Synthesis of 7,11,12-Trimethylbenz[a]anthracene

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Reaction of 1-naphthylmagnesium bromide with 3-methylphthalic anhydride gave an 86% yield of a mixture of mostly 2-methyl-6-(1-naphthoyl)benzoic acid (**2**) and a little 3-methyl-2-(1-naphthoyl)benzoic acid (**3**). Heating this mixture with 80% sulfuric acid gave mostly **3** in 75% yield. Reduction of **3** with hydriodic acid and phosphorus in acetic acid yielded 99% of 4-methyl-3-(1-naphthylmethyl)phthalide (**4**), which was reduced by boiling with aqueous potassium hydroxide, activated zinc–copper couple, and pyridine to 3-methyl-2-(1-naphthylmethyl)benzoic acid (**5**) in 95% yield. Ring closure by heating in acetic acid with catalytic zinc chloride yielded 94% of 7-acetoxy-11-methylbenz[*a*]anthracene (**6**), which was oxidized to 11-methyl-7,12-benz[*a*]anthraquinone (**7**) in 82% yield. Treatment of **7** with methyllithium followed by dimethyl sulfate afforded 64% of a pure isomer of 7,12-dihydro-7,12-dimethoxy-7,11,12-trimethylbenz[*a*]anthracene (**9**). On treatment of **9** with sodium pure 7,11,12-trimethylbenz[*a*]anthracene was produced in 45% yield.

The fact that 7-methylbenz[*a*]anthracene (7-MBA) is the most potent carcinogen of the monomethylbenz[*a*]-anthracenes is well-known.[1] When a methyl group is placed in the 12-position also, the resulting hydrocarbon, 7,12-dimethylbenz[*a*]anthracene (DMBA), is considerably more carbinogenic. To account for this my working hypothesis for many years has been that, since the steric effect of the methyl group in the 12-position forces the molecule to be nonplanar,[2] this effect is largely responsible for the increased activity of DMBA.

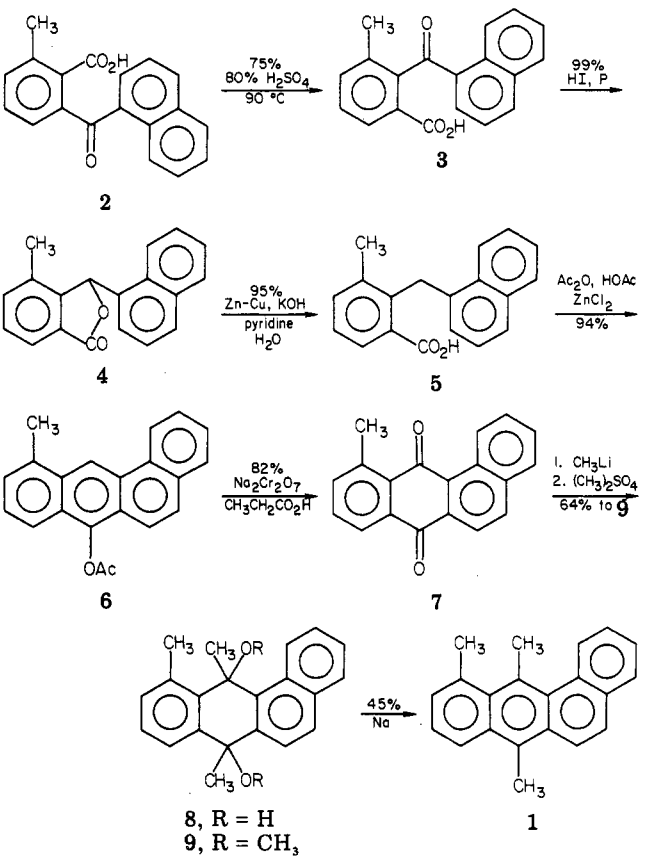
Recent work[3] on the rate of detritiation of strained (nonplanar) methylated phenanthrenes compared to the rate for unstrained (planar) analogues shows that the rates for the strained compounds are greater than expected.

Before the advent of the diol epoxide theory of carcinogenic activity, we prepared 1,7,12-trimethylbenz[*a*]-anthracene[4] (TMBA) since the extra methyl group in the 1-position should make the molecule more strained and more noncoplanar than DMBA. However TMBA proved completely inactive,[5] a fact that supports the diol epoxide of the bay region theory.

In this paper, I report the synthesis of 7,11,12-trimethylbenz[*a*]anthracene[6] (**1**), as shown in Scheme I. This compound was prepared because the 11-methyl group should buttress the 12-methyl group[7] and so make 1 more strained and more carcinogenic than DMBA. The methyl group in the 11-position should not seriously interfere with the formation of an epoxide in the 1,2-position as does the 1-methyl group in 1,7,12-TMBA.

The reaction of 1-naphthylmagnesium bromide with 3-methylphthalic anhydride[8] produced a mixture of 2-methyl-6-(1-naphthoyl)benzoic acid (**2**), and 3-methyl-2-(1-naphthoyl)benzoic acid (**3**), in 86% yield. The unwanted isomer, **2**, was formed in by far the greater amount. However, by heating the mixture of acids with 80% H_2SO_4 at 85–90 °C about 75% of pure **3** could be obtained.[9]

Scheme I



Reduction of **3** to 3-methyl-2-(1-naphthylmethyl)benzoic acid (**5**), was best accomplished in two stages: (1) reduction with hydriodic acid and phosphorus to the lactone, 4; (2) reduction with activated zinc (see Experimental Section for details) and alkali. Ring closure of **4** to 11-methyl-7-benz[*a*]anthryl acetate (**6**), followed by oxidation afforded the desired 11-methylbenz[*a*]anthra-7,12-quinone (**7**). Direct cyclization of **2** and/or **3** to quinone had to be avoided because of the Hayashi rearrangement,[10] which would result in the unwanted 8-methylquinone.

Conversion of **7** to **8** by reaction with methyllithium proved quite erratic as the stability of the diols was

(1) For a review of much of the early evidence see J. C. Arcos and M. F. Argus in "Chemical Induction of Cancer," Vol. IIA, Academic Press, New York, 1974, p 31.

(2) For the latest X-ray structure and discussion of DMBA see D. W. Jones and J. M. Sowden, *Cancer Biochem. Biophys.*, 281 (1976).

(3) H. V. Ansell and R. Taylor, *J. Org. Chem.*, **44**, 4946 (1979).

(4) M. S. Newman and W. M. Hung, *J. Med. Chem.*, **20**, 179 (1977).

(5) Unpublished experiments by J. A. and E. C. Miller, McArdle Cancer Research Laboratory, University of Wisconsin, Madison, WI.

(6) Compoumd 1 has been synthesized (W. E. Bachmann and J. M. Chemerda, *J. Org. Chem.*, **6**, 36 (1941)), but no mention of the testing of 1 could be found.

(7) For quantitative data on the buttressing effect involving heats of combustion see H. A. Karnes, B. D. Kybett, J. L. Margrave, H. H. Wilson, and M. S. Newman, *J. Am. Chem. Soc.*, **87**, 5554 (1965).

(8) M. S. Newman and V. Lee, *J. Org. Chem.*, **42**, 1478 (1977).

(9) Compare S. J. Cristol and J. L. Caspar, *J. Org. Chem.*, **33**, 2020 (1968).

(10) M. S. Newman and K. G. Ihrman, *J. Am. Chem. Soc.*, **80**, 3652 (1958).

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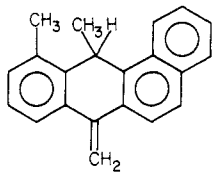
markedly affected by the solvent used for crystallization. Low melting diols, mp 150–178 °C, proved quite poor in yielding dimethoxy compound **9**, mp >205 °C. Accordingly, the acidic methanol method used previously[6] was abandoned in favor of treatment of the dilithio salt of **8** with dimethyl sulfate to yield **9** directly. The conversion of **9** to **1** by treatment with sodium also proved erratic. In the early synthesis the reaction of powdered sodium with **9** was stated[6] to give a deep brown solution which yielded 85% of **1**, mp 99.5–103 °C. After extensive purification[6] **1**, mp 102–103.5 °C, was obtained in unstated yield. In my experience, whenever the reaction mixture was deep brown purification of crude **1** was quite difficult and took place only with great loss of material. However, if slightly less than 2 equiv of sodium were used with **9**, the reaction mixture was pale yellow and purification of **1** was relatively easy. The deep brown color is undoubtedly due to the addition of excess sodium to **1** formed by elimination of two methoxy groups from **9**. When the mixture is worked up a small amount of 7,12-dihydro-7,11,12-trimethylbenz[*a*]anthracene is formed, the separation of which from **1** causes problems.[11] Attempts to aromatize the dihydro compound were unpromising.

In attempts to convert the diol mixture, **8**, to **1** by treatment with stannous chloride–hydrochloric acid[12] an unpromising mixture of compounds was obtained from which no **1** was isolated but a small amount of **10** was



10

obtained. I was unable to convert **10** to **1** by heating with Pd–C at 200 °C or warming with trifluoroacetic acid.

I have submitted samples of pure **1** for cancer tests and also for X-ray crystallographic study.[13] Preliminary studies[5] involving subcutaneous injection show that **1** is more active as a carcinogen than DMBA. **Added in Proof:** On injection subcutaneously into groups of 16 female outbred CD(SD) rats from the Charles River Laboratory, Wilmington, MA, 4 μmol of 7,12-dimethylbenz[*a*]-anthracene in trioctanoin solution induced sarcomas in 7 rats by 7 months and 11 rats by 8 months, while 7,11,12-trimethylbenz[*a*]anthracene caused 11 sarcomas in 7 months and 15 by 8 months.[5]

Experimental Section[14]

3-Methyl-2-(1-naphthoyl)benzoic Acid (3). The Grignard reagent prepared from 61 g of 1-bromonaphthalene and 9.8 g of pure sublimed Mg in 350 mL of ether and 50 mL of benzene using the ethylene bromide technique[15] was added to a stirred solution of 46 g of 3-methylphthalic anhydride[8] in 500 mL each of benzene and ether at 40 ± 3 °C (by use of a cooling bath) in 10 min. After $^1/_2$ h the mixture was worked up as usual to yield 70.48 g (85.6%) of a mixture of **3** and 2-methyl-6-(1-naphthoyl)benzoic acid (**2**), mp 145+ °C. This acid mixture was finely ground in a mortar and added (69.0 g) to a stirred solution at 87 °C of 500 mL of concentrated H_2SO_4 in 212 g of water (about 80–81% H_2SO_4 by weight). This deep purple mixture was held at 85–90 °C for 30 min, cooled a bit, and poured on 2 L of cracked ice. The yellow solid was collected, washed well with water, and treated with 500 mL of dilute KOH. Filtration through Celite gave a clear filtrate, which was poured in excess dilute HCl. The off-white solid was collected, washed well with water, pressed fairly dry with a rubber dam, and dried in a vacuum oven overnight. Recrystallization from 500 mL of boiling acetic acid yielded 47.3 g of pure **3**, mp 232–233 °C. Anal. (Galbraith) Calcd for $C_{19}H_{14}O_3$: C, 78.6; H, 4.9. Found: C, 78.8; H, 5.2. Concentration of the mother liquor to 125 mL yielded 6.4 g of impure **3**, which did not all dissolve in boiling acetic acid. The insoluble acid did not melt by 250 °C and was discarded. A further 4.8 g of pure **3**, mp 232–233 °C, was obtained from this filtrate (total yield 75.5%). By recrystallization of the neutral product from ethyl methyl ketone there was obtained 3 g of a mixture of 8-methyl- and 11-methylbenz-[*a*]anthraquinones, mp 150–163 °C, which could not readily be separated into pure isomers.

4-Methyl-3-(1-naphthylmethyl)phthalide (4). A magnetically stirred mixture of 37.50 g of **3**, 500 mL of acetic acid, 90 mL of 55% HI, and 7 g of red phosphorus was held at reflux for 5 h. To the dark cooled mixture was added a small amount of 50% H_3PO_2. In a few minutes the iodine color had disappeared and the mixture was filtered. The filtrate was rotary evaporated and the mixture was treated with dilute K_2CO_3. The insoluble lactone was collected, washed, and dried to yield 34.94 g (99%) of **4**, mp 158–161 °C, good enough for the next step. A pure sample, mp 162–163 °C, *m/e* 274, was obtained by crystallization from acetic acid.

3-Methyl-2-(1-naphthylmethyl)benzoic Acid (5). Activated zinc was prepared by reacting 110 g of powdered zinc with 200 mL of 15% HCl in a mortar. The zinc was ground from time to time for 20 min, washed with water, and then treated with a solution of 1.14 g of hydrated copper sulfate in 30 mL of water. This zinc was placed in a 2-L three-necked flask with 700 mL of 10% KOH, 85 mL of pyridine, and 13.78 g of **4**. After stirring for 16 h at reflux and cooling a bit, water was added until the pyridine layer was gone. The mixture was filtered and the filtrate added to excess HCl. The dried colorless solid obtained was crystallized from about 150 mL of 1-propanol to yield 12.72 g (95%) of **5**, mp 199.5–201.0 °C, in two crops. The shiny zinc collected was pyrophoric if air was drawn over it by suction.

7-Acetoxy-11-methylbenz[*a*]anthracene (6). In the best of several experiments a solution of 17.30 g of **5** in 60 mL of acetic acid and 35 mL of acetic anhydride containing 1.3 g of $ZnCl_2$ was held at reflux for 50 min, cooled to about 90 °C, and treated with water to hydrolize the anhydride so that the temperature did not rise above 95 °C. On cooling of 17.13 g of **6**, mp 172.5–173.0 °C *m/e* 332, crystallized. A second crop, mp 171–172 °C, 0.65 g, obtained by diluting the mother liquor, made the total yield 94%.

11-Methyl-7,12-benz[*a*]anthraquinone (7). In the best of several experiments 19 g of powdered $Na_2Cr_2O_7 \cdot 2H_2O$ was added all at once to a hot solution of 15.40 g of pure **6** in 75 mL of propionic acid[6] in a 250-mL Erlenmeyer flask with rapid swirling by hand. After heating at gentle reflux for 20 min spontaneous crystallization caused a more violent reflux. After 10 min of further heating the mixture was diluted with 20 mL of acetic acid. After cooling, the quinone was collected, washed with cold acetic acid, and recrystallized from propionic acid (or 1-propanol) to yield 11.51 g (82%) of **7**, mp 191.5–192.0 °C (lit.[6] mp 192–194 °C), as yellow elongated prisms which became slightly green if exposed to light.[16] The quinone in the mother liquors of the above operations was a mixture that did not readily become purer on recrystallization.

7,12-Dihydro-7,12-dihydroxy-7,11,12-trimethylbenz[*a*]-anthracene (8). I could not duplicate the results[6] on addition of methylmagnesium iodide to **7**. In the best of several experiments in which the yield and melting point of crude **8** differed widely, 27 mL of 1.6 M methyllithium (Aldrich) was added during 3 min to a magnetically stirred solution of 5.10 g of **7** in 500 mL

(11) Compare J. Pataki, C. Duguid, P. W. Rabideau, H. Huisman, and R. G Harvey, *J. Med. Chem.*, **14**, 940 (1971).
(12) M. S. Newman and K. Kanakarajan, *J. Org. Chem.*, **45**, 3523 (1980).
(13) Dr. D. W., Jones, University of Bradford, England.
(14) All melting points are uncorrected. All dry ether used was freshly distilled from *n*-BuMgBr. The term "worked up in the usual way" means that an ether–benzene solution of the product was washed with dilute acid and/or base and saturated NaCl and filtered through a cone of dry $MgSO_4$.
(15) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).
(16) Samples of this quinone, isolated from various reaction mixtures involving treatment of **7** with organometallic reagents, did not turn green on exposure to light and air.

of benzene and 75 mL of ether containing 4.35 g of tetramethylethylenediamine (TMEDA) at about 30 °C. The mixture at first turned dark brown but soon the color lightened and some suspended solid was present. After 25 min, 5 mL of methanol was added and then some 20% acetic acid. After the usual workup, which concluded with a wash with K_2CO_3, the solvent was rotary evaporated below 40 °C. The crude product was crystallized from a mixture of benzene and hexane to yield 3.00 g (53%) of **8**, mp 182–185 °C. It was difficult to get more pure **8** from the mother liquor as the stereoisomeric diol was not nearly as stable as the form, mp 182–185 °C, isolated.

7,12-Dihydro-7,12-dimethoxy-7,11,12-trimethylbenz[*a*]anthracene (9). In the best of several experiments 15 mL of 1.5 M methyllithium (Aldrich) was added in 3 min to a magnetically stirred solution of 3.00 g of pure **8** in 100 mL of pure dry THF. The mixture warmed to 40 °C and gas was evolved. After 5 min no more gas was evolved and a pale yellow suspension was present. A solution of 2.8 g of dimethyl sulfate in 5 mL of THF was added and the mixture stirred at reflux for 7 h. After removal of THF by rotary evaporation and the usual workup there was obtained 2.65 g (81%) of **9**, mp 208–211 °C, as colorless prisms from benzene–alcohol; MS, m^+/e 332.178400; calcd for $C_{23}H_{24}O_2$, 332.177619. The preferable route to **9** involved reaction of **7** with methyllithium in THF followed directly by treatment with dimethyl sulfate. In the best experiment a solution of 9.50 g of **7** in 330 mL of THF was treated with 50 mL of 1.5 M methyllithium during 10 min. After 30 min the ice cooled mixture was treated with 9.5 g of dimethyl sulfate in 20 mL of THF. The mixture was refluxed for 7 h. After a workup as described above, there was obtained 7.39 g (64%) of colorless **9**, mp 209.5–212.0 °C, from benzene–alcohol.

7,11,12-Trimethylbenz[*a*]anthracene (1). In a 100-mL round-bottomed one-neck flask from which toluene had been boiled was added 0.480 g of clean sodium that was then powdered by melting under hot toluene by vigorous shaking. The toluene was then forced out by dry nitrogen. Then 40 mL each of dry benzene and ether, a dried magnetic stirrer, 3.480 g of pure **9**, and some pieces of dried cracked glass were added. A glass stopper was fitted and secured. After stirring at room temperature for 19 h, no sodium was visible in a pale yellow suspension of sodium methylate. In cases where an excess of sodium or less pure **9** (containing an isomer) was used the reaction mixture was deep brown and the yield was poorer because purification to pure **1** was difficult. The reaction mixture was treated with 2% acetic acid and worked up as usual. The crude product was treated with 2.3 g of picric acid in benzene alcohol. The dark picrate was passed through a column of Al_2O_3 to remove the picric acid. Crystallization from benzene–alcohol yielded a total of 1.29 g (45%) of pure **1**: mp 101.5–102.0 °C; NMR ($CDCl_3$; $(CH_4)_4Si$) δ 3.00 (s, 6 H, 7- and 11-CH_3), 3.28 (s, 3 H, 12-CH_3).

Bachmann and Chemerda reported mp 102–103.5 °C for **1**. In my experience a hydrocarbon in the benz[*a*]anthracene series with such a wide melting point range is impure. Pure **1** has a very sharp melting point. In an experiment aimed at converting **8** to **1** by acidic reduction[17] in the presence of $SnCl_2$ an unpromising mixture of compounds was produced from which pure **1** was never obtained. A small amount of a compound, **10**, mp 127.0–127.5 °C, was obtained as colorless crystals. MS and NMR indicated **10** to be 7,12-dihydro-12-methyl-7-methylenebenz[*a*]anthracene: NMR ($CDCl_3$; $(CH_4)_4Si$) δ 1.40 (d, J = 4 Hz, 3 H, 12-CH_3), 2.60 (s, 3 H, 11-CH_3), 5.03 (q, J = 4 Hz, H, 12-H), 7.50 (d, J = 3 Hz, 7-CH_2); MS, m^+/e 270.141695; calcd for $C_{21}H_{18}$ 270.140843. Compound **10** might have an alternate structure in which the 7 CH_2 and 12 CH_3H groups are interchanged. We prefer the structure of **10** named because of steric reasons. Attempts to isomerize **10** to **1** by heating with Pd–C (200 °C) or warming with a trace of CF_3COOH failed as mixtures of several compounds were obtained.

Registry No. **1**, 74845-57-1; **2**, 38119-05-0; **3**, 86785-12-8; **4**, 86785-13-9; **5**, 86802-66-6; **6**, 86785-14-0; **7**, 60184-76-1; **8**, 86785-15-1; **9**, 86785-16-2; **10**, 86785-17-3; 1-bromonaphthalene, 90-11-9; 3-methylphthalic anhydride, 4792-30-7; 8-methylbenz[*a*]anthraquinone, 86785-18-4.

(17) M. S. Newman and K. Kanakarajan, *J. Org. Chem.*, **45**, 230 (1980).

(18) For similar problems in conversion of over crowded polymethylanthracenes see R. J. Crawford, S. Levine, R. M. Elofson, and R. B. Sandin, *J. Am. Chem. Soc.*, **79**, 3153 (1957).