surface. The hydrocarbon molecules are apparently held in the mixed films in two principal ways:

(a) In a two dimensional solution which the hydrocarbon molecules can enter or leave reversibly; the logarithm of the mole fraction of hydrocarbon held in such solution, at film pressures below 15 dynes, varies linearly with the pressure applied to the film by the movable barrier (Fig. 4 and Table IV). At any given pressure the extent of this solubility depends on the structure of both the hydrocarbon and the sterol.

(b) In association complexes with sterol molecules; one hydrocarbon molecule apparently is held between two appropriately oriented sterol molecules. For such association to occur the hydrocarbon must have a favorable molecular configuration with respect to ring system and side chain. Any influence which favors a high degree of orientation among the solvent sterol molecules, such as low temperature or the presence of a third film component which leads to advantageous packing, favors this association. Any influence which disrupts the sterol orientation, such as high temperature, unfavorable sterol substituents or double bonds, or presence of an improperly packing third film component, detracts from the possibilities for formation of such hydrocarbon–sterol complexes (Figs. 5, 7, 8).

4. The molecular areas have been determined for most of the hydrocarbons studied (Table II) and compared with the dimensions of the same hydrocarbon molecules in the crystal, as obtained from previously published X-ray data (Table III).

Molecular areas for certain representative hydrocarbons have also been determined at temperatures from 8° to 40° (Table VI).

5. It is suggested that the solution type of interaction may possibly have some significance in the transport of polycyclic hydrocarbons in the animal organism. The association type of interaction, which is especially pronounced when the hydrocarbon–sterol films contain a fat, stearic acid, or a phosphatide as a third component, may possibly provide a mechanism whereby the polycyclic hydrocarbons may be bound into, and act as a modifying influence in biological structures.

INDIANAPOLIS, INDIANA RECEIVED SEPTEMBER 3, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of 9,10-Dimethyl-1,2-benzanthracene and of a Thiophene Isolog

BY REUBEN B. SANDIN[1] AND LOUIS F. FIESER

Among the numerous homologs and dimethylene derivatives of 1,2-benzanthracene which have been tested for carcinogenic activity, those exhibiting the highest potency are cholanthrene, 20-methylcholanthrene, and 9,10-dimethyl-1,2-benzanthracene. The 10-methyl derivative falls somewhat below these hydrocarbons in general ability to evoke tumors rapidly in various tissues, and among the other isomers 9-methyl-1,2-benzanthracene comes next in the order of potency.[2] It would be interesting to know whether the structural specificity discernible in the hydrocarbon series is manifested among compounds of analogous structure in which one of the four benzenoid nuclei is replaced by a heterocyclic ring having aromatic characteristics. The synthesis of a thiophene isolog of one of the above potently carcinogenic hydrocarbons was undertaken both from this point of view and in order to provide a basis for interpreting such biological results as may be obtained with the recently synthesized pyridine isolog of 20-methylcholanthrene.[3] Since this substance differs from the hydrocarbon in being basic as well as in possessing a heterocyclic ring, a control substance was desired representing a variation of only one of these two features.

As a likely starting point for the synthesis of a compound of the desired type having a thiophene ring in place of the terminal linear ring of a *meso*-alkyl-1,2-benzanthracene, the condensation of α-thienylmagnesium iodide with 1,2-naphthalic anhydride was investigated. A keto acid mixture was produced in moderately good yield, and it was found possible to separate the higher melting isomer (II) readily as the crystalline sodium salt and to isolate the isomer I from the mother liquor.

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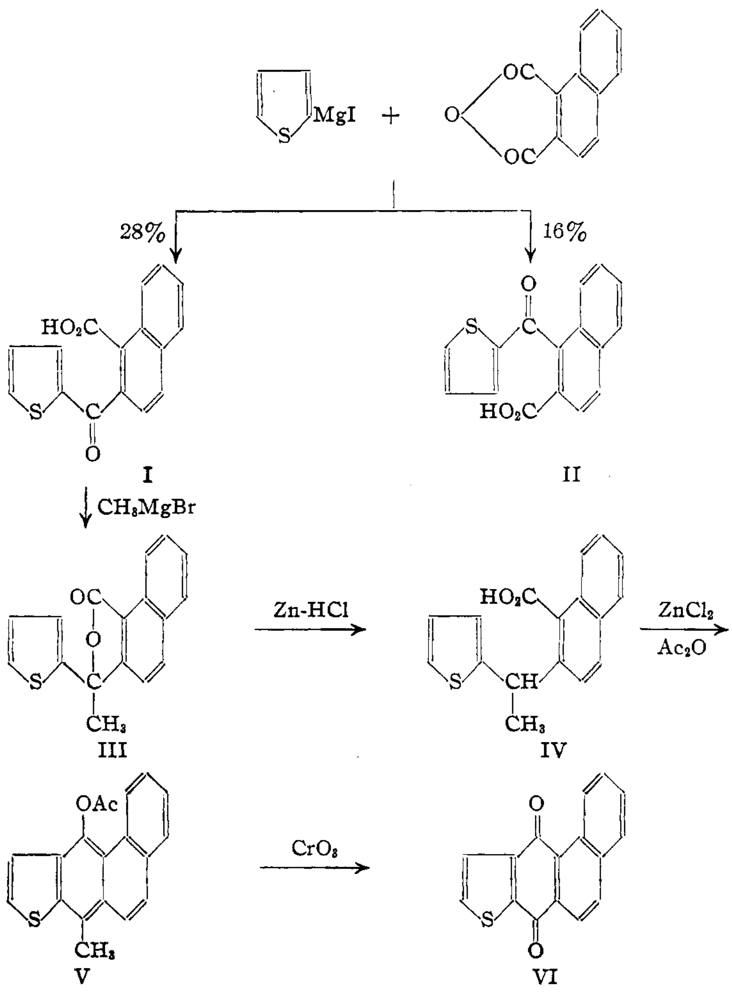
[1] Fellow of the Rockefeller Foundation on leave from the Department of Chemistry, University of Alberta, Canada.

[2] For a summary of most of the pertinent data, see Fieser, *Am. J. Cancer*, **34**, 37 (1938).

[3] Fieser and Hershberg, THIS JOURNAL, **62**, 1640 (1940).

The structures follow from the results of decarboxylation of the acids in the presence of copper. The higher melting acid gave a liquid ketone, whereas the isomer I gave a solid product identified as β-naphthyl α-thienyl ketone by direct comparison with a sample of this substance synthesized as described by Thomas and Couderc.[4] α-Naphthyl α-thienyl ketone is reported by these investigators to be a liquid. The condensation of the α-thienyl Grignard reagent with 1,2-naphthalic anhydride follows the course established for various arylmagnesium halides. Thus the situation is analogous to that found with *o*-tolylmagnesium bromide,[5] both with respect to the proportion of isomers and the melting point relationship between them.



The more abundant isomer, 2-α-thenoyl-1-naphthoic acid (I), was utilized as the starting material in an attempt to synthesize the isolog of 10-methyl-1,2-benzanthracene. On condensing the free keto acid with excess methylmagnesium bromide by the procedure of Fieser and Newman,[5] a crystalline lactone (III) was obtained in 66% yield. Reduction to IV was accomplished in excellent yield by a procedure described by Newman[6] for a comparable case, and cyclization of the acid with zinc chloride and acetic acid anhydride[7] was nearly quantitative. All attempts to reduce the resulting acetate V, however, were unsuccessful. Various methods were tried but gave only dark tars. For orientation of experiments to be presented below, 4-acetoxy-9-methyl-5,6-benzthiophanthrene (V) was converted to the quinone VI by oxidation with chromic acid. The yield was very low, but 5,6-benz-4,9-thiophanthrenequinone was isolated without difficulty by extraction of an ethereal solution of the reaction mixture with alkaline hydrosulfite and oxidation of the hydroquinone.

We then sought to replace the acetoxyl group of V by methyl by cleavage with a Grignard reagent, isomerization of the anthranol, and Grignard methylation according to Fieser and Hershberg.[7] Although this method was found by Newman[8] to be applicable to the strictly analogous synthesis of 9,10-dimethyl-1,2-benzanthracene, we obtained from V only a high melting product evidently arising from the condensation of the anthranol and anthrone.[7] The next trial consisted in an attempt to apply to the present case the excellent method developed by Bachmann and Chemerda[9] for the synthesis of 9,10-dimethyl-1,2-benzanthracene and related hydrocarbons. This consists in condensing 1,2-benzanthraquinone with excess methyl Grignard reagent, isolating the diol VII, converting this by treatment with methanol and hydrogen chloride into the dimethyl ether VIII, and converting the ether into the hydrocarbon by interaction with sodium. A benzthiophanthrenequinone

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[4] Thomas and Couderc, *Bull. soc. chim.*, [4] **23**, 288 (1918).

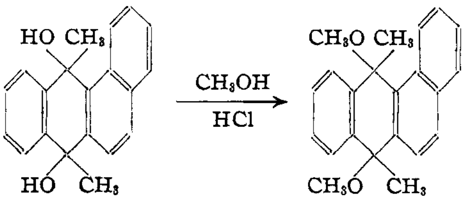
[5] Fieser and Newman, THIS JOURNAL, **58**, 2376 (1936).

[6] Newman, *ibid.*, **60**, 1368 (1938).

[7] Fieser and Hershberg, *ibid.*, **59**, 1028 (1937).

[8] Newman, *ibid.*, **60**, 1141 (1938).

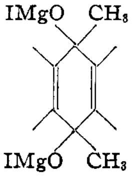
[9] Bachmann and Chemerda, *ibid.*, **60**, 1023 (1938).



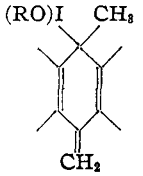
VII VIII

preparation obtained as described below was put through the exact procedure of Bachmann and Chemerda, and numerous variations thereof, with entirely unpromising results, although their synthesis of 9,10-dimethyl-1,2-benzanthracene could be duplicated without difficulty. The diol presumably formed in the first step invariably failed to crystallize and subsequent processing gave only tars. It seemed possible that in the thiophanthrene series the diol may suffer dehydration, with subsequent polymerization, and ways of avoiding such a process were sought. One variation consisted in an attempt to convert the magnesium iodide derivative of the diol directly into the dimethyl ether by interaction with methanol and hydrogen chloride, and this afforded in about 10% yield a crystalline substance containing, according to the analysis, only one atom of oxygen. In seeking an explanation of this curious result, we investigated the behavior of the derivative of the known diol VII under similar conditions. The ether–benzene solution obtained by the action of excess methylmagnesium iodide on 1,2-benzanthraquinone was treated with mixtures of hydrochloric acid with methanol or methanol–acetic acid, and under suitable conditions it was found possible to isolate considerable amounts of a bright yellow, crystalline, highly sensitive compound which contains iodine. By pouring the Grignard solution into a methanol–hydriodic acid mixture at 0° and later adding acetic acid as a precipitant, the iodo compound was obtained in over-all yields from the quinone as high as 70%.

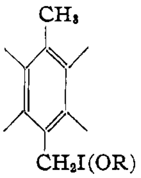
The iodo derivative was found to react quantitatively with sodium methoxide or ethoxide to give stable ethers having one atom of oxygen and corresponding in other respects to the substance obtained in the benzthiophanthrenequinone series. The analyses of the halide and of the two ethers all pointed to a composition requiring formulation of the central ring as in either (b) or (c). An iodo compound of the type (b) could arise from the diol magnesium iodide derivative (a) by the replacement of one OMgI group by iodine and the elimination of the other by a process of dehydration.



(a)



(b)



(c)

The structure (c) could arise from (b) by a sequence of α,γ-shifts. Since the 1,2-benz ring renders the molecule unsymmetrical, there are four possible structures. A distinction between types (b) and (c), however, was easily made by ultraviolet absorption spectroscopy. The spectrum of the ethoxy derivative in absolute alcohol, kindly determined by Dr. R. N. Jones, is of the characteristic 1,2-benzanthracene type and corresponds very closely with that of the 9,10-dimethyl compound, as shown in Table I.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA OF 1,2-BENZANTHRACENE DERIVATIVES

	9-Methyl-10-ethoxymethyl		9,10-Dimethyl[10]	
Band	λ, Å.	log E_m	λ, Å.	log E_m
A	2630	4.56	2625	4.50
B	2715	4.59	2735	4.58
C	2830	4.85	2850	4.80
D	2945	4.93	2965	4.90
F	(3240)	3.54	(3300)	..
G	3420	3.83	3450	3.83
H	3600	3.94	3640	3.94
I	3760	3.84	3840	3.83
J and K	3960	3.13	3900(K)	..

The central ring is therefore aromatic (c) and not constituted as in (b), which would certainly give rise to quite different absorption characteristics. Formulation (c) accords well with the behavior of the iodo compound on reduction. The reaction was accomplished by a method which appears to be novel and which has considerable practical significance. This consists in heating the iodo compound in dioxane with stannous chloride and hydrochloric acid for a brief period and diluting the solution with water. Very pure 9,10-dimethyl-1,2-benzanthracene separated in nearly quantitative yield. This reduction procedure has since been found to afford a very satisfactory method of preparing the 10-methyl compound from 10-chloromethyl-1,2-benzanthracene.[11]

There remained the determination of the respective *meso* positions occupied by the methyl and by the iodomethyl or alkoxymethyl groups. The most inviting course open for establishing the

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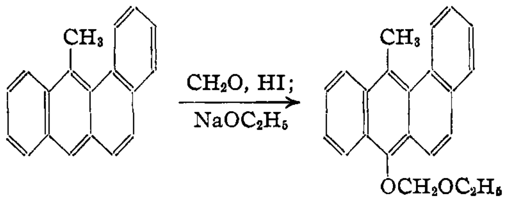
(10) R. N. Jones, THIS JOURNAL, **62**, 148 (1940).

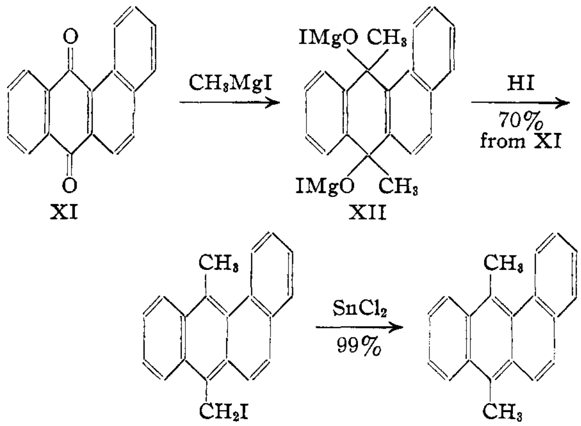
(11) Wood and Fieser, *ibid.*, **62**, 2674 (1940).

structure seemed to lie in the synthesis of one of the isomers from 9-methyl-1,2-benzanthracene and formaldehyde. Although Badger and Cook[12] were not successful in an attempt to isolate the product of the chloromethylation of this hydrocarbon, we thought that an ether or other derivative might be obtainable in amounts sufficient for the present purpose. The iodo derivative encountered above has such a favorably low solubility and so pronounced a tendency to crystallize, that in a re-investigation of the reaction the expedient was tried of adding hydriodic acid to a solution of the hydrocarbon (IX) and either trioxymethylene or chloromethyl ether in acetic acid at room temperature. Bright yellow crystals of an iodo compound soon began to appear and the yield of satisfactory material amounted to no less than 90% of the theoretical. For identification the substance was converted into 9-methyl-10-ethoxymethyl-1,2-benzanthracene (X), which proved to be identical with the above ethyl ether. The iodo compound itself decomposes when heated and is not suitable for melting point comparison, but the product of iodomethylation and that resulting from the interaction of the diol magnesium derivative were entirely similar in crystalline form, solubility, and reactivity.



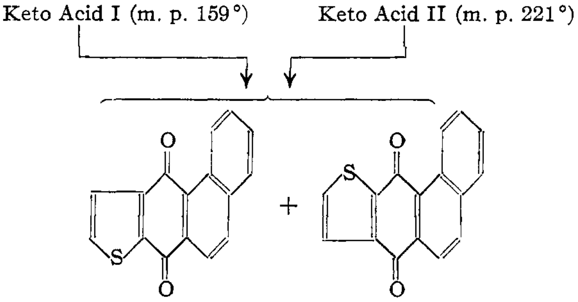
IX X

The novel series of reactions encountered can thus be formulated as shown in the chart. This constitutes a new and useful synthesis of the very potently carcinogenic[13] 9,10-dimethyl-1,2-benzanthracene. Very satisfactory hydrocarbon can be prepared rapidly from an available starting material (XI) in 69% yield in three operations requiring no purification of intermediates. The preparation has been conducted repeatedly with the same results. The iodide XIII offers interesting possibilities for further synthetic operations, which are being investigated. Both this synthesis and the iodomethylation reaction are being extended to other cases. Attention may be called to an observation recorded in the Experimental Part indicating that 9,10-dimethyl-1,2-benzanthracene, when brought into contact with alumina in benzene solution, is capable of rather rapid conversion to the peroxide[14] even in the ordinary diffused light of the laboratory.



XI XII XIII XIV

The new synthetic method was found well suited to the preparation of a thiophene isolog of the hydrocarbon XIV. The most promising source of a suitable quinone starting material seemed to be by the cyclization of one of the isomeric thenoylnaphthoic acids I and II. After various other methods of ring closure had been tried without success, it was found that both acids can be cyclized very smoothly by the action of phosphorus pentoxide in nitrobenzene at 165°, a method described by Cook.[15] Whereas normal cyclization of 2-α-thenoyl-1-naphthoic acid (I) would give the quinone VI, and ring closure of 1-α-thenoyl-2-naphthoic acid (II) would afford the isomer XV, both acids gave the same product. One or both reactions therefore involves a rearrangement of the type encountered by Hayashi[16] and elucidated by Cook.[15] Cook observed rearrangements to occur on cyclization of both 1-α-naphthoyl- and



VI (m. p. 167°) XV (not isolated)

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[12] Badger and Cook, *J. Chem. Soc.*, 802 (1939).

[13] Bachmann, Kennaway and Kennaway, *Yale J. Biol. Med.*, **11**, 97 (1938).

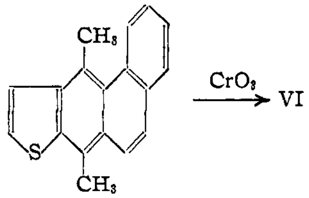
[14] Cook, Martin and Roe, *Nature*, **143**, 1020 (1939).

[15] Cook, *J. Chem. Soc.*, 1472 (1932).

[16] Hayashi, *ibid.*, 2516 (1927); 1513, 1520, 1524 (1930).

1-β-naphthoyl-2-naphthoic acid by the phosphorus pentoxide–nitrobenzene method and showed that the reactions must involve an exchange between the aroyl radical and the hydroxyl of the carboxylic acid group, probably proceeding through the lactol form of the acid. In the present case such a rearrangement would lead to the interconversion of the acids I and II. Since quinone preparations of exactly the same character were obtained from the two pure acids and from the unseparated mixture of the isomers, it is probable that an equilibrium between them is established prior to the loss of water. The quinone preparation was not altered greatly by ordinary crystallization and melted at 178–180°. By repeated recrystallization from dilute solution, small amounts of material of the same composition could be separated melting as high as 200°. The product thus appears to be a mixture of isomers in which the lower melting substance predominates. The pure isomer VI was prepared as described above and found to melt at 166.5–167°, or some eleven degrees below the melting point of the mixture. When an equal part of the latter was mixed with VI there was no depression below 167° and the melting point was raised to an intermediate level. While these observations are not conclusive, they indicate that the mixture consists in large part of 5,6-benz-4,9-thiophanthrenequinone, VI.

Since the quinone mixture could not be separated satisfactorily, it was submitted as such to the new synthesis. This proceeded very smoothly, the metal derivative produced by interaction with methylmagnesium iodide giving, on treatment with hydrogen iodide, a crystalline iodo compound which could be reduced readily with stannous chloride. The total crude product, obtained in excellent yield, had a wide melting point range and may well have been a mixture of isomers. The chief constituent, however, crystallized well and was easily isolated in a pure form of constant melting point. The structure was established by oxidation of the pure substance with chromic acid, for this gave a sharply melting product identical with 5,6-benz-4,9-thiophanthrenequinone (VI). The product of the synthesis is therefore 4,9-dimethyl-5,6-benzthiophanthrene, XVI. Tests for carcinogenicity with this compound and with the above alkoxymethyl derivatives are being conducted by Drs. Shields Warren and C. E. Dunlap.



XVI

Experimental Part[17]

1,2-Benzanthracene Series

9-Methyl-10-iodomethyl-1,2-benzanthracene (XIII)

(a) **From 1,2-Benzanthraquinone.**—To a solution of the Grignard reagent from 1.0 g. of magnesium and excess methyl iodide in 20 cc. of anhydrous ether and 20 cc. of benzene was added 1.0 g. of 1,2-benzanthraquinone.[12] The quinone went into solution on stirring at room temperature for thirty minutes, and after standing overnight at 5° the transparent, tan-colored solution was poured dropwise and with continual stirring into a solution (cooled to 0°) of 12 cc. of hydriodic acid (sp. gr. 1.7) in 40 cc. of methanol. Glacial acetic acid (40 cc.) was then added. The iodomethyl compound slowly separated as bright yellow crystals and in an almost pure condition; yield, 1.04 g. (70%). The substance is very sparingly soluble in cold acetic acid but dissolves readily in cold benzene or dioxane. Attempted crystallization from benzene always resulted in the liberation of iodine. The substance darkens rapidly when exposed to light. It has no melting point but when heated begins to darken at about 99° with considerable decomposition, sometimes with visible loss of iodine. Samples could not be dried satisfactorily for microanalysis, for some decomposition invariably occurred. A suitable method of macroanalysis was found which consisted in treating a large (0.5 g.) air-dried sample with excess sodium ethylate in absolute ethanol and determining the amount of sodium iodide formed by precipitating silver iodide and weighing it. Analyses were conducted using both sodium ethoxide and sodium methoxide and the corresponding ethers were identified. 9-Methyl-10-ethoxy-1,2-benzanthracene was isolated in one analysis in 90% yield.

Anal. Calcd. for $C_{20}H_{15}I$: I, 33.25. Found: I, 33.04, 33.24.

(b) **By Iodomethylation of 9-Methyl-1,2-benzanthracene.**—The required hydrocarbon was prepared according to Newman.[18] A solution of 0.25 g. of 9-methyl-1,2-benzanthracene in 30 cc. of glacial acetic acid was treated at room temperature with 8 cc. of chloromethyl ether, followed by 10 cc. of hydriodic acid (sp. gr. 1.7). After standing for one hour at 0°, there was obtained 0.35 g. of bright yellow crystals of the iodo compound. In another experiment trioxymethylene was used with equally good results. The iodo compound on treatment with sodium ethoxide as described below gave an ether melting at 126–127°, which showed no depression of the melting point when mixed with the sample prepared from the iodo compound obtained by method (a).

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[17] Microanalyses by Lyon Southworth. All melting points are corrected.

[18] Newman, THIS JOURNAL, 59, 1003 (1937).

9-Methyl-10-methoxymethyl-1,2-benzanthracene was prepared by adding 0.52 g. of the iodomethyl compound XIII (a) to a solution of 1 g. of sodium methoxide in 50 cc. of absolute methanol. After refluxing for one hour, the mixture was diluted with 500 cc. of water, affording 0.32 g. (88%) of a pale yellow solid. Crystallized from methanol, it formed pale yellow needles, m. p. 120–121°.

Anal. Calcd. for $C_{21}H_{18}O$: C, 88.07; H, 6.33. Found: C, 88.17; H, 6.66.

9-Methyl-10-ethoxymethyl-1,2-benzanthracene was obtained in 95% yield from XIII (a) by the same procedure. Crystallization from ethanol gave fine, pale yellow needles, m. p. 126–127°.

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.70. Found: C, 87.98; H, 6.92.

9,10-Dimethyl-1,2-benzanthracene.—A solution of 1.05 g. of 9-methyl-10-iodomethyl-1,2-benzanthracene in 60 cc. of dioxane containing 3 cc. of concentrated hydrochloric acid was added to a solution of 10 g. of stannous chloride crystals in 50 cc. of dioxane and 30 cc. of concentrated hydrochloric acid. It is necessary to use a very strongly acidic medium in order to avoid the formation of tar. After being refluxed gently for five minutes, the originally dark yellow solution became pale yellow; the solution was allowed to stand for one-half hour and then diluted with 500 cc. of water. After standing overnight to allow the precipitated hydrocarbon to coagulate, there was collected 0.71 g. (99%) of only faintly colored 9,10-dimethyl-1,2-benzanthracene, m. p. 120–122°. A sample crystallized from alcohol melted at 122–123° and did not depress the melting point of material prepared by the procedure of Bachmann and Chemerda.[9] It formed a red dipicrate melting unsharply at 102–106° (compare 103–106°[8]).

9,10-Dimethyl-1,2-benzanthracene Peroxide.—A sample of the hydrocarbon (m. p. 122–123°) which had been purified through the dipicrate and then crystallized from alcohol was dissolved in benzene and passed through a tower of alumina three times. The melting point was found to have risen to 152–162°, and analysis of this product indicated that oxygen had been taken up. The oxygenated material was dissolved in benzene and allowed to stand in contact with a small amount of alumina, with exposure to air, for forty-eight hours. The solution was filtered and evaporated and the residue crystallized from alcohol. This afforded compact, colorless crystals which melted at 194–195° with decomposition and gas evolution.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.54; H, 5.79.

The substance gave a positive test for a peroxide when heated with sodium iodide solution and acetic acid. The melting point agrees with that of the product obtained by Cook, Martin and Roe[14] by photo-oxidation, and the composition indicates that the substance is similar to the peroxide of 9,10-dimethyl-1,2,5,6-dibenzanthracene described by Bachmann and Chemerda.[19] We cannot as yet say whether the alumina behaves as a catalyst of the peroxidation, functions by removing an inhibitor of the reaction, or is merely incidental. The only light concerned in the above experiment was the diffused daylight of a basement laboratory.

Benzthiophanthrene Series

Reaction of 1,2-Naphthalic Anhydride with α-Thienylmagnesium Iodide.—Following the procedure of Fieser and Newman,[5] the Grignard reagent prepared from 24 g. of α-iodothiophene,[20] 3.5 g. of magnesium and 100 cc. of ether was filtered under nitrogen pressure and forced all at once into a well-stirred solution of 20 g. of sulfur-free 1,2-naphthalic anhydride[21] in 300 cc. of warm, thiophene-free benzene. A yellow complex separated at once. The mixture was refluxed for two hours, cooled, treated with dilute hydrochloric acid, and the benzene layer was separated and extracted thoroughly with sodium carbonate solution. Acidification of the combined soda extracts afforded 25 g. of crude keto acid mixture, and two crystallizations from acetic acid gave 15.0 g. of a mixture of isomers (m. p. 141–156°) which could not be separated into the components by the use of acetic acid or benzene. A separation was easily accomplished by preparing a hot saturated solution of the sodium salts and allowing this to cool slowly; the salt of the acid II separated in a crystalline condition, while that of I remained in solution.

1-α-Thenoyl-2-naphthoic Acid (II).—The acid liberated from the crystalline salt after one crystallization from acetic acid melted at 220–221° and consisted of colorless microneedles; yield 4.5 g. (16%). The melting point was unchanged on recrystallization.

Anal. Calcd. for $C_{16}H_{10}O_3S$: C, 68.08; H, 3.57. Found: C, 68.02; H, 3.86.

2-α-Thenoyl-1-naphthoic acid (I) was obtained from the aqueous mother liquor and crystallized from acetic acid. There resulted 8 g. (28%) of a colorless crystalline powder melting at 158–159.5°.

Anal. Calcd. for $C_{16}H_{10}O_3S$: S, 11.36. Found: S, 11.42.

Decarboxylation of the Acids.—The reaction proceeded smoothly on a small scale (1–2 g.) using basic copper carbonate as the catalyst. The acid I afforded a product identical with β-naphthyl α-thienyl ketone[4] (melting point and mixed melting point 87–88°), while the acid II gave an oil which failed to solidify.

Lactone of 2-[α-Hydroxy-α-(α′-thienyl)-ethyl]-1-naphthoic Acid (III).—This compound was obtained readily from the keto acid I according to the procedure of Fieser and Newman,[5] using methylmagnesium bromide. The yield of material melting at 109–110° was 66%. A sample crystallized to constant melting point from alcohol formed small, colorless plates, m. p. 112–113°.

Anal. Calcd. for $C_{17}H_{12}O_2S$: C, 72.78; H, 4.32. Found: C, 72.74; H, 4.58.

2-[α-(α′-Thienyl)-ethyl]-1-naphthoic acid (IV) was prepared by reduction of the lactone essentially according to Newman,[6] the yield of almost pure acid being practically quantitative. The purified substance separated from alcohol in a crystalline crust and melted at 132–134°.

Anal. Calcd. for $C_{17}H_{14}O_2S$: S, 11.36. Found: S, 11.38.

4-Acetoxy-9-methyl-5,6-benzthiophanthrene (V).—Cyclization of the acid IV with zinc chloride in acetic acid-

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[19] Bachmann and Chemerda, THIS JOURNAL, **61**, 2358 (1939).

[20] Minnis, "Organic Syntheses," Vol. XII, 1932, p. 44.

[21] Hershberg and Fieser, *ibid.*, Vol. XVIII, 1938, p. 59.

anhydride[7] afforded the acetate, m. p. 184–186°, in close to the theoretical yield. A sample recrystallized from acetic acid formed small, straw-colored needles, m. p. 186–187°.

Anal. Calcd. for $C_{19}H_{14}O_2S$: C, 74.46; H, 4.61. Found: C, 74.66; H, 4.83.

Attempts were made to reduce the acetate using sodium hydroxide and zinc dust activated with copper sulfate,[22] both with and without the use of toluene, but only red tars were encountered. The unsuccessful attempt to apply the synthesis of Fieser and Hershberg[7] has been noted; the only solid product was a grayish, sparingly soluble substance melting in the range 260–270°.

5,6-Benz-4,9-thiophanthrenequinone, VI (L. F. F.) (a) **From the Acetate V.**—A solution of 0.5 g. of the acetate V in 10 cc. of glacial acetic acid was kept at or near the boiling point during the addition in small portions of 1.9 g. of powdered potassium dichromate. The oxidation proceeded smoothly and a small amount of the dichromate persisted on digesting the mixture at the boiling point for a few minutes after the addition. On addition of water a sticky product was precipitated, and since crystallization tests seemed unpromising this was dissolved in ether and the solution was filtered from a small residue, washed with mineral acid, dried and clarified with Norit. The solution was washed once with alkali and then extracted with 2% potassium hydroxide containing sodium hydrosulfite. This gave an orange-yellow vat liquor and discharged the yellow color from the ether layer. The alkaline liquor was drawn off into a separatory funnel under ether, neutralized with acetic acid, and the organic material was extracted into the ether layer. After three washings with sodium carbonate solution, the ether layer was shaken with silver oxide and magnesium sulfate and the filtered solution evaporated to dryness. Crystallization of the residue from acetic acid gave about 50 mg. of rather poorly formed crystals in two crops, m. p. 163–164° and 162–163°. Sublimation just below the melting point at 3 mm. gave material melting at 164–166°. This crystallized from alcohol, in which the substance is moderately soluble, in the form of fibrous orange needles which filled the liquid, m. p. 166.5–167°, and a further crystallization from dilute acetic acid did not alter the melting point. The substance gives a brownish-purple solution in concentrated sulfuric acid and an orange-yellow vat.

Anal.[23] Calcd. for $C_{16}H_8O_2S$: C, 72.71; H, 3.05. Found: C, 73.05, 73.01; H, 3.42, 3.39.

(b) **From 4,9-Dimethyl-5,6-benzthiophanthrene.**—A solution of 120 mg. of the hydrocarbon (m. p. 158–159°) in 4 cc. of glacial acetic acid was treated with 0.7 g. of potassium dichromate and the mixture was heated at the boiling point with stirring for seven minutes. Dilution with water gave a granular orange precipitate which, however, became tarry when dried at 100°. The material was therefore taken up in ether and the quinone was separated by vatting and processed exactly as in (1). Vacuum sublimation afforded 20 mg. of reddish-yellow crystalline material, m. p. 162–163°, and on one crystallization from alcohol the quinone formed fine orange needles, m. p. 166–166.5°, and showed no depression when mixed with the sample (a).

Cyclization of the Keto Acids I and II.—A mixture of 8 g. of phosphorus pentoxide and 4 g. of 1-α-thenoyl-2-naphthoic acid (II) dissolved in 40 cc. of nitrobenzene was heated with constant stirring for one hour in an oil-bath maintained at 160–165°. The hot mixture was poured into water and the solvent steam distilled. After cooling, the dark brown solid product was collected and washed, and extracted repeatedly with small quantities of boiling glacial acetic acid. By adding water to the combined extracts the **benzthiophanthrenequinone mixture** separated as a bright yellow or orange-yellow precipitate. The yield varied from 1.75 to 2.60 g. (46–68%). The crude material melted at 175–177° with preliminary sintering. Three crystallizations from glacial acetic acid, which were attended with considerable loss of material, gave orange needles melting at 178–180°. The color reactions were as described for pure VI. When a mixture of equal parts of the quinone preparation, m. p. 178–180°, and of VI (m. p. 166.5–167°) was heated in a capillary tube the melting point was 169.5–170.5°.

Anal. Calcd. for $C_{16}H_8O_2S$: C, 72.71; H, 3.05; S, 12.13. Found: S, 12.05.

The results were essentially the same as described when 2-α-thenoyl-1-naphthoic acid (I) was used as starting material, or when the mixture of acids I and II (m. p. 141–156°) was employed, the thrice crystallized products melting at 178–180° and giving no depression when mixed with the above sample. Several attempts were made to effect a separation of isomers, or to remove a possible contaminant by treatment with potassium dichromate in acetic acid. The latter process produced little change in the melting point and the composition remained the same (found: C, 72.94; H, 3.28); four more crystallizations raised the melting point to 199–201° (found: C, 72.59; H, 3.36). The material from the acid mixture likewise gave small crops of quinone, m. p. 190–192°, and a minute amount of material melting at 197–199° (found: C, 72.76; H, 3.25). On attempting to isolate a pure isomer from the mother liquors the same slow rise in melting point was encountered.

4,9-Dimethyl-5,6-benzthiophanthrene (**XVI**).—One gram of the crude benzthiophanthrenequinone preparation obtained from the mixture of keto acids was treated with methylmagnesium iodide and the solution was poured into hydriodic acid and methanol exactly according to the procedure described for the case of 1,2-benzanthraquinone. The iodo compound separated on adding acetic acid as a light tan, crystalline product. It was reduced with stannous chloride in dioxane by the method detailed above. The precipitated material consisted of 0.85 g. of light brown crystals melting over the range of 130–145°. It was dissolved in benzene and passed through a tower of alumina, which adsorbed much colored material. On evaporation of the filtrate and crystallization of the product four times from glacial acetic acid (moderately soluble), there was obtained 0.22 g. (22%) of beautiful, faintly yellow plates, m. p. 156–159°. One more crystallization raised the melting point to 158–159° and further purification by crystallization on through the picrate produced no further change.

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[22] Martin, THIS JOURNAL, 58, 1438 (1936); Fieser and Seligman, *ibid.*, 60, 170 (1938).

[23] Microanalysis by Dr. Carl Tiedcke.

Anal. Calcd. for $C_{18}H_{14}S$: C, 82.40; H, 5.38; S, 12.22. Found: C, 82.64; H, 5.52; S, 12.21.

The **picrate** was prepared from the above purified sample and crystallized from alcohol. It formed purplish black microneedles, m. p. 135.5–137°.

Anal. Calcd. for $C_{18}H_{14}S \cdot C_6H_3O_7N_3$: N, 8.55. Found: N, 8.33.

When the synthesis was repeated using the quinone resulting from cyclization of the pure higher melting keto acid (II), the same dimethyl compound was produced; melting point and mixed melting point, 157–159° (found: C, 82.17; H, 5.70).

Methylmethoxymethylbenzthiophanthrene.—This substance was first encountered in an early experiment in which the solution obtained from methylmagnesium iodide and the benzthiophanthrenequinone mixture was treated at 0° with methanol and a few drops of concentrated hydrochloric acid. Processing of the tarry reaction mixture afforded a small amount of a solid product which after purification from methanol formed pale yellow needles, m. p. 121–122°.

Anal. Calcd. for $C_{19}H_{16}OS$: C, 78.05; H, 5.51. Found: C, 78.12; H, 5.44.

An ether of the same melting point and mixed melting point was later obtained in 25% yield from the quinone by treatment of the iodo compound with sodium methoxide in hot methanol. The most likely structure is that of 4-methyl-9-methoxymethyl-5,6-benzthiophanthrene.

Summary

A novel sequence of reactions which provides a very convenient route to 9,10-dimethyl-1,2-benzanthracene and related compounds was encountered in the course of an unsuccessful attempt to apply known methods of synthesis to the problem of preparing thiophene isologs of certain carcinogenic hydrocarbons. The Grignard derivative resulting from the action of methylmagnesium iodide on 1,2-benzanthraquinone, when treated directly with methanol, hydriodic acid and acetic acid, affords 9-methyl-10-iodomethyl-1,2-benzanthracene, and this can be reduced very smoothly to the hydrocarbon with stannous chloride in dioxane.

The intermediate 10-iodomethyl compound was also synthesized in 90% yield by a second novel reaction consisting in the iodomethylation of 9-methyl-1,2-benzanthracene.

The first series of reactions was applied successfully to the synthesis of 4,9-dimethyl-5,6-benzthiophanthrene, although some complications arose from the occurrence of a keto acid rearrangement in the cyclization reaction employed for the preparation of the benzthiophanthrenequinone required as starting material.

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The Alkylation of Benzene with *d-s*-Butyl Alcohol

BY CHARLES C. PRICE AND MARION LUND

The purpose of the present investigation was to determine the stereochemical course for certain cases of alkylation of the Friedel–Crafts type involving reactions at an asymmetric carbon atom. The boron fluoride and aluminum chloride catalyzed alkylations of benzene with *s*-butyl alcohol were chosen since, in each case, the reaction has been reported to proceed without isomerization of the alkyl group.[1]

The alkylation of benzene with *dl-s*-butyl alcohol in the presence of one equivalent of either of these catalysts gave *dl-s*-butylbenzene in yields of 50–60%. In two experiments using *d-s*-butyl alcohol ($[\alpha]^{20}\text{D}$ +11.05° and +11.36°) with boron fluoride as the catalyst, the *s*-butylbenzene formed was levorotatory ($[\alpha]^{20}\text{D}$ −0.15° and −0.16°) but with aluminum chloride as the catalyst the product was a racemic mixture.

The sign of rotation of the active *s*-butylbenzene does not necessarily indicate the configuration of the asymmetric carbon atom involved, although the change of sign during alkylation would at least lead one to suspect the possibility of a Walden inversion. It is interesting to note in this connection that Sprung and Wallis[2] observed no change in the sign of rotation after the rearrangement of the *s*-butyl group in *d-s*-butyl phenyl, *m*-cresyl and *p*-cresyl ethers by mixtures of sulfuric and acetic acids or zinc chloride and acetic acid. Here again, of course, the sign of rotation may have no relation to the configuration of the asymmetric carbon atom. Both cases,

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(1) (a) McKenna and Sowa, THIS JOURNAL, **59**, 470 (1937); (b) Huston and Hsieh, *ibid.*, **58**, 439 (1936).

(2) Sprung and Wallis, *ibid.*, **56**, 1715 (1934); Gilbert and Wallis, *J. Org. Chem.*, **5**, 184 (1940).