Anal. Calcd for $C_{27}H_{34}N_4O_4S$: C, 63.51; H, 6.71; N, 10.97. Found: C, 63.45; H, 6.53; N, 10.96.

The free biuret **15** was obtained on treating a solution of 10.20 g (0.02 mol) of **12** in 50 ml of dichloromethane with dry hydrogen chloride gas for 1 h. The residue obtained after evaporating the solvent was treated with methanol leaving colorless plates of **15**, which were filtered off and washed with methanol: 7.4 g (90%) of **15**; mp 140 °C (MeOH); ir ($CHCl_3$) 1720, 1680 cm^{-1} (C=O); ^{13}C NMR ($CDCl_3$) δ 153.3 and 150.4 ppm (carbonyl C).

Anal. Calcd for $C_{21}H_{19}N_3O_4S$: C, 61.61; H, 4.68; N, 10.27. Found: C, 61.09; H, 4.76; N, 10.13.

B. From 1,3-Diphenyldiazetidine-2,4-dione (14) and *p*-Toluenesulfonamide. A solution of 0.01 mol of **14**, *p*-toluenesulfonamide, and triethylamine each in 25 ml of chloroform was kept at 80 °C for 23 h while the progress of the reaction was followed by ir (disappearance of C=O bands of the diazetidine-2,4-dione at 1770 cm^{-1}). The salt **12** was separated from the reaction solution by adding diethyl ether. Thus 2.2 g (43%) of **12** was obtained, identical with a sample prepared under A.

A mixture of 0.01 mol of **14** and *p*-toluenesulfonamide was heated in 10 ml of DMF for 20 h to 120 °C, while the disappearance of **14** was followed by ir. The resulting brown solution yielded, on gradual dilution with water, fractions of 2.2 g of *N,N'*-diphenylurea, mp 245 °C (identical in ir comparison with an authentic sample), and 0.9 g of *N,N*-dimethyl-*N'*-(*p*-toluenesulfonyl)formamidine, mp 134–135 °C (lit.[11] 135–137 °C), ir ($CHCl_3$) 1625 cm^{-1} (C=N).

C. From *N*-Phenyl-*N'*-(*p*-toluenesulfonyl)urea and Phenyl Isocyanate. On adding 0.4 g (0.004 mol) of triethylamine to a suspension of 1.1 g (0.0038 mol) of *N*-phenyl-*N'*-(*p*-toluenesulfonyl)urea in 10 ml of chloroform, salt formation with solvation of the starting material takes place. After 0.45 g (0.0038 ml) of phenyl isocyanate was added the solution was heated to reflux for 3–4 h while the progress of the reaction was followed by ir (disappearance of the –N=C=O band at 2260 cm^{-1}). The resulting solution was diluted with diethyl ether, causing separation of 1.05 g (54%) of **12**, identical with a sample prepared under A.

Registry No.—**1a**, 59812-63-4; **1b**, 59812-64-5; **1c**, 59812-65-6; **1d**, 59812-66-7; **1e**, 59812-67-8; **1f**, 59812-68-9; **2**, 59812-69-0; **3** (R' = *p*-$CH_3C_6H_4$), 59812-79-2; **7**, 59812-80-5; **10a**, 59812-70-3; **10b**, 59812-71-4; **10c**, 59812-72-5; **11a**, 59812-73-6; **11b**, 59812-74-7; **11c**, 59812-75-8; **11d**, 59812-76-9; **11e**, 59812-77-0; **11f**, 59812-78-1; **12**, 59812-82-7; **14**, 1025-36-1; **15**, 59812-81-6; RNCO (R = Me), 624-83-9; RNCO (R = Ph), 103-71-9; RNCO (R = *p*-$CH_3C_6H_4$), 622-58-2; RNCO (R = *m*-$CH_3C_6H_4$), 621-29-4; RNCO (R = *p*-ClC_6H_4), 104-12-1; RNCO (R = $PhCH_2$), 3173-56-6; R'SO_2NCO (R' = *p*-ClC_6H_4), 5769-15-3; R'O_2NCO (R' = *p*-$CH_3C_6H_4$), 4083-64-1; R'SO_2NH_2 (R' = Ph), 98-10-2; R'SO_2NH_2 (R' = *p*-$CH_3C_6H_4$), 70-55-3; 1,2-dimethylimidazole, 1739-84-0; *N*-methyl-*N'*-(*p*-toluenesulfonyl)urea, 13909-69-8; *N*-phenyl-*N'*-(*p*-toluenesulfonyl)urea, 13909-63-2; *N,N'*-diphenylurea, 102-07-8.

References and Notes

(1) H. Ulrich and R. Richter in "Newer Methods of Preparative Organic Chemistry", Vol. 6, W. Foerst, Ed., Verlag Chemie, Weinheim/Bergstr., Germany, 1971, p 280.
(2) G. N. Holcomb, T. J. Silhavy, and R. E. Counsell, *J. Org. Chem.*, **37**, 3357 (1972).
(3) G. N. Holcomb, L. A. Klemm, T. J. Silhavy, and R. E. Counsell, *J. Pharm. Sci.*, **62**, 1379 (1973).
(4) Other isocyanate oligomerizations involving 1,2-dimethylimidazole have been described recently: R. Richter and H. Ulrich, *Synthesis*, 463 (1975).
(5) W. Bartmann, *Chem. Ber.*, **100**, 2938 (1967).
(6) H. Ulrich, B. Tucker, and A. A. R. Sayigh, *Angew. Chem.*, **80**, 281 (1968).
(7) This was confirmed by ir and ^1H NMR analysis. Attempted mass spectral analysis failed owing to extensive fragmentation; no parent ion could be detected.
(8) R. Richter, *Tetrahedron Lett.*, 5037 (1968).
(9) R. Huisgen, K. Herbig, and M. Morikawa, *Chem. Ber.*, **100**, 1107 (1967).
(10) All melting points are uncorrected. Analyses were by Galbraith Laboratories, Knoxville, Tenn.; ir spectra were determined using a Perkin-Elmer 625 spectrophotometer; ^1H NMR spectra were determined with a Varian T-60 and ^{13}C NMR spectra with a Varian CFT20 spectrophotometer using $CDCl_3$ or Me_2SO-d_6 as solvents and tetramethylsilane as internal standard.
(11) R. Albrecht, G. Kresze, and B. Mlakar, *Chem. Ber.*, **97**, 483 (1964).

Fluoroxytrifluoromethane Reactions with Polynuclear Arenes. A New Route to Fluorinated K-Region Ketones

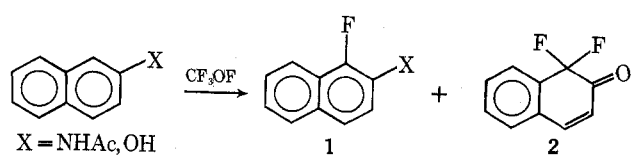
Timothy B. Patrick,* Mary H. LeFaivre,[1a] and Thomas E. Koertge[1b]

Chemistry Department, Southern Illinois University, Edwardsville, Illinois 62026

Received April 5, 1976

Reactions between 9-(*N*-acetylamino)phenanthrene (**3**), 5-(*N*-acetylamino)benzo[*c*]phenanthrene (**5**), 5-methoxy-7,12-dimethylbenz[*a*]anthracene (**7**), and fluoroxytrifluoromethane (CF_3OF) yielded 10,10-difluorophenanthren-9(10*H*)-one (**4**, 40%), 6-fluorobenzo[*c*]phenanthren-5(6*H*)-one (**6**, 30%), and 6-fluoro-7,12-dimethylbenz[*a*]anthracen-5(6*H*)-one (**8**, 45%), respectively, as the major products. Compounds **6** and **8** were found to exist predominantly as the K-region ketone instead of the usual K-region phenol; steric and fluorine electronic effects are used to explain the preference for the ketonic tautomer.

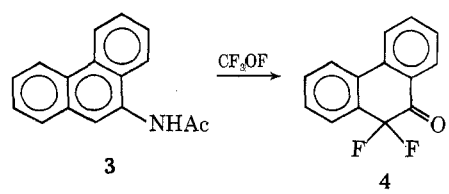
Previous work on fluoroxytrifluoromethane (CF_3OF) reactions with polynuclear aromatic systems has revealed reactions which include monofluorination, *gem*-difluorination, and oxidation.[2] Thus certain 2-substituted naphthalene derivatives reacted with CF_3OF to produce 1-fluoro substituted naphthalenes (**1**) and 1,1-difluoronaphthalen-2(1*H*)-one (**2**).



9-Substituted anthracenes produced only the oxidation product anthraquinone. Further studies of CF_3OF reactions with higher polynuclear arenes were pursued to determine (1) the orientation and extent of fluorination, (2) the synthetic utility, and (3) the properties of the derived products.

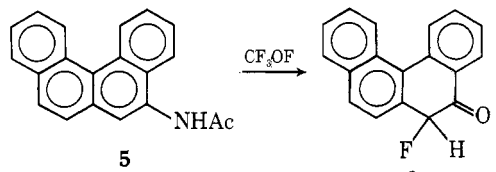
Results

9-(*N*-Acetylamino)phenanthrene (**3**) reacted with CF_3OF in chloroform solution at room temperature to yield a mixture of 9,10-phenanthraquinone (3%), 10,10-difluorophenanthren-9(10*H*)-one (**4**, 40%), and an unidentified high-melting



material. No evidence was obtained for the presence of a monofluorination product. The *gem*-difluoro ketone **4** shows carbonyl absorption in the infrared spectrum at 1700 cm^{-1}; compound **2** had previously been observed to contain absorption at 1700 cm^{-1} for the carbonyl group.[2]

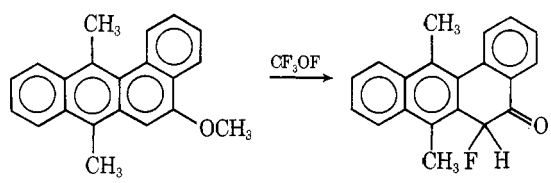
The reaction between CF_3OF and 5-(*N*-acetylamino)benzo[*c*]phenanthrene (**5**) produced a dark oil which, after several chromatographic purifications, furnished 6-fluorobenzo[*c*]-phenanthren-5(6*H*)-one (**6**) in 30% yield. Compound **6** showed



5 6

carbonyl absorption in its infrared spectrum at 1720 cm^{-1}; no hydroxyl absorption was observed.

When 5-methoxy-7,12-dimethylbenz[*a*]anthracene (**7**) and CF_3OF were allowed to react, the major identifiable product, isolated in 45% yield, was 6-fluoro-7,12-dimethylbenz[*a*]-anthracen-5(6*H*)-one (**8**). Compound **8** displayed carbonyl



7 8

absorption at 1700 cm^{-1} and some detectable hydroxyl absorption at 3390 cm^{-1}.

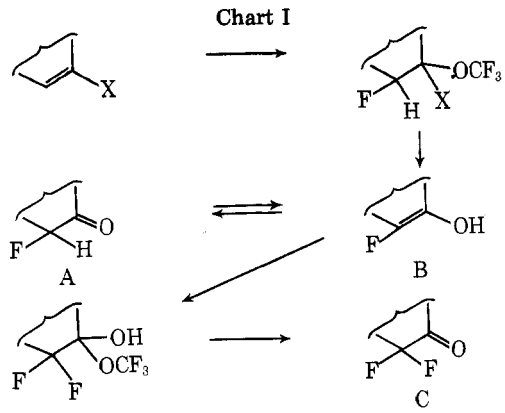
A material balance of 80–100% was found in all reactions with intractable, high-melting material accounting for the unidentified portion of the reactions. In the case of **7**, an empirical formula for the material was determined from elemental analysis as C_5H_3OF; the material did not have enough volatility for a mass spectral investigation.

Fluoroxy reactions with several unsubstituted polynuclear aromatic systems were also attempted. Naphthalene and phenanthrene were found unreactive; benz[*a*]anthracene afforded a small amount of viscous oil with an empirical formula of $C_{18}H_{12}F_8$ but structure elucidation has been unsuccessful; anthracene was converted into anthraquinone in 70% yield.

Discussion

Fluoroxytrifluoromethane is a powerful reagent for effecting electrophilic fluorination, addition, and oxidation.[3] The present findings can be interpreted as combined electrophilic substitution–oxidation processes. However, an addition–oxidation path as shown in Chart I is also attractive (X = NHAc, OCH_3).

Chart I



In this path, the K-region bond undergoes addition of CF_3OF followed by oxidation to the fluoro ketone A which is in equilibrium with the fluorophenol B. A steric effect in **6** and **8** renders the K region relatively olefinic in nature.[4] The fluorine atom destabilizes the olefin-like[5] system such that the keto form predominates and reaction stops at this point. In the absence of the steric effect, the K-region phenolic tautomer (B) predominates and a second addition occurs; subsequent oxidation affords the α,α-difluoro ketone C. Previous results with 2-naphthol show that both the monofluorophenol and α,α-difluoro ketone can be isolated: the aromatic character of the naphthalene system possibly retards the addition reaction. The ir and NMR spectra of **6** and **8** show that the keto structure is highly predominant in **6** while **8** contains a small but detectable (ir) amount of phenol tautomer.

Keto tautomers have previously been reported present in significant amount in 5-hydroxy-[4,6] and 6-hydroxy-7,12-dimethylbenz[*a*]anthracene (DMBA).[7] The 5-hydroxy isomer exists in approximately 1:1 equilibrium with its ketonic tautomer.[4] The dominance of the keto form in both **6** and **8** can be explained using a combination of steric and fluorine electronic effects. The close proximity of two fused benzene rings in benzo[*c*]phenanthrene renders the system nonplanar;[8] the K region thus loses some resonance stabilization and gains olefinic character. Substitution of a fluorine atom in the K region destabilizes the olefinic bond through electron repulsion[5] thus causing **6** to exist in the keto form. 5-Hydroxybenzo[*c*]phenanthrene, without the fluorine substituent, exists as the phenolic tautomer.[9] Similar reasoning for increased olefinic character of the K region in 5-hydroxy-DMBA, which has internal strain from the interaction of the 12-methyl group and the 1 proton,[10] has been evoked.[4] 5-Hydroxybenz[*a*]-anthracene, without the steric crowding, exists as the phenolic tautomer.[6] Thus the strain in 5-hydroxy-DMBA accounts for the increased ketone content and the fluorine substituent effect in 6-fluoro-5-hydroxy-DMBA (**8**) can explain the dominance of the keto tautomer in this system.

The K-region keto structure has been suggested as an important intermediate in the carcinogenic activity of DMBA.[4] Although initial carcinogenic activity tests have not supported this suggestion,[7] thorough testing of the suggestion has not been completed. The reactions between CF_3OF and the polynuclear arenes described in this study constitute a novel route to K-region ketones. More in-depth study of K-region ketones and their role in carcinogenic activity is now possible.

Experimental Section

All temperature readings are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. NMR spectra were determined on a Varian T-60 spectrometer using tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were obtained on a Varian MAT-111 spectrometer (80 eV); samples were introduced using a direct inlet probe. Infrared spectra were determined on a Perkin-Elmer Model 337 grating spectrophotometer using polystyrene for calibration. Fluoroxytrifluoromethane was obtained from PCR, Inc., Gainesville, Fla., or prepared according to literature procedures.[11] Reagent grade chloroform was used in all reactions. TLC was performed using Mallinkrodt SilicAR.

General Procedure. 10,10-Difluorophenanthren-9(10*H*)-one (4). To a solution of 9-(*N*-acetylamino)phenanthrene[12] (0.25 g, 1.06 mmol) in 75 ml of chloroform contained in a 200-ml, round-bottomed flask open to the atmosphere was added with stirring at ambient temperature a slow stream of CF_3OF gas (9.6 mmol) until TLC analysis showed only a trace of starting material remaining (1 h). The contents were then stirred and nitrogen gas was used to facilitate the removal of excess CF_3OF. A white, high-melting (>400 °C) substance, 0.075 g, was removed by filtration.

The concentrated filtrate was chromatographed on a 26.5 × 2.5 cm Florisil column (benzene) yielding, after sublimation and recrystallization (hexane), 87.3 mg (40%) of slightly yellow **4**: mp 100–102 °C; ir (KBr) 1700 cm^{-1} (C=O); NMR (CCl_4) δ 7.2–8.1 (aromatic); MS *m/e* (rel intensity) 230 (M, 92), 211 (92), 200 (100). Anal. Calcd for $C_{14}H_8F_2O$: C, 73.1: H, 3.5; F, 16.4. Found: C, 73.4; H, 3.6; F, 16.4.

Chloroform eluent furnished 12.5 mg (6.3%) of 9,10-phenanthraquinone identified by comparison with authentic material, mp 205 °C (lit.[13] mp 208.5–210 °C). Further elution gave 65 mg of unreacted **3**.

A reaction attempted at −20 °C gave only unchanged starting material.

6-Fluorobenzo[*c*]phenanthren-5(6*H*)-one (6). A solution of 0.21 g (0.72 mmol) of 5-(*N*-acetylamino)benzo[*c*]phenanthrene[14] in 75 ml of chloroform was treated with 2.4 g of CF_3OF according to the above procedure. After removal of residual gas and concentration on a rotary evaporator, 0.34 g of crude oil was obtained. Preparative TLC (500 μ, 20 × 5 cm slide, $CHCl_3$) showed the presence of several substances from which the major component **6** (R_f 0.39) was isolated as an oil (57.7 mg, 30%) which slowly crystallized over a period of 2 months: mp 85–88 °C (yellow crystals); ir (neat) 1730 (C=O), 730 cm^{-1}; NMR ($CDCl_3$) δ 4.43 (1 H, benzylic proton, d, J_{HF} = 48 Hz), 7.4–8.0 (10 H, m, aromatic); MS *m/e* (rel intensity) 262 (M, 100), 243 (14), 232 (21), 149 (38). Anal. Calcd for $C_{18}H_{11}FO$: C, 82.4; H, 4.2; F, 7.3. Found: C, 82.1; H, 4.5; F, 7.7.

6-Fluoro-7,12-dimethylbenz[*a*]anthracen-5(6*H*)-one (8). 6-Methoxy-7,12-dimethylbenz[*a*]anthracene[15] (0.25 g, 0.66 mmol) in 75 ml of chloroform was reacted with 1.0 g of CF_3OF. A brown solid (0.059 g) was obtained by filtration: mp >400 °C; empirical formula, C_5H_3FO; mass spectrum not attainable owing to low volatility; ir (KBr) broad, diffuse absorptions.

The concentrated filtrate furnished a dark oil which gave four fractions by TLC (300 μ, 20 × 5 cm, 1:1 $CHCl_3$–hexane): (1) R_f 0.074, 9.1 mg, identical with above described high melting point material; (2) R_f 0.50, 26 mg, unidentified; (3) R_f 0.79, 87 mg (45%) of **8**; (4) R_f 0.95, 59 mg, recovered **7**.

Compound **8** gave the following properties: mp 159–160 °C; ir (KBr) 3390 (OH), 1700 (C=O), 890, 745, 710 cm^{-1} (aromatic); NMR ($CDCl_3$) δ 1.42 (3 H, s, 7-CH_3), 2.88 (3 H, s, 12-CH_3), 4.0 (1 H, d, benzylic, J_{HF} = 84 Hz), 7.3–8.2 (8 H, m, aromatic); MS *m/e* (rel intensity) 290 (M, 7), 275 (22), 271 (7), 260 (100), 245 (50). Anal. Calcd for $C_{20}H_{15}FO$: C, 82,8; H, 5.2; F, 6.6 Found: C, 83.0; H, 5.2; F, 6.5.

Fraction 2 showed a broad melting range of 140 to >300 °C. Analytical TLC indicated the presence of **8** and the substance(s) in fraction 1.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. M.H.L. was supported by a research assistantship from the Graduate School, Southern Illinois University.

Registry No.—**3,** 4235-09-0; **4,** 59830-28-3; **5,** 4176-51-6; **6,** 59830-29-4; **7,** 53306-03-9; **8,** 59830-30-7; CF_3OF, 373-91-1.

References and Notes

(1) (a) Taken in part from the M.S. Thesis of M.H.L., Southern Illinois University, 1976; (b) Petroleum Research Fund Undergraduate Fellow.
(2) T. B. Patrick and E. C. Hayward, *J. Org. Chem.*, **39,** 2120 (1974).
(3) C. M. Sharts and W. A. Sheppard, *Org. React.*, **21,** 125 (1974).
(4) M. S. Newman and D. R. Olsen, *J. Am. Chem. Soc.*, **96,** 6207 (1974).
(5) R. D. Chambers, "Fluorine in Organic Chemistry", Wiley, New York, N.Y., 1973, p 142.
(6) R. G. Harvey, S. H. Goh, and C. Cortez, *J. Am. Chem. Soc.*, **97,** 3468 (1975).
(7) A. Dipple, L. S. Levy, and P. T. Lype, *Cancer Res.*, **35,** 652 (1975).
(8) F. H. Herbstein and G. M. S. Schmidt [*J. Chem. Soc.*, 3302 (1954)] have established the nonplanarity of benzo[*c*]phenanthrene by x-ray analysis.
(9) M. S. Newman and J. Blum, *J. Am. Chem. Soc.*, **86,** 503 (1964). A sample provided by Dr. Newman was reexamined using ir and NMR; no evidence for ketone presence was found.
(10) D. Sayre and P. H. Friedlander [*Nature (London)*, **187,** 139 (1960)] have found large deviation from planarity in DMBA by x-ray analysis.
(11) M. Lustig, A. R. Pitochelli, and J. K. Ruff, *J. Am. Chem. Soc.*, **89,** 2841 (1967); T. B. Patrick and R. L. Bain, unpublished work on apparatus modification.
(12) R. DeRidder and R. H. Martin, *Bull. Soc. Chim. Belg.*, **69,** 534 (1960); mp (reported) 207.8–208.8 °C, mp (observed) 207.5–208.5 °C.
(13) R. Wendland and J. LaLonde, "Organic Syntheses", Collect. Vol IV, N. Rabjohn, Ed., Wiley, New York, N.Y., 1963, p 757.
(14) M. S. Newman and J. Blum, *J. Am. Chem. Soc.*, **86,** 1835 (1964); mp (reported) 216–217 °C, mp (observed) 219–220 °C.
(15) We thank Dr. Newman for the sample of **7** used in this work, ref 4.

2,4-Dihydroxyphenanthrenes and Derived Ethers. Regioselective Etherification of Acetates

H. E. Zaugg* and D. A. Dunnigan

Division of Pharmacology and Medicinal Chemistry, Abbott Laboratories, North Chicago, Illinois 60064

Received May 10, 1976

Etherification of the two phenanthrene diacetates **3** and **11** using a large alkyl halide in the presence of anhydrous K_2CO_3 in refluxing dry acetone is much more regioselective at the 2 position than is the direct alkylation of the monosodium salts of the corresponding phenanthrenediols **2** and **10.** However, this regioselectivity unaccountably disappears when methyl iodide is used as the alkylating agent. Also, when the steric hindrance provided by the 5 position is diminished by conversion to the nonplanar 9,10-dihydrophenanthrene system, regioselective etherification of the diacetate (i.e., **20**) no longer occurs. End products of the present work were prepared as carbocyclic analogues of the cannabinoids. Although none shows appreciable central nervous system activity, some of the chemistry used in their preparation may be useful for the syntheses of certain antifungal phytoalexins which are known to be ethers of 2,4-dihydroxy-9,10-dihydrophenanthrenes.

In extension of our work[1] in the cannabinoid field, some 2,4-disubstituted phenanthrenes and corresponding 9,10-dihydro derivatives were prepared as carbocyclic analogues of the pharmacologically potent heterotricyclic substances. Although none of the analogues exhibited appreciable central nervous system activity, some of the chemistry described here should be applicable to improved syntheses in the area of the antifungal phytoalexins, orchinol, hircinol, and loroglossol. These have been shown to be methyl ethers of 9,10-dihydro-2,4,5(7)-trihydroxyphenanthrene.[2,3]

The key intermediate **2** for this work was provided by a modification of a reported method.[4] By treating crude keto ester **1** with methanesulfonic acid at room temperature instead of polyphosphoric acid at 150 °C, the 6% reported yield of **2** was increased to nearly 60%.

Selective ether formation at the less hindered 2 position of **2** was initially approached by simple alkylation of the monosodium salt in hexamethylphosphoramide (HMPA). Under these conditions 3-*p*-fluorophenylpropyl bromide (3-FPB) gave a 53% yield of the desired monoether **4** and a 34% yield of the diether **6.** Column chromatography was necessary for the isolation of both products even though none of the mo-