Studies on Polycyclic Thiaarenes: Part II [1]. An Improved Synthesis of Phenanthro[1,2-*b*]thiophene and a Synthesis of Acenaphtho[1,2-*b*]naphtho-[2,3-*d*]thiophene, a Novel Polynuclear Thiaarene

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An improved synthesis of phenanthro[1,2-*b*]thiophene (**6**) from 1-chloro-3,4-dihydrophenanthrene-2-aldehyde (**2**) by condensation with thioglycolate followed by hydrolysis, decarboxylation and dehydrogenation is described. A new polycyclic thiophene derivative **14** has also been prepared from acenaphthothiophene (**7**) by Friedel-Craft's reaction with phthalic anhydride followed by lactonisation of the keto carboxylic acid **9** and then reduction and finally cyclisation of the resultant aldehyde **13**.

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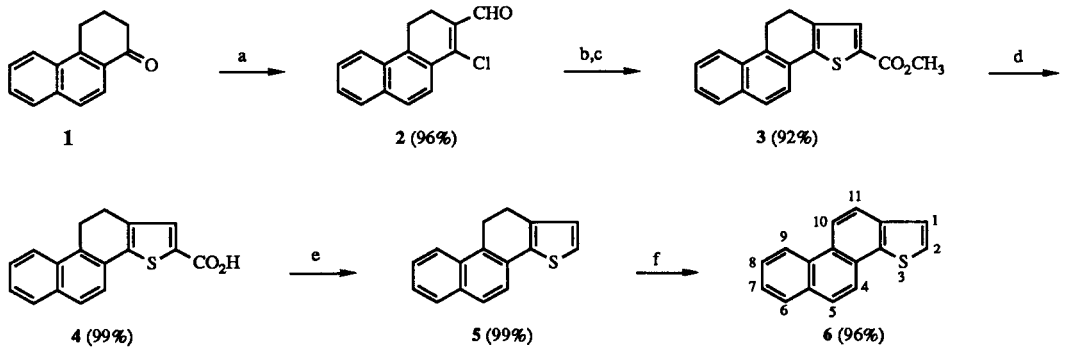
The great similarities in physical and chemical properties between thiophene and benzene and between their corresponding derivatives have been the subject of much speculation until the concept of bioisosterism was developed [2,3]. The two groups -CH=CH- and -S- have been called ring equivalents and are presently considered as 'bioisosters' by medicinal chemists [2].

Polyaromatic hydrocarbons (PAH) which are important environmental pollutants have been widely studied in the last few decades with regard to their mutagenic and/or carcinogenic activity [4]. However analogous sulphur heterocycles (in which one benzene ring of the PAH has been replaced by a thiophene ring) which have been found to occur concomitantly with PAH in numerous mixtures of coal derived products [5,6] and shale oils [7] *etc.* were not investigated in detail so far as their mutagenic properties are concerned. Although prior to the early seventies some studies revealed that polycyclic thiophene derivatives are carcinogenic [8,9], we still know very little about the biological properties of these heterocyclic molecules as compared to those of related PAH, mostly due to lack of standards. In the last few years there has been a tremendous development in the synthesis and biological evaluation of polynuclear thiaarenes all around the world particularly in the United States by Castle *et al* [10].

Recently Castle *et al* [11,12] have reported the synthesis of several phenanthrothiophenes and their tetracyclic isomeric analogues. They have shown, that tetracyclic thiophene derivatives are mutagenic [13-15] in the saturated Ames or in the pre-incubation Ames test. Phenanthro[3,4-*b*]thiophene was found to possess approximately same mutagenic potency in the Ames test as benzo[*a*]pyrene. In an another report Croisy *et al* [16] have also inferred that several polycondensed thiophenes are more carcinogenic in mice than the analogous hydrocarbons.

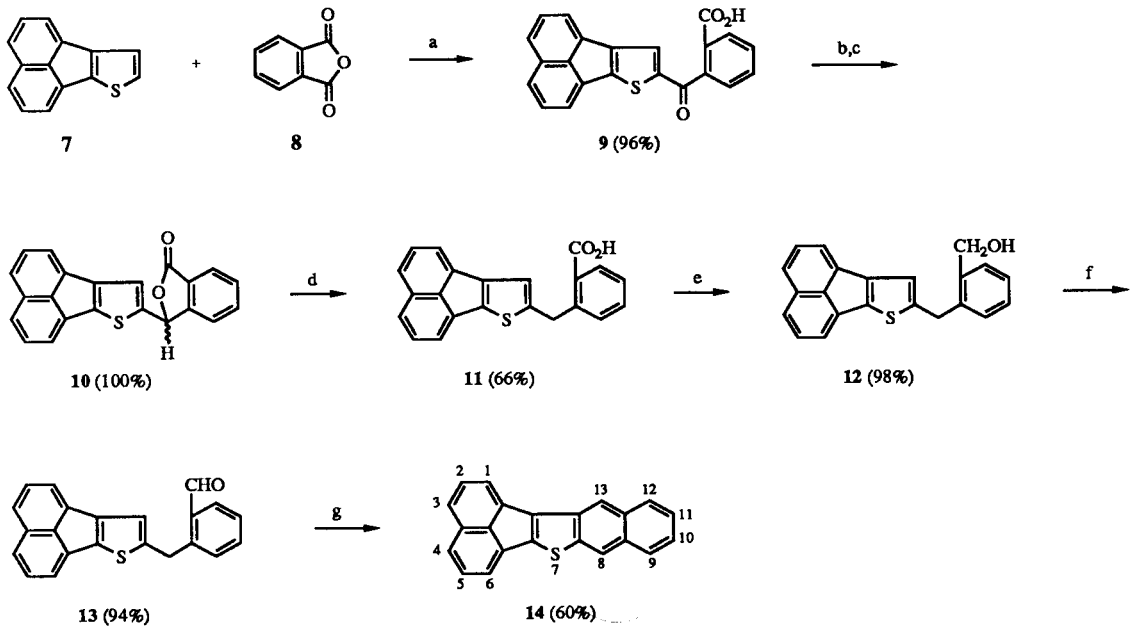
Prompted by the importance and hence the need for newer methods for the synthesis of thiaarenes we undertook in devising a simple route to such compounds in high yields. Though the isolation of phenanthro[1,2-*b*]thiophene [17] from coal tar was reported in the late seventies,

Scheme I



a, $POCl_3$/DMF/35°-50°C
b, $SHCH_2CO_2CH_3/Et_3N$/Py/45-50°
c, 50% aq KOH/20-25°C
d, aq alcoholic KOH/EtOH/reflux
e, Cu-chromite (cat)/quinoline/reflux
f, DDQ/benzene/reflux

Scheme II



however, a literature survey shows, only one synthesis of the compound in about 32% yield by the photocyclization of 1-(1'-naphthyl)-2-(3'-thienyl)ethylene [11]. In our present work we have developed a route for the synthesis of phenanthro[1,2-*b*]thiophene (**6**) [18] and an another novel polynuclear thiaarene, acenaphtho[1,2-*b*]naphtho[2,3-*d*]thiophene (**14**). The synthetic strategy for compound **6** is outlined in Scheme I.

Thus the ketone **1** was converted *via* the Vilsmeir-Haack reaction to 1-chloro-3,4-dihydrophenanthrene-2-aldehyde (**2**) [19] which was condensed with methyl thioglycolate/triethylamine in pyridine followed by ring closure with 50% aqueous potassium hydroxide to obtain methyl 10,11-dihydrophenanthro[1,2-*b*]thiophene-2-carboxylate (**3**) in 92% yield. Saponification of **3** with aqueous alcoholic potassium hydroxide produced the acid **4** which followed by decarboxylation with copper-chromite in boiling quinoline afforded 10,11-dihydrophenanthro[1,2-*b*]thiophene (**5**) in almost quantitative yield. Aromatization of **5** with DDQ furnished phenanthro[1,2-*b*]thiophene (**6**) in 96% yield which was found to be identical with the sample reported by Castle *et al* [11]. All the compounds were characterized by the usual spectroscopic methods as well as by elemental analysis.

The unique feature of Scheme I is the ready availability of the starting material, extremely good yield and high purity of the products formed. Thus we believe that this method is superior in every respect to the previously reported method [11].

Synthesis of **14**, a hitherto unknown thiophene derivative was accomplished from acenaphtho[1,2-*b*]thiophene (**7**) as an extension of our previous work [1]. The compound was synthesized as outlined in Scheme II.

Acenaphtho[1,2-*b*]thiophene (**7**) on reaction with phthalic anhydride/aluminum chloride in nitrobenzene at 0-5° gave the keto acid 8-(2'-carboxybenzoyl)acenaphtho[1,2-*b*]-thiophene (**9**) in about 96% yield. All attempts to reduce the keto acid **9** to the acid **11** by zinc amalgam/hydrochloric acid, hydrazine hydrate/potassium hydroxide/diethyleneglycol, triethylsilane/trifluoroacetic acid or zinc/sodium hydroxide met with failure. Finally the acid **11** was obtained *via* the sodium borohydride reduction of the keto-acid **9** followed by hydrogenolysis of the lactone **10**. The acid **11** was reduced to the alcohol **12** by LAH in ~99% yield. Oxidation of the alcohol **12** with chromic oxide-pyridine complex produced the aldehyde **13** which was cyclized with PPA at 120-130° to produce acenaphtho[1,2-*b*]-naphtho[2,3-*d*]thiophene (**14**) as a red solid in 60% yield.

The elemental analyses as well as the spectral data of the final compound and also of the intermediates are in agreement with the assigned structures.

EXPERIMENTAL

Melting points (uncorrected) were determined in a metal bath or in a sulphuric acid bath. Elemental analyses were performed by R. S. I. C., Lucknow, India. All solvents used were of reagent grade. The nmr spectra were recorded at Varian EM 390 (90 MHz), Brucker (250 MHz) and Jeol (100 MHz) instruments. The ir spectra were recorded with a Perkin-Elmer 883 spectrometer.

1-Chloro-3,4-dihydrophenanthrene-2-aldehyde (**2**).

To an ice cooled solution of DMF (5 ml), phosphorus oxychloride (1.63 g, 10.6 mmoles) was added dropwise and stirred at 0-5° for 10 minutes. To this a solution of **1** (1.02 g, 5.2 mmoles) in 15 ml of DMF was added dropwise maintaining the temperature below 5-10°. The mixture was stirred at 0-5° for 1 hour and then allowed to attain room temperature gradually. Stirring was continued at room temperature for 15 hours and then at 45-50° for 1 hour. The complex was then poured in ice cold sodium acetate solution and stirred for 5-10 minutes and kept at freezing temperature for 1-1.5 hours. The light yellow solid which separated was filtered, washed well with water and dried to produce 1.2 g (96%) of **2**. Recrystallization from petroleum ether (60-80°) furnished light yellow crystals of **2**, mp 88-89°; ir (potassium bromide): ν max 1665 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.5 (t, 2H), 3.05 (t, 2H), 7.3-8.0 (m, 6H), 10.25 (s, 1H) ppm.

Anal. Calcd. for $C_{15}H_{11}OCl$: C, 74.23; H, 4.54. Found: C, 73.98; H, 4.26.

Methyl 10,11-Dihydrophenanthro[1,2-*b*]thiophene-2-carboxylate (**3**).

To a stirred solution of the chloroformyl derivative **2** (500 mg, 2.06 mmoles) and methyl thioglycolate (240 mg, 2.26 mmoles) in 5 ml of pyridine at 0-5°, triethylamine (300 mg, 2.97 mmoles) was added dropwise. The reaction mixture was stirred at 45-50° for 1 hour, 20 minutes and then cooled to 20°. An aqueous solution of 50% potassium hydroxide (1 ml) was added and stirred vigorously for a further 20 minutes. The reaction mixture was poured into ice water and the colorless solid which separated was filtered and dried in air to give 555 mg (92%) of **3**, mp 132-133° (ethanol); 1705 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.9 (t, 2H), 3.35 (t, 2H), 3.9 (s, 3H), 7.35-8.10 (m, 7H) ppm.

Anal. Calcd. for $C_{18}H_{14}O_2S$: C, 73.47; H, 4.76. Found: C, 73.40; H, 4.66.

10,11-Dihydrophenanthro[1,2-*b*]thiophene-2-carboxylic Acid (**4**).

To a solution of **3** (350 mg, 1.19 mmoles) in 15 ml of ethanol, 5% aqueous potassium hydroxide solution (10 ml) was added and refluxed for 5 hours. Excess ethanol was distilled off and the residue was diluted with water, extracted with ethyl acetate to remove neutral matter (if any), treated with active charcoal and filtered hot. Acidification of the filtrate with concentrated hydrochloric acid afforded the desired solid. It was filtered, washed well with water, dried and recrystallized from ethyl acetate to produce 330 mg (99%) of **4** as a faint yellow solid, mp 270-271°; ir (potassium bromide): ν max 1650, 2950 cm^{-1}.

Anal. Calcd. for $C_{17}H_{12}O_2S$: C, 72.86; H, 4.29. Found: C, 72.72; H, 4.10.

10,11-Dihydrophenanthro[1,2-*b*]thiophene (**5**).

The acid **4** (220 mg, 0.86 mmole) was refluxed with quinoline (7 ml) in the presence of copper-chromite (catalytic amount) for 5 hours and then filtered to separate the catalyst. The filtrate was poured in ice cooled concentrated hydrochloric acid (10 ml), diluted with water and extracted with ether. The organic layer was successively washed with diluted hydrochloric acid, 5% sodium bicarbonate solution, water and dried (sodium sulphate). Removal of the solvent afforded a brown viscous oil which on purification by column chromatography [alumina/petroleum ether (60-80°)] furnished 185 mg 99% of **5** as a colorless solid, mp 125-126° (petroleum ether); ^1H nmr (deuteriochloroform): δ 2.95 (t, 2H), 3.3 (t, 2H), 6.95 (d, 1H), 7.15 (d, 1H), 7.25-8.25 (m, 6H) ppm.

Anal. Calcd. for $C_{16}H_{12}S$: C, 81.36; H, 5.08. Found: C, 81.01; H, 4.86.

Phenanthro[1,2-*b*]thiophene (**6**).

A 100 mg (0.42 mmole) sample of **5** was refluxed with DDQ (100 mg, 0.44 mmole) in 5 ml of dry benzene for 3.5 hours. After cooling to room temperature, it was filtered through a neutral alumina column and eluted with benzene. Removal of the solvent afforded shining colorless solid (95 mg, 96%), mp 170-171° (petroleum ether) (lit [11] mp 168-170°).

8-(2'-Carboxybenzoyl)acenaphtho[1,2-*b*]thiophene (**9**).

To an ice cooled mixture of acenaphtho[1,2-*b*]thiophene (**7**) [1] (2.4 g, 11.5 mmoles) and phthalic anhydride (1.7 g, 11.5 mmoles) in dry nitrobenzene (50 ml) was added anhydrous aluminum chloride (3.0 g, 22.5 mmoles) in 4-5 batches. The mixture was stirred at 0-5° for 3 hours and then at room temperature for overnight. The complex was decomposed with ice water and the nitrobenzene was removed by steam distillation. The crude keto acid thus separated was redissolved in potassium carbonate solution and extracted with benzene to remove neutral matter (if any). The aqueous layer was treated with active charcoal and filtered. The filtrate on acidification with hydrochloric acid afforded the keto acid **9** as a bright yellow solid 3.95 g, (96%), mp 261-262° (ethanol); ir (potassium bromide): ν max 1630, 1660, 3400 cm^{-1}.

The methyl ester derivative had ^1H nmr (deuteriochloroform): δ 3.70 (s, 3H), 7.2-8.25 (m, 11H) ppm.

Anal. Calcd. for $C_{22}H_{12}O_3S$: C, 74.16; H, 3.37. Found: C, 73.92; H, 3.13.

8-(3'-Oxo-1',3'-dihydroisobenzofuran-1'-yl)acenaphtho[1,2-*b*]thiophene (**10**).

To a solution of the keto acid **9** (230 mg, 0.65 mmole) in 25 ml of 1*N* sodium hyroxide solution, sodium borohydride (75 mg, 2 mmoles) was added in 3 batches. The mixture was stirred at 70-80° for 1 hour and then at room temperature overnight. It was then acidified with concentrated hydrochloric acid and stirred for an additional 30 minutes. The yellow solid which separated was filtered and washed well with water. The crude product thus obtained was dissolved in benzene and filtered through a short column of neutral alumina. Removal of solvent furnished the lactone **10** as a yellow solid, yield ~220 mg (100%), mp 194-195°; ir (potassium bromide): ν max 1750 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.65 (s, 1H), 7.3-7.8 (m, 10H), 7.95 (d, 1H) ppm.

Anal. Calcd. for $C_{22}H_{12}O_2S$: C, 77.65; H, 3.53. Found: C, 77.28; H, 3.25.

8-(2'-Carboxybenzyl)acenaphtho[1,2-*b*]thiophene (**11**).

A slow stream of hydrogen was passed through a refluxing solution of the lactone **10** (400 mg, 1.18 mmoles) in 15 ml of acetic acid containing 10% Pd-C catalyst (250 mg) for 3 hours. The catalyst was filtered out, the filtrate was concentrated under reduced pressure and diluted with water. The yellow solid which separated was filtered, dried to give 265 mg (66%) of the acid **11** which was recrystallized from acetic acid or chloroform to produce bright yellow needles, mp 206-207° (acetic acid); ir (potassium bromide): 1682 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.66 (s, 2H), 7.28-8.0 (m, 11H) ppm.

Anal. Calcd. for $C_{22}H_{14}O_2S$: C, 77.19; H, 4.09. Found: C, 77.02; H, 3.91.

8-(2'-Hydroxymethylbenzyl)acenaphtho[1,2-*b*]thiophene (**12**).

To a suspension of LAH (75 mg, 2 mmoles) in dry ether (20 ml), an etherial solution (30 ml) of the acid **11** (90 mg, 0.26 mmole) was added dropwise. The mixture was stirred under nitrogen at 50-60° for 2 hours. The complex was decomposed with ice water, acidified with 10% hydrochloric acid and extracted with ether. The organic layer was thoroughly washed with 5% sodium bicarbonate solution, water and dried (sodium sulphate). Removal of solvent afforded the crude alcohol **12** which was dissolved in benzene and filtered through alumina column. After usual work up it gave 85 mg (98%) of yellow solid, mp 118-119°; ir (potassium bromide): ν max 2922, 3032, 3258 cm^{-1}; ^1H nmr (deuteriochloroform and deuterium oxide): δ 4.36 (s, 2H), 4.76 (s, 2H), 7.05-7.80 (m, 11H) ppm.

8-(2'-Formylbenzyl)acenaphtho[1,2-*b*]thiophene (**13**).

To a stirring suspension of chromium trioxide (300 mg, 3 mmoles) in dry pyridine (3 ml) was added dropwise a solution of the alcohol **12** (150 mg, 0.46 mmole) in pyridine (4 ml). Stirring was continued for 2.5 hours at room temperature and then filtered. Filtrate was diluted with water and extracted with choroform. The chloroform layer was successively washed with diluted hydrochloric acid, diluted sodium bicarbonate solution and finally with water. After the usual work up it gave 140 mg (94%) of the aldehyde **13** as a viscous light yellow brown mass which was used directly in the next step without further purification; ir (potassium bromide): ν max 1694 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.8 (s, 2H), 7.25-8.40 (m, 11H), 10.2 (s, 1H) ppm.

Acenaphtho[1,2-*b*]naphtho[2,3-*d*]thiophene (**14**).

The above aldehyde **13** (133 mg, 0.43 mmole) was stirred with PPA (10 g) at 80-100° for 40 minute. After cooling to room temperature, the red complex was decomposed with ice water and extracted with chloroform. The organic layer was washed with diluted sodium carbonate solution, water and dried (sodium sulphate). Removal of the solvent gave the crude product which was purified by column chromatography (alumina/petroleum ether, 60-80°) to furnish **14** as a brick red solid, yield 75 mg (60%), mp 181-182° (ethanol); ^1H nmr (deuteriochloroform): δ 7.45-8.05 (m, 9H), 8.1 (d, 1H), 8.35 (s, 1H), 8.6 (s, 1H) ppm; ms: (m/z) 308 (M^+), 279, 167, 149, 113.

Anal. Calcd. for $C_{22}H_{12}S$: C, 85.71; H, 3.90. Found: C, 85.54; H, 3.63.

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[19] Compound **2** was previously reported by P. Cagniant, P. Perin, G. Kirsch and D. Cagniant, *C. R. Hebd. Seances Acad. Sci.*, **277C**, 37 (1973) in 92% yield as pale yellow leaflets from alcohol, mp 86.5°, from the Vilsmeier reaction of 1,2,3,4-tetrahydrophenanthren-1-one. No procedural details were given by the French authors.