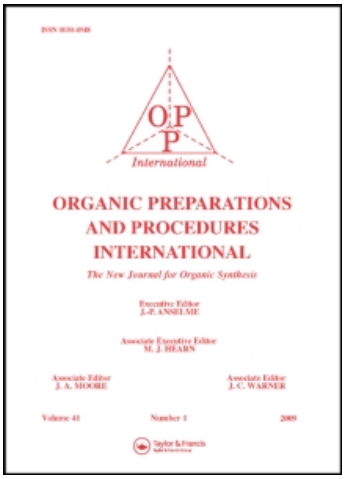

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SYNTHESIS OF 1,4-DIMETHOXYBENZ[a]ANTHRACENES AND OF 7,10-DIMETHOXYCHOLANTHRENES†

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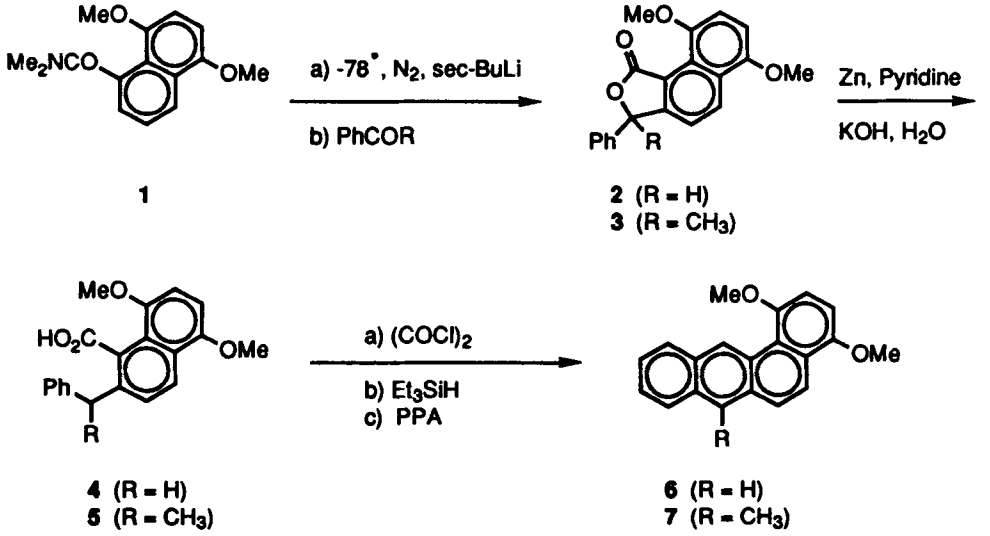
Methylcholanthrenes and benz[a]anthracenes are well known carcinogenic hydrocarbons. syn and anti Diolepoxides of these are of interest as metabolic products[1] leading to cancer. In seeking to provide an alternate route[2] to such metabolites, we thought that the chemistry by which 1,4-naphthoquinone was converted into diolepoxides of naphthalene[3] might be extended to benz[a]anthracene and cholanthrene intermediates. In this paper the syntheses of several 1,4-dimethoxybenz[a]anthracenes and 7,10-dimethoxycholanthrenes are described as well as the conversion of 1,4-dimethoxy-7,12-dimethylbenz[a]anthracene to 7,12-dimethyl-1,4-benz[a]anthraquinone.

The benz[a]anthracene synthesis started by treatment of the 2-lithio derivative of the dimethylamide of 5,8-dimethoxy-1-naphthoic acid (1),[2] with benzaldehyde (or acetophenone) to yield after hydrolysis of the crude reaction mixture, 5,8-dimethoxy-2-(α-hydroxybenzyl)-1-naphthoic



1

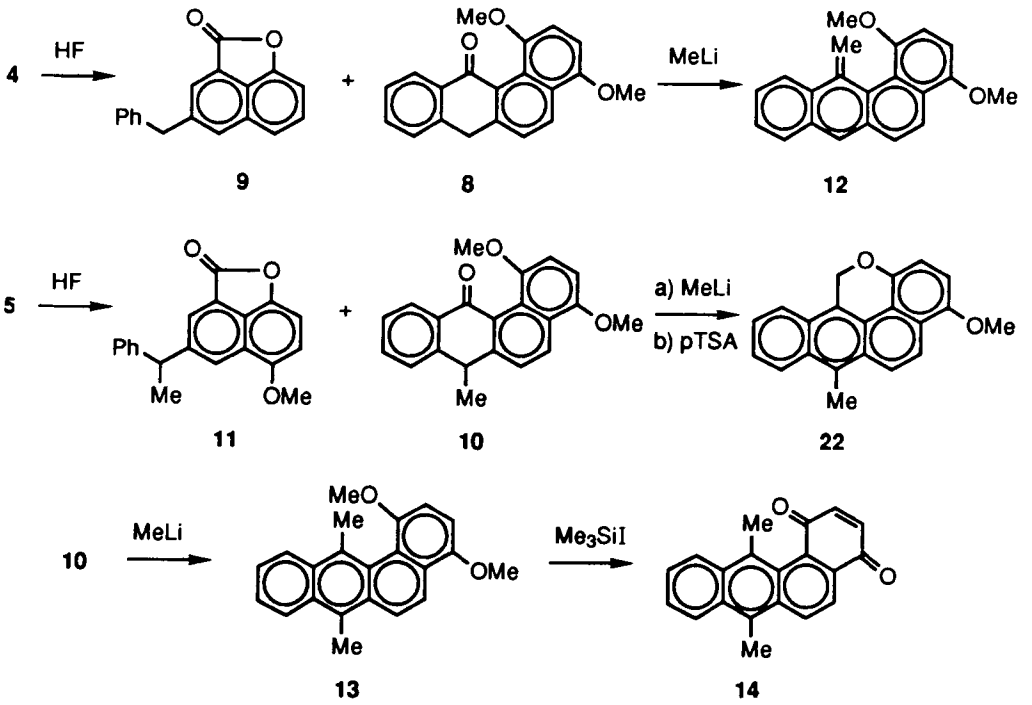
2 (R = H)
3 (R = CH_3)

4 (R = H)
5 (R = CH_3)

6 (R = H)
7 (R = CH_3)

acid lactone (2, 87%), and 5,8-dimethoxy-2-(α-hydroxy-α-methylbenzyl)-1-naphthoic acid lactone (3, 63%). Reduction of these lactones with alkaline zinc systems afforded the corresponding acids 4, and 5 in high yields. The acid chloride of 4 was reacted with triethylsilane to afford the crude aldehyde which was immediately treated with polyphosphoric acid to obtain 28% of pure 1,4-dimethoxybenz[a]anthracene (6). Similarly, acid 5 yielded 24% of pure 1,4-dimethoxy-7-methylbenz[a]anthracene (7).

On treatment of 4 with HF, a 69% yield of pure 1,4-dimethoxy-12-benz[a]anthracenone (8), was obtained. Chromatography of the mother liquors afforded a small amount of unexpected 2-benzyl-8-hydroxy-5-methoxy-1-naphthoic acid lactone (9). Treatment of 5 with HF resulted in 1,4-dimethoxy-7-methyl-12-benz[a]anthracenone (10), in 74% yield, with 18% of the unexpected 2-(α-methyl-benzyl)-8-hydroxy-5-methoxy-1-naphthoic acid lactone (11). Treatment of 8 with methyllithium afforded 82% of pure 1,4-dimethoxy-12-methylbenz[a]anthracene, (12). Treatment of 10 with methyllithium gave an 84% yield of pure 1,4-dimethoxy-7,12-dimethylbenz[a]anthracene (13),[5] which on treatment with trimethylsilyl iodide[4] led in high yield to 7,12-dimethyl-1,4-benz[a]anthraquinone (14).[8]



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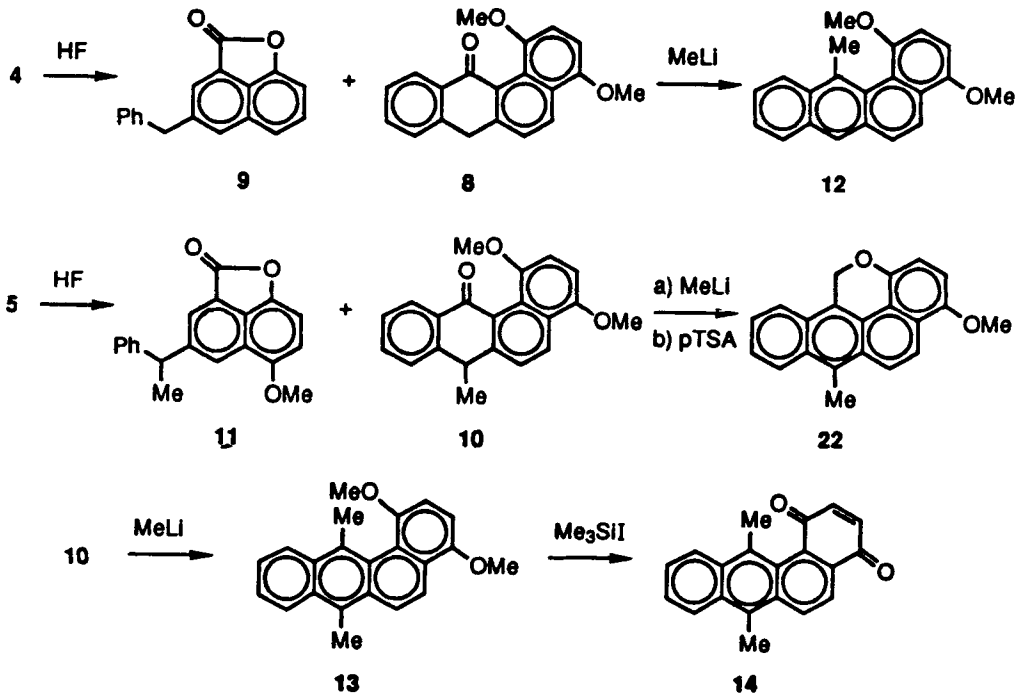
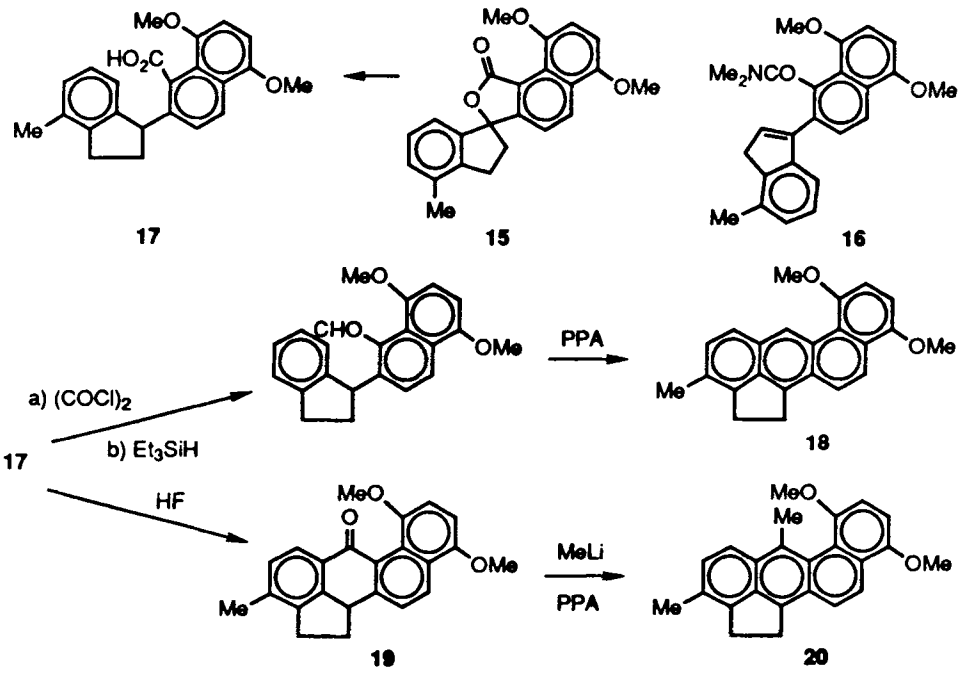


The condensation of the 2-lithio derivative of N,N-dimethyl-5,8-dimethoxy-1-naphthamide (1), with 2,2-dideutero-4-methylindanone[2a] afforded 68% of the lactone of 2-(1-hydroxy-4-methylindan-1-yl)-5,8-dimethoxy-1-naphthoic acid (15), in addition to 21% of N,N-dimethyl 2-(4-methyl-1-indenyl)-5,8-dimethoxy-1-naphthamide (16). When N,N-diethyl 5,8-dimethoxy-1-naphthamide[5] was used instead of the N,N-dimethylamide an 18% yield of 15 and 56% of the diethyl analog of 16 (21), were obtained. In agreement with Harvey[2a] the dideuteroindanone gave better yields than the hydrogen analog. Reduction of 15 yielded 94% of the acid 17, which on treatment similar to that used in the conversion of 4 (or 5) to 6 (or 7) afforded 58% of 7,10-dimethoxy-3-methylcholanthrene (18). Reactions of 17 similar to those by which 4 (or 5) was converted into 12 (or 13) yielded 74% of 7,10-dimethoxy-3-methylcholanthrene-6-one (19), and therefrom 7,10-dimethoxy-3,6-dimethylcholanthrene (20).



Further studies on the conversions of 6, 7, 12, 13, 18 and 20 to quinones were not possible because of the termination of the grant.†

EXPERIMENTAL SECTION[7]

All new compounds had IR, Mass and ^1H NMR spectra consistent with the proposed structures. Microanalyses were performed by Galbraith Microanalytical Laboratories. The term "worked up as usual" means that an ether-benzene solution of the reaction products was washed with dilute acid and/or alkali and then with saturated brine and filtered through anhydrous $MgSO_4$. All melting points are uncorrected. All chromatography was carried out using silica gel or neutral alumina and suitable solvent mixtures.

N,N-Dimethyl-5,8-dimethoxy-1-naphthamide (1).- A mixture of 23.2 g (0.1 mole) of 5,8-dimethoxy-1-naphthoic acid[4] 100 mL of benzene, 0.2 mL of dimethylformamide and 17.0 g (0.11 mole) of thionyl chloride was heated at reflux for 4 hrs. After rotary evaporation of volatile substances the crude acid chloride in 100 mL of benzene was added to a stirred solution of 13.5 g (0.25 mole) of dimethylamine in 100 mL each of ether and benzene. After stirring overnight the mixture was washed with cold water and 5% $NaHCO_3$ to yield 24.3 g (94%) of amide 1, mp 91-92°, ^1H NMR: d 2.67 (s, 3H), 316 (s, 3H), 3.88 (s, 3H), 3.95 (s, 3H) 6.76 (AB doublet, J = 8.5 Hz, 2H), 7.32-7.35 (m, 1H), 7.43-7.51 (m, 1H), 8.23-8.27 (m, 1H); MS: m/e 259 (M^+).

5,8-Dimethoxy-2-(a-hydroxybenzyl)-1-naphthoic Acid Lactone (2).- To a stirred solution of 14.35 g (0.05 mole) of 1 in 400 mL of ether and 200 mL of THF containing 6.4 g of tetramethylethylenediamine (TMEDA) at -78° was added dropwise a solution of sec-butyllithium in cyclohexane (1.3 M, 43 mL, 0.056 mole). After 1 hr, 7.95 g (0.075 mole) of benzaldehyde in 100 mL of ether was added during 30 min. After 2 hrs at -78° the mixture was allowed to come to room temperature overnight. After addition of 50 mL of saturated ammonium chloride, the usual workup yielded 13.1 g (87%) of pure yellow 2, mp. 153-154° ^1H NMR: d 3.97 (s, 3H), 4.05 (s, 3H), 6.35 (s, 1H), 7.42 (m, 6H), 8.55 (d, J = 8.64 Hz 1, H); MS: m/e 320 (M^+).

5,8-Dimethoxy-2-(a-hydroxy-a-methylbenzyl)-1-naphthoic Acid Lactone (3).- In a procedure similar to that which describes the preparation of 2 acetophenone was used instead of benzaldehyde. The crude product was purified by chromatography to yield 63% of pure 3, mp. 93-94°. ^1H NMR: d 2.1 (s, 3H), 3.98 (s, 3H), 4.05 (s, 3H), 6.7 (AB doublet, J = 8.6 Hz, 2H), 7.21-7.45 (m, 6H), 8.53 (d, 2H, J = 8.65 Hz); MS: m/e 334 (M^+).

2-Benzyl-5,8-dimethoxy-1-naphthoic Acid, (4).- A mixture of 6.4 g of 2, 6.4 g of powdered zinc (activated by 20 min reaction with 10% hydrochloric acid and a little copper sulfate), 500 mL of 15% aqueous potassium hydroxide, and 200 mL of pyridine was refluxed for 20 hrs. The acid product was crystallized from chloroform to yield 5.8g (90%) of pale yellow crystals of 4, mp. 210-211°; ^{1}H NMR: δ 3.92 (s, 3H) 3.94 (s, 3H), 4.23 (s, 2H), 6.80 (AB doublet J = 8.5 Hz, 2H), 7.17-7.30 (m 1 6H), 8.19 (d, J = 8.73 Hz, 1H), MS: m/e 322 M^+.

5,8-Dimethoxy-2-(α-methylbenzyl)-1-naphthoic Acid, (5).- When 3 was used in place of 2 a similar procedure produced 88% of 5,[5] mp. 204-205°.

1,4-Dimethoxybenz[a]anthracene, (6).- Treatment of 1.61 g of 4 with 2.54 g of oxalyl chloride in 30 mL of CH_2Cl_2 at reflux for 2 hrs gave an acid chloride to which was added a solution of 0.63 g of triethylsilane in 10 mL of CCl_4. After 2 hrs at reflux, the crude aldehyde formed was immediately treated with PPA at 100° for 30 min. to produce crude 6. On chromatography over neutral alumina in hexane-ether, there was obtained 0.40 g (28%) of pure 6, mp 189-190°; ^{1}H NMR: δ 4.01 (s, 3H), 4.16 (s, 3H), 7.11 (AB doublet, J = 8.77 Hz 2H), 7.49-7.57 (m, 2H), 7.82 (d, J = 8.3 Hz, 1H), 8.00-8.13 (m, 1H), 8.15 (d, J = 6.7 Hz, 2H), 8.35 (s, 1H), 10.24 (s, 1H); MS: m/e 288 (M^+).

1,4-Dimethoxy-7-methylbenz[a]anthracene 7.- From 5 in a similar way was obtained a 24% yield of 7, mp 130-131°; ^{1}H NMR: δ 3.12 (s, 3H), 4.02 (s, 3H), 4.13 (s, 3H), 7.09 (AB doublet, J = 8.76 Hz, 2H), 7.51-7.63 (m, 2H), 8.13-8.38 (m, 3H) 8.31 (d of d, J = 1.26 Hz and 8.6 Hz, 1H).

1,4-Dimethoxy-12-benz[a]anthracenone (8).- On warming a solution of 0.644 g of 4 in 20 mL of HF for 1 hr most of the HF evaporated. The crude oily product was crystallized from benzene-hexane to yield 0.42 g (69%) of 8, mp. 121-122°; ^{1}H NMR: δ 3.93 (s, 3H), 4.03 (s, 3H), 7.18 (AB doublet J = 8.74 Hz, 2H), 7.5-7.62 (m, 2H), 7.68 (d, J = 8.3 Hz, 1H), 7.88 (s, 1H), 7.95-8.00 (m, 2H), 8.7-8.75 (m, 1H), 10.62 (s, 1H); MS: m/e 304 (M^+). By chromatography of the products in the mother liquors, there was isolated a small yield of the lactone of 2-benzyl-8-hydroxy-5-methoxy-1-naphthoic acid (9), mp 95-96°, as pale yellow crystals; ^{1}H NMR: δ 3.09 (s, 2H), 4.00 (s, 3H), 7.02 (AB doublet, J = 8.6 Hz H, 2H), 7.35-8.07 (m, 6H), 8.36-8.40 (m, 1H); MS: m/e 290. On similar treatment of 5, there were obtained 74% of 1,4-dimethoxy-7-methylbenz[a]anthrace-none (10),[5] mp. 144-145°, and 18% the lactone of 8-hydroxy-5-methoxy-2-(α-methylbenzyl)-1-naphthoic acid (11),[5] mp. 128-130°.

1,4-Dimethoxy-12-methylbenz[a]anthracene (12).- To a stirred solution at 0-5° of 1.52 g of (8) in 150 mL of benzene under nitrogen was added 9 mL of 1.4 M methyllithium in ether. After the mixture was refluxed for 10 hrs there was isolated 1.24 g (82%) of yellow (12), mp 124-125°, ^{1}H NMR: δ 3.00 (s, 3H), 3.92 (s, 3H), 3.99 (s, 3H), 6.86 (AB doublet, J = 8.8 Hz, 2H), 7.25-7.31 (m, 1H), 7.44-7.5 (m, 2H), 7.65 (s, 2H), 7.69-7.88 (m, 2H); MS: 302. In a similar way 1,4-dimethoxy-7,12-dimethylbenz[a]anthracene[5] (13), mp 105-106°, ^{1}H NMR: δ 2.83 (s, 3H), 3.01 (s, 3H), 3.92 (s, 3H), 4.0 (s, 3H), 6.96 (q, 2H), 7.55 (M, 2H), 7.90 (M, 2H), 8.26 (m,2H) was obtained in 84% yield from (10). When the crude product (obtained by reaction of one equivalent of methyllithium in ether at 0° with 10) was heated in benzene with 1 g of toluenesulfonic acid there was isolated in 66% yield yellow plates, mp 229-230°, of the cyclic ether of 1-hydroxy-12-hydroxymethyl-4-methoxy-7-methylbenz[a]anthracene, (22), ^{1}H NMR: δ 3.08 (s, 3H), 4.0 (s, 3H), 6.07 (s, 2H), 7.01 (AB doublet, J = 8.6 Hz, 2H), 7.55-7.65 (m, 2H) 7.96-8.05 (m, 3H< 8.32-8.58 (m, 1H) together with 16% of 13.

7,12-Dimethyl-1,4-benz[a]anthraquinone (14).- To a solution of 1.58 g of (13) in 30 mL of acetonitrile under nitrogen was added 5.0 g of trimethylsilyl iodide. After refluxing for 48 hrs chromatography over alumina using hexane-ethyl acetate afforded 0.45 g of 13 along with 0.93 g (92% based on recovered 13) of 14, mp 199-200°.[6]

2-(1-Hydroxy-4-methylindan-1-yl)-5,8-dimethoxy-1-naphthoic Acid Lactone (15). To a mixture of 80 mL of ether, 20 mL of tetrahydrofuran, 1.28 g of TMEDA, and 2.59 g of 1 under nitrogen at -78° was slowly added 8.6 mL of 1.3 M sec-butyllithium. After 2 hrs at -78° a solution of 1.6 g of 2,2-dideutero-4-methylindanone in 20 mL of ether and 30 mL of THF was added during 30 min. After a further 2 h the mixture was allowed to come to room temperature overnight. Addition of saturated ammonium chloride and the usual workup yielded a crude mixture which was chromatographed over silica gel using hexane-ethyl acetate to yield 2.45 g (68%) of yellow 15, mp. 167-168°, ^{1}H NMR: δ 2.37 (s, 3H), 2.7 (T, J=7.6 Hz, 2H), 307-3.46 (m, 4H), 3.99 (s, 3H), 4.05 (s, 3H), 66 (d, J = 7.5 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 7.03-7.36 (m, 4H) 8.58 (d, J=8.6 Hz, 1H), and 0.81 g (21%) of N,N-dimethyl 2-(4-methyl-1-indenyl)-5,8-dimethoxy-N,N-dimethyl-1-naphthoic acid amide (16), mp. 140-141°. When the N,N-diethylamide similar to 1 was used a poor yield (18%) of 15 was obtained and a 56% yield of the N,N-diethylamide (21), mp 186-187°, corresponding to 16 was

obtained. If nondeuterated 4-methylindanone were used a poorer yield of 16 was obtained as described earlier.[2a]

5,8-Dimethoxy-2-(4-methylindan-1-yl)-1-naphthoic Acid (17).- The lactone, 15, 3.6 g was reduced essentially as described for the formation of 4 to yield 3.4 g of 17, mp 202-203°, ^{1}H NMR: δ 2.09-2.25 (m, 1H), 2.36 (s, 3H), 2.69-3.15 (m, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 2.69-3.15 (m, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 4.8 (T, J = 8.4 Hz, 1H), 6.74-7.38 (m, 6H), 8.21 (d, J = 8.9 Hz 1H).

7,10-Dimethoxy-3-methylcholanthrene (18).- The acid 17, was converted into 18, ^{1}H NMR: δ 2.47 (s, 3H), 3.44-3.48 (m, 2H), 3.77-3.82 (m, 2H), 4.0 (s, 3H), 4.13 (s, 3H), 7.02 (AB doublet J = 8.7 Hz, 2H), 7.3 (d, J = 9.4 Hz, 1H), 7.74-7.80 (M, 2H), 8.09 (d, J = 9.4 Hz, 1H), 9.99 (s, 1H), in 58% yield essentially as the acids 4 and 5 were converted into 6 and 7.

7,10-Dimethoxy-3,6-dimethylcholanthrene (20).- The acid 17, was converted in 74% yield to pure 3-methyl-7,10-dimethoxycholanthren-6-one, mp 198-201°, (19), with HF as in the case of acids 4 and 5 to form 8 and 10. Treatment of 0.334 g of (19) at 0° with excess methyllithium for 15 hrs or heating the crude reaction product (obtained by reacting 19) with one equivalent of methyllithium in ether) with benzene and p-toluenesulfonic acid afforded after chromatographic purification 0.30 g (85%) of 20, mp 212-213°, ^{1}H NMR: δ 1.26 (s, 3H), 2.48 (s, 3H), 3.46-3.50 (m, 2H), 3.77-3.82 (m, 2H) 4.02 (s, 3H), 4.14 (s, 3H), 7.08 (AB doublet, J = 8.7 Hz, 2H) 7.35 (d, J = 9.4 Hz, 1H), 7.79-7.85 (m, 2H), 8.15 (d, J = 9.4 Hz, 1H).

Table 1. Elemental Analyses Data of Compounds 1-22

Compound	Calculated(Found) C,	H	N
1, $C_{15}H_{17}NO_3$	C, 69.5(69.6)	H, 6.6(6.5)	N, 5.4(5.3)
16, $C_{25}H_{25}NO_3$	C, 77.5(77.6)	H, 6.5(6.4)	N, 3.6(3.6)
21, $C_{27}H_{29}NO_3$	C, 78.1(78.2)	H, 7.0(6.9)	N, 3.4(3.5)
2, $C_{20}H_{16}O_4$	C, 75.0(75.1)	H, 5.0(5.0)	
3, $C_{21}H_{18}O_4$	C, 75.5(75.5)	H, 5.4(5.3)	
4, $C_{20}H_{18}O_4$	C, 74.5(74.7)	H, 5.6(5.5)	
6, $C_{20}H_{16}O_2$	C, 83.3(83.3)	H, 5.6(5.6)	
7, $C_{21}H_{18}O_2$	C, 83.4(83.4)	H, 6.0(5.3)	
8, $C_{20}H_{16}O_3$	C, 78.5(78.5)	H, 5.3(5.3)	
9, $C_{19}H_{14}O_3$	C, 78.6(78.8)	H, 4.8(5.0)	
11, $C_{20}H_{16}O_3$	C, 78.9(78.7)	H, 5.3(5.3)	
12, $C_{21}H_{18}O_2$	C, 83.4(83.5)	H, 6.0(6.1)	
15, $C_{23}H_{20}O_4$	C, 76.2(76.8)	H, 5.6(5.4)	
17, $C_{23}H_{22}O_4$	C, 76.2(76.3)	H, 6.1(6.2)	
18, $C_{23}H_{20}O_3$	C, 84.1(84.2)	H, 6.1(6.0)	
19, $C_{23}H_{20}O_3$	C, 80.2(80.5)	H, 5.8(5.7)	
20, $C_{24}H_{22}O_2$	C, 84.2(84.3)	H, 6.4(6.5)	
22, $C_{21}H_{16}O_2$	C, 84.0(84.1)	H, 5.3(5.4)	

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†† Postdoctoral Research Associate.

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