h]P (XIV).



The UV spectrum of the mixture of XIII and XIV is virtually identical with those of DB[a,h]P and its other fluoro derivatives; neither λ_{max} nor the molar absorptivities are significantly affected. HPLC analysis (reversed phase C-18 column; acetonitrile-water gradient) showed it to contain two components in a ratio of about 87:13. The 270 MHz proton NMR spectrum showed 2-fluoro-DB[a,h]P to be the major product. We infer the minor component to be the 4-fluoro isomer. Extreme insolubility problems have thus far impeded preparative separation and complete characterization of the individual isomers. However, the fluorine-19 NMR spectrum of the mixture revealed two resonances downfield from external C_6F_6 (ratio ca. 1:4) whose shifts are consistent with expectation.

Attempted Synthesis of 2,9-Difluoro-DB[a,h]P

Our initial work on the synthesis of 2-fluoro-DB[a,h]P appeared to have shown cyclization affording a single product. Based on this indication, we attempted synthesis of 2,9-difluoro-DB[a,h]P *via* a double cyclization. Reaction of 1,5-dichloronaphthalene with excess m-fluorobenzoyl chloride in the presence of aluminum chloride gave 1,5-dichloro-4,8-bis(m-fluorobenzoyl)naphthalene, which upon treatment with KOH and quinoline afforded a mixture of three isomeric difluorodiones. Reduction (Al/cyclohexanol) gave a product deduced to contain the DB[a,h]P chromophore on the basis of its UV spectrum. HPLC analysis showed it to consist of three components (relative amounts ca. 6:3:1), presumably 2,9-difluoro-DB[a,h]P, 2,11-difluoro-DB[a,h]P and 4,11-difluoro-DB[a,h]P. The 270 MHz proton NMR spectrum confirmed the presence of a mixture, but could not be further analyzed. Insolubility problems prevented preparative separation and characterization of the constitutents.

Attempted Synthesis of 1,8-Difluoro-DB[a,h]P

o-Fluorobenzoyl chloride was condensed with 1,5-dichloronaphthalene, giving 1,5-dichloro-4,8-di(o-fluorobenzoyl)-naphthalene (XV). The latter, on treatment with KOH/quinoline, underwent cyclization to a dione, presumed to be 1,8-difluoro-DB[a,h]P-7,14-dione (XVI).* However, reduction of XVI under a variety of conditions afforded, not the expected 1,8-difluoro-DB[a,h]P, but a complex mixture whose extreme insolubility prevented isolation of its constituents. Mass spectral analysis of the mixture revealed a peak at m/e 328, consistent with a difluoro-DB[a,h]P, along with two other peaks of comparable intensity at m/e 320 and m/e 302, most probably 1-fluoro-DB-[a,h]P and DB[a,h]P.

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*The compound was characterized as a dione by development of a red color when it dissolved in sodium hydrosulfite and by its extremely high melting point (>300°C). Moreover, elemental analysis was consistent with the formula $C_{24}H_{10}O_2F_2$ (see Experimental section).

NMR Spectra of Fluorinated DB[a,h]Ps

The structures of 2-fluoro-, 3-fluoro and 3,10-difluoro-DB[a,h]P were established by computer simulation of their proton NMR spectra at 79.5 and 270 MHz and comparison with those of DB[a,h]P. At 270 MHz, the proton NMR spectrum of DB[a,h]P is well-resolved, nearly first-order, and easily assignable. The bay-region protons H-4* and H-9 resonate at δ8.99 (broad doublet, J=8.7 Hz) and δ8.94 (sharp doublet, J=9.4 Hz), respectively, while the mesoanthracenic proton H-7 occurs as a singlet at δ8.65. At somewhat higher field, H-6 appears as one half of an AB quartet (δ8.31; J=9.4), and H-1 gives rise to a broadened doublet at δ8.29 (J=8.7). At highest field, H-2 (δ7.75) and H-3 (δ7.81) appear as a complex multiplet.

Incorporation of fluorine leads to an upfield shift of protons ortho to it of between 0.2 and 0.5 ppm and, in the monofluorinated derivatives, to a lifting of the degeneracies of the otherwise symmetry-equivalent proton pairs. Chemical shift assignments are summarized in Table I.

The upfield shift of protons ortho to fluorine is variable and appears to increase with increasing carbon-carbon π-bond order. Thus, in 2-fluoro-DB[a,h]P, H-1 experiences a greater upfield shift (-0.5 ppm; bond order 0.72) than does H-3 (-0.2; bond order 0.61), while in 3-fluoro-DB[ah,]P, H-4 is shifted further upfield (-0.44 ppm; bond order 0.71) than H-2 (-0.2 ppm; bond order 0.61). We have observed similar behavior in the isomeric DB[a,i]P series. [12]

While most other shifts are unaffected by fluorine substitution, significant variations are observed in several cases. The K-region protons (H-5,12) which form part of the bay region are shifted upfield by 0.18 ppm in 3,10-DB[a,h]P, while only one (presumably H-5) is so shifted in 3-fluoro-

*Owing to the symmetry of DB[a,h]P, H-4 and H-11 are equivalent; here, as in the other proton-positions, only one member of each pair is listed.

TABLE 1

Proton Chemical Shifts of Fluorinated Dibenzo[a,h]pyrenes

Proton	DB[a,h]P	2-fluoro	3-fluoro	3,10-difluoro
1	δ 8.29	δ7.81	δ8.28	δ8.28
2	7.75	--	7.55	7.55
3	7.81	7.59	--	--
4	8.99	8.89	8.56	8.56
5	8.94	9.02	8.76	8.76
6	8.31	8.32	8.30	8.30
7	8.65	8.69	8.65	8.65
8	8.29	8.30	8.29	8.28
9	7.75	7.75	7.75	7.55
10	7.81	7.81	7.81	--
11	8.99	8.97	8.99	8.56
12	8.94	9.02	8.94	8.76
13	8.31	8.35	8.31	8.30
14	8.65	8.58	8.65	8.65

TABLE 2

Ionization Potentials of Fluorinated Dibenzo[a,h]pyrenes

Compound	Experimental (UV)	Calculated (SCF-MO)
DB[ah]P	7.00 eV	6.79 eV
2-fluoro	7.02	6.77
3-fluoro	---	6.75
3,10-difluoro	7.02	6.72

DB[a,h]P. In the 2-fluoro isomer both H-5 and H-12 experience nearly identical deshieldings of -0.08 ppm. Similarly, the mesoanthracenic protons (H-7 and H-14) are virtually degenerate and unshifted in 3-fluoro-DB[a,h]P, but differ by 0.11 ppm in the 2-fluoro isomer. If these fluorine-induced shifts are indicative of electron density changes, then fluorine appears capable of exerting electronic effects across considerable distances, as we found in our studies of deuteriodeprotonation of the fluoro-DB[a,i]Ps. [13]

Ionization Potentials of Fluorinated DB[a,h]Ps

The UV absorption frequencies of polycyclic aromatic hydrocarbons are known to correlate linearly with their ionization potentials [7,14]. We have found this same correlation to extend to fluoroaromatics as well [15], and have thus determined the ionization potentials of 2-fluoro-, 3-fluoro- and 3,10-difluoro-DB[a,h]P. The results (Table II) indicate fluorine substitution to have a negligible effect on the ease of ionization of DB[a,h]P, in good agreement with the results of self-consistent field molecular calculations [15].

Effect of Fluorine on Carcinogenic Activity of DB[a,h]P

3,10-Difluoro-DB[a,h]P and 3-fluoro-DB[a,h]P were tested for activity as tumor initiators on mouse skin, along with DB[a,h]P, at the 0.2 mg dose level [17]. Fluorination of both bay-region benzo rings of DB[a,h]P leads to almost total loss of activity, while blockage of only one of the two bay-region benzo rings has essentially no effect on carcinogenicity, consistent with expectation based on the bay-region theory of PAH carcinogenesis. However, the virtual identity of the ionization potentials indicates that ease of ionization cannot be a determinative step in metabolic activation, as the one-electron oxidation hypothesis would seem to require.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary apparatus, and were uncorrected.

Elemental analyses were performed by Guelph Chemical Laboratories, Ontario.

NMR spectra were obtained on one of two instruments: a Varian Associates FT-80A Fourier transform NMR spectrometer (^{13}C, 20.0 MHz; ^{1}H, 79.5 MHz; ^{19}F, 74.8 MHz) or a Bruker WH-270 Fourier transform NMR spectrometer (^{1}H, 270 MHz).

Mass spectra of the supposed 1,8-difluoro DB[a,h]P were taken on a Finnigan 3200D quadrupole mass spectrometer by Cambridge Analytical Associates, Watertown, Massachusetts.

UV spectra were taken on a Cary 14 UV-VIS spectrometer in 1 cm cells, using ethanol as solvent.

1,5-Dichloro-4-benzoylnaphthalene (V), nc

A mixture of anhydrous aluminum chloride (1.4g) and freshly distilled benzoyl chloride (1.4g) was melted on a soft flame. The mixture was cooled and then refluxed with carbon disulfide (8 ml) for 10-15 minutes and cooled. 1,5-Dichloronaphthalene (2 g) was added and the mixture was refluxed for 2-3 hours. It was then cooled and decomposed with ice and hydrochloric acid and filtered. The solid residue was washed with dilute sodium hydroxide solution (5%), water, and dried. The solid product was purified by passing through a short-packed alumina column. It was recrystallized from a ether-hexane mixture, yield 2.6 g, (86%), M.P. 111°C.

Anal. Calcd. for $C_{17}H_{10}Cl_2O$: C, 67.79; H, 3.34.
Found: C, 67.45; H, 3.31%.

1,5-Dichloro-4(benzoyl)-8-(p-fluorobenzoyl)naphthalene (VI), nc

A mixture of (V) (1 g), $AlCl_3$ (2 g) and p-fluorobenzoyl chloride (1.5 g) was heated in an oil bath with stirring for 18 hrs at 160-180°. It was cooled and decomposed with ice and hydrochloric acid. The solid residue was filtered off and washed thoroughly with sodium hydroxide solution (5%) and then with water, dried, and recrystallized from CH_2Cl_2-ether. Yield 1.1 g (80%), M.P. 228.5°.

Anal. Calcd. for $C_{24}H_{13}Cl_2FO_2$: C, 68.10; H, 3.09; F, 4.49.
Found: C, 67.74, H, 3.35; F, 4.27%.

1,5-Dichloro-4,8-bis(p-fluorobenzoyl)naphthalene (II), nc

A mixture of anhydrous aluminum chloride (3.4 g) and p-fluorobenzoyl chloride was heated to a melt on a soft flame and cooled. Carbon disulfide (15 ml) was added to the solid mixture which was refluxed on a water bath for 20 minutes. The mixture was cooled and 1,5-dichloronaphthalene (2 g) was added to it. It was refluxed for 3-4 hours after which the carbon disulfide was distilled off. The solid was then heated in an oil bath maintained at 160-180° for 24 hrs. The reaction mixture was decomposed with ice-hydrochloric acid, filtered, and washed sequentially with 5% sodium hydroxide solution and water, then dried. The compound was purified by passing through a short-packed alumina column using CH_2Cl_2 as solvent, and recrystallized from methylene chloride-ether. Yield, 3.8 g, 84%; m.p. 21.8°.

Anal. Calcd. for $C_{24}H_{12}Cl_2F_2O_2$: C, 65.32; H, 2.74; F, 8.61.
Found: C, 65.07: H, 2.60; F, 8.42%.

3 Fluorodibenzo[b,def]chrysene-7,14-dione
(3-Fluoro-dibenzo[a,h]pyrene-7,14-dione, (VII), nc

A mixture of quinoline (20 ml), potassium hydroxide and (VI) (1.5 g) was refluxed for 15-20 minutes and then cooled. The mixture was steam distilled and then filtered. The orange-yellow residue so obtained was washed with water and the solid was treated with sodium hydrosulfite (4 g) in sodium hydroxide solution (4 g in 200 ml water) [16]. The deep red solution was filtered, then aerated. The residue was collected by filtration, washed with water, and dried. The orange-yellow solid so obtained was recrystallized from dichlorobenzene to yield the quinone VII (560 mg, 45%).

Anal. Calcd. for $C_{24}H_{11}FO_2$: C, 82.27; H, 3.16; F, 5.42.
Found: C, 82.16; H, 3.12: F, 5.28%.

3,10-Difluorodibenzo[b,def]chrysene-7,14-dione
(3,10-Difluorodibenzo[a,h]pyrene-7,14-dione, III), nc

This compound was prepared from II (as described above (II)) (for VII) in 40% yield, m.p. > 400°.

Anal. Calcd. for $C_{24}H_{10}F_2O_2$: C, 78.26; H, 2.73.
Found: C, 78.96; H, 2.74%.

3-Fluorodibenzo[b,def]chrysene
(3-Fluorodibenzo[a,h]pyrene, VIII), nc

A mixture of dried cyclohexanol (10 ml) and aluminum turnings (0.5 g) was refluxed with a catalytic amount of mercuric chloride [17]. To the opalescent solution so obtained, the quinone VII (100 mg), was added and the mixture was refluxed for 48 hrs. Cyclohexanol was removed by vacuum distillation and the residual cyclohexanol was removed by steam distillaion of the mixture in sodium hydroxide solution (5%, 100 ml). Sodium hydrosulfite (2 g) was added to the mixture which was then filtered, and the resulting precipitate washed with water and dried. The yellow solid so obtained was purified by column chromatography on a neutral alumina column using benzene as eluant. After removal of the solvent the solid was recrystallized from benzene to give yellow crystals. Yield 70 mg. (77%), m.p. 298-99°.

Anal. Calcd. for $C_{24}H_{12}F_2$: C, 89.98; h, 4.09; f, 5.93
Found: C, 90.27; H, 3.92; F, 5.73

3,10-Difluorodibenzo[b,def]chrysene, nc
(3,10-Fluorodibenzo[a,h]pyrene,IV) was prepared from III following the same procedure for VIII, in 60% yield. Recryst. from benzene, m.p. 318°C (dec).

Anal. Calcd. for $C_{24}H_{12}F_2$: C, 85.10; H, 3.57
Found: C, 85.43; H, 3.63%.

3-(p-Fluorobenzoyl)-7H-benz[de]anthracene-7-one(IX), nc

A mixture of 5.2 g of 10-methyleneanthrone [18] and 6.7 g of ß-chloro-p-fluoropropiophenone (Aldrich), 6 g of CH_3COOK and 35 ml of nitrobenzene was stirred and refluxed for 2.5 hours at 180-190°C. It became very dark. Upon cooling a solid mass precipitated and was filtered after triturating with methanol. Washing with methanol then with water gave 7.0 g of a yellow solid (yield 85%). Recrystallization from nitrobenzene or acetic acid gave yellow crystals, m.p. 225.5°C.

Anal. Calcd. for $C_{24}H_{13}FO_2$: C, 81.81; H, 3.72, F, 5.39
Found: C, 81.73; H, 3.92; F, 5.51%.

3-Chloro-1-(3-fluorophenyl)-1-propanone(β-chloro-m-fluoropropiophenone), nc

A solution of 17.5 g (0.1 mol. 11.2 ml) of mobromofluorobenzene in 50 ml anhydrous ether was added to 2.4 g magnesium in ether under N_2 with stirring. To complete the reaction, the mixture was refluxed for 30 minutes.

To this mixture was added 9.5 g of $CdCl_2$ in 20 ml benzene, and refluxing was continued for one hour. The ether was then distilled off and replaced by benzene, then 12.7 g (9.5 ml) of 3-chloropropionyl chloride in 30 ml benzene were added and the mixture was stirred for 2 hours at 25-35°.

After adding ice and H_2SO_4 the organic layer was separated, the water layer extracted with benzene and the combined benzene solutions washed with water and Na_2CO_3, then dried over Na_2SO_4, filtered and the benzene evaporated to give an oily residue which was purified by flash chromatography using CH_2Cl_2 as solvent for elution. After evaporation of the solvent, 6 g of the pure ketone were obtained (32% yield) as white crystals, M.P. 51-52°.

Anal. Calcd. for C_9H_8ClFO: C, 57.93; H, 4.32; Cl, 19.00; F, 10.18.
Found: C, 57.99; H, 4.33; Cl, 19.04; F, 10.29%.

3-(3-Fluorobenzoyl)-7H-benz[de]anthracene-7-one, nc (3-(m-fluorobenzoyl)benzanthrone,(X) was prepared from the above ketone (3.35 g) and 10-methyleneanthrone (2.6 g) by the same procedures described for the p-isomer. 3.0 g (73%) of a yellow substance were obtained. Recrystallization from nitrobenzene gave yellow crystals, m.p. 218-219°.

Anal. Calcd. for $C_{24}H_{13}FO_2$: C, 81.81; H, 3.72; F, 5.39.
Found: C, 81.63; H, 3.98; F, 5.28%.

2-Fluorodibenzo[b,def]chrysene-7,14-dione(XI) and 4-fluorodibenzo[b,def]chrysene-7,14-dione(XII):

Cyclization of 3-(m-fluorobenzoyl)benzanthrone(X) using $AlCl_3$ and NaCl at 180°-200° [17] yielded a mixture of two isomeric quinones, XI (85-90%) and XII(10-15%), which melted at 400°C (approximately).

Anal. Calcd. for $C_{24}H_{11}FO_2$: C, 82.28; H, 3.16, F, 5.42.
Found: C, 82.48; H, 3.08, F, 5.35%.

1,5-Dichloro-4,8-di(o-fluorobenzoyl)naphthalene(XV) was prepared from 1,5-dichloronaphthalene and o-fluorobenzoyl chloride in 85% yield. M.p. 258-9° (from CH_2Cl_2).

Anal. Calcd. for $C_{24}H_{12}Cl_2F_2O_2$: C, 65.32; H, 2.74; F, 8.61.
Found: C, 65.40; H, 2.68; F, 8.25%.

1,8-difluorodibenzo[b,def]chrysene-7,14-dione(XVI) was prepared from (XV) by KOH-quinoline cyclization in 30% yield. M.p. 362-3° (from xylene).

Anal. Calcd for $C_{24}H_{10}F_2O_2$: C, 78.26; H, 2.73; F, 10.31.
Found: C, 78.14; H, 2.98; F, 10.05.

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