unreacted sulfamide is best accomplished using alkali metal hydroxides.

***N*-[*N*-(*Triphenylphosphoranylidene*)*sulfamoyl*]-*N'*-*alkylureas* (*3a–e*).** Bis(2-methoxyethyl) ether (100 mL of practical grade), **2** (20.6 g, 0.048 mol), and the appropriate amine (ca. 0.110 mol) were added to a two-necked flask (300 mL) fitted with a mechanical stirrer and reflux condenser. The heterogeneous mixture was stirred for 10 min at room temperature and then heated to 112 °C (oil bath temperature) at which point the solid had dissolved to give a yellow solution. After 10 min at 112 °C, a white solid precipitated. Heating was continued for 1 h and then the mixture was cooled and suction filtered and the white solid washed with water and dried in vacuo. Recrystallization from suitable solvents gave analytically pure material (Table I). In the case of gaseous amines, the amine was passed directly into the reaction mixture until precipitation of the derivative occurred.

***N*-[*N*-(*Triphenylphosphoranylidene*)*sulfamoyl*]-*S*-*methylisothiourea* (*4*).** An intimate mixture of **1** (66.5 g, 0.177 equiv) and *S*-methylisothiourea hydrogen sulfate (37.0 g, 0.266 equiv) was added in portions and with vigorous stirring to saturated aqueous potassium carbonate (250 mL) contained in a two-necked flask (1000 mL) equipped with a mechanical stirrer. After stirring for 45 min, acetone (250 mL) was added and the mixture stirred at room temperature for 27 h. Analysis of the mixture by TLC indicated the absence of **1**. Water (200 mL) was added and the mixture stirred for a short time. Filtration of the mixture, followed by drying of the solid in vacuo gave 70.1 g of **4** (92.8%).

***N*-[*N*-(*Triphenylphosphoranylidene*)*sulfamoyl*]-*N'*-*methylguanidine* (*5a*).** Powdered, crude **4** (20.0 g, 0.047 mol) and triethylene glycol (205 mL, purified grade) were placed in a two-necked flask (500 mL) equipped with a magnetic stirrer, reflux condenser, and a gas dispersion tube connected via a trap and three-way stopcock to a lecture bottle of methylamine (Matheson). The mixture was stirred and heated in an oil bath to a bath temperature of 120 °C, effecting nearly complete dissolution of **4**. Methylamine, in a current of nitrogen, was then added at a moderate rate until the evolution of methyl mercaptan had ceased (about 2 h), as indicated by lead acetate paper; the solution was pale green at this point. Stirring was stopped and the solution, which turned yellow upon cooling, was decanted from a small amount of insoluble residue and added to water (700 mL) with vigorous stirring. A fine, white powder separated which gave, after filtering and drying in vacuo over P_2O_5, 11.3 g (58.7%) of **5a**. The other alkylguanidines were prepared similarly except that bis(2-methoxyethyl) ether was used as solvent.

Acknowledgment

We thank Mr. Malcolm Stone of A. H. Robins Co. for the elemental analyses.

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Received for review March 20, 1978. Accepted May 31, 1978.

Synthesis of Potentially Estrogenic Carcinogens: 7,12-Dimethylbenz[*a*]anthracene-3,9-diol

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Previously no diphenolic derivatives of the powerful mammary carcinogen, 7,12-dimethylbenz[*a*]anthracene have been reported. The present report concerns the synthesis of 7,12-dimethylbenz[*a*]anthracene-3,9-diol from 4-methoxyphthalic anhydride and 6-methoxy-2-bromonaphthalene. This compound has the potential to behave both as an estrogen and as a carcinogen.

7,12-Dimethylbenz[*a*]anthracene (DMBA) has been employed for many years as a useful tool in the induction of mammary tumors in rodents (*1*). The susceptibility of these tumors to hormonal influences, particularly by estrogens, prompted this laboratory to investigate the properties of polycyclic hydrocarbon diols, the hydroxy groups of which are superimposable with those of the potent experimental carcinogenic estrogen diethylstilbestrol and the naturally occurring estrogen 17β-estradiol.

This laboratory first prepared benz[*a*]anthracene-3,9-diol (BA-3,9-diol) (*2*) as a model compound with which to pursue the concept that polycyclic hydrocarbon diols of proper architecture will behave as estrogens. The compound BA-3,9-diol did indeed display estrogenic activity as evidenced by bioassay. The compound also inhibited the binding of 17β-estradiol to the 8S binding protein of rat uterine cytosol at an intensity similar to that of the known estrogen inhibitor, Nafoxidine hydrochloride (*3*).

The present report concerns the synthesis of 7,12-dimethylbenz[*a*]anthracene-3,9-diol. The scheme outlined for the acquisition of this compound (Scheme I) is similar to that used previously for the preparation of methyl-substituted derivatives (*4*) and hydroxy-substituted derivatives (*5*) of DMBA. The reaction of 4-methoxyphthalic anhydride with the Grignard reagent prepared from 6-methoxy-2-bromonaphthalene gave the isomeric acids 2-(6-methoxy-2-naphthoyl)-4-methoxybenzoic acid (**1**) and 2-(6-methoxy-2-naphthoyl)-5-methoxybenzoic acid (**1a**). The structure of acid **1** was established by decarboxylation to 3-methoxyphenyl 6-methoxy-2-naphthyl ketone (**7**) which was reduced by sodium borohydride to 2-(6-methoxy-2-naphthyl)-3-methoxybenzyl alcohol (**8**). The alcohol **8** was also synthesized from 3-methoxybenzaldehyde and the Gringnard reagent prepared from 2-bromo-6-methoxynaphthalene (Scheme II)

The keto acid **1** reacted with methylmagnesium iodide to give the lactone 3-methyl-3-(6-methoxy-2-naphthyl)-5-methoxyphthalide (**2**) which was reduced with Zn(Cu) in base to the acid 2-[2-(6-methoxy-2-naphthyl)ethyl]-4-methoxybenzoic acid (**3**). Cyclization of the acid **3** in HF gave 3,9-dimethoxy-7-methylbenz[*a*]anthr-12-one (**4**). Reaction of the ketone **4** with me-

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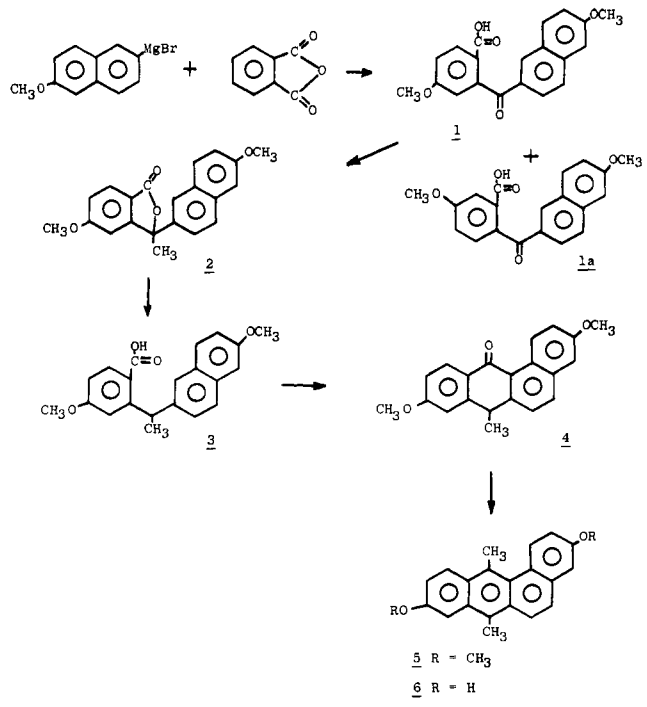
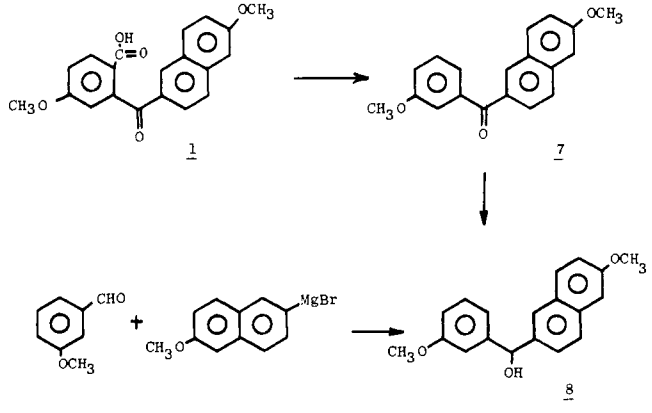
Scheme I



Scheme II



thylmagnesium iodide followed by dehydration gave 3,9-dimethoxy-7,12-dimethylbenz[*a*]anthracene (**5**). The free diphenol 7,12-dimethylbenz[*a*]anthracene-3,9-diol (**6**) was obtained by cleavage of the ether with boron tribromide.

Experimental Section

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The IR spectra of all compounds were consistent with the proposed structures. Elemental analyses (C, H) within ±0.4% of the theoretical values were submitted for review and were performed by Atlantic Microlab, Atlanta, Ga.

2-(6-Methoxy-2-naphthoyl)-4-methoxybenzoic acid (1) and 2-(6-Methoxy-2-naphthoyl)-5-methoxybenzoic acid (1a). To a solution of 43 g (0.241 mol) of 4-methoxyphthalic anhydride in 300 mL of anhydrous benzene was added a solution of 6-methoxy-2-naphthylmagnesium bromide obtained from 58.8 g (0.248 mol) of 6-methoxy-2-bromonaphthalene and 6.03 g 0.248 mol) of magnesium turnings. The resultant solution was heated at reflux for 3 h and then the solvent was removed in vacuo. The residue from evaporation was partitioned between 10% HCl and ethyl acetate. The organic layer was separated, washed with water, and extracted with saturated sodium bicarbonate solution. The latter extract was cooled in an ice bath, acidified with concentrated HCl, and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and concentrated in vacuo to give 40.5 g (50%) of a mixture of the two isomeric naphthoylbenzoic acids **1** and **1a** as a yellow solid. This mixture was fractionally recrystallized from benzene and gave 13.7 g (17%) of 2-(6-methoxy-2-naphthoyl)-4-methoxybenzoic acid (**1**) and 6.4 g (8%) of 2-(6-methoxy-2-naphthoyl)-5-methoxybenzoic acid (**1a**). Analytical samples of the two isomers were obtained by crystallization from benzene.

2-(6-Methoxy-2-naphthoyl)-4-methoxybenzoic acid (**1**), mp 215–217 °C. Anal. ($C_{20}H_{16}O_5$) C, H. 2-(6-Methoxy-2-naphthoyl)-5-methoxybenzoic acid (**1a**), mp 206–208 °C. Anal. ($C_{20}H_{16}O_5$) C, H.

3-Methyl-3-(6-methoxy-2-naphthyl)-5-methoxyphthalide (2). To a refluxing solution of 8.5 g (0.025 mol) of 2-(6-methoxynaphthoyl)-4-methoxybenzoic acid (*1*) in 160 mL of 1:1 benzene–THF was added an ethereal solution of methylmagnesium iodide prepared from 10.81 g (0.076 mol) of methyl iodide and 1.85 g (0.076 mol) of magnesium turnings. The resultant yellowish suspension was heated at reflux for 1 h and then the solvent was removed in vacuo. The residue from evaporation was poured into a mixture of ice/10% HCl and extracted with ethyl acetate. The organic layer was washed with water, extracted with 5% K_2CO_3, washed with water, dried ($MgSO_4$), and concentrated in vacuo to give a dark foam. This crude lactone was chromatographed on a 4.5 × 20 cm silica gel (80–200 mesh) column using benzene to pack the column. Increasing concentrations of ethyl acetate in benzene were used to elute the purified phthalide **2**, as a yellow oil which solidified on standing to give 5.0 g (60%) of product. Crystallization from ethanol afforded the analytical sample as white needles, mp 99–100 °C. Anal. ($C_{21}H_{18}O_4$) C, H.

2-[2-(6-Methoxy-2-naphthyl)ethyl]-4-methoxybenzoic acid (3). A mixture of 4.5 g (0.014 mol) of 3-methyl-3-(6-methoxy-2-naphthyl)-5-methoxyphthalide (**2**) in 225 mL of 10% aqueous KOH and 45 mL of pyridine was added to 27 g of Zn(Cu) couple (prepared as per Fieser, "Organic Reagents", Vol. 1, p 1293), and the mixture was refluxed for 20 h. After cooling to room temperature the solution was decanted from the metal, acidified with concentrated HCl, and again extracted with ethyl acetate. The organic solution was washed with water, dried ($MgSO_4$), and concentrated in vacuo and gave 3.84 g (85%) of crude 2-[2-(6-methoxy-2-naphthyl)ethyl]-4-methoxybenzoic acid (**3**) as a white solid. A single crystallization from ethyl acetate/heptane gave an analytically pure product, mp 197–199 °C. Anal. ($C_{21}H_{20}O_4$) C, H.

3,9-Dimethoxy-7-methylbenz[a]anthr-12-one (4). A solution of 3.84 g (0.011 mol) of the tricyclic acid **3**, in 45 mL of anhydrous HF was allowed to evaporate at room temperature for 20 min. The dark solution was then poured onto ice and extracted with benzene. The benzene was washed with water, 5% K_2CO_3, and again with water, dried ($MgSO_4$), and concentrated in vacuo to give 2.78 g (78%) of tetracyclic ketone **4**, as a yellow solid. Crystallization from ethyl acetate afforded an analytical sample of 3,9-dimethoxy-7-methylbenz[*a*]-anthr-12-one (**4**), as yellow needles, mp 151–152 °C. Anal. ($C_{21}H_{18}O_3$) C, H.

3,9-Dimethoxy-7,12-dimethylbenz[a]anthracene (5). To a refluxing solution of 2.67 g (8.39 mol) of ketone **4**, in 25 mL of anhydrous THF was added an ethereal Grignard solution of CH_3MgI derived from 0.41 g (16.8 mmol) of magnesium turnings and 2.30 g (16.8 mmol) of methyl iodide. The resultant yellowish suspension was refluxed for 1 h and the solvent was removed in vacuo. The residue from evaporation was poured onto a mixture of 10% HCl/ice and extracted into benzene. The organic layer was washed with water, dried ($MgSO_4$), and concentrated in vacuo to give the crude hydroxy derivative. This material was refluxed in 100 mL of benzene containing 500 mg of 4-toluenesulfonic acid hydrate for 1 h, extracted with saturated

$NaHCO_3$ washed with water, dried ($MgSO_4$), and concentrated in vacuo to give the crude benzanthracene derivative **5**, as a dark fluorescent syrup. This crude material was chromatographed on a 4.5 × 20 cm silica gel column (80–200 mesh) using benzene as eluent. Crystallization from ethanol gave 340 mg (13%) of the desired product as orange fluorescent needles, mp 152–153.5 °C. Anal. ($C_{22}H_{20}O_2$) C, H.

3,9-Dihydroxy-7,12-dimethylbenz[a]anthracene (6). To a stirred solution of 110 mg (0.348 mmol) of 3,9-dimethoxy-7,12-dimethylbenz[*a*]anthracene (**5**) in 15 mL of benzene was added a solution of 1.5 mL of BBr_3 in 5 mL of benzene. The solution was refluxed for 1 h, poured onto crushed ice, and extracted with ethyl acetate. The organic solution was washed with 6 × 50 mL of water, dried ($MgSO_4$), and concentrated in vacuo to give a dark solid. Recrystallization three times from ethanol gave 15 mg (15%) of the diol **6** which crystallized with 1.5 molecules of ethanol, mp 274–276 °C dec. Anal. ($C_{23}H_{25}O_{2.5}$) C, H. The free diol was obtained when the sample was dried in vacuo for 4 h at 100 °C. Anal. ($C_{20}H_{16}O_2$) C, H.

Structure Proof of 2-(6-Methoxy-2-naphthoyl)-4-methoxybenzoic Acid (1). A mixture of 1.0 g (3.0 mmol) of ketoacid **1** and 100 mg of $CuSO_4$ in 25 mL of quinoline was refluxed for 3 h. The reaction mixture was cooled to room temperature, poured onto crushed ice/10% HCl, and extracted with ether. The organic solution was extracted with 10% HCl to remove the quinoline, washed with water, dried ($MgSO_4$), and concentrated in vacuo to give 840 mg of crude ketone **7**. Chromatography on silica gel using 5% ethyl acetate in benzene afforded a solid which was recrystallized from ether/heptane to give 579 mg (66%) of analytically pure 3-methoxyphenyl 6-methoxy-2-naphthyl ketone **7**, mp 93–94 °C. Anal. ($C_{19}H_{16}O_3$) C, H.

The above ketone **7** was reduced with $NaBH_4$ in methanol to afford the corresponding 2-(6-methoxy-2-naphthyl)-3-methoxybenzyl alcohol which upon recrystallization from heptane/ethanol gave white needles, mp 97–98 °C. Anal. ($C_{19}H_{16}O_3$) C, H.

The carbinol **8** was identical in all respects with synthetic material obtained from the condensation of 3-methoxybenzaldehyde and 6-methoxy-2-naphthylmagnesium bromide; IR spectra were superimposable and mixture melting point of the two samples was not depressed.

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Received for review March 22, 1978. Accepted May 31, 1978. This investigation was supported by Grant No. CA22001, awarded by the National Cancer Institute, Department of Health, Education and Welfare.