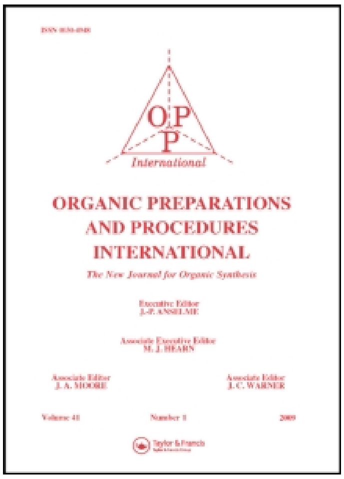

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SYNTHESIS OF 6,7,12-TRIMETHYLBENZ[a]ANTHRACENE 6,7-, AND 6,12-DIHETHYLBENZ[a]ANTHRACENE

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SYNTHESIS OF 6,7,12-TRIMETHYLBENZ[a]ANTHRACENE 6,7-, AND 6,12-DIMETHYLBENZ[a]ANTHRACENE

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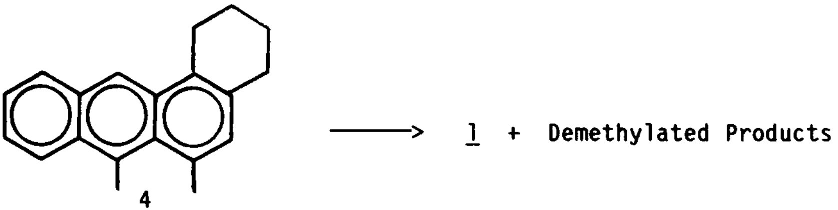
Methyl substitution in the benz[a]anthracene ring system often profoundly alters the tumorigenic properties of the parent hydrocarbon.[1,2] This paper reports improved syntheses of three methylated benz[a]anthracenes: 6,7- and 6,12-dimethylbenz[a]anthracene (1 and 2) and 6,7,12-trimethylbenz[a]anthracene (3). Syntheses of compounds 1 and 2 in poor yields (3% of 1 and 9% of 2) were first reported by Fieser and Jones,[3] from dehydrogenation of the saturated angular ring analogs 4 and 5 with Pd/C and sulfur. Pataki *et al.*[4,5] subsequently reported the synthesis of 1, 2, and 3 in overall yields of 35%, 27%, and 20%, respectively. We now report modified procedures which afford overall yields of 1, 2, and 3 of 57%, 35% and 37%, respectively from synthetically available 6a and 6b.[3]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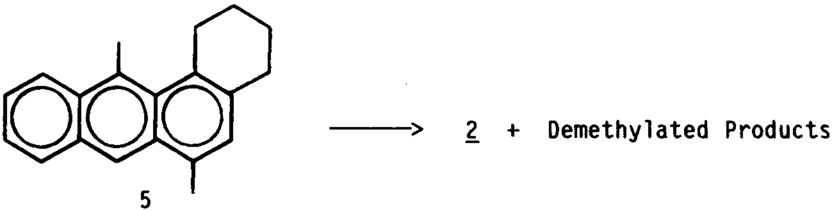
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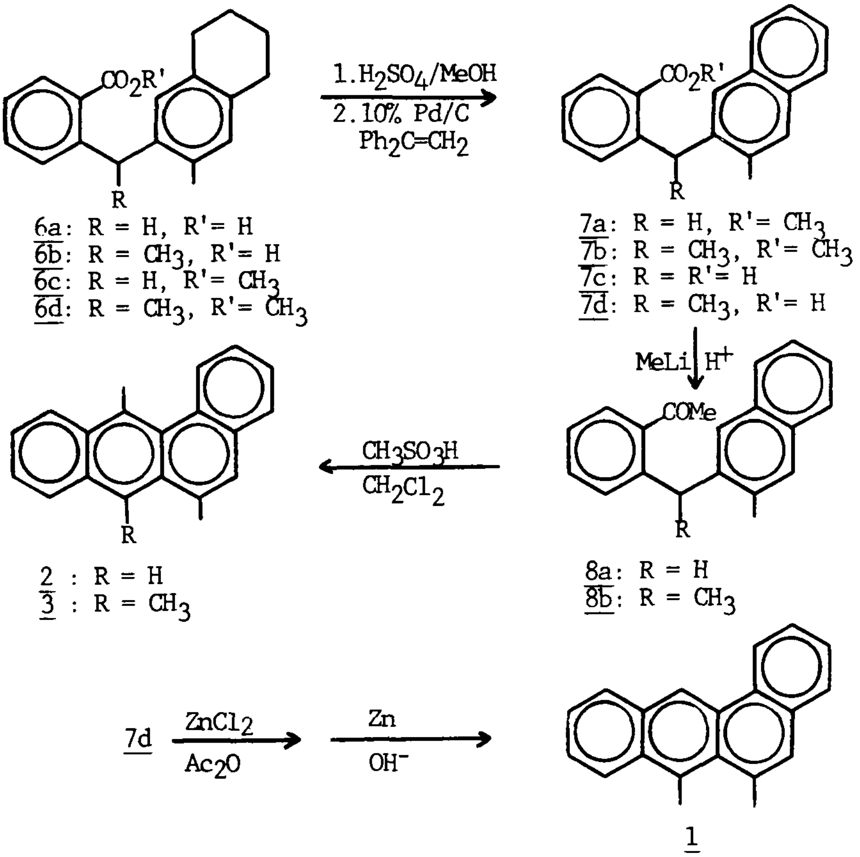
We circumvented the problem of low yield dehydrogenation reactions by performing the dehydrogenation before the benz[a]anthracene system was assembled. Esterification of the acids 6a and 6b[6] followed by dehydrogenation using sulfur, DDQ,[7,8] and 10% Pd/C afforded good yields of naphthalene esters 7a and 7b. Saponification of the esters afforded the acids 7c and 7d which were readily converted to the substituted acetophenones 8a and 8b by treatment with methyllithium. Cyclization of 8a and 8b using dilute methanesulfonic acid[9,10] afforded the desired hydrocarbons 2 and 3 in 55% overall yield and 50% overall yield, respectively (from 7c and 7d). On the other hand, reaction of acid 7d with $ZnCl_2$ and acetic anhydride in acetic acid followed by reduction with Zn in toluene afforded compound 1 in 76% yield.



6a: R = H, R'= H
6b: R = CH_3, R'= H
6c: R = H, R'= CH_3
6d: R = CH_3, R'= CH_3

7a: R = H, R'= CH_3
7b: R = CH_3, R'= CH_3
7c: R = R'= H
7d: R = CH_3, R'= H

8a: R = H
8b: R = CH_3

2 : R = H
3 : R = CH_3

1

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected as are reported boiling points. Elemental analyses were performed by Mrs. Ruby Ju of the Department of Chemistry. IR measurements were obtained on a Perkin-Elmer Model 337 spectrophotometer. ^1H NMR spectra at 60 MHz were recorded on a Hitachi Perkin Elmer R-24B instrument at ambient temperature and are referenced to tetramethylsilane as an internal standard.

2-(1,2,3,4-Tetrahydro-6,α-dimethyl-7-naphthylmethyl)benzoic Acid (6b).- A mixture of 450 g (6.73 mol) of granulated Zn (amalgamated), 40 mL of H_2O, 195 mL of conc HCl, 45 mL of acetic acid, and 2-(1,2,3,4-tetrahydro- 6,α-dimethyl-7-naphthylmethyl-6-ol)benzoic lactone (8.8 g, 30 mmol)[3] in 100 mL of toluene was stirred under reflux for 50 hrs. After cooling, the aqueous layer was separated, washed with ether, and the combined organic extracts were washed with 10% Na_2CO_3. Acidification with conc HCl gave 8.2 g (92%) of a white solid, mp. 164-165°, which was recrystallized from ethyl acetate, mp. 165-166°, lit.[3] mp. 165-166°.

Methyl 2-(1,2,3,4-tetrahydro-6-methyl-7-naphthylmethyl)benzoate (6c).- A mixture of 26 g (93 mmol) of 2-(1,2,3,4-tetrahydro-6- methyl-7-naphthylmethyl)benzoic acid (6a),[3] 7 g (71 mmol) of conc sulfuric acid, 24 g (750 mmol) of methanol, and 112 ml of 1,2-dichloroethane was heated to reflux for 72 hrs. After cooling, 500 mL of ether was added and the organic layer was separated, washed with water, 5% aq $NaHCO_3$, and satd salt solution. After the organic layer was dried ($MgSO_4$), the solvent was removed to give 26 g (96%) of a clear pale yellow oil.

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.58; H, 7.54

Found: C, 81.63; H, 7.62

IR: 1725 (C=O, ester) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.55-8.05(m, 6H), 4.30(s, 2H), 3.80(s, 3H), 2.40-2.90(m, 4H), 2.15(s, 3H), 1.55-1.95(m, 4H).

Methyl 2-(1,2,3,4-tetrahydro-6-α-dimethyl-7-naphthylmethyl)benzoate (6d).- As described for the synthesis of 6c, a mixture of 13.2 g (44.8 mmol) of

6b, 14 mL of methanol, 400 mL of 1,2-dichloroethane, and 2.7 mL of conc H_2SO_4 was refluxed for 72 hrs. Similar workup afforded 13.5 g (98%) of a solid, mp. 82-83°.

Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.77; H, 7.86

Found: C, 81.67; H, 7.62

IR: 1720 (C=O, ester) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.70-7.95(m, 6H), 4.95-5.40 (q, 1H), 3.82(s, 3H), 2.50-2.90(m, 4H), 2.00(s, 3H), 1.45-1.90(m, 7H).

Methyl 2-(3-methyl-2-naphthylmethyl)benzoate (7a).- A mixture of 0.1 g of 10% palladium on charcoal, 2.6 g (8.8 mmol) of 6c, 3.6 g (20 mmol) of 1,1-diphenylethylene and 10 mL of 1-methylnaphthalene was dehydrogenated at 290° for 6 hrs. After cooling, benzene was added and the catalyst was removed by filtration. Benzene was removed under reduced pressure and 1-methylnaphthalene, 1,1-diphenylethane, and 1,1-diphenylethene were removed on a Kugel Rohr apparatus (80°, 0.05 mm). The resulting oil was distilled (180°, 0.05 mm) to give a yellow oil which solidified to afford 2.1 g (82%) of a white solid, mp. 87-88°.

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25

Found: C, 82.80; H, 6.35

IR: 1730 (C=O, acid) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.60-7.85(m, 10H), 4.29(s, 2H), 3.40(s, 3H), 2.09(s, 3H).

Methyl-2-(3,α-dimethyl-2-naphthylmethyl)benzoate (7b).- As described for the synthesis of 7a, 0.1 g of 10% palladium on charcoal, 4.0 g (13 mmol) of 6d, 5.4 g (30 mmol) of 1,1-diphenylethylene, and 10 mL of 1-methylnaphthalene were allowed to react for 6 hrs. Similar workup afforded a pale yellow oil which solidified to a white solid. Recrystallization from methanol gave 3.4 g (85%) of white crystals mp. 92-93°.

Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86: H, 6.62

Found: C, 83.02; H, 6.81

IR: 1720 (C=O, ester) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.85-7.90(m, 10H), 5.10-5.55(q, 1H), 3.75(s, 3H), 2.15(s, 3H), 1.55-1.75(d, 3H).

<u>2-(3-Methyl-2-naphthylmethyl)benzoic Acid</u> (<u>7c</u>).- A solution of 4.0 g of KOH pellets (85%), 10.7 g (36.8 mmol) of <u>7a</u> in 110 mL of 95% ethanol was refluxed for 3 hrs. The ethanol was removed and water was added to dissolve the residue. The aqueous solution was extracted with ether and then acidified with conc HCl. The white precipitate was collected, washed with water, and dried to give 9.7 g (95%) of <u>7c</u>, mp. 165-168°. An analytical sample, mp. 167-168°, was obtained by recrystallization from ethyl acetate.

<u>Anal</u>. Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84

Found: C, 82.47; H, 5.71

IR: 1680-1725 (C=O, acid) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.10-8.15(m, 10H), 4.61(s, 2H), 2.50(s, 3H).

<u>2-(3,α-Dimethyl-2-naphthylmethyl)benzoic Acid</u> (<u>7d</u>).- As described for the synthesis of <u>7c</u> a mixture of 5.0 g of KOH (85%), 10.7 g (35.1 mmol) of <u>7b</u>, and 170 mL of 95% EtOH was refluxed for 7 hrs. Similar workup afforded 10.1 g (90%) of a white solid, mp. 210-212°. An analytical sample, mp. 213-215°, was obtained by recrystallization from ethyl acetate.

<u>Anal</u>. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25

Found: C, 82.74; H, 6.19

IR: 1670-1715 (C=O, acid) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.00-8.00(m, 10H), 5.20-5.60(q, 1H), 2.20(s, 3H), 1.50-1.70(d, 3H).

<u>2-(3-Methyl-2-naphthylmethyl)acetophenone</u> (<u>8a</u>).- To a solution of 6.50 g (23.5 mmol) of <u>7c</u> in 300 mL of dry ether was added 50 mL (71 mmol; 4% solution in ether) of methyllithium. After stirring for 1 hr. the reaction mixmixture was poured over 400 mL of ice water containing 5 mL of conc H_2SO_4. After a conventional workup 6.5 g of the solid obtained was chromatographed on neutral alumina with benzene to afford 4.10 g (64%) of a white solid,

mp. 81-82.5°. Recrystallization from methanol afforded an analytical sample, mp. 84-85°.

Anal. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61

Found: C, 87.58; H, 6.40

IR: 1680 (C=O, ketone) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.85-7.80(m, 10H), 4.32(s, 2H), 2.38(s, 3H), 2.25(s, 3H).

6,12-Dimethylbenz[a]anthracene (2).- A solution of 0.40 g (1.46 mmol) of 8a in 20 mL of a 50:50 mixture of methylene chloride:methanesulfonic acid was stirred at room temperature for 24 hrs. The product was chromatographed on neutral alumina (benzene), to yield 0.27 g (73%) of 2 as a white solid,

mp. 73-74.5°, lit.[3] mp. 75-75.5°. ^1H NMR ($CDCl_3$): δ 7.10-8.40 (m, 10H), 3.05(s, 3H), 2.45(s, 3H).

2-(3,α-Dimethyl-2-naphthylmethyl)acetophenone (8b).- As described for the synthesis of 8a, to a solution of 1.2 g (4.1 mmol) of 7d in 50 ml of dry ether was added 20 mL (28.4 mmol; 4% solution in ether) of methyl- lithium. Chromatography afforded 0.84 g (71%) of a white solid, mp. 91-92°.

Anal. Calcd for $C_{21}H_{20}O$: C, 87.45; H, 7.03

Found: C, 87.15; H, 7.21

IR: 1680 (C=O, ketone) cm^{-1}. ^1H NMR: δ 7.12-8.00(m, 10H), 5.05-5.40(q, 1H), 2.42(s, 3H), 2.28 (s, 3H), 1.62-1.75(d, 3H).

6,7,12-Trimethylbenz[a]anthracene (3).- As described for the synthesis of 2, a solution of 0.50 g (1.7 mmol) of 8b in 30 mL of a 50:50 mixture of methylene chloride/methanesulfonic acid was stirred at room temperature for 48 hrs. Similar workup gave 0.33 g (70%) of a pale yellow solid,

mp. 188-190°, lit.[4,5] mp. 179-180°.

Anal. Calcd for $C_{21}H_{18}$: C, 93.29; H, 6.73

Found: C, 93.30; H, 6.72

^{1}H NMR($CDCl_3$): δ 7.05-8.25(m, 9H), 3.05(s, 3H), 2.85(s, 3H), 2.55(s, 3H).

6,7-Dimethylbenz[a]anthracene (1).- A mixture of 3.9 g (13 mmol) of 7d, 0.32 g (1.8 mmol) of zinc chloride, 20 mL of acetic anhydride and 24 mL of acetic acid was refluxed for 1.5 hrs. Water was added to the cooled reaction mixture and the precipitate was dissolved in ether. The ether was washed with water and dried ($MgSO_4$). Removal of the solvent afforded a yellow oil which was purified on a Kugel Rohr apparatus (180°, 0.05 mm) to afford 3.8 g of a pale yellow oil. Reactive Zn was prepared by swirling 18.7 g (286 mmol) of Zn dust with 0.8 g of $CuSO_4$ dissolved in 30 mL of water. The aqueous layer was decanted and to the residual Zn was added 200 mL of 10% NaOH solution and 3.8 g of the oil dissolved in 70 mL of toluene. The reaction mixture was refluxed for 40 hrs. After cooling toluene was added, and the product was chromatographed on neutral alumina (benzene), to afford 2.6 g (76% from 7d) as a pale yellow solid, mp. 114-115°. Recrystallization from EtOH/benzene gave light yellow needles, mp. 114.5-115.5°, lit.[3] mp. 114-114.4°. Picrate, mp. 162.5-163.5°.

^{1}H NMR ($CDCl_3$): δ 7.05-8.20(m, 10H), 2.85(s,3H), 2.55(s,3H).

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