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SYNTHESIS OF MONOFLUOROBENZO[c]PHENANTHRENES

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SUMMARY

Synthesis of 1-, 2-, 3- and 4-fluorobenzo[c]phenanthrenes by photocyclization of appropriate ß-naphth-1-yl fluorostyrenes is described. An improved synthesis of 6-fluorobenzo[c]phenanthrene was developed. Partial photochemical debromination occured upon cyclization of 2-bromo-7-fluorobenzo[c]phenanthrene.

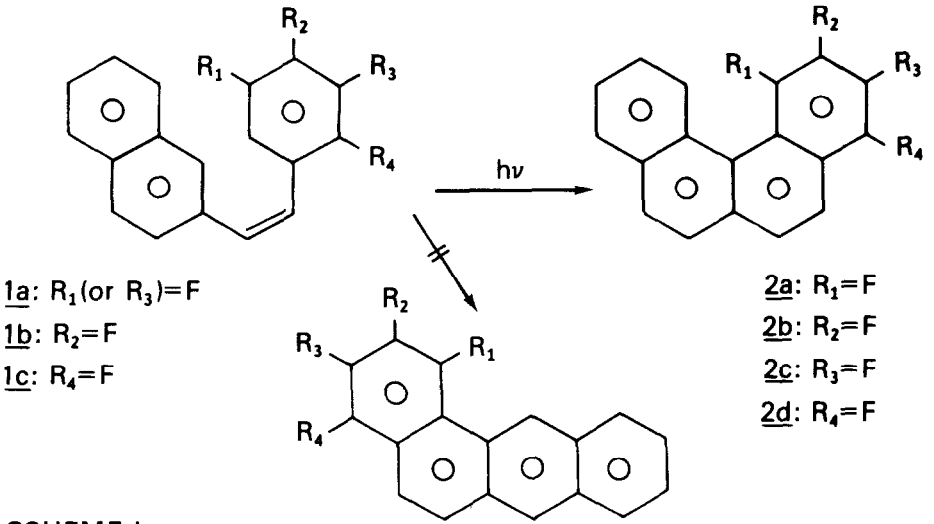
INTRODUCTION

In the past several years, considerable advances have been made in defining the metabolic activation pathways responsible for the carcinogenic activity of the polycyclic aromatic hydrocarbons (PAH s) [1,2]. Monofluorinated hydrocarbons have proved to be important tools in these studies. The presence of a fluorine substituent on either carbon of a formal aromatic double bond either blocks or greatly inhibits the rate of oxidative metabolism of an aromatic hydrocarbon to arene oxide at that position. [3,4]. Previously, Bergmann and Blum [5] had prepared benzo[a]anthracenes (BA) and benzo[c]phenanthrenes (B[c]Ph) fluorinated at their K-regions to test the K-region theory of the Pullmanns [6]. Newman and collaborators [7] prepared numerous fluoro and methyl substituted BA s in an attempt to explain the carcinogenicity of this PAH. Since the formulation of the 'bay-region' theory by Jerina et al. [3,8], fluorine-substituted PAH's have been used as a probe of this theory as well. The 'bay-region' theory predicts that diol epoxides on saturated, angular benzo-rings will have the highest chemical and biological activity when the epoxide forms part of a bay-region of the PAH. Fluorine substitution on the crucial benzo-ring should block the formation of bay-region diol epoxides, and thus markedly reduce the biological activity of the PAH. Boger et al. [9] found that 10-fluorodibenzo[a,i]-pyrene was much less tumorigenic than the parent hydrocarbon and that 2,10-difluoro derivative was noncarcinogenic in accord with the predictions of the theory. 1-fluoro-5-methyl- and 3-fluoro-5-methylchrysene are only marginally active as carcinogens whereas 6-fluoro-5-methyl and 9-fluoro-

5-methyl are as potent as 5-methylchrysene [10]. In the latter two hydrocarbons, the fluorine is not on the critical benzo-ring. Huberman and Slaga compared the tumor-initiating activity of dimethylbenzo[a]anthracene (DMBA) with several of its fluoro derivatives on mouse skin. The results clearly demonstrated the importance of the 'bay region'; i.e., 1- and 2-fluoro DMBA were much less active than DMBA [11] As part of our continuing investigations into the generality of the "bay-region" theory, we wished to study the four benzo-ring monofluorinated B[c]Ph. Although direct fluorination of B[c]Ph, perhaps with XeF_2 [12], might represent a convenient synthesis of F-B[c]Ph, separation and purification of the various isomers was anticipated to be difficult. Since a range of amino substituted B[c]Ph s were not readily available and since the Schiemann reaction was reported not to work on 5-amino-B[c]Ph [5], photocyclization of variously fluorinated β-naphth-1-yl styrenes was deemed the method of choice for the present syntheses. We report here the synthesis of 1-, 2-, 3-, 4- and 6-fluorobenzo[c]phenanthrene. The latter compound is particularly interesting for carcinogenesis studies since the fluorine atom is located on one of the two K-regions (5,6 bond). Retardation of metabolism at one K-region might be expected to enhance formation of bay-region diol epoxides and thereby to increase its carcinogenicity relative to B[c]Ph.

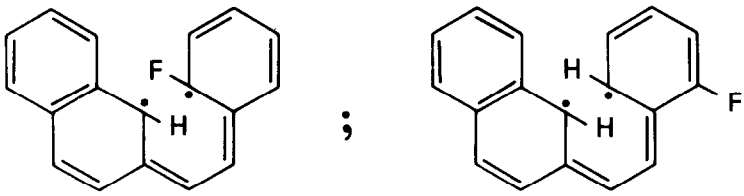
RESULTS and DISCUSSION

The synthesis of the benzo-ring monofluorobenzo[c]phenanthrenes is summarized in Scheme I.



SCHEME I

β-naphth-1-yl-fluorostyrenes were readily obtained by Wittig condensation between the triphenyl phosphorium salt of β-bromomethylnaphthalene and various isomeric fluorobenzaldehydes. Photocyclization in cyclohexane provided the desired fluorobenzo[c]phenanthrenes. Although photocyclization in two directions is possible [13], no evidence for the formation of BA derivatives (3) was found. In the case of 1a where two different diradical intermediates (see below) are possible, loss of fluorine to form B[c]Ph was not detected.

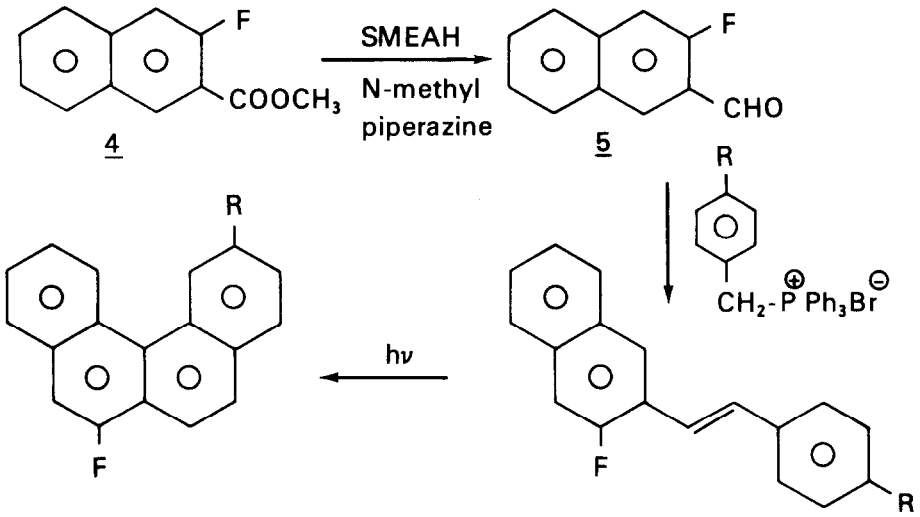


SCHEME II

When β-naphth-1-yl-3-fluorostyrene (1a) was irradiated, two products (2a and 2c) were obtained in the ratio of 1:2, respectively. Because of their great polarity differences (the out-of-plane fluorine atom probably increases the dipole moment of 2a compared to 2c), these two compounds could be separated easily by HPLC.

Previously, Marx and Bergmann [14] reported the synthesis of 6-fluorobenzo[c]phenanthrene. We improved their yield by using a slightly different route. Commercially available 2-amino-3-naphthoic acid was esterified quantitatively with 1-methyl-3-p-tolyltriazene [15] and the ester was caused to undergo a Schiemann reaction to form the fluoro ester 4. This ester was reduced quantitatively to 2-fluoro-3-naphthaldehyde by the novel reagent sodium bis-(2-methoxy ethoxy) aluminium hydride (SMEAH)-N-methylpiperazine system at RT [16]. Wittig reaction of 5 with benzyltriphenyl phosphonium chloride provided α-fluoro-β-naphth-1-yl-styrene (6a) which was photocyclized to the desired compound 7a.

Physical properties of the new β-naphth-1-yl-fluorostyrenes and fluorobenzo[c]phenanthrenes are summarized in Table I. ^{19}F-NMR spectra of the fluorobenzo[c]phenanthrenes show the expected coupling constants for ortho (J≃12Hz) and meta (J≃6 Hz) coupling. A through-space fluorine-hydrogen coupling (J ($F-H_{12}$) = 14 Hz) was observed in 1-fluoro B[c]Ph as previously reported by Mallory et al. [17]. Details of their synthesis have yet to be reported.



SCHEME III

In anticipation of a study of the metabolism of 6-fluorobenzo[c]phenanthrene, 2-bromo-7-fluorobenzo[c]phenanthrene was prepared in the hope that the bromine could be replaced by tritium to provide radioactive 6-fluoro benzo[c]phenanthrene. A mixture of cis- and trans-β-(3'-fluoronaphth)-yl-4-bromostyrene (obtained from p-bromobenzyltriphenyl phosphonium bromide and compound 5) was irradiated in cyclohexane to give the desired 2-bromo-7-fluorobenzo[c]phenanthrene [7b] along with 6-fluorobenzo[c]phenanthrene. When the photocyclization was monitored with time 7a was found to form at the expense of 7b. Irradiation of pure 7b lead to the formation of 7a. Although photochemical dehalogenations of aromatic bromides and iodides are well known [18], debromination of a very similar system, β-naphth-1-yl-4-bromostyrene, was not noted by LeGuen and Taylor [19]. Reduction of 7b with palladium on carbon in the presence of an excess of KOH and 1 atm of hydrogen cleanly produced 7a without detectable loss of fluorine or reduction of the aromatic system.

Initial studies on the metabolic activation of B[c]Ph and its five fluorinated derivatives with rat liver microsomes in the presence of S. typhimurium strains TA98 and TA100 have indicated that all of the compounds could be activated to mutagens. The most active substrate for causing these mutations was 3-F-B[c]Ph. In contrast, preliminary results of initiation-

promotion studies on mouse skin have indicated that 6-F-B[c]Ph is the most tumorigenic compound in the group (unpublished observations, A. Wood and W. Levin). This latter result is in accord with our expectation that the presence of the 6-fluoro group could result in a higher percentage of metabolic formation of the 3,4-dihydrodiol with a bay-region double bond. Preliminary studies of the metabolism of B[c]Ph (unpublished observations Y. Ittah and D. M. Jerina) have indicated that the 3,4-dihydrodiol is indeed one of the metabolites of this hydrocarbon.

EXPERIMENTAL

All melting points were determined on a Thomas Kofler-type micro hot plate and are uncorrected. ^{1}HNMR and ^{19}F-NMR spectra were run on a Jeol FX-100 instrument in $CDCl_3$ solution with Me_4Si or hexafluorobenzene as internal standards. UV spectra were recorded on a Cary 14 in spectrograde methanol. Mass Spectra were determined with a Finnigan 1015D and Hitachi RMU-6 spectrometers.

2-Fluoro-3-naphthaldehyde

Freshly distilled N-methylpiperazine (4ml, 36 mmol) in 10 ml of toluene was added dropwise at RT and under N_2 to 10 ml of SMEAH (Aldrich, 70%) in 10 ml of toluene. The clear, colorless solution was stirred until hydrogen evolution stopped. This solution was added dropwise at RT to a solution of 2-fluoro-3-carbomethoxynaphthalene (612mg, 3mmol) in 25 ml toluene. After 25 min water and acid were added and the products were extracted into benzene. The residue obtained after evaporation of solvent was recrystallized from methanol to provide colorless leaves; 465 mg (89%), mp 64-65°.

β-Naphth-2-ylfluorostyrenes

n-Butyl lithium (10 mmol) in 50 cc of ether was added under nitrogen to a stirred suspension of the triphenyl phosphonium salt of β-bromomethyl naphthalene (4.84 g, 10 mmol). The deep orange mixture was stirred overnight at RT and 1.24 g (10 mmol) of fluorobenzaldehyde was added. The color disappears upon the addition. After refluxing the mixture for one hour, the solids were filtered from the hot solution and washed with hot ether. Evaporation of the filtrates to dryness provided a white-creamy residue. Trituration of the residue with cold methanol left the trans-isomer as a solid and removed most of the cis-isomer. Yields and m.p. are summarized in Table I.

TABLE I

Physical properties of β-naphth-1-yl-fluorostyrenes and fluorobenzo[c]phenanthrenes

Compound	Yield[c] (mp)	UV in methanol λmax^{d} ($\varepsilon max \times 10^{-4}$)	^{19}F NMR in $CDCl_3$ δ(ppm); J(Hz)
trans-β-naphth-1-yl o-fluorostyrene(1a)	51(136-8[a])		43.89
trans-β-naphth-1-yl-m-fluorostyrene(1b)	79(127-8[b])		48.33
trans-β-naphth-1-yl-p-fluorostyrene(1c)	58(151-2[a])		47.60
trans-β-(3'-fluoronaphth)-1-yl-p-bromostyrene(6a)	52(148-9[a])		
4-fluoro B[c]Ph (2d)	48(73-75[b])	282(6.51), 272(5.30)	40.01; $J(H_2\text{-}F) = 6$; $J(H_3\text{-}F) = 11$
3-fluoro B[c]Ph (2c)	43(68-69[a])	282(7.18), 271(5.27)	46.82; $J(H_1\text{-}F) = 5.8$; $J(H_2\text{-}F) = 12$; $J(H_4\text{-}F) = 11$
2-fluoro B[c]Ph (2b)	56(67-8[b])	280(6.24), 270(4.20)	49.60; $J(H_1\text{-}F) = 12$; $J(H_3\text{-}F) = 12$; $J(H_4\text{-}F) = 6.5$
1-fluoro B[c]Ph (2a)	22(68-9[a])	282(6.68), 273(5.46)	62.98; $J(H_2\text{-}F) = 13$; $J(H_3\text{-}F) = 5.8$; $J(H_{12}\text{-}F) = 14$
6-fluoro B[c]Ph (7a)	64(72-73[a])	281(5.64), 272(5.09)	36.47; $J(H_5\text{-}F) = 10.8$
2-bromo-7-fluoro B[c]Ph (7b)	24[e](128-9[a])	285(7.23), 274(6.02)	
Benzo[c]phenanthrene		281(8.33), 270(5.83)	

a - recrystallized from methanol; b - recrystallized from n-hexane; c - yield of last step for isolated compound; d - λ units in nm; e - together with debrominated product (26%).

Analysis Cald. for $C_{18}H_{13}F$		C = 87.06	H = 5.28	F = 7.65
	Found 3a	C = 86.87	H = 5.49	F = 7.44
	3b	C = 86.83	H = 5.48	F = 7.73
	3c	C = 87.36	H = 5.42	F = 7.39

Monofluorobenzo[c]phenanthrenes

A solution of 250 mg (1 mmol) of the ß-naphthylstyrene and 20 mg iodine in cyclohexane (300 cc) was irradiated with a 250-W medium pressure mercury lamp through a quartz filter for 6 hr. Evaporation of the solvent provided a yellow oil which was dissolved in 10cc cyclohexane. This solution was filtered through a small silica gel column to remove polar by-products. The column was further eluted with 250cc n-hexane. The nearly pure residue after evaporation of the solvents was dissolved in hexane and repurified on a 25 cm Whatman Magnum-9 silica column using n-hexane as eluent: k'_{2a} = 2.1; k'_{2b} = 1.6; k'_{2c} = 1.5; k'_{2d} = 2.3. Each compound was further purified by elution from a 50 cm Whatman Magnum-9 ODS-2 column using acetonitrile as eluent.

Analysis Cald. for $C_{18}H_{11}F$		C = 87.77	H = 4.50	F = 7.72
	Found 4a	C = 87.67	H = 4.83	
		C = 87.52	H = 4.62	F = 7.63
		C = 87.54	H = 4.63	
		C = 87.97	H = 4.53	

When 6b was irradiated two products having the characteristic B[c]Ph chromophore (λmax $\sim$ 280 nm) were obtained. They could be cleanly separated on a Whatman ODS-2 column (50 x 0.92 cm) using acetonitrile as eluent (9.9 ml/min). By MS, NMR and comparison with an authentic sample the less retained produce (k' = 4.6) was identified as 6-fluorobenzo[c]phenanthrene (7a) while the more retained product (k' = 7.0) was the desired 2-bromo-7-fluorobenzo[c]phenanthrene (7b).

Hydrohalogenesis of 2-bromo-7-fluorobenzo[c]phenanthrene (7b)

To a stirred solution of 5 mg of 7b in 5cc methanol containing 2mg of KOH, 2mg of 10% palladium on charcoal were added. Hydrogen was passed at atmospheric pressure over the mixture for 30 min. The solids were filtered and washed with methanol. After evaporation of the methanol the residue was chromatographed on a Silica TLC plate (50 x 20 cm, 2mm thickness) to provide 4.5 mg (90%) of pure 6-fluorobenzo[c]phenanthrene.

m.p. 72-73°C (unchanged when mixed with an authentic sample of 7a). The MS shows no detectable formation of over reduced products.

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