Synthesis of Potential Metabolites of 7,12-Dimethylbenz[*a*]anthracene

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The acetates of 9-hydroxy- and 10-hydroxy-7,12-dimethylbenz[*a*]anthracene, two new phenolic derivatives of the potent carcinogen 7,12-dimethylbenz[*a*]anthracene, from 4-methoxyphthalic anhydride and 1-bromonaphthalene have been synthesized.

More and more experimental evidence is accumulating that the carcinogenic polycyclic aromatic hydrocarbons do not exert their carcinogenicity per se, but that they must be activated metabolically in the host organism, and that one or several of the produced metabolites are the ultimate carcinogens (*2, 3, 7*). Information relevant to the process of chemical carcinogenesis may be derived from these metabolites if they are available in sufficient quantities for experimental work. We now wish to report synthesis of 9-hydroxy- and 10-hydroxy-7,12-dimethylbenz[*a*]anthracenes, potential metabolites of 7,12-dimethylbenz[*a*]anthracene.

Reaction of 4-methoxyphthalic anhydride (*6*) with 1-naphthylmagnesium bromide afforded a mixture of the isomeric acids **1** and **2** in 54% yield. They were separated by fractionated crystallization from benzene or glacial acetic acid. The proportion 2-(1-naphthoyl)-5-methoxybenzoic acid (**1**) to 2-(1-naphtholy)-4-methoxybenzoic acid (**2**) was 1:4.5. The structure of the acids was proved by decarboxylation of **1** to 1-methoxybenzoylnaphthalene (*4, 5*) prepared independently from anisocyanide and 1-naphthylmagnesium bromide. 2-[1-Hydroxy-1-(1-naphthyl)ethyl]-5-methoxybenzoic acid lactone (**3**) was prepared from **1** with methylmagnesium bromide. Reduction of **3** with zinc and aqueous alkali gave 2-[1-(1-naphthyl)ethyl]-5-methoxybenzoic acid (**5**). Cyclization of **5** with anhydrous HF led to 9-methoxy-12-methylbenz[*a*]anthr-7-one (**7**). 9-Methoxy-7,12-dimethylbenz[*a*]anthracene (**9**) was obtained from **7** with methylmagnesium bromide and treatment of the crude reaction product with *p*-toluenesulfonic acid. **9** was demethylated with thioethoxide ion in dimethylformamide (*1*) to **9a** which was not isolated but acetylated directly to **9b.**

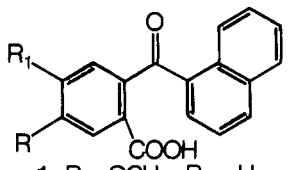
By the same sequence of reactions, **2,** through the intermediates **4, 6,** and **8,** was transformed into 10-methoxy-7,12-dimethylbenz[*a*]anthracene (**10**). Demethylation of **10** gave crude **10a,** acetylated to **10b.**

Experimental Section

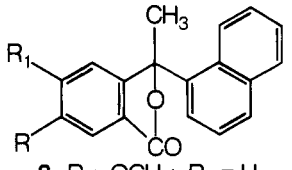
Melting points were determined in open capillary tubes on a Buchi melting point apparatus and are not corrected. The NMR spectra were taken in $CDCl_3$ solution on a Varian F-60 instrument; chemical shifts (δ) are expressed in parts per million downfield from internal tetramethylsilane. Microanalyses were performed by Robertson Laboratory, Florham Park, N.J. Elemental analyses were within ±0.3% of the theoretical values and were submitted for review.

2-(1-Naphthoyl)-5-methoxybenzoic Acid (1) and 2-(1-Naphthoyl)-4-methoxybenzoic Acid (2). 1-Naphthylmagnesium bromide (prepared from 6.17 g (0.0298 mol) of 1-bromonaphthalene and 0.78 g (0.032 g-atom) of Mg) in 50 ml of Et_2O was added to a solution of 4.83 g (0.027 mol) of 4-methoxyphthalic anhydride (*6*) in 100 ml of benzene. The solution was heated to reflux for 3 h and, after cooling, decomposed with 2 N HCl. The organic phase was extracted with 5% Na_2CO_3 solution. The extract was made acid with 2 N HCl and the precipitate was filtered off. After drying, the product was fractionally crystallized from benzene. The less soluble **2,** mp 199–201 °C, was obtained in 3.6-g (44.5%) yield. From the more soluble fractions, 0.7 g (9.5%) of **1,** mp 178–180 °C, was isolated. Separation of the two acids could be also achieved by crystallization from glacial acetic acid.

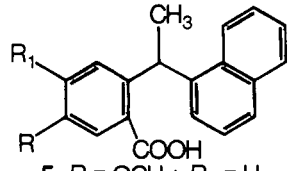
1-p-Methoxybenzoylnaphthalene. (a) From Anisocyanide. 1-Naphthylmagnesium bromide (prepared from 8.49 g (0.041 mol) of 1-bromonaphthalene) in 50 ml of Et_2O was added to 5 g (0.037 mol) of anisocyanide in 50 ml of benzene. The solution was refluxed for 1 h, chilled, and decomposed by slow addition of 100 ml of 2 N HCl. The organic phase was diluted with $CHCl_3$ and filtered through a column of 80 g of silica gel. The solution was evaporated and the residue crystallized from *i*-PrOH to give 2.80 g of the title compound, mp 100–102.5 °C (lit. (*4*) mp 100–101°) (*5*).



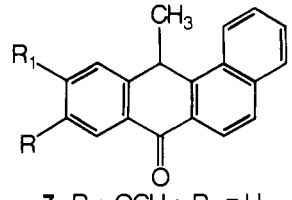
1, R = OCH_3; R_1 = H
2, R = H; R_1 = OCH_3



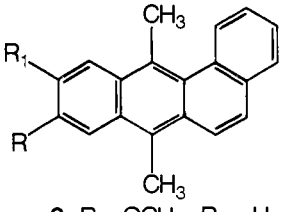
3, R = OCH_3; R_1 = H
4, R = H; R_1 = OCH_3



5, R = OCH_3; R_1 = H
6, R = H; R_1 = OCH_3



7, R = OCH_3; R_1 = H
8, R = H; R_1 = OCH_3



9, R = OCH_3; R_1 = H
9a, R = OH; R_1 = H
9b, R = OAc; R_1 = H
10, R = H; R_1 = OCH_3
10a, R = H; R_1 = OH
10b, R = H; R_1 = OAc

(b) From 1. **1** (100 mg) was melted with 72 mg of $CuCO_3 \cdot Cu(OH)_2$. The melt was taken up in 3 ml of quinoline and the solution was refluxed for 0.5 h. After cooling, the solution was diluted with $CHCl_3$, washed with 2 N HCl, dried, and evaporated. The residue (67 mg) was chromatographed on 5 g of silica gel. The material eluted with benzene–$CHCl_3$ crystallized from *i*-PrOH. The 1-*p*-methoxybenzoylnaphthalene obtained (22 mg) melted at 100.5–102.5 °C and was identical with the product from anisocyanide (mixture melting point).

2-[1-Hydroxy-1-(1-naphthyl)ethyl]-5-methoxybenzoic Acid Lactone (3). Acid 1 (5.9 g; 0.019 mol) was suspended in 20 ml of benzene with stirring and 10 ml of a 3 M solution of MeMgBr

Table I. NMR (δ) Values of Substituents

Compound	C9-OMe	C10-OMe	C7-Me	C12-Me
7	3.86	—	—	1.46; 1.57
8	—	3.93	—	1.57; 1.70
9	3.99	—	3.30	2.99
10	—	4.00	3.24	2.99
9b	—	—	3.32	2.99
10b	—	—	3.13	2.83

in Et_2O was added. After warming to reflux for 1 h, the solution was cooled and decomposed by addition of 2 N HCl. The organic layer was washed with 5% $NaHCO_3$ solution and H_2O and dried and the solvents were removed under reduced pressure. The residue gave from EtOH 3.04 g (52%) of **3,** mp of the analytical sample 160–162.5 °C.

2-[1-(Naphthyl)ethyl]-5-methoxybenzoic Acid (5). Lactone **3** (2.75 g; 0.009 mol) was dissolved in 50 ml of EtOH and to the solution 2.7 g of NaOH in 5.5 ml of H_2O was added. The alcohol was evaporated, to the residue 8 ml of concentrated NH_4OH, 50 ml of H_2O, and 6.4 g of Zn dust were added, and the mixture was refluxed for 16 h with stirring. The hot solution was then filtered through Celite and acidified. The precipitate was dissolved in benzene, the solution was washed with H_2O and dried and the solvent was evaporated. The residue crystallized from dilute AcOH, yield 2.3 g (38%). The analytical sample melted at 178–180 °C.

9-Methoxy-12-methylbenz[a]anthr-7-one (7). A solution of 2.0 g of **5** in 20 ml of anhydrous HF was allowed to evaporate in a hood overnight. The residue was dissolved in EtOAc, washed with 5% aqueous Na_2CO_3 and H_2O, and dried. The evaporation residue (1.72 g) was chromatographed on 50 g of Florisil. The benzene eluate gave from EtOH 600 mg (32%) of crystalline **7.** The analytical sample had a mp of 133.5–135 °C.

9-Methoxy-7,12-dimethylbenz[a]anthracene (9). To a solution of 600 mg of **7** in 10 ml of benzene 5 ml of 3 M MeMgBr in Et_2O was added. The solution was heated to reflux for 1 h, then chilled, and decomposed with 2 N HCl. Some insoluble material was dissolved by addition of $CHCl_3$. Conventional workup provided a residue which was dissolved in 50 ml of benzene and refluxed with 1.0 g of *p*-TsOH for 0.5 h. After cooling, the dark solution was washed with H_2O, dried, and concentrated to a small volume to give 297 mg of crystalline **9.** Melting point of the analytical sample was 208–209.5 °C.

9-Acetoxy-7,12-dimethylbenz[a]anthracene (9b). A solution of 200 mg (0.69 mmol) of **9** in 8 ml of dimethylformamide was refluxed with 142 mg (1.72 mmol) of freshly prepared sodium ethylmercaptide for 3 h in a nitrogen atmosphere. The cooled mixture was diluted with 2 N HCl and extracted with CH_2Cl_2. The extract was washed with 2 N aqueous NaOH and H_2O, and dried. The evaporation residue was heated with 5 ml of pyridine and 2 ml of acetic anhydride 1 h on the steam bath. Addition of water to the cooled solution precipitated the acetate which was filtered off, washed well with H_2O, and dried. Crystallization from benzene–hexane gave 90 mg (41%) of pure **9b,** mp 185–186 °C.

2-[1-Hydroxy-1-(1-naphthyl)ethyl]-4-methoxybenzoic Acid Lactone (4). To a stirred suspension of 10.4 g (0.033 mol) of **2** in 50 ml of anhydrous benzene, 50 ml of a 3 M MeMgBr solution in Et_2O was added, and the solution was refluxed for 1 h. After cooling, the solution was decomposed with 2 N HCl. Part of the lactone crystallized and was removed by filtration. The remaining organic phase was worked up in the usual manner. The combined products were recrystallized from CH_2Cl_2 to yield 7.21 g (73%) of **4,** mp 208.5–210.5 °C.

2-[1-(Naphthyl)ethyl]-4-methoxybenzoic Acid (6). To a solution of 3.15 g of **4** in 50 ml of EtOH 3.15 g of NaOH in 6.5 ml of H_2O was added, and the alcohol was evaporated. The residue was dissolved in 55 ml of H_2O and 9 ml of concentrated NH_4OH, and 7.1 g of Zn dust was added. The mixture was stirred and heated to reflux for 16 h. The solution was filtered and acidified. The mixture was extracted with EtOAc, the extract was washed with H_2O, dried, and evaporated to a small volume. On cooling, 3.0 g (96%) of **6** crystallized. The analytical sample had a melting point of 222–223 °C.

10-Methoxy-12-methylbenz[a]anthr-7-one (8). Three grams of **6** was dissolved in 30 ml of anhydrous HF and the solution was allowed to evaporate overnight. The residue was dissolved in EtOAc and worked up in the usual manner. Crystallization from benzene–EtOH gave 2.76 g (94%) of **8,** mp 136–138 °C. The analytical sample had the same melting point.

10-Methoxy-7,12-dimethylbenz[a]anthracene (10). Ketone **8** (2.25 g) in 30 ml of benzene was treated with 10 ml of 3 M MeMgBr solution in Et_2O for 1 h at reflux temperature. The reaction product was worked up in the same way as for **9,** yield 2.0 g (94%) of **10,** mp 137–138 °C.

10-Acetoxy-7,12-dimethylbenz[a]anthracene (10b). A solution of 2.0 g (6.9 mmol) of **10** in 80 ml of dimethylformamide was heated to reflux with 1.4 g (17.2 mmol) of freshly prepared sodium mercaptide for 3 h in a nitrogen atmosphere. Workup was the same as in the case of compound **9.** The crude phenol was acetylated with 15 ml of pyridine and 10 ml of acetic anhydride. The acetate **10b** was recrystallized from benzene–hexane, yield 1.5 g (72%), mp 117–119 °C.

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