# Synthesis of Novel Furan and Thiophene PAH'S Related to Acephenanthrylene



Edward Lee-Ruff* and Ying-Sheng Chung

Department of Chemistry, York University,
Toronto, Ontario, M3J 1P3, Canada

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The total syntheses of furan and thiophene PAH's related to acephenanthrylene are reported. Cyclobutanones which were obtained by [2 + 2] addition of ketenes with 2,3-dihydrofuran or 2,3-dihydrothiophene regioselectively could be converted into angular PAH skeleton molecules by rearrangements with polyphosphoric acid. 2,3-Dichloro-5,6-dicyanobenzoquinone was applied for aromatization to achieve the formation of PAH's.

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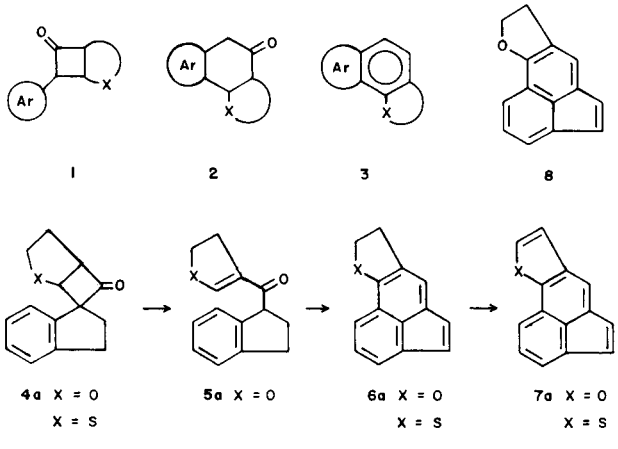
The occurrence of polynuclear aromatic hydrocarbons (PAHs) in the environment and their toxicological properties has prompted wide studies in both the environmental and toxicology fields [1]. Recently a number of cyclopentene annelated PAHs have been found to exhibit moderate to high levels of mutagenic activity [2]. Of particular interest have been the derivatives of cyclopenta [*c,d*] pyrene, a non-bay region hydrocarbon, shown to possess significant levels of activity in the Ames test. The metabolic activation of these derivatives takes place by way of a peripherally fused cyclopentene epoxide and subsequent binding of the epoxide to nucleophilic sites in cellular macromolecules [3].

Moderate to strong mutagenic properties have also been associated with the secoderivatives aceanthrylene and acephenanthrylene [4]. In contrast to the carbocyclic systems relatively little is known about biological properties of sulphur and oxygen heterocyclic analogues of mutagenic and carcinogenic PAHs primarily because of the lack of standards. In this study we report the synthesis of two novel oxygen and sulphur heterocyclic derivatives related to acephenanthrylene using an approach we have developed recently for the synthesis of carbocyclic PAHs. The method is based on the use of cyclobutanones **1** as intermediates and the observation that such strained ketones undergo regioselective $\beta$-ring opening reactions to give $\beta$-tetralones **2** which can be readily converted to angularly fused polynuclear aromatic hydrocarbons with a terminally fused heterocyclic ring system **3**. In our present study we report the synthesis of the novel heterocycles **7a** and **b** using this approach.

The starting tetracyclic cyclobutanones **4a** and **b** were prepared by cycloadditions of indenylidene ketene with dihydrofuran and dihydrothiophene [5] respectively. The regioselectivity of ketene cycloadditions with enol ethers



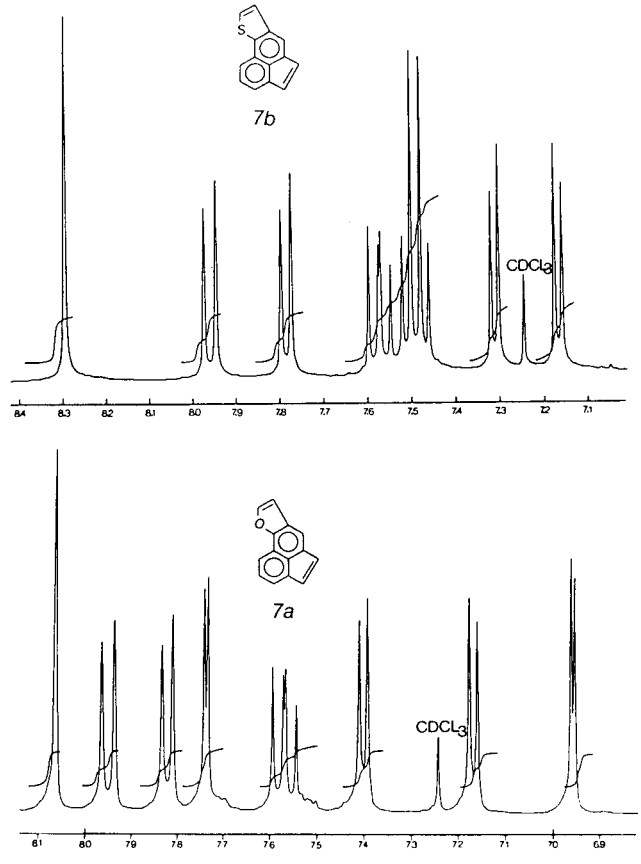




Figure 1. The nmr spectra of furanoacenaphthylene **7a** and thiophenoacenaphthylene **7b**.

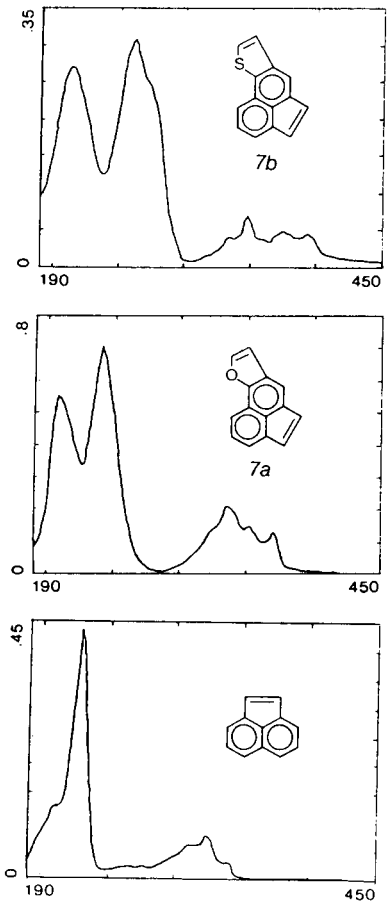



Figure 2. The uv spectra of furanoacenaphthylene **7a**, thiophenoacenaphthylene **7b** and acenaphthylene.

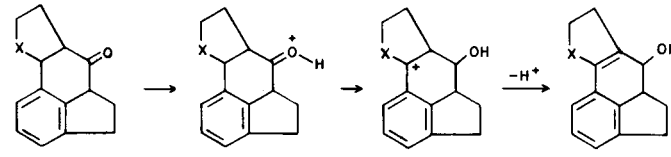
and thioethers is well-defined from previous studies [6] and involves bond formation of the more nucleophilic $\beta$-carbon of the heterocycle olefin with the carbonyl carbon of ketene. The stereochemistry of **4a** and **b** however has not been assigned unambiguously but it has no bearing on the eventual preparation of the PAHs. Evidence from previous studies on the stereochemistry of unsymmetrical ketene cycloadditions point to an orthogonal $2\pi s$ and $2\pi a$ transition state in which the more bulky of the two ketene substituents ends up in the endo position. In our reaction only stereoisomer was isolated in each case and the configurational assignments are based on previous stereochemical studies. The rearrangement of **4a** and **b** directly to **6a** and **b** respectively could be achieved using polyphosphoric acid (PPA). The isolated yields were 31% for the dihydrothiophene system and 10% for the furan system. By-products in the case of furans appeared to be products derived from ring opening of the tetrahydrofurans ring. The yield of **6a** could be improved by carrying out the transformation using shorter reaction times. Alternatively reaction of **4a** with phosphorus pentoxide in bezene led to the unsaturated ketone **5a** which could be cyclized to **6a** with polyphosphoric acid. The complete aromatization of **6a** and **b** was achieved by dehydrogenation with two equivalents of 2,3-dichloro-5,6-dicyanobenzoquinone in refluxing benzene solution to produce **7a** and **b** respectively in yields ranging from 22% to 50%.

For the furano-derivative, the half-dehydrogenation product **8** could be isolated when the dehydrogenation was carried out at room temperature. It is of interest to note that dehydrogenation of the cyclopentene ring in these systems is more facile than the dehydrofuran ring. The regiochemistry of the furan ring was confirmed for **8** by the observation of long-range coupling between the benzilic $\beta$-hydrogens in the furan ring (at higher field in the nmr spectrum) and the proximal benzene proton appearing as a slightly coupled singlet (triplet J = 1.5 Hz).

The nmr spectra of **7a** and **b** (Figure 1) quite clearly indicate the first-order multiplicities for the aromatic signals and are consistent with the assigned structures (Figure 1). Furthermore the uv spectra of both **7a** and **7b** resemble that of acenaphthylene (Figure 2). The mass spectra of both of these compounds showed the parent ions as base peaks in the fragmentation pattern.

It is of interest to note the unusual rearrangement dehydration reaction associated with the transformation of **4** to **7**. We propose that an intermediate tetracyclic ketone **9** is involved as an intermediate by analogy with other cyclobutanone transformations initiated by acid [8].

Scheme 1




9 10 11

Hydride transfer from the benzylic carbon to carbonyl could occur by a 1,3 shift giving rise to cation **10**. The driving force is likely the additional stabilization of charge by both heteroatom and benzene delocalization. Deprotonation of such an intermediate would lead to the unsaturated alcohol **11** which is followed by an acid-catalyzed dehydration step (Scheme 1). We have previously noticed a similar transformation involving a bicyclic cyclobutanone fused to a tetrahydrofuran ring [9].

These particular PAH heterocycles are of interest in view of current toxicological studies of PAHs with peripherally fused cyclopentenes. Current investigations are in progress to test these compounds for mutagenic activity. Furthermore this approach represents a novel method for the preparation of polycyclic derivatives with a terminal heterocycle.

## EXPERIMENTAL

Melting points were determined on a Reichert melting point apparatus and were uncorrected. Infrared spectra were recorded on a Unicam SP 1000 instrument as thin films. Ultraviolet spectra were measured on Unicam SP 800-A spectrometer and Hewlett Packard 8451A Diode Array spectrophotometer. Proton and $^{13}C$ nmr spectra were recorded on a Bruker AM-300 spectrometer using deuteriochloroform solutions with tetramethylsilane as internal standard. All nmr data are given as chemical shifts in ppm from tetramethylsilane. Mass spectra were recorded on a V.G. Micromass 16F spectrometer at 70 ev. elemental analyses were performed by Guelph Chemical Laboratories Limited. Indene and dihydrofuran were obtained from Aldrich and not further purified. Dihydrothiophene was prepared according to the procedure of Sosnovsky [5]. The pyrolysis of the α-benzoylperoxytetrahydrothiophene was carried out at 125° using a vacuum train with liquid nitrogen traps. Yield of dihydrothiophene was 71%.

1*H*-Indene-3-carboxylic Acid.

A modification of the procedure described by Noland *et al* [10] was used. The dry ice was replaced by a cylinder containing predried carbon dioxide. Isolated yield was 54%.

Indane-1-carboxylic Acid.

Hydrogenation of 1*H*-indene-3-carboxylic acid was carried out with 0.174 moles of substrate in 150 ml of ethanol using a medium pressure hydrogenator (Parr pressure reaction apparatus) with 60 psi pressure of hydrogen. The catalyst used was palladium on carbon. After filtering off the catalyst, the filtrate was evaporated to give 0.174 moles of indanecarboxylic acid, mp 54-55° (lit 57-58°); ir: 1710 $cm^{-1}$ (C = O stretch); nmr: δ 11.65 ppm (COOH, S, 1H).

Indane-1-carboxylic Acid Chloride.

A mixture consisting of indane-1-carboxylic acid (0.0242 mole) 6 ml of thionyl chloride was heated to reflux for 2½ hours. The reaction was monitored by following the disappearance of the carbonyl peak in the ir spectrum of the starting material. The unreacted thionyl chloride was evaporated and the crude reaction mixture was used without purification for the next step; ir: 1800 $cm^{-1}$ (CO of acid chloride).

Spiro[2-oxabicyclo[3.2.0]heptan-6-one-7,1'-indane] **4a**.

To a solution of 0.0432 mole of indane-1-carboxylic acid chloride in 60 ml of anhydrous ether was added 0.0476 mole of triethylamine and 0.1084 mole of dihydrofuran in 15 ml of anhydrous ether. The addition was carried out in an atmosphere of dry nitrogen. A precipitate was formed immediately. The reaction mixture was left to stir at room temperature for an additional 1½ hours after which it was filtered and the filtrate washed with 200 ml of 10% hydrochloric acid, 200 ml of saturated sodium carbonate solution and 200 ml of water. The solution was dried over anhydrous magnesium sulfate and evaporated to yield 0.0384 mole of white crystalline **4a** (recrystallized from hexane), mp 62-64°; ir: ν (CO) = 1780 $cm^{-1}$; nmr: 7.23 (4H, S), 4.73 (1H, d), 4.12 (3H, m), 3.05 (2H, m), 2.30 (4H, m); ms: 214 ($m^+$), 144 ($M^+$-$C_4H_6O$), 69 ($C_4H_5O^+$).

*Anal.* Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.59; H, 6.86.

Spiro[2-thiabicyclo[3.2.0]heptan-6-one-7,1'-indane] **4b**.

To a cooled solution (ice-water bath) of 0.049 mole of 2,3-dihydrothiophene and 0.022 mole of indane-1-carboxylic acid chloride in 80 ml of anhydrous ether was added to a solution of 0.024 mole of triethylamine in 15 ml of anhydrous ether under nitrogen. After addition the reaction mixture was brought to room temperature and stirred for 40 minutes. An additional 60 ml of ether was added and the solution was washed with 200 ml of 10% hydrochloric acid, 200 ml of saturated bicarbonate solution and 200 ml of water. The organic layer was dried over anhydrous magnesium sulfate and the solvent evaporated. The residue was chromatographed by flash chromatography giving 0.019 mole (81%) of oily **4b** (eluent: 10% ethyl acetate in 60-80 petroleum ether); nmr: 7.16-7.30 (4H, m), 4.32 (1H, t), 4.17 (1H, d), 2.91-3.17 (2H, m), 2.69-2.91 (2H, m), 2.36 (1H, m), 1.76-2.19 (2H, m), 0.75-1.04 (1H, m); ms: 230 ($m^+$), 144 ($M^+$-$C_4H_6S$); ir: 1765 $cm^{-1}$ (C = O stretch cyclobutanone).

*Anal.* Calcd. for $C_{14}H_{14}OS$: C, 73.01; H, 6.13. Found: C, 72.72; H, 6.53.

4,5,7,8-Tetrahydroacenaphtho[5,4-*b*]furan **6a**.

A solution of 6.4 X $10^{-3}$ moles of the cyclobutanone **4a** in 30 ml of chloroform and excess polyphosphoric acid (PPA) was heated to reflux in an atmosphere of nitrogen for 30 hours. To the cooled solution was added distilled water and the organic layer was washed with distilled water, dried over anhydrous magnesium sulfate, filtered and evaporated to give a residue which was chromatographed by thin-layer chromatography (silica gel/benzene) to give 5.9 x $10^{-4}$ moles (9.1%) of yellow crystalline material mp 96-97°; nmr: 7.42 (1H, d), 7.34 (1H, s), 7.21 (1H, t), 7.14 (1H, d), 4.55 (2H, t), 3.34 (2H, t), 3.25 (4H, m); uv: λ (ε x $10^{-4}$) 240 (4.39), 274 (0.36), 284 (0.42), 296 (0.38), 324 (0.15), 338 (0.24); ms: 196 ($H^+$), 195 ($M^+$-H), 165 ($M^+$-$CH_3O$).

*Anal.* Calcd. for $C_{14}H_{12}O$: C, 85.7; H, 6.2. Found: C, 85.6; H, 6.2.

1-[4',5'-Dihydro-3'-furoyl]indane **5a**.

To a solution of ketone **4a** (0.0042 mole) in 60 ml of benzene was added 0.012 mole of phosphorus pentoxide. The reaction mixture was stirred for 24 hours at room temperature at which point the C = O absorption at 1780 $cm^{-1}$ in the ir spectrum of **4a** disappeared. The suspension was filtered and the filtrate washed with cold water, dried and evaporated to give crystalline **5a** (0.0022 mole, 53%), mp 110-112°; ir: 1610, 1630 (C = O and C = C stretch of enol ether); nmr 7.03-7.40 (4H, m), 7.35 (1H, s), 4.51 (2H, t), 4.39 (1H, t), 3.13 (1H, m), 2.87 (3H, m), 2.35 (2H, m); uv: λ (ε x $10^{-4}$) 206 (1.30), 270 (1.61): ms: 214 ($M^+$), 97.

*Anal.* Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.54; H, 6.66.

Conversion of **5a** to **6a**.

A solution consisting of 2.85 x $10^{-3}$ mole of ketone **5a** in 15 ml of chloroform and excess polyphosphoric acid was heated at reflux for 65 hours. The reaction mixture was worked up in the usual manner and the residue was chromatographed on the (silica gel/benzene) to give 2.7 x $10^{-4}$ mole of yellow crystals identical in spectroscopic properties and mp with a sample of **6a** prepared above.

Acenaphtho[5,4-*b*]furan **7a**.

A solution of 8.9 x $10^{-4}$ moles of **6a** and 3.9 x $10^{-3}$ mole of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in 30 ml of dry benzene was heated to reflux in an atmosphere of nitrogen for 2 hours. The reaction mixture was concentrated and passed through an alumina column (benzene) to give 1.93 x $10^{-4}$ moles (21%) of yellow crystalline material mp 46-48°; nmr 8.06 (1H, s), 7.95 (1H, d), 7.83 (1H, d), 7.75 (1H, d), 7.57 (1H, dxd), 7.40 (1H, d), 7.17 (1H, d), 6.96 (1H, d); ms: 192 ($M^+$, base peak), 164, 163, 96, 82; uv: λ (ε x $10^{-4}$) 208 (2.64), 242 (3.36), 320 (0.56), 336 (1.01), 352 (0.71), 370 (0.62).

*Anal.* Calcd. for $C_{14}H_8O$: C, 87.48; H, 4.20. Found: C, 87.02; H. 4.32.

When the above reaction was repeated at room temperature instead of reflux and worked up in identical way the half dehydrogenated product **8** was obtained as the major product, mp 91-93°; nmr 7.71 (1H, d), 7.70 (1H, d), 7.64 (1H, s long range coupled t), 7.43 (1H, dxd), 7.18 (1H, d), 7.05 (1H, d); ms: 194 ($M^+$); uv: λ (ε x $10^{-4}$) 206 (3.08), 240 (3.69), 312 (0.87), 326 (1.22), 348 (1.15), 364 (1.30).

*Anal.* Calcd. for $C_{14}H_{10}O$: C, 86.57; H, 5.19. Found: C, 86.26; H, 5.40.

4,5,7,8-Tetrahydroacenaphtho[5,4-*b*]thiophene **6b**.

A mixture of 1.02 x $10^{-3}$ moles of ketone **4b** and 4.6 g of polyphosphoric acid was heated and stirred at 100° for 2 minutes then quenched with ice water and extracted with chloroform. The organic layer was washed with aqueous sodium carbonate and distilled water, dried over anhydrous magnesium sulfate and evaporated to give a residue which was chromatographed by tlc (silica gel/10% benzene in hexanes). The major fraction **6b** (0.32 x $10^{-3}$ moles) was an olive coloured crystalline material, mp 93-95°; nmr: 7.46 (1H, d), 7.42 (1H, s), 7.31 (1H,

dxd), 7.19 (1H, d), 3.39 (6H, m), 3.31 (2H, m); ms: 212 ($M^+$) (base peak), 211 ($M^+$-H); uv: λ (ε x $10^{-4}$) 220 (6.05), 234 (5.26), 260 (11.03), 284 (1.71), 294 (2.22), 306 (1.76).

*Anal.* Calcd. for $C_{14}H_{12}S$: C, 79.20; H, 5.70. Found: C, 79.02; H, 5.93.

Acenaphtho[5,4-*b*]thiophene **7b**.

A solution of 1.04 x $10^{-3}$ mole of 2,3-dichloro-5,6-dicyanobenzoquinone and 0.47 x $10^{-3}$ mole of **6b** in 5 ml of distilled benzene was heated under reflux in a nitrogen atmosphere for 40 minutes. The reaction mixture was concentrated and passed through a short alumina column. The non-polar fraction (benzene eluent) was further purified on tlc (10% benzene in hexanes, silica gel) to yield 48 mg (49%) of yellow-orange crystalline material **7b**, mp 71-73°; nmr: 8.30 (1H, s), 7.97 (1H, d), 7.78 (1H, d), 7.58 (1H, dxd), 7.52 (1H, d), 7.48 (1H, d), 7.31 (1H, d), 7.17 (1H, d): ms: 208 ($M^+$, base peak); uv: 214, 262, 348, 376, 394, 422 nm.

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