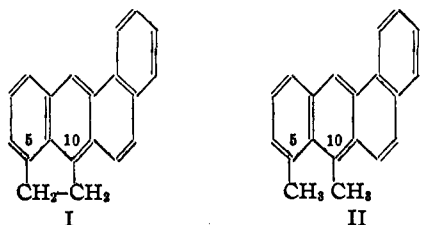


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of 1,2-Benzanthracene Derivatives Related to Cholanthrene

BY LOUIS F. FIESER AND MELVIN S. NEWMAN¹

Of the various hydrocarbons known to possess cancer-producing properties, the most potent are methylcholanthrene and cholanthrene (I).² In the regularity and rapidity with which they produce tumors in experimental mice these substances so far outshadow all of the many other derivatives of 1,2-benzanthracene thus far investigated (largely by Cook and co-workers³) that it is a matter of considerable interest to attempt to define the features of structure responsible for their striking activity. Clearly the methyl group present in methylcholanthrene in the 6-position of the 1,2-benzanthracene nucleus is relatively unimportant, for cholanthrene is as active, or very nearly as active, as methylcholanthrene.² Of other carcinogenic derivatives of the itself inactive 1,2-benzanthracene the 5-methyl compound is weakly active, the 5,6-dimethyl and 5,6-trimethylene derivatives are slightly more so, and the 8,9-dimethylene compound shows some activity,³ but none of these hydrocarbons is comparable with cholanthrene (I) in potency. It should be possible to determine whether the special activity of



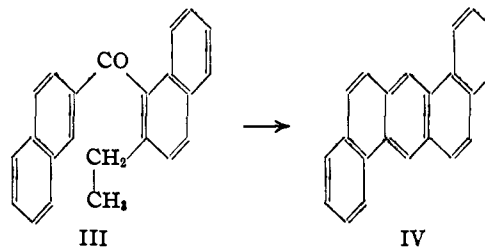
cholanthrene is associated with the presence of the five-membered ring including carbon atoms 5 and 10, or merely with the presence of alkyl substituents at these positions, by investigating the biological actions of 5,10-dimethyl-1,2-benzanthracene, II. With this end in view we undertook the synthesis of the latter hydrocarbon and of the likewise interesting 10-methyl-1,2-benzanthracene.

Considering the success of the modified Elbs reaction developed by one of us with Seligman^{3b} for the preparation of cholanthrenes, it seemed possible that 10-methyl anthracenes or benzanthra-

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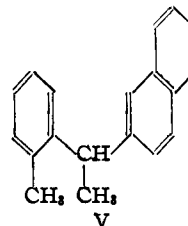
(2) For reviews and references, see (a) Cook, *Ber.*, **69A**, 38 (1936); (b) Fieser, "The Chemistry of Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, 1936, pp. 81-110.(3) Shear, *J. Biol. Chem.*, **114**, lxxxix (1936).

cenes might be obtainable by the pyrolysis of suitable *o*-ethyl diaryl ketones, for example 2-ethyl-3-methylphenyl- α -naphthyl ketone. As a preliminary trial of the reaction in a simple case, the ketone (III) from α -naphthoyl chloride and



β -ethylnaphthalene was submitted to pyrolysis, but the resulting hydrocarbon, obtained in a yield quite good for such reactions, proved to be identical with 1,2,5,6-dibenzanthracene (IV), indicating the loss of a methyl group from the 10-position. Similarly the ketone from 2,5-dimethylbenzoyl chloride and β -ethylnaphthalene gave in small amounts an unidentified hydrocarbon having the composition of a monomethyl rather than a trimethyl 1,2-benzanthracene. This type of reaction was therefore abandoned, although from more recent work in this Laboratory (A. M. Seligman) it appears that in some cases the condensation proceeds without degradation of an *n*-alkyl group.

As another possible approach we investigated a method used by Cook and Haslewood⁴ for the synthesis of cholanthrene. α -(*o*-Tolyl)- α -(2-naphthyl)-ethane, V, was prepared by the addition



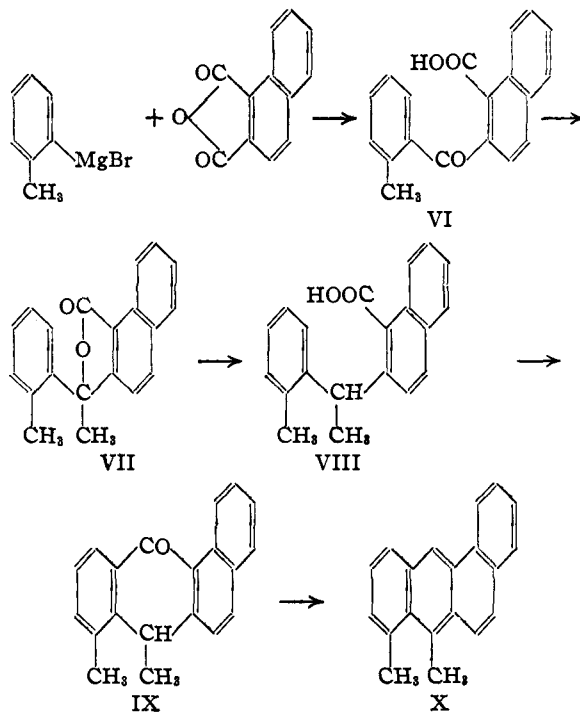
of *o*-tolylmagnesium bromide to methyl β -naphthyl ketone, dehydration of the resulting carbinol, and hydrogenation of the olefin. Attempts were made to introduce a carboxyl group in the 1-position of the naphthalene nucleus by the bromination of the hydrocarbon and carbona-

(4) Cook and Haslewood, *J. Chem. Soc.*, 770 (1935).

tion of the Grignard reagent, and by the hypochlorite oxidation of the (crude) acetyl derivative obtained by the Friedel and Crafts reaction, but a crystalline acid was not isolated. On submitting the acid mixture obtained by the first procedure to cyclization and reduction, there was isolated in very small amount through the picrate a hydrocarbon having the expected composition of a dimethylbenzanthracene, but the substance did not have the properties of a pure individual.

Following these unpromising results a successful synthesis was developed starting with 1,2-naphthalic anhydride (naphthalene-1,2-dicarboxylic anhydride), a compound easily prepared synthetically in any desired quantity.⁵ On reaction with one mole of *o*-tolylmagnesium bromide this gave a mixture from which the desired keto acid VI was easily isolated in 40% yield. Reaction at the more hindered carbonyl group took place to a less extent, only about 3% of the isomeric 2-*o*-tolyl-1-naphthoic acid being isolated. The structures of the acids were established by decarboxylation to the known *o*-tolyl α - and β -naphthyl ketones.⁶ 1,2-Naphthalic anhydride thus behaves in the Grignard reaction⁷ much as it does in the Friedel and Crafts condensation with hydrocarbons.⁸ On condensing the anhydride with cumene, Cook⁹ isolated the keto acids resulting from condensation at the β - and α -carbonyl groups, respectively, in 23 and 10% yields.

The addition of the methyl Grignard reagent to the ketonic group of 2-*o*-tolyl-1-naphthoic acid (VI) was at first accomplished by using the ester, but about 20% of the keto acid usually was recovered unchanged and no more than 50% of the material utilized was converted into the desired reaction product, 2-(α -hydroxy-*o*, α -dimethylbenzyl)-1-naphthoic acid lactone (VII). The yield was considerably improved by treating the keto acid (VI) itself with two moles of methylmagnesium iodide, and when methylmagnesium bromide was employed no appreciable amount of acid was recovered and the yield of good product rose to 86%. The lactone VII exists in two apparently polymorphic modifications. Attempts



to prepare 2-(*o*, α -dimethylbenzyl)-1-naphthoic acid (VIII) by the reduction of the lactone with zinc dust and alkali were unpromising, but as Martin¹⁰ has shown recently that γ -phenylbutyrolactone can be reduced to γ -phenylbutyric acid with amalgamated zinc and hydrochloric acid, this method was tried. The desired acid was obtained in this way in excellent yield (76%) and purity and the reaction proceeded particularly smoothly in acetic acid solution. The acid VIII was cyclized with concentrated sulfuric acid at room temperature to an anthrone (IX) which was not isolated in a pure condition but reduced with zinc dust and alkali to the desired 5,10-dimethyl-1,2-benzanthracene (X). The hydrocarbon was obtained in good yield and was easily purified.

10-Methyl-1,2-benzanthracene was prepared by using phenylmagnesium bromide in the first step of the synthesis and proceeding as above. The free 2-benzoyl-1-naphthoic acid gave a good yield in the Grignard reaction and the normal ester, prepared with the use of diazomethane, gave a moderately satisfactory result. It was observed that the substance obtained by esterifying the acid with alcohol-hydrogen chloride and described in the literature³ as methyl 2-benzoyl-1-naphthoate does not react with methylmagnesium iodide, except possibly to undergo hydrolysis.

(5) Fieser and Hershberg, *THIS JOURNAL*, **57**, 1851 (1935).

(6) Fieser and Martin, *ibid.*, **58**, 1443 (1936).

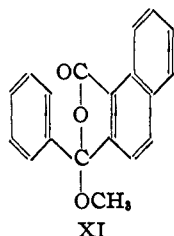
(7) The preparation of *o*-aroyl carboxylic acids by the addition of Grignard reagents to symmetrical aromatic anhydrides has been investigated recently by Weizmann, E. Bergmann and F. Bergmann, *J. Chem. Soc.*, 1367 (1935); see also Weizmann and E. Bergmann, *ibid.*, 567 (1936).

(8) Waldmann, *J. prakt. Chem.*, **127**, 195 (1930); **131**, 71 (1931).

(9) Cook, *J. Chem. Soc.*, 456 (1932).

(10) Martin, *THIS JOURNAL*, **58**, 1438 (1936).

The substance is thus regarded as the lactol ether XI. The formation of such a compound in the Fischer esterification reaction is in striking contrast to the behavior of *o*-benzoylbenzoic acid.¹¹



In the hope of introducing a long aliphatic chain in the 10-position, the keto acid VI or its methyl ester was treated with octadecylmagnesium bromide, but the only product isolated proved to be the lactone of the hydroxy acid resulting from the reduction of the carbonyl group of VI to a carbinol group by the reagent. This was reduced further with zinc and acid to 2-*o*-tolylmethyl-1-naphthoic acid, and the identical substance was obtained by the action of the same reagents on the keto acid VI. This acid was put through the remaining steps of the synthesis and afforded the known 5-methyl-1,2-benzanthracene.¹² A reducing action also was noticed in a preliminary study of the reaction of ethylmagnesium bromide with 2-*o*-tolyl-1-naphthoic acid (VI), but in this case some addition also occurred.

While the reducing action of at least certain alkyl Grignard reagents imposes some limits on the synthetic method, it may be possible to avoid this difficulty by reversing the order of the two Grignard reactions. We hope to investigate this possibility and to explore other applications of the synthesis.

The new hydrocarbons are being tested for carcinogenic activity by Dr. M. J. Shear, and although the experiments have been in progress only for a comparatively short time the preliminary results are of considerable interest. 5,10-Dimethyl-1,2-benzanthracene was injected subcutaneously into mice, using approximately 10 mg. of the crystalline material per animal. Severe ulceration at the site of injection was noted in all of the mice after the first month. After three and one-half months tumors had been produced in seven of fifteen mice, the first two tumors making their appearance at the end of two and one-half months. From these results it ap-

pears that the new hydrocarbon is at least roughly comparable in carcinogenic activity with the most potent of the compounds previously investigated, namely, methylcholanthrene, cholanthrene and 3,4-benzpyrene,¹³ and that it is considerably more powerful in its action than any of the known monomethyl or dimethyl derivatives of 1,2-benzanthracene.² 5-Methyl-1,2-benzanthracene, injected subcutaneously into twenty mice in 5-mg. dosages, produced no noticeable effect in thirty-seven days, while 10-methyl-1,2-benzanthracene in the same dosage produced either ulceration, thickening of the tissue, or both, in thirteen of twenty mice during the same period.

From the present indications, it appears that the five-membered ring characteristic of the cholanthrene system is of importance in contributing to the carcinogenic potency of hydrocarbons of this type only in that it includes carbon substituents at the 5- and 10-positions. The presence of the intact ring is by no means essential, for simple alkyl groups at these positions produce nearly the same effect. Substitution at the meso position 10 seems to be particularly important, and it is interesting to note that 3,4-benzpyrene may be regarded as a 1,2-benzanthracene derivative with a carbon substituent at one of the meso positions (9). Heretofore the hypothesis that cancer-producing hydrocarbons may be formed in the organism by the abnormal metabolism of cholesterol or of bile acids has found support in the demonstration that two different bile acids can be transformed by chemical means into methylcholanthrene,² and in the striking circumstance that this outstandingly potent hydrocarbon carries as a mark of its possible origin the cyclopenteno ring characteristic of the sterols. While the possibility of the biological formation of methylcholanthrene remains undisputed, if, to be sure, quite unestablished, the observation that comparable activity is exhibited by a simpler hydrocarbon lacking both the C₂₀-methyl group and the cyclopenteno ring characteristic of the sterols, and of a type not likely to arise in the process of metabolism, weakens somewhat the circumstantial evidence favoring acceptance of the hypothesis.

(13) In previous publications from this Laboratory the carcinogenic hydrocarbon isolated from coal tar by J. W. Cook, C. L. Hewett and I. Hieger has been referred to as "1,2-benzpyrene," in accordance with the system of numbering originally employed by the discoverers of the substance. Following a plea for unanimity from the editor of "Beilstein," and in agreement with Dr. J. W. Cook, we will employ hereafter the numbering system for pyrene favored in Germany and used in *Chemical Abstracts*, according to which the carcinogenic hydrocarbon becomes 3,4-benzpyrene.

(11) H. Meyer, *Monatsh.*, **25**, 475 (1904); **28**, 1231 (1907).

(12) Cook, *J. Chem. Soc.*, 1592 (1933).

Experimental Part¹⁴

Pyrolysis of 1-(2-Naphthoyl)-2-ethylnaphthalene (III).— β -Ethylnaphthalene, b. p. 122–125° (14 mm.), picrate, yellow needles, m. p. 76.5–77° from alcohol, was prepared in 52% yield by the Clemmensen–Martin procedure¹⁰ and condensed with β -naphthoyl chloride with aluminum chloride in carbon bisulfide solution. The crude ketone, b. p. 235–240° (2–2.5 mm.), resulted in 91% yield but did not crystallize, and on pyrolysis at 425–430° for one and one-half hours 6 g. of the material gave 1.3 g. (23%) of a hydrocarbon melting at 261–262° and identified by analysis and mixed melting point determinations as 1,2,5,6-dibenzanthracene.

Pyrolysis of 1-(2,5-Dimethylbenzoyl)-2-ethylnaphthalene.—2,5-Dimethylacetophenone was prepared more satisfactorily than previously reported¹⁵ by adding 45 g. of aluminum chloride during one and one-half hours to a stirred solution at 0° of 31 g. of *p*-xylene and 25 g. of acetyl chloride in 450 cc. of carbon bisulfide. After three hours at 0° with stirring, twelve hours at 0–5°, and one to two hours at 25°, the light yellow complex was collected with suction, washed with carbon bisulfide, and decomposed with dilute hydrochloric acid. A small additional amount of the ketone was recovered from the filtrate and the combined product distilled at 106.2° (14 mm.), yield 40.8 g. (95%). The ketone was converted to 2,5-dimethylbenzoic acid, m. p. 132–133°, with potassium hypochlorite from the commercial calcium salt in 93% yield by the general procedure reported.¹⁶ The acid chloride (b. p. 101.5° at 11–12 mm.), prepared with thionyl chloride, was condensed with β -ethylnaphthalene as above and the ketone, b. p. 188–192° (2 mm.), yield 84%, was pyrolyzed at 450–455° for fifteen minutes. From 5.9 g. of the ketone 1.3 g. of hydrocarbon, m. p. 124–126°, was obtained after two crystallizations from alcohol. This yielded a picrate which after two crystallizations from benzene–ligroin formed red needles, m. p. 155–156°, and had the composition of a methylbenzanthracene picrate.

Anal. Calcd. for C₁₉H₁₄C₈H₇O₇N₄: C, 63.68; H, 3.64. Found: C, 63.93, 63.86; H, 3.80, 3.60.

Attempted Synthesis from α -(*o*-Tolyl)- α -(2-naphthyl)ethane, V.—The Grignard reagent from 94 g. of *o*-bromotoluene, 13.4 g. of magnesium, and 500 cc. of ether was added to 85 g. of methyl β -naphthyl ketone in 225 cc. of benzene during one and one-half hours and after distilling the ether the benzene solution was refluxed for one hour. After hydrolysis with dilute hydrochloric acid the carbinol was heated at 200–250° to effect dehydration and the resulting α -(*o*-tolyl)- α -(2-naphthyl)ethene was distilled at 2 mm., giving 83 g. (68%) of a colorless oil which immediately crystallized. Recrystallization from alcohol gave colorless prisms, m. p. 66–66.5°.

Anal. Calcd. for C₁₉H₁₆: C, 93.40; H, 6.60. Found: C, 93.51; H, 6.57.

Hydrogenation of the olefin proceeded smoothly in gla-

cial acetic acid solution with Adams catalyst and the resulting liquid hydrocarbon boiled at 177–179° (1.5–2 mm.), yield 86%. In attempted Friedel and Crafts condensations of the hydrocarbon with acetyl chloride under various conditions, naphthalene was always obtained as a fore-run, there was much resinous material, and the portion boiling in the range 160–200° (1.5–2 mm.) yielded no appreciable amount of acid on hypochlorite oxidation in aqueous medium or in pyridine,¹⁷ or by other methods.¹⁸ Chloroacetylation was also unsuccessful.

In other experiments the hydrocarbon V was brominated according to Cook and Haslewood⁴ and the product was treated with pyridine, converted into the Grignard reagent, and this was carbonated and submitted to hydrogenation, as described by these authors. The acidic material obtained did not crystallize, even when seeded later with the pure acid VI. After several preliminary tests, cyclization was effected by warming the crude acid mixture for one-half hour with 90% sulfuric acid at 40°. The solid material which precipitated on treatment with ice was boiled with zinc dust and alkali for ten hours with added toluene. The resulting product yielded a picrate which after repeated crystallization formed apparently homogeneous, red needles, m. p. 152–153°, but the hydrocarbon recovered from it, although it formed excellent pale yellow needles from alcohol, melted over the range 149–168°.

Anal. Calcd. for C₂₀H₁₆: C, 93.70; H, 6.30. Found: C, 93.56; H, 6.53. Picrate, calcd.: C, 64.32; H, 3.95; N, 8.66. Found: C, 64.56; H, 4.08; N, 8.53.

The product does not correspond at all with the pure 5,10-dimethyl-1,2-benzanthracene described below and as the yield was very poor the substance was not investigated further.

Synthesis of 5,10-Dimethyl-1,2-benzanthracene

Reaction of 1,2-Naphthalic Anhydride with *o*-Tolylmagnesium Bromide.—The 3,4-dihydronaphthalene-1,2-dicarboxylic anhydride was prepared with the use of sodium ethylate as described by Fieser and Hershberg⁵ and with the same yield (81%) when employing as much as 254 g. of ethyl γ -phenylbutyrate. With large quantities it was found convenient to powder the sodium under xylene by simply agitating the mixture with a Hershberg wire stirrer.¹⁹ The dehydrogenation was conducted as described,⁵ using 213.5 g. of material. The product twice distilled and once crystallized from benzene was sulfur-free and suitable for the Grignard reaction; yield 163.5 g. (77.5%). The mother liquor afforded 11.5 g. of anhydride of the same melting point but giving a slight test for sulfur.

After a number of trials and variations the following procedure for the addition reaction was adopted as the most satisfactory. The Grignard reagent prepared from 19 g. of *o*-bromotoluene, 3.5 g. of magnesium, and 100 cc. of ether was filtered through a plug of glass wool under nitrogen pressure and forced *all at once* under pressure of the gas into a well-stirred (Hershberg stirrer) solution of 20 g. of sulfur-free 1,2-naphthalic anhydride in 400 cc. of warm thiophene-free benzene. A yellow complex

(17) Fuson, Lewis and DuPuis, *ibid.*, **54**, 1114 (1932).

(18) Babcock, Nakamura and Fuson, *ibid.*, **54**, 4407 (1932); Kröhnke, *Ber.*, **66**, 604 (1933).

(19) Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 313 (1936).

(14) All melting points are corrected unless otherwise noted, using the precision apparatus of Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 312 (1936). Analyses by Mrs. G. M. Wellwood.

(15) Claus and Wollner, *Ber.*, **18**, 1856 (1885); Freund, Fleischer and Gofferje, *Ann.*, **414**, 1 (1916).

(16) Fieser, Holmes and Newman, *This Journal*, **58**, 1055 (1936).

separated immediately. The mixture was heated with stirring, the ether was allowed to distil, and the benzene was then kept refluxing for two hours. After cooling and treating with dilute hydrochloric acid, the benzene layer was diluted with 200 cc. of ether and extracted thoroughly with potassium carbonate solution. The residual ether-benzene solution contained no easily recovered products (some anhydride was obtained in early runs with less efficient stirring). The combined carbonate extracts were acidified and the keto acid mixture was taken into ether and the solution was washed with saturated sodium chloride solution and evaporated. A solution of the residue in 150 cc. of hot benzene was treated with 20–30 cc. of warm hexane to produce a saturated solution, and the crystalline material (m. p. 130–145°) which separated on standing overnight was taken up in 50 cc. of glacial acetic acid. After standing for twelve to sixteen hours (no longer) the dense, diamond-shaped prisms of 2-*o*-toluyl-1-naphthoic acid (VI) which separated were collected; yield 11–12.5 g. (38–43%), m. p. 147–149°. This material was used for the next step. A sample for analysis was crystallized to constant melting point from glacial acetic acid, m. p. 149.5–150.5°.

1-*o*-Toluyl-2-naphthoic acid, m. p. 210–211°, was obtained from the first acetic acid mother liquor and purified by repeated recrystallization from the solvent. It forms heavy diamond-shaped prisms resembling those of VI; yield about 1 g. (3%).

Anal. Calcd. for $C_{19}H_{14}O_2$: C, 78.60; H, 4.86. Found (VI): C, 78.69; H, 5.05. (Isomer): C, 78.17, 78.31; H, 4.83, 5.29.

Methyl 2-*o*-Toluyl-1-naphthoate was obtained in 97% yield as a very viscous, pale yellow oil, b. p. 215–216° (2.5 mm.), by refluxing the acid with methyl alcohol-hydrogen chloride for five hours. An ester similar in appearance and in its behavior in the Grignard reaction was obtained using diazomethane.

Decarboxylation of the Acids.—The reaction proceeded well on a small scale (0.5 g.) using as catalyst a small amount of the blue copper salt of the appropriate acid and heating a mixture of the salt and free acid in a bath at 230–245°. After about ten minutes the product of decarboxylation was distilled at 9 mm. pressure and taken into hexane. The ketones crystallized slowly but well. The acid VI afforded a product identical with Martin's¹⁰ *o*-toluyl- β -naphthyl ketone, m. p. and mixed m. p. 67–68°, while 1-*o*-toluyl-2-naphthoic acid gave *o*-tolyl α -naphthyl ketone, m. p. and mixed m. p. 51.5–52.5°.

Lactone of 2-(α -Hydroxy-*o*, α -dimethylbenzyl)-1-naphthoic Acid, VII.—The condensation of methyl 2-*o*-toluyl-1-naphthoate with slightly more than one equivalent of methylmagnesium iodide, filtered through a plug of glass wool under nitrogen and added inversely, was tried in ether, ether-benzene and ether-xylene at temperatures from 25 to 100° for two to three hours with nearly the same results. After decomposing the reaction mixture with dilute hydrochloric acid the organic layer was washed with water and extracted with potassium carbonate solution. The carbonate extract yielded 15–18% of the original keto acid resulting from the hydrolysis of the ester, and the ether or ether-benzene solution on drying and removing the solvent gave the lactone, which was crystallized from

benzene-alcohol or benzene-hexane. The lactone apparently is formed directly in the course of the reaction or during the hydrolysis of the magnesium derivative; hydrolysis of the keto ester also occurs prior to the working up of the reaction mixture. The yields were from 40 to 51%, based on the acid consumed. Methyl zinc chloride gave none of the desired reaction product.

When the free keto acid was used and treated in benzene-ether solution with two equivalents of methylmagnesium iodide, distilling the ether and refluxing four or five hours, 10–40% of the acid was recovered unchanged and the yield of lactone, allowing for the recovery, rose to 70–80%. The most satisfactory results were obtained using methylmagnesium bromide and employing a considerable excess of the reagent (using the ester, an excess of Grignard reagent caused a decrease in the yield). For the preparation of the reagent 0.032 mole of magnesium was covered with ether and methyl bromide was introduced slowly by distillation until the magnesium was very nearly all dissolved. The solution was filtered under nitrogen pressure and added gradually to a benzene-ether solution of 0.01 mole of 2-*o*-toluyl-1-naphthoic acid. A white precipitate of the $MgBr$ -salt separated and changed to a greenish-yellow and then a bright yellow complex. After stirring for three and one-half hours at room temperature, the mixture was refluxed for one-half hour and treated with dilute acid. The potassium carbonate extract contained no appreciable quantity of keto acid, and the lactone was obtained in a good condition in 86% yield.

The lactone dissolves readily in benzene and crystallizes well after the addition of either alcohol or hexane. At first the substance was obtained in a low-melting form which separated as large, flat, elongated, transparent prisms, or as small needles, m. p. 103–104°. In later experiments a second modification appeared more frequently, either alone or together with the low-melting form. This separated as long, square, transparent prismatic rods, m. p. 119–120°. When a solution of the pure low-melting form was seeded with the other material either the high-melting form crystallized directly or a mixture melting between 110 and 117° resulted and gave the pure high-melting form only on further crystallization. On one occasion the low-melting form was obtained as clusters of needles on seeding a solution of the high-melting modification, but usually it was difficult to obtain any but the high-melting form once it had been isolated.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.30; H, 5.60. Found (m. p. 103–104°): C, 83.25; H, 5.62; (m. p. 119–120°): C, 83.43; H, 5.90.

2-(*o*, α -Dimethylbenzyl)-1-naphthoic Acid, VIII.—Using Martin's modification¹⁰ of the Clemmensen method, 0.9 g. of the lactone VII was refluxed with a mixture of 40 g. of amalgamated zinc, 20 cc. of water, 40 cc. of toluene, 10 cc. of glacial acetic acid, and 40 cc. of concentrated hydrochloric acid for twenty-one hours, adding two 30-cc. portions of concentrated acid. The organic material was collected in toluene-ether and the reduction product obtained by extraction with potassium carbonate solution. Unchanged lactone was recovered in a good condition from the toluene-ether. The results were variable, for in one case the pure reduction product was obtained in 80% yield and no lactone was recovered, while more usually 20–26% of

starting material was recovered and the yield, allowing for this, was 40–76%. It seems better to use a homogeneous solution. Using 1.5 g. of lactone, 50 g. of amalgamated zinc, 50 cc. of glacial acetic acid and 25 cc. of concentrated hydrochloric acid, and refluxing for eleven hours with the dropwise addition of 150 cc. more acid during this period, the nearly pure reduction product, isolated as above and crystallized from benzene–hexane, amounted to 1.15 g. (76%).

A sample of the acid recrystallized for analysis from benzene–hexane formed clusters of transparent prisms, m. p. 183.5–184°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.72; H, 6.25. Found: C, 82.71; H, 6.30.

5,10-Dimethyl-1,2-benzanthracene.—To 10 cc. of concentrated sulfuric acid at 20° 0.8 g. of powdered 2-(*o*, α -dimethylbenzyl)-1-naphthoic acid was added with swirling, and after five minutes the material had all dissolved to an orange solution. After two hours this was poured onto 100 g. of crushed ice, and after standing for two hours at 0° the precipitated, light yellow anthrone was collected and washed with water. As the substance is very sensitive and alterable, the moist anthrone was at once transferred to a flask and a mixture of the substance with 2 g. of zinc dust, 10 g. of sodium hydroxide, and 100 cc. of water was refluxed vigorously for six hours. The yellow, at first oily, material gradually disappeared and gave way to light-colored crystals of the hydrocarbon. The mixture was treated with excess hydrochloric acid to dissolve most of the zinc, and the crude product was collected, dried and crystallized from benzene–alcohol. The yield of colorless material melting at 146–147°, uncorr., was 0.45 g. (64%).

The hydrocarbon forms a picrate which separates from benzene as deep reddish-black flat needles, m. p. 173.7–174.2°. The hydrocarbon regenerated from the purified picrate crystallized from benzene–alcohol or benzene–hexane as colorless plates, m. p. 147–147.5°, having an intense blue fluorescence in ultraviolet light.

Anal. Calcd. for $C_{20}H_{18}$: C, 93.70; H, 6.30. Found: C, 93.72; H, 6.64. Picrate, calcd. for $C_{20}H_{18} \cdot C_6H_5O_7N_3$: C, 64.32; H, 3.95; N, 8.66. Found: C, 64.13; H, 3.74; N, 8.82.

Synthesis of 10-Methyl-1,2-benzanthracene

Reaction of 1,2-Naphthalic Anhydride with Phenylmagnesium Bromide.—The Grignard reaction was carried out as above and the chief reaction product, 2-benzoyl-1-naphthoic acid, was isolated in 80% yield. The pure substance melted at 141.8–142.8° (Waldmann⁸ and v. Braun²⁰ report the value 139–140°, uncorr.), and gave β -benzoylnaphthalene, m. p. 82–83°, on decarboxylation. The isomeric 1-benzoyl-2-naphthoic acid, m. p. 223.5–224.5° (Waldmann,⁸ 219–220°, uncorr.), seemed to be present to a greater extent than in the case noted above.

Waldmann⁸ obtained these two acids by the Friedel and Crafts condensation of 1,2-naphthalic anhydride with benzene, and he reports that the esterification of 2-benzoyl-1-naphthoic acid with methyl alcohol and hydrogen chloride gave an ester, m. p. 153–154°, uncorr. We prepared the substance by this method (m. p. 156–156.5°) and found that after being refluxed for four hours in ben-

zene–ether with one equivalent of methylmagnesium iodide, no addition occurred and after saponification nearly all of the material was recovered as 2-benzoyl-1-naphthoic acid. The compound therefore is regarded as the lactol ether XI. The true methyl 2-benzoyl-1-naphthoate, prepared using diazomethane, was found to react normally with the Grignard reagent. The substance forms slender colorless needles from methyl alcohol, or better from hexane, m. p. 72.5–73.5°.

Anal. Calcd. for $C_{19}H_{14}O_2$: C, 78.60; H, 4.86. Found: C, 78.38; H, 5.16.

Lactone of 2-(α -Hydroxy- α -methylbenzyl)-1-naphthoic Acid.—The reaction of the normal ester with one equivalent of methylmagnesium iodide was conducted as above. No acid was recovered and the yield of purified lactone was 56%. On treating the free acid in benzene–ether with three equivalents of methyl bromide and refluxing for three and one-half hours, no appreciable amount of acid was recovered and the lactone was obtained in a very satisfactory condition in 89% yield. Once recrystallized from benzene–alcohol, the substance formed colorless prisms, m. p. 173.8–174.2°.

Anal. Calcd. for $C_{19}H_{14}O_2$: C, 83.18; H, 5.15. Found: C, 83.49; H, 5.34.

2-(α -Methylbenzyl)-1-naphthoic Acid.—On reducing the lactone with amalgamated zinc and acid in the presence of toluene 33% of the lactone was recovered and 90% of the material consumed was obtained as the acid. Using dilute acetic acid the process was simpler and the yield of acid based on the lactone taken was 74%. The acid gives well-formed prisms from benzene–hexane but these contain solvent which is lost only with difficulty. After drying in vacuum at 60° for three hours the product sintered at 118° and melted at 122–124°, and after two crystallizations from glacial acetic acid it finally formed dense prisms melting at 128–129°. This melting point is reached at once when the solvated material is melted and then crystallized from acetic acid.

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.76; H, 6.32.

10-Methyl-1,2-benzanthracene was prepared from the above acid exactly as described for the higher homolog, the total yield of pure product, collected partly as such and partly as the picrate, being 66%. The hydrocarbon crystallizes from benzene–hexane as long, flat, very nearly colorless needles, m. p. 140.2–140.8°, bright blue fluorescence in ultraviolet light. Slender needles are formed from benzene–alcohol. The picrate separates from benzene as dark red needles, m. p. 173.5–174°.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.17; H, 5.83. Found: C, 94.08; H, 6.03. Picrate, calcd. for $C_{19}H_{14} \cdot C_6H_5O_7N_3$: C, 63.68; H, 3.64. Found: C, 63.47; H, 3.87.

Other Experiments; 5-Methyl-1,2-benzanthracene

2-(*o*-Toluyloxy)-1-naphthoic Acid with Ethyl- and with Octadecyl-magnesium Bromide.—The reaction of the ester of the above acid with octadecylmagnesium bromide proceeded very poorly and better results were obtained by treating the free acid in benzene–ether with three equivalents of the reagent. In contrast with the experiences above the complex in this case dissolved completely. The

(20) v. Braun, Manz and Reinsch, *Ann.*, **466**, 277 (1929).

material from the neutral fraction of the reaction mixture was refluxed for one hour with alcoholic potassium hydroxide, and from the alkaline extract there was obtained on acidification and crystallization (28% yield) a substance identified as the lactone of 2-(α -hydroxy-*o*-methylbenzyl)-1-naphthoic acid. The substance forms colorless, pearly plates from benzene-hexane, m. p. 157-157.8°.

Anal. Calcd. for $C_{19}H_{14}O_2$: C, 83.18; H, 5.15. Found: C, 83.23, 83.16; H, 5.27, 5.32.

From the residue unsaponified in the above treatment there was isolated in small amount a substance having the properties of *n*-hexatriacontane, pearly white plates, m. p. 77-78°.

A reducing action also was observed in the reaction of 2-(*o*-toluyl)-1-naphthoic acid (free acid) with ethylmagnesium bromide (3 equivalents), but in this case some of the normal reaction product also was isolated. The neutral fraction from the reaction mixture was first crystallized from a rather dilute solution in benzene-hexane, when crystals of 2-(α -hydroxy-*o*-methylbenzyl)-1-naphthoic acid lactone were deposited in nearly pure condition and in 34% yield. The material in the mother liquor was recovered and crystallized from alcohol, affording fairly pure 2-(α -hydroxy-*o*-methyl- α -ethylbenzyl)-1-naphthoic acid lactone in 23% yield. On further crystallization from alcohol the substance formed thin hexagonal plates, m. p. 124-125°.

Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.41; H, 6.00. Found: C, 83.24; H, 6.13.

2-(*o*-Methylbenzyl)-1-naphthoic Acid.—This was obtained in 38% yield by the Clemmensen-Martin reduction of 2-(α -hydroxy-*o*-methylbenzyl)-1-naphthoic acid lactone and also, in very poor yield, by the zinc amalgam acid reduction of 2-*o*-toluyl-1-naphthoic acid in acetic acid solution. Attempted reduction with zinc dust and alkali was unsuccessful. The acid forms clusters of small, thick needles from benzene-hexane, m. p. 144-145°.

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.56; H, 6.05.

5-Methyl-1,2-benzanthracene was obtained by cyclization and reduction exactly as described above, the yield of purified product being 78%. Crystallized from benzene-hexane, the hydrocarbon formed fluorescent, colorless plates, m. p. 158.5-159.1°; picrate, m. p. 165.8-166.3°. Cook¹² reports the melting point 157.5-158.5°, uncorr., for the hydrocarbon and 163-163.5°, uncorr., for the picrate.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.17; H, 5.83. Found: C, 93.80; H, 6.20.

Summary

A rather general method is described for the synthesis of substituted 1,2-benzanthracenes, with or without a methyl group at the 10-position, starting with 1,2-naphthalic anhydride (naphthalene-1,2-dicarboxylic anhydride) and an arylmagnesium halide. The methyl group is introduced if desired by the reaction of the free 2-aryol-1-naphthoic acid with an excess of ethylmagnesium bromide. The 5-methyl, 10-methyl and 5,10-dimethyl derivatives of 1,2-benzanthracene have been prepared in this way for comparison with the carcinogenically active 5,10-dimethylene derivative (cholanthrene). Preliminary results of biological tests indicate that 5,10-dimethyl-1,2-benzanthracene has cancer-producing properties and is comparable in potency with methylcholanthrene, cholanthrene and 3,4-benzpyrene.

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The Synthesis of Phenanthrene and Hydrophenanthrene Derivatives. VII. 5,9-Dimethoxy-1',3'-diketo-1,2-cyclopentenophenanthrene

BY L. F. FIESER AND E. B. HERSHBERG

In continuation of other work^{1,2} it seemed desirable to prepare for bio-assay a methoxylated derivative of the previously described 1',3'-diketo-1,2-cyclopentenophenanthrene.² It was thought that the keto acid I would afford a convenient starting point for the synthesis of such a compound, but, although this acid was obtained in nearly quantitative yield by the condensation of 1,5-dimethoxynaphthalene with succinic anhydride, an unexpected difficulty was encountered

(1) Part IV. Fieser and Hershberg, *THIS JOURNAL*, **58**, 2314 (1936).

(2) Part VI. Fieser, M. Fieser and Hershberg, *ibid.*, **58**, 2322 (1936).

in the reduction of the substance with amalgamated zinc and hydrochloric acid, using toluene with or without the addition of acetic acid.³ Considerable resinification occurred and the desired product of normal reduction (II) was isolated in only 20-25% yield from the distillable material present, although it crystallized well and could be separated readily from more soluble substances. The acid was converted successfully by the sequence of reactions previously described² into 5,9-dimethoxy-1',3'-diketo-1,2-cyclopentenophenanthrene (III), although an unexpected

(3) Martin, *ibid.*, **58**, 1438 (1936).