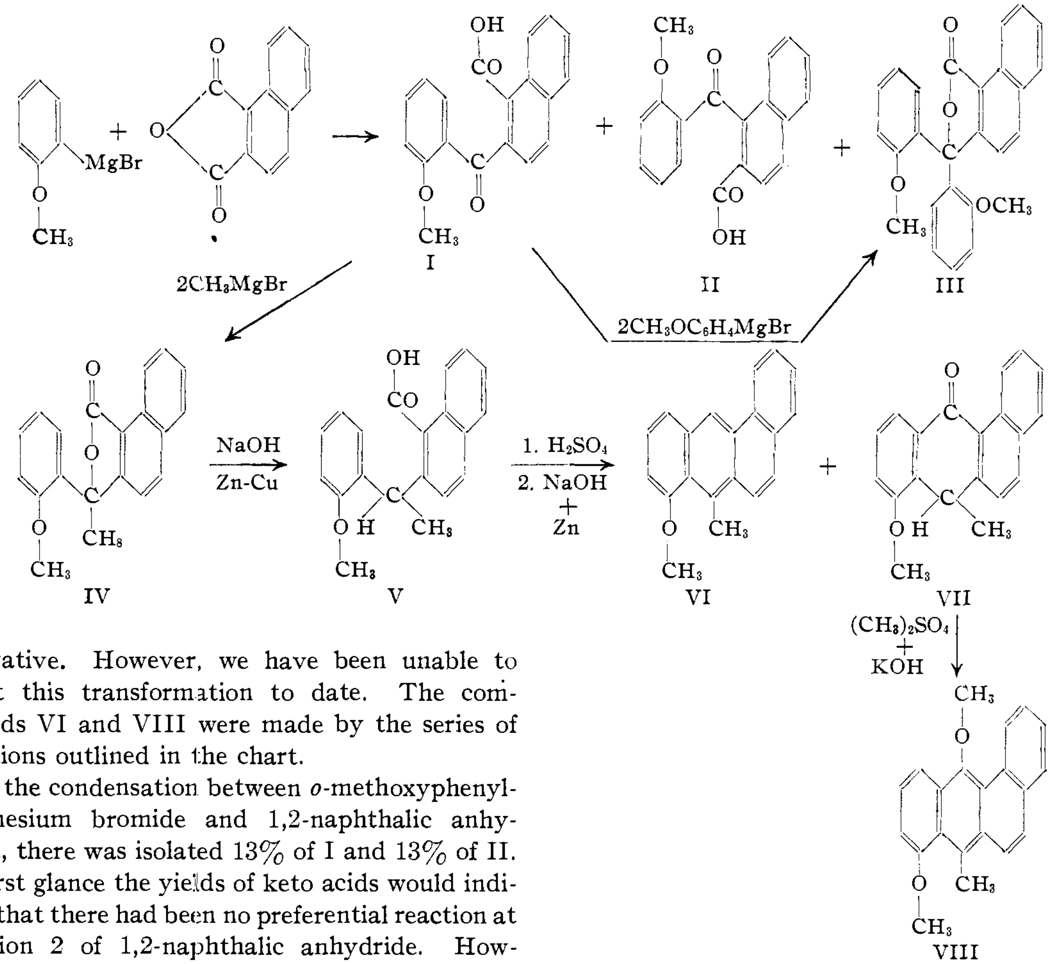
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Synthesis of 5-Methoxy-10-methyl-1,2-benzanthracene and Related Compounds[1]

BY MELVIN S. NEWMAN AND PAUL H. WISE

In continuation of a program[2] designed to study the effect on the carcinogenic action of 10-methyl-1,2-benzanthracene produced by introduction of functional groups at various positions, we have prepared 5-methoxy-10-methyl-1,2-benzanthracene, VI, and 5,9-dimethoxy-10-methyl-1,2-benzanthracene, VIII. Originally, we intended to demethylate VI to 5-hydroxy-10-methyl-1,2-benzanthracene and to proceed from this interesting compound to the corresponding amino derivative. However, we have been unable to effect this transformation to date. The compounds VI and VIII were made by the series of reactions outlined in the chart.



In the condensation between *o*-methoxyphenylmagnesium bromide and 1,2-naphthalic anhydride, there was isolated 13% of I and 13% of II. At first glance the yields of keto acids would indicate that there had been no preferential reaction at position 2 of 1,2-naphthalic anhydride. However, from the neutral fraction of the reaction products there was isolated 17% of III, the structure of which was proved by its synthesis from the reaction of two molecules of *o*-methoxyphenylmagnesium bromide with I. This modified the ratio of products resulting from reaction at position 2 to products resulting from reaction at position 1 to 2.3. This ratio is only approximate for it was exceedingly difficult to separate I and II by crystallization, both acids having about the same melting point. The structures of these two acids were established by decarboxylation to *o*-methoxyphenyl 2-naphthyl ketone and *o*-methoxyphenyl 1-naphthyl ketone, respectively, two new ketones synthesized for comparison by condensation of *o*-methoxyphenylmagnesium

---

(1) Part of the material herein presented was communicated at the Cincinnati meeting of the American Chemical Society, 1940, before the Division of Organic Chemistry. This material is largely contained in the Thesis presented by P. H. W. to The Ohio State University in partial fulfillment of the requirements for the Ph.D. degree, June, 1940.

(2) Previous papers in this series include the following: (a) Newman and Orchin, THIS JOURNAL, **60**, 586 (1938); (b) Newman, *ibid.*, **60**, 1368 (1938); (c) Newman and Orchin, *ibid.*, **61**, 244 (1939).

bromide with the appropriate naphthonitrile.

It is of interest to point out significant differences in behavior of *o*-methoxyphenylmagnesium bromide, *o*-tolylmagnesium bromide,[3] and *o*-chlorophenylmagnesium bromide[2b] on reaction with 1,2-naphthalic anhydride under almost identical conditions. With the *o*-tolyl reagent the above ratio was about 17 and with the *o*-chloro reagent the ratio was high (but not exactly determined). Furthermore, the amount of lactone formation (compounds similar to III) was appreciable only in the case of the *o*-methoxy reagent. Possible explanations of these effects must wait further experimental evidence concerning the effect of steric hindrance on the condensation of Grignard reagents with unsymmetrical anhydrides of the *o*-phthalic type.[4]

Having once isolated I in a pure condition, the remaining steps in the synthesis proceeded in excellent yield to the final product, VI. Many attempts to demethylate VI to the corresponding hydroxy compound failed. These included heating with hydrogen iodide or hydrogen bromide in acetic acid, pyrolysis at 180° with methylmagnesium iodide,[5] boiling in benzene with aluminum chloride,[6] and heating with methyl alcoholic potassium hydroxide at 210 to 230°.[7]

After tests covering ten months, it is reported that VI showed no carcinogenic activity when tested by subcutaneous injection in ten mice.[8] Tests on VIII are now being carried out by Professor E. von Haam at The Ohio State University.

Experimental[9]

Reaction of 1,2-Naphthalic Anhydride with *o*-Methoxyphenylmagnesium Bromide.—To a well-stirred solution of 33.3 g. of 1,2-naphthalic anhydride[10] in 600 cc. of dry benzene at 50° was added all at once 140 cc. of 1.2 *M* *o*-methoxyphenylmagnesium bromide in ether. After refluxing for three hours and stirring overnight at room temperature, the mixture was treated with dilute hydrochloric acid. The crude acid fraction, 31.1 g. (60.5%), was crystallized from 400 cc. of acetic acid to yield 22.2 g. (43%) of crystalline acid, m. p. 166–190°. Similar products from other runs were united and fractionally crystallized from acetone–benzene and from alcohol, separation of crystals by hand being employed wherever practical. In this way both 2-*o*-methoxybenzoyl-1-naphthoic acid, I, and 1-*o* methoxybenzoyl-2-naphthoic acid, II, were isolated in almost pure condition in 13% yields (based on starting anhydride). The analytical sample of I melted at 193.8–194.6° and that of II at 193.0–194.4°. Mixed melting points showed large depressions.

Anal.[a] Calcd. for $C_{19}H_{14}O_4$: C, 74.5; H, 4.6. Found, I: C, 74.6; H, 4.8. Found, II: C, 74.4; H, 4.7.

From the neutral fraction of the above run was isolated 18.8 g. of a mixture of yellow crystals (unchanged anhydride) and white crystals (lactone III). This was easily separated by heating with ammonium hydroxide, the unchanged anhydride being converted thereby into a water soluble compound and the lactone III being unaffected. In this way 11.4 g. (17%) of III melting at 229–232°, was isolated. A sample recrystallized for analysis from dioxane separated as dense colorless prisms, m. p. 232.2–232.5°.

Anal.[a] Calcd. for $C_{26}H_{20}O_4$: C, 78.7; H, 5.1. Found: C, 78.4, 78.4; H, 5.1, 5.2.

Proof of Structure—2-*o*-Methoxybenzoyl-1-naphthoic Acid, I.—As in previous cases,[2a,b,c] the keto acid, 0.50 g., was decarboxylated to yield 0.267 g. (62%) of almost colorless prisms, m. p. 74.5–76.0°, of *o*-methoxyphenyl 2-naphthyl ketone. This ketone proved identical with that prepared in 74% yield by condensation of *o*-methoxyphenylmagnesium bromide with 2-naphthonitrile. A sample recrystallized from alcohol for analysis melted at 74.6–75.6°.

Anal.[b] Calcd. for $C_{18}H_{14}O_2$: C, 82.4; H, 5.4. Found: C, 82.6; H, 5.2.

Proof of Structure—1-*o*-Methoxybenzoyl-2-naphthoic Acid, II.—When 0.50 g. of II was decarboxylated the yield and purity of the product was less than in the case of I. Only 0.090 g. (21%) of pure *o*-methoxyphenyl 1-naphthyl ketone, m. p. 75–76°, was obtained. This did not depress the melting point of the *o*-methoxyphenyl 1-naphthyl ketone prepared in 87% yield by condensation of *o*-methoxyphenylmagnesium bromide with 1-naphthonitrile but did depress the melting point of *o*-methoxyphenyl 2-naphthyl ketone to a large extent. The analytical sample melted at 76.0–76.5°.

Anal.[b] Calcd. for $C_{18}H_{14}O_2$: C, 82.4; H, 5.4. Found: C, 82.1; H, 5.5.

Proof of Structure—Lactone of 2-[*o*-Methoxy-α-hydroxy-α-(*o*-methoxyphenyl)-benzyl]-1-naphthoic Acid, III.—To a solution of 1.186 g. of I in 75 cc. of hot benzene was added 7.5 cc. of 1.0 *M* *o*-methoxyphenylmagnesium bromide solution. A yellow solid complex separated at first but after refluxing for four hours gradually changed to a clear yellow-brown solution. After standing for five hours longer, the reaction mixture was treated with dilute acid, and, from the neutral fraction there was isolated 1.168 g. (76%) of III, m. p. 230.6–232.2°. After recrystallization, a sample did not depress the melting point of pure III obtained from the reaction of *o*-methoxyphenylmagnesium bromide with 1,2-naphthalic anhydride.

---

[3] Fieser and Newman, THIS JOURNAL, **58**, 2376 (1936).

[4] See, for example, Newman and McCleary, *ibid.*, **63**, 1542 (1941).

[5] Smith, Ungnade and Irwin, *ibid.*, **62**, 142 (1940).

[6] Cason and Fieser, *ibid.*, **63**, 1256 (1941).

[7] Dodds, Goldberg, Lawson and Robinson, *Nature*, **141**, 247 (1938).

[8] Private communication from L. F. Fieser.

[9] All melting points corrected. All benzene used was thiophene-free and dry. Analyses marked (a) M. Renoll, Ohio State University; (b) J. H. Walker, Ohio State University, W.P.A. Project No. 65-1-42-89; (c) D. Mowry, Ohio State University; (d) B. Lord, Ohio State University.

[10] Hershberg and Fieser, "Organic Syntheses," Vol. XVIII, 1938, p. 59.

Lactone of 2-(*o*-Methoxy-α-hydroxy-α-methylbenzyl)-1-naphthoic Acid, IV.—In a typical run, 17.5 cc. of 1.96 *M* methylmagnesium bromide was added to a suspension of 5.0 g. of I in 300 cc. of benzene and 50 cc. of ether. After refluxing for four hours, the mixture was treated with dilute acid and the products separated into acidic and neutral fractions. There was recovered from the acid fraction 0.92 g. (18%) of I and from the neutral fraction 3.90 g. (78% or 96% if based on acid used) of dense colorless prisms, m. p. 128.5–129.5°, of IV. A sample for analysis, recrystallized from alcohol, melted at 129.6–130.6°.

Anal.[b] Calcd. for $C_{20}H_{16}O_3$: C, 78.9; H, 5.3. Found: C, 79.2, 79.1; H, 5.3, 5.0.

2-(*o*-Methoxy-α-methylbenzyl)-1-naphthoic Acid, V.—A solution containing 3.1 g. of IV, 4.4 g. of sodium hydroxide, and 4 cc. of water in 40 cc. of alcohol was refluxed for eight hours during the last fifteen minutes of which 20 cc. of alcohol was distilled. The remainder was diluted with 20 cc. of hot water and poured into a flask containing 5.0 g. of zinc dust (activated with copper sulfate) and 15 cc. of 55% sodium hydroxide solution. After refluxing for one day, the solution was decanted from the zinc, acidified, and the organic products taken up in ether. On extraction with sodium carbonate, acidification, and crystallization from benzene, 2.82 g. (90%) of the acid, V, was obtained as colorless prisms, m. p. 187–188°. The analytical sample melted at 188.8–189.6°.

Anal.[b] Calcd. for $C_{20}H_{18}O_3$: C, 78.4; H, 5.9. Found: C, 78.4; H, 5.7.

5-Methoxy-10-methyl-1,2-benzanthracene, VI.—In the best of several experiments, in which the concentration of sulfuric acid used was approximately 85, 90 and 95%, 2.12 g. of V was powdered and dissolved in 22 cc. of 90% sulfuric acid. After one-half hour at room temperature, the clear red solution was poured onto ice. The pale yellow anthrone was collected immediately on an iced funnel and reduced by refluxing for twenty hours with a mixture of 10 g. of sodium hydroxide, 130 cc. of water, and 3 g. of zinc dust activated with copper sulfate. After dilution to 200 cc. with water, the solid was collected, dried, and extracted with hot acetone. The filtered acetone solution was concentrated and the acetone replaced with alcohol. Further concentration and cooling yielded 1.30 g. of a mixture of crystalline compounds. This was treated in benzene–alcohol (1:4) with a 10% excess of *s*-trinitrobenzene. The deep red crystalline derivative was fractionally recrystallized from the same solvent mixture to yield 1.30 g. of pure *s-trinitrobenzenate* of VI as red needles, m. p. 204.6–205.2°. This represents a 40% yield calculated from V.

Anal.[b] Calcd. for $C_{26}H_{19}O_7N_3$: C, 64.3; H, 4.0; N, 8.7. Found: C, 64.5; H, 3.7; N, 8.8.

Pure VI was obtained from the above by chromatographic adsorption using activated alumina. It crystallized from benzene–petroleum ether as pale yellow needles, m. p. 131.0–132.2°, which showed a brilliant blue-violet fluorescence in ultraviolet light. When crystallized from alcohol the material invariably separated as a mixture of plates and needles having a green fluorescence in ultraviolet light.

Anal.[b] Calcd. for $C_{20}H_{16}O$: C, 88.2; H, 5.9. Found: C, 88.4; H, 5.8.

The picrate crystallized from benzene–alcohol as deep purple-black needles, m. p. 187.0–188.4°.

Anal.[b] Calcd. for $C_{26}H_{19}O_8N_3$: C, 62.3; H, 3.8; N, 8.4. Found: C, 62.2; H, 3.7; N, 8.2.

5-Methoxy-10-methyl-1,2-benz-9-anthrone, VII.—Frequently the crude reaction product resulting from the cyclization and reduction of V above described was contaminated with clusters of pale yellow prisms. These were separated mechanically and after two recrystallizations from alcohol melted at 158.0–159.0° and did not fluoresce in ultraviolet light.

Anal.[b] Calcd. for $C_{20}H_{16}O_2$: C, 83.3; H, 5.6. Found: C, 83.6, 83.7; H, 5.6, 5.7.

5,9-Dimethoxy-10-methyl-1,2-benzanthracene, VIII.—This compound was obtained in best yield by treating the crude anthrone, VII, resulting from cyclization of 1.50 g. of V with dimethyl sulfate and potassium hydroxide in alcoholic solution. The crude product, VIII, after purification by conversion to the picrate, recrystallization, and chromatographic adsorption on activated alumina, yielded 0.27 g. (18%) of pure pale yellow plates of VIII, m. p. 136.2–137.2°, having a brilliant blue-violet fluorescence in ultraviolet light.

Anal.[c] Calcd. for $C_{21}H_{18}O_2$: C, 83.4; H, 6.0. Found: C, 83.2, 83.3; H, 6.0, 5.8.

The picrate separated as brown needles, m. p. 128.8–130.0°, from benzene–alcohol.

Anal.[c] Calcd. for $C_{27}H_{21}O_9N_3$: C, 61.0; H, 4.0. Found: C, 61.1, 61.3; H, 4.0, 4.0.

The *s*-**trinitrobenzene derivative** formed deep red needles, m. p. 146.2–146.8°, from benzene–alcohol.

Anal.[d] Calcd. for $C_{27}H_{21}O_8N_3$: N, 8.2. Found: N, 7.9, 7.9.

Summary

o-Methoxyphenylmagnesium bromide is shown to react preferentially at the 2 position of 1,2-naphthalic anhydride. By reaction with methylmagnesium bromide, followed by reduction, cyclization, and further reduction, 2-*o*-methoxybenzoyl-1-naphthoic acid is converted into 5-methoxy-10-methyl-1,2-benzanthracene.

COLUMBUS, OHIO RECEIVED JUNE 5, 1941