Experimental Section

Nuclear magnetic resonance (NMR) data were obtained on a Perkin-Elmer R12A spectrometer and high-performance liquid chromatography (HPLC) data were obtained on a Dupont Model 850 chromatograph under reversed-phase conditions on a Zorbax ODS column, 4.6 mm × 25 cm, using a 0.25 M triethylammonium phosphate (TEAP, pH 3.5)/CH_3CN (97:3) system and monitoring at 230 nm. Microanalyses were performed by Galbraith Laboratories, Inc. Chemical-ionization mass spectrometric analyses were performed on a Finnigan 3200 quadrupole mass spectrometer at the University of Virginia, using methane as the reagent gas.

(*R*)-2-Bromo-4-methylpentanoic Acid (3a). Treatment of D-leucine (**6a**, 16.4 g, 125 mmol) with nitrosyl bromide,[6] followed by distillation of the crude product, gave 15.1 g (62%) of purified **3a**: bp 97–98 °C (0.25 mm); $[\alpha]^{22}_D$ +38.2 (*c* 2, methanol) [lit.[7] (*S* isomer) $[\alpha]^{27}_D$ −34° (methanol)].

(*S*)-2-Bromo-3-phenylpropanoic Acid (3b). Compound **3b** was prepared in the same manner as **3a** in 63% yield: bp 144–145 °C (0.35 mm); $[\alpha]^{25}_D$ −10.0° (*c* 2, methanol) [lit.[8] $[\alpha]^{20}_D$ −9.9° (*c* 5, absolute ethanol)]; ^1H NMR ($CDCl_3$) δ 3.36 (m, 2 H), 4.45 (m, 1 H), 7.29 (s, 5 H), 10.20 (s, 1 H).

***N,O,S*-Triacetyl-L-cysteinol (7).** L-Cysteine (**8**, 10.0 g, 83 mmol) was reduced by the procedure of Anhoury et al.[9] The crude cysteinol obtained was acetylated with acetic anhydride/sodium acetate to give 7.51 g (39%) of **7**: mp 95–97 °C; $[\alpha]^{25}_D$ −42.6° (*c* 2, water) [lit.[10] mp 101–102 °C, $[\alpha]^{25}_D$ −45° (*c* 1.9, water)]; ^1H NMR ($CDCl_3$) δ 1.95 (s, 3 H), 2.06 (s, 3 H), 2.35 (s, 3 H), 3.11 (m, 2 H), 4.15 (m, 3 H), 6.90 (br, 1 H).

***N,O,S*-Triacetyl-D-cysteinol (9).** Compound **9** was prepared in the same manner as described for its enantiomer **7**: mp 96–97 °C, $[\alpha]^{25}_D$ +43.7° (*c* 2, water).

D-Serψ(CH$_2$NH)L-Leu (4a). Compound **7** (1.50 g, 6.44 mmol) was hydrolyzed in 60 mL of 1.7 N HCl at 90 °C under an atmosphere of nitrogen for 72 h. The solvent was removed under reduced pressure and residual water was removed by azeotropic distillation with absolute ethanol. The crude cysteinol hydrochloride (**2**) was dissolved in 20 mL of absolute ethanol containing NaOEt (17.34 mmol). To this solution was added **3a** (0.38 g, 4.46 mmol) in 5 mL of absolute ethanol. The reaction mixture was stirred for 72 h at room temperature followed by evaporation of the solvent. The residue was dissolved in water, acidified with 6 N HCl, and extracted with ether. The aqueous portion was neutralized with 2 N NaOH and diluted to 150 mL with deionized water. This solution was desalted on a 2 × 20 cm column of Dowex 1 × 8, according to the procedure of Drêze et al.[11] The ninhydrin-positive fractions were pooled and the solvent was removed under reduced pressure. The residue was crystallized from 47.5% ethanol to give 0.70 g (70%) of D-Serψ(CH$_2$NH)L-Leu (**4a**): mp 179–180 °C; $[\alpha]^{22}_D$ −53.7° (*c* 2.5, water); ^1H NMR (D_2O) δ 0.90 (d, 6 H), 1.60 (m, 3 H), 2.95 (m, 2 H), 3.48 (m, 2 H), 3.78 (m, 2 H); CI/CH_4 mass spectrum, (M + 1)/*e* (relative intensity) 222 (100), 205 (50), 204 (39), 159 (46), 149 (27), 117 (49). Anal. Calcd for $C_9H_{19}NO_3S$: C, 48.83; H, 8.67; N, 6.33; S, 14.48. Found: C, 48.68; H, 8.77; N, 6.33; S, 14.38. Compound **4a** elutes near the position of phenylalanine during automatic amino acid chromatography of the single column type (ninhydrin constant is 0.45 times that of leucine).

Compounds **1a** and **4b** were obtained in the same manner.

L-Serψ(CH$_2$NH)L-Leu (1a): mp 180–181 °C; $[\alpha]^{22}_D$ −5.4° (*c* 1.5, water); ^1H NMR (D_2O) δ 0.91 (d, 6 H), 1.62 (m, 3 H), 2.95 (m, 2 H), 3.50 (m, 2 H), 3.80 (m, 2 H); CI/CH_4 mass spectrum, (M + 1)/*e* (relative intensity) 222 (100), 205 (36), 204 (22), 159 (36), 149 (14), 117 (13). Compound **1a** elutes near the position of phenylalanine during automatic amino acid chromatography of the single column type (ninhydrin constant is 0.54 times that of leucine).

D-Serψ(CH$_2$NH)D-Phe (4b): mp 173–174 °C; $[\alpha]^{25}_D$ −13.3° (*c* 2, water); ^1H NMR (D_2O) δ 2.82 (m, 2 H), 3.13 (m, 2 H), 3.50 (m, 2 H), 3.78 (m, 2 H), 7.40 (s, 5 H); CI/CH_4 mass spectrum, (M + 1)/*e* (relative intensity) 256 (77), 238 (100), 193 (21), 175 (19), 149 (23), 133 (26), 105 (25). Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.44; H, 6.72; N, 5.49; S, 12.55. Found: C, 56.19; H, 6.94; N, 5.53; S, 12.33. Compound **4b** elutes 17 min after phenylalanine during automatic amino acid analysis of the single column type (ninhydrin constant is 0.52 times that of leucine).

Boc-D-Serψ(CH$_2$NH)L-Leu (11). D-Serψ(CH$_2$NH)L-Leu (**4a**) was converted to **11** by standard procedures using di-*tert*-butyl dicarbonate:[4] mp 149–150 °C; $[\alpha]^{25}_D$ −88.6° (*c* 2, methanol); ^1H NMR ($CDCl_3$/Me_2SO-d_6) δ 0.90 (d, 6 H), 1.45 (s, 9 H), 1.69 (m, 3 H), 2.80 (m, 2 H), 3.34 (m, 1 H), 3.65 (m, 3 H), 5.62 (br, 1 H). Anal. Calcd for $C_{14}H_{27}NO_5S$: C, 52.32; H, 8.47; N, 4.36; S, 9.96. Found: C, 52.50; H, 8.63; N, 4.23; S, 9.80.

Boc-D-Serψ(CH$_2$NH)D-Phe (12). Compound **12** was prepared in the same manner as **11**: mp 120–121 °C; $[\alpha]^{25}_D$ +39.9° (*c* 2, methanol); ^1H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 2.80 (m, 2 H), 3.10 (m, 2 H), 3.45 (m, 1 H), 3.65 (m, 2 H), 3.72 (m, 1 H), 5.25 (br, 1 H), 5.93 (br, 2 H), 7.23 (s, 5 H). Anal. Calcd for $C_{17}H_{25}NO_5S$: C, 57.44; H, 7.10; N, 3.94; S, 9.01. Found: C, 57.21; H, 7.18; N, 3.79; S, 9.14.

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Registry No. **1a**, 76999-47-8; **2**, 77057-91-1; **3a**, 42990-28-3; **3b**, 35016-63-8; **4a**, 76999-48-9; **4b**, 76999-49-0; **5**, 77057-92-2; **6a**, 328-38-1; **6b**, 61-90-5; **7**, 76999-50-3; **8**, 52-90-4; **9**, 76999-51-4; **10**, 921-01-7; **11**, 76999-52-5; **12**, 76999-53-6.

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Synthesis of Angular Ring Methoxy-5-methylchrysenes and 5-Methylchrysenols[1]

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Methylated chrysenes contribute to the tumor initiation and complete carcinogenic activity of tobacco smoke and have also been detected in coal-liquefaction products.[2,3] Their concentration in the latter exceeds that of chrysene and is much higher than observed in tobacco smoke. Methylated chrysenes may also contribute to the mutagenicity of other energy-related materials.[4] Among the six possible monomethylchrysene isomers, 5-methylchrysene (**1**) is a potent carcinogen with activity approximately equal to that of benzo[*a*]pyrene. By comparison, chrysene is only weakly carcinogenic.[3,5]

The formation of vicinal dihydrodiol epoxides in the angular rings (positions 1–4 and 7–10 of **1**) of polynuclear aromatic hydrocarbons (PAH) appears to be a major activation process.[6-10] A related metabolic pathway, gen-

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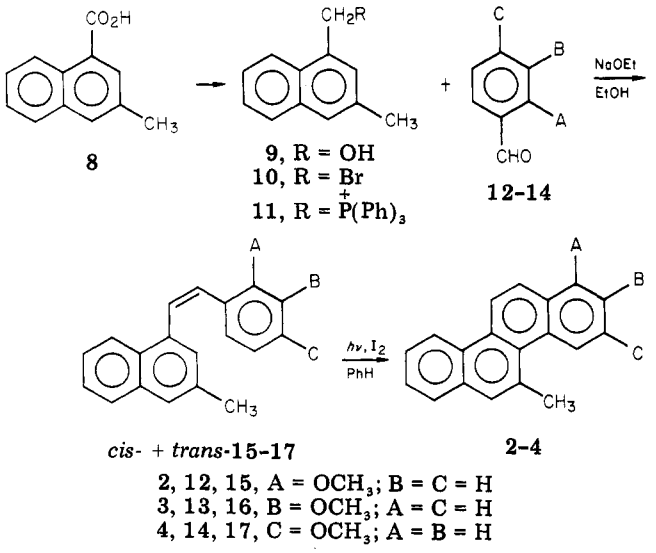
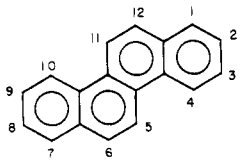
Scheme I



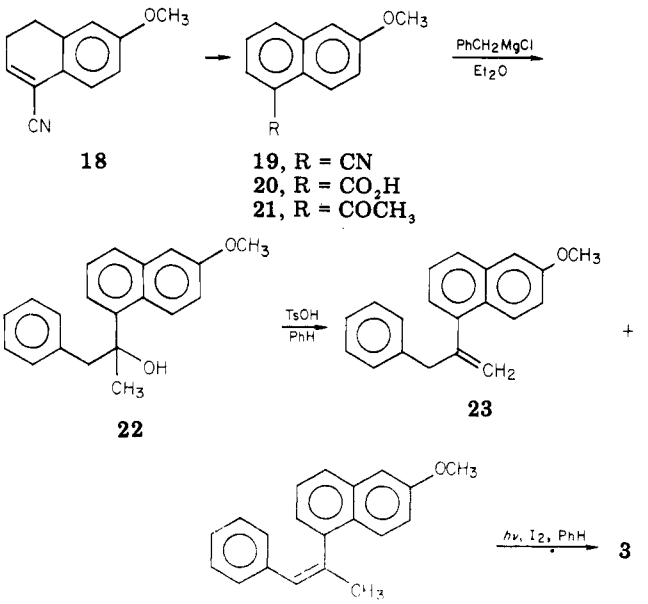
erally resulting in detoxified products, is the formation of phenols by nonenzymatic rearrangement of arene oxides.[11] These phenolic derivatives are often the major metabolites of PAH and can be used as an index of overall metabolism of and exposure to PAH. In this report, we describe the syntheses of the angular ring methoxy-5-methylchrysenes **2–7** and their conversion to the corresponding 5-methylchrysenols. The syntheses of the monomethoxychrysenes have been described,[12] but there have been no previous syntheses of the important angular ring monooxygenated derivatives of **1**.



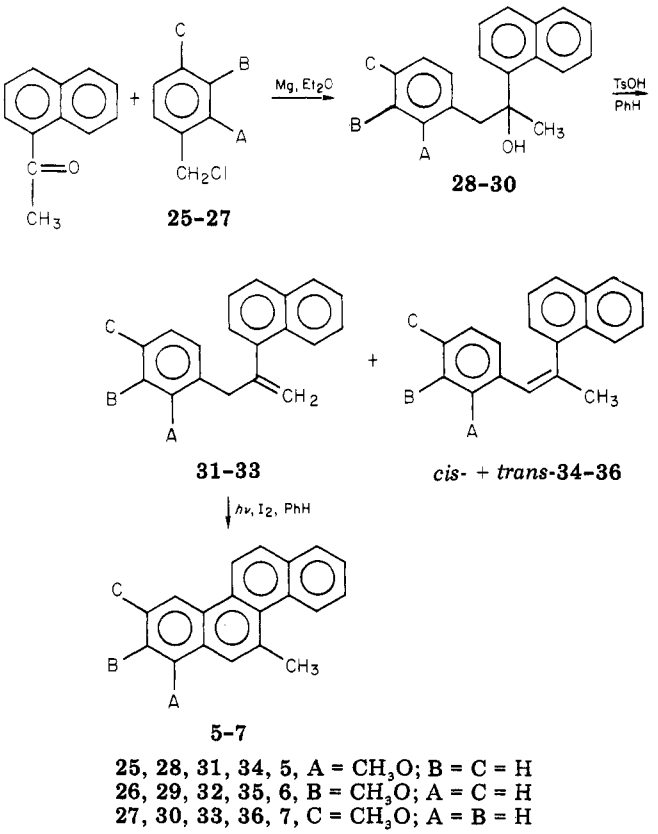
1, 5-CH_3
2, 1-CH_3O-5-CH_3
3, 2-CH_3O-5-CH_3
4, 3-CH_3O-5-CH_3
5, 7-CH_3O-5-CH_3
6, 8-CH_3O-5-CH_3
7, 9-CH_3O-5-CH_3

The syntheses of compounds **2–4** are summarized in Scheme I. 3-Methyl-1-naphthoic acid (**8**) was converted to the phosphonium salt **11** which was the precursor to the three alkenes **15–17** via condensations with the appropriate methoxybenzaldehyde **12–14**. Photochemical ring closure of **15–17** gave **2–4**. Ring closure of **15** and **17** could only give one product; however, photolysis of **16** could have given either 2-methoxy-5-methylchrysene (**3**) or 4-methoxy-5-methylchrysene. Therefore, an alternative synthesis for **3** was devised, as outlined in Scheme II. In this sequence, the position of the methoxy group was unequivocal through the use of **18** as starting material. Conversion of **18** to a mixture of **23** and **24**, followed by photolysis, gave **3**. The product obtained in the photolysis of **16** was identical with that obtained from **24**. There was no evidence of contamination by 4-methoxy-5-methylchrysene,

Scheme II



Scheme III



indicating that **3** was produced selectively in the closure reaction of **16**, presumably due to steric factors.

For the synthesis of **5–7** (Scheme III), the appropriate alkenes **34–36** were prepared from 1-acetonaphthone and *o*-, *m*-, or *p*-methoxybenzylmagnesium chloride. In the dehydration reactions, the exocyclic methylene isomers **31–33** were also produced, as observed in the dehydration of **22**, and previously in the 5-methylchrysene series.[13]

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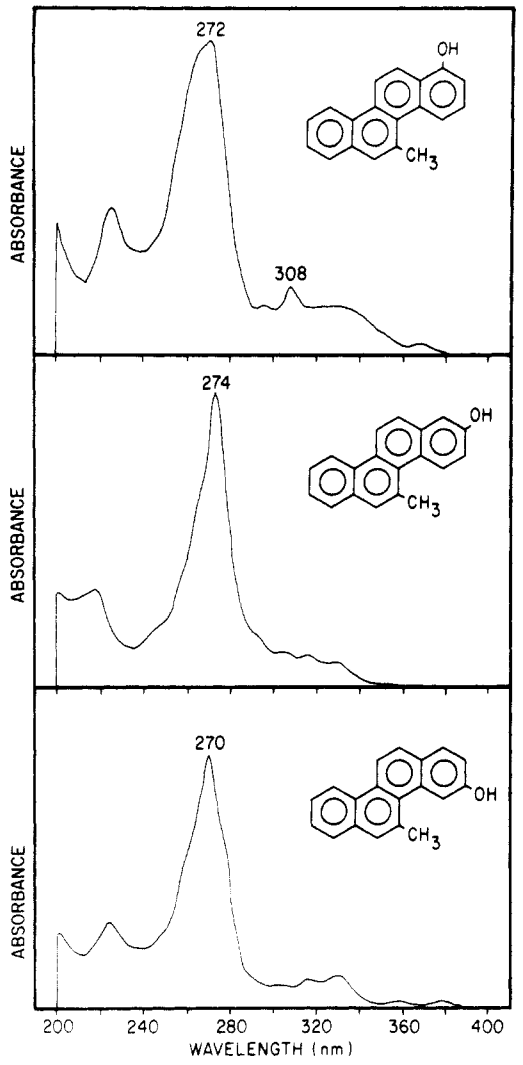

Figure 1. UV spectra of 1-hydroxy-5-methylchrysene, 2-hydroxy-5-methylchrysene, and 3-hydroxy-5-methylchrysene.

The exocyclic isomers do not photocyclize.[13] Photolysis of each mixture of endocyclic and exocyclic alkenes gave methoxychrysenes **5–7**. In the photolysis of **32** and **35**, **6** was produced exclusively in analogy to the results described above.

Compounds **2–7** were converted cleanly to the corresponding 5-methylchrysenols by cleavage with BBr_3. The 5-methylchrysenols were purified by crystallization and/or by HPLC. Since UV spectra are useful for identification of metabolites, the spectra of 1-, 2-, and 3-hydroxy-5-methylchrysenes are presented in Figure 1. These spectra are similar to those of 7-, 8-, and 9-hydroxy-5-methylchrysenes, respectively. By use of reverse-phase HPLC, 1-, 3-, 7-, and 9-hydroxy-5-methylchrysenes can be separated as illustrated in Figure 2. Under these conditions, 8-hydroxy-5-methylchrysene coelutes with 3-hydroxy-5-methylchrysene and 2-hydroxy-5-methylchrysene elutes slightly later than 9-hydroxy-5-methylchrysene (relative retention volumes 0.81 and 0.82; 1-hydroxy-5-methylchrysene 1.00). The major phenolic metabolites of **1** formed by rat liver 9000 × g supernatant have been tentatively identified as 9-hydroxy-5-methylchrysene, 7-hydroxy-5-methylchrysene, and 1-hydroxy-5-methylchrysene.[10]

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 267 spectrometer in Nujol mulls (solids) or as liquid films. ^1H NMR spectra were determined with a Hitachi Perkin-Elmer Model R-24 spectrometer in $CDCl_3$ solution with Me_4Si as internal reference. Mass spectra and combined GLC–mass spectra were recorded with a Hewlett-Packard Model 5982A mass spectrometer. GLC was done with a Hewlett-Packard Model 5711 instrument equipped with a flame-ionization detector and an 8 ft × $^1/_8$ in. column filled with 10% OV-17 on gas Chrom Q, 80–100 mesh. A flow rate of 40 mL/min of He and an oven temperature of 250 °C were used. TLC was done with 0.25-mm silica gel 60 F_{254} (Merck) glass plates. High-pressure liquid chromatography (HPLC) was performed with a Waters Associates Model ALC/GPC-202 high-speed liquid chromatograph equipped with a Model 6000A solvent delivery system, a Model 660 solvent programmer, a Model U6K septumless injector, and a 6 mm × 30 cm μBondapak/C_{18} column with elution by 65% CH_3OH–35% H_2O at 2 mL/min. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

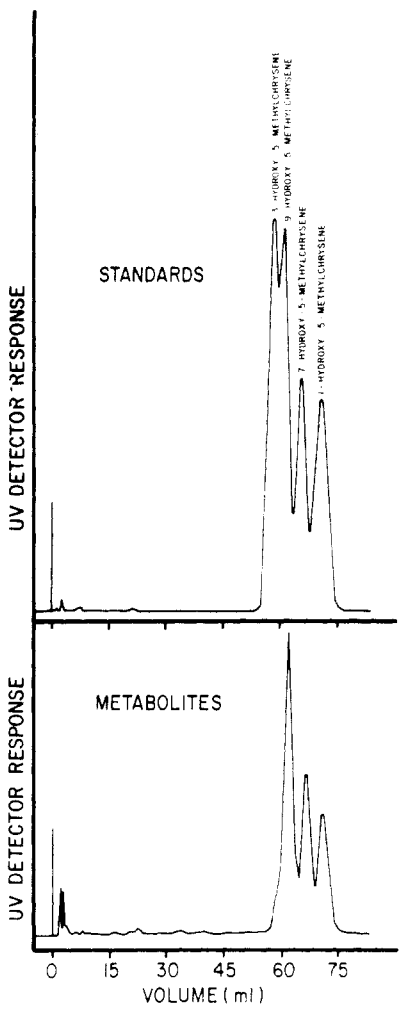

Figure 2. Separation by HPLC of hydroxy-5-methylchrysene standards and phenolic metabolites of 5-methylchrysene.

1-(Hydroxymethyl)-3-methylnaphthalene (9). A mixture of 3-methyl-1-naphthoic acid (**8**; 0.9 g, 0.005 mol)[14] and $LiAlH_4$ (0.18 g, 0.005 mol) in Et_2O (100 mL) was refluxed for 3 h. After cooling and acidification with 2 N HCl, the Et_2O layer was separated and the aqueous layer further extracted with Et_2O. The combined organic extracts were washed with H_2O, dried ($MgSO_4$), and concentrated to give a colorless solid. Recrystallization of the product from benzene gave pure **9** (0.6 g, 70%): mp 79–80 °C; IR (Nujol) 3400 cm^{-1}; NMR δ 2.25 (s, 1 H), 2.40 (s, 3 H), 4.90 (s, 2 H), 7.2–8.0 (m, 6 H); mass spectrum, *m/e* (relative intensity) 172 (M^+, 100), 143 (80), 128 (70), 115 (45).

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1-(Bromomethyl)-3-methylnaphthalene (10). The alcohol **9** (0.5 g, 0.003 mol), PBr_3 (1 mL, 0.011 mol), and Et_2O (25 mL) were heated under reflux for 3 h, cooled, and poured into H_2O (150 mL). The Et_2O layer was separated and the aqueous layer extracted with Et_2O (2 × 25 mL). The combined Et_2O layers were washed with H_2O, dried ($MgSO_4$), and concentrated to give an oil which solidified on standing. Recrystallization of the crude product from petroleum ether gave pure **10** (0.5 g, 70%): mp 68–69 °C; NMR δ 2.50 (s, 3 H), 4.85 (s, 2 H), 7.3–8.3 (m, 6 H); mass spectrum *m/e* (relative intensity) 236 (M^+, 10), 234 (10), 155 (100).

1-(3-Methyl-1-naphthyl)-2-(3-methoxyphenyl)ethylene (16). A solution of **10** (0.47 g 0.002 mol) and 0.52 g (0.002 mol) of triphenylphosphine in 30 mL of benzene was heated under reflux for 5 h and cooled. Filtration gave 0.6 g of the phosphonium salt **11**.

To a stirred solution of **11** (0.5 g, 0.001 mol) and 3-methoxybenzaldehyde (0.136 g, 0.001 mol) in 15 mL of EtOH was added a solution of 0.001 mol of NaOEt in 10 mL of EtOH. This was stirred at room temperature for 2 h and then diluted with brine and extracted with CH_2Cl_2. The organic solution was washed (H_2O), dried ($MgSO_4$), and concentrated. Silica gel chromatography of the resulting oil, with elution by CH_2Cl_2/hexane, gave **16** (0.2 g, 73%) as a mixture of cis and trans isomers; NMR δ 2.35 (s, 1.92 H, trans CH_3), 2.45 (s, 1.08 H, cis CH_3), 3.30 (s, 1.92 H, trans OCH_3), 3.75 (s, 1.08 H, cis OCH_3), 6.5–8.0 (m, 12 H). According to analysis by GLC–MS, *cis*-**16** (35%) eluted in 6.5 min and gave *m/e* (relative intensity) 274 (M^+, 100), 259 (40), 243 (30); *trans*-**16** eluted in 16.5 min and gave *m/e* (relative intensity) 274 (M^+, 100), 259 (40), 243 (30). The tentative assignment of the cis and trans isomers of **16** is by analogy of their GLC retention times to those cited in ref 13 for similar compounds. In a similar manner, the alkenes **15** and **17** were prepared from the corresponding aldehydes.

1-Cyano-6-methoxynaphthalene (19). To a solution of **18**[15] (1.5 g, 0.008 mol) in dry benzene (50 mL) under N_2 was added 2,3-dihydro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.8 g, 0.008 mol) with stirring, and the resulting solution was refluxed for 2 h. The reaction mixture was cooled, filtered, and concentrated. The residue was dissolved in CH_2Cl_2 and chromatographed on silica gel. Elution with CH_2Cl_2/hexane (20:80) afforded **19**: mp 78–79 °C (lit.[16] mp, 78–80 °C); 1.2 g (85%): IR (Nujol) 2200 cm^{-1}; NMR δ 3.90 (s, 3 H), 7.2–8.2 (m, 6 H); mass spectrum, *m/e* (relative intensity) 183 (M^+, 100), 140 (100), 168 (10).

6-Methoxy-1-naphthoic Acid (20). A solution of the nitrile **19** (1.0 g, 0.0054 mol), MeOH (25 mL), NaOH (0.8 g, 0.022 mol), and H_2O (1 mL) was refluxed for 20 h. The reaction mixture was diluted with H_2O, extracted with CH_2Cl_2, acidified, and then extracted again with CH_2Cl_2. The organic solution was washed with H_2O, dried ($MgSO_4$), and concentrated to give 0.8 g (80%) of **20** which was sufficiently pure to be used in the subsequent step: mp 178–179 °C (lit.[16] mp 182 °C); IR (Nujol) 1680 cm^{-1}; NMR δ 3.80 (s, 3 H), 7.0–8.0 (m, 5 H), 8.7 (d, 1 H, J = 7 Hz); mass spectrum, *m/e* (relative intensity) 202 (100), 185 (15).

6-Methoxy-1-acetonaphthone (21). To a stirred solution of 1.01 g (0.005 mol) of **20** in 32 mL of Et_2O at 0 °C under N_2 was added 15 mL (0.011 mol) of 0.75 M methyllithium in Et_2O. The reaction mixture was stirred for 24 h at 0 °C, poured into 30 mL of saturated aqueous NH_4Cl, and extracted with Et_2O. The combined Et_2O extracts were washed with saturated aqueous $NaHCO_3$ and H_2O, dried, and concentrated to afford 0.9 g of a yellow oil. Column chromatography of this material on silica gel with CH_2Cl_2 as eluant gave 0.8 g (80%) of **21**: NMR δ 2.50 (s, 3 H), 3.70 (s, 3 H), 7.0–7.8 (m, 5 H), 8.7 (d, 1 H, J = 7 Hz); mass spectrum, *m/e* (relative intensity) 200 (M^+, 70), 185 (100).

2-(6-Methoxy-1-naphthyl)-1-phenyl-2-propanol (22). The ketone **21** (1.0 g, 0.005 mol) in Et_2O was added at 0 °C to a solution of benzylmagnesium chloride prepared from benzyl chloride (0.9 g, 0.007 mol) and Mg (0.17 g, 0.007 mol) in Et_2O (100 mL). The mixture was stirred under N_2 overnight while warming to room temperature. After the mixture was cooled to 0 °C, saturated aqueous NH_4Cl (50 mL) was added. The aqueous layer was extracted with Et_2O and the combined Et_2O solutions were washed with H_2O, dried ($MgSO_4$), and concentrated. Chromatography on silica gel, with elution by CH_2Cl_2/hexane, gave 1.1 g (75%) of **22**: IR (film) 3400 cm^{-1}; NMR δ 1.70 (s, 3 H), 2.15 (br s, 1 H), 3.50 (d, 2 H), 4.00 (s, 3 H), 7.0–7.9 (m, 10 H), 8.85 (d, 1 H).

By use of the same general method, **28–30** were synthesized by reaction of the appropriate Grignard reagents (prepared from **25–27**) and acetonaphthone. **28**: yield 70%; NMR δ 1.75 (s, 3 H), 2.05 (s, 1 H), 3.35 (dd, 2 H), 3.65 (s, 3 H), 6.6–7.8 (m, 10 H), 8.6–8.8 (m, 1 H). **29**: yield 80%; NMR δ 1.70 (s, 3 H), 2.10 (s, 1 H), 3.40 (dd, 2 H), 3.50 (s, 3 H), 6.5–8.0 (m, 10 H), 8.5–8.8 (m, 1 H). **30**: yield 64%; NMR δ 1.70 (s, 3 H), 2.01 (s, 1 H), 3.50 (dd, 2 H), 3.70 (s, 3 H), 6.6–8.0 (m, 10 H), 8.6–8.8 (m, 1 H).

Dehydration of 22 and 28–30. To 1.1 g (0.004 mol) of alcohol **22** in 150 mL of benzene was added 20 mg of *p*-toluenesulfonic acid. The mixture was heated under reflux for 2 h, using a Dean–Stark trap, and then extracted with 25 mL of 10% $NaHCO_3$. The benzene layer was separated, washed with H_2O (2 × 25 mL), dried ($MgSO_4$), and concentrated, leaving a mixture of **23** and **24** (0.9 g, 90%); NMR δ 2.35 (s, 1.5 H, CH_3), 3.65 (s, 1.0 H, CH_2), 3.85 (s, 3 H), 5.15 (d, 1.0 H, $=CH_2$), 6.9–8.1 (m, 11 H). In a similar manner, dehydration of **28–30** gave 80–92% of mixtures of the exocyclic olefins **31–33** and the endocyclic olefins **34–36**.

2-Methoxy-5-methylchrysene (3). A solution of 0.8 g (0.0029 mol) of **23** and **24** and 5 mg of I_2 in 1 L of dry benzene was stirred and dry air was bubbled through the solution. This was irradiated with a Hanovia 250-W medium-pressure mercury lamp, using a Corex filter. The reaction was followed by GLC; after 20 h, 70% of **23** and **24** had reacted. Removal of the solvent gave 240 mg of a light yellow oil which was chromatographed on silica gel with elution by CH_2Cl_2/hexane to give 200 mg of crude **3**, which was recrystallized from EtOH to give pure **3** (160 mg, 20%).

In a similar manner, the alkenes **15–17** and **31–36** were converted to the corresponding chrysene derivatives, **2–7** which were recrystallized from ethanol and had the following melting points (°C): **2**, 124–125; **3**, 148–150; **4**, 144–146; **5**, 104–106; **6**, 147–148; **7**, 94–96. NMR spectra of **2–7** were similar; each had the following: δ 3.00–3.20 (s, 3 H, CH_3), 3.85–4.00 (s, 3 H, OCH_3), 6.7–8.1 (m, 7 H), 8.3–9.1 (m, 3 H). Mass spectra of **2–7** had *m/e* (relative intensity) 272 (M^+, 100), 257, 239, 202. Anal. Calcd for $C_{20}H_{16}O$: C, 88.23; H, 5.88. Found: (**2**) C, 88.15; H, 5.99; (**3**) C, 88.05; H, 5.76; (**4**) C, 88.38; H, 6.14; (**5**) C, 88.35; 6.02; (**6**) C, 88.29; H, 6.08; (**7**) C, 88.35; H, 6.01.

***p*-Methoxybenzyl Chloride (27).** A solution of 6.9 g (0.05 mol) of *p*-methoxybenzyl alcohol in 20 mL of $SOCl_2$ was heated under reflux for 1 h. Excess $SOCl_2$ was distilled; distillation of the crude product gave 6.5 g (83%) of **27**: bp 76–80 °C (0.5 mm); NMR δ 3.65 (s, 3 H), 4.35 (s, 2 H), 6.75 (d, 2 H, J = 7 Hz), 7.30 (d, 2 H, J = 7 Hz).

The chlorides **25** and **26** were prepared in a similar manner. **26**: yield 75%; NMR δ 3.95 (s, 3 H), 4.70 (s, 2 H), 6.9–7.5 (m, 4 H). **25**: yield 70%; NMR δ 3.85 (s, 3 H), 4.70 (s, 2 H), 6.8–7.4 (m, 4 H).

Conversion of Methoxy-5-methylchrysenes to Hydroxy-5-methylchrysenes. To a stirred solution of **3** (54 mg, 0.0002 mol) in 10 mL CH_2Cl_2 was added dropwise over a period of 10 min, a solution of boron tribromide (50 mg, 0.0002 mol) in 5 mL of CH_2Cl_2 at 0 °C under N_2. Stirring was continued for an additional 2 h. Ice-cold H_2O (50 mL) was then added. After the contents were neutralized with 10% $NaHCO_3$, the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 phases were dried ($MgSO_4$) and concentrated. The residue was recrystallized from CH_2Cl_2–hexane to give 2-hydroxy-5-methylchrysene: mp 186–187 °C; 30 mg (60%); NMR ($CDCl_3$/Me_2SO) δ 3.25 (s, 3 H), 7.2–8.1 (m, 6 H), 8.5–8.9 (m, 3 H), 9.60 (s, 1 H); mass spectrum, *m/e* (relative intensity) 258 (M^+, 100); UV (MeOH) λ_{max} 274 (ε 103 525). In a similar manner, **2** and **4–7** were converted to the corresponding hydroxy-5-methylchrysenes (mp, °C, UV (MeOH) λ_{max} (ε), nm): 1-hydroxy-5-methylchrysene, 162–164, 272 (54 105); 3-hydroxy-5-methylchrysene, 163–165, 270 (79 280); 7-hydroxy-5-methylchrysene, 148–150, 269 (47 250); 8-hydroxy-5-methylchrysene, 165–167, 267 (167 000); 9-hydroxy-5-methylchrysene, 168–170; 266 (63 595).

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Registry No. **2**, 77028-87-6; **3**, 77028-88-7; **4**, 77028-89-8; **5**, 77028-90-1; **6**, 77028-91-2; **7**, 77028-92-3; **8**, 5774-05-0; **9**, 77028-93-4; **10**, 64977-27-1; **11**, 77028-94-5; **12**, 135-02-4; **13**, 591-31-1; **14**, 123-11-5; *cis*-**15**, 77028-95-6; *trans*-**15**, 77028-96-7; *cis*-**16**, 77028-97-8; *trans*-**16**, 77028-98-9; *cis*-**17**, 77028-99-0; *trans*-**17**, 77029-00-6; **18**, 6398-50-1; **19**, 77029-01-7; **20**, 36112-61-5; **21**, 58149-89-6; **22**, 77029-02-8; **23**, 77029-03-9; *cis*-**24**, 77029-04-0; *trans*-**24**, 77029-05-1; **25**, 7035-02-1; **26**, 824-98-6; **27**, 824-94-2; **28**, 77029-06-2; **29**, 77029-07-3; **30**, 77029-08-4; **31**, 77029-09-5; **32**, 77029-10-8; **33**, 77029-11-9; *cis*-**34**, 77029-12-0; *trans*-**34**, 77029-13-1; *cis*-**35**, 77029-14-2; *trans*-**35**, 77029-15-3; *cis*-**36**, 77029-16-4; *trans*-**36**, 77029-17-5; benzyl chloride, 100-44-7; 1-acetylnaphthalene, 941-98-0; *p*-methoxybenzyl alcohol, 105-13-5; *o*-methoxybenzyl alcohol, 612-16-8; *m*-methoxybenzyl alcohol, 6971-51-3; 2-hydroxy-5-methylchrysene, 77029-18-6; 1-hydroxy-5-methylchrysene, 67411-85-2; 3-hydroxy-5-methylchrysene, 72427-02-2; 7-hydroxy-5-methylchrysene, 67411-84-1; 8-hydroxy-5-methylchrysene, 77029-19-7; 9-hydroxy-5-methylchrysene, 67411-83-0.

Nature of the Reaction of Thiamin in the Presence of Low Concentrations of Sulfite Ion. Competitive Trapping

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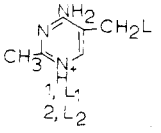
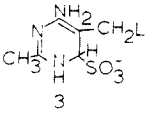
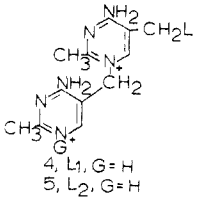
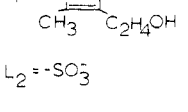
Nucleophilic substitution of thiamin (1), vitamin B_1, by sulfite ion gives pyrimidinium sulfonate **2** and the corresponding free thiazole.[1] Although this reaction was first reported in 1935 it was not until 1977 that a mechanism was advanced: one sulfite ion adds to the pyrimidinium ring, made electrophilic by protonation, to give intermediate **3**. A second sulfite ion, the one appearing in the observed product, then reacts either with **3** or with another intermediate formed from **3**, i.e., by loss of the leaving group (L) from **3**. Expulsion of the first sulfite gives product.[2]









Confirmation of the involvement of the second sulfite ion in this scheme was reported recently in a significant kinetic study.[3] Doerge and Ingraham demonstrated that at constant thiamin concentration reduction of the sulfite ion concentration leads to a change in kinetic order from one to two for sulfite ion.[3] However, the sigmoidal pH-dependent reactivity of the intermediate(s) detected when the second sulfite ion is kinetically important was not explained.

We provide an explanation for the observed pH-dependent reactivity of the intermediate observed by Doerge and Ingraham and isolate a product, not previously detected, which supports our interpretation.

Results and Discussion

We suggest that as the sulfite ion concentration is reduced in a series of experiments involving thiamin, another nucleophile begins to compete with sulfite ion for intermediate. This nucleophile under the conditions employed by Doerge and Ingraham is thiamin. In support of this are reports relating to other conditions: pyridine, a nucleophile similar in basicity to the conjugate base of **1**, can be made to compete with sulfite ion in the formation of substitution products to give a derivative of **1** having a pyridine ring as substituent L.[2,4]

Consideration of our suggestion that thiamin and sulfite ion both compete for intermediate leads to an explanation of the observed sigmoidal pH dependent reactivity of the intermediate, given by k_2/k_3 in ref 3. This apparent rate constant ratio contains pH-dependent terms to reflect the fractional amount of each nucleophile present in its reactive, basic form as the acidity of the reaction medium is varied. The fractional amount of nucleophile present as its reactive base is given by $K_a/([H] + K_a)$; appropriate pK_a values are 4.7 (HB) and 6.9 (HSO_3^-). Our eq 1 which

$$\frac{k_2}{k_3} = \left(\frac{k_B}{k_S}\right)\left(\frac{\text{fraction free 1}}{\text{fraction free } SO_3^{2-}}\right)[1]_0 \qquad (1)$$

has a linear form reproduces the previously unexplained observations and establishes a new rate constant ratio given by the slope which is pH independent (correlation coefficient 0.989). This slope, k_B/k_S, reflecting the relative abilities of the two competing nucleophiles to trap intermediate, is roughly 10^{-4}. Hence, only under conditions where **1** is present in large excess over sulfite ion is **1** able to compete with the strongly nucleophilic sulfite ion.

We sought support for our analysis of kinetic data by carrying out a product study. As a way to solve the practical problem of maintaining a very small concentration of sulfite ion in solution so that thiamin might successfully compete with it and yet achieve conversion to products in an amount suitable for isolation we elected to employ $CaSO_3$. This sparingly soluble salt ($K_{sp} = 1.1 \times 10^{-7}$ at 18 °C[5]) acts as a "buffer", keeping a low, roughly constant amount of sulfite ion in solution, compensating for the loss due to formation of sulfonic acid product.

A 2.4 M solution of **1** when briefly heated with $CaSO_3$ gives rise to **5** which we have isolated in very low yield. This material contains two pyrimidine rings. One of these is bonded to the methylene side chain of **1** in place of the thiazole leaving group. This new bond to the quaternized pyrimidine ring is logically produced in a trapping reaction because a control shows that no significant reaction takes place in the absence of sulfite ion. Although we would have liked to isolate bispyrimidine **4** where L is a thiazole ring instead of a sulfonato group as with **5**, this was not possible. Other studies making use of independently synthesized **4** and **5** (G = CH_3) show that **4** is much more reactive than **1**.[6] In other words, the product produced in a trapping

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