Synthesis of Fluoranthenо[1,2-*b*]thiophene and Fluoranthenо[3,2-*b*]thiophene, Isosteres of Benzofluoranthenes

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The total syntheses of fluoranthenо[1,2-*b*]thiophene and fluoranthenо[3,2-*b*]thiophene are reported. The common cyclobutanone intermediate which was obtained by [2 + 2] addition of fluorenylidene ketene with 2,3-dihydrothiophene underwent regioselectively α or β ring opening to lead to linear or angular PAC skeleton molecules under desired conditions. 2,3-Dichloro-5,6-dicyanobenzoquinone was applied for aromatization to achieve the formation of PAC's. These two isosteres exhibit very similar uv/visible spectra to benzo[*a*] and [*b*]fluoranthenes respectively. Spectroscopic data used for their structural assignments is also discussed.

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Introduction.

The sulfur content in fossil fuels represents a significant component with much of the sulfur bound as organosulfur derivatives [1]. Under reducing conditions during the combustion of petroleum, coal and other fuels polycyclic aromatic hydrocarbons (PAH) are among the principal byproducts. Under the same conditions fuel-bound sulfur becomes incorporated into stable thiophene condensed aromatic derivatives. Environmental concerns of the presence and toxic nature of PAH have recently been extended to sulfur polycyclic aromatic compounds (PAC). Sulfur isosteres of carcinogenic PAH's have been shown to exhibit levels of mutagenic activity comparable with their PAH isosteres [2].

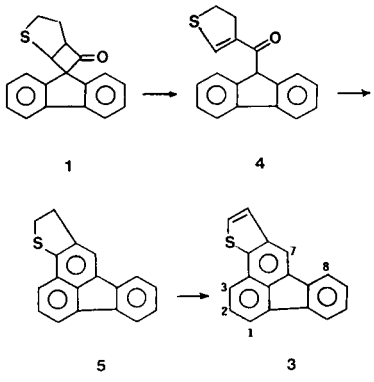
Cyclopentene fused PAH's such as cyclopenta[*c,d*]pyrene have been found to be common environmental contaminants and show levels of mutagenic and carcinogenic activity that are comparable with those of benzo[*a*]pyene [3]. More recently it has been shown that some of the more simple cyclopentene PAH's such as aceanthrylene and acephenanthrylene exhibit moderate levels of toxicity which correlate with the stabilization energies of the suspected carbocation intermediates produced from the cyclopenta epoxide metabolites [4,5]. In contrast to the carbocyclic systems relatively little is known about the biological properties of sulfur heterocyclic analogs of mutagenic and carcinogenic PAH's primarily due to the lack of standards [6]. Recently we have prepared a number of novel cyclopentene-fused polycyclic aromatic thiophenes with the objective of studying their environmental presence and toxicological properties [7,8].

Our approach to the preparation of PAH's fused with non-benzenoid ring systems involves the use of cyclobutanone intermediates obtained from aryl ketene cycloolefin cycloadditions and their regioselective ring-opening and ortho-annelation reactions [9]. In view of the toxicity associated with benzo[*b*]fluoranthene and related derivatives [10] we were interested in extending the cyclobutanone methodology for the preparation of non-benzenoid terminal ring annelated PAC's to include thiophene isosteres of both benzo[*a*] and benzo[*b*]fluoranthenes. This note describes the preparation of both fluoranthenо[1,2-*b*]thiophene **2** and fluoranthenо[3,2-*b*]thiophene **3** from a common cyclobutanone intermediate.

Results and Discussion.

The key intermediate in the synthesis was the fluorenylidene ketene cycloadduct **1** of 2,3-dihydrothiophene which was prepared by generating 9-fluorenylidene ketone "*in situ*" (from 9-fluorenylcarbonylchloride by dehydrochlorination with triethylamine) with a 2.4 equivalent excess of 2,3-dihydrothiophene" [11]. The regiochemistry of the crystalline cycloadduct was assigned on the basis of nmr spectral data as well as previous observations of ketone/enol ether and thioether cycloadditions [12,13]. Cyclobutanones possessing a positive charge stabilizing group at C-3 undergo regioselective β-ring opening under acidic conditions [9]. Treatment of ketone **1** with triflic acid at room temperature gave the unsaturated ketone **4** in 90% yield. *Ortho*-ring annelation to the dihydrothiophene **5** could be accomplished with polyphosphoric acid or triflic acid. Slightly better yields of **5** were obtained with polyphosphoric acid. This particular transformation involves a formal dehydration which has been observed for a related system [7] and rationalized in terms of a hydride transfer mechanism. Dehydrogenation of **5** to **3** could be readily effected with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in 69% yield. Thiophene **3** was produced as a yellow crystalline compound (mp 133-135°) and exhibited an uv/visible spectrum very similar to that of benzo[*b*]fluoranthene indicating the similarity between thiophene and benzene rings in acting as conjugating chromophores. Further confirmation of the structural integrity of **3** was obtained from both the 1-D and 2-D (COSY) ^{1}H nmr spectra. Furthermore Nuclear Overhauser Enhancement difference spectra and its 2-D version (NOESY) established the non-coupled proximal hydrogens relationships at the peri or bay-region positions [14].

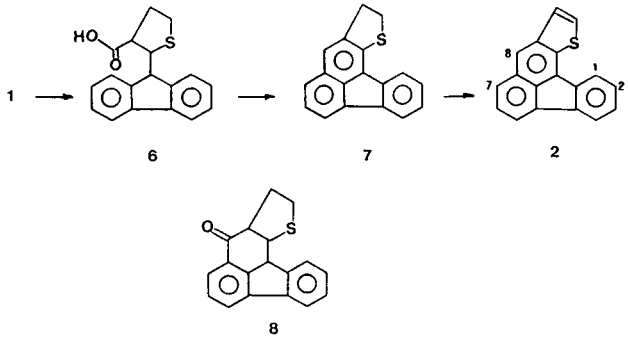
Scheme 1



The preparation of the linear thiophene **2** was based on the regiospecific α ring-opening reactions previously observed for α-arylcyclobutanones [9]. Treatment of ketone **1** with potassium hydroxide gave carboxylic acid **6** in almost quantitative yield. Most efficient dehydrative cyclization (*ortho*-annelation) of **6** was effected by treating a neat sample of **6** with polyphosphoric acid at 110°. The double dehydration product (dihydrothiophene) **7** was produced in this manner in 99% yield. It is presumed that ketone **8** is an intermediate in the acid-catalyzed dehydration and ring annelation, however, it was not possible to observe this intermediate under the reaction conditions.

Standard treatment of dihydrothiophene **7** with DDQ produced the desired linear-fused thiophene **2** in 88% yield. Thiophene **2** was a pale yellow crystalline material which exhibited an uv/visible absorption spectrum very similar to benz[*a*]fluoranthene. The proton assignments were based on 1-D and 2-D ^{1}H nmr spectra including COSY and NOESY methods [15].

Scheme 2



In summary both novel sulphur isosteres **2** and **3** of benz[*a*]fluoranthene and benz[*b*]fluoranthene were prepared from a common cyclobutanone intermediate. The use of α-arylcyclobutanones as precursors to polycyclic aromatic heterocycles appears to be a general route to PAC's possessing terminal non-benzenoid rings. The bioassay of both thiophenes **2** and **3** are to be performed and compared with the activity of their benzofluoranthene analogs.

EXPERIMENTAL

Melting points (mp) were determined on a Reicher melting point apparatus and were uncorrected. Infrared (ir) spectra were recorded on a Unicam SP-1000 instrument as thin films or potassium bromide pellets. Ultraviolet (uv) spectra were measured on a Unicam SP800-A spectrometer and Hewlett Packard 8451A diode array spectrophotometer. Proton nmr spectra were recorded on a Bruker AM-300 spectrometer at 300 MHz using samples dissolved in deuteriochloroform containing 1% TMS as an internal standard. All nmr values are reported as chemical shifts δ in ppm downfield from TMS. Mass spectra were recorded on a VG Micromass 16F spectrometer. High resolution mass spectrometry was performed at the McMaster Regional Centre for Mass Spectrometry using a VG ZAB-E instrument in the EI mode at 70eV. Elemental analyses were performed by Guelph Chemical Laboratories Limited. 2,3-Dihydrothiophene was prepared according to the method of Sosnovsky [11].

Tetracyclic Ketone **1**.

A mixture of 8 g (38.1 mmoles) of 9-fluorenecarboxylic acid and 12 ml of thionyl chloride was heated to 50° and kept stirring until all the carboxylic acid was dissolved. Excess thionyl chloride was evaporated under reduced pressure. Without further purification, the acid chloride was used in the 2 + 2 reaction below.

A mixture of 8.5 g (98.8 mmoles) of 2.3 dihydrothiophene and 6 ml (41.9 mmoles) of triethyl amine in 60 ml dry dichloromethane was cooled to 0°. To the mixture, a solution of above acid chloride in 80 ml of dry dichloromethane was added dropwise under nitrogen. The ice/water bath was removed to allow the reaction to warm up to room temperature. The reaction mixture was kept stirring for an additional 3 hours. The ammonium salt was filtered off. The filtrate was washed successively with water (100 ml), 10% hydrochloric acid (100 ml), saturated sodium bicarbonate solution (60 ml), and water (100 ml), dried over magnesium sulfate, filtered, and solvent removed to afford a yellow solid (8.6 g). The solid was column flash chromatographed on silica gel (dichloromethane:carbon tetrachloride (60:40) eluant) to yield cyclobutanone **1** as white crystals (8.2 g, 29.5 mmoles).

Cyclobutanone **1** can be recrystallized from benzene. During recrystallization, some decomposition to 9-fluorenecarboxylic acid occurred upon heating, yield, 77% (from 9-fluorenecarboxylic acid), mp, decomposed at 140-142° to 9-fluorenecarboxylic acid; ^{1}H nmr (deuteriochloroform): δ 7.71-7.75 (m, 2H), 7.64 (d, J = 7.3 Hz, 1H), 7.51 (d, J = 7.0 Hz, 1H), 7.32-7.46 (m, 4H), 4.78 (t, J = 8.2 Hz, 1H), 4.50 (d, J = 8.7 Hz, 1H), 3.13-3.29 (m, 2H), 2.89 (dd, J = 5.0 Hz and 13.3 Hz, 1H), 2.08-2.22 (m, 1H); ir: 1780 (C=O), 1450, 740 cm^{-1}; ms: m/z (relative intensity) 278 (M+, 12), 250 (11), 192 (100), 164 (88), 85 (34).

Anal. Calcd. for $C_{18}H_{14}OS$: C, 77.67; H, 5.07; S, 11.52. Found: C, 78.03; H, 5.37; S, 11.82.

Tricyclic Unsaturated Ketone **4**.

Ten drops of trifluoroacetic acid was added to a solution of 315 mg (1.13 mmoles) of cyclobutanone **1** in 20 ml of dry dichloromethane. The reaction mixture was stirred for 20 minutes, then poured onto ice/water. The aqueous layer was separated. The organic layer was washed successively with saturated sodium bicarbonate solution (20 ml × 2) and water (20 ml × 2), dried over

magnesium sulfate, filtered, solvent removed giving 65 mg (0.23 mmole) of unsaturated ketone **4** which was recrystallized from absolute ethanol. The mother liquid was column chromatographed on silica gel (dichloromethane:carbon tetrachloride (80:20) eluant) to yield another 220 mg (0.79 mmole) of ketone **4**, yield, 91%, mp 157-159°; ^{1}H nmr (deuteriochloroform): δ 7.79 (d, J = 7.8 Hz, 2H), 7.40-7.47 (m, 4H), 7.31 (t, J = 7.5 Hz, 2H), 6.81 (s, 1H); 5.16 (s, 1H), 3.18 (t, J = 9.0 Hz, 2H), 2.95 (t, J = 9.0 Hz, 2H); ir: 1640 (C=O), 1550, 745, 735 cm^{-1}; uv: λ (ε × 10^{-4}), 216 (2.66), 264 (1.68), 304 (1.36), 322 (1.54); ms: m/z (relative intensity) 278 (M+, 35), 165 (47), 113 (100), 85 (22), 45 (33). A satisfactory elemental analysis could not be obtained since this compound undergoes decomposition during one day upon standing.

Dihydrothiophene **5** from Polyphosphoric Acid Reaction of Ketone **4**.

Unsaturated ketone **4** (180 mg, 0.65 mmole) was added to 10 g of preheated (100°) polyphosphoric acid and stirred for 4 minutes. The reaction mixture was poured onto ice/water and extracted with dichloromethane. The organic layer was washed successively with saturated sodium bicarbonate solution and water, dried over magnesium sulfate, filtered, solvent removed to afford 130 mg yellow solid which was column chromatographed (silica gel, hexanes:benzene (80:20) eluant) to yield 108 mg (0.42 mmole) of the dihydrothiophene derivative **5** as yellow fluoroscent crystals, yield, 64%, mp 115-117°; ^{1}H nmr (perdeuteriobenzene): δ 8.11 (d, J = 7.4 Hz, 1H), 7.74 (d, J = 7.3 Hz, 1H), 7.64 (d, J = 6.9 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.32 (dd, J = 6.9 and 8.0 Hz, 1H), 7.27 (t, 1H), 7.20 (t, 1H), 7.08 (s, 1H), 2.81-2.84 (m, 2H), 2.73-2.79 (m, 2H); uv: λ (ε × 10^{-4}), 232 (4.01), 256 (2.84), 278 (2.11), 284 (2.21), 294 (1.97), 330 (0.68), 346 (1.24), 364 (0.80), 382 (0.95); ms: m/z (relative intensity) 260 (M+, 100), 258 (83), 226 (13), 215 (14), 129 (21).

Anal. Calcd. for $C_{18}H_{12}S$: C, 83.04; H, 4.65. Found: C, 83.38; H, 4.89.

Dihydrothiophene **5** *via* Triflic Acid Reaction of **1**.

Eight drops of trifluoroacetic acid was added to a solution of 200 mg (0.72 mmole) cyclobutanone **1** in 20 ml of dry benzene. The reaction mixture was stirred for 20 minutes at room temperature then heated to reflux and stirred for an additional 1.5 hours. The reaction mixture was poured onto ice/water. The aqueous layer was separated and the organic layer was washed successively with saturated sodium bicarbonate (20 ml) and water (20 ml), dried over magnesium sulfate, filtered, solvent removed to afford 152 mg yellow solid which was column chromatographed (silica gel, hexanes; benzene (80:20) eluant) to yield 83 mg (0.32 mmole) dihydrothiophene derivative **5** identical with a sample prepared above.

Fluorantheno[3,2-*b*]thiophene **3**.

A solution of 200 mg (0.77 mmole) dihydrothiophene derivative **5** in 15 ml of dry benzene was added to a solution of 200 mg (0.88 mmole) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 20 ml of dry benzene dropwise under nitrogen gas. The mixture was heated to reflux for 1 hour and allowed to cool followed by solvent evaporation. The reaction mixture was passed through a short column of neutral alumina and eluted with benzene. The solvent was evaporated to afford 157 mg which was recrystallized from absolute ethanol to yield 42 mg (0.16 mmole) of yellow thiophene derivative **3**. The mother liquid was applied on two preparative silica gel tlc plates (hexane:benzene (90:10) eluant) to yield 94 mg (0.36 mmole) of thiophene derivative PAH **3** along with 8 mg of unreacted starting material **5**, yield, 69%, mp 133-135°; ^{1}H nmr (perdeuteriobenzene): δ 8.04 (d, J = 7.5 Hz, 1H), 7.86 (s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 6.9 Hz, 1H), 7.37 (dd, J = 6.9 and 8.2 Hz, 1 H), 7.28 (dt, Jd = 1.04 Hz, Jt = 7.5 Hz, 1H), 7.21 (dt, J_d = 1.04 Hz, J_t = 7.5 Hz), 7.07 (d, J = 5.6 Hz, 1H), 6.93 (d, J = 5.6 Hz, 1H); ^{1}H nmr (deuteriochloroform): δ 8.35 (s, 1H), 7.98-8.03 (m, 4H), 7.66 (dd, J = 6.9 and 8.2 Hz, 1H), 7.60 (d, J = 5.6 Hz, 1H), 7.57 (d, J = 5.6 Hz, 1H), 7.50 (dt, J_d = 1.04 Hz, J_t = 7.5 Hz, 1H), 7.43 (dt, J_d = 1.04 Hz, J_t = 7.5 Hz, 1H); uv: λ (ε × 10^{-4}), 210 (2.95), 238 (3.13), 270 (4.53), 300 (0.34), 346 (0.38), 364 (0.34), 398 (0.68); ms: m/z (relative intensity) 258 (M+, 100), 213 (22), 129 (41); high resolution ms: m/e Calcd: 258.0503. Found: 258.0496.

Carboxylic Acid **6**.

A solution of 140 mg (2.5 mmoles) potassium hydroxide in 25 ml of 95% ethanol was heated to reflux for a few minutes, then 320 mg (1.15 mmoles) of cyclobutanone **1** was added. The mixture was stirred under reflux for 2.5 hours. The ethanol was evaporated under reduced pressure. The potassium salt was then dissolved in water and extracted with dichloromethane to remove unreacted starting material. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with dichloromethane. Combined the organic layers and dried over magnesium sulfate, filtered, and solvent removed to afford 340 mg (1.15 mmoles) carboxylic acid, yield, 100%, mp 159.5-161°; ^{1}H nmr (deuteriochloroform): δ 8.05 (d, J = 7.5 Hz, 1H), 7.74 (t, J = 8.3 Hz, 2H), 7.53 (d, J = 7.4 Hz, 1H), 7.23-7.44 (m, 4H), 4.66-4.70 (m, 1H), 4.29 (d, J = 3.3 Hz, 1H), 2.82-2.88 (m, 2H), 2.27-2.31 (m, 1H), 2.11-2.17 (m, 1H), 1.95-2.03 (m, 1H); ir: 3400 (OH), 1700 cm^{-1} C=O); ms: m/z (relative intensity) 296 (M+, 37), 165 (85), 131 (100), 87 (31), 85 (27), 45 (15); high resolution ms: m/e Calcd: 296.0871. Found: 296.0873.

Fluorantheno[1,2-*b*]thiophene.

Three hundred mg (1.01 mmoles) of carboxylic acid **6** was added to 15 g of preheated (110°) polyphosphoric acid and stirred for 1.5 hours (until all carboxylic acid crystals disappeared) and poured onto ice/water. The resulting aqueous solution was extracted with dichloromethane. The organic layers were combined and washed successively with saturated sodium bicarbonate solution (50 ml), and water (50 ml), dried over magnesium sulfate, filtered. The solvent evaporated under reduced pressure to yield 270 mg yellow solid dihydrothiophene derivative **7** which was recrystallized from absolute ethanol to yield 130 mg (0.5 mmole) as yellow crystals. The mother liquid was applied on 2 preparative silica gel tlc plates (hexanes:benzene (80:20) eluant) to afford 132 mg (0.51 mmole) of dihydrothiophene derivative **7** along with 2.5 mg of highly fluoroscent compound which was identified to be thiophene derivative PAH **2**, yield, 99%, mp 128-129.5°; ^{1}H nmr (perdeuteriobenzene): δ 7.75 (d, J = 8.2 Hz, 1H), 7.69 (t, J = 6.7 Hz, 2H), 7.55 (d, J = 6.9 Hz, 1H), 7.19-7.28 (m, 4H), 2.94-3.00 (m, 2H), 2.83-2.88 (m, 2H); uv: λ (ε × 10^{-4}), 226 (3.36), 250 (3.03), 282 (1.71), 302 (1.15), 314 (1.32), 334 (0.54), 378 (0.81), 406 (0.80); ms: m/z (relative intensity) 260 (M+, 6), 258 (100), 226 (15), 215 (11), 213 (18), 129 (23), 59 (24), 28 (67).

Anal. Calcd. for $C_{18}H_{12}S$: C, 83.04; H, 4.65. Found: C, 83.31; H, 4.81.

A solution of 160 mg (0.62 mmole) of dihydrothiophene deriva-

tive **7** in 10 ml of dry benzene was added to a solution of 180 mg (0.80 mmole) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 15 ml of dry benzene dropwise under nitrogen gas. The reaction mixture was heated to reflux for 1.25 hours, cooled to room temperature. After removal of the solvent, the reaction mixture was then passed through a short aluminum oxide (neutral) column and eluted with benzene. The solvent was evaporated to yield 142 mg of yellow solid which was recrystallized from absolute ethanol to give: 1st crop 51 mg (0.20 mmole), 2nd crop 26 mg (0.10 mmole) of yellow thiophene derivative PAH **2**. The mother liquid was applied on 2 preparative silica gel tlc plates (hexanes:benzene (90:10) eluant) to afford 62 mg (0.24 mmole) PAH **2**, yield, 88%; mp 115-116°; ^{1}H nmr (perdeuteriochloroform): δ 7.83 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.73 (dm, 1H), 7.66 (dm, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.31 (dd, J = 7.2 and 8.0 Hz, 1H), 7.20-7.24 (m, 2H), 7.13 (d, J = 5.3 Hz, 1H), 7.00 (d, J = 5.3 Hz, 1H); ^{1}H nmr (deuteriochloroform): δ 8.27 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.89-7.96 (m, 3H), 7.71 (dd, J = 7.2 and 8.0 Hz, 1H), 7.60 (d, J = 5.3 Hz, 1H), 7.57 (d, J = 5.3 Hz, 1H), 7.38-7.41 (m, 2H); uv: λ ($\epsilon \times 10^{-4}$), 226 (3.46), 238 (3.08), 264 (3.08), 280 (3.42), 300 (2.46), 350 (1.06), 366 (1.09); ms: m/z (relative intensity) 258 (M+, 100), 213 (16%), 129 (34%).

Anal. Calcd. for $C_{18}H_{10}S$: C, 83.69; H, 3.90. Found: C, 84.01; H, 3.90.

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[14] NOESY experiments (perdeuteriobenzene as solvent) showed that the singlet at 7.86 ppm (assigned to H-7) was correlated with a doublet at 7.75 ppm, which by COSY experiments was assigned to H-8.

[15] NOESY experiments (perdeuteriobenzene as solvent) indicated that the singlet at 7.78 ppm (assigned to H-8) showed a cross peak to a doublet at 7.83 ppm, which by COSY experiments was assigned to H-7.