Synthesis of Pyreno[*b*]thiophenes

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The synthesis of all the isomers of pyreno[*b*]thiophene namely, pyreno[1,2-*b*]thiophene, pyreno[2,1-*b*]thiophene and pyreno[4,5-*b*]thiophene is described. Their spectral characteristics are also discussed.

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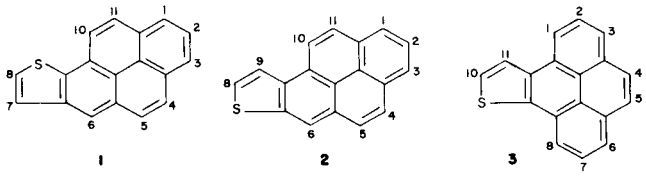
The presence of polycyclic aromatic hydrocarbons (PAH) in coal derived products and their mutagenic activity have been extensively studied (la,b). Recently from this as well as other laboratories (2-4) it has been shown that many commercial PAH materials derived from coal contain sulfur heterocycles as major impurities in which one aromatic ring has been replaced by a thiophene ring. However, the mutagenic and carcinogenic potential of these sulfur compounds are rarely reported because of the difficulties encountered in obtaining pure samples from coal in sufficient amounts. Therefore, we have initiated a systematic synthetic effort to obtain authentic specimens of polycyclic thiophenes in high purity in order to compare their mass spectra with those obtained from coal derived products and to test their mutagenic activity. Thus we can identify polycyclic thiophenes occuring in coal with certainty.

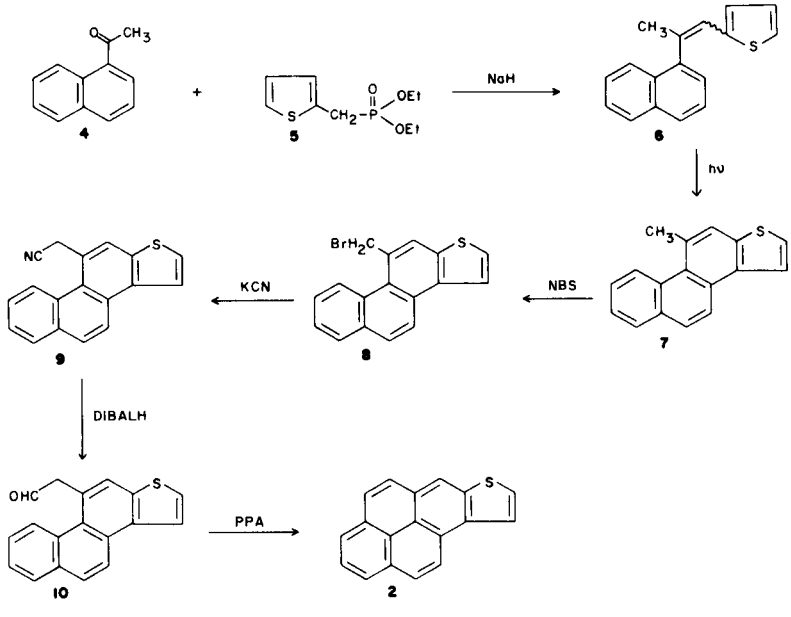
There are three different thiophene isomers which can result when a thiophene ring is fused to a pyrene ring. Of these, pyreno[1,2-*b*]thiophene (**1**) has been reported by Tilak, *et al* (5). The other two isomers, namely pyreno[2,1-*b*]thiophene (**2**) and pyreno[4,5-*b*]thiophene (**3**) have been prepared as described below.



1 **2** **3**

The synthesis of pyreno[2,1-*b*]thiophene is depicted in Scheme I. 10-Methylphenanthro[2,1-*b*]thiophene (**7**), a key intermediate, was prepared by photocyclization of 2-[2-methyl-2-(1-naphthylethenyl]thiophene (**6**), from which the required compound can be made by homologation of an easily funtionalizable methyl group. The olefin **6** was prepared by a Wadsworth-Emmons reaction between diethyl 2-thenylphosphonate (**5**) and 1-acetylnaphthalene. The compound **6** appeared to be a mixture of *cis* and *trans* isomers as evidenced by the presence of two methyl signals at δ 2.19 and δ 2.48 in the nmr spectrum. The bromination of **7** with *N*-bromosuccinimide in the presence of benzoyl peroxide as a radical initiator gave exclusively bromomethylphenanthrothiophene (**8**). The bromine atom in **8** was replaced by a one carbon nucleophile required for ring closure at C-1 of the phenanthrene ring. Thus the reaction of **8** with potassium cyanide in a phase transfer

Scheme I



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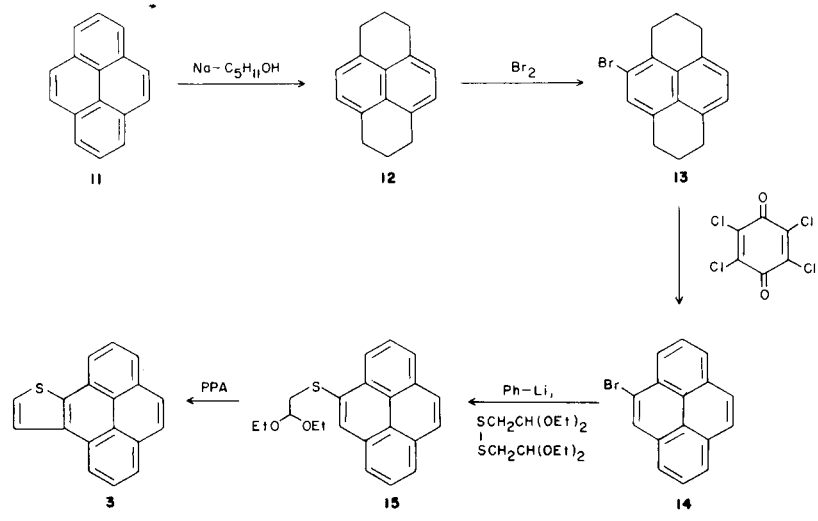
Scheme II



medium gave 10-cyanomethylphenanthrothiophene (**9**). The cyano compound **9** was reduced to the aldehyde with diisobutylaluminum hydride and the resulting aldehyde was cyclized with polyphosphoric acid to the desired compound **2**.

The steps involved in the synthesis of pyreno[4,5-*b*]-thiophene are depicted in Scheme II. The pyrene was converted to 4-bromo-1,2,3,6,7,8-hexahydropyrene (**13**) by reduction with sodium in amyl alcohol followed by bromination using literature methods (6,7). The reaction of 4-bromopyrene **14** with phenyllithium gave 4-prenyllithium and the latter on reaction with 2,2,2′,2′,-tetraethoxydiethyl disulfide yielded *w*-diethoxyethyl-4-prenyl sulfide (**15**). We were, however, unsuccessful in our attempt to make the lithio derivative of **13**. The diethyl acetal **15** was cyclized with polyphosphoric acid to pyreno[4,5-*b*]thiophene [**3**], though in poor yield.

The fusion of the thiophene ring at different positions of the pyrene ring caused deshielding of the peri protons around the thiophene ring. This deshielding caused diagnostic differences among all three isomers. In pyreno[1,2-*b*]thiophene, proton H-6 was more deshielded and gave a singlet at δ 8.70. The most deshielded protons H-6 and H-10 of pyreno[2,1-*b*]thiophene gave a singlet at δ 8.56 and a doublet (J = 8 Hz) at δ 8.60, respectively. The most deshielded proton, H-1 of pyreno[4,5-*b*]thiophene appeared at δ 8.70 as a doublet (J = 10 and 2.5 Hz) due to coupling with its *ortho* and *meta* protons. There is no characteristic difference in the uv absorption pattern in all three isomers and these spectra are similar to that of benzo[*a*]pyrene.

EXPERIMENTAL

Ir spectra were recorded on a Beckman Acculab-2 Spectrometer. ^{1}H Nmr spectra were obtained on a Varian EM 390 Spectrometer and a JEOL FX 90Q spectrometer in the solvents indicated. Chemical shifts are reported in ppm from TMS as an internal reference and are given in δ units. Mass spectra were recorded on a Hewlett Packard model 5980 A mass spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

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

This compound was prepared starting from 3-bromopyrene according to Tilak's procedure (5), m.p. 145° (lit 145-146°); ir (potassium bromide): 3040 (s), 1590 (s), 1420 (s), 1320 (s), 840 (s), 820 (s), 700 (s); nmr (deuteriochloroform): 8.70 (s, H-6, 1H), 8.48-7.59 (m, H-1, H-2, H-3, H-4, H-5, H-7, H-8, H-10, H-11, 9H); ms: 258 (M^+, 100), 226 (M^+-32, 8), 200 (M^+-58, 2); uv (cyclohexane): λ max nm (log ε), 220 (4.56), 258 (4.67), 264 (4.73), 272 (4.69), 284 (4.69), 296 (4.60), 310 (3.79), 325 (4.04), 340 (4.42), 360 (4.63), 370 (4.05), 390 (3.93).

2-[2-Methyl-2-(1-naphthyl)ethenyl]thiophene (**6**).

Sodium hydride (50% oil suspension, 3 g, 62.5 mmoles) was placed in 1,2-dimethoxyethane (200 ml). The slurry was cooled to 20° and diethyl 2-thenylphosphonate (9.36 g, 40 mmoles) was added dropwise with stirring. After addition, the solution was stirred at room temperature for about one hour until the gas evolution had ceased. To the yellow solution, maintained below 25°, was added dropwise 1-acetylnaphthalene (Aldrich, contains 30% 2-acetylnaphthalene). The reaction mixture was stirred at room temperature for an additional hour and then refluxed for 0.5 hour. After cooling, the reaction mixture was decomposed with a large excess of water and the product was extracted with benzene. The benzene, after drying over sodium sulfate, was removed and the residue was chromatographed over a silica gel column using hexane as an eluant to give 5.5 g (82%) as a pale greenish yellow oil; nmr (deuteriochloroform): 2.19 and 2.48 (s, CH_3, 3H), 6.5-8.3 (m, 1 olefinic proton, 10 aromatic protons, 11H).

10-Methylphenanthro[2,1-*b*]thiophene (**7**).

A solution of 2-[2-methyl-2-(1-naphthyl)ethenyl]thiophene (1.24 g, 5 mmoles) and iodine (0.05 g) in cyclohexane (500 ml) was irradiated for four hours with a 450 Watt Hanovia medium pressure mercury lamp through a Corex filter. During the course of reaction a slow stream of air was also passed through the solution. The solvent was evaporated *in vacuo* and the residue was chromatographed over a silica gel column using hexane as the eluant to give white crystals which were recrystallized from hexane, yield 0.23 g (18.5%), m.p. 121-122°; nmr (deuterio-

chloroform): 3.3 (s, CH_3, 3H), 7.5-8.2 (m, H-2, H-4, H-5, H-6, H-7, H-8, 6H), 8.35 (d, H-3, J = 9 Hz, 1H), 9.0 (near dd, H-9, J = 9 Hz, 1H).

Anal. Calcd. for $C_{17}H_{12}S$: C, 82.22; H, 4.87; S, 12.91. Found: C, 82.48; H, 4.78; S, 12.63.

10-Bromomethylphenanthro[2,1-*b*]thiophene (**8**).

A mixture of *N*-bromosuccinimide (0.89 g), 10-methylphenanthro[2,1,-*b*]thiophene (1.24 g, 5 mmoles), benzoyl peroxide (0.01 g) in dry benzene (50 ml) was gently refluxed for two hours. The reaction mixture was cooled in an ice bath and succinimide was separated by suction filtration. The last traces of imide were removed by shaking the filtrate with an ice-cooled sodium hydroxide (5%) solution followed with water. The organic layer was dried over sodium sulfate, evaporated and the residue was washed with hexane (10 ml) and was then recrystallized from hexane-benzene (2:1) to give (1.22 g, 75%) of colorless needles, m.p. 147°; nmr (deuteriochloroform): 5.30 (s, CH_3, 3H), 7.67 (d, J = 5 Hz, H-5, 1H), 7.62-7.79 (m, H-7, H-8, 2H), 7.91 (d, J = 10 Hz, H-5, 1H), 7.92-8.05 (m, H-6, 1H), 8.00 (d, J = 6 Hz, H-3, 1H), 8.23 (s, H-11, 1H), 8.30 (d, J = 10 Hz, H-4, 1H), 9.05 (near dd, J = 1 and 7 Hz, H-9, 1H).

Anal. Calcd. for $C_{17}H_{11}BrS$: C, 62.40; H, 3.39; S, 9.80. Found: C, 62.62; H, 3.54; S, 9.67.

10-Cyanomethylphenanthro[2,1-*b*]thiophene (**9**).

A mixture of **8**, (1.13 g, 5 mmoles) potassium cyanide (2.5 g) in a mixture of benzene (100 ml) and water (15 ml) with 10 drops of Aliquat-336 (tricarprylylmethyl ammonium chloride) was refluxed for 2.5 hours. After the addition of 100 ml of benzene, the benzene layer was separated, washed successively with water, 10% hydrochloric acid and water. After drying over sodium sulfate, the benzene was removed under reduced pressure. The residue was crystallized from benzene-ethanol (1:1) giving pale yellow needles (0.86 g, 63%), m.p. 155-157°; ir (potassium bromide): 2260 (C≡N); nmr (deuteriochloroform): 4.56 (s, CH_2-CN, 2H), 7.65 (d, J = 6 Hz, H-2, 1H), 7.59-7.76 (m, H-7, H-8, 2H), 7.88 (d, J = 10 Hz, H-5, 1H), 7.98 (d, J = 6 Hz, H-3, 1H), 8.03 (near dd, J = 4 Hz, H-6, 1H), 8.24 (s, H-11, 1H), 8.30 (d, J = 1 Hz, H-4, 1H), 8.44 (near dd, J = 6 Hz, H-9, 1H).

Anal. Calcd. for $C_{18}H_{11}NS$: C, 79.09; H, 4.06; N, 5.13: S, 11.73. Found: C, 78.96; H, 4.20; N, 5.13; S, 11.83.

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

Diisobutylaluminium hydride (25% solution in toluene, 2 ml, 3 mmoles) was added to a solution of **9** (0.5 g, 1.83 mmoles) in dry benzene (15 ml). The mixture was stirred at room temperature for two hours. Dilute hydrochloric acid was added and the product was extracted with chloroform. The evaporation of the dried extracts over sodium sulfate, gave an aldehyde as an oil which slowly crystallized; ir (neat): 1720 (C=O). A mixture of the above aldehyde and polyphosphoric acid (10 g) was heated on a steam bath for one hour. The reaction mixture was poured into ice water and extracted with chloroform. The chloroform was washed successively with water and sodium carbonate solution, dried over sodium sulfate and evaporated. The residue was chromatographed on a silica gel column using hexane as the eluant giving pale yellow leaflets (0.1 g, 21%, m.p. 156-157°. The picrate was obtained as brown needles, m.p. 198°; ir (potassium bromide): 3040 (s), 1580 (s), 1245 (m), 862, 835, 820, 740; uv (cyclohexane): λ max nm (log ε) 247 (4.64), 256 (4.67), 268 (4.19), 280 (4.45), 291 (4.59), 323 (3.67), 336 (4.13), 352 (4.51), 372 (4.69), 386 (3.62); nmr (deuteriochloroform): 7.75 (d, J = 5.5 Hz, H-8, 1H), 8.0-8.27 (m, H-1, H-2, H-3, H-4, H-5, H-9, 6H), 8.56 (s, H-6, 1H), 8.60 (d, J = 8 Hz, H-10, 1H); ms: 258 (M^+, 100), 226 (M^+-32, 10), 200 (M^+-58, 2).

*Anal.*Calcd. for $C_{18}H_{10}S$: C, 83.37; H, 3.90; S, 12.41. Found: C, 83.59; H, 3.89; S, 12.27.

S-1,2,3,6,7,8-hexahydropyrene (**12**).

This compound was prepared by the reduction of pyrene following Cook and Hewlett's procedure (6) with sodium in amyl alcohol, m.p. 132° (lit 132-133°).

4-Bromo-1,2,3,6,7,8-hexahydropyrene (**13**).

Hexahydropyrene was brominated with bromine in glacial acetic acid according to the procedure of Streitweiser (7) m.p. 120° (lit 127°).

4-Bromopyrene (**14**).

Streitweiser's procedure (7) was followed for dehydrogenation of hexahydropyrene m.p. 130° (lit 138°).

Pyreno[4,5-*b*]thiophene (**3**).

4-Bromopyrene (2.5 g, 9 mmoles) dissolved in dry benzene (15 ml) and diluted with dry ether (30 ml) was treated with phenyllithium (6 ml, 1.85 *M* solution) and the reaction mixture was allowed to stand overnight. The prenyllithum was separated as a yellow solid. The solvent was decanted and the solid was washed with ether 2-3 times. The solid was then suspended in ether and treated with the solution of 2,2,2',2'-tetraethoxydiethyl disulfide (8) (2.5 g, 9 mmoles) and the reaction mixture was stirred overnight. The reaction was decomposed with water and the ether layer was separated. The aqueous layer was extracted again with ether. The combined ether layers were dried over sodium sulfate and concentrated to give an oil which was used for the next step. The above oil was dissolved in chlorobenzene (100 ml) and refluxed with polyphosphoric acid (10 g) for 0.5 hour. The chlorobenzene was decanted and the residue was washed three times with chlorobenzene. The chlorobenzene was removed *in vacuo* and the residue was chromatographed on a silica gel column using hexane as the eluant. The solid obtained was crystallized from hexane to give yellow crystals (0.1 g, 5%), m.p. 185°; ir (potassium bromide): 3040 (s), 1580 (s), 820 (s), 710 (s); nmr (deuterioacetone): 8.70 (dd, J = 10 and 2.5 Hz, H-1, 1H), 8.53-7.36 (m, H-2, H-3, H-4, H-5, H-6, H-7, H-8, H-10, H-11, 9H); ms: 258 (M^+, 100), 226 (M^+-32, 12), 200 (M^+-58, 2); uv (hexane): λ max nm (log ε): 223 (4.59), 250 (4.50), 260 (4.45), 284 (4.51), 288 (4.49), 316 (4.14), 330 (4.36), 348 (4.49), 367 (3.62).

Anal. Calcd. for $C_{18}H_{10}S$: C, 83.37; H, 3.90; S, 12.41. Found: C, 83.35; H, 3.91; S, 12.12.

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