Synthesis and Mutagenicity of 5,11-Dimethylchrysene and Some Methyl-Oxidized Derivatives of 5-Methylchrysene[1]

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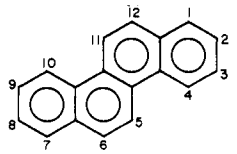
A series of compounds structurally related to the carcinogen and mutagen 5-methylchrysene (1) was synthesized and tested for mutagenicity toward *S. typhimurium* TA 100. The compounds prepared were 5,11-dimethylchrysene (2), 5-(hydroxymethyl)chrysene (3), 5-(acetoxymethyl)chrysene (4), 5-carbomethoxychrysene (5), 5-(hydroxymethyl)-1,2,3,4-tetrahydrochrysene (6), 5-carbomethoxy-1,2,3,4-tetrahydrochrysene (7), and 5*H*-chryseno[4,5-*bcd*]pyran-5-one (31). When tested in the presence of rat liver homogenate, 1 and 2 were active while 3–7 were less mutagenic than 1; 31 was highly mutagenic. The mutagenicity of 1 and 2 contrasts with the low activity of 5,12-dimethylchrysene, which supports the generalization that the structural requirements favoring activity are a bay-region methyl group and a free peri position, both adjacent to an unsubstituted angular ring. The low activity of 3–7 indicates that methyl oxidation is not an important activation process for 1. This agrees with previous studies in which the major proximate mutagen and carcinogen of 1 was identified as 1,2-dihydro-1,2-dihydroxy-5-methylchrysene.

Methylated polynuclear aromatic hydrocarbons (PAH) are often more mutagenic and carcinogenic than the parent compounds.[2] For example, 5-methylchrysene (1) is a

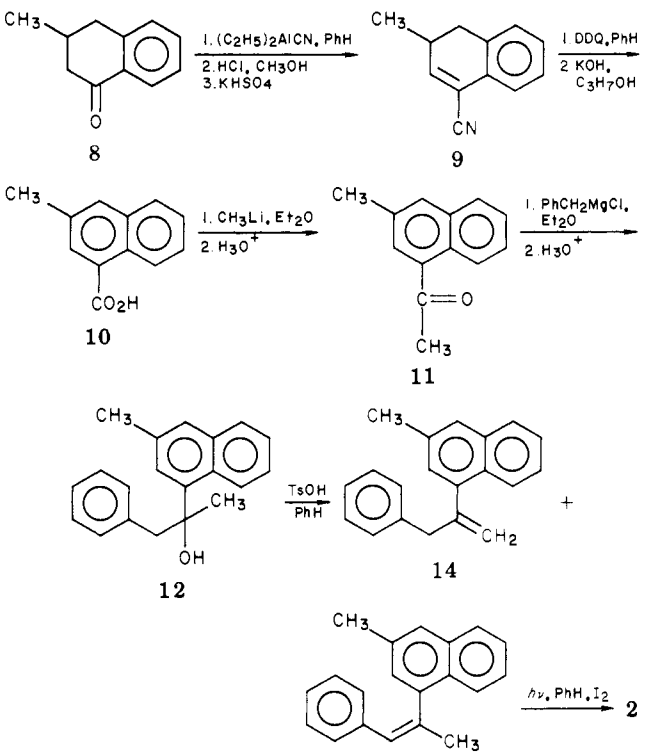


1, 5-CH_3
2, 5,11-$(CH_3)_2$
3, 5-CH_2OH
4, 5-CH_2OAc
5, 5-CO_2CH_3
6, 1,2,3,4-tetrahydro-5-CH_2OH
7, 1,2,3,4-tetrahydro-5-CO_2CH_3

potent carcinogen and mutagen, while chrysene and the other monomethylchrysene isomers are only weakly active or inactive.[3,4] Metabolic and structure–activity studies in the methylchrysene series indicate that the structural features favoring carcinogenicity are a bay-region methyl group and a free peri position, both adjacent to an unsubstituted angular ring[5] and that 1,2-dihydro-1,2-dihydroxy-5-methylchrysene is a major proximate mutagen and carcinogen of 1.[6-8] This agrees with investigations of other PAH, including chrysene,[9,10] which indicate that angular ring dihydrodiol epoxides having one carbon terminus of the epoxide ring in the "bay region" of the molecule are major ultimate carcinogens and mutagens.[11] However, certain methylated PAH, such as 7,12-dimethylbenz[*a*]anthracene and 3-methylcholanthrene, may have another activation pathway, i.e., hydroxylation of a methyl or methylene carbon followed by formation of a bay-region dihydrodiol epoxide.[12-14] It has also been suggested that conjugates of hydroxymethyl derivatives of PAH may be involved in activation.[15] In the present study, 5,11-dimethylchrysene (2) was synthesized to further test the structural requirements for mutagenicity and carcinogenicity in the methylchrysene series. Compounds 3–5 were prepared to assess the possible involvement of methyl oxidation in mutagenesis by 1. This concept was further tested by mutagenicity assays of 6 and 7 which could not be further activated by formation of a 1,2-dihydrodiol, as in 1 and 3. Tetrahydro derivatives 6 and 7 also provided a possible synthetic entry to the major proximate mutagen and carcinogen of 1, 1,2-dihydro-1,2-dihydroxy-5-methylchrysene.

Synthesis. The synthesis of 2 is outlined in Scheme I. The key intermediate was 3-methyl-1-naphthoic acid (10), which was prepared by an improved route.[16] Conversion of 10 to ketone 11, followed by reaction with benzylmagnesium chloride and dehydration, gave *cis*- and *trans*-13 and the *exo*-methylene isomer 14.[17] Photolysis of a mixture of 13 and 14 gave 2.

Scheme I



The syntheses of methyl-oxidized derivatives 3–7 are outlined in Scheme II. Photolysis of 16 or 17 afforded chrysene-5-carboxylic acid (18) or 5, respectively, in 60% yields,[18] which were higher than we generally obtained when 1 and related compounds were prepared from methyl-substituted α-styrylnaphthalenes.[17,19] Reduction of 5 gave 3, which was acetylated to yield 4. This preparation of 3 was superior to its synthesis from 1 by benzylic bromination and hydrolysis.

The tetrahydro compounds 6 and 7 were prepared starting from 19. However, the yield of 7 from the photolysis of 21 was only 7% in contrast to the higher yields obtained in the photolyses of 16 and 17. As shown in

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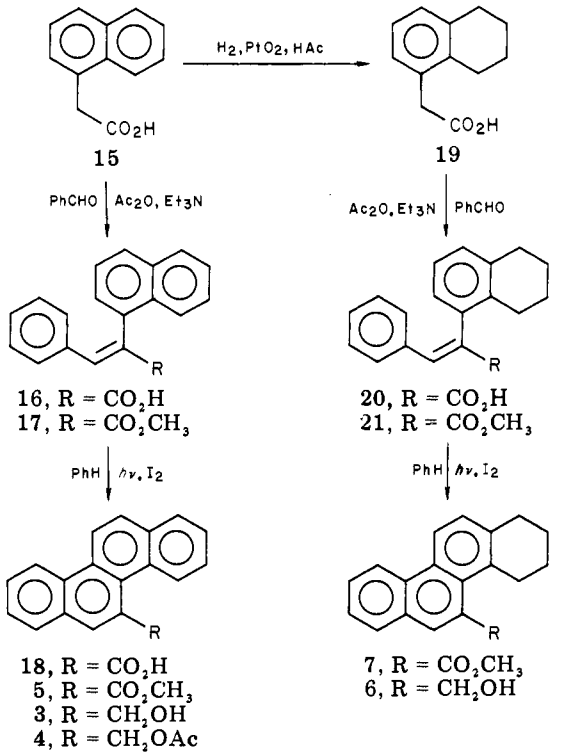
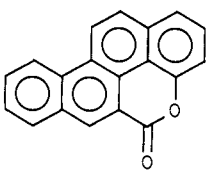
Scheme II



Scheme III, attempted preparation of 5-methyl-1,2,3,4-tetrahydrochrysene (**28**) by the analogous sequence failed, since **26** did not cyclize.

The reduction of 5-(hydroxymethyl)-1,2,3,4-tetrahydrochrysene (**6**) was investigated since **28** was not obtained by photolysis and was a potential precursor to 3,4-dihydro-5-methylchrysene, a critical intermediate in the synthesis of 1,2-dihydro-1,2-dihydroxy-5-methylchrysene. However, hydrogenolysis of **6** gave predominantly 1,2,3,4,5,6-hexahydro-5-methylchrysene (**27**) and only traces of **28**. Reduction of the 5,6 double bond in **6** may have resulted from unfavorable steric interactions in **28**.

Another approach to 3,4-dihydro-5-methylchrysene was treating 1,2,3,4,5,6-hexahydro-5-methylchrysene (**27**) with 2,3-dihydro-5,6-dicyano-1,4-benzoquinone (DDQ).[20] However, this resulted in aromatization of the 1–4 ring; the major product was **29**. These results contrast with those observed when 1,2,3,4,5,6-hexahydrochrysene was reacted with DDQ. In that case, 3,4,5,6-tetrahydrochrysene was obtained selectively and was converted to 1,2-dihydro-1,2-dihydroxychrysene.[21] The reaction of **7** with DDQ was also studied. While the major product was **5**, up to 25% of **31** was also isolated.



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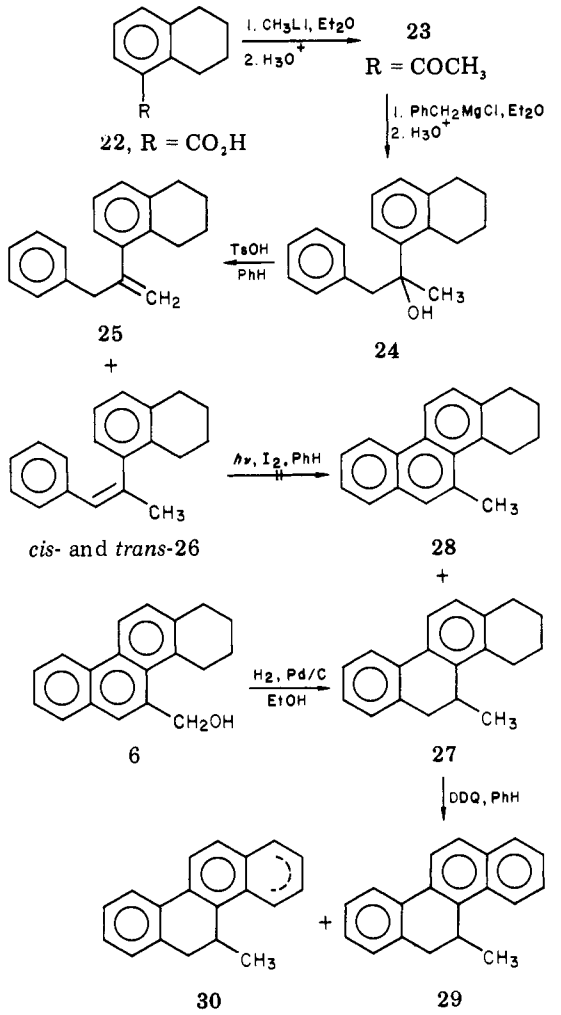
Mutagenicity Assays. All compounds were tested for mutagenicity toward *S. typhimurium* TA 100 in the presence of rat liver homogenate; **1** was not mutagenic toward TA 98. The results are summarized in Table I. 5,11-Dimethylchrysene (**2**) was more mutagenic than 5-methylchrysene (**1**). In contrast, a previous study showed that 5,12-dimethylchrysene was less mutagenic toward *S. typhimurium* TA 100 than was **1**.[17] These results support

Scheme III



the generalization that the structural requirements favoring mutagenicity and carcinogenicity of methylated polynuclear aromatic hydrocarbons are a bay-region methyl group and a free peri position, both adjacent to an unsubstituted angular ring. Both **1** and **2** fulfill these requirements, while 5,12-dimethylchrysene does not, due to the presence of a methyl group at peri position 12. Similar results have been obtained in comparative assays of **1**, **2**, and 5,12-dimethylchrysene for tumor-initiating activity.[22] Inhibition of carcinogenicity by peri substitution has also been observed in other systems.[22,23]

None of the methyl-oxidized derivatives **3**–**7** were as mutagenic as **1**. In contrast, 1,2-dihydro-1,2-dihydroxy-5-methylchrysene induced 1350 His^+ revertants/plate in *S. typhimurium* TA 100 after a dose of 50 μg.[24] These results are in agreement with our previous studies and indicate that oxidation of the methyl group of **1** is not an important activation step. However, 5-(hydroxymethyl)chrysene (**3**) is one of the major metabolites formed from **1** in vitro by rat liver homogenates.[7] The high mutagenicity of lactone **31** is of interest since this compound is analogous to the mutagenic and carcinogenic PAH benzo[*a*]pyrene; **31** was inactive in the absence of liver homogenate.

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

Table I. Mutagenic Activity toward *S. typhimurium* TA 100 of Compounds Related to 5-Methylchrysene

no.	compd	His$^+$ revertants/plate[a,b] 5 μg	10 μg	20 μg	50 μg	100 μg
1	5-methylchrysene	156	235	373	381	354
2	5,11-dimethylchrysene	255	329	464	640	564
3	5-(hydroxymethyl)chrysene	170	238	188	185	162
4	5-(acetoxymethyl)chrysene	145	215	211	185	147
5	5-(carboxymethyl)chrysene	179	215	216	195	214
6	5-(hydroxymethyl)-1,2,3,4-tetrahydrochrysene	135	144	180	182	159
7	5-(carboxymethyl)-1,2,3,4-tetrahydrochrysene	136	151	162	175	164
31	5*H*-chryseno[4,5-*bcd*]pyran-5-one	413	608	649	661	669

[a] Average Me_2SO control = 108 His$^+$ revertants/plate. [b] Each value is the average of four trials.

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. Gas–liquid chromatography 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 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. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and were within ±0.3% of the calculated values.

1-Cyano-3-methyl-3,4-dihydronaphthalene (9). A solution of 5.6 g (0.035 mol) of 3-methyl-1-tetralone (**8**)[25] in 30 mL of dry toluene was cooled to −20 °C with stirring under N_2. A cooled solution of diethylaluminum cyanide[26] in benzene (Alfa Division, Ventron Corp., 1.2 M, 70 mL) was added with a syringe, and the resulting mixture was kept at −15 °C for 2 h and then added to a mechanically stirred solution of 150 mL concentrated HCl and 250 mL of CH_3OH at −70 °C. Stirring was continued for 1.5 h, and the resulting mixture was poured into a mixture of 200 mL of concentrated HCl and 1 L of ice–water and extracted with CH_2Cl_2 (3 × 500 mL). The combined organic phases were washed twice with H_2O (500 mL), dried ($MgSO_4$), and evaporated at 20 °C from a flask containing 55 mg of *p*-toluenesulfonic acid. The residue was obtained as a pale-yellow oil (7.4 g), which was distilled (from 200 mg of powdered $KHSO_4$) to yield the crude dihydronitrile **9**, bp 87–90 °C (0.1 mm). The crude product was purified by chromatography on a column of silica gel with elution by hexane–CH_2Cl_2 (90:10) to give pure **9**: yield 3.0 g (50%); IR (film) 2220 cm^{-1}; NMR δ 1.2–1.4 (m, 3 H), 2.5–3.1 (m, 3 H), 6.8 (d, 1 H, J = 2 Hz), 7.2–7.7 (m, 4 H); MS m/e (relative intensity) 169 (M^+, 60), 154 (100).

3-Methyl-1-naphthoic Acid (10). A mixture of dihydronitrile **9** (1.69 g, 0.01 mol) and DDQ (2.37 g, 0.01 mol) in dry benzene (50 mL) was heated under reflux for 3 h. Precipitated dihydro-2,3-dichloro-5,6-dicyano-1,4-benzoquinone was collected, and the filtrate was evaporated to leave a brown solid (1.6 g). Chromatography on a column of silica gel (40 g) with hexane as eluant gave 1-cyano-3-methylnaphthalene: yield 1.5 g (89%); mp 51–52 °C; IR (Nujol) 2220, 1600 cm^{-1}; NMR δ 2.60 (s, 3 H), 7.5–7.8 (m, 5 H), 8.2–8.4 (m, 1 H); MS m/e (relative intensity) 167 (M^+, 100), 154 (30), 139 (32).

A mixture of 1-cyano-3-methylnaphthalene (1.6 g, 0.01 mol), 1.7 g of 85% aqueous KOH, and 50 mL of 1-propanol was refluxed for 80 h. The cooled mixture was poured into 300 mL of H_2O and the amide (0.15 g) was filtered, mp 225–226 °C. The acid **10** (1.3 g, 70%) was precipitated on acidification of the filtrate, and after two recrystallizations from 95% EtOH formed colorless needles: mp 172–174 °C (lit.[16] 172–174 °C); IR (Nujol) 3350, 1720 cm^{-1}; MS m/e (relative intensity) 186 (M^+, 100), 169 (59), 141 (70).

3-Methyl-1′-acetonaphthone (11). To a stirred solution of **10** (0.93 g, 0.005 mL) in 50 mL of Et_2O under N_2 was added a solution of 6 mL of 1.7 M methyllithium (Alfa Division, Ventron Corp.). The reaction mixture was stirred for 12 h and then quenched with H_2O. The Et_2O layer was washed with H_2O, saturated aqueous $NaHCO_3$, and again with H_2O, dried ($MgSO_4$), and concentrated. The crude product was chromatographed on silica gel with elution by chloroform–hexane (50:50), yielding 0.9 g (93%) of 3-methyl-1-acetonaphthone (**11**): IR (Nujol) 1675 cm^{-1}; NMR δ 2.45 (s, 3 H), 2.65 (s, 3 H), 7.2–7.8 (m, 5 H), 8.5–8.8 (m, 1 H); MS m/e (relative intensity) 184 (M^+, 54), 169 (100), 141 (80), 115 (80).

2-(3-Methyl-1-naphthyl)-1-phenyl-2-propanol (12). A solution of **12** (0.9 g, 0.005 mol) in 30 mL of dry Et_2O was added to a cold solution of benzylmagnesium chloride prepared from 0.17 g of Mg, 0.76 g (0.006 mol) of benzyl chloride, and 50 mL of Et_2O. The mixture was stirred at 20 °C for 1 h, refluxed for 5 h, and then stirred overnight at 20 °C. Aqueous NH_4Cl (20 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined Et_2O solutions were washed with H_2O (3 × 50 mL), dried ($MgSO_4$), and evaporated. The oily residue (2 g) was chromatographed on 50 g of silica gel with elution by 3:1 hexane–CH_2Cl_2 to give 1.5 g (54%) of **12** (colorless liquid): IR (film) 3350 cm^{-1}; NMR δ 1.80 (s, 3 H), 2.45 (s, 3 H), 2.90 (s, 1 H), 3.50 (q, 2 H, J = 12 Hz), 7.0–7.8 (m, 9 H), 7.6–7.9 (m, 1 H), 8.6–8.9 (m, 1 H); MS m/e (relative intensity) 91 (100).

Dehydration of 12. A solution of **12** (1.0 g, 0.0036 mol) and a catalytic amount of *p*-toluenesulfonic acid in 150 mL of dry benzene was refluxed for 3 h using a Dean–Stark trap. The solvent was removed, and the oil obtained (0.96 g) was chromatographed on silica gel with elution by hexane–CH_2Cl_2 (80:20) to give 0.9 g (98%) of product as a mixture of **13** (cis and trans) and **14**. According to analysis by GLC–MS, the *exo*-methylene isomer **14** (60%) eluted in 4.0 min and gave MS m/e (relative intensity) 258 (M^+, 28), 167 (100). The geometrical isomers of **13** eluted at 3.8 and 5.5 min and gave identical MS m/e (relative intensity) 258 (M^+, 95), 243 (100); NMR δ 2.3 (m, 4.4 H, CH_3 of **13** and **14**), 3.7 (s, 0.8 H, CH_2 of **14**), 5.1 (d, 0.8 H, $=CH_2$ of **14**), 6.9–7.9 (m, 12 H).

5,11-Dimethylchrysene (2). A solution of 800 mg (0.0035 mol) of the above alkene mixture and 50 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 monitored by GLC. Complete reaction required 40 h. The mixture was filtered and the filtrate concentrated in vacuo. The residue was chromatographed on a silica gel column with 4:1 hexane–$CHCl_3$ to give 80 mg of **2**. Further purification required chromatography on silica gel with hexane and recrystallization from ethanol to give colorless needles: mp 125–126 °C (55 mg, 7%); NMR δ 3.0 (s, 6 H), 7.3–7.9 (m, 8 H), 8.3–8.6 (m, 2 H); MS m/e (relative intensity) 256 (100), 241 (52). Anal. ($C_{20}H_{16}$) C, H.

2-(1-Naphthyl)-3-phenylpropenoic Acid (16). The acid was prepared from **15** (5.58 g, 0.03 mol) and benzaldehyde (3.2 g, 0.03 mol) under conditions similar to those described below for **20**: yield 73%; mp 163–164 °C (lit.[18] 164 °C); IR (Nujol) 1675 cm^{-1}; NMR δ 6.8–7.7 (m, 12 H), 8.0 (s, 1 H), 10.7 (br s, 1 H); MS m/e (relative intensity) 274 (M^+, 40), 229 (100).

5-Carbomethoxychrysene (5). A mixture containing 1.35 g (0.005 mol) of **16**, 3.3 g (0.025 mol) of K_2CO_3, and 1.26 g (0.01 mol) of dimethyl sulfate in 200 mL of dry acetone was refluxed for 3 h. After filtration, the filtrate was evaporated to afford **17** as a white solid, mp 78–79 °C (1.3 g), which was used as such for further reaction: IR (Nujol) 1710 cm^{-1}; NMR δ 3.70 (s, 3 H), 7.0–8.0 (m, 12 H), 8.01 (s, 1 H).

Photolysis of 1.0 g of **17** for 10 h under conditions described above for the preparation of **2** gave **5**, which was purified by crystallization from ethanol to yield 0.6 g (60%): mp 159–160 °C; NMR δ 3.95 (s, 3 H), 7.4–8.4 (m, 9 H), 8.6 (d, 2 H, J = 7 Hz); MS m/e (relative intensity) 286 (M^+, 100), 258 (58), 226 (70), 227 (60). Anal. ($C_{20}H_{14}O_2$) C, H.

5-(Hydroxymethyl)chrysene (3). The alcohol **3** was prepared from **5** (0.286 g, 0.001 mol) as described below for preparation of **6**; **3** (mp 124–126 °C) was obtained in 85% yield after purification by crystallization from CH_2Cl_2–hexane: NMR δ 2.15 (br s, 1 H), 5.40 (s, 2 H), 7.5–8.2 (m, 8 H), 8.6–8.9 (m, 3 H); MS m/e (relative intensity) 258 (M^+, 100), 239 (40), 229 (80). Anal. ($C_{19}H_{14}O$) C, H.

5-(Acetoxymethyl)chrysene (4). Acetyl chloride (27 mg, 0.00035 mol) in methylene chloride (5 mL) was added dropwise to a stirred solution of the alcohol **3** (80 mg, 0.0003 mol) and triethylamine (35 mg, 0.00035 mol) in methylene chloride (10 mL) and stirred overnight. The reaction mixture was washed (H_2O) and dried ($MgSO_4$). Concentration provided crude **4**, which was recrystallized from CH_2Cl_2–hexane to give 55 mg (59%): mp 91–93 °C; IR (Nujol) 1730 cm^{-1}; NMR δ 2.20 (s, 3 H), 5.85 (s, 2 H), 7.5–8.2 (m, 8 H), 8.5–8.8 (m, 3 H); MS m/e (relative intensity) 300 (M^+, 70), 258 (45), 239 (100). Anal. ($C_{21}H_{16}O$) C, H.

5,6,7,8-Tetrahydro-1-naphthylacetic Acid (19). A solution of 1-naphthylacetic acid (**15**; 18.6 g, 0.01 mol) in 150 mL of acetic acid was hydrogenated for 4 h in the presence of 1.8 g of PtO_2 under a pressure of 30 psi. The catalyst was filtered and washed thoroughly with additional portions of acetic acid. The filtrate was poured into H_2O. The precipitate was filtered and washed with H_2O and hexane. The product was crystallized from cyclohexane: mp 161 °C (lit.[27] 162 °C); yield 15 g (80%); IR (Nujol) 1700 cm^{-1}; NMR δ 1.7–2.0 (m, 4 H), 2.5–2.9 (m, 4 H), 3.65 (s, 2 H), 7.10 (s, 3 H), 10.6 (s, 1 H); MS m/e (relative intensity) 190 (M^+, 40) 131 (100).

2-[1-(5,6,7,8-Tetrahydronaphthyl)]-3-phenylpropenoic Acid (20). A slurry of **19** (19.0 g, 0.1 mol), 10 mL of acetic anhydride (10 mL), triethylamine (10 mL), and benzaldehyde (10.6 g, 0.1 mol) was heated with stirring at 160 °C for 2 h. To the cool, but liquid, reaction mixture was added 20 mL of concentrated HCl. The resulting solid was transferred to a separatory funnel with methylene chloride, washed with H_2O (3 × 150 mL), and extracted with 10% aqueous NaOH (3 × 200 mL). The basic extract was acidified with acetic acid to precipitate 18.0 g (64%) of **20** (recrystallized from cyclohexane: mp 171 °C; IR (Nujol) 3340, 1670 cm^{-1}; NMR δ 1.7–1.9 (br s, 4 H), 2.4–2.6 (br s, 2 H), 2.7–2.9 (br s, 2 H), 7.0–7.3 (m, 8 H), 7.9 (s, 1 H); MS m/e (relative intensity) 278 (M^+, 60), 200 (100). Anal. ($C_{19}H_{18}O_2$) C, H.

Methyl 2-[1-(5,6,7,8-Tetrahydronaphthyl)]-3-phenylpropenoate (21). The ester was prepared by reaction of **20** (2.78 g, 0.01 mol) with dimethyl sulfate as described above for **17**; **21** was obtained in 80% yield after purification by crystallization from CH_2Cl_2–hexane: mp 59–60 °C; IR (Nujol) 1710 cm^{-1}; NMR δ 1.6–1.8 (m, 4 H), 2.3–2.5 (m, 2 H), 2.6–2.8 (m, 2 H), 3.80 (s, 3 H), 6.9–7.4 (m, 8 H), 7.9 (s, 1 H); MS m/e (relative intensity) 292 (M^+, 90), 260 (50), 145 (100).

5-Carbomethoxy-1,2,3,4-tetrahydrochrysene (7). A solution of 2.9 g (0.01 mol) of the ester **21** and 200 mg of I_2 in 3 L of dry benzene was irradiated for 40 h in the usual way. The solvent was removed and the residue was chromatographed on 60 g of silica gel. Elution with hexane–chloroform (90:10) gave **7** (250 mg). Recrystallization of **7** from absolute ethanol yielded light-yellow crystals: mp 95–96 °C (200 mg, 7%); IR (Nujol) 1710 cm^{-1}; NMR δ 1.5–2.0 (br s, 4 H), 2.6–3.1 (br s, 4 H), 3.90 (s, 3 H), 7.2–7.9 (m, 5 H), 8.3–8.6 (m, 2 H); MS m/e (relative intensity) 290 (M^+, 45), 258 (100). Anal. ($C_{20}H_{18}O_2$) C, H.

5-(Hydroxymethyl)-1,2,3,4-tetrahydrochrysene (6). A solution of 72 mg (0.00025 mol) of **7** in 3 mL of anhydrous THF was added dropwise during 5 min to a stirred suspension of 39 mg of $LiAlH_4$ in 10 mL of THF. The mixture was stirred for 90 min at 20 °C and 4 h at 70 °C, cooled, diluted cautiously with H_2O, and extracted with ethyl acetate. The ethyl acetate solution was dried ($MgSO_4$) and concentrated to afford 64 mg of **7**: mp 104–106 °C (CH_2Cl_2–hexane); NMR δ 1.6–1.9 (br s, 4 H), 1.95 (s, 1 H), 2.7–2.9 (br s, 2 H), 3.1–3.3 (br s, 2 H), 5.0 (s, 2 H), 7.1–7.7 (m, 5 H), 8.3–8.5 (m, 2 H); MS m/e (relative intensity) 262 (M^+, 40), 244 (50), 216 (100), 215 (100).

5,6,7,8-Tetrahydro-1-naphthoic Acid (22). A mixture of 1-naphthoic acid (3.4 g, 0.02 mol) in acetic acid (30 mL) was hydrogenated in the presence of PtO_2 at 42 psi for 6 h. The suspension was heated to boiling before filtration of the catalyst and the latter was washed with additional hot acetic acid and poured into H_2O. The solid acid was filtered and washed with H_2O and hexane. The product was crystallized from acetic acid to provide **22** (2.4 g, 68%) as white needles: mp 151–152 °C (lit.[28] 150–151 °C); IR (Nujol) 1700 cm^{-1}; NMR δ 1.5–2.0 (br s, 4 H), 2.6–2.9 (br s, 2 H), 3.1–3.4 (br s, 2 H), 7.2–7.6 (m, 3 H); MS m/e (relative intensity) 176 (M^+, 82), 159 (100).

5,6,7,8-Tetrahydro-1-acetonaphthone (23). The acid **22** was converted in 84% yield to the ketone **23** as described above for **11**. The ketone was a colorless oil: bp 88–90 °C (0.5 mm) [lit.[28] 152–155 °C (19 mm)]; NMR δ 1.5–2.0 (m, 4 H), 2.50 (s, 3 H), 2.6–3.0 (m, 4 H), 7.0–7.5 (m, 3 H); MS m/e (relative intensity) 174 (M^+, 78), 159 (100), 131 (59).

3-Phenyl-2-[1-(5,6,7,8-tetrahydronaphthyl)]-2-propanol (24). Benzylmagnesium chloride was prepared from Mg (0.37 g, 0.015 mol) and benzyl chloride (1.9 g, 0.015 mol) and allowed to react with ketone **23** (2.0 g, 0.012 mol) as described above for the synthesis of **12**. The alcohol **24** was obtained in 84% yield as a liquid and used as such in the next step: NMR δ 1.5 (s, 3 H), 1.6–2.0 (m, 5 H), 2.6–3.2 (m, 6 H), 6.9–7.4 (m, 8 H).

3-Phenyl-1-(5,6,7,8-tetrahydronaphthyl)-2-propene (26). The carbinol **24** (2.2 g, 0.0082 mol) was dehydrated as described for **12** and afforded a mixture of **25** and **26** (cis and trans). According to analysis by GLC–MS, the *exo*-methylene isomer **25** (45%) eluted in 12.8 min and gave MS m/e 248 (M^+, 28), 233 (100), while the geometrical isomers of **26** eluted at 12.5 and 16.0 min and gave identical MS, m/e (relative intensity) 248 (M^+, 38), 233 (100): NMR of the mixture δ 1.7–2.1 (m, 4 H), 2.1 (d, 2 H, CH_3 of *cis*- and *trans*-**26**), 2.6–3.0 (m, 4 H), 3.60 (s, 1 H, CH_2 of **25**), 5.1 (d, 1 H, $=CH_2$ of **28**), 6.9–7.8 (m, 9 H).

Reduction of 5-(Hydroxymethyl)-1,2,3,4-tetrahydrochrysene (6). Catalytic hydrogenation of 26 mg of the alcohol **6** in 10 mL of ethanol (catalytic amount of HCl) over 5 mg Pd/C (10%) for 2 min at 6 psi afforded 20 mg (65%) of 1,2,3,4,5,6-hexahydro-5-methylchrysene (**27**) as a colorless liquid: NMR δ 0.9 (d, 3 H, J = 7 Hz), 1.6–1.9 (m, 4 H), 2.6–3.4 (m, 7 H), 7.0–7.7 (m, 6 H); GLC showed the presence of one peak at the retention time of 6.4 min; MS m/e (relative intensity) 248 (M^+, 82), 233 (100).

The above reaction was repeated under different conditions, using 5 mg of Pd/C (10%) for 1 min at 0.5 psi. According to analysis by GLC–MS, the hexahydro compound **27** (43%) eluted in 6.4 min and gave MS m/e (relative intensity) 248 (M^+, 82), 233 (100). The other product [tetrahydro compound **28** (56.3%)] eluted at 16.5 min and gave MS m/e (relative intensity) 246 (M^+, 80), 231 (100).

Action of DDQ on 1,2,3,4,5,6-Hexahydro-5-methylchrysene (27). A mixture of the hexahydro compound **27** (20 mg, 0.0008 mol) and DDQ (18 mg, 0.0008 mol) in dry benzene under N_2 was warmed at 50 °C for 15 min. GLC–MS analysis showed three peaks with retention times of 6.4, 7.0, and 8.0 min, which were identified as **27**, **30** (minor), and 5,6-dihydro-5-methylchrysene (**29**) (major), respectively. After the addition of 1 more equiv of DDQ, the remaining hexahydro compound **27** was converted to **29** as the major product. The structure of **29** was confirmed by comparison of its GLC retention time and MS to those of a reference sample.[29]

Action of DDQ on 5-Carbomethoxy-1,2,3,4-tetrahydrochrysene (7). The tetrahydro compound **7** (145 mg, 0.0005 mol) was allowed to react with 27 mg (0.001 mol) of DDQ in 10 mL of refluxing benzene for 15 min under N_2. The resulting mixture was chromatographed on 20 g of silica gel with elution by hexane–chloroform (80:20) to give **5**: yield 90 mg (64%); mp 159–160 °C. Further elution with chloroform provided **31**: yield 35 mg (25%); mp 225–226 °C; IR (Nujol) 1730 cm^{-1}; NMR δ 7.5–7.8 (m, 6 H), 8.2–8.6 (m, 4 H); MS m/e (relative intensity) 270 (M^+, 100), 242 (10). Anal. ($C_{19}H_{10}O_2$) C, H.

Mutagenicity Assays. Mutagenicity studies were performed using *S. typhimurium* tester stains TA 100 (TA 1535/pKM101) provided by Dr. Bruce Ames of the University of California, Berkeley. The S-9 fraction employed for microsomal activation was obtained from the livers of male Fischer-344 rats weighing

300–350 g which had been treated 5 days prior to sacrifice with 500 mg/kg Aroclor 1254. The S-9 fraction was prepared by centrifugation of the liver homogenate (25% in 0.15 M KCl) at 9000*g* for 15 min as described by Ames et al.[30] The S-9 fraction was filter sterilized at 4 °C using a 600-mL Millipore pressure filtration apparatus equipped with 0.45-μm Swinex filter (Millipore Corp., Bedford, Mass.). Each microsomal preparation was checked for sterility on nutrient agar prior to storage at −80 °C. The S-9 mix contained, per milliliter, 100 μmol of potassium phosphate buffer, pH 7.4; 8 μmol of $MgCl_2$; 1.65 μmol of KCl; 5 μmol of glucose 6-phosphate; 4 μmol of $NADP^+$; and 0.5 mL of S-9 fraction.

The procedure of Ames et al.[30] was employed in performing these assays. In summary, various concentrations of chrysenes in 50 μL of dimethyl sulfoxide (Me_2SO) were added to 0.1 mL of an overnight nutrient broth culture of the bacterial tester strain. After the addition of 200 μL of S-9 mix and 2 mL of molten top agar at 45 °C, the contents were mixed and poured on minimal glucose agar plates. Percent survivors for all compounds assayed was determined by employing dilutions of bacterial broth under identical conditions, with the exception that excess histidine was added to the top agar. No significant toxicity toward the bacteria was observed for the compounds assayed. All compounds were analyzed by high-pressure LC, GLC, and/or TLC prior to mutagenicity assays; in all cases, purity was greater than 99%.

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Synthesis and Biological Activity of Carboxyl-Terminus Modified Prostaglandin Analogues

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A series of PGE_2, 16,16-dimethyl-PGE_2, and $PGF_{2\alpha}$ analogues modified at the carboxyl terminus with tetrazole, amide, acylurea, imide, and sulfonimide functionalities was evaluated for uterine stimulant, bronchodilator, hypotensive, gastric antisecretory, and diarrheal activity. These compounds were prepared by modification of the Corey prostaglandin synthesis utilizing as a key step condensation of known hemiacetals with the ylide derived from the requisite substituted phosphonium salts. Structure–activity relationships suggest that a proton at the C-1 position appears necessary for agonist activity and the acidity of this proton has a relatively greater influence on activity than pendant steric bulk. Noteworthy are the tissue-selective bronchodilator activity of *N*-acetyl-PGE_2-carboxamide and the selectivity for uterine tissue of *N*-methanesulfonyl-PGE_2-carboxamide, 2-decarboxy-2-(tetrazol-5-yl)-16,16-dimethyl-PGE_2, *N*-acetyl-16,16-dimethyl-PGE_2-carboxamide, and *N*-methanesulfonyl-16,16-dimethyl-PGE_2-carboxamide.

Achievement of tissue selectivity and metabolic stability has emerged as a necessary requirement for the realization of the potential therapeutic utility of prostaglandins. In pursuit of this objective, numerous prostaglandin analogues modified in the *n*-amylcarbinol side chain or cyclopentane ring have been prepared.[1,2] One line of research pursued

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