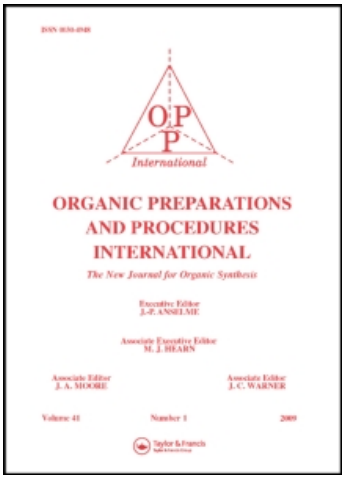

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A MODIFIED APPROACH IN THE SYNTHESIS OF 5- AND 6-METHYLBENZ[a]ANTHRACENES

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A MODIFIED APPROACH IN THE SYNTHESIS OF 5- AND 6-METHYLBENZ[a]ANTHRACENES

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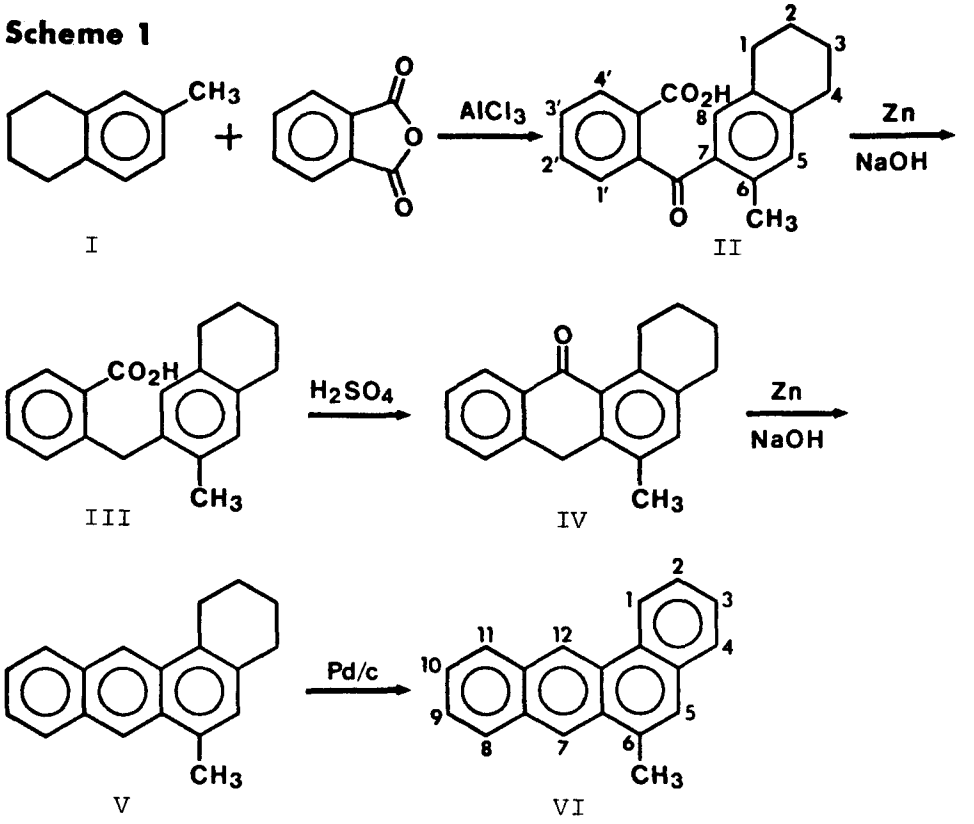
Polycyclic aromatic hydrocarbons (PAHs) are common particulate environmental pollutants and many have been found to be carcinogenic in experimental animals. The twelve isomeric methylbenz[a]anthracenes (MBAs) have been synthesized and their carcinogenicity has been tested.[1] The effect of the methyl substituent on the biotransformation of MBAs is not clearly understood.[2] Detailed metabolic studies require large quantities of hydrocarbon and the simplest procedures to date for the synthesis of 5- and 6-methylbenz[a]anthracenes (IX and VI) have been reported by Newman (see Scheme 1).[3] The synthesis of the starting material, 6-methyltetralin (I), prepared[3] by Clemmensen-Martin reduction of 7-methyl-1-tetralone, requires at least four steps beginning with succinoylation of toluene.[4] It was also obtained[4] by catalytic hydrogenation of 2-methylnaphthalene with Raney nickel catalyst (1800 psig and 130-135°). We now report that hydrogenation of 2-methylnaphthalene over PtO_2 occurs readily at 40 psig, (25°) in 81% yield; PtO_2 was previously found to be superior to Pd/C in preparing the tetrahydro-PAH by hydrogenation of the terminal benzo ring of PAHs.[5]

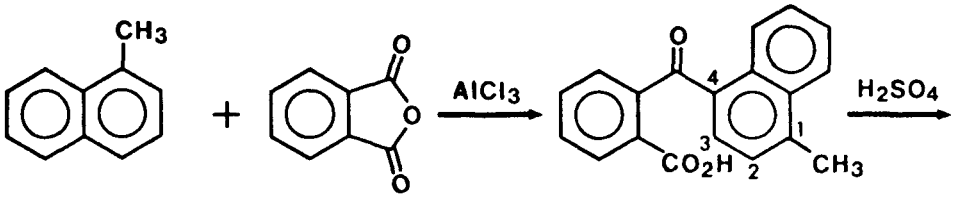
Compound VI was then synthesized according to Scheme 1. We also employed the dehydrogenation reagent, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[6] in the conversion of 1,2,3,4-tetrahydro-6-methylbenez[a]anthracene (V) to 6-methylbenz[a]anthracene (VI).

Scheme 1

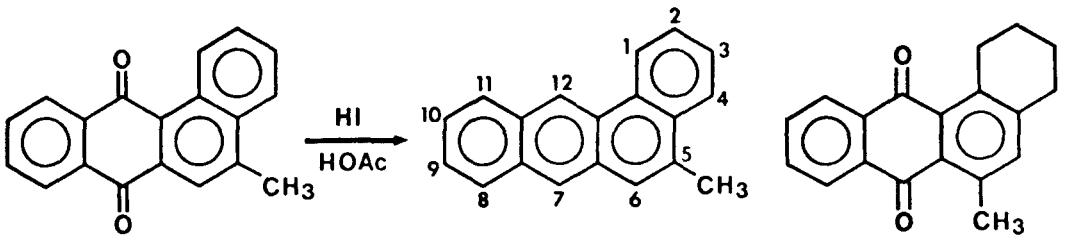


The procedure for the synthesis of 5-methylbenz[a]anthracene (IX) reported by Newman[3] is similar to that used for 6-MBA; however dehydrogenation as the last step was not necessary since 1-methylnapthalene was used as the starting material. Our modified method (Scheme 2) requires one step less than the procedure of Newman.[3] The keto acid VII was synthesized according to a known procedure.[3] Cyclization by concentrated sulfuric acid afforded 5-methylbenz[a]anthracene-7,12-dione (VIII) in a 55% yield. Reduction of VIII with HI in acetic acid afforded IX in a 96% yield. Thus, this three-step modified method provides IX in an overall yield of 48%.

Scheme 2



VII



VIII IX X

Though cyclization of the keto acid VII by H_2SO_4 afforded the quinone VIII in good yield, conversion of keto acid II to quinone X by several acidic catalysts failed.[3] A probable explanation for the reactivity difference between these two keto acids (II and VII) is that cyclization of II occurs by electrophilic aromatic substitution to a benzenoid substrate whereas cyclization of VII is to a naphthalenoid aromatic ring. Compound VI was also prepared in a 94% yield by reduction of 6-methylbenz[a]anthracene-7, 12-dione with HI in acetic acid. The result further confirms the generality of this procedure using HI as the reducing agent.[7] The structures of keto acids II and VII were previously determined by chemical oxidation to fragments of known structures[4]. By ^1H NMR spectral analysis, we have confirmed the substitution pattern. In compound VII, an ortho coupling (7.4 Hz) between H_2 and H_3 was observed and H_2 also exhibited a benzylic coupling of 0.8 Hz which was characteristic of an aromatic proton meta to a methyl group. For compound II, only one proton (H_5) exhibited a nuclear Overhauser enhancement (NOE) when the methyl protons were saturated. This measurement

showed that H_5 was ortho to the methyl substituent, but H_8 was not. Furthermore, when the methylene protons of the corresponding acid III were saturated, the other proton (H_8) exhibited an NOE.

EXPERIMENTAL

^1H NMR spectra were recorded with a Jeol MH 100 or a Bruker WH 270 spectrometer with Me_4Si as an internal standard. Mass spectra were obtained on a Finnigan Model 4023 gas chromatograph-mass spectrometer system, via solid probe insertion, by electron impact ionization at 70 ev and an ion source temperature of 250°C. Melting points are uncorrected. Catalytic hydrgenation experiments were conducted in a Parr apparatus.

Platinum (IV) oxide and 10% Pd/c catalysts were purchased from Ventron Corp. 2-Methylnaphthalene (Aldrich) was purified by chromatography on silica gel, eluted with hexane prior to use. HI (57% aqueous solution) was purchased from Fisher Chemical Co. 6-Methylbenz[a]anthracene-7,12-dione was obtained from Alfred Bader Chemicals.

6-Methyltetralin (I).- A mixture of 2-methylnaphthalene (40g, 0.28 mol) in ethyl acetate (25 ml) was hydrogenated over PtO_2 (2.1 g)in a Parr apparatus at ambient temperature at 42 psig for 20 hrs. The crude reaction product was filtered through Celite and washed several times with acetone, and the solvent was evaporated. Upon vacuum distillation of the residue, 33g (81% yield) of 6-methyltetralin was obtained at 60-62°/1 mm, lit.[4] bp. 226-227°/1 atm , as a colorless oil.

NMR(100 MHz,CCl_4): δ 1.58-1.90 (m,4,$H_{2,3}$), 2.21 (s,3,CH_3), 2.44-2.87 (m,4, $H_{1,4}$) and 6.45-6.93 ppm (m,3, $H_{5,7,8}$).

6-Methyl-1,2,3,4-tetrahydro-BA (V).- Succinoylation of I with anhydrous $AlCl_3$ in benzene at 65° for 15 hrs using Newman's procedure[3] gave keto acid II in 85% yield, mp. 168-170° (benzene-hexane), lit.[3] mp. 167.5-168°.

NMR(270 MHz,acetone-d_6): δ 2.05-2.07 (m,4,$H_{2',3'}$), 2.53 (s,3,CH_3), 2.53-2.58 (m,2,H_1 or H_4). 2.72-2.76 (m,2,H_4 or H_1), 6.89 (s,1,H_8), 6.99 (s,1,H_5) and 7.42-8.03 (m,4,$H_{1'-4'}$), ($J_{5,8}$=1.0 Hz).

Reduction of keto acid II with Zn/NaOH afforded acid III as colorless solid (88% yield) mp. 167-169°, lit.[3] mp. 167-169°.

Mass spectrum: m/e 280 (M^+); NMR (270 MHz, $CDCl_3$): δ 1.74-179 (m,4,$H_{2,3}$), 2.14 (s,3,CH_3), 2.65-2.73 (m,4,H_1, $_4$),6.66 (s,1,H_5) 6.88 (s,1,H_8), 7.00-7.03 (d,1 H), 7.26-7.40 (t,1 H), 7.42- 7.45 (t,1 H), and 8.08-8.12 ppm (dd,1 H).

Upon cyclization of III with conc. sulfuric acid at ambient temperature overnight followed by the usual workup, crude anthrone derivative IV was obtained:

NMR(100 MHz,$CDCl_3$): δ 1.66-2.0 (m,4,$H_{2,3}$),2.36 (s,3,CH_3), 2.68-3.04 (m,2, H_4), 3.24-3.56 (m,2,H_1), 4.12 (s,2,CH_2), 7.28 (s,1,H_5), 7.40-7.75 (m,3,H_{8-10}), and 8.36 ppm (apparent d,1,H_{11}).

The crude IV was reduced by refluxing with activated zinc and sodium hydroxide solution, providing V in 65% yield, mp. 81.5-83° (benzene-methanol), lit.[4] mp. 82.3-82.9°

Mass spectrum: m/e 246 (M^+); NMR(100 MHz,$CDCl_3$): δ 1.72-2.07 (m,4,$H_{2,3}$) 2.60-2.85 (m,2,H_4),2.70 (s,3,CH_3), 3.02-3.24 (m,2,H_1), 6.99-8.12 (m,5, $H_{5,8-11}$), and 8.43 ppm (apparent s,2,$H_{7,12}$).

6-Methylbenz[a]anthracene (VI).- (a) Catalytic dehydrogenation of V (2.0 g) with 10% Pd/C (200 mg) under conditions described by Newman, afforded crude VI; VI was purified by passage through a Florisil column and eluted with hexane followed by crystallization from benzene-methanol;1.22 g (62%) of colorless needles, mp. 126-127° lit.[3] mp. 126.2-127.2°.

Mass spectrum: m/e 242 (M^+); NMR(270 MHz,$CDCl_3$): δ 2.82 (apparent s,3,CH_3), 7.56 (apparent s,1,H_5), 7.56-8.16 (m,7,$H_{2-4,8-11}$), 8.52 (s,1,H_7), 8.82 (dd, 1,H_1), and 9.21 ppm (1,s,H_{12}).

(b) A solution of V (1.23g, 5 mmol) and DDQ (1.25 g,5.5 mmol) in benzene (60 ml) was refluxed under N_2 for 1 hr. After conventional workup, VI was obtained (0.8 g, 66% yield).

(c) A mixture of 6-methylbenz[a]anthracene-7,12-dione (136 mg, 0.5 mmol) and 57% HI (0.5 ml) in glacial acetic acid (8 ml) was heated to reflux

for 6 hrs. The resulting solution was poured into a sodium bisulfite solution. The precipitate was collected by filtration. Upon purification by Florisil column chromatography, 114 mg (94%) of VI was obtained.

o-(1-Methyl-4-Naphthoyl)-benzoic Acid (VII)[3].- Succinoylation of 1-methylnaphthalene (107 g) with anhydrous $AlCl_3$ in benzene using Newman's procedure[3] afforded keto acid VII in 92% yield, mp. 172-173° (benzene).

Mass spectrum: m/e 290(M^+); NMR(270 MHz,acetone-d_6): δ 2.73 (s,3,CH_3), 7.29-7.35 (ABM_3 spin system, 2, $H_{2,3}$), 7.56-7.80 (m,5 H), 8.03-8.17 (m,2 H), and 9.08-9.13 (m,1 H).

5-Methylbenz[a]anthracene-7,12-dione (VIII).- Keto acid VII (1.0 g,3.45 mmol) in conc. H_2SO_4 (60 ml) was stirred at ambient temperature for 5 days. The reaction mixture was poured onto icewater. The preciptate was collected by filtration and purified by elution with benzene from a Florisil column, affording 512 mg (55% yield) of VIII, mp. 178-179°, lit.[8] mp. 179°.

Mass spectrum: m/e 272 (M^+), NMR(100 MH_z,$CDCl_3$): δ 2.80 (s,3,CH_3), 7.1-8.3 (m,8,aromatic), 9.5-9.7 ppm (m,1,H_1).

5-Methylbenz[a]anthracene (IX).- A mixture of 5-methylbenz[a]anthracene-7,12-dione (VIII) (272 mg, 1 mmol) and 57% HI (1.0 ml) in glacial acetic acid (12 ml) was refluxed for 6 hrs. After workup and purification as described for the synthesis of VI from 6-methylbenz[a]anthracene-7,12-dione, IX was obtained (2.61 mg, 96% yield), mp. 156-157° (benzene-methanol), lit.[3] mp. 155.9-156.9°.

Mass spectrum: m/e 242 (m^+); NMR (270 MHz, acetone-d_6): δ 2.72 (d from ortho benzylic coupling, 3, CH_3), 7.5-8.3 (m,8,$H_{2-4,6,8-11}$), 8.40 (s,1,H_7), 9.02 (d,1,H_1), and 9.38 ppm (s,1,H_{12}). The H_4 and H_6 resonances could be assigned from NOE difference spectrum following saturation of the methyl group; 7.74 (s,1,H_6) and 8.08 ppm (d,1,H_4).

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