THE JOURNAL OF Organic Chemistry

VOLUME 43, NUMBER 13

JUNE 23, 1978

Syntheses of 1-, 2-, 3-, 4-, 6-, 9-, and 10-Hydroxy-7,12-dimethylbenz[*a*]anthracenes

Melvin S. Newman,* J. M. Khanna,[1] K. Kanakarajan,[1] and S. Kumar[1]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received November 25, 1977

The condensation of 8-methyoxy-1-naphthyllithium with phthalic anhydride produced 2-(8-methoxy-1-naphthoyl)benzoic acid (**4**), which was converted by two routes into 1-methoxy-7,12-dimethylbenz[*a*]anthracene (**2**). Similarly, 7-methoxy-1-naphthylmagnesium iodide and 5-methoxy-1-naphthylmagnesium iodide were reacted with phthalic anhydride to produce 2-(7-methoxy-1-napthoyl)benzoic acid (**12**) and 2-(5-methoxy-1-napthoyl)benzoic acid (**13**), respectively. These were converted into 2-methoxy- (**20**) and 4-methoxy-7,12-dimethylbenz[*a*]anthracene (**21**). Reaction of 3-methoxy-7,12-benz[*a*]anthraquinone (**24**) with methyllithium yielded 7,12-dimethyl-7,12-dihydroxy-7,12-dihydrobenz[*a*]anthracene (**25**), which was converted to 7-chloromethyl-3-methoxy-12-methylbenz[*a*]anthracene (**26**), in turn reduced to 3-methoxy-7,12-dimethylbenz[*a*]anthracene (**27**). Reaction of the Grignard reagent prepared from 2-(*o*-bromophenyl)-4,4-dimethyl-2-oxazoline with 3-methoxy-2-napthyl methyl ketone followed by hydrolysis afforded the lactone of 2-[1-hydroxy-1-(3-methoxy-2-naphthyl)ethyl]benzoic acid (**32**), which was converted into 6-methoxy-7,12-dimethylbenz[*a*]anthracene (**29**). Ring closure of 2-(4-methoxybenzyl)-1-naphthoic acid (**42**) yielded 12-acetoxy-10-methoxybenz[*a*]anthracene (**43**), readily oxidized to 10-methoxy-7,12-benz[*a*]anthraquinone (**44**), from which 10-methoxy-7,12-dimethylbenz[*a*]anthracene (**38**) was synthesized. All of the methoxy-7,12-dimethylbenz[*a*]anthracenes were cleaved to the corresponding hydroxy compounds by heating with sodium ethyl mercaptide.

The arene oxide concept concerning the metabolism of polycyclic aromatic hydrocarbons has long been advanced.[2] Since arene oxides are very prone to rearrange into a mixture of the two related isomeric phenols,[2] the isolation of epoxides from in vitro or in vivo metabolism studies might be difficult. Accordingly, the synthesis of all of the nuclear monohydroxylated 7,12-dimethylbenz[*a*]anthracenes was undertaken in order that known compounds, or suitable derivatives thereof, would become available to use as standards, the carcinogenicity and mutagenicity of each could be determined, and the tendency of each to react with methanolic HCl as its ketonic isomer could be assessed.[3]

Although the synthesis of 1-hydroxy-7,12-dimethylbenz[*a*]anthracene (**1**) and the corresponding methoxy compound (**2**) was accomplished, as shown in Scheme I, these compounds were extremely unstable; the hydroxy compound (**1**) turned into a dark brown material even when protected from light and air, and the methoxy compound (**2**) polymerized to a large extent during the final step of its synthesis (although when pure, it is stable). The synthetic routes shown in Scheme I seem straightforward, but experimental difficulties (owing to the steric effect of the methoxy group in the 8 position of the naphthalenic intermediates) were severe.

Since 8-methoxy-1-iodonaphthalene[4] (**3**) would not form a Grignard reagent, lithiation yielded a reagent which condensed with phthalic anhydride to yield **4** (71%). As **4** was recovered unchanged on attempted reaction with methylmagnesium iodide, it was reacted with excess methyllithium to yield the desired lactone which was reduced directly to **5** (overall yield from **4** was 96%). Under the usual conditions **5** was inert to the action of CH_3Li. However, when tetramethylethylenediamine (TMEDA) was added, reaction occurred to yield the ketone **6** (70%). Cyclization with polyphosphoric acid (PPA) afforded 1-methoxy-DMBA[5] (**2**) in fair yield accompanied by high molecular weight material.

In an alternate synthesis, **5** was cyclized to the anthrone **7**, which on treatment with CH_3Li afforded, unexpectedly, the relatively stable adduct **8**, which could be dehydrated to a mixture of the methylene compound **9** and **2**. Under certain conditions more **9** was formed than **2**. However, **9** readily changes to **2**. When **8** or **2** was heated with sodium ethylmercaptide reagent[6] followed by acidification, **1** was produced.

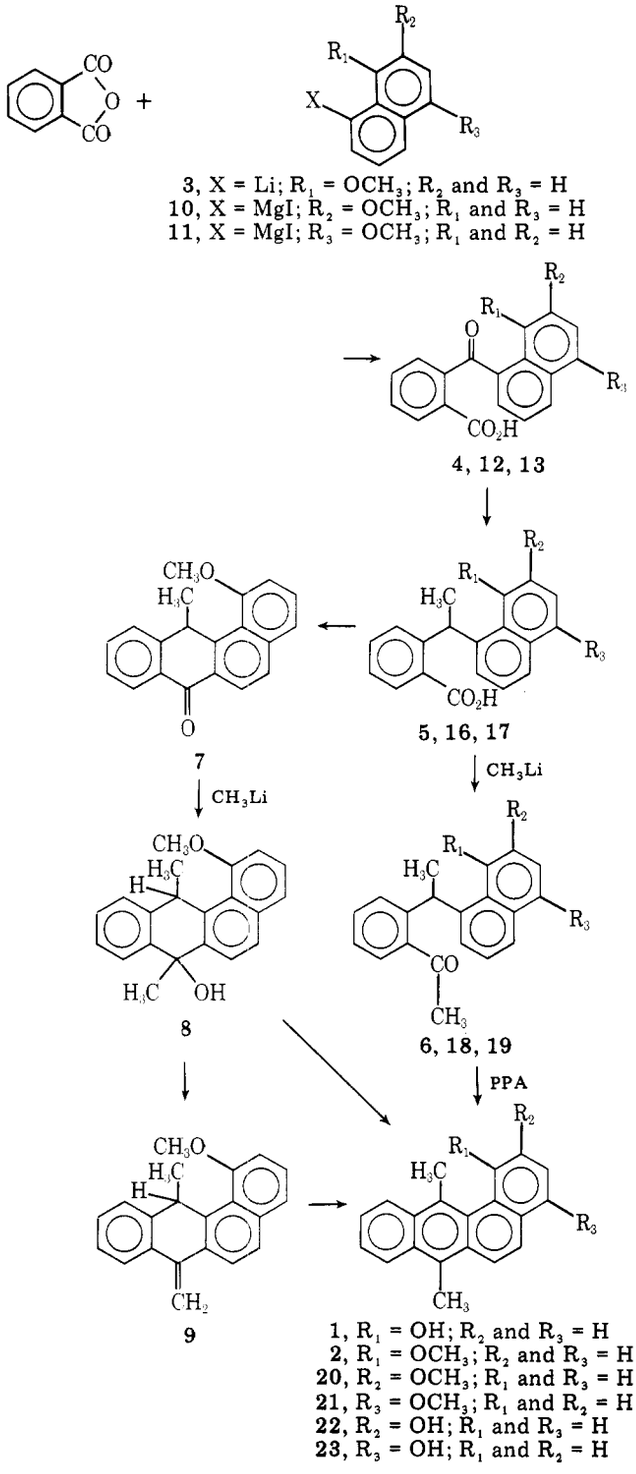
The syntheses of 2-hydroxy- (**22**) and 4-hydroxy-DMBA (**23**) are outlined in Scheme I.

The required 1-iodo-7-methoxynaphthalene[7] (**10**) was prepared from 7-methoxy-1-tetralone[8] via the oxime which on treatment with acetic anhydride and PPA at 65–70 °C for 6 min yielded 1-acetylamino-7-methoxynaphthalene in 85% yield. This intramolecular oxidation–reduction reaction occurred much more readily than the conversion of the oxime of 1-tetralone to 1-acetylaminonaphthalene, which required[9] heating for 30 min at 80 °C. Diazotization of the corresponding amine hydrochloride led to **10**. The remaining steps from **10** to **20** were accomplished in about 50% overall yield. In a similar way, 1-iodo-5-methoxynaphthalene[10] (**11**) was converted into **21** in about 36% overall yield.

We had planned to synthesize **28** by a route similar[11] to that shown in Scheme I starting from 6-methoxy-1-iodonaphthalene. However, all attempts to convert the oxime of 6-methoxy-1-tetralone into 1-acetylamino-6-methoxynaphthalene failed,[9] and the alternate route shown in Scheme II worked

0022-3263/78/1943-2553$01.00/0

Scheme I

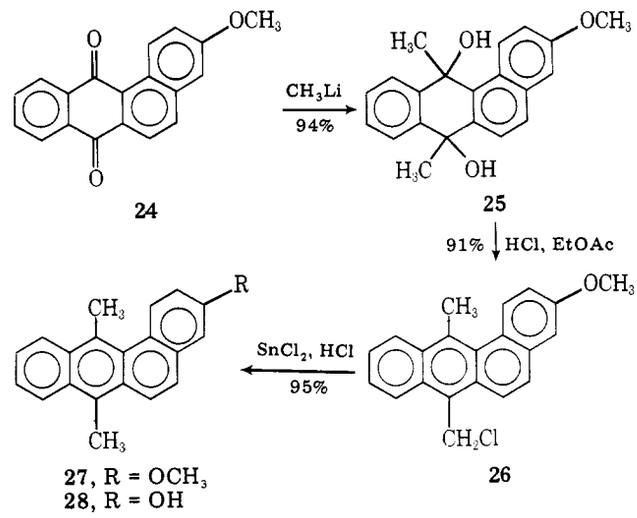


extremely well.

An improved synthesis of 6-methoxy-DMBA[12] (**29**) has been developed by reacting the Grignard reagent of 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline[13] (**30**) with 3-methoxy-2-naphthyl methyl ketone[14] (**31**) followed by appropriate treatment[15] to yield, after three steps, **29**, as shown in Scheme III.

Hydrolysis of the condensation product of the Grignard reagent[13] prepared from **30** and **31**[14] yielded **32** (60%), which was converted into **34** (84% overall from **32**). Attempted cyclization of **34** to **29** with polyphosphoric acid as described for a similar case[3] gave poor results, which undoubtedly stemmed from the facts that ring closure must occur meta to a methoxy group and demethylation of the ether function occurred.

Scheme II



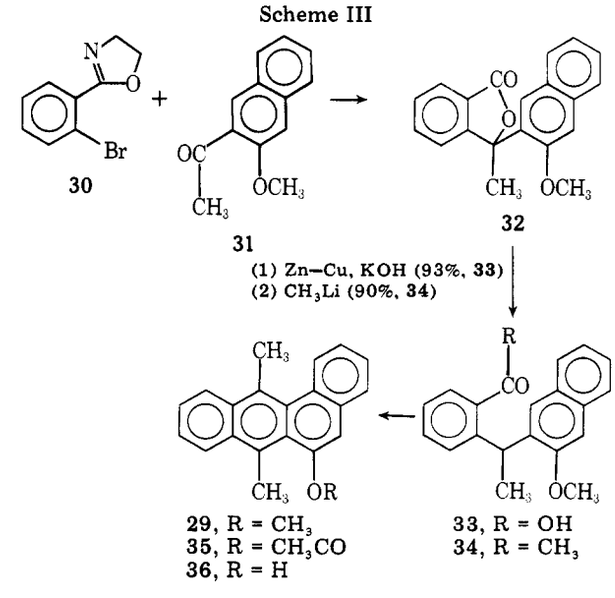
Cyclization of **34** with HBr–acetic acid followed by acetylation of the crude product afforded 63% of **35**. This treatment was necessary because demethylation occurred during the cyclization. Treatment of **35** with methanolic HCl afforded **29**, identical with that synthesized by an alternate route.[3]

The attempted coversion of **29** to **36** as described[6] proved difficult because of the great instability[3] of **36**. However, the acetate **35** was readily obtained.[3] In the IR spectra of crude samples of **36**, ketonic as well as hydroxylic bands were observed (compare with ref 3).

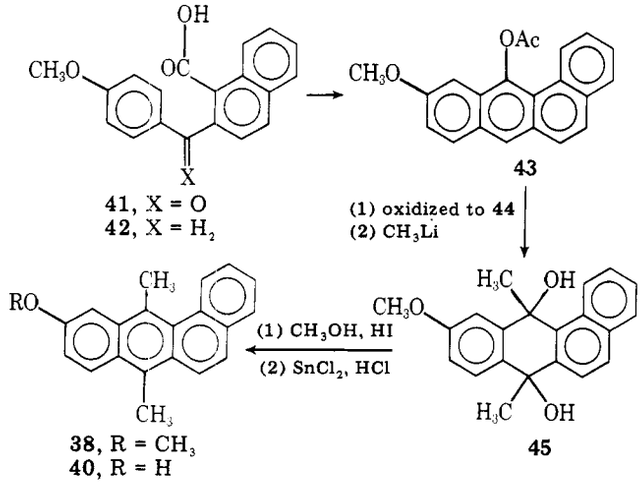
The syntheses of 9-methoxy- (**37**) and 10-methoxy-DMBA (**38**) by a sequence of reactions starting with 4-methoxyphthalic anhydride and 1-naphthylmagnesium bromide have been reported.[16] However, the synthesis of **37** by this route uses 2-(1-naphthoyl)-5-methoxybenzoic acid, formed in less than 10% yield.[16] We have synthesized **37** and **38** by a route[15] which does not require the separation of the isomeric acids formed in the above-mentioned Grignard reaction. We have also synthesized **38** by an alternate route,[18] shown in Scheme IV, which allows for functionalization at the 7-methyl group if desired.

All of the methoxy-DMBA compounds (**2, 20, 27, 21, 29, 37,** and **38**) were converted into the corresponding hydroxy-DMBA compounds (**1, 22, 28, 23, 36, 39,** and **40**) essentially as described.[6,12] Of the phenols, only **36** and 5-hydroxy-DMBA[12] gave ketonic IR bands and were converted in high yield to the corresponding methyl ethers on treatment, under

Scheme III



Scheme IV



standard conditions, with 0.1 N methanolic HCl at room temperature for 7 h.[12] The other phenols gave only 0–6% of methyl ethers under these conditions. Thus, the steric strain in the DMBA derivatives results in abnormal reactivity involving the ketonic isomer only when the oxygenated moiety is in the 5 and 6 positions (compare with other results[12]).

Experimental Section[19]

2-(8-Methoxy-1-naphthoyl)benzoic Acid* (4). To a stirred solution of 15.0 g of **3**[4] in 250 mL of ether was added 40 mL of a 1.6 M ethereal butyllithium solution. After 0.5 h at room temperature, this solution was added to a stirred solution of 8.0 g of phthalic anhydride in 100 mL of freshly distilled THF. After being held at reflux for 72 h, the cooled mixture was treated with dilute HCl and the acidic component was crystallized once from $CHCl_3$–benzene to produce 11.5 g (71%) of **4**, mp 228–230 °C.

2-[α-(8-Methoxy-1-naphthyl)ethyl]benzoic Acid* (5). To a solution of 20.0 g of **4** in 350 mL of ether was added 140 mL of 1.6 M methyllithium. After 48 h at reflux, the cooled mixture was acidified with HCl and most of the THF was removed on a rotary evaporator. To the neutral portion of the reaction product, isolated as usual, was added 100 g of zinc, 1.5 g of $CuSO_4$, 75 mL of pyridine, and 1 L of 10% KOH. The vigorously stirred mixture was heated at reflux for 20 h, cooled, and filtered. The filtrate was acidified with HCl, and the acid product, after crystallization from benzene–petroleum ether, amounted to 19.2 g (96%) of **5**, mp 194–195 °C.

2-[α-(8-Methoxy-1-naphthyl)ethyl]acetophenone* (6). In the best of several runs, 35 mL of 1.84 M methyllithium was added dropwise to a solution of 5.0 g of **5** in 200 mL of ether containing 5 g of TMEDA. After a 24-h reflux the neutral fraction was crystallized from ethanol to yield 3.5 g (70%) of **6**, mp 119–121 °C. From the acid portion was recovered 1.2 g (24%) of **5**.

7,12-Dimethyl-7-hydroxy-1-methoxy-7,12-dihydrobenz[a]anthracene* (8). A mixture of 2.40 g of **5**, 0.5 g of $ZnCl_2$, and 50 mL of CF_3CO_2H was held at reflux for 3 h, cooled, and poured on ice. The reaction product was chromatographed over silica gel (benzene) to yield 1.70 g (75%) of an oil (anthrone **7** from IR analysis), which was treated with excess CH_3Li in ether for 20 h at room temperature. The reaction product on crystallization from benzene–petroleum ether yielded 1.35 g (56% from **5**) of **8**, mp 191–195 °C dec. By TLC analysis the material in the mother liquor contained **8**, **9**, and **2**.

1-Methoxy-12-methyl-7-methylene-7,12-dihydrobenz[a]anthracene (9). A solution of 1.00 g of **5** in 25 mL of anhydrous HF was poured on ice after 1 h. To the crude anthrone **7**, isolated as usual, was added excess CH_3Li in ether at room temperature. After 20 h the mixture was acidified with dilute HCl and the dried product was chromatographed over alumina (benzene–petroleum ether, ca. 1:3) to yield 450 mg (48%) of **9**, *m/e* 286,[20] from the first 5 fractions and then 200 mg (21%) of **2**: mp 138–140 °C; *m/e* 286. The remaining material was of high molecular weight. The NMR[21] spectrum of **9** [δ 1.50 (d, 3, OCH_3), 4.05 (s, 3, OCH_3), 5.70–5.75 (m, 3, $=CH_2$, 12-H), and 7.3 (m, 9, ArH)] and an IR band at 1620 cm^{-1} indicate the methylene feature. Because of the ready rearrangement of **9** to **2**, no elemental analysis was attempted.

1-Methoxy-7,12-dimethylbenz[a]anthracene* (2). Method A. A stirred mixture of 1.50 g of **6**, and 30 mL of PPA was heated on a steam bath for 40 min and poured on ice. Mass spectral analysis of the crude reaction product isolated in the usual way showed high molecular weight impurities. Chromatography over basic alumina using benzene–petroleum ether (1:3) afforded 800 mg of pale yellow **2** from the first 10 fractions (25 mL each): mp 138–140 °C; NMR δ 2.80 (s, 3, 7-CH_3), 3.00 (s, 3, 12-Me), 3.85 (s, 3, OCH_3), 7.3 (m, 9, ArH).

Method B. A solution of 225 mg of **8** and 10 mg of *p*-toluenesulfonic acid in 10 mL of benzene was held at reflux for 1 h, cooled, washed with dilute NaOH, and dried over Na_2SO_4. The product was chromatographed as in method A to yield 100 mg (47%) of pure **2**.

1-Hydroxy-7,12-dimethylbenz[a]anthracene (1). A mixture of 500 mg of **2** in 10 mL of dimethylformamide with the sodium ethyl mercaptide formed[6] from 500 mg of ethyl mercaptan and NaH in 5 mL of dimethylformamide was heated at 155 °C for 2 h and poured on ice. The crude product was chromatographed over silica gel using ether to yield a homogeneous fraction which did not solidify on removal of solvent (all saturated with N_2 in this work). The pale yellow viscous **1**, *m/e* 272, obtained in 75% yield (350 mg) could not be obtained crystalline. It was hygroscopic, and a solid sample, mp 60–70 °C (unsharp), was obtained. Analysis indicated 0.5 molecule of water of hydration. The solid rapidly turned dark brown. No **2** was obtained on standard treatment[3] with CH_3OH–HCl.

2-(7-Methoxy-1-naphthoyl)benzoic Acid* (12). A solution of 9.4 g of ethylene dibromide in 200 mL of ether[22] was added during 3 h to a stirred mixture of 14.2 g of **10**[5] and 2.4 g of sublimed Mg in 200 mL of ether. After 1 h this Grignard reagent was added to a stirred solution of 8.8 g of phthalic anhydride in 100 mL of THF. After 20 h at room temperature, a conventional workup yielded 11.0 g (68%) of **12**, mp 154–155 °C, after one crystallization from benzene–petroleum ether (bp 35–55 °C).

2-[α-(7-Methoxyl-1-naphthyl)ethyl]benzoic Acid* (16). A Grignard reagent prepared from 21.3 g of CH_3I, 3.6 g of Mg, and 450 mL of ether was added dropwise to a solution of 17.5 g of **12** in 500 mL of ether. After being held at reflux for 24 h, the cooled mixture was worked up as usual to yield 16.0 g of lactone **14**, which was stirred at reflux with 840 mL of 10% KOH, 84 mL of pyridine, and 105 g of Zn dust (activated with 1 g of $CuSO_4$) for 24 h. The acidic fraction of the product was crystallized from benzene–petroleum ether to yield 12.0 g (69%) of **16**, mp 170–172 °C.

2-[α-(7-Methoxyl-1-naphthyl)ethyl]acetophenone* (18). To a solution of 5.0 g of **16** in 200 mL of ether was added 35 mL of 1.8 M CH_3Li. After 20 h at reflux the mixture was worked up as usual to yield **18** as colorless crystals, mp 104–105 °C, in almost quantitative yield. No unreacted **16** was recovered.

2-Methoxy-7,12-dimethylbenz[a]anthracene (20). A mixture of 6.0 g of **18** and 120 mL of PPA was heated on a steam bath for 45 min. A conventional workup afforded 5.3 g of **20**, mp 131–132 °C (lit.[23] mp 131–132.5 °C), after crystallization from benzene–petroleum ether or methanol.

2-Hydroxy-7,12-dimethylbenz[a]anthracene* (22). Demethylation of 2.4 g of **20** by heating at 155–160 °C for 3 h with C_2H_5SNa[6] afforded 1.7 g (89%) of **22**, mp 115–117 °C. A freshly vacuum sublimed sample melted at 122–124 °C and was pale yellow. On standing, the color darkens and the melting point becomes lower and broader.

2-(5-Methoxy-1-naphthoyl)benzoic Acid* (13). By reacting 5-iodo-1-methoxynaphthalene[10] (**11**) with phthalic anhydride essentially as described for the synthesis of **12**, **13** was obtained, mp 184–185 °C, on crystallization from benzene in 70% yield.

2-[1-Hydroxy-1-(5-methoxy-1-naphthyl)ethyl]benzoic Acid Lactone* (15). The Grignard reagent prepared from 4.2 g of Mg and MeI in ether was added to a solution of 15.0 g of **13** in 300 mL of benzene and 300 mL of ether. After 20 h at reflux a conventional workup yielded 14.0 g (93%) of **15**, mp 159–161 °C, on crystallization from ether–petroleum ether.

2-[α-(5-Methoxy-1-naphthyl)ethyl]benzoic Acid* (17). Reduction of 15.0 g of **15** as described for **14** afforded 11.5 g (77%) of **17**, mp 170–171 °C, on crystallization from benzene–petroleum ether.

2-[α-(5-Methoxy-1-naphthyl)ethyl]acetophenone* (19). Treatment of 7.65 g of **17** in ether with 65 mL of 1.4 M methyllithium as described for **16** yielded 6.80 g (89%) of **19**, mp 132–134 °C, on crystallization from ethanol.

4-Methoxy-7,12-dimethylbenz[a]anthracene (21). After heating a solution of 6.08 g of **19** in 105 mL of PPA on a steam bath for 35 min, a conventional workup followed by chromatography over alumina yielded 94% of **21**, mp 120–121 °C (lit.[24] mp 121 °C), on crystallization from methanol.

4-Hydroxy-7,12-dimethylbenz[a]anthracene (23). On treatment of 1.00 g of **21** with C_2H_5SNa as described above for **20**, 0.80 g (84%) of **23** was obtained, mp 164–154 °C (lit.[24] mp 164–165 °C), on crystallization from benzene. All solvents used in the preparation of **23** were saturated with N_2.

3-Methoxy-7,12-benz[*a*]anthraquinone* (24). A solution of 2.50 g of 12-acetoxy-3-methoxybenz[*a*]anthracene (mp 165–167 °C), prepared as described[11] (mp 166–167 °C), and 3.3 g of $Na_2Cr_2O_7$ in 60 mL of acetic acid was boiled for 15 min, cooled, and diluted with 60 mL of dilute H_2SO_4. The precipitate was chromatographed over basic alumina eluting with $CHCl_3$ to yield 2.25 g (95%) of **24,** mp 162–163 °C, on crystallization from benzene–petroleum ether.

7,12-Dimethyl-7,12-dihydroxy-3-methoxy-7,12-dihydrobenz[*a*]anthracene* (25). A solution of CH_3Li (0.04 mol) in ether was added to a suspension of 2.88 g (0.01 mol) of **24** in 150 mL of 1:1 benzene–ether at room temperature. After being held at reflux for 15 h, the mixture was treated with aqueous NH_4Cl and the product isolated as usual. After recrystallization from benzene–petroleum ether, 3.00 g (94%) of **25** was obtained, mp 135–140 °C, as a mixture of isomers suitable for the next step.

7-Chloromethyl-3-methoxy-12-methylbenz[*a*]anthracene* (26). Dry HCl was passed into a solution of 2.30 g of **25** in 30 mL of dry ethyl acetate at 0 °C. After 5 h at 0 °C, 2.10 g (91%) of **26,** mp 149–150 °C, before and after recrystallizaion from benzene–petroleum ether, was collected by filtration.

3-Methoxy-7,12-dimethylbenz[*a*]anthracene* (27). A solution of 2.0 g of **26** in 50 mL of dioxane containing 10 g of stannous chloride and 10 mL of concentrated HCl was heated on a steam bath for 1 h. The crude product obtained as usual was chromatographed over a short column of basic alumina to yield 1.7 g (95%) of **27,** mp 128–129 °C, suitable for demethylation. A pale yellow analytical sample, mp 131–132 °C, was obtained with little loss on crystallization from benzene–petroleum ether.

3-Hydroxy-7,12-dimethylbenz[*a*]anthracene* (28). Demethylation of 1.00 g of **27** was carried out as described for the preparation of **22** to yield 0.90 g of **28,** mp 165–166 °C, on crystallization from N_2-saturated chloroform–petroleum ether. A colorless analytical sample, mp 167–168 °C, was prepared by sublimation at 160 °C and 1 mm.

3-Methoxy-2-naphthyl Methyl Ketone (31). To a stirred suspension at room temperature of 20.2 g of 2-methoxy-3-naphthoic acid, prepared in 71% yield essentially as described,[14] in 400 mL of ether was added 108 mL of 1.84 M methyllithium during 1 h. After being stirred at reflux for 16 h, the reaction mixture was worked up as usual to yield 13.0 g (86% based on recovery of 5.0 g of starting acid by alkaline extraction) of **31:** bp 134–136 °C (0.2 mm); mp 42–44 °C (lit.[25] mp 48 °C).

2-[1-Hydroxy-1-(3-methoxy-2-naphthyl)ethyl]benzoic Acid Lactone (32). To the Grignard reagent prepared from 5 g of 2-(*o*-bromophenyl)-4,4-dimethyl-2-oxazoline[13] (**30**) in THF using sublimed magnesium was added a solution of 4.4 g of **31** in THF at room temperature. After being stirred for 16 h at 15–20 °C and at reflux for 1 h, a conventional workup afforded a crude oil which was heated at reflux for 18 h with 100 mL of 8% ethanolic H_2SO_4. After dilution with water the mixture was worked up as usual to yield an oil from which 3.2 g (53%) of colorless crystals of **32,** mp 159–162 °C, was obtained. An analytical sample, mp 165–165.5 °C, was obtained on crystallization from ethanol with little loss.

***o*-[1-(3-Methoxy-2-naphthyl)ethyl]benzoic Acid* (33).** On reduction by refluxing a stirred mixture of 3.0 g of **32,** 20 g of Zn (activated by acid washing and treatment with 200 mg of $CuSO_4$), 130 mL of 10% KOH, and 12 mL of pyridine for 20 h, 2.8 g (93%) of colorless **33** was obtained, mp 177–179 °C, by a conventional workup. An analytical sample, mp 179–180 °C, was obtained by recrystallization from benzene–petroleum ether.

***o*-[1-(3-Methoxy-2-naphthyl)ethyl]acetophenone* (34).** As in the case of the above synthesis of **31, 33** was converted to pure **34,** mp 127–128 °C, in 90% yield.

6-Acetoxy-7,12-dimethylbenz[*a*]anthracene (35). A mixture of 0.6 g of **34,** 6 mL of acetic acid, and 6 mL of 48% HBr was held at reflux for 15 min. Isolation of the product as usual gave 0.5 g of a light yellow solid which was dissolved in 10 mL of pyridine and 5 mL of acetic anhydride. After 18 h at room temperature, water was added and the product, isolated by ether extraction as usual, was crystallized twice from ether to yield 400 mg (63%) of **35,** mp 138–139 °C. A mixture melting point with 138–139 °C material prepared as described[3] was not depressed. The IR and NMR spectra were identical.

6-Methoxy-7,12-dimethylbenz[*a*]anthracene* (29). In one experiment the crude product obtained by treating **34** with HBr as described above was treated with 0.1 M methanolic HCl at room temperature for 24 h to yield 40% of pure **29:** melting and mixture point with another sample,[3] 140–141 °C; IR and NMR spectra were identical.

In as much as the experiment describing the synthesis of **29** was inadvertently omitted,[3] it is given here. A mixture of 3.0 g of *o*-[α-(3-methoxy-1-naphthyl)ethyl]acetophenone (**27**) (numbering is the same as that in ref 3) and 60 g of PPA was stirred at 85 °C for 2 h. Workup, including chromatography over neutral alumina, afforded 1.4 g (50%) of **29,** mp 140–141 °C.

A solution of 0.337 g of pure **35** in 20 mL of 0.1 N methanolic HCl was allowed to stand at room temperature for 7 h. The volatile matter was removed under reduced pressure, and the product was taken up in ether. After three washings with 3% KOH (no material recoverable from the aqueous washings), the dried ether solution afforded 0.308 g (ca. 100%) of light yellow solid, mp 135–137 °C. One recrystallization from ether afforded 0.273 g (90%) of pure **29,** mp 140–141 °C.

4-Methoxy-2-(1-naphthoyl)benzoic Acid. When an ether–benzene solution of 1-naphthylmagnesium bromide was added to a solution of 4-methoxyphthalic anhydride in ether, a mixture of ketoacids was obtained. When an aqueous alkaline solution of these acids was just acidified with acetic acid, 4-methoxy-2-(1-naphthoyl)-benzoic acid, mp 191–193 °C, was obtained in 61% yield. Recrystallization from benzene afforded pure acid, mp 198–199 °C (lit.[16] mp 199–201 °C), with little loss. The dilute acetic acid filtrate on acidification with HCl yielded a solid which on recrystallization from benzene afforded 5-methoxy-2-(1-naphthoyl)benzoic acid, mp 158–159 °C (lit.[16] mp 178–180 °C; a sample sent by Dr. Pataki melted at 172–178 °C alone and mixed with our 158–159 °C acid, a polymorphic form, as seeding with Dr. Pataki's sample raised the melting point to 172–178 °C).

2-[1-Hydroxy-1-(1-naphthyl)ethyl]-4-methoxybenzoic Acid Lactone. To a solution at 0 °C of lithiated 2-(*p*-methoxyphenyl)-4,4-dimethyl-2-oxazoline, prepared as described[15] from 10.25 g (0.05 mol) of oxazoline in 150 mL of ether, was added a solution of 8.5 g (0.05 mol) of methyl 1-naphthyl ketone in 50 mL of ether during 5 min. After 18 h at room temperature and 10 h at reflux, the cooled mixture was treated with 50 mL of water and worked up as usual. A solution of the product in 300 mL of 8% ethanolic H_2SO_4 was refluxed for 18 h, after which time the ethanol was removed under reduced pressure. The product, isolated after the usual workup, was heated at reflux with 100 mL of 20% aqueous NaOH and 100 mL of ethanol. From the neutral portion of the reaction products was isolated 3.5 g (41%) of starting ketone by vacuum distillation. Acidification of the aqueous alkaline layer afforded 8.2 g (53%; 90% based on recovered 4-methoxybenzoic acid) of lactone, mp 195–203 °C, after trituration with $NaHCO_3$ solution to remove *p*-methoxybenzoic acid. Recrystallization from methanol yielded pure lactone; mp and mmp 205–206 °C with lactone prepared as described.[16] The crude lactone was suitable for reduction to 4-methoxy-2-(1-naphthylethyl)benzoic acid as described.[16]

Reaction of 4-Methoxyphenylmagnesium Bromide with 1,2-Naphthalic Anhydride. This reaction was carried out essentially as described[23] except that pure sublimed magnesium was used. An 80% yield of a mixture of **41** and its isomer was obtained (lit.[23] 58%). Separation began by refluxing in methanolic HCl for 12 H (1.2 L of methanol for 74 g of acids). A conventional workup afforded 74 g of a mixture of methyl esters. A solution of the esters in 350 mL of concentrated H_2SO_4 was held at room temperature for 2 h and then poured on ice. By treatment of the organic products with 2% KOH, 42 g (45% based on 1,2-naphthalic anhydride) of 2-(4-methoxybenzoyl)-1-naphthoic acid (**41**), mp 169–173 °C, was obtained which on one crystallization from benzene–acetone yielded pure **41,** mp 176–178 °C (lit.[23] mp 179.5–181 °C), with little loss. From the neutral fraction 20.0 g (21%) of methyl 1-(4-methoxybenzoyl)-2-naphthoate, mp 135–136 °C, was obtained. Alkaline hydrolysis yielded pure 1-(4-methoxybenzoyl)-2-naphthoic acid, mp 216–217 °C (lit.[23] mp 212–216 °C), in high yield.

2-(4-Methoxybenzyl)-1-naphthoic Acid* (42). Reduction of 18.1 g of **41** as described for *o*-benzoylbenzoic acid[26] yielded 13.7 g (93% based on recovery of 2.5 g of **41**) of the lactone of 2-(1-hydroxy-4-methoxyphenylmethyl)-1-naphthoic acid, mp 133–134 °C. Reduction of 13.5 g of the lactone with 60 g of activated zinc dust (washing with 10% HCl followed by treatment with ammoniacal $CuSO_4$), 200 mL of 30% KOH, and 300 mL of ethylene glycol by boiling for 48 h afforded 12.9 g (96%) of **42,** mp 150–152 °C, suitable for the next step. An analytical sample, mp 155–156 °C, was obtained with little loss by crystallization from benzene–petroleum ether.

12-Acetoxy-10-methoxybenz[*a*]anthracene* (43). A solution of 12.0 g of **42,** 0.7 g of $ZnCl_2$, 240 mL of HOAc, and 90 mL of Ac_2O was boiled for 90 min, and the cooled solution was poured into 1 L of water. The solid which separated was collected by filtration and washed with water and dilute $NaHCO_3$ to yield 12.0 g (92%) of **43,** mp 180.5–181.5 °C. An analytical sample, mp 183–184 °C, was obtained with little loss by crystallization from benzene–petroleum ether.

A solution of 12.0 g of **43** and 16.3 g of $K_2Cr_2O_7$ in 280 mL of HOAc

was refluxed for 45 min, cooled, and added to 1 L of 10% H_2SO_4. The yellow solid which separated was collected, washed with water, and dried to give 10.0 g (92%) of 10-methoxy-7,12-benz[*a*]anthraquinone* (**44**), mp 168–169 °C, suitable for further use. Recrystallization from acetic acid yielded pure **44**, mp 171.5–172.0 °C, with little loss.

7,12-Dihydroxy-7,12-dimethyl-10-methoxy-7,12-dihydrobenz[*a*]anthracene* (45). To a solution of 9.0 g (0.03 mol) of **44** in 270 mL of benzene was added 65 mL (0.09 mol) of 1.4 M CH_3Li in ether during 5 min. After 18 h at reflux, saturated NH_4Cl solution was added and the mixture worked up as usual to yield 9.2 g (95%) of **45**, which showed no carbonyl group in the IR spectrum. A colorless analytical sample, mp 175.5–176.5 °C, was obtained by crystallization from benzene–petroleum ether and benzene alone with little loss.

10-Methoxy-7,12-dimethylbenz[*a*]anthracene (**38**) was obtained by adding a solution of 7.0 g of **45** in 400 mL of methanol dropwise during 25 min to a solution at 0 °C of 75 mL of 70% HI in 100 mL of methanol. After 1 h at 5 °C the solid which had separated was collected and dissolved in 400 mL of dioxane and 30 mL of concentrated HCl. This solution was added to a solution of 70 g of $SnCl_2$ in 300 mL of dioxane and 210 mL of concentrated HCl. On holding at reflux for 30 min the color changed from dark orange-yellow to light yellow. The cooled reaction mixture was added to 3 L of water. The crude solid obtained was dissolved in 70 mL of hexamethylphosphoramide (HMPA) containing a solution of 2 g of NaOH in 5 mL of water and 2 mL of methyl iodide. After 7 h the mixture was diluted with water and the product extracted with ether to yield 4.3 g of solid. Chromatography over basic alumina afforded 4.0 g (62% from **45**) of **38**, mp 135–136 °C (lit.[23] mp 136–137 °C), identical with the **38** produced by the alternate synthesis.

9-Hydroxy-7,12-dimethylbenz[*a*]anthracene* (39) and 10-Hydroxy-7,12-dimethyl-benz[*a*]anthracene (40). Demethylation of **37** and **38** as described[6] afforded 79% of **39** as pale yellow crystals, mp 197–198 °C, and 87% of **40** as pale yellow crystals, mp 133–134 °C (lit.[17] mp 122–123 °C; light tan), respectively, after chromatography and recrystallization.

Registry No.—**1**, 66240-13-9; **2**, 66240-14-0; **3**, 51179-24-9; **4**, 66240-15-1; **5**, 66240-16-2; **6**, 66240-17-3; **7**, 66240-1-4; **8**, 66240-19-5; **9**, 66240-20-8; **10** halide derivative, 66240-21-9; **11** halide derivative, 61735-51-1; **12**, 66240-22-0; **13**, 66240-23-1; **14**, 66240-24-2; **15**, 66240-25-3; **16**, 66240-26-4; **17**, 66240-27-5; **18**, 66240-28-6; **19**, 66240-29-7; **20**, 66240-30-0; **21**, 16277-49-9; **22**, 66240-31-1; **23**, 14760-53-3; **24**, 63216-11-5; *cis*-**25**, 66239-99-4; *trans*-**25**, 66240-00-4; **26**, 66240-01-5; **27**, 66240-02-6; **28**, 57266-83-8; **29**, 53306-04-0; **30**, 32664-13-4; **31**, 17056-94-9; **32**, 66240-03-7; **33**, 66240-04-8; **34**, 66240-05-9; **35**, 53306-06-2; **37**, 62078-52-8; **38**, 62064-35-1; **39**, 66240-06-0; **40**, 62064-38-4; **41**, 66240-07-1; **42**, 66240-08-2; **43**, 66240-09-3; **44**, 66240-10-6; **45**, 66240-11-7; 12-acetoxy-3-methoxybenz[*a*]anthracene, 66240-12-8; 2-methoxy-3-naphthoic acid, 883-62-5; 1-naphthyl bromide, 90-11-9; 4-methoxyphthalic anhydride, 28281-76-7; 4-methoxy-2-(1-naphthoyl)benzoic acid, 62064-28-2; 5-methoxy-2-(1-naphthoyl)benzoic acid, 62064-27-1; 2-[1-hydroxy-1-(1-naphthyl)ethyl]-4-methoxybenzoic acid lactone, 62064-30-6; oxazoline, 504-77-8; methyl 1-naphthyl ketone, 1333-52-4; 4-methoxyphenyl bromide, 104-92-7; 1,2-naphthalic anhydride, 5343-99-7; methyl 1-(4-methoxybenzoyl)-2-naphthoate, 66239-96-1; 1(4-methoxybenzoyl)-2-naphthoic acid, 66239-97-2; 2-(1-hydroxy-4-methoxyphenylmethyl)-1-naphthoic acid lactone, 66239-98-3.

References and Notes

(1) Postdoctoral Research Associates. The funds for this research were provided by Grant CA07394 from the National Cancer Institute, DHEW.
(2) For a review, see D. M. Jerina and J. W. Daly, "Drug Metabolism from Microbe to Mann", Taylor and Francis, London, 1976, p 13ff. See also D. M. Jerina, H. Yagi, and J. W. Daly, *Heterocycles*, **1**, 267 (1973).
(3) M. S. Newman, V. Sankaran, and D. R. Olson, *J. Am. Chem. Soc.*, **8**, 3237 (1976).
(4) B. M. Graybill and D. A. Shirley, *J. Org. Chem.*, **31**, 1221 (1966).
(5) DMBA refers to 7,12-dimethylbenz[*a*]anthracene throughout the paper.
(6) G. I. Feutrill and R. W. Mirrington, *Tetrahedron Lett.*, 1327 (1970).
(7) W. E. Bachmann and W. J. Horton, *J. Am. Chem. Soc.*, **69**, 58 (1947).
(8) D. G. Thomas and A. H. Nathan, *J. Am. Chem. Soc.*, **70**, 331 (1948).
(9) M. S. Newman and W. H. Hung, *J. Org. Chem.*, **38**, 4073 (1973).
(10) J. Lockett and W. F. Short, *J. Chem. Soc.*, 787 (1939).
(11) Compare: D. C. C. Smith, *J. Chem. Soc.*, 673 (1962).
(12) M. S. Newman, V. Sankaran, and D. R. Olson, *J. Am. Chem. Soc.*, **98**, 3237 (1976).
(13) A. I. Meyers, D. L. Temple, D. Haidukewych, and E. D. Mihelich, *J. Org. Chem.*, **39**, 2787 (1974).
(14) S. V. Sunthanken and H. Gilman, *J. Org. Chem.*, **16**, 18 (1951).
(15) M. S. Newman and S. Kumar, *J. Org. Chem.*, **43**, 370 (1978).
(16) J. Pataki and R. F. Balick, *J. Chem. Eng. Data*, **22**, 114 (1977).
(17) C. E. Morreal and V. Alks, *J. Chem. Eng. Data*, **22**, 118 (1977).
(18) M. S. Newman and V. Sankaran, *Tetrahedron Lett.*, 2067 (1977).
(19) All melting points are uncorrected. The term "worked up as usual" means that an ether–benzene solution of the products was washed with dilute HCl and/or alkali and then with saturated NaCl and dripped through a cone of anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator, and the residue was treated as indicated. All compounds gave NMR and IR spectra consistant with the formula, and the mass spectra were performed by C. R. Weisenberger on an MS9 instrument made by A.E.I. All new compounds marked with an asterisk gave analyses (by M-H-W Laboratories, Garden City, Mich., and the Galbraith Laboratory, Knoxville, Tenn.) within ±0.30% of theory.
(20) We thank Mr. R. Weisenberger for the mass spectra.
(21) All NMR spectra were taken in $CDCl_3$ using Me_4Si as a standard.
(22) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).
(23) R. M. Peck, *J. Am. Chem. Soc.*, **78**, 997 (1956).
(24) The synthesis of **7** by an alternate route has been reported by J. W. Flesher, S. Soedigdo, and D. R. Kelley, *J. Med. Chem.*, **10**, 932 (1967).
(25) H. Wahl, *C. R. Hebd. Seances Acad. Sci.*, **206**, 521 (1938).
(26) M. S. Newman, *J. Org. Chem.*, **26**, 2630 (1961).

Structure Relation of Conjugated Cycloalkenones and Their Ketals

Dan Becker,* Naphtali C. Brodsky, and Jacob Kalo

Department of Chemistry, Technion-Israel Institute of Technology, Haifa, 32000, Israel

Received November 14, 1977

The degree of double bond shift during ketalization was studied on cycloalkenone systems. It was found that the shift was dependent on ring size and the location of substituents.

Introduction

In the framework of research carried out in our laboratory,[1] we attempted to develop a new and efficient method for the synthesis of 4,4-disubstituted cycloenones according to Scheme I.

A necessary requirement for success is the shift of the double bond to the β,γ position during the conversion of the ketone into the ketal. The fact that the double bond migrates on ketalization was discovered by Fernholz and Stavely[2] in 1937 and applied in syntheses of natural products.[3,4] Although

Scheme I