Journal of Fluorine Chemistry, *24* (1984) 249–261

Received: March 28, 1983; accepted: June 4, 1983

SYNTHESIS AND ^{1}H AND ^{13}C NMR SPECTRA OF 7-FLUORO-, 9-FLUORO- AND 11-FLUORO-BENZO[B]FLUORANTHENES

D.J. SARDELLA*, P.K. GHOSHAL AND E. BOGER#

Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02167, (U.S.A.).

SUMMARY

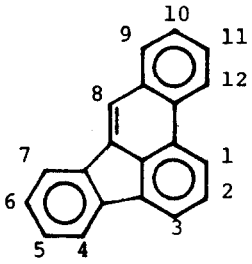
We have synthesized 7-fluoro-, 9-fluoro- and 11-fluoro-benzo[b]fluoranthene as part of a study designed to locate the molecular sites involved in the metabolic activation of the carcinogenic parent hydrocarbon. Analysis of the proton NMR spectra reveals the effect of fluorine substitution to be almost entirely localized in the substituted ring, the principal exception being a strong deshielding of opposing protons in sterically crowded sites (i.e., peri or pseudo-bay regions).

INTRODUCTION

In recent years, numerous studies of the *in vitro* metabolic activation of polycyclic aromatic hydrocarbons have supported the bay-region theory of carcinogenicity. [1] However, virtually all studies have involved alternant π-systems, with almost no attention having been given to nonalternant systems, which differ from alternant aromatics both in shape and in their electron density distributions, and which generally exhibit considerably greater reactivity. [2]

#Deceased April 30, 1983.

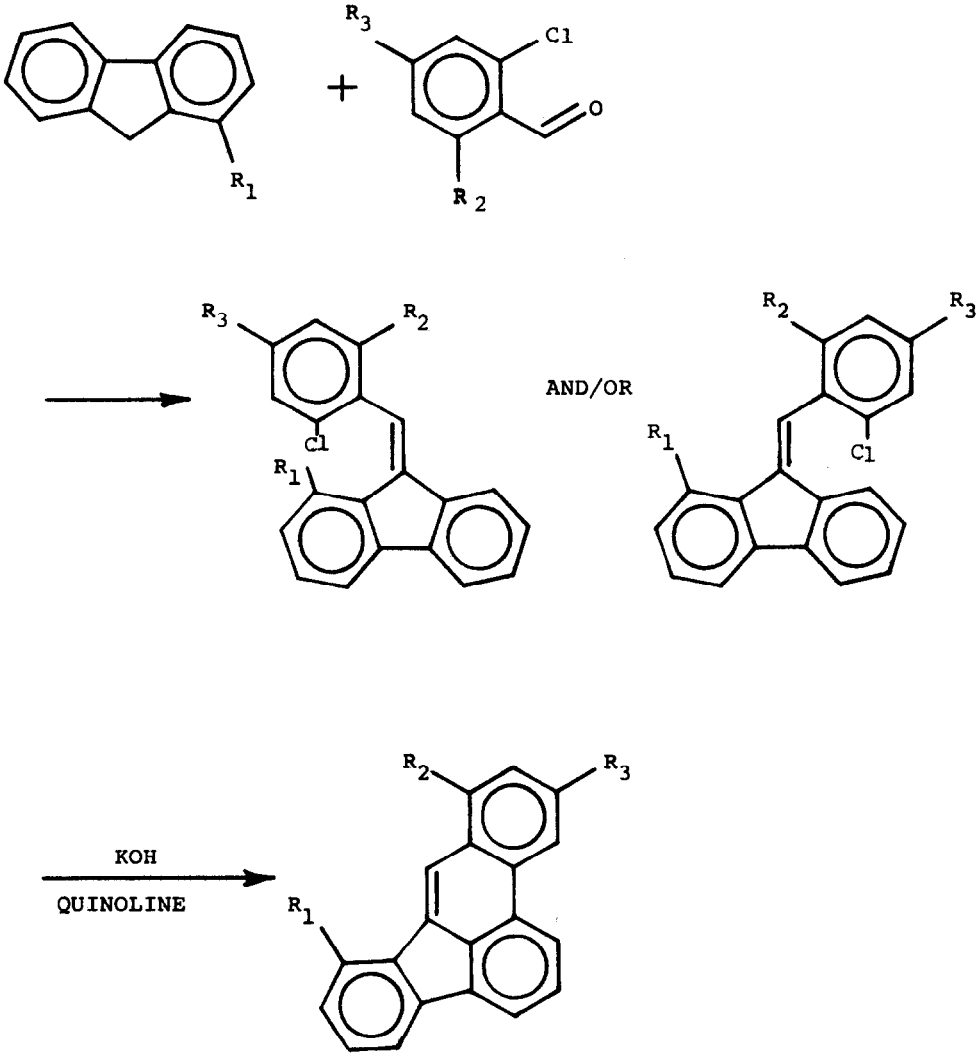
0022-1139/83/$3.00



Benzo[b]fluoranthene, found in urban air, gasoline engine exhaust, cigarette smoke and European rivers at levels comparable to benzo[a]pyrene, [3] is known to be carcinogenic in laboratory animals. [4] A study of its in vitro metabolic activation by rat liver microsomes indicated that the dihydrodiol formed was not the 9, 10-dihydrodiol expected to be the proximate metabolite according to the bay-region theory. [5] To identify the molecular site (or sites) involved in metabolic activation, we have applied the fluorine substitution methodology, [6] and report in this paper the synthesis, characterization and NMR spectra of the 7-, 9-, and 11-fluorobenzo[b]-fluoranthenes [7,8].

RESULTS AND DISCUSSION

The pentacyclic ring systems of 7-fluorobenzo[b]fluoranthene (I), 9-fluorobenzo[b]fluoranthene (II) and 11-fluorobenzo[b]fluoranthene (III) are conveniently accessible via the reaction sequences shown in Chart I. Base-catalyzed condensation of a fluorene derivative with an o-chlorobenzaldehyde affords a fluorinated 9-(o-chlorobenzylidene)fluorene which, upon treatment with KOH in refluxing quinoline, [9] undergoes cyclization and aromatization to yield a fluorinated benzo[b]fluoranthene. Products were characterized by elemental analysis, ^{13}C NMR spectra, ^{1}H NMR Spectra (see below) and, in the case of the fluorinated benzo[b]fluoranthenes, by comparison of their UV spectra with that of the parent compound.



		R_1	R_2	R_3
I	7-fluoro	F	H	H
II	9-fluoro	H	F	H
III	11-fluoro	H	H	F

Scheme 1

9-Fluorobenzo[b]fluoranthene (II)

Condensation of fluorene with 2-chloro-6-fluorobenzaldehyde (effected by potassium t-butoxide in t-butyl alcohol) afforded 9-(2-chloro-6-fluorobenzylidene)fluorene (65%). Cyclization-aromatization (KOH/quinoline) gave II in 63.5% yield. The UV spectrum of II was virtually identical with that of benzo[b]-fluoranthene, consistent with our observations in the dibenzo-[a,i]pyrene and dibenzo[a,h]pyrene series that fluorine substituents have almost no effect on the position and intensity of the electronic spectrum [9].

The presence and position of the fluorine substituent in II were confirmed by the observed ^{13}C-^{19}F couplings. Thus, in addition to the directly-bonded coupling (J_{CF} = 270 Hz), the ^{13}C spectrum exhibited one two-bond (J_{CF} = 21.2 Hz), one three-bond (J_{CF} = 8.8 Hz) and one four-bond coupling (J_{CF} = 3.9 Hz) to protonated carbons, which were similar in magnitude to the analogous couplings in 1-fluoronaphthalene [10]. Moreover, we also observed a 7.6 Hz coupling to the peri carbon, C-8, like that seen in 1-fluoronaphthalene.

Final structure determination rested on the analysis of the proton NMR spectrum of II and its comparison with the spectrum of benzo[b]fluoranthene.

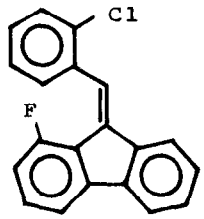
11-Fluorobenzo[b]fluoranthene (III)

11-Fluorobenzo[b]fluoranthene (III) was prepared by condensation of fluorene with 2-chloro-4-fluorobenzaldehyde, followed by cyclization-aromatization of the resulting 9-(2-chloro-4-fluorobenzylidene)fluorene. The overall yield was 23%.

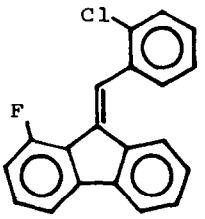
As in the case of II, CF couplings confirmed the position of the fluorine. Here we observed two ortho CF couplings (23.8 and 22.0 Hz, to C-10 and C-12 respectively) and a single meta CF coupling (8.8 Hz) to a bay-region carbon, placing fluorine at C-11, as anticipated. This conclusion was reinforced by our analysis of the proton spectra.

7-Fluorobenzo[b]fluoranthene (I)

In principle, the base-catalyzed reaction of 1-fluorofluorene with 2-chlorobenzaldehyde may afford two isomers, (E)- and (Z)- 1-fluoro-9-(2-chlorobenzylidene)fluorene:



(Z-)



(E-)

In fact, the reaction proceeded smoothly to give a single product, as evidenced both from the sharp melting point (72-74°) and the ^{13}C NMR spectrum, which exhibited only eight resonances attributable to protonated carbons: four singlets due to the carbons in the unfluorinated rings, and four-doublets due to the carbons ortho, meta and para to fluorine as well as the exocyclic benzylidene carbon. While the spectra did not permit unambiguous assignment of configuration, steric considerations suggest (E)-1-fluoro-9-(2-chlorobenzylidene) fluorene as the more likely structure.

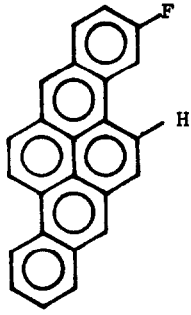
Treatment of the intermediate with KOH in refluxing quinoline led to a product identified as a benzo[b]fluoranthene on the basis of its UV spectrum. Its ^{13}C NMR spectrum showed fluorine to be coupled to carbons ortho, meta and para to it, as well as to C-8, across the pseudo-bay region. Final structure assignment came from analysis of the proton NMR spectra.

NMR Spectra

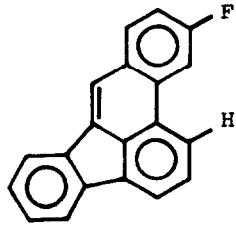
The proton NMR spectra of the three isomeric fluorobenzo-[b]fluoranthenes were obtained at 79.5 and 270 MHz. In all three cases, the 79.5 MHz spectra, arising from eleven non-equivalent protons (some influenced by and/or coupled to the fluorine - a twelfth spin) spanned a range of less than 1.5

ppm and were virtually uninterpretable, owing to extensive peak overlap within the tightly-coupled spin systems. However, at 270 MHz spectral dispersion was sufficient to allow approximate assignment of most resonances by first-order analysis. Final analysis was then accomplished by computer simulations of the XABC (the fluorinated ring) and ABCDLMN (the remaining protons, except for H-8, an easily-assigned intense singlet) subspectra which were added together to generate the total spectrum, using the program SIMEQ [11]. No iterative analyses were done. When the visual fit between experimental and computer-simulated spectra appeared satisfactory, the chemical shifts were scaled down and the spectra recalculated at 79.5 MHz. Good agreement between simulated and experimental spectra at both frequencies was taken as indicative of a satisfactory analysis. The chemical shifts thus obtained are summarized in Table I, along with those reported for the parent benzo[b]fluoranthene in CS_2 by Jones et al. [8].

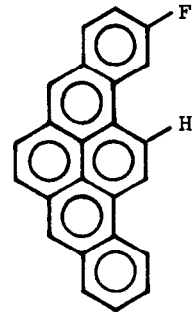
The data indicate fluorine to exert two main influences on the proton chemical shifts. First, within the substituted ring, protons ortho to fluorine are shifted upfield by approximately 0.3 ppm (the exact shift is related to the carbon-carbon π-bond order), while para protons move upfield by about half as much. Meta protons are essentially unaffected. Secondly, fluorine in sterically-congested sites (i.e., at C-7 or C-9) causes a strong downfield shift of H-8 (0.40 ppm in 9-fluorobenzo[b]fluoranthene and 0.29 ppm in 7-fluorobenzo[b]fluoranthene) which is likely due to sterically-induced deshielding [12]. The smaller shift in the 7-fluoro isomer probably reflects the slightly greater H-F internuclear distance in that case (2.8 A versus 2.4 A, measured from Dreiding models). Most other protons experience negligible fluorine-induced shifts, except for H-1 in 11-fluorobenzo[b]fluoranthene, which shifts upfield by 0.16 ppm, behavior consistent with our observations in both 3-fluorodibenzo[a,h]pyrene (IV) and 2-fluorodibenzo[a,i]pyrene (V) where H-14 and H-5, which bear the same spatial relationship to fluorine, experience upfield shifts of 0.16 and 0.18 ppm respectively.



IV



III



V

Table I.

Proton Chemical Shifts of Benzo[b]fluoranthene and Its 7-, 9- and 11-Fluoro Derivatives

Proton	Parent[a]	I 7-Fluoro[b]	II 9-Fluoro[b]	III 11-Fluoro[b]
1	8.24	8.39	8.31	8.18
2	7.58	7.61	7.67	7.63
3	7.77	7.90	7.84	7.87
4	7.72	7.67	7.80	7.83
5	7.24	7.33	7.33	7.35
6	7.26	7.06	7.30	7.37
7	7.78	--	7.90	7.85
8	7.99	8.28	8.39	7.96
9	7.85	7.99	--	7.85
10	7.47	7.59	7.23	7.28
11	7.52	7.63	7.51	--
12	8.45	8.57	8.30	8.11

[a] In CS_2; Jones et al., Spectrochim. Acta, 30A, 489-501(1979).

[b] In $CDCl_3$; this work.

The effects of steric deshielding of H-8 in 7-fluoro- and 9-fluorobenzo[b]fluoranthene are also discernable in their ^{13}C NMR spectra, which show upfield shifts of C-8. Thus, whereas the chemical shift of C-8 in the unhindered 11-fluoro isomer is δ120.6, its shifts in the 7-fluoro and 9-fluoro isomers are δ117.2 and δ113.2, respectively, consistent with the idea that Van der Waals repulsion between fluorine and H-8 results in a flow of electrons from H-8 toward C-8, leading to a shielding increase.

In summary, both proton and carbon NMR spectral data indicate fluorine substituents to affect primarily the electron distribution within the substituted ring, although there are indications that some longer-range effects are possible, particularly in sterically congested sites.

EXPERIMENTAL

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

Elemental analyses were performed by either Galbraith Laboratories or Guelph Chemical Laboratories.

NMR Spectra were obtained on one of two instruments: a Varian Associates FT-80A Fourier transform NMR spectrometer equipped with a broadband tunable probe and operating at either 20.00 MHz (^{13}C) or 79.54 MHz (^{1}H), or a Bruker WH-270 Fourier transform NMR Spectrometer operating at 270 MHz (^{1}H).

Proton spectra were taken on samples whose concentrations were in the range of 10-20 mg/ml $CDCl_3$, with TMS used as internal reference. Typically 5-20 FID's were accumulated, with a 30-second delay after each 45° pulse, and a 16K data set. No exponential multiplication was performed before transformation.

Carbon spectra were obtained on samples whose concentrations were approximately 50-100 mg/ml. Pulse widths were in the range 10-15 μsec (45-67°) and the delay between pulses was 4-5 sec. The sweep width was 4000 Hz and the number of data points was 16K. Typically, 9000 spectra were accumulated and a slight line-broadening applied before transformation to improve the signal-to-noise ratio. The chemical shifts were referred to chloroform-d (δ76.9).

1-Fluoro-9-(2-chlorobenzylidene)fulvene (nc)

To a warmed solution of potassium t-butoxide (1.85 g) in t-butyl alcohol (100 ml) under nitrogen was added 2.8 g of 1-fluorofluorene [13] in small portions, with stirring. After having been heated under reflux for one hour, the solution was cooled to 10-15° and to it was added dropwise and with stirring a solution of o-chlorobenzaldehyde (2.1 g in 20 ml t-butyl alcohol). The reaction mixture was stirred at 10-15° for one hour, then heated under reflux for three hours, at which time solvent was partially removed, the mixture cooled to room temperature and acidified with ice-cold 3N HCl. It was extracted with ether, the ether extract washed with water, dried (Na_2SO_4), and the solvent removed in vacuo. The resulting product was purified by flash chromatography [14] on neutral alumina (9:1 petroleum ether: benzene eluant), then recrystallization from petroleum ether to yield 4.2g (90%) of product.m.p. 72-74°. Analysis: calculated for $C_{20}H_{12}Cl$ F: C, 78.30%; H 3.94%; F 6.19%. Found: C, 78.44%; H 3.84%; F 6.24%.

7-Fluorobenzo[b]fluoranthene (I)(nc)

One gram of 1-fluoro-9-(2-chlorobenzylidene)fluorene and three grams of KOH in quinoline (30 ml) were heated under reflux for three hours [9]. The reaction mixture was cooled to room temperature and most of the quinoline removed by steam distillation. The resulting material was cooled, then acidified with cold 3N HCl, after which it was filtered, washed with water and dried (Na_2SO_4). Chromatography over silica gel with 4:1 petroleum ether: benzene eluant afforded 7-fluorobenzo[b]fluoranthene (390 mg; 44.2%). Recrystallization from benzene-petroleum ether gave pure product, mp 148-149°, whose UV spectrum was very similar to that of the parent hydrocarbon. Analysis: calculated for $C_{20}H_{11}F$: C, 88.87%; H, 4.10%; F, 7.03%; Found: C, 89.07%; H, 4.11%; F, 6.91%.

9-(2-Chloro-6-fluorobenzylidene)fluorene (nc)

Five grams of fluorene was added portionwise, to a warm, stirred solution of potassium t-butoxide (3.74 g) in t-butyl alcohol (100 ml) under a nitrogen atmosphere. The reaction mixture was then heated under reflux for an hour and cooled to 10-15°. A solution of 2-chloro-6-fluorobenzaldehyde (4.7 g) in 20 ml of t-butyl alcohol was added dropwise, with stirring. When addition was complete, the reaction mixture was stirred for an hour, then heated under reflux for three hours. Solvent was removed and the resulting solution made acidic with ice-cold HCl (3N). The solution was extracted (Et_2O) and the ether extract dried (Na_2SO_4). Removal of solvent afforded a liquid which, upon repeated chromatography (neutral alumina; 1:9 ether: petroleum ether), yielded 5.9 g (64%) of product. Recrystallization from petroleum ether gave pure product, m.p. 100-101°. Analysis: calculated for $C_{20}H_{12}Cl$ F, C, 78.30%; H, 3.94. Found: C, 78.30%; H, 4.10%.

9-Fluorobenzo[b]fluoranthene (II) (nc)

A mixture of 9-(2-chloro-6-fluorobenzylidene)fluorene (1.0 g), and 3 g of KOH in 30 ml quinoline was heated under reflux for 3 hours, after which the reaction mixture was allowed to cool to room temperature and the quinoline removed by steam distillation [9]. The remaining mixture was cooled, then acidified (cold 3N HCl). The solid was filtered, washed with water and dried. Chromatography on silica gel (9:1 petroleum ether: benzene) yielded 560 mg of 9-fluorobenzo[b]fluoranthene (63.5%). Recrystallized from benzene-petroleum ether, m.p. 149-150°. Analysis: calculated for $C_{20}H_{11}F$: C 88.87%, H 4.10%, F 7.03%. Found: C 88.89%, H 4.10%, F 6.50%.

9-(2-Chloro-4-fluorobenzylidene)fluorene (nc)

Fluorene (3.3 g) was dissolved in portions in a stirred solution of potassium t-butoxide (2.35 g) in t-butyl alcohol (100 ml) under nitrogen. After being heated under reflux for

one hour the solution was cooled to 10-15° and a solution of 2-chloro-4-fluorobenzaldehyde in t-butyl alcohol (3.2 g in 20 ml) added dropwise. The mixture was stirred for one hour, then heated under reflux for 3 hours. Solvent was removed, the residue acidified with ice-cold 3N HCl and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), and the solvent removed *in vacuo*. The resulting material (5.4 g;88.5%) was purified by column chromatography on neutral alumina (9:1 petroleum ether: benzene) and recrystallization from petroleum ether. m.p. 78-79°. Analysis: calculated for $C_{20}H_{12}ClF$: C 78.30%, H 3.94%, F 6.19%. Found: C 78.05%, H 4.04%, F 6.34%.

11-Fluorobenzo[b]fluoranthene (III) (nc)

A solution of 9-(2-chloro-4-fluorobenzylidene)fluorene (1.0 g) and KOH (3.0 g) in 30 ml of quinoline was heated under reflux for 3 hours [9]. The solution was cooled to room temperature, quinoline removed by steam distillation and the residue acidified with cold 3N HCl. The solid was filtered, washed with water and dried. It was then chromatographed on neutral alumina (4:1 petroleum ether-benzene) and recrystallized from benzene-petroleum ether to yield 235 mg of 11-fluorobenzo[b] fluoranthene (27%). m.p. 142-143°. Analysis: calculated for $C_{20}H_{11}F$: C 88.87%, H 4.10. Found: C 88.83%, H 3.94%.

CONCLUSIONS

The isomeric 7-, 9- and 11-fluorobenzo[b]fluoranthenes have been synthesized and characterized. NMR spectra suggest that the effect of fluorine substitution is limited largely to the substituted rings. Skin painting tests have shown all three fluoroderivatives to be less carcinogenic than the parent hydrocarbon, although all three retain significant carcinogenic activity [7]. Consistent with this observation, *in vitro* metabolic activation studies have indicated fluorine substitution to reduce the amount of dihydrodiol metabolites formed, but not to eliminate them altogether [7].

ACKNOWLEDGEMENTS

This work was supported by grant no. CA 23454 awarded by the National Cancer Institute (DHHS). The Varian Associates Model FT-80A NMR Spectrometer was purchased in part by NIH Biomedical Research Support grants. High-field NMR spectra were obtained at the NMR Facility for Biomolecular Research located at the Francis Bitter National Magnet Laboratories, MIT and funded by Grant No. RR0095 (Division of Research Resources, NIH) and Contract No. C-670 (NSF).

REFERENCES

1 (a) R.G. Harvey, Accts. Chem. Res., 14, (1981), 218-226.

(b) D.R. Thakker, W.Levin, H. Yagi, M. Tada, A.H. Conney and D.M. Jerina, A. Bjorseth and A.J. Dennis, (Eds.), in Polynuclear Aromatic Hydrocarbons: Chemistry and Biological Effects, Raven Press, New York (1980), pp. 267-286.

(c) S.S. Hecht, E.J. LaVoie, V. Bedenko, D. Hoffmann, D.J. Sardella, E. Boger, and R.E. Lehr, M. Cooke and A.J. Dennis, (Eds.), in Polynuclear Aromatic Hydrocarbons: Chemical Analysis and Biological Fate, Battelle Press, Columbus (1981), pp. 43-54.

2 An exception is the study of the metabolic activation of dibenzo[a,e]fluoranthene: O. Perin-Roussel, M. Croisy-Delcey, J. Mispelter, S. Saguem, O. Chalvet, B. Ekert, J. Fouquet, P. Jacquinon, J.M. Lhoste, B. Muel and F.E. Zajdela, Cancer Res., 40, (1980), 1742-1749.

3 (a) J.E. Baum, H.V. Gelboin and P.O.P. T'so, (Eds.), in Polycyclic Hydrocarbons and Cancer, Vol.1, Academic Press, New York, (1978), pp. 45-70.

(b) D. Hoffmann and E.L. Wynder, A.C. Stern, (Ed.), in Air Pollution, Third Edition, Vol. II, Academic Press, New York, pp. 361-455.

(c) E.L. Wynder and D. Hoffmann, Tobacco and Tobacco Smoke, Academic Press, New York (1967).

(d) J. Borneff and H. Kunte, Arch. Hyg. Bakteriol., 149, (1965), 226.

(e) J. Borneff and H. Kunte, Ibid, 148, (1964), 585.

4 (a) E.L. Wynder and D. Hoffmann, Cancer, 12, (1959), 1194-1199.

(b) A. Lacassagne, N.P. Buu-Hoi, F. Zajdela, D. Lavit-Lamy and O. Chalvet, Acta Unio Int. Contra Cancrum, 19, (1963), 480-496.

5 S.S. Hecht, E. LaVoie, S. Amin, V. Bedenko and D. Hoffmann, A. Bjorseth and A.J. Dennis, (Eds.), in Polynuclear Aromatic Hydrocarbons: Chemistry and Biological Effects, Raven Press, New York (1980), pp. 417-433.

6 (a) J.A. Miller, E.C. Miller and G.C. Finger, Cancer Res., 13, (1953), 93.

(b) M.S. Newman, R.I. Freudenthal and P.W. Jones, (Eds.), in Polynuclear Aromatic Hydrocarbons: Chemistry, Metabolism and Carcinogenesis, Raven Press, New York, (1976), pp. 203ff.

7 The results of skin-painting tests and metabolic activation studies have been reported. E.J. LaVoie, S. Amin, A. Juchatz, S.S. Hecht, D. Hoffmann, D.J. Sardella and E. Boger, AACR Abstracts, 23, (1982), 85, No. 332.

8 The 220 MHz proton NMR Spectrum of the parent benzo[b] fluoranthene has been analyzed: D.W. Jones, R.S. Matthews and K.D. Bartle, Spectrochim. Acta, 30A, (1979), 489-501.

9 D.J. Sardella, P.K. Ghoshal and E. Boger, J. Fluorine Chem., 20, (1982), 459-473.

10 (a) F.J. Weigert and J.D. Roberts, J. Am. Chem. Soc.,93, (1971), 2361-2369.

(b) P.E. Hansen, A. Berg, H.J. Jakobsen, A.P. Manzara and J. Michl, Org. Magn. Reson.,10, (1977), 179-187.

11 Varian Associates research programs software package.

12 D.M. Grant and B.V. Cheney, J. Am. Chem. Soc., 89, (1967), 5315-5318.

13 E.K. Weisburger and J.H. Weisburger, J. Org. Chem., 18, (1953), 864.

14 W.C. Still, M. Kahn and A. Mitra, Ibid., 43, (1978), 2923.