Synthesis of Some Tricyclic Analogs of Tetracycline

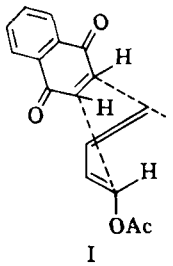
By HOWARD J. SCHAEFFER and GIRISH B. CHHEDA

Several tricyclic analogs of the tetracyclines were prepared through the Diels-Alder reaction. 1,4-Naphthoquinone was combined with 1-acetoxy-1,3-butadiene to give the adduct, 1-acetoxy-1,4,4a,9a-tetrahydroanthraquinone-9,10. Hydride reduction of the key adduct gave 1-acetoxy-1,4,4a,9,9a,10-hexahydro-9-hydroxy-10-ketoanthracene. This product, after several subsequent reactions, gave two isomeric 1,4,4a,-9,9a,10 - hexahydro - 9 - hydroxy - 9 - O - (2′ - tetrahydropyranyl) - 1,10 - dioxoanthracenes. The attempted Diels-Alder condensation of these isomers with 1-acetoxy-1,3-butadiene did not generate tetracyclic isomers. The synthesis and stereochemical assignment of these and other tricyclic compounds are described.

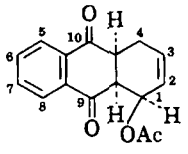
A NUMBER OF the attempted syntheses of linear tetracyclic compounds related to the naturally occurring antibiotics have employed multiple Claisen or Michael-type condensations for the construction of one or more rings of the desired tricyclic or tetracyclic compounds (1–4). It appeared that linear tetracyclic compounds could be synthesized from a properly activated intermediate by the Diels-Alder reaction. Therefore, using model compounds, we initiated a study of the synthesis of certain tricyclic and tetracyclic compounds in which the Diels-Alder reaction is employed.

The reaction of 1-acetoxy-1,3-butadiene (5) with 1,4-naphthoquinone was chosen as the first step in our study. The condensation of the diene and 1,4-naphthoquinone proceeded smoothly in refluxing benzene solution to give the adduct (II) in good yield (6, 7). The facile condensation of the diene with 1,4-naphthoquinone suggested that the diene must be predominantly *trans*, since it has been established that *cis*-1-substituted dienes are extremely sluggish in the Diels-Alder reaction and generally undergo polymerization (8–10).

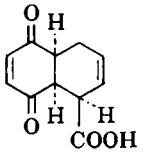
The spatial configuration of the adduct (II) has been assigned on the following grounds. On the basis of the well-known stereospecificity of the Diels-Alder reaction, we can assume that the newly formed ring in the adduct was *cis*-fused. The combination of the diene and quinone should proceed through the transition state (I) generally accepted for the Diels-Alder reaction, and thus would lead to an adduct with the stereochemistry as shown in II.[1] The steric orientation of the hydrogen at C_1 with respect to bridgehead hydrogens is capable of being derived from the classic "Alder-Stein Rules" (11). Few examples of similar steric situation can be cited. Woodward and his associates (12) have established that the adduct prepared from vinylacrylic acid and quinone has the stereochemistry shown in III.



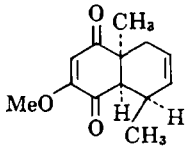
I



II

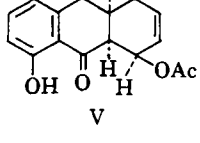


III



IV

Bloom (13) has proved that the stereochemistry of the adduct prepared from *p*-methoxytoluquinone and piperylene is correctly described by structure IV. Inhoffen and his associates (14) have made similar assumptions in assigning the stereochemistry of the adduct prepared from juglone[2] and 1-acetoxy-1,3-butadiene as shown in V.



V

From this knowledge we are most probably justified in assigning the stereochemical configurations of the three asymmetric centers in the adduct as shown in II.

Some preliminary studies with the key adduct (II) served to characterize its functions and gave valuable information about its reactivity in acidic and basic media. Treatment of the adduct with dilute solutions of methanolic ammonia or sodium

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[1] The chemical name for the adduct, according to the numbering shown in II, is 1-acetoxy-1,4,4a,9a-tetrahydroanthraquinone-9,10. This numbering of the tricyclic compounds is followed throughout the text.

[2] Juglone is 5-hydroxynaphthaquinone-1,4.

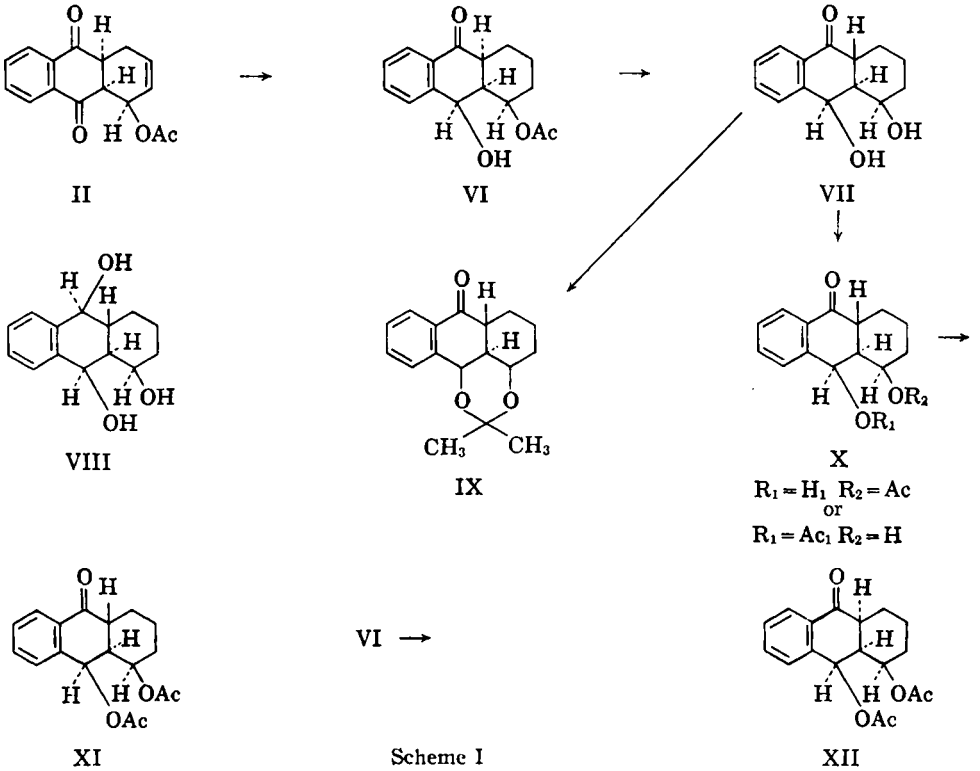
methoxide in methanol resulted in spontaneous elimination of acetic acid with concomitant oxidation of the alicyclic ring to give a quantitative yield of anthraquinone-9,10. These results establish that the acetate group of II cannot be removed until the activating effects of the keto groups have been removed. Therefore, a number of attempts were made to convert the ketone functions into their corresponding ketal by allowing II to react with ethyl orthoformate or with ethylene glycol catalyzed with *p*-toluenesulfonic acid or boron trifluoride; however, in all cases the only product which was isolated was anthraquinone-9,10.

Several attempts were made to convert the tricyclic adduct into a tetracyclic adduct by allowing II to react with an excess of 1-acetoxy-1,3-butadiene or 2,3-dimethyl-1,3-butadiene with and without a catalytic amount of aluminum chloride, but the only product which could be isolated was anthraquinone-9,10. Thus, it became apparent that a reduced form of adduct II would be more valuable for further synthetic studies.

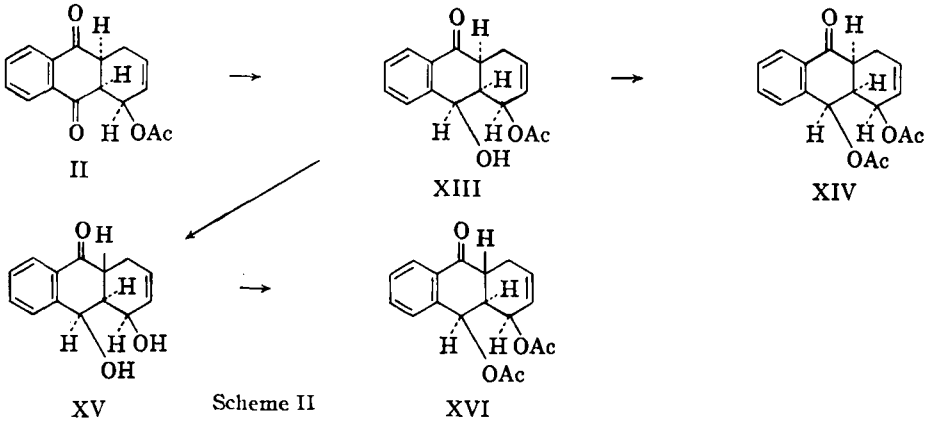
When II was hydrogenated using a palladium-on-charcoal catalyst, not more than 2 mol. equivalents of hydrogen could be introduced. A tetrahydro derivative (VI) of the adduct was obtained in a 45% yield, suggesting reduction of the double bond and of only one keto group. The infrared spectrum supported this data, in that it exhibited carbonyl absorption at 1690 cm.$^{-1}$ and an hydroxyl peak at 3450 cm.$^{-1}$; in addition, the ester carbonyl peak was lowered to 1715 cm.$^{-1}$ from 1740 cm.$^{-1}$ in the adduct (II). This lowering was probably due to the hydrogen bonding between the generated hydroxyl and the carbonyl group of the acetate, thus indicating that the reduction might have occurred at C_9. To establish that the reduced product had the structure VI, rather than the alternate possibility in which the hydrogenation had occurred at C_{10}, it was converted into a diol (VII) by treatment with a solution of methanolic ammonia. The limited solubility of the diol (VII) in boric acid solutions thwarted the study of changes in pH of boric acid solutions containing the diol (VII).

In addition to the indication from infrared spectra, certain preliminary chemical studies suggested that in the catalytic reduction of the adduct (II), the hydroxyl group was generated at C_9. To establish unequivocally that the hydroxyl group of acetoxy alcohol (VI) was located at C_9, we studied the preparation of an isopropylidene derivative in a model compound which definitely had hydroxyls at C_1 and C_9. The model compound was the triol (VIII) which was readily prepared in good yields by catalytic reduction of the diol (VII) with a rhodium-on-alumina catalyst. When the triol was stirred in an acetone solution containing anhydrous copper sulfate and a catalytic amount of sulfuric acid, an excellent yield of the desired isopropylidene derivative was obtained. Similarly, when the diol (VII) was stirred with acetone using a method identical to that for the model compound, a good yield of the isopropylidene derivative (IX) of the diol was obtained. The infrared spectra of the isopropylidene derivatives exhibited characteristic absorption at 1380 cm.$^{-1}$ for *gem*-dimethyl group. These results established that the structure VII was correct for the diol and that the acetoxy alcohol obtained by catalytic reduction of the adduct II had structure VI.

We found that during the alkaline methanolysis of acetoxy alcohol VI the *cis*-ring juncture was equili-



Scheme I



Scheme II

brated to *trans*. This was demonstrated as follows. The diol VII, when treated with one equivalent of acetic anhydride in pyridine gave a monoacetate (X) which melted at 145–146°. The infrared spectrum supported its gross structure since it exhibited peaks at 3490, 1735, and 1660 cm.$^{-1}$. The monoacetate (X) was thus clearly different from the acetoxy alcohol (VI) obtained from the adduct (II). The monoacetate (X) was reacetylated with excess acetic anhydride in pyridine; a diacetate (XI) was obtained, m.p. 172°. Similarly, when acetoxy alcohol (VI) was acetylated, a different diacetate (XII) was obtained, m.p. 158°. The infrared spectra of these two diacetates showed peaks for acetate and carbonyl groups but were not identical. The production of two different diacetates can be rationalized if it is assumed that during the removal of the acetate, the *cis*-ring juncture of VI underwent isomerization to *trans*. Parenthetically, it was found that the methanolysis of acetoxy alcohol (VI) by sodium methoxide gave the same isomerized diol (VII).

The introduction of asymmetry at C_9 in VI through catalytic reduction necessitates the assignment of configuration of this center relative to the configuration at the other asymmetric centers. Most probably the attack during catalytic reduction would occur on the convex face of the adduct (II), and thus the stereochemical orientation of the asymmetric centers in the acetoxy alcohol (VI) would be as depicted in VI.

Methanolysis of acetoxy alcohol (VI) by methanolic ammonia resulted in isomerization of position C_{4a}. Hence, the stereochemistry of the diol would be as assigned in formula VII. Because of this isomerization, the structure X for monoacetate is questionable with respect to the relative positions of acetate and hydroxy group. However, the stereochemistry of monoacetate would remain as shown in formula X. Stereochemically, the diacetates XI and XII differ at positions C_{4a}, XI being *trans*-fused and XII being *cis*-fused.

The stereochemical assignments of the triol (VIII) follow from that of the diol (VII), with the assumption that the attack during the reduction of C_{10} would occur on the α-face of the diol. Similarly, the steric orientations of the isopropylidene diol IX and the isopropylidene triol are capable of being derived from the parent compounds. The formation of six-membered isopropylidene derivatives from the diol and the triol besides proving the relative positions of hydroxyls offers support to the assignment of the *cis* configuration to the C_1 and C_9 hydroxyls.

After observing the results of the catalytic hydrogenation of the adduct (II), we became interested in investigating the chemical reduction of II. When the adduct was allowed to react with an excess of lithium aluminium hydride, two products were obtained: (*a*) an acetoxy alcohol (XIII) and (*b*) a product whose elemental analysis indicated that it was a diol.[3] The acetoxy alcohol (XIII) exhibited a peak at 1715 cm.$^{-1}$ for ester carbonyl and at 1690 cm.$^{-1}$ for a ketone. The position of acetate absorption was again lowered due to hydrogen bonding as it was in the hydroxy acetate (VI), suggesting that most probably the ketone which was in the vicinity of acetate has been reduced. To establish the position of the hydroxyl group in XIII, it was converted to the diol (XV) by treatment with methanolic ammonia. The diol (XV), when stirred in acetone containing copper sulfate and a catalytic amount of sulfuric acid, formed the isopropylidene derivative which exhibited infrared absorptions at 1380 cm.$^{-1}$ for the *gem*-dimethyl group, at 1690 cm.$^{-1}$ for carbonyl, and at 1660 cm.$^{-1}$ for a double bond. The formation of the isopropylidene derivative thus established the structure of the reduction product as that shown in XIII.

The preparation of the acetoxy alcohol (XIII) by lithium aluminum hydride reduction of II resulted in variable and frequently low yield of the desired product. Therefore, other methods of reduction of II were sought. After several variations, it was found that sodium borohydride reduction of II gave the acetoxy alcohol (XIII) in 65% yield.

For stereochemical studies, the alcohol (XIII) and the diol (XV) were allowed to react with an excess acetic anhydride in pyridine. The alcohol XIII gave a diacetate (XIV), m.p. 182°, and showed the expected peaks at 1735 cm.$^{-1}$ for ester carbonyl, at 1690 cm.$^{-1}$ for a ketone, and 1650 cm.$^{-1}$ for a double bond. However, the diacetate (XVI) obtained from the diol (XV) melted at 160–161° and exhibited the corresponding peaks at 1745, 1680, and 1660 cm.$^{-1}$ in its infrared spectrum. These results indicate that alcohol XIII underwent

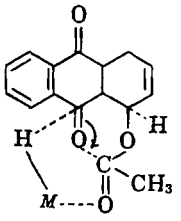
[3] Since we were interested mainly in the acetoxy alcohol (XIII), extensive structural work was not carried out on the diol. It was shown, however, that the diol was not merely deacetylated XIII (see text for structural studies on XIII).

an isomerization from a *cis*-ring juncture to a *trans* one during the treatment with methanolic ammonia in preparation of the diol (XV). That XIII had a *cis*-ring juncture was shown by the fact that catalytic hydrogenation of the double bond in XIII gave VI in excellent yields.

The assignment of the stereochemistry of the hydroxyl at C_9 in XIII is based on the following considerations. It has been shown by Beyler and Sarett (15) that reduction of *cis*-1,4-diketodecalin with lithium aluminum hydride gives only that diol in which the hydroxyl groups are *trans* to the bridgehead hydrogen atoms. Furthermore, it can be assumed from Cram's principle of asymmetric reduction (16) that the attacking group would enter from the least hindered side of the molecule. These data permitted us to assign the stereochemistry of the product obtained by the lithium aluminum hydride reduction of the adduct (II) as that shown in XIII. Inhoffen and his associates have also shown that the ring junctures remain *cis* after lithium aluminum hydride reduction of similar type of compounds (14).

The stereochemistry of the diol (XV) has been assigned as shown in XV from its progenitor XIII, which isomerizes at C_{4a} during ester hydrolysis. Thus, the diacetates XIV and XVI should be epimers at C_{4a}, diacetate XIV being *cis*-fused. The formation of an isopropylidene derivative from diol (XV) supported the *cis* orientation of C_1 and C_9 hydroxyls. In addition, XV on catalytic hydrogenation of the double bond was converted into VII, thereby supporting the assignment of the *trans*-ring juncture in XV.

The results of catalytic as well as chemical reduction of the adduct II indicate that the C_9 carbonyl is far more reactive than the C_{10} carbonyl, in spite of its being partially shielded by the C_1 acetoxy group. These observations prompt us to suggest that there may be participation by a neighboring acetoxy group in these reductions. For example, in the case of reductions with metal hydrides the adduct (II) may pass through the transition state



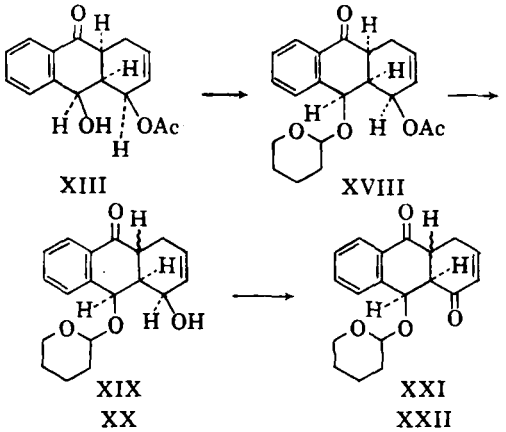
XVII

XVII wherein a six-membered ring may be formed. Inhoffen and his colleagues (14) have observed similar cases in the Grignard reactions of the quinone adducts with 1-acetoxy-1,3-butadiene.

For the attempted synthesis of tetracyclic compounds, the acetoxy alcohol (XIII) was a key intermediate, since it is substituted in a manner that ring C could be converted into a dienophile. As a preliminary study for preparing tetracyclic compounds, we attempted to condense 1-acetoxy-1,3-butadiene with the acetoxy alcohol (XIII); however, only starting material was recovered. The use of aluminum chloride to catalyze this condensation did not give better results. To carry out the reactions contemplated for the construction of a suitable intermediate which could serve as a good dienophile in Diels-Alder reaction, it became necessary to block the free hydroxyl group of acetoxy alcohol (XIII). When a slurry of acetoxy alcohol in anhydrous ether was stirred with 5 mol. equivalents of dihydropyran using *p*-toluenesulfonic acid as a catalyst, excellent yields of blocked material (XVIII) were obtained. Our choice of pyran as a blocking group was based on the fact that it would be stable if basic media, but easily removed in acid. The blocked ester (XVIII), as expected, did not show absorption for hydroxyl group in infrared spectrum, but exhibited other predicted absorptions for an ester, ketone, and ether. As expected, when XVIII was allowed to react with lithium aluminum hydride, the keto group at C_{10} and the acetoxy group at C_1 were reduced to alcohol functions.

When the pyranylated ester (XVIII) was hydrolyzed with 1 mol. equivalent of sodium hydroxide, two isomeric alcohols were obtained in almost equal yields (XIX and XX). The combined yield of the two isomers was about 40%. The residual syrup contained more of the low melting isomer (XX), as shown by infrared and oxidation studies, but it was difficult to separate by crystallization. The use of sodium methoxide and potassium hydroxide did not increase the yields of alcohols. Methanolic ammonia and *n*-butylamine did not remove the ester.

Isomerization studies were done in an attempt to determine the stereochemical differences of these two alcohols. When a methanol solution of the alcohol XIX was equilibrated in presence of 1 mol. equivalent of sodium hydroxide at reflux temperatures, 84% of the unchanged alcohol XIX was recovered. In a similar experiment on the isomer XX the recovery of unchanged alcohol was very low. These experiments, though inconclusive, indicate that the high melting isomer XIX may be *trans*-fused and the isomer XX may be *cis*-fused.



XIII XVIII

XIX XXI

XX XXII

It was necessary to oxidize the free hydroxyl to obtain a dienophile from these alcohols. When the high melting alcohol (XIX) was stirred with a chromium trioxide–pyridine complex in pyridine solution, a crystalline oxidation product (XXI) was obtained in moderate yield. The product melted at 113° and exhibited infrared absorption at 1680 $cm.^{-1}$ for carbonyl, 1620 $cm.^{-1}$ for a double bond, and 1135 $cm.^{-1}$ for ether. When the low melting alcohol (XX) was oxidized by a similar procedure, a different oxidation product (XXII) was obtained. This product has a melting point of 146–147°, and

it displayed infrared absorptions at 1690, 1675 cm.$^{-1}$ for carbonyl, and 1120 cm.$^{-1}$ for ether. The formation of two different oxidation products (XXI and XXII) from the two isomeric alcohols (XIX and XX) suggests that the alcohols as well as the oxidation products differ most probably in ring juncture.

Attempted Diels-Alder reaction of XXI with 1-acetoxy-1,3-butadiene under a wide variety of reaction conditions did not give the corresponding tetracyclic compound; a product which was formed in low yield in this reaction had an empirical formula of $C_{19}H_{20}O_4$ and appears to be a stereoisomer of the starting material (XXI). The attempted Diels-Alder reaction of XXII and 1-acetoxy-1,3-butadiene resulted in decomposition if high temperatures were employed, and the desired product could not be isolated. At low temperatures no reaction occurred. Thus, neither XXI nor XXII served as a useful dienophile in the Diels-Alder reaction.

EXPERIMENTAL[4]

1 - Acetoxy - 1,2,3,4,4a,9,9a,10 - octahydro - 9-hydroxy-10-ketoanthracene (VI).—A solution of 2.70 Gm. (10.0 mmoles) of II (6) in 200 ml. of ethanol was hydrogenated using 0.270 Gm. of a 5% palladium-on-charcoal catalyst in a Parr hydrogenator at an initial pressure of 38.8 p.s.i. Hydrogenation was continued until no more hydrogen was absorbed (19.2 mmoles). The catalyst was removed by filtration; the pale yellow filtrate was decolorized with charcoal and evaporated *in vacuo*. The syrupy residue was crystallized from a mixture of benzene-hexane and gave 1.26 Gm. (45.9%) of the desired product, m.p. 126°. After three recrystallizations of the crude material from a mixture of benzene-hexane, the analytically pure material was obtained, m.p. 130–131°. γ in cm.$^{-1}$ (KBr): 3450 (OH); 1715 (C=O acetate); 1690 (C=O). $\lambda_{max.}^{ethanol}$ 249.5 mμ, ($\epsilon \times 10^{-3}$) 7.06.

Anal.[5]—Calcd. for $C_{16}H_{18}O_4$: C, 70.04; H, 6.61. Found: C, 70.18; H, 6.64.

1,2,3,4,4a,9,9a,10 - Octahydro - 1,9 - dihydroxy-10-ketoanthracene (VII).—To a solution of 5.49 Gm. (20.0 mmoles) of VI in 50 ml. of methanol was added 100 ml. of 3.7% (w/v) ammonia in methanol. The mixture was allowed to stand at room temperature for 40 hours. The pink solution was decolorized with charcoal; the filtrate was evaporated under reduced pressure and gave 4.13 Gm. of crystalline solid. After crystallization from methanol, the crude product gave 2.12 Gm. of the desired product, m.p. 163°. Concentration of the mother liquor gave an additional 1.08 Gm. of the same material, m.p. 163°; yield, 3.20 Gm. (70.0%). After three recrystallizations of the crude material from methanol, the pure sample was obtained, m.p. 162–163°. γ in cm.$^{-1}$ (KBr): 3250 (OH); 1685 (C=O); 1600 (aromatic). $\lambda_{max.}^{ethanol}$ 247 mμ, ($\epsilon \times 10^{-3}$) 12.2.

Anal.—Calcd. for $C_{14}H_{16}O_3$: C, 72.29; H, 6.94. Found: C, 72.64; H, 7.06.

1,2,3,4,4a,9,9a,10 - Octahydro - 1,9,10 - trihydroxyanthracene (VIII).—A solution of 1.16 Gm. (5.00 mmoles) of VII in 200 ml. of ethanol was hydrogenated using 0.116 Gm. of rhodium-on-alumina catalyst in a Parr hydrogenator at an initial pressure of 50 p.s.i. The uptake of hydrogen stopped when 5.05 mmoles has been absorbed. The catalyst was removed by filtration, and the colorless filtrate was evaporated *in vacuo*. The white crystalline residue was recrystallized from a mixture of methanol-water and gave 0.782 Gm. of the desired product, m.p. 221°. Concentration of the mother liquor gave an additional 92 mg. of the desired product, m.p. 220°. The yield was 0.874 Gm. (74.6%).

Three recrystallizations of the crude product from methanol-water gave the analytical material, m.p. 220–221°. γ in cm.$^{-1}$ (KBr): 3200–3250 (OH); 2925 (CH).

Anal.—Calcd. for $C_{14}H_{18}O_3$: C, 71.79; H, 7.75; Found: C, 71.67; H, 7.82.

Isopropylidene Derivative of 1,2,3,4,4a,9,9a,10-Octahydro-1,9,10-trihydroxyanthracene.—To a solution of 0.117 Gm. (0.499 mmole) of VIII in 55 ml. of acetone were added 1 drop of sulfuric acid and 200 mg. of anhydrous copper sulfate. The reaction mixture was stirred for 72 hours at room temperature. After removing the copper sulfate by filtration, the filtrate was concentrated *in vacuo* at 20° to about half of the original volume. The concentrate was poured into 25 ml. of cold 2% sodium bicarbonate solution and refrigerated overnight. The white crystalline product was isolated by filtration, 0.070 Gm. (51.2%), m.p. 162–163°. The mother liquor was extracted with ether which, after drying over magnesium sulfate, then evaporation *in vacuo* yielded 0.028 Gm. of the crystalline material, m.p. 162–163°. The total yield was 0.098 Gm. (71.5%).

After three recrystallizations of the crude product from ethanol-water the analytically pure product was obtained, m.p. 162°. γ in cm.$^{-1}$ (KBr): 3500 (OH); 1385 (*gem*-dimethyl); 1110 (C—O—C).

Anal.—Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.47; H, 8.14.

Isopropylidene Derivative of 1,2,3,4,4a,9,9a,10-Octahydro-1,9-dihydroxy-10-ketoanthracene (IX).—To a solution of 0.232 Gm. (1.00 mmole) of VII in 15 ml. of acetone were added 1 drop of sulfuric acid and 0.065 Gm. of anhydrous copper sulfate; the reaction mixture was stirred for 66 hours at room temperature. After removing the copper sulfate by filtration, the filtrate was poured into 15 ml. of cold 2% sodium bicarbonate solution and refrigerated for 1 hour. The white crystalline product was isolated by filtration: yield, 0.178 Gm. (64.9%), m.p. 155°. The mother liquor was extracted with ether which was then evaporated *in vacuo*. Recrystallization of the solid residue from ethanol-water yielded 0.024 Gm., m.p. 153°. The yield was 0.202 Gm. (73.7%) of the desired material.

Recrystallization of the crude material from ethanol-water gave the analytical sample, m.p. 156°. γ in cm.$^{-1}$ (KBr): 1685 (C=O); 1600 (aromatic); 1380 (*gem*-dimethyl); 1105 (C—O—C).

Anal.—Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.11; H, 7.49.

iso - 1(9) - Acetoxy - 1,2,3,4,4a,9,9a,10 - octahydro-9(1) - hydroxy - 10 - ketoanthracene (X).—To a solution of 2.32 Gm. (10.0 mmoles) of VII in 25 ml. of pyridine was added 0.992 ml. (1.07 Gm., 1.05 mmoles) of acetic anhydride. The reaction mixture

[4] The ultraviolet spectra were determined on a Perkin-Elmer model 4000 A spectrophotometer; the infrared spectra were determined on a Perkin-Elmer 137 spectrophotometer. The melting points were determined on a Kofler Heizbank and are corrected.

[5] The analyses reported in this paper were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

was allowed to stand at room temperature for 47 hours and then heated under reflux for 20 minutes. The reaction solution was poured into ice-water and was left in a refrigerator for 40 hours. The desired monoacetate crystallized and was isolated by filtration; yield, 1.43 Gm. (52.2%), m.p. 137–138°.

Two recrystallizations of the crude product from benzene-hexane raised the melting point to 145–146°. γ in cm.$^{-1}$ (KBr): 3490 (OH); 1735 (C=O ester); 1660 (C=O); 1600 (aromatic); 1225 (C—O—ester).

Anal.—Calcd. for $C_{16}H_{18}O_4$: C, 70.04; H, 6.61. Found: C, 70.68; H, 6.69.

iso - 1,9 - Diacetoxy - 1,2,3,4,4a,9,9a,10 - octahydro-10-ketoanthracene (XI) (Equilibrated).—To a solution of 0.274 Gm. (1.00 mmole) of X in 2 ml. of pyridine was added 0.3 ml. of acetic anhydride. The reaction mixture was allowed to stand at room temperature for 1 day, then poured into ice-water. After refrigeration for 2 hours, the white crystalline product was isolated by filtration; 0.294 Gm. (93.0%), m.p. 174°. Recrystallization of this material from benzene-hexane gave 0.220 Gm. (69.5%) of the desired product, m.p. 174°. Concentration of the mother liquor gave an additional 0.030 Gm. of the same material, m.p. 174°. The yield was 0.250 Gm. (79.2%).

Two recrystallizations of the crude product from ethanol gave the analytical material, m.p. 172°. γ in cm.$^{-1}$ (KBr): 1735 (C=O ester); 1680 (C=O); 1600 (phenyl); 1230 (C—O ester).

Anal.—Calcd. for $C_{18}H_{20}O_5$: C, 68.33; H, 6.37. Found: C, 68.04; H, 6.41.

1,9 - Diacetoxy - 1,2,3,4,4a,9,9a,10 - octahydro-10-ketoanthracene (XII) (Nonequilibrated).—To a solution of 0.274 Gm. (1.00 mmole) of VI in 2 ml. of pyridine was added 0.3 ml. of acetic anhydride. The reaction mixture was allowed to stand at room temperature for 1 day, then poured into ice-water. After refrigeration for 2 hours, the white crystalline product was isolated by filtration (0.291 Gm.), m.p. 148°. After recrystallization of the crude product, 0.150 Gm. (m.p. 159°) of the desired product was obtained. The filtrate, after concentration, gave 0.030 Gm. of the desired material, m.p. 155°. The yield was 0.180 Gm. (56.5%).

After two recrystallizations of the crude material from ethanol, the pure product was obtained, m.p. 158–159°. γ in cm.$^{-1}$ (KBr): 1740 (C=O ester); 1675 (C=O); 1600 (aromatic); 1225 (C—O—ester). $\lambda_{max.}^{ethanol}$ 247.5; ($\epsilon \times 10^{-3}$), 11.0.

Anal.—Calcd. for $C_{18}H_{20}O_5$: C, 68.33; H, 6.37. Found: C, 68.35; H, 6.49.

1 - Acetoxy - 1,4,4a,9,9a,10 - hexahydro - 9 - hydroxy-10-ketoanthracene (XIII).—To a stirred solution of 0.283 Gm. (7.50 mmoles) of sodium borohydride in 100 ml. of 95% ethanol was added with stirring over a period of 4 to 5 minutes a warm solution (at 40°) of 4.05 Gm. (15.0 mmoles) of II in 160 ml. of 95% ethanol. The reaction mixture was then stirred for 2 hours at room temperature. After cooling the reaction mixture in an ice bath, about 20 Gm. of ice and 60 ml. of water were added. After 5 minutes of additional stirring, 15 ml. of 5% hydrochloric acid was added; the whole reaction mixture was stirred for 15 minutes. The mixture was then cooled and filtered to remove the insoluble anthraquinone, 0.490 Gm. (15.7%). Concentration of the filtrate to a volume of about 80 ml. caused the crystallization of the desired product which was isolated by filtration; yield, 2.65 Gm. (65.0%) of XIII, m.p. 146–147°.

Two recrystallizations of the crude material from benzene-hexane gave the pure product, m.p. 149–150°. γ in cm.$^{-1}$ (KBr): 3490 (OH); 1715 (C=O, ester); 1690 (C=O); 1650 (C=C, sh); 1600 (aromatic); 1240 (C—O—ester). $\lambda_{max.}^{ethanol}$ 250, ($\epsilon \times 10^{-3}$) 9.09. TLC (silica gel) ($CHCl_3$) one spot.

Anal.—Calcd. for $C_{16}H_{14}O_4$: C, 70.57; H, 5.92. Found: C, 70.37; H, 6.12.

Lithium Aluminum Hydride Reduction of 1-Acetoxy-1,4,4a,9a-tetrahydroanthraquinone-9,10.—To a refluxing solution of 8.11 Gm. (30.0 mmoles) of II in 470 ml. of ether was added with stirring a slurry of 1.13 Gm. (30.0 mmoles) of lithium aluminum hydride in 550 ml. of ether over a period of 20 minutes. At the end of 2.5 hours of refluxing with stirring, the reaction mixture was cooled and 200 ml. of cold water was added, followed by the addition of 55 ml. of 5% hydrochloric acid. The mixture was stirred for a few minutes and then separated; the aqueous layer was extracted with ether (6 × 100 ml.). The organic phase, combined with ethereal extracts, was washed with 5% sodium bicarbonate solution (3 × 20 ml.), dried over magnesium sulfate, then concentrated *in vacuo* to about 40 ml. The precipitate of the crystalline diol, *iso*-1,4,4a,9,9a,10-hexahydro-1,9-dihydroxy-10-ketoanthracene, was isolated by filtration; yield 1.93 Gm. (27.9%), m.p. 163–164°.

The mother liquor gave, after concentration and cooling, 0.966 Gm. (11.8%) of XIII; m.p. 147–148°.

Two recrystallizations of the diol from methanol gave the pure product, m.p. 165–166°. γ cm.$^{-1}$ (KBr): 3470, 3325 (OH); 1665 (C=O); 1650 (C=C sh); 1600 (aromatic). TLC (silica gel) ($CHCl_3$) one spot.

Anal.—Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.12. Found: C, 72.85; H, 6.19.

1,4,4a,9,9a,10 - Hexahydro - 1,9 - dihydroxy - 10-ketoanthracene (XV).—To a solution of 2.72 Gm. (10 mmoles) of XIII in 100 ml. of methanol was added 75 ml. of 3.7% (w/v) ammonia in methanol. After allowing the reaction mixture to stand at room temperature for 23 hours, the solution was filtered to remove 150 mg. of anthraquinone. The filtrate was evaporated *in vacuo;* the crude residue was dissolved in methanol, decolorized with charcoal, then allowed to crystallize from methanol. The desired product was isolated by filtration; yield, 1.43 Gm., m.p. 170°. The mother liquor after concentration gave 0.203 Gm. of the same diol, m.p. 168–169°; the total yield of the diol was 1.63 Gm. (70.8%).

After two recrystallizations of the crude product from methanol-water, the analytical sample was obtained, m.p. 171–172°. γ in cm.$^{-1}$ (KBr): 3390 (OH); 1685 (C=O), 1650 (C=C sh); 1600 (aromatic). $\lambda_{max.}^{ethanol}$ 250; ($\epsilon \times 10^{-3}$) 10.7. TLC (silica gel) ($CHCl_3$) one spot.

Anal.—Calcd. for $C_{14}H_{14}O_3$; C, 73.02; H, 6.13. Found: C, 72.96; H, 6.22.

Isopropylidene Derivative of 1,4,4a,9,9a,10-Hexahydro-1,9-dihydroxy-10-ketoanthracene.—To a solution of 231 mg. (1.00 mmole) of XV in 25 ml. of acetone was added 1 drop of concentrated sulfuric acid and 150 mg. of anhydrous copper sulfate. The reaction mixture was stirred for 66 hours at room

temperature. The copper sulfate was removed by filtration, the filtrate was poured into 20 ml. of cold 1% sodium bicarbonate solution. After cooling the solution, the crystalline white solid which separated was isolated by filtration; yield 111 mg., m.p. 154°. The filtrate was extracted with ether, which was then evaporated *in vacuo*. The residue, after two recrystallizations from ethanol-water yielded 26 mg. of the desired material, m.p. 151°. The total yield of the isopropylidene derivative was 137 mg. (51.0%).

Recrystallization of the crude material first from ethanol-water and then from acetone-water gave the analytical sample, m.p. 155–156°. γ in cm.$^{-1}$ (KBr): 1380, 1200, 773 (C-$(CH_3)_2$); 1690 (C=O); 1660 (C=C); 1600 (aromatic). $\lambda_{max.}^{ethanol}$ 247, ($\epsilon \times 10^{-3}$) 11.8.

Anal.—Calcd. for $C_{17}H_{18}O_3$; C, 75.53; H, 6.71. Found: C, 75.15; H, 7.01.

1,4,4a,9,9a,10 - Hexahydro - 1,9 - diacetoxy - 10-ketoanthracene (XIV).—To a solution of 504 mg. (1.85 mmoles) of XIII in 8 ml. of pyridine was added 2 ml. of acetic anhydride. The reaction mixture was allowed to stand at room temperature for 48 hours, then poured into 20 ml. of cold water. The mixture rapidly crystallized when placed in a cold room for 4 hours. The crystalline XIV was isolated by filtration; yield, 537 mg. (96.0%), m.p. 180°.

Recrystallization of the crude material from ethanol gave the analytical sample, m.p. 182°. γ in cm.$^{-1}$ (KBr): 1735 (C=O ester); 1690 (C=O); 1650 (C=C sh); 1260 (C—O— ester).

Anal.—Calcd. for $C_{18}H_{18}O_5$: C, 68.77; H, 5.77. Found: C, 68.93; H, 5.56.

iso - 1,4,4a,9,9a,10 - Hexahydro - 1,9 - diacetoxy-10-ketoanthracene (XVI).—To a solution of 224 mg. (0.974 mmole) of XV in 5 ml. of pyridine was added 1 ml. of acetic anhydride. The reaction mixture was allowed to stand at room temperature for 48 hours, then poured into 15 ml. of cold water. The solution, which crystallized immediately, was cooled in a refrigerator for a 4.5-hour period and filtered. A 241-mg. (79.0%) quantity of white needles of XVI, m.p. 160–161°, was obtained. Recrystallization of the crude product from ethanol did not change the melting point. γ in cm.$^{-1}$ (KBr): 1745 (C=O ester); 1680 (C=O); 1660 (C=C sh); 1225 (C—O— ester).

Anal.—Calcd. for $C_{18}H_{18}O_5$: C, 68.77; H, 5.77. Found: C, 68.86; H, 5.98.

1 - Acetoxy - 1,4,4a,9,9a,10 - hexahydro - 9 - hydroxy - 9 - O - (2′ - tetrahydropyranyl) - 10 - ketoanthracene (XVIII).—A mixture of 6.87 Gm. (0.025 mole) of XIII, 10.5 Gm. (0.125 mole) of dihydropyran, and 0.15 Gm. of *p*-toluenesulfonic acid in 25 ml. of anhydrous ether, was stirred for 5 hours at room temperature. At the end of 5 hours, the reaction was chilled in an ice-bath and the desired product was isolated by filtration, washed with ether, and dried *in vacuo* at room temperature; yield 4.83 Gm., m.p. 129°. The filtrate was washed with 5% sodium bicarbonate solution (2 × 5 ml.), then with water (2 × 5 ml.). The ethereal solution was then dried over magnesium sulfate and evaporated *in vacuo* to a thick syrup which crystallized after cooling. The crystalline product was isolated by filtration; 2.20 Gm., m.p. 120–122°. Recrystallization of this crude material (2.20 Gm.) gave 1.66 Gm. of desired product, m.p. 129–130° in three crops. Thus the total yield of XVIII was 6.49 Gm. (73.0%).

Three recrystallizations of the crude product from methanol-water gave the analytical sample, m.p. 130°. γ in cm.$^{-1}$ (KBr): 1750 (C=O ester); 1695 (C=O); 1655 (C=C sh); 1600 (aromatic); 1235 (C—O ester); 1075, 1030 (—C—O—C ether). TLC (silica gel) ($CHCl_3$) one spot.

Anal.—Calcd. for $C_{21}H_{24}O_5$: C, 70.76; H, 6.79. Found: C, 70.92; H, 6.97.

1,4,4a,9,9a,10 - Hexahydro - 1,9,10 - trihydroxy-9 - O - (2′ - tetrahydropyranyl)anthracene.—To a stirred suspension of 570 mg. (15.0 mmoles) of lithium aluminum hydride in 170 ml. of ether was added over a period of 2 minutes a solution of 3.56 Gm. (10.0 mmoles) of XVIII in 170 ml. of ether. After stirring for 8 hours at room temperature, the reaction mixture was chilled and 150 ml. of water was added. The mixture was stirred for 30 minutes, and 1% hydrochloric acid (100 ml.) was added; stirring was continued for an additional 15 minutes. The aqueous layer was separated from the ether phase and extracted with ether (3 × 100 ml.). The ether extracts were combined and washed with 2.5% sodium bicarbonate solution (2 × 40 ml.) and then with water (2 × 50 ml.). The ether was dried over magnesium sulfate and evaporated *in vacuo* to a syrupy residue (3.48 Gm.). The residue was triturated with ether which caused the crystals of a desired product to appear. Filtration of the mixture gave 1.03 Gm. (32.6%) of crystalline white material, m.p. 158–160°. For analysis a small sample was recrystallized first from benzene and then from methanol; m.p. 161–162°. γ in cm.$^{-1}$ (KBr): 3300 (broad) (OH); 1650 (C=C); 1010 (C—O—C ether).

Anal.—Calcd. for $C_{19}H_{24}O_4$: C, 72.12; H, 7.64. Found: C, 72.11; H, 7.41.

1,4,4a,9,9a,10 - Hexahydro - 1,9 - dihydroxy 9 - O - (2′ - tetrahydropyranyl) - 10 - ketoanthracene (XIX) and (XX).—To a solution of 10.7 Gm. (30.0 mmoles) of XVIII in 300 ml. of methanol was added a solution of 1.26 Gm. (31.5 mmoles) of sodium hydroxide in a mixture of 105 ml. of methanol and 45 ml. of water. The reaction solution was heated under reflux for 6 hours. The mixture was cooled and filtered to remove anthraquinone (60 mg.). The filtrate was diluted with water (400 ml.) and concentrated under reduced pressure to about 500 ml. which caused the crystallization of the yellow product, 5.51 Gm. melting over a wide range (122–128°). The filtrate was extracted with ether (5 × 200 ml.), and the combined extracts were washed with water (2 × 100 ml.). The ether was dried over magnesium sulfate and evaporated *in vacuo*. There was obtained 3.40 Gm. of a residual oil.

Recrystallization of 5.51 Gm. of the yellow product and crystallization of the syrup from methanol gave in two crops 1.60 Gm. (17.2%) of the high melting alcohol (XIX), m.p. 159–161°.

Several recrystallizations of the crude high melting alcohol (XIX) from methanol gave a pure product, m.p. 162–163°. γ in cm.$^{-1}$ (KBr): 3500 (OH); 1695 (C=O); 1660 (C=C sh); 1600 (aromatic); 1120, 1020 (C—O—C pyran). $\lambda_{max.}^{ethanol}$ 251, ($\epsilon \times 10^{-3}$) 10.7. TLC (silica gel) ($CHCl_3$) one spot.

Anal.—Calcd. for $C_{19}H_{22}O_4$: C, 72.58; H, 7.05. Found: C, 72.52; H, 7.07.

After separation of the above high melting isomer (XIX), the mother liquors, when allowed to crystallize further, gave 2.04 Gm. (21.5%) of another isomer (XX), m.p. 127–128°.

For analysis, a small sample of low melting alcohol (XX) was recrystallized five times from methanol. There was obtained a pure product, m.p. 128–129°. γ in cm.$^{-1}$ (KBr): 3500 (OH); 1680 (C=O); 1650 (C=C sh); 1040, 1060, 1120 (—C—O—C pyran); $\lambda_{max.}^{ethanol}$ 247, ($\epsilon \times 10^{-3}$) 11.0. TLC (silica gel) ($CHCl_3$) one spot.

Anal.—Calcd. for $C_{19}H_{22}O_4$: C, 72.58; H, 7.05. Found: C, 72.85; H, 7.30.

1,4,4a,9,9a,10 - Hexahydro - 9 - hydroxy - 9 - O-(2′ - tetrahydropyranyl) - 1, 10 - dioxoanthracene (XXI).—To a solution of 1.88 Gm. (6.00 mmoles) of XIX in 30 ml. of pyridine was added 61 ml. of solution of chromium trioxide-pyridine complex (17) in pyridine containing 1.19 Gm. (11.9 mmoles) of chromium trioxide (three times the required quantity). The dark brown reaction mixture was then stirred for 10 hours at room temperature. Ether (250 ml.) was added to the reaction mixture which was then stirred for 10 minutes. The precipitated red material was removed by filtration. The filtrate was washed with water (2 × 100 ml.), dried over magnesium sulfate, evaporated *in vacuo*, and gave 1.45 Gm. of residual syrup. The residue was dissolved in ethanol, treated with charcoal, and allowed to crystallize. There was obtained 1.01 Gm. (54.0%) of crystalline product, m.p. 108–110°. Two recrystallizations of the crude product from ethanol gave the pure product, m.p. 111–113° (oil bath). γ in cm.$^{-1}$ (KBr): 1680 (C=O); 1620 (C=C); 1600 (aromatic); 1250, 1135, 1035 (—C—O—C ether); $\lambda_{max.}^{ethanol}$ 235 (broad), ($\epsilon \times 10^{-3}$) 13.2. TLC (silica gel) ($CHCl_3$) one spot.

Anal.—Calcd. for $C_{19}H_{20}O_4$: C, 73.05; H, 6.45. Found: C, 73.27; H, 6.56.

A chloroform solution of 1,4,4a,9,9a,10-hexahydro-9-hydroxy-1,10-dioxoanthracene XXI was shaken with 5% hydrochloric acid and then evaporated *in vacuo* to a syrupy residue. Crystallization of the residue gave a 1,4,4a,9,9a-10-hexahydro-9-hydroxy-1,10-dioxoanthracene, m.p. 152–153°.

Recrystallization of this product from methanol gave the pure product, m.p. 155–156°. γ in cm.$^{-1}$ (KBr): 3525 (H); 1690 (CO=O); 1660 (C=O conjugated); 1600 (aromatic); 1620 (C=C sh).

Anal.—Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.29. Found: C, 73.36; H, 5.44.

1,4,4a,9,9a,10 - Hexahydro - 9 - hydroxy - 9 - O-(2′ - tetrahydropyranyl) - 1, 10 - dioxoanthracene (XXII).—By an oxidation procedure similar to that used for XIX, 2.51 Gm. (8.00 mmoles) of XX gave 2.04 Gm. of a semisolid residue. Recrystallization of the residue from ethanol gave 1.11 Gm. (44.8%) of XXII, m.p. 144–145°. Two recrystallizations of the crude material from ethanol gave a sample for analysis, m.p. 146–147°. γ in cm.$^{-1}$ (KBr): 1690, 1675, (C=O). 1620 (C=C weak); 1600 (aromatic); 1300, 1120, 1030 (C—O—C ether); $\lambda_{max.}^{ethanol}$ 247, ($\epsilon \times 10^{-3}$) 11.2.

Anal.—Calcd. for $C_{19}H_{20}O_4$: C, 73.05; H, 6.45. Found: C, 73.18; H, 6.47.

Attempted Diels-Alder Reaction of 1,4,4a,9,9a,10-Hexahydro - 9 - hydroxy - 9 - O - (2′ - tetrahydropyranyl)-1,10-dioxoanthracene (XXI).—A mixture of 234 mg. (0.750 mmole) of XXI and 448 mg. (4.50 mmoles) of 1-acetoxy-1,3-butadiene in 20 ml. of benzene containing 10 mg. of hydroquinone was heated in a steel bomb at 130° for 66 hours. The cooled reaction mixture was evaporated *in vacuo*. The residue was triturated with cyclohexane, and a small amount of insoluble material was removed by filtration. Hexane was added to the filtrate which caused the separation of 12 mg. (3.5%) of a crystalline product, m.p. 137–140°. Two recrystallizations of the crude product from ether–petroleum ether gave the analytical sample which appears to be a stereoisomer of the starting material (XXI), m.p. 147–149°. γ in cm.$^{-1}$ (KBr): 1690 (C=O); 1650 (C=C sh); 1600 (aromatic).

Anal.—Calcd. for $C_{19}H_{20}O_4$: C, 73.05; H, 6.45. Found: C, 73.10; H, 6.61.

No further pure products could be obtained from the filtrate.

Conversion of 1-Acetoxy-1,4,4a,9,9a,10-hexahydro-9-hydroxy-10-ketoanthracene (XIII) into 1-Acetoxy - 1,2,3,4,4a,9,9a,10 - octahydro - 9 - hydroxy-10-ketoanthracene (VI).—A solution of 1.09 Gm. (4.00 mmoles) of XIII in 200 ml. of ethanol was hydrogenated using 108 mg. of 5% palladium-on-charcoal catalyst in a Paar hydrogenator at an initial pressure of 50 p.s.i. Hydrogenation was continued until no more hydrogen was absorbed. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo*. There was obtained 1.10 Gm. (101%) of crude crystalline residue. The crude material was recrystallized from methanol and gave 641 mg. (58.8%) of 1-acetoxy-1,2,3,4,4a,9,9a,10-octahydro-9-hydroxy-10-ketoanthracene (VI), m.p. 127–128°. An additional recrystallization of the product from ethanol gave the pure material, m.p. 128–129°, mixed m.p. 128–129° *with* an authentic sample of VI.

Conversion of 1,4,4a,9,9a,10-Hexahydro-1,9-dihydroxy-10-ketoanthracene (XV) into 1,2,3,4,4a,9,-9a,10 - Octahydro - 1,9 - dihydroxy - 10 - ketoanthracene (VII).—By a hydrogenation procedure similar to that described above, 161 mg. (0.693 mmoles) of XV was hydrogenated and gave 75 mg. (47%) of crude VII, m.p. 156–159°. Two recrystallizations of the crude product from methanol gave the pure sample, m.p. 162–163°, mixed m.p. 162–163°, with an authentic sample of VII.

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