cm^{-1}; ^1H NMR, see Table I; ^{13}C NMR, see Table II.

13-Acetyl-7-(2,2,2-trichloroethyloxycarbonyl)baccatin III (13). Compound **12** (200 mg, 0.26 mmol), 4-(dimethylamino)-pyridine (15 mg), and acetic anhydride (0.4 mL) in dry acetonitrile (4.0 mL) was heated to 75 °C and kept at this temperature for 6 h. Usual workup and purification by preparative TLC (4:1 hexane–ethyl acetate) yielded **13** as a white solid; 0.15 g (71%); mp 239.5–241 °C dec; FABMS, m/z 803/805 (MH^+); IR 1770, 1740 cm^{-1}; ^1H NMR, see Table I; ^{13}C NMR, see Table II.

13-Acetylbaccatin III (10). Compound **13** (74 mg) was treated with Zn dust (100 mg) in MeOH–AcOH (1:1, 2.0 mL) at 40 °C for 10 min, and the reaction was worked up by filtering, evaporating the salts in vacuo, redissolving in CH_2Cl_2, and refiltering to remove Zn salts. The product **10** was obtained as a white powder (50 mg, 83%'); recrystallization (MeOH) gave mp 222.5–225 °C: $[\alpha]^{23}_D$ −59.6° (c 0.02, MeOH); FABMS, m/z (relative intensity) 651 (MNa^+, 7), 629 (MH^+, 22), 611 ($MH^+ - H_2O$, 2), 569 (MH^+ – AcOH, 11), 551 (MH^+ – AcOH – H_2O, 18), 509 (MH^+ – 2AcOH, 15), 135 (17), 119 (25), 105 (100); m/z 629.2541 (MH^+; $C_{33}H_{41}O_{12}$ requires 629.2599); IR 1760, 1740, 1725, 1670, 1570, 1390, 1295, 1120, 1090, 1060, 1000, 720 cm^{-1}; ^1H NMR, see Table I; ^{13}C NMR, see Table II.

7,13-Diacetylbaccatin III (15). A mixture of baccatin III (0.15 g, 0.51 mmol), acetic anhydride (1.5 mL), 4-(dimethylamino)-pyridine (8 mg), and pyridine (0.125 mL) was heated at 75 °C for 3 h. Workup by standard procedures and purification by PTLC yielded **15**: 0.085 g (49%); mp 234–236 °C; FABMS, m/z (relative intensity) 693 (25, MMa^+), 671(15, MH^+), 611 (12, $MH^+ - CH_3COOH$), 593 (3, $MH^+ - CH_3COOH - H_2O$), 551 (10, $MH^+ - 2CH_3COOH$), 533 (4), 525 (6), 517 (17), 459 (90), 433 (100); IR 1750, 1765 cm^{-1}; ^1H NMR, see Table I; ^{13}C NMR, see Table II.

Acknowledgment. We thank Dr. M. Suffness (National Cancer Institute) and Dr. F. E. Boettner (Polysciences Inc.) for gifts of taxol and partially purified taxol fractions, respectively, and Dr. R. G. Powell for samples of baccatin III and baccatin V. We acknowledge the assistance of the staffs of the Midwest Center for Mass Spectrometry and the Middle Atlantic Mass Spectrometry Laboratory with mass spectral measurements. Financial support from the American Cancer Society (Grant CH-268) is gratefully acknowledged.

Registry No. **1a**, 33069-62-4; **2**, 27548-93-2; **7**, 31077-81-3; **8**, 103150-32-9; **10**, 76446-91-8; **11**, 32981-90-1; **12**, 103150-33-0; **13**, 103150-34-1; **15**, 92950-44-2.

Fluorination of Activated Aromatic Systems with Cesium Fluoroxysulfate

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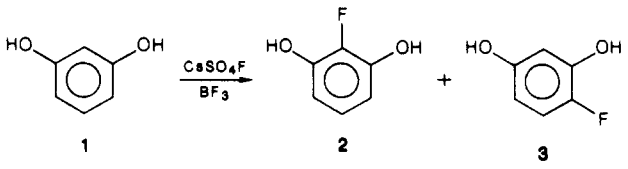
We have previously described the reactions between activated aromatics and fluoroxytrifluoromethane, CF_3OF.[1,2] The use of CF_3OF as a fluorination agent has declined because of the development of safer and more readily available hypofluorites. Rozen et al. have described the preparation and reactions of acetyl and trifluoroacetyl hypofluorites.[3] Appleman et al.[4] have reported the isolation and reactions of cesium and rubidium fluoroxysulfate, and Zupan et al.[5] have applied the use of cesium fluoroxysulfate ($CsSO_4F$) in several organic systems; both groups have reported detonations of $CsSO_4F$. Because of the ease of preparation of $CsSO_4F$, its mild reaction conditions, and its relatively long shelf life,[4,5] we conducted a study of the reaction of $CsSO_4F$ with several activated aromatic systems. This study parallels the experiments we reported several years ago with CF_3OF. We now report the new results with $CsSO_4F$ and a comparison with the previous CF_3OF studies.

In order to determine optimum reaction conditions for fluorination we chose the boron trifluoride catalyzed reaction between $CsSO_4F$ and resorcinol.[4a] The best reaction conditions proved to be an initial substrate to $CsSO_4F$ ratio of 1:1 with four drops of boron trifluoride etherate in acetonitrile solution at room temperature. Reaction time (3–12 h) was determined by substrate reactivity. Thus resorcinol (**1**) reacted with $CsSO_4F/BF_3$ for 3 h to give a mixture of 2-fluororesorcinol (**2**) and 4-fluororesorcinol (**3**).



1 2 3

$CsSO_4F/1$	% 2	% 3
1	4	21
1.3	13	40
2	25	27

The substitution ortho to the hydroxyl groups is in accord with previous results of Appleman.[4] Fluorination at the 4-position predominates over fluorination at 2-position, but the amount of the 2-substitution may be increased by increasing the amount of $CsSO_4F$. Rozen has shown that fluorination of 1,3-dimethoxybenzene with CH_3COOF produces only 4-substitution without 2-substitution and has attributed the result to steric hinderance at the 2-position.[3d] In our case, apparently the association of the $CsSO_4F$ with the phenolic hydroxyl groups permits formation of some 2-isomer **2**.[4b]

We attempted several reactions between piperonal and $CsSO_4F$, but we were unable to detect any fluorination product. Rozen, in a study of the piperonal–CH_3COOF reaction observed addition of CH_3COOF to the 1,2-bond. His results showed the dual mechanistic nature of CH_3COOF: transfer of fluorine ions and addition.[3d] We have previously shown that CF_3OF adds to the aromatic nucleus of pyrenol.[6] The addition of $CsSO_4F$ to the aromatic nucleus is apparently a much less desirable process than is the addition of CH_3COOF or CF_3OF.

Reaction of 17β-estradiol (**4**) and $CsSO_4F/BF_3$ provided a clean and simple preparation of two fluorinated isomers: 2-fluoro-17β-estradiol (**5**) and 4-fluoro-17β-estradiol (**6**). Both fluorinated isomers were useful in the study of cancer therapy with estrogens.[7,8] The present synthesis is especially attractive because the products are produced in

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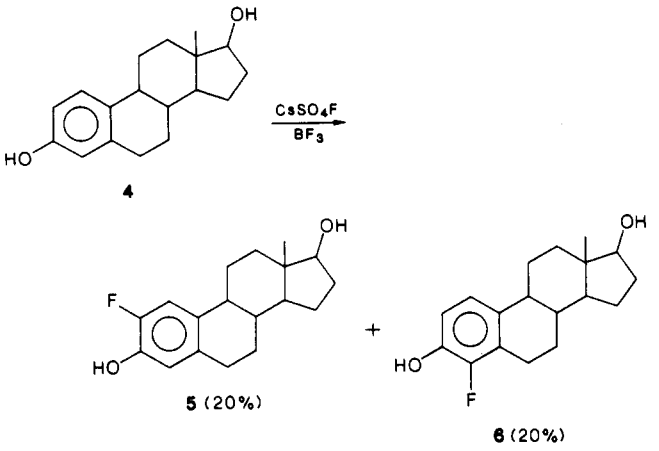
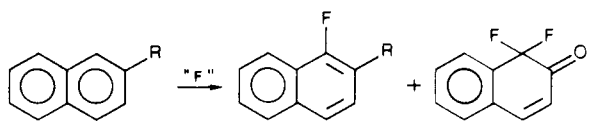


one step. Other syntheses of these compounds require the preparation and isolation of intermediate 17β-estradiol derivatives.[8,9] The reaction of 17β-estradiol with CF_3OF produced only low yields of unidentifiable materials in our hands. However, Barton, Hesse, et al. have reported that estrone 3-methyl ether and estrone 3-acetate are both smoothly fluorinated by CF_3OF to give fluorinated dienones from ipso fluorination and a small amount of the fluorinated phenols.[10,11]

2-(N-Acetylamino)naphthalene (7) and 2-hydroxynaphthalene (8) showed similar behavior with $CsSO_4F/BF_3$, forming predominantly 1-fluoro-2-X-naphthalene 9 and lesser amounts of 1,1-difluoro-2-oxo-1,2-dihydronaphthalene (10). Reaction of substrates 7 and 8 with



7 or 8 9 10

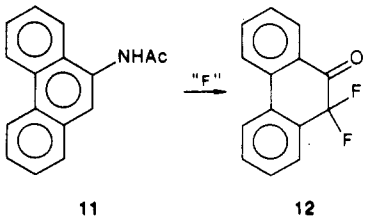
	R	"F"	% 9	% 10
7	NHAc	$CsSO_4F$	58	21
7	NHAc	CF_3OF[1]	25	43
8	OH	$CsSO_4F$	50	13
8	OH	CF_3OF[1]	14	20

CF_3OF leads to the same products (9 and 10), but 10 is the major component in this case. These results point out that CF_3OF and $CsSO_4F$ have inherent differences in their reactivity and possibly in their mechanism of reaction also.

9-(N-Acetylamino)phenanthrene (11) reacted with $CsSO_4F/BF_3$ to give 9,9-difluoro-10-oxo-9,10-dihydrophenanthrene (12). Compound 12 is produced in higher yield from the reaction of 11 with CF_3OF.

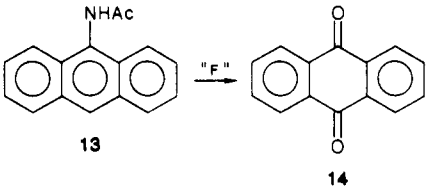
9-(N-Acetylamino)anthracene (13) is not fluorinated with either $CsSO_4F/BF_3$ or CF_3OF; instead both reagents cause oxidation to produce 9,10-anthraquinone (14).

5-(N-Acetylamino)benzo[c]phenanthrene (15) and its 5-hydroxy analogue (16) react with $CsSO_4F$ to give the difluorination product, 6,6-difluoro-5-oxo-5,6-dihydrobenzo[c]phenanthrene (17). Previous studies of the reaction of CF_3OF with 15 and 16 showed only monofluorination in each case without observation of any 17.[2]



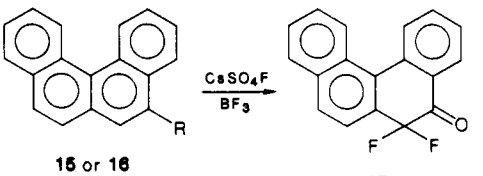
11 12

"F"	% 12
$CsSO_4F$	22
CF_3OF[2]	40



13 14

"F"	% 14
$CsSO_4F$	75
CF_3OF[1]	95



15 or 16 17

	R	% 17
15	NHAc	10
16	OH	24

Mechanistically, the neutral hypofluorites, CF_3OF[12,13] and CH_3COOF,[3] have received much more attention than has the anionic hypofluorite, $CsSO_4F$.[4,5] Both CF_3OF and CH_3COOF are characterized in their mechanisms as having components of (a) ionic transfer of fluorine to a region of high electron density, (b) free-radical transfer of the fluorine atom, and (c) addition of the elements of the molecular hypofluorite. The limited mechanistic studies of $CsSO_4F$ indicate that it is similar to the neutral hypofluorites in possessing ionic fluorination and free radical fluorination pathways, but its addition chemistry is much less evident. Our results would also indicate that the addition of $CsSO_4F$ is uncompetitive with the ionic and free-radical fluorination paths.

In summary, the results show that both $CsSO_4F$ and CF_3OF produce very similar products from the substrate systems studied, with variations in the amounts of mono- vs. difluorination products. Our experience shows that $CsSO_4F$ is much more easily handled and less expensive than CF_3OF. We have observed no adverse reactions or explosions with the preparation or use of $CsSO_4F$, but care should be exercised when handling hypofluorite compounds.

Experimental Section

Caution. $CsSO_4F$ has been reported to explode on contact with metal surfaces. $CsSO_4F$ was prepared by the method of Appleman et al.[4b] in 2–3-g batches and stored at −10 °C. Acetonitrile, reagent grade, was obtained from Fisher Chemical Co., distilled, and stored over 3-Å molecular sieves. Starting materials 7, 8, and 13 were available from previous research.[2,6] 17β-Estradiol was obtained from Sigma Chemical Co. Products 9, 10, 12, and 14 were identified by comparison of IR and NMR spectral properties. Compounds 5 and 6 were prepared according to the method of Utne.[8]

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Nuclear magnetic resonance spectra were obtained on a JOEL FX-90 Q spectrometer operating at 22.5 MHz for carbon (Me_4Si), 84.7 MHz for fluorine ($CFCl_3$), and 89.8 MHz for proton ($CDCl_3$) in either $CDCl_3$ on acetone-d_6 solutions. HPLC separations were accomplished on a Perkin-Elmer series LC-1 system with a Perkin-Elmer LC-75 spectrophotometric detector and a Whatman Partisil M9 10/50 or Whatman Partisil M9 10/50 ODS-2 column with HPLC grade solvents as specified. Mass spectra were obtained by Rich Berger at the Washington University School of Medicine, St. Louis. Melting points were obtained on a Thomas-Hoover capillary apparatus.

General Procedure. Cesium fluoroxysulfate (1 mmol) was added to 25 mL of dry acetonitrile in a small plastic vial, and the resulting solution was flushed with nitrogen for several minutes. The aromatic compound (1 mmol) was added to the stirred solution, and the solution was flushed again with nitrogen. Four drops of boron trifluoride etherate were added, and the vial was closed, wrapped in aluminum foil, and allowed to stir for 3 h in the dark, at which time an additional 1 mmol of cesium fluoroxysulfate was added to the solution. The vial was again closed, wrapped in aluminum foil, and allowed to stir for 3 more h for highly activated aromatic compounds or overnight for the less activated aromatic compounds. The solution was transferred to a large test tube and placed on a centrifuge for 2 min. The liquid was decanted and evaporated on a Büchi evaporator. The crude product was transferred to a smaller flask, using acetone, in which the cesium salts are insoluble, and the acetone was evaporated. The crude product was placed under vacuum to remove all remaining traces of solvent. The crude product was first analyzed by ^{19}F NMR.

Resorcinol (1). Two monofluorination products were isolated by HPLC on a Partisil M9 10/50 column with a 2:1 mixture of hexane–ethyl acetate at a flow rate of 4 mL/min. 2-Fluororesorcinol (**2**) was obtained as an oil (64%): ^1H NMR (acetone-d_6) δ 8.31 (OH), 6.66 (m, 1 H), 6.32 (m, 2 H); ^{19}F NMR ϕ −139.8 ppm; mass spectrum, m/e calcd 128, found 128. Anal. Calcd for $C_6H_5FO_2$: C, 56.25; H, 3.91. Found: C, 56.20; H, 3.73. 4-Fluororesorcinol (**3**): mp 98–99 °C (32%); ^1H NMR (acetone-d_6) δ 8.29 (s, 2 H, OH), 6.26–6.90 (m, 3 H, Ar); ^{13}C NMR (acetone-d_6) δ 105.6 (J_{CF} = 2.4 Hz), 106.8 (J_{CF} = 6.1 Hz), 116.6 (J_{CF} = 19.5 Hz) 145.6 (J_{CF} = 229.5 Hz), 146.1 (J_{CF} = 14.6 Hz), 155.0 (J_{CF} = 0 Hz) ppm; ^{19}F NMR (acetone-d_6) ϕ −145.88 ppm; mass spectrum, m/e calcd 128, found 128. Anal. Calcd for $C_6H_5OF_2$: C, 56.25; H, 3.91. Found: C, 56.35; H, 3.77.

17β-Estradiol (4) produced two products, which were isolated by HPLC on a Partisil M9 10/50 ODS-2 column with a 10:1.1:1 mixture of hexane–methylene chloride–isopropyl alcohol at a flow rate of 2.5 mL/min. 2-Fluoro-17β-estradiol (**5**) (20%): mp 174–175 °C (lit.[8] mp 173–175 °C); ^{19}F NMR ϕ −138.4 (d) ppm. 4-Fluoro-17β-estradiol (**6**) (20%): mp 189–190 °C (lit.[8] mp 189–191 °C); ^{19}F NMR ϕ −137.0 (m) ppm. Both **5** and **6** were characterized by comparison with authentic samples.[8]

2-(*N*-Acetylamino)naphthalene (7) produced, after column chromatography on alumina with methylene chloride, 1-fluoro-2-(acetylamino)naphthalene (**9**, R = NHAc) (58%) [mp 118–120 °C (lit.[1] mp 120–121 °C); ^{19}F NMR ϕ −141.7 ppm] and 1,1-difluoro-2-oxo-1,2-dihydronaphthalene (**10**) (21%) [mp 49–50 °C (lit.[1] mp 49–50); ^{19}F NMR ϕ −101.5 ppm].

2-Hydroxynaphthalene (8) produced **9** (R = OH) (50%), mp 74–75 °C (lit.[1] mp 74–75 °C), and **10** (13%).

9-(*N*-Acetylamino)phenanthrene (11) gave after purification on alumina (benzene), 9,9-difluoro-10-oxo-9,10-dihydrophenanthrene (**12**) (22%): mp 93–94 °C (lit.[2] mp 100–102 °C); ^{19}F NMR ϕ −103.6 ppm.

9-(*N*-Acetylamino)anthracene (13) gave only 9,10-anthraquinone (**14**) (75%), mp 283–284 °C (authentic sample mp 283–284 °C).

5-(*N*-Acetylamino)benzo[*c*]phenanthrene (15) and 5-hydroxybenzo[*c*]phenanthrene (16)[14] gave, after chromatography on alumina (benzene), 6,6-difluoro-5-oxo-5,6-dihydrobenzo[c]phenanthrene (**17**) in 10% and 24% yields, respectively: mp 93–94 °C; ^1H NMR ($CDCl_3$) δ 7.47–8.64 (m, Ar); ^{19}F NMR ϕ −110.7 ppm; ^{13}C NMR ($CDCl_3$) 108.5 (t, J = 246 Hz) 121.5, 126.1, 126.7, 128.3, 128.7, 129.5, 130.6, 181.4 (C=O) ppm; mass spectrum, m/e calcd 280, found 280. Anal. Calcd for $C_{18}H_{10}FO_2$: C, 77.14; H, 3.57. Found: C, 77.01; H, 3.72.

Registry No. **1**, 108-46-3; **2**, 103068-40-2; **3**, 103068-41-3; **4**, 50-28-2; **5**, 16205-32-6; **6**, 1881-37-4; **7**, 581-97-5; **8**, 135-19-3; **9** (R = NHAc), 19580-15-5; **9** (R = OH), 51417-63-1; **10**, 51417-64-2; **11**, 4235-09-0; **12**, 59830-28-3; **13**, 37170-96-0; **14**, 84-65-1; **15**, 4176-51-6; **16**, 38063-26-2; **17**, 103068-42-4; $CsSO_4F$, 70806-67-6; piperonal, 120-57-0.

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Synthesis of Volatile, Fluorescent 7-Methylguanine Derivatives via Reaction with 2-Substituted Fluorinated Malondialdehydes

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Many carcinogens that are alkylkating agents react with DNA to give a wide range of alkylated purine and pyrimidine bases. Carcinogenic methylating agents such as methyl methanesulfonate (MMS), *N*-methyl-*N*-nitrosourea (MNU), and dimethylnitrosamine (DMN) give rise to 7-methylguanine (7-MeG) as the major product of reaction with DNA and other nucleic acids.[1] Thus, the determination of 7-MeG in physiological fluids and tissues is of major importance given the wide range of methylating agents to which man may be exposed.

The analysis of 7-MeG or related compounds is made particularly difficult by the chemical properties of naturally occurring purines. Guanine and its alkylated derivatives are typically nonvolatile, insoluble in organic solvents, and lacking in intense native fluorescence or other spectroscopic properties which could be exploited in analytical methods.

As part of our studies in in vivo methylation we required a sensitive and selective method of derivatization to enable the determination of 7-MeG by gas chromatography–mass spectrometry (GC–MS).[2] The results of our attempts to prepare novel derivatives of 7-MeG are summarized in this paper.

Some years ago Moschel and Leonard[3] found that 2-substituted malondialdehydes reacted with guanine to give highly fluorescent 1,N^2-prop-2-en-2-yl-1-ylideneguanine derivatives (Scheme I). We reasoned that substitution at N^7 of guanine would not dramatically affect the reaction.

Reichardt and his co-workers[4] have synthesized a large number of 2-substituted malondialdehydes that still retain their characteristic chemical reactivity, indicating that a wide range of substitution at C-2 can be tolerated. From the point of view of analytical methodology the use of a pentafluorophenyl group at C-2 would be very useful for negative ion GC–MS or electron capture detection, and we

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