

2',3',4',3,4-Pentahydroxychalcone (III).—Five and four-hundredths grams of gallacetophenone and 4.2 g. of protocatechuic aldehyde in 10 cc. of alcohol, condensed with 85 g. of 60% potassium hydroxide, gave 3.2 g. (39% yield) of pure 2',3',4',3,4-pentahydroxychalcone. The chalcone separated from 50% alcohol as yellow microscopic crystals, melting at 249°. Russell and Todd² obtained this chalcone as a deep orange-red microcrystalline solid melting at 233° by saponification of 2',3',4',3,4-pentabenzoyloxychalcone.

From the acid mother liquor saturated with sodium chloride, the unchanged gallacetophenone and protocatechuic aldehyde were recovered by extraction with ethyl acetate.

2',3',4',3,4-Pentabenzoyloxychalcone was prepared by dissolving 0.5 g. of the chalcone in 10 cc. of a 50-50 benzoyl chloride-pyridine mixture and heating in a hot water-bath for two hours. After diluting the reaction mixture

with water and extracting with ether, followed by washing the ether extract with cold alcohol, the pentabenzoate separated from hot alcohol as a white powder melting at 85°, as given by Russell and Todd.

Summary

The preparation of the polyhydroxychalcones by a direct condensation of the appropriate hydroxyacetophenone and aromatic aldehyde is described. 2',3,4-Trihydroxychalcone and 2',3',4',3,4-pentahydroxychalcone have been obtained in yields of 46 and 39%, respectively. Ring closure was effected with the former by refluxing with acidulated alcohol to give 3',4'-dihydroxyflavanone.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

9-Methyl-1,2,5,6-dibenzanthracene

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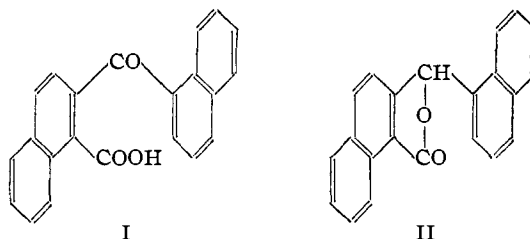
In view of the marked cancer-producing properties of 10-methyl-1,2-benzanthracene and the moderate activity displayed by 9-methyl-1,2-benzanthracene¹ it seemed of interest to synthesize for comparison the *meso*-methyl derivative of 1,2,5,6-dibenzanthracene. All previously studied homologs of this moderately powerful carcinogen, including the 9,10-dimethyl derivative, are less active than the parent hydrocarbon, whereas the introduction of a methyl group into either or both *meso*-positions of the inactive 1,2-benzanthracene favors the development of carcinogenic potency.^{1,2}

As starting material for the synthesis of 9-methyl-1,2,5,6-dibenzanthracene we employed 2-(α -naphthoyl)-1-naphthoic acid, I. This was obtained as the chief product of the reaction between 1,2-naphthalic anhydride and α -naphthylmagnesium bromide. A reaction product isolated in smaller amounts corresponded in melting point and in the melting point of the lactol acetate with the isomeric 1-(α -naphthoyl)-2-naphthoic acid synthesized in a different manner by Cook,³ and the structure of the new acid follows from the observation that it is an isomer of this substance.

(1) For a summary of the literature and biological tests see Fieser, *Am. J. Cancer*, **34**, 37 (1938).

(2) Additional data on the carcinogenic action of 9,10-dimethyl-1,2-benzanthracene are given by W. E. Bachmann, E. L. Kennaway and N. M. Kennaway, *Yale J. Biol. Med.*, **11**, 97 (1938).

(3) Cook, *J. Chem. Soc.*, 1472 (1932).

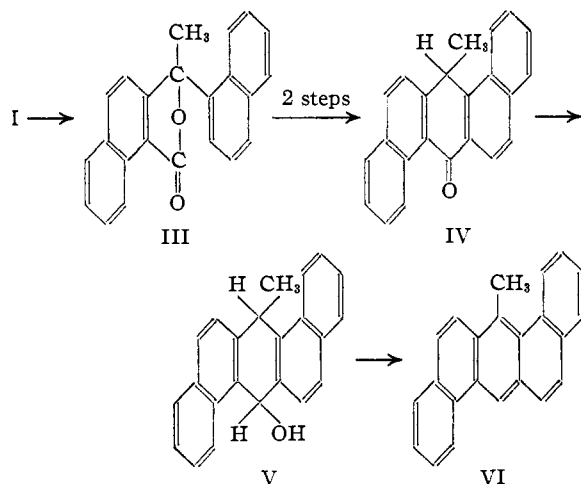


Since both *meso*-positions of the desired hydrocarbon are equivalent, two routes were open for the introduction of the methyl group starting with keto acid I. The reduction of the acid was investigated with the idea of proceeding through the anthranyl acetate and the anthrone,⁴ but the results were unpromising. Treatment with zinc and alkali led only to resins. High pressure hydrogenation over copper chromite catalyst at temperatures at which the naphthalene rings were not attacked to an appreciable extent gave as a principal crystalline product the lactone II. A very small amount of the fully reduced 2-(α -naphthylmethyl)-1-naphthoic acid was isolated from the acidic fraction, and small amounts of the same substance were obtained from the lactone II by Clemmensen reduction and by reduction with zinc and alkali following Newman's⁵ procedure. The yields, however, were too low to be practical.

(4) Fieser and Hershberg, *THIS JOURNAL*, **59**, 1028 (1937).

(5) Newman, *ibid.*, **60**, 1368 (1938).

We therefore turned to the method of Fieser and Newman⁶ and found that a methyl group can be introduced smoothly by the action of excess Grignard reagent on the keto acid I giving the lactone III. This was reduced in good yield by



the Clemmensen–Martin method and the resulting acid was cyclized smoothly with zinc chloride in acetic acid–anhydride.⁴ In contrast to the behavior noted in the synthesis of *meso*-methyl compounds in the 1,2-benzanthracene series,^{4,7} the product of the cyclization was the non-fluorescent anthrone, IV, and not the anthranil acetate, which was prepared from IV for comparison.

The difference may be due merely to the sparing solubility of the pentacyclic compound, for it crystallizes from the reaction mixture at the boiling point. Cyclization with sulfuric acid gave the same product (IV), but less smoothly than by the above process. The anthrone on reduction with zinc and alkali according to Martin⁸ was converted into the dihydride V. This is stable in a basic medium and can be obtained pure by crystallization from aqueous pyridine. When warmed in alcohol containing a small amount of hydrochloric acid it was dehydrated easily to 9-methyl-1,2,5,6-dibenzanthracene, VI. The best samples of the hydrocarbon had an appreciable melting point range (192–194.5°, *corr.*) but nevertheless seemed homogeneous, the same melting point being found for various samples and remaining unchanged on purification by chromatographic adsorption, sublimation, and recovery from the sharply melting trinitrobenzene derivative.

(6) Fieser and Newman, *THIS JOURNAL*, **58**, 2876 (1936).

(7) Newman, *ibid.*, **60**, 1141 (1938).

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

Experimental Part

2-(α -Naphthoyl)-1-naphthoic Acid (I) and Isomer.—The Grignard reagent from 20.4 g. of α -bromonaphthalene (b. p. 138–139.5° at 13–14 mm.) and 2.6 g. of magnesium in thiophene-free benzene (300 cc.)–ether (95 cc.) was added during five hours to a warm, stirred solution of 15 g. of 1,2-naphthalic anhydride (m. p. 166–166.5°, very faint test for sulfur) in 300 cc. of benzene. The ether was removed by distillation and the yellow mixture refluxed for two and one-half hours and allowed to stand overnight. After acid hydrolysis the organic layer and ether extract were mixed with 250 cc. of 5% sodium carbonate solution and steam distilled to remove solvents and naphthalene. The dark solution was clarified with Norite and poured into 25 cc. of hydrochloric acid and 50 cc. of water. The precipitated acid when dried was almost colorless (22 g., m. p. 157–161°). One crystallization from benzene gave 11.3 g. (45.8%) of colorless acid, m. p. 174–178°; the mother liquor gave higher melting crops containing the 2-naphthoic acid.

After several crystallizations of the first crop from various solvents the acid I was obtained in a satisfactory condition melting constantly at 183.5–184°, *corr.* The most satisfactory solvent for crystallization is benzene, from which the acid separates in glistening scales containing solvent of crystallization. These crystals melt at about 120°, with resolidification; the solvent can be removed completely by drying at 90° in vacuum.

Anal. Calcd. for $C_{22}H_{14}O_3$: C, 80.97; H, 4.32. Found: C, 80.60; H, 4.38.

The lactol acetate, prepared by heating the keto acid I with acetic anhydride and pyridine, crystallized from alcohol as colorless prisms, m. p. 179.5–181°, *corr.*

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.25; H, 4.38. Found: C, 77.92; H, 4.68.

In addition to the acid I, which was the main reaction product, there was isolated smaller amounts of 1-(α -naphthoyl)-2-naphthoic acid,³ m. p. 244–245°, *corr.*; lactol acetate, m. p. 197.5–198.5°, *corr.* The constants correspond satisfactorily with the uncorrected values reported by Cook.³

Reduction of the Acid I.—The hydrogenation (of 1–2 g. samples) was conducted in the presence of copper chromite catalyst at 80–140 atmospheres pressure and 150–180°. A neutral fraction, amounting to about one-fourth of the total product, gave after repeated crystallization from ethyl acetate–hexane a small amount of 2-(α -naphthylhydroxymethyl)-1-naphthoic acid lactone (II), which formed colorless, granular crystals, m. p. 170.5–171°, *corr.* There appears to be a needle-form which melts first at 166.5°, *corr.*, with transformation to the other form melting at the higher temperature.

Anal. Calcd. for $C_{22}H_{14}O_2$: C, 85.14; H, 4.55. Found: C, 85.03; H, 4.84.

From the acidic fraction of the hydrogenation, which constituted about three-fourths of the whole, there was isolated with considerable difficulty a small amount of 2-(α -naphthylmethyl)-1-naphthoic acid as granular crystals, m. p. 193–194°, *corr.*

Anal. Calcd. for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.22; H, 5.29.

Smaller amounts of the same acid were obtained by the reduction of the lactone by the methods mentioned in the introduction.

2- α -(α -Hydroxy- α -1'-naphthylethyl)-1-naphthoic Acid Lactone (III).—A warm solution of 4 g. of the keto acid I (m. p. 174–178°) in benzene (200 cc.)–ether (200 cc.) was added during two hours to the Grignard reagent prepared from 2 g. of magnesium and excess methyl chloride (started with methyl iodide). The ether was distilled off and after refluxing for two hours acid was added in the usual way. The organic layer yielded but little acidic material on extraction with soda; concentration to about 25 cc. gave 3.1 g. (78%) of colorless product, m. p. 188–190°. After two crystallizations from benzene the lactone formed granular crystals, m. p. 194.5–195°, corr. (constant).

Anal. Calcd. for $C_{23}H_{18}O_2$: C, 85.16; H, 4.97. Found: C, 84.72; H, 5.15.

2- α -(α -1'-Naphthylethyl)-1-naphthoic Acid.—A mixture of 3.1 g. of the lactone III (m. p. 189–190°), 100 cc. of glacial acetic acid, 120 g. of amalgamated zinc, 120 cc. of hydrochloric acid, and 25 cc. of toluene was refluxed vigorously for thirty hours, during which time 300 cc. more acid was added. The toluene layer, combined with a benzene extract of the aqueous layer, was washed with water and extracted with 2.5% sodium hydroxide. Under proper conditions the sodium salt of the reduction product could be caused to separate on standing in large mica-like plates, but it was found expedient to precipitate the free acid directly. The dried solid was colorless; m. p. 212–217°, yield 2.3 g. (73.5%). Purified by crystallization from glacial acetic acid and from alcohol, the acid formed prisms, m. p. 221–222°, corr.

Anal. Calcd. for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found: C, 84.57; H, 5.70.

9-Methyl-1,2,5,6-dibenz-10-anthrone (IV).—The reduced acid (990 mg.) was dissolved in 3.2 cc. of a 40% solution of acetic anhydride in glacial acetic acid and a pinch of zinc chloride added. After boiling gently for about two minutes a crystalline product began to separate. After cooling, there was collected 694 mg. (74%) of pale yellow anthrone, m. p. 204–205°. Dilution of the mother liquor with water gave 231 mg. of acidic material, and when treated as before it afforded 187 mg. of anthrone; total yield, 94%. Recrystallized from benzene and from acetic acid–anhydride, the substance formed colorless prismatic needles, m. p. 203.5–204.5°, corr. The anthrone shows no fluorescence in benzene solution. Cyclization of the acid with concentrated sulfuric acid (procedure, ref. 6) proved less satisfactory, but after repeated crystallization the sample had the same crystalline form and nearly the same m. p. (no depression) as above.

Anal. Calcd. for $C_{23}H_{18}O$: C, 89.58; H, 5.23. Found: C, 89.56; H, 5.63.

9-Methyl-1,2,5,6-dibenzanthranthyl-10-acetate was prepared by heating 300 mg. of the anthrone in 7 cc. of acetic anhydride containing pyridine (5 drops) for one hour, concentrating the solution, and allowing it to cool; yield, 291 mg. (85%), m. p. 187–190°. The acetate crystallizes well from benzene–hexane, forming small, faintly yellow needles, m. p. 192–192.5°, corr. When pure it shows a strong fluorescence in benzene solution.

Anal. Calcd. for $C_{25}H_{18}O_2$: C, 85.69; H, 5.18. Found: C, 85.59; H, 5.28.

9-Methyl-9,10-dihydro-1,2,5,6-dibenz-10-anthranol (V).—The anthrone (190 mg.) was refluxed with 25 cc. of 10% sodium hydroxide, 430 mg. of zinc dust, and 5 cc. of toluene for about eleven hours. On cooling, a solid product crystallized from the toluene layer; this was collected, taken into benzene, and after clarifying the solution with Norite and concentrating to about 20 cc. there was obtained 140 mg. (73%) of fibrous white needles. The substance is very sensitive to traces of acid but can be recrystallized repeatedly from alcohol containing a small quantity of potassium hydroxide. This purification gave needles, m. p. 226–227° corr. (soft-glass capillary), but on combustion a considerable inorganic residue was left. Four crystallizations of the crude product from pyridine–water mixtures gave colorless needles; this sample melted at 215–220° in soft-glass capillaries but melted below 200° in acid-washed Pyrex capillaries. Combustion of this material left a residue corresponding to approximately 0.26% of sodium hydroxide in the sample.

Anal. Calcd. for $C_{23}H_{18}O$: C, 89.00; H, 5.84. Found (corrected for residue): C, 89.31; H, 6.01.

9-Methyl-1,2,5,6-dibenzanthracene (VI).—The hydrocarbon was first prepared from crude anthrone obtained by cyclization with sulfuric acid as described by Fieser and Newman.⁶ The moist material was reduced with zinc and alkali as above and the crude solid separating from the toluene layer was treated with dilute hydrochloric acid with the object of removing the zinc. The material was then crystallized from benzene (Norite), giving nearly colorless plates of the hydrocarbon, m. p. 188–190°; the over-all yield from the acid was about 50%. The hydrocarbon was also obtained by crystallization of the dihydroanthranol V from alcohol containing a small amount of hydrochloric acid; the hydrocarbon separated from the hot solution in a crystalline condition.

Samples of the hydrocarbon purified by repeated crystallization from various solvents, adsorption on an alumina column and elution, sublimation in high vacuum, and recovery from the pure trinitrobenzene derivative had the same properties. The purest material forms glistening mica-like plates, m. p. 192–194.5°, corr. On repeated remelting in the capillary tube the substance darkened and melted lower. The substance is nearly colorless, having a very faint yellowish tinge.

Anal. Calcd. for $C_{23}H_{18}$: C, 94.48; H, 5.52. Found: C, 94.12, 94.35%; H, 5.77, 5.46.⁹

The **picrate** (orange) was rather unstable and not easily obtained as good crystals; the best material from benzene–hexane melted at 186–186.5°. The trinitrobenzene derivative was more stable and after several crystallizations from benzene–hexane it was obtained as bright orange-red needles, m. p. 178.5–179°, corr. It dissociates to a considerable extent in alcohol and yields the free hydrocarbon when crystallized from acetic acid.

Summary

9-Methyl-1,2,5,6-dibenzanthracene has been synthesized from 1,2-naphthalic anhydride by

(9) Microanalysis by Herbert S. Wight.

application of the method of Fieser and Newman. An alternate method was found impractical because of the difficulty of reducing 2-(α -naphthoyl)-1-naphthoic acid. The hydro-

carbon is being tested for carcinogenic activity.

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Studies on Lignin and Related Compounds. XXXVIII. The Effect of Solvents in the Grignard Analysis for Active Hydrogen and Carbonyl

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It was the purpose of this investigation to ascertain the effect of using solvents such as dioxane and pyridine in the analysis for active hydrogen and carbonyl³ using Grignard reagent. This became necessary because of the present extended application of the Grignard machine to the study of lignins, which are, for the most part, not sufficiently soluble in other solvents to ensure complete reaction.

Even with these, the reactions of compounds containing a variety of reactive groups are often incomplete. The results show that pyridine is much more satisfactory than dioxane. Thus, cellulose acetate in dioxane reacts with less than half the amount of Grignard reagent required by theory, and pentaacetylglucose with less than one-third, although in pyridine the latter consumes two-thirds of the theoretical amount. While it is not surprising that low carbonyl values should be obtained with these polyacetyl compounds, the discrepancies may not be owing entirely to incomplete reaction. This reservation is suggested by the anomalous behavior of catechol diacetate. While the latter reacts normally and completely in xylene, active hydrogen and a lower carbonyl value are found when pyridine is used. This same effect is found accentuated in dioxane. The source of this active hydrogen is being investigated. Regardless of this abnormal behavior it is certain that a compound such as glucose does not react completely with methyl iodide Grignard reagent in dioxane although a close approximation (4.6 active hydrogen per mole) to the theoretical value is obtained in pyridine and in quinoline (4.2 active hydrogen per mole).

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(2) Holder of a Bursary and Studentship under the National Research Council of Canada, 1936-1938.

(3) Kohler, Fuson and Stone, *THIS JOURNAL*, **49**, 3181 (1927); Kohler and Richtmyer, *ibid.*, **52**, 3736 (1930).

The carbonyl group in carboxylic acids is also not indicated quantitatively by the Grignard reagent in dioxane. Benzoic acid consumes only half of the theoretical amount required for formation of the ketone, and cinnamic acid none at all. In pyridine, on the other hand, benzoic acid reacts normally (1 active hydrogen, one addition) while cinnamic acid consumes 0.8 mole of RMgX. In xylene, however, the reaction seems to go beyond the ketone stage (1.23 moles per mole).

From these results it can be said that dioxane is an unsatisfactory solvent for the Grignard analysis except in cases where reasonably predictable incompleteness of reaction can, by comparison with complete reaction, be employed to give an insight into structure. It has been used in this way with lignins to differentiate reactive carbonyl groups from the inert carboxylic acids.

Grignard analyses of vanillin types at first seemed to indicate that reaction was incomplete in dioxane and in isoamyl ether only because of precipitation of the magnesium phenoxide. Similar results were obtained with isovanillin, although analysis of each of these compounds in pyridine indicated one active hydrogen and one carbonyl. The isovanillin likewise reacted normally in xylene. In confirmation of the incomplete reaction in dioxane, 63% of the vanillin was recovered from the reaction product in this solvent. In agreement with these results, the hydroxyl group of 3-methoxy-4-hydroxyacetophenone reacted completely with the methyl iodide Grignard reagent in dioxane, but the ketone group did not react at all. In xylene both active hydrogen and carbonyl reacted, while the value for active hydrogen found in pyridine was augmented as a result of a slight amount of enolization. When veratraldehyde was used to substantiate these results it was found that it reacted normally (one carbonyl) in xylene