(S)-1-Phenyl-2-hydroxyethyl (2R,3R,4R)-3,4-Epoxy-4-methyltetrahydropyran-2-yl Ether (10a). To a solution of **9** (185 mg, 0.789 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added MCPBA (200 mg, 0.9 mmol). The reaction was maintained at 0 °C for 18 h. The reactiom mixture was poured into saturated aqueous $NaHCO_3$ (15 mL), and the aqueous layer extracted was with EtOAc (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel 60 (100 g) with 50% EtOAc/hexanes as eluent gave the syn epoxide **10a** (183 mg, 0.731 mmol, 93%) as a viscous oil homogenous by TLC, R_f 0.15 (50% EtOAc/hexanes): $[\alpha]^{28}_D$ +123.01° (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3663, 3475, 3011, 2922; ^1H NMR ($CDCl_3$) δ 1.39 (3, s), 1.83–1.98 (2, m), 3.02 (1, s), 3.07 (1, d, J = 3.1 Hz), 3.46–3.94 (4, m), 4.84–4.90 (2, m), 7.27–7.40 (5, m); ^{13}C NMR ($CDCl_3$) δ 21.80 (CH_3), 29.80 (CH_2), 56.14 (C), 56.71 (CH_2), 58.30 (CH), 67.12 (CH_2), 79.32 (CH), 91.35 (CH), 127.08 (CH), 128.16 (CH), 128.51 (CH), 138.16 (C).

The anti epoxide **10b** (14 mg, 0.056 mmol, 7%) was also isolated as a viscous oil homogenous by TLC, R_f 0.20, (50% EtOAc/hexanes): ^1H NMR ($CDCl_3$) δ 1.42 (3, s), 1.75–1.89 (1, m), 1.98–2.12 (1, m), 2.95 (1, s), 3.41–3.53 (1, m), 3.66–3.88 (4, m), 4.83 (1, s), 4.87 (1, dd, J = 3.7, 8.0 Hz), 7.35 (5, m); ^{13}C NMR ($CDCl_3$) δ 23.36 (CH_3), 28.83 (CH_2), 55.98 (CH_2), 56.38 (C), 57.57 (CH), 67.23 (CH_2), 81.06 (CH), 94.29 (CH), 126.93 (CH), 128.35 (CH), 128.62 (CH), 137.75 (C).

(S)-1-Phenyl-2-hydroxyethyl (2R,4R)-4-Hydroxy-4-methyltetrahydropyran-2-yl Ether (11). To a suspension of $LiAlH_4$ (30 mg, 0.79 mmol) in THF (1.5 mL) at 0 °C was added a solution of epoxide **10a** in THF (3 mL) dropwise via syringe. The mixture was stirred at ambient temperature for 8 h and then quenched by successive additions of water (30 μL), 10% aqueous NaOH (30 μL), and water (90 μL). The mixture was filtered through Celite and concentrated in vacuo. Chromatography of the residue on silica gel 60 (100 g) with EtOAc as eluent gave the product **11** (144 mg, 0.571 mmol, 80%) as an oil that crystallized upon cooling, mp 83–84 °C: R_f 0.31 (EtOAc); $[\alpha]^{25}_D$ +184.11° (*c* 1.41, EtOH); IR ($CHCl_3$) cm^{-1} 3435, 3009, 2971, 2931; ^1H NMR ($CDCl_3$) δ 1.22 (3, s), 1.60–1.89 (4, m), 3.55–3.87 (4, m), 4.30 (1, dt, J = 3.0, 11.9 Hz), 4.49 (1, s), 4.84 (2, s), 7.33 (5, s); ^{13}C NMR ($CDCl_3$) δ 29.80 (CH_3), 37.89 (CH_2), 40.92 (CH_2), 56.38 (CH_2), 66.78 (CH_2), 67.03 (C), 78.41 (CH), 94.47 (CH), 127.10 (CH), 128.21 (CH), 128.55 (CH), and 137.58 (C).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.58; H, 7.88.

(4R)-4-Hydroxy-4-methyltetrahydropyran-2-one (1). To a solution of **8a** (100 mg, 0.396 mmol) in THF (5 mL) was added 10% aqueous HCl (3 mL). The mixture was stirred for 0.5 h, then poured into saturated aqueous $NaHCO_3$ (20 mL), and extracted with hot EtOAc (10 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel 60 (75 g) with EtOAc as eluent gave the lactol as a colorless liquid homogenous by TLC, R_f 0.25 (EtOAc). This material was subjected to oxidation without characterization.

To a suspension of PCC (215 mg, 1.00 mmol) and freshly ground 3-Å sieves (230 mg) in CH_2Cl_2 (1.5 mL) was added a solution of the above lactol in CH_2Cl_2 (2 mL). The mixture was stirred for 7 h at ambient temperature. Ether (10 mL) was added with vigorous stirring. Filtration of the mixture through silica gel 60 (15 g) with ether as eluent gave (*R*)-mevalonolactone (**1**) (39 mg, 0.30 mmol, 76%), which exhibited identical physical and spectral properties when compared to a sample of authentic racemic material (Aldrich): R_f 0.31 (EtOAc); $[\alpha]^{27}_D$ -20.0° (*c* 0.85, EtOH); lit.[3a] $[\alpha]_D$ -23° (*c* 0.32, EtOH); IR ($CHCl_3$) cm^{-1} 3431, 3013, 2973, 1729; ^1H NMR ($CDCl_3$) δ 1.39 (3, s), 1.91 (2, m), 2.50 (1, d, J = 17 Hz), 2.67 (1, d, J = 17 Hz), 2.88 (1, s), 4.30–4.42 (1, m), 4.56–4.68 (1, m); ^{13}C NMR ($CDCl_3$) δ 29.53 (CH_3), 35.68 (CH_2), 44.54 (CH_2), 66.15 (CH_2), 67.93 (C), 171.04 (C).

Similarly, hydrolysis of pyranoside **11** (130 mg, 0.515 mmol) and oxidation with PCC (275 mg, 1.25 mmol) and 3-Å sieves (300 mg) gave **1** (49 mg, 0.38 mmol, 74%), $[\alpha]^{26}_D$ -20.1° (*c* 1.0, EtOH).

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Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra of all new compounds (24 pages). Ordering information is given on any current masthead page.

A Novel Reaction between Acetone and the Benzo[*c*]phenanthrene K-Region *o*-Quinone Containing a Peri-Fluoro Substituent

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Polycyclic aromatic hydrocarbons, the ubiquitous environmental pollutants, are bioactivated by cytochromes P450 and epoxide hydrolase to carcinogenic bay-region diol epoxides[1,2] but are detoxified by the same enzymes to K-region dihydrodiols. Interestingly, the weak carcinogen, 6,7-difluorobenzo[*c*]phenanthrene[3,4] (**1**), is predominantly metabolized by rat liver cytochromes P450 to the K-region quinone **2** (Scheme I).[4] In this paper, we describe a novel and surprisingly facile reaction of the fluoroquinone **2** with acetone that was discovered during our studies on the oxidative metabolism of **1**. We found that the K-region quinone **2** reacts readily with aqueous acetone[5] at 25 °C to exclusively form a pair of aralkyl acetomethyl ethers (**4**, **5**) in the absence of added catalyst or light (Scheme I). Additionally, we observed that the ether **4** converted to the regioisomer ether **5** in aqueous organic solutions under ambient conditions. Both, the formation of regioisomeric ethers (**4**, **5**) from the quinone as well as the rearrangement of one aralkyl acetomethyl ether to its regioisomer are novel reactions.

Oxidative metabolism of **1** at its K region by rat liver cytochromes P450 yielded the quinone **2** (0.1 M potassium phosphate buffer containing MeCN (5% v/v), pH 7.4, 37 °C, 20 min). When MeCN was replaced with acetone (5% v/v) as a cosolvent for the hydrocarbon substrate, two new products were formed at the expense of the quinone as indicated by HPLC analysis. Subsequently, we synthesized the quinone **2** and observed that it reacted quantitatively with aqueous acetone[5] at 25 °C to yield the same two products. The assignment of the structures **4** and **5** to the early and late eluting products (cf. Experimental Section for HPLC conditions) and the proposed mechanism of their formation are described.

High-resolution mass spectra (EI) of the ethers **4** and **5** gave molecular ions at m/z = 334.1007 and 334.1016, respectively, and established their molecular formula as $C_{21}H_{15}O_3F$ (calcd m/z = 334.1005). The molecular formula suggests addition of elements of acetone to the quinone **2**. The UV spectra of **4** and **5** in MeOH/H_2O (4/1) (HPLC mobile phase) had absorption maxima at 228 and 266 nm, respectively. The deconvoluted FTIR spectrum of each

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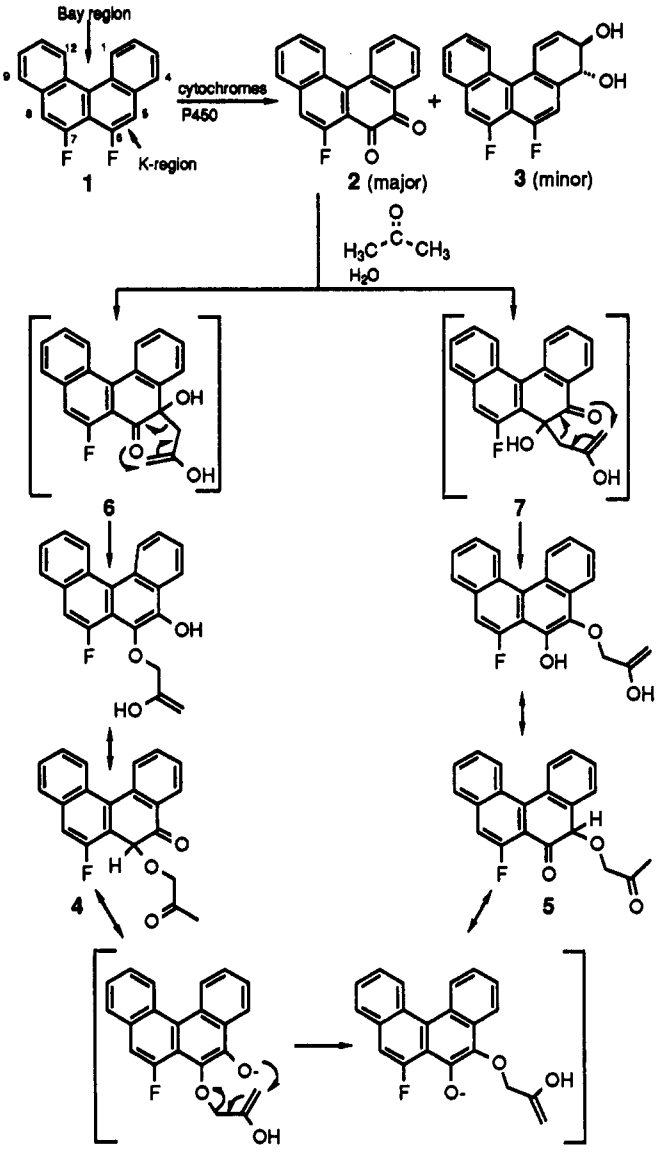
Scheme I. Proposed Mechanism for the Formation of the Regioisomeric Ethers 4 and 5 from the Metabolic Intermediate 2



product showed two carbonyl stretching frequencies (1707 and 1725 cm^{-1} for **4**, 1710 and 1725 cm^{-1} for **5**), indicative of the presence of two carbonyl groups in each compound. In addition, characteristic branched C–O–C stretch bands were observed at 1143–1105 cm^{-1}. ^1H NMR and ^{19}F NMR spectra of the two products allowed unequivocal assignment of their structures. The presence of a singlet between 2.10 and 2.20 ppm and of a pair of geminally coupled doublets centered near 3 ppm clearly indicated the presence of the CH_2COCH_3 moiety in both **4** and **5**. The 4-bond long-range coupling of the methine 1) was (H-6) in

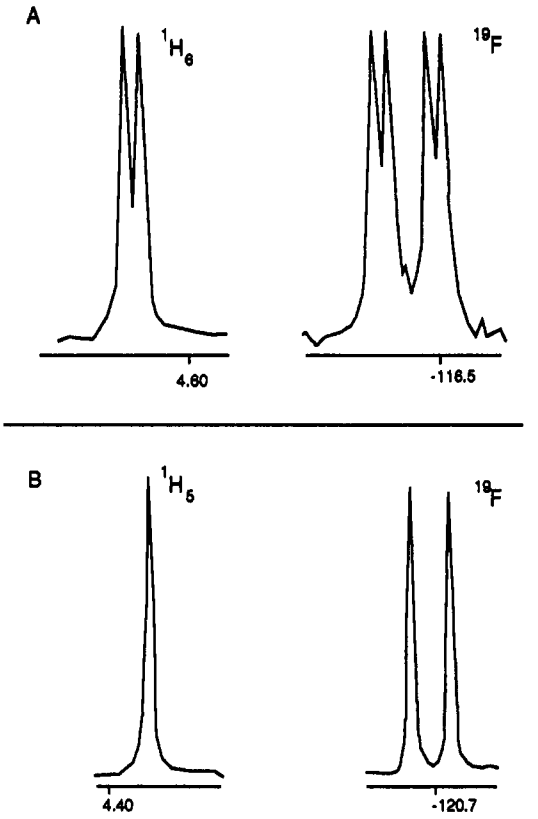


Figure 1. ^{19}F and partial ^1H NMR spectra of **4** (A) and **5** (B). The doublet at 4.62 ppm in the ^1H NMR spectrum and the doublets of doublet at −116.49 ppm in the ^{19}F NMR spectrum of **4** (A) are indicative of the 4-bond long-range coupling between H-6 and F-7 in this compound.

4 to the peri-fluorine (Figure 1) was confirmed by heteronuclear decoupling and established the position of the acetomethyl moiety at C-6. The 4-bond coupling also provided key evidence for the ether linkage between the acetomethyl group and the benzylic C-6 position. The alternative product, i.e. the aldol condensation product **6** shown in Scheme I, would not have the C–H linkage at C-6 and hence, would not be consistent with the observed coupling. As expected, the ^1H and ^{19}F NMR spectra of **5** did not show long-range coupling between the methine proton (H-5) and the fluorine at C-7 (Figure 1). The proximity of the methine proton in **5** (H-5) to H-4 was established by NOE. The structures **4** and **5** were thus assigned to the early and late eluting products, respectively, formed by condensation of acetone with the quinone **2**. Based on integration of the ^1H NMR signals of the product mixture, it appears that the ethers **4** and **5** are formed in a ratio of 1:2.

Attempts to isolate pure **4** by reversed-phase HPLC always resulted in a mixture of **4** and **5**, whereas the same method allowed the isolation of pure **5**. This observation indicated that a net conversion of **4** to **5** occurred during reversed-phase chromatography. Subsequently, we found that the equilibrium between **4** and **5** slowly ($t_{1/2}$ = 90 h) established from pure **4** (isolated by normal-phase HPLC) such that **5** accounted for >95% of the equilibrium mixture. The observed net conversion of **4** to **5** shown in Scheme I presumably occurs by a mechanism analogous to that observed for formation of ethers **4** and **5** from the corresponding aldol intermediates **6** and **7**.

We postulate that acetone, in the presence of water, reacts with the fluoroquinone **2** to form the aldol intermediates **6** and **7**. These undergo spontaneous retro-Claisen type [3,3]-sigmatropic rearrangement to form the

(1) Thakker, D. R.; Yagi, H.; Levin, W.; Wood, A. W.; Conney, A. H.; Jerina, D. M. *Bioactivation of Foreign Compounds*; Academic Press: New York, 1985; p 177.

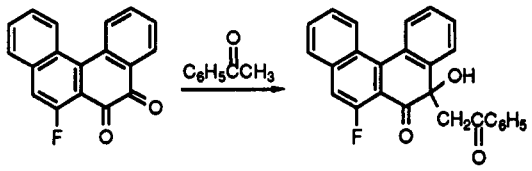
(2) Bay region is defined as the sterically hindered region in polycyclic aromatic hydrocarbons as exemplified by the region enclosed between positions 1 and 12 of 6,7-difluorobenzo[c]phenanthrene (1) in Scheme I. The K region is defined as the double bond in polycyclic aromatic hydrocarbons that is flanked by two aromatic rings (cf. Scheme I).

(3) Mirsadeghi, S.; Prasad, G. K. B.; Whittaker, N.; Thakker, D. R. *J. Org. Chem.* **1989**, *53*, 309.

(4) Patrick, M.; Levin, W.; Wood, A. W.; Mirsadeghi, S.; Thakker, D. R. *Proc. Am. Assoc. Cancer Res.* **1990**, *31*, 112.

(5) The reaction proceeds in the presence of as little as 0.3% water (w/v).

Scheme II. Formation of Aldol Product 8 from Fluoroquinone 2 and Acetophenone[6]



2 8 (predominant product)

regioisomeric acetomethyl ethers **4** and **5** (Scheme I). This mechanism invokes the presence of enol tautomers **6** and **7**. Although the enol tautomers are expected to be present in extremely low concentration, we believe that their mere presence is sufficient to account for the observed rearrangements. In fact, this proposed mechanism is further substantiated by the observed net conversion of **4** to **5** in aqueous organic solvents (cf. Scheme I). Although we do not have direct evidence for the formation of the aldol intermediates, their presence was indirectly established by carrying out a similar reaction between the fluoroquinone **2** and acetophenone. We predicted that a reaction between **2** and acetophenone would stop after initial aldol condensation, because the aldol product would be incapable of undergoing [3,3]-sigmatropic rearrangement. As predicted, reaction between **2** and acetophenone resulted in the formation of an aldol adduct (**8**) as the major product (Scheme II).[6] In general, [3,3]-sigmatropic rearrangements are under thermodynamic control, and proceed irreversibly to form carbonyl products from vinyl ethers (Claisen rearrangement).[7] While examples of retro-Claisen rearrangements have been reported,[8] these rearrangements generally occur at elevated temperatures or in the presence of a catalytic amount of Lewis acid.

The formation of acetone adducts with an *o*-quinone, such as 9,10-phenanthraquinone, under harsh conditions[9,10] or via imine intermediates[11-13] have been reported. In some cases the structures of these adducts were not unequivocally established,[9,11,12] whereas, in other cases[10,13] they were reported as aldol products. To our knowledge, this is the first report of a facile reaction between acetone and an *o*-quinone without any added catalysts other than water. Equally interesting is our proposal that aldol products formed from a K-region *o*-quinone spontaneously rearrange by a retro-Claisen type [3,3]-sigmatropic rearrangement to form acetomethyl ethers.

Experimental Section

General. High-resolution MS were obtained at a resolution of 10 000 over a range of 50–400 amu with perfluorokerosene as a standard. Proton-decoupled ^{19}F spectra were obtained with a spectrometer equipped with a ^{19}F-[^{1}H] duplexer filter. FTIR spectra were obtained with a spectrometer equipped with a MCT broad band detector with 2-cm^{-1} resolution. Resolution was enhanced by the Gaussian deconvolution method supplied by the instrument software. A HPLC equipped with a diode-array detector was used for analytical assays. Effluent was monitored at 254 nm. Acetophenone and HPLC-grade acetone were purchased from Aldrich and were used without further purification.

7-Fluorobenzo[*c*]phenanthrene-5,6-quinone (2). The method of Cook was adapted for preparation of **2**.[14] 6-Fluorobenzo[*c*]phenanthrene (75 mg, 0.30 mmol) and $Na_2Cr_2O_7{\cdot}2H_2O$ (90 mg, 0.30 mmol) were dissolved in glacial acetic acid (10 mL) and heated at 75 °C for 65 h. The mixture was cooled and added dropwise to cold 0.1 M Na_2CO_3 (100 mL). The product was extracted into $CHCl_3$ (3 × 30 mL), and the residue was concentrated and dissolved in MeCN for purification by HPLC (Zorbax ODS column (2.1 × 25 cm) eluted with 75/25 MeCN/H_2O at 10 mL/min). The fluoroquinone **2** eluted at 13.5 min and was isolated in 7.5% yield (6.32 mg, 0.023 mmol); mp 193.5–195 °C; HRMS (EI) *m/z* calcd for $C_{18}H_9O_2F$ 276.0586, found 276.0585 (M^+); MS (EI) *m/z* 276 (M^+), 248 (M^+ – CO), 220 (M^+ – 2CO); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 3 H, H_8, $H_{10,11}$ ($H_{2,3}$)), 7.69, 7.79 (t, dt, 2 H, $H_{2,3}$ ($H_{10,11}$)), 7.86 (d, J = 8.1 Hz, 1 H, H_9 (H_4)), 8.05 (d, J = 8.1 Hz, 1 H, H_4 (H_9)), 8.14 (dd, J = 7.5, 1.2 Hz, 1 H, H_1), 8.51 (d, J = 8.4 Hz, 1 H, H_{12}); ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$ = 0 ppm) δ –118.59 (d, $J_{F,8}$ = 11.0 Hz); UV λ_{max} (85/15 MeOH/H_2O) 270.5 nm. The major product eluting at 16.0 min was identified as benzo[*c*]phenanthrene-5,6-quinone: mp 177–9 °C (lit.[14] mp 187–188 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (dt, J = 7.5, 0.6 Hz, 1 H), 7.65 (m, 2 H), 7.7 (m, 3 H), 7.9 (m, 2 H), 8.15 (m, 3 H), 8.59 (d, J = 8.4 Hz, 1 H); MS (EI) *m/z* 258 (M^+), 230 (M^+ – CO), 202 (M^+ – 2CO); UV λ_{max} (85/15 MeOH/H_2O) 276.5, 297.5 (shoulder) nm.

Reaction of 7-Fluorobenzo[*c*]phenanthrene-5,6-quinone with Acetone. Fluoroquinone **2** reacted with excess acetone/water (90% v/v) to completion at 37 °C in 12 h in the absence of light. Product formation was monitored by HPLC on a Zorbax ODS column (0.46 × 25 cm) eluted with a linear gradient of 50/50 MeOH/H_2O to 100% MeOH (0.8 mL/min) over 40 min (t_R (min): **2**, 27; **4**, 23.5; **5**, 25). The products **4** and **5** were eluted by normal-phase HPLC (Zorbax SIL column (0.94 × 25 cm) eluted with 90/10 hexanes/THF (THF freshly distilled over LAH) at 2.5 mL/min). The assignments of the ^1H chemical shifts for **4** and **5** were made from 2D NMR spectra, and determinations of the coupling constants were from highly digitized 1D NMR spectra.

Characterization of 6-[(2′-Oxopropyl)oxy]-7-fluorobenzo[*c*]phenanthren-5(6*H*)-one (4): ^1H NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 3 H, $COCH_3$), 2.71 (d, J = 14.30 Hz, 1 H, OCH_aH_b), 3.40 (d, 1 H, OCH_aH_b), 4.62 (d, $J_{6,F}$ = 3.49 Hz, 1 H, H_6), 7.48 (dt, J = 7.65, 1.3 Hz, 1 H, H_{11}), 7.55 (m, 3 H, $H_{3,8,10}$), 7.75 (dt, J = 7.66, 1.46 Hz, 1 H, H_2), 7.82 (dd, J = 8.04, 0.85 Hz, 1 H, H_4), 7.98 (dd, J = 7.75, 1.33 Hz, 1 H, H_9), 8.01 (d, J = 7.97 Hz, 1 H, H_1), 8.41 (d, 1 H, H_{12}); ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$ = 0 ppm) δ –116.49 (dd, $J_{F,8}$ = 11.84, $J_{F,6}$ = 3.33 Hz, confirmed by decoupling studies); FTIR (cm^{-1}) 1726, 1707 (C=O str), 1143, 1105 (branched C—O—C str); HRMS (EI) *m/z* calcd for $C_{21}H_{15}O_3F$ 334.1005, found 334.1007; MS (EI) *m/z* 334 (M^+), 277 (M^+ – C_3H_5O), 249 (M^+ – $C_4H_5O_2$), 220 (M^+ – $C_5H_6O_3$), 201 (M^+ – $C_5H_6O_3F$); UV λ_{max} (80/20 MeOH/H_2O) 228.5, 259.5 (shoulder) nm.

Characterization of 5-[(2′-Oxopropyl)oxy]-7-fluorobenzo[*c*]phenanthren-6(5*H*)-one (5): ^1H NMR (500 MHz, $CDCl_3$) δ 2.10 (s, 3 H, $COCH_3$), 3.00 (d, J = 15.69 Hz, 1 H, OCH_aH_b), 3.25 (d, 1 H, OCH_aH_b), 4.39 (s, 1 H, H_5), 7.44 (m, 2 H, $H_{3,10}$), 7.55 (overlapping d and t, J = 8.31, $J_{8,F}$ = 10.43 Hz, 2 H, $H_{8,11}$), 7.64 (t, J = 7.28 Hz, 1 H, H_2), 7.86 (m, 2 H, $H_{1,4}$), 7.91 (m, 1 H, H_9), 8.57 (d, J = 8.57 Hz, 1 H, H_{12}); NOE 3.7% enhancement of H_4 (7.86 ppm) upon irradiation of H_5 (4.38 ppm); ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$ = 0 ppm) δ –120.69 (d, $J_{F,8}$ = 10.15 Hz, confirmed by decoupling studies); FTIR (cm^{-1}) 1726, 1710 (C=O str); 1150, 1114 (branched C—O—C str); HRMS (EI) *m/z* calcd for $C_{21}H_{15}O_3F$ 334.1005, found 334.1016; MS (EI) *m/z* 334 (M^+), 277 (M^+ – C_3H_5O), 249 (M^+ – $C_4H_5O_2$), 220 (M^+ – $C_5H_6O_3$), 201 (M^+ – $C_5H_6O_3F$); UV λ_{max} (80/20 MeOH/H_2O) 266 nm.

(6) While two regioisomeric products are possible, **8** has been assigned as the 6-oxo isomer based on the similarity of its chromophore with that of **5** (see the Experimental Section). Acetophenone adduct **8** was characterized as an aldol product by the loss of $M^+ - H_2O$ that was not observed for **4** or **5**. Fragment at 276 ($M^+ - C_6H_5COCH_3$) was observed for **8**. Aldol adducts have consistently fragmented to yield (M^+ – $RCOCH_3$), R = C_6H_5, CH_3; whereas ether adducts with acetone have consistently fragmented to yield ($M^+ - CH_3COCH_2^{\bullet}$) (unpublished results).

(7) Mertzner, P.; Pham, T. N.; Vialle, J. *Nouv. J. Chim.* **1978**, *2*, 179 and references cited therein. Beslin, P.; Lagain, D.; Vialle, J. *J. Org. Chem.* **1980**, *45*, 2517.

(8) Boeckman, R. K., Jr.; Flann, C. J.; Poss, K. M. *J. Am. Chem. Soc.* **1985**, *107*, 4359.

(9) Japp, F. R.; Streatfeild, F. W. *J. Chem. Soc.* **1882**, 270.

(10) Constenla, M. A.; Chaverri, A. *Rev. Latinoamer. Quim.* **1971**, *2*, 58.

(11) Humphry-Baker, R. A.; Salisbury, K.; Wood, G. P. *J. Chem. Soc., Perkin Trans. 2* **1978**, 659.

(12) Japp, F. R.; Miller, N. H. J. *J. Chem. Soc.* **1885**, 10.

(13) Constenla, M. A.; Vega, F. *Rev. Latinoamer, Quim.* **1985**, *16*, 20.

(14) Cook, J. W. *J. Chem. Soc.* **1931**, 2524.

Reaction of 7-Fluorobenzo[c]phenanthrene-5,6-quinone with Acetophenone. The reaction of 2 (0.75 mg, 2.7 μmol), acetophenone (200 μL, 1.7 mmol), and H_2O (200 μL) in MeCN (1 mL) at 37 °C after a prolonged period of time (several days), yielded predominantly one product in quantity sufficient for characterization. Excess acetophenone was removed under a stream of argon followed by high vacuum. The product (8) was purified by HPLC (Zorbax SIL column (0.94 × 25 cm) eluted with 75/25 CH_2Cl_2/ethyl acetate at 4 mL/min): t_R (min) 17; HRMS (EI) m/z calcd for $C_{26}H_{17}O_3F$ 396.1162, found 396.1155; MS (EI) m/z 396 (M^+), 378 ($M^+ - H_2O$), 349 ($M^+ - H_2O - CHO$), 276 ($M^+ - C_6H_5COCH_3$), 248 ($M^+ - CO - C_6H_5COCH_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.36 (d, 1 H, J = 15.90 Hz, CH_aH_b), 4.01 (d, 1 H, CH_aH_b), 4.46 (s, 1 H, OH), 7.3-8.7 (14 H, aromatic); UV λ_{max} (90/10 MeOH/H_2O) 264.5 nm. The minor acetophenone adduct was not isolated in quantities sufficient for NMR but had a similar UV spectrum to the ether 4, UV λ_{max} (90/10 MeOH/H_2O) 228.5, 258.5 (shoulder) nm.

Conversion of the Ether 4 to Its Regioisomer 5. A small amount of the pure ether 4 dissolved in 4/1 acetone/H_2O (500 μL) containing 2-methylnaphthalene (125 μg, internal standard) was added to an amber screw-top vial, and the mixture was maintained at 25 °C. Samples (10 μL) were assayed by HPLC (Zorbax ODS column (0.46 × 25 cm) eluted with a linear gradient of 75/25 MeOH/H_2O to 100% MeOH at 1.1 mL/min over 15 min): t_R (min) 4, 5.6; 5, 6.0; 2-methylnaphthalene, 11.9.

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Supplementary Material Available: ^1H and ^{19}F spectra of the fluoroquinone 2 and the ethers 4 and 5 and results of ^{19}F-[^1H] heteronuclear decoupling experiments (4, 5) and of the NOE experiment (5) (6 pages). Ordering information is given on any current masthead page.

2(*S*),3-Pyridinediyl Thiocarbonate Reagent. Reactions with Amines

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Activated derivatives of carbonic acid may be regarded as bifunctional acylating reagents for the preparation of carbonate esters, ureas, carbamates, mixed carbonic anhydrides, carboxylic acids, esters, ketones, aldehydes, and other derivatives following two successive reactions with appropriate nucleophiles. Examples of such useful reagents include phosgene or triphosgene,[1] carbonyldiimidazole,[2] (alkyloxy)- or (aryloxy)carbonyl chlorides,[3,4] (α-haloalkyloxy)carbonyl chlorides,[5] dialkyl dicarbonates,[6] 2,2′-carbonylbis(3,5-dioxo-4-methyl-1,2,4-oxadiazolidine),[7] and others.[8] We also note that several diactivated ester derivatives of carbonic acid have been applied as acylating reagents in organic synthesis. Known carbonates of this type include bis(*p*-nitrophenyl),[9] 1,2,2,2-tetrachloroethyl *N*-succinimidyl,[10] and the di-2-pyridyl.[11] Comparable applications of cyclic carbonic acid esters such as the *o*-(4-nitrophenylene) carbonate,[12] 4,6-diphenylthieno[3,4-*d*]-1,3-dioxol-2-one 5,5-dioxide[13] or the 1,2(*S*)-pyridinediylium thiocarbonate[14] have not been often reported and merit further notice. Given the expected stability and convenient handling of such reagents, and in view of recent demand for more specific and less toxic chemicals[15] coupled with ongoing development of automated synthetic procedures,[16] we seek new cyclic diesters of carbonic acid as alternative diacylating reagents. In this paper we report the synthesis of a novel cyclic carbonate ester of 2(1*H*)-thioxo-3-pyridinol: 2(*S*),3-pyridinediyl thiocarbonate (2-oxo-1,3-oxathiolo[4,5-*b*]pyridine, 1, or PTC) and its regiospecific reactions with several primary and secondary amines.

Table I. Preparation of Disubstituted Ureas[a]

urea	N,N′-substituents	reaction solvent	isolated yield,[b] %
2a	dicyclohexyl	THF	93
2a	dicyclohexyl	H_2O	91
2b	diphenyl	C_6H_6	91
2c	dibenzyl	EtOAc	91
2d	diallyl	THF	90
2e	phenylallyl	THF	81

[a] Reaction 2. [b] Of ureas listed in ref 17.

Table II. Preparation of 2-Thioxopyrid-3-yl Carbamates[a]

carbamate	N-substit R	N-substit R′	react cond[b]	isol yield, %
3a	H	c-hexyl	A	81
3b	H	allyl	A	75
3c	*N*-piperidinyl		B	87
3d	*N*-pyrrolidinyl		B	91

[a] Reaction 3. [b] A: Dropwise addition of amine in THF at room temperature for 3 h. B: Rapid addition of amine in THF at room temperature for 3 h.

Results and Discussion

2(*S*),3-Pyridinediyl Thiocarbonate. Treatment of 2(1*H*)-thioxo-3-pyridinol (HOPyS) with carbonyldiimidazole (Im_2CO)[2] or 1,1′-carbonylbis(2-methylimidazole)

(1) (a) Hirschmann, R.; Schwam, H.; Strachan, R. G.; Schoenewaldt, E. F.; Barkemeyer, H.; Miller, S. M.; Conn, J. B.; Garsky, V.; Veber, D. F.; Denkewalter, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 2746-2754. (b) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894-895.

(2) Staab, H. A. *Angew, Chem., Int. Ed. Engl.* **1962**, *1*, 351-367.

(3) (a) Vaughan, J. R., Jr.; Osato, R. L. *J. Am. Chem. Soc.* **1951**, *73*, 3547. (b) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1966**, *88*, 1338-1339.

(4) Anderson, G. W.; McGregor, A. C. *J. Am. Chem. Soc.* **1957**, *79*, 6180.

(5) Sennyey, G.; Barcelo, G.; Senet, J.-P.; Bensoam, J.; Loffet, A. *Synthesis* **1986**, *8*, 627.

(6) (a) Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 730-732. (b) Moroder, L.; Hallett, A.; Wunsch, E.; Keller, O.; Wersin, G. *Hoppe-Seyler Z. Physiol. Chem.* **1976**, *357*, 1651-1653.

(7) Denarie, M.; Grenouillat, D.; Malfroot, T.; Senet, J.-P.; Sennyey, G.; Wolf, P. *Tetrahedron Lett.* **1987**, *28*, 5823-5826.

(8) (a) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1964**, *86*, 1839. (b) Nagasawa, T.; Narita, K.; Isowa, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1269.

(9) (a) Wieland, T.; Heinke, B.; Vogeler, K. *Liebigs Ann. Chem.* **1962**, *655*, 189. (b) Glatthard, R.; Matter, M. *Helv. Chim. Acta* **1963**, *46*, 795.

(10) Jaouadi, M.; Martinez, J.; Castro, B.; Barcelo, G.; Sennyey, G.; Senet, J.-P. *J. Org. Chem.* **1987**, *52*, 2364-2367.

(11) Kim, S.; Ko, Y. K. *J. Chem. Soc., Chem. Commun.* **1985**, 473.

(12) (a) Fife, T. H.; McMahon, D. *J. Org. Chem.* **1970**, *35*, 3699-3704. (b) Laufer, D. A.; Doyle, K.; Zhang, X. *Org. Prep. Proced. Int.* **1989**, 771-776.

(13) Kirstgen, R.; Olbrich, A.; Rehwinkel, H.; Steglich, W. *Liebigs Ann. Chem.* **1988**, 437-440.

(14) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939-941.

(15) Haffin, J. *Chem. Eng. News* **1987**, *65*, 26.

(16) (a) Frisbee, A. R.; Nantz, M. H.; Kramer, G. W.; Fuchs, P. L. *J. Am. Chem. Soc.* **1984**, *106*, 7143-7145. (b) Kramer, G. W.; Fuchs, P. L. *Chem. Tech.*, in press (and references cited therein).

(17) Weast, R. C., Astle, M. J., Eds. *CRC Handbook of Data on Organic Compounds*, Vol. 2; CRC Press: Boca Raton, 1985.

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