Similar three-step spectroscopic examinations[43] were carried out for 4,5-phenanthrenediol and 1,6,8-tribromo-2,5-phenanthrenediol which were oxidized to purple and yellow solutions, respectively, but the spectra of these solutions were without character. Reduction afforded colorless solutions with spectra identical to that before reduction.

1,3,6,8-Tetrabromo-4,5-phenanthrenediol and 2,5-phenanthrenediol were oxidized to afford purple and yellow solutions, respectively. Both solutions gave spectra without character and no reduction experiments were attempted.

Assignment of Structures.—In our assignment of structure to the Fremy's salt oxidation products we bank heavily on the assumption that oxidation in which a new hydroxyl group results always occurs *ortho* or *para* to an existing hydroxyl group in the compound being oxidized. This assumption, to date, is supported by all available evidence.[18] Furthermore, if the hydroxyl group is present in the 2 position (or equivalent 7 position) we assume that oxidation will occur preferentially in the 1 position rather than the 3 position.

4,5-Dihydroxyphenanthrene (4,5-PH_2).—In addition to the method of synthesis[16] the hydroxyl groups are undoubtedly in the 4 and 5 positions because of the absence of proton resonances between τ 1.0 and 1.5 in the nmr spectrum[44] and that of the precursor, 4,5-dimethoxyphenanthrene.[45]

5-Hydroxy-1,4-phenanthrenequinone (IV).—This structure was assigned to the Fremy's salt oxidation product of 4,5-PH_2 (III) on the assumption that oxidation would take place *para* to one of the hydroxyl groups. We have shown that 4-phenanthrol yields 1,4-phenanthrenequinone. The failure to obtain a quinoxaline derivative on treatment with *o*-phenylenediamine is evidence against an *o*-quinone structure for IV. The nmr spectrum[44] is also consistent with the assigned structure but does not rule out the 5-hydroxy-3,4-phenanthrenequinone structure. The structure of 5-acetoxy-1,4-phenanthrenequinone follows from IV.

7-Hydroxy-1,2-phenanthrenequinone (VI).—The Fremy's salt oxidation product of V was assigned structure VI on the assumption (stated above) that Fremy's salt oxidizes hydroxy compounds in the *ortho* or *para* positions,[18] and on the nature of the acetylation reactions and nmr spectral data. Fieser[4] showed that 1,2-phenanthrenequinone yields 1,2,4-triacetoxyphenanthrene under Thiele conditions (acetic anhydride and H_2SO_4) and 1,2-diacetoxyphenanthrene on reductive acetylation. On comparable treatment VI yields the tetraacetate VIII and triacetate VII (see above).

The nmr spectrum of VIII had one proton as a doublet centered at τ 0.9. This is attributed to splitting of the 5 proton by the 6 proton. The remaining protons need no comment.[44] The nmr spectrum of VII had two protons as four peaks centered at τ 1.7. This is attributed to the fact that the 4 and 5 protons are nonequivalent and each is split by the 3 and 6 protons, respectively. The remaining protons need no comment.[44]

Finally, the ultraviolet spectrum of VI (see above) is similar to that of 1,2-phenanthrenequinone which has λ_{max} at 222 mμ (log ϵ 4.62), 282 (4.38), 315 (385), and 375 (3.43).

7-Hydroxy-1,4-phenanthrenequinone (X).—This oxidation product of 2,5-dihydroxyphenanthrene (IX) might be 7-hydroxy-1,2-P, 5-hydroxy-1,2-P, or 7-hydroxy-3,4-P on the basis of our assumptions concerning Fremy's salt oxidations. We believe structure X is correct because the ultraviolet spectrum is similar to that of 1,4-phenanthrenequinone and, also, because 4-phenanthrol is oxidized by Fremy's salt to 1,4-phenanthrenequinone rather than to 3,4-phenanthrenequinone.

For the assignment of structure to the brominated dihydroxyphenanthrenes, we assume that bromination occurs only in positions *ortho* and *para* to the existing hydroxyl groups. Furthermore, hydroxyl groups in the 2 and 7 positions direct only to the 1 and 8 positions, respectively. The analogy for this argument is that 2-naphthol brominates in the 2 position but not in the 3 position.

(43) Spectra data of diols are listed with description of syntheses.

(44) The nmr spectral data are in the Ph.D. thesis of R. L. Childers.

(45) J. A. Pople, W. G. Schneider, and H. J. Bernstein ["High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 248–250] list the 4,5 protons of phenanthrene in the τ 1.0–1.5 region.

The Syntheses of 3,4-Dimethoxy-9,10-dimethyl-1,2-benzanthracene and 9,10-Dimethyl-1,2-benzanthra-3,4-quinone[1]

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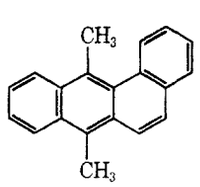
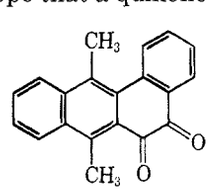
The synthesis of 3,4-dimethoxy-9,10-dimethyl-1,2-benzanthracene (V) started with the condensation of *o*-acetylbenzoic acid with 1,2-dimethoxynaphthalene in 90% methanesulfonic acid to yield 3-methyl-3-(3,4-dimethoxy-1-naphthyl)phthalide (VI), followed by conventional steps to yield V. The synthesis of 9,10-dimethyl-1,2-benzanthra-3,4-quinone (II) was accomplished by hydroxylation of 9,10-dimethyl-1,2-benzanthracene (I) to 3,4-dihydro-3,4-dihydroxy-9,10-dimethyl-1,2-benzanthracene (VIII), followed by treatment of VIII with acetic anhydride and dimethyl sulfoxide to yield II. Other attempts to prepare II by more traditional methods failed.

One of the most powerful carcinogenic hydrocarbons is 9,10-dimethyl-1,2-benzanthracene (I), but little information as to the mechanism by which it induces cancer is available.[3] In the hope that a quinone related to I might prove to be an inhibitor or a promoter of the production of cancer by I, we have attempted to develop routes for the synthesis of such quinones. Herein is reported the synthesis of 9,10-dimethyl-1,2-benzanthra-3,4-quinone (II).



I



II

Our first attempt to prepare II was by oxidation of 3-methoxy-9,10-dimethyl-1,2-benzanthracene (III), prepared essentially as described,[4] as oxidation of 9-methoxyphenanthrenes to 9,10-phenanthraquinones has been effected.[5] When oxidation of III to II proved unsuccessful, attempts were made to demethylate III to 3-hydroxy-9,10-dimethyl-1,2-benzanthracene (IV) prior to oxidation. However, we were unable to isolate IV. Actually IV has never been isolated although re-

(1) This research was supported by funds from the U. S. Public Health Service Grant No. CA-07394.

(2) This research is taken from the Ph.D. thesis of C. C. Davis, The Ohio State University, 1966.

(3) See N. H. Cromwell, *Am. Scientist*, **53**, 213 (1965), for references and discussion.

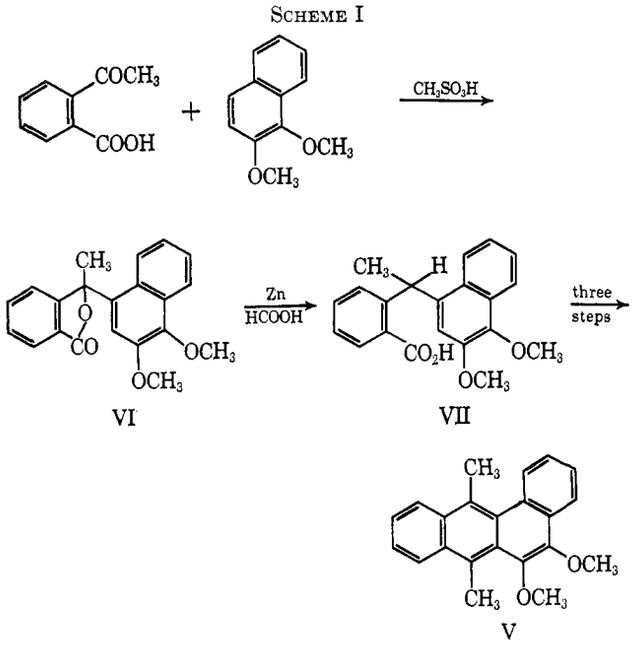
(4) W. M. Smith, Jr., E. F. Pratt, and H. J. Creech, *J. Am. Chem. Soc.*, **73**, 319 (1951).

(5) L. Ruzicka and H. Waldman, *Helv. Chim. Acta*, **15**, 907 (1932).

action mixtures supposedly containing IV were subjected to the Bucherer reaction to yield the corresponding 3-amino compound.[4] All of our attempts to oxidize mixtures resulting from demethylation experiments gave no trace of quinone.[6]

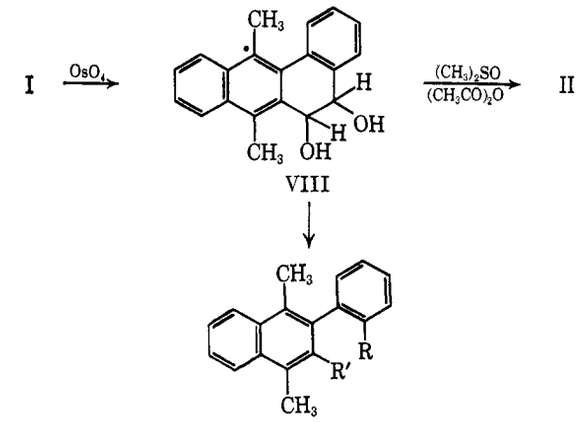
We next prepared 3,4-dimethoxy-9,10-dimethyl-1,2-benzanthracene (V) in the hope that either V or the corresponding 3,4-dihydroxy compound could be oxidized to II. Attempts to convert V into II by demethylation and subsequent oxidation failed. The synthesis of V is of interest in that the first step involved the condensation of *o*-acetylbenzoic acid with 1,2-dimethoxynaphthalene using methanesulfonic acid (90%) to yield 3-methyl-3-(3,4-dimethoxy-1-naphthyl)phthalide (VI). This step was patterned after a similar reaction of phthalaldehydic acid with benzene using concentrated sulfuric acid[7] and represents the first use of *o*-acetylbenzoic acid in such condensations. In the present case, the use of methanesulfonic acid was markedly superior to that of sulfuric acid as no oxidation or sulfonation of the dimethoxynaphthalene occurred. The remaining steps followed conventional procedures described in the Experimental Section (See also Scheme I).

SCHEME I



The synthesis of II was finally accomplished by oxidation of 3,4-dihydro-3,4-dihydroxy-9,10-dimethyl-1,2-benzanthracene (VIII). This route was chosen as 1,2-benzanthra-3,4-quinone had been prepared by chromic acid oxidation[8] of 3,4-dihydro-3,4-dihydroxy-1,2-benzanthracene[9] and I had been converted into VIII.[10] After many unsuccessful attempts to oxidize VIII to II, success was finally achieved by treatment with dimethyl sulfoxide and acetic anhydride, a reagent

SCHEME II



IX, R = COOH; R' = $CONH_2$ ⟶ X, R = R' = $COOCH_3$

system recently used for the oxidation of secondary alcohols to ketones (see Scheme II).[11,12]

The quinone II was converted into the corresponding quinoxaline derivative by treatment with *o*-phenylenediamine and into V by reduction with zinc and alkali followed by methylation of the crude diol with dimethyl sulfate. The dimethoxy compound thus produced was identical with V produced by the synthesis starting from 1,2-dimethoxynaphthalene.

The dihydrodiol VIII was converted *via* the acid amide IX as described[10a] into the diacid by deamination and the latter was esterified to yield X.

Dehydration of VIII yielded a reaction mixture which on treatment with alkali and dimethyl sulfate yielded a methoxy compound which was shown to be identical with 3-methoxy-9,10-dimethyl-1,2-benzanthracene (III) prepared as described.[4] Interestingly only III was obtained. No sign of the formation of the isomeric 4-methoxy compound was obtained. The selective loss of the 4-hydroxyl group is probably the result of a steric effect as greater release of strain is provided by loss of the 4-hydroxyl group because of the methyl group at the 10 position.

Several attempts to cyclize X to II by means of reaction with sodium[13] were made because of the successful cyclization of a series of methylated dimethyl 6,6'-dimethyldiphenates by this means.[14] However, no trace of II was found in any reaction.

Experimental Section[15]

3-Methoxy-9,10-dimethyl-1,2-benzanthracene (III).—3-Methyl-3-(4-methoxy-1-naphthyl)phthalide was prepared as de-

(6) These attempts involved mainly Fremy's salt, potassium nitrosodisulfonate; see H. J. Teuber and H. Limdner, *Ber.*, **92**, 932 (1959), and earlier references.

(7) V. W. Floutz, *J. Org. Chem.*, **25**, 643 (1960), and references therein.

(8) C. J. Collins, J. G. Burr, Jr., and D. N. Hess, *J. Am. Chem. Soc.*, **73**, 5176 (1951).

(9) J. W. Cook and R. Schoental, *J. Chem. Soc.*, 170 (1948).

(10) (a) H. I. Hadler and A. C. Kryger [*J. Org. Chem.*, **25**, 1896 (1960)] prepared VIII[9] as did (b) E. Boyland and P. Sims [*Biochem. J.*, **95**, 780 (1965)]. Both groups reported unsuccessful attempts to oxidize VIII to II.

(11) J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965). Our attention to this method was called by Mr. J. B. Hughes, The Ohio State University, to whom we extend heartfelt thanks.

(12) By treatment with this reagent, an almost quantitative yield of duroquinone was obtained from the corresponding hydroquinone but, when hydroquinone itself was used, a dark mixture of products was the result. In one attempt we failed to obtain 2,3-butanedione from 2,3-butanediol with the same reagent. We thank Mr. Frederick Hetzel for performing these experiments.

(13) G. Wittig and H. Zimmerman, *Ber.*, **86**, 629 (1953).

(14) Unpublished results by H. Karnes, The Ohio State University.

(15) All melting points were uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer. Nuclear magnetic resonance spectra (nmr) were obtained with a Varian Model A-60 spectrometer at 60 Mc with tetramethylsilane as an internal reference. The phrase "treated in the usual manner" means that the organic solvent layer was washed successively with water and saturated sodium chloride solution and filtered through anhydrous magnesium sulfate, and the solvent was distilled under reduced pressure.

scribed.[4] Reduction of this in 98% yield to 2-(α-4-methoxy-1-naphthylethyl)benzoic acid was accomplished by the zinc dust–aqueous formic acid method.[16] The conversion of this acid into III was essentially as described.[4] Oxidation of III with chromic acid, acid permanganate, alkaline peroxide, peracetic acid, trifluoroperacetic acid, and selenium dioxide gave such complex mixtures that no pure substance of quinone character was isolated. All attempts to isolate the 3-hydroxy compound after treatment of III with HBr in dioxane,[4] HBr (47% aqueous and anhydrous) in acetic acid at reflux under nitrogen for 1–2 hr, HI (47%) in acetic acid as above, and boron tribromide in methylene chloride[17] gave complex mixtures from which no pure substance was isolated.

3-Methyl-3-(3,4-dimethoxy-1-naphthyl)phthalide (VI).—To a solution of 10.4 g of *o*-acetylbenzoic acid[18] in 40 ml of 90% methanesulfonic acid[19] was added 11.70 g of 1,2-dimethoxynaphthalene. After 12 hr at room temperature the mixture was treated with 800 ml of water. After the usual work-up, 14.1 g (67%) of crude VI was obtained from the neutral fraction. Recrystallization from toluene–petroleum ether (bp 65–110°) and ether–petroleum ether (bp 30–60°) afforded 10.34 g (50%) of colorless crystalline VI: mp 127.5–128.0°, infrared absorption at 5.71 μ.

Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.4; H, 5.4. Found: C, 75.4; H, 5.3.

2-(α-2,3-Dimethoxy-1-naphthylethyl)benzoic Acid (VII).—A mixture of 6.00 g of VI, 90 ml of 90% formic acid, 12 g of zinc dust, and 12 ml of water was held at reflux for 12 hr. The acidic portion of the reaction products afforded crude VII in quantitative amount. Recrystallization from toluene–petroleum ether (bp 65–110°) with almost no loss afforded the analytical sample of VII: mp 152.0–154.0°, infrared absorption at 5.89 μ.

Anal. Calcd for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0. Found: C, 74.9; H, 6.0.

3,4-Dimethoxy-9,10-dimethyl-1,2-benzanthracene (V).—To 6.38 g of VII in a polyethylene bottle was added 100 ml of anhydrous hydrogen fluoride with swirling. After 20 min the mixture was cautiously poured on cracked ice. A solution of the neutral product in 125 ml of dry toluene was added to a stirred solution of 0.05 mole of CH_3MgBr in 100 ml of ether. After stirring at room temperature for 12 hr, dilute HCl was added and the product was worked up as usual. The entire product was dissolved in 100 ml of toluene and heated at reflux for 1.5 hr after adding a small amount of *p*-toluenesulfonic acid. The resulting product was chromatographed on silica gel to yield a yellow oil which afforded 3.30 g (55%) of pale yellow, crystalline V, mp 51.8–52.5°, from hexane–toluene (100:1) at −80°. This product had the following ultraviolet absorption spectrum: $\lambda_{max}^{C_2H_5OH}$ 219 mμ (log ε 4.5), 228 (4.53), 249 (4.22), 271 (4.59), 283 (4.52), 295 (4.71), and 306 (4.73).

Anal. Calcd for $C_{22}H_{20}O_2$: C, 83.5; H, 6.4. Found: C, 83.7; H, 6.4.

(16) R. L. Letsinger, J. D. Jamison, and A. S. Hussey, *J. Org. Chem.*, **26**, 97 (1961).

(17) J. F. McOmie and M. L. Watts, *Chem. Ind.* (London), 1658 (1963).

(18) Prepared as described by H. L. Yale, *J. Am. Chem. Soc.*, **69**, 1547 (1947).

(19) We thank the Pennsalt Manufacturing Co. for a gift of 90% methanesulfonic acid.

In 11 attempts[20] at demethylation of V to the corresponding diol no success was attained.

9,10-Dimethyl-1,2-benzanthra-3,4-quinone (II).—9,10-Dimethyl-1,2-benzanthracene was prepared as described[21] and converted into 3,4-dihydro-3,4-dihydroxy-9,10-dimethyl-1,2-benzanthracene (VIII), mp 172.5–173.5°, by hydroxylation with osmium tetroxide as described.[10a] To a stirred solution of 10.0 g of VIII in 250 ml of dimethyl sulfoxide at room temperature was added 100 ml of acetic anhydride. The solution became pale yellow after 1 hr, light red after 3 hr, and dark red after 46 hr. This solution was then diluted with 500 ml of water and the resultant mixture was extracted with 200-ml portions of 4:1 hexane–benzene. After treatment in the usual way, a red oily residue was obtained on removal of solvent. Two crystallizations from acetone afforded 4.34 g (47%) of red II: mp 152.0–153.0°; ultraviolet absorption at $\lambda_{max}^{C_2H_5OH}$ 216 mμ (log ε 4.56), 249 (4.51), 270 (4.59), 281 (4.63), and 304 (4.22).

Anal. Calcd for $C_{20}H_{14}O_2$: C, 83.9; H, 4.9. Found: C, 83.9; H, 4.9.

The quinoxaline derivative of II formed deep yellow crystals, mp 170.5–172.5°.

Anal. Calcd for $C_{26}H_{18}N_2$: C, 87.1; H, 5.1; N, 7.8. Found: C, 87.1; H, 5.2; N, 7.8.

On addition of 10 ml of 20% KOH solution to a mixture containing 0.20 g of II and 0.2 g of zinc dust in 50 ml of 95% ethanol the color immediately became dark brown. After 15 min at reflux the cooled (0°) mixture was treated successively with 10 ml of dimethyl sulfate and 20 ml of 20% KOH solution. The solution on heating to reflux was now pale yellow. The cooling and treatment with dimethyl sulfate and KOH were repeated and the mixture was refluxed for 25 min. After the usual work-up, 0.22 g of a light yellow oil was obtained which showed 7 spots on tlc, one spot having the same mobility as that of V. This component was isolated by preparative tlc on silica gel with benzene–hexane, as eluent, in 14% yield. This was shown to be identical with V by its spectral properties.

Methyl 3-(*o*-Carbomethoxyphenyl)-1,4-dimethyl-2-naphthoate (X).—A solution of 5.40 g of 3-(*o*-amidophenyl)-1,4-dimethyl-2-naphthoic acid, prepared as described[10a] in 130 ml of dioxane containing 4 ml of concentrated H_2SO_4 was cooled to 0° and treated with 7 ml of isoamyl nitrite. After 45 min at 0° 3 ml of water was added and the mixture was warmed until gas evolution ceased. The resulting dark solution was worked up as usual to produce a dark oil which contained much starting amide acid as indicated by infrared analysis. Accordingly the oil was dissolved in 200 ml of acetic acid containing 4 ml of concentrated H_2SO_4 and treated at 20° with 4 g of sodium nitrite during 15 min. After conventional work-up a dark oil was obtained which was treated with diazomethane. Decolorization by charcoal followed by chromatography over 100 g of alumina yielded 2.84 g (48%) of colorless X, mp 110.0–110.5°.

Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.8; H, 5.8. Found: C, 75.8; H, 5.6.

The nmr spectra of all of the compounds reported were consistent with the assigned structures.

(20) See the Ph.D. thesis of C. C. Davis, p 35, for details.

(21) See R. B. Sandin and L F. Fieser, *J. Am. Chem. Soc.*, **62**, 3098 (1940).