R.D. in methanol (*c* 0.086): $[\alpha]_{700}$ +74°, $[\alpha]_{589}$ +112°, $[\alpha]_{341.5}$ +2097°, $[\alpha]_{294}$ −2733°, $[\alpha]_{260}$ −1762°; λ_{max}^{EtOH} 314 mμ, log ε 2.03.

(+)-**Camphor** (Eastman Kodak Co.), R.D. in methanol (*c* 0.10): $[\alpha]_{700}$ +5°, $[\alpha]_{589}$ +23°, $[\alpha]_{312.5}$ +2009°, $[\alpha]_{265}$ −3305°, $[\alpha]_{255}$ −2590°.

3α-Chlorocamphor[43] (F. V. Brutcher), R.D. in methanol (*c* 0.095): $[\alpha]_{700}$ +68°, $[\alpha]_{589}$ +95°, $[\alpha]_{331}$ +1798, $[\alpha]_{292.5}$ −1437°, $[\alpha]_{250}$ +603°.

3β-Chlorocamphor[43] (F. V. Brutcher), R.D. in methanol (*c* 0.097): $[\alpha]_{700}$ +22°, $[\alpha]_{589}$ +35°, $[\alpha]_{330}$ +1810°, $[\alpha]_{285}$ −2170°, $[\alpha]_{250}$ −1093°.

3,3-Dichlorocamphor (F. V. Brutcher) R.D. in methanol (*c* 0.101): $[\alpha]_{700}$ +21°, $[\alpha]_{589}$ +43°, $[\alpha]_{339}$ +1951°, $[\alpha]_{292.5}$ −2609°, $[\alpha]_{260}$ −1945°.

3α-Bromocamphor[43] (F. V. Brutcher), R.D. in methanol (*c* 0.107): $[\alpha]_{700}$ +84°, $[\alpha]_{589}$ +131°, $[\alpha]_{335}$ +1970°, $[\alpha]_{290}$ −1472°, $[\alpha]_{260}$ −177°.

3,3-Dibromocamphor (F. V. Brutcher), R.D. in methanol (*c* 0.10): $[\alpha]_{700}$ +23°, $[\alpha]_{589}$ +39°, $[\alpha]_{345}$ +1455°, $[\alpha]_{297.5}$ −2200°, $[\alpha]_{270}$ −1730°.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE MCARDLE MEMORIAL LABORATORY, THE MEDICAL SCHOOL, UNIVERSITY OF WISCONSIN]

The Synthesis of the Mono- and Dihydroxy Derivatives of 1,2,5,6-Dibenzanthracene Excreted by the Rabbit and of Other Hydroxylated Dibenzanthracene Derivatives[1]

BY JOHN A. LABUDDE AND CHARLES HEIDELBERGER

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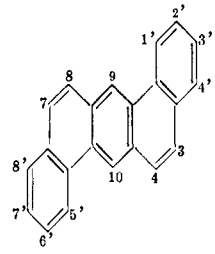
Two metabolites of 1,2,5,6-dibenzanthracene excreted by rabbits after administration of this polycyclic hydrocarbon have been characterized by synthesis as 2′-hydroxy- and 2′,6′-dihydroxy-1,2,5,6-dibenzanthracene. In addition, derivatives of 4,8-dihydroxy- and 4,7-dihydroxy-1,2,5,6-dibenzanthracene have been prepared, and a new synthesis of 3,7-dihydroxy-1,2,5,6-dibenzanthracene is described. All the monohydroxy isomers of 1,2,5,6-dibenzanthracene are now known as the result of the synthesis of four new monohydroxy derivatives of this hydrocarbon.

In 1937, Levi and Boyland[2] reported the isolation of a dihydroxy-dibenzanthracene derivative from the urine of rabbits maintained on a diet containing 0.16% of 1,2,5,6-dibenzanthracene. The same compound was obtained by Dobriner, Rhoads and Lavin[3] from the urine and feces of rabbits injected subcutaneously or intramuscularly with dibenzanthracene. A different metabolite, isolated by Dobriner, *et al.*,[3] from the urine and feces of mice or rats injected with dibenzanthracene, was identified by synthesis as 4′,8′-dihydroxy-1,2,5,6-dibenzanthracene by Cason and Fieser.[4] Cook and Schoental,[5] in a re-investigation of the metabolism of dibenzanthracene in rabbits, isolated a second phenolic metabolite from the feces, which they believed was a monohydroxy derivative of the hydrocarbon. Since studies concerning hydrocarbon carcinogenesis utilizing 1,2,5,6-dibenzanthracene are being carried out actively in this Laboratory,[6-8] we undertook the characterization of the two rabbit metabolites, not only for the purpose of determining the positions in the dibenzanthracene molecule hydroxylated by rabbits, a species relatively resistant to hydrocarbon carcinogenesis, but also in the interest of learning more about the chemistry of dibenzanthracene and of relieving the chemical literature of the embarrassment of two rather simple uncharacterized compounds. In the work reported here both rabbit metabolites were again isolated to provide samples for comparison with synthetic products,[9] and the metabolites were characterized by synthesis as 2′-hydroxy- and 2′,6′-dihydroxy-1,2,5,6-dibenzanthracene. In addition, a number of other hydroxylated dibenzanthracene derivatives were prepared, and all of the monohydroxy-dibenzanthracene isomers are now known.



Initially we focused our attention on the dihydroxy metabolite, because more information concerning its structure was available. Levi and Boyland[2] had converted this compound to the corresponding dihydroxy-dibenz-9,10-anthraquinone, thereby eliminating the 9- and 10-positions as sites for the hydroxyl groups. They also concluded from the stability of the metabolite to air oxidation that the hydroxyl groups were not *ortho* or *para* to each other. In the present work 9,10-dihydroxy- and 3,4-dihydroxy-1,2,5,6-dibenzanthracene, prepared by reduction of the corresponding dibenzanthraquinones, were too unstable to be isolated as such and were therefore converted to the 9,10-dimethyl ether and the 3,4-diacetate X, respectively. A comparison of these two synthetic products with the corresponding derivatives of the dihydroxy metabolite demonstrated their non-

(1) This work was supported in part by a grant-in-aid from the Wisconsin Division of the American Cancer Society and in part by a grant, C-1132, from the National Cancer Institute, National Institutes of Health, Public Health Service.

(2) A. A. Levi and E. Boyland, *Chemistry & Industry*, **15**, 446 (1937).

(3) K. Dobriner, C. P. Rhoads and G. I. Lavin, *Proc. Soc. Exptl. Biol. Med.*, **41**, 67 (1939).

(4) J. Cason and L. F. Fieser, THIS JOURNAL, **62**, 2681 (1940).

(5) J. W. Cook and R. Schoental, *J. Chem. Soc.*, 9 (1952).

(6) C. Heidelberger, H. I. Hadler and G. Wolf, THIS JOURNAL, **75**, 1303 (1953).

(7) C. Heidelberger and M. Moldenhauer, *Cancer Research*, **16**, 442 (1956).

(8) P. M. Bhargava and C. Heidelberger, THIS JOURNAL, **78**, 3671 (1956).

(9) We thank Professor Eric Boyland for a sample of the dihydroxy rabbit metabolite, part of which we converted to the diacetoxy-dibenz-9,10-anthraquinone.

identity with the metabolite. Since the hydroxy metabolite of dibenzanthracene excreted by rats and mice was a symmetrical compound, it appeared likely that the dihydroxy rabbit metabolite was also symmetrical. In addition to 4′,8′-dihydroxy-1,2,5,6-dibenzanthracene,[4] Cason and Fieser[10] had previously synthesized the 9,10-quinone of 3,7-dihydroxy-1,2,5,6-dibenzanthracene, and Hornig[11] had prepared 3′,7′-dihydroxy-1,2,5,6-dibenzanthracene, all of which were different from the rabbit metabolite. Of the three remaining symmetrical derivatives, 4,8-dihydroxy-, 2′,6′-dihydroxy- and 1′,5′-dihydroxy-1,2,5,6-dibenzanthracene, the evidence indicated that the metabolite was the 4,8-dihydroxy isomer for the following reasons: When Boyland, *et al.*,[12] oxidized the 9,10-quinone of the metabolite under the same conditions used by Cook[13] to oxidize 1,2,5,6-dibenz-9,10-anthraquinone to anthraquinone tetracarboxylic acid, none of this product could be isolated, and they concluded that at least one of the hydroxyl groups was in the anthracene portion of the dibenzanthracene ring system. On the basis of spectrographic evidence Boyland, *et al.*,[12] suggested that the hydroxyl groups might be located in the 4- and 8-positions. They found that the ultraviolet absorption spectrum of 1,2,5,6-dibenz-9,10-anthraquinone had an absorption maximum at 390 mμ. (Subsequently we have determined that the corresponding maximum for 3,7-dihydroxy-1,2,5,6-dibenz-9,10-anthraquinone[14] is at 398 mμ.) However, this maximum was shifted to 454 mμ for the 9,10-quinone of the metabolite. Similarly they found[12] that the corresponding absorption maximum at 323 mμ for 9,10-anthraquinone was at 347 mμ for 2,6-dihydroxy-9,10-anthraquinone, but was shifted to 423 mμ for 1,5-dihydroxy-9,10-anthraquinone. These data strongly indicated to them that the hydroxyl groups in the metabolite occupied the 1- and 5-positions of the anthracene nucleus, *i.e.*, that the metabolite was 4,8-dihydroxydibenzanthracene.

Our preliminary work on the preparation of derivatives of dibenzanthracene not only provided another indication that the metabolite was the 4,8-dihydroxy isomer but also seemed to afford a method for the synthesis of this compound. Cook and Schoental[15] had treated 1,2,5,6-dibenzanthracene with osmium tetroxide to obtain the 3,4-dihydrodiol Ia which upon acid dehydration yielded a phenol to which they assigned the structure of IIIc on the basis of analogy with other compounds prepared by this method. In an effort definitively to characterize this monohydroxy derivative, we repeated its synthesis and oxidized it in the form of the acetate IIIa to the corresponding 9,10-quinone IVa. This quinone, when dissolved in alkali, gave a deep blue color identical with the color in alkali of the 9,10-quinone of the dihydroxy metabolite which the spectral data indicated was the 4,8-dihydroxy derivative. Since Cason and Fieser[10] had found that 3,7-dihydroxy-1,2,5,6-dibenz-9,10-anthraquinone did not show this color reaction, it appeared that the blue color in alkali might be a result of interaction between an ionized hydroxyl group in the 4 (*peri*) position and the adjacent keto group of the dibenz-9,10-anthraquinones. These findings suggested that the monohydroxy compound IIIc was actually 4-hydroxydibenzanthracene and formed the basis of our first attempt to synthesize 4,8-dihydroxy-1,2,5,6-dibenzanthracene by dehydration of 3,4,7,8-tetrahydrotetrahydroxy-1,2,5,6-dibenzanthracene (Fig. 1).

The procedure of Cook and Schoental[15] for the preparation of Ia led to considerable quinone formation, but refluxing the osmium tetroxide adduct of dibenzanthracene with chloroform, acetic anhydride and pyridine gave the dioldiacetate Ib in fairly good yield. This latter method was also used for the preparation of Va and Vb. Later it became apparent that the conversion was actually catalyzed by acidic impurities present in the chloroform, and the procedure was revised to include a catalytic amount of concentrated hydrochloric acid, as described for the preparation of Ib. The osmium tetroxide addition product of Ib was prepared and converted to the tetraacetate IIb which upon hydrolysis and exposure to air gave dibenz-3,4,7,8-anthraquinone VIII. Hydrolysis of IIb under nitrogen to the tetrol IIa and dehydration with acid gave 3,7-dihydroxydibenzanthracene rather than the desired 4,8-dihydroxy isomer. The product was identified, after conversion to the diacetoxyquinone VIIa by a mixed m.p. determination with an authentic sample of 3,7-diacetoxy-1,2,5,6-dibenz-9,10-anthraquinone.[14] In addition, the infrared spectra of VIIb and authentic 3,7-dihydroxy-1,2,5,6-dibenz-9,10-anthraquinone were identical. The possibility still existed that the monohydroxy derivative IIIc was the 4-hydroxy isomer, since the course of dehydration might have proceeded differently with the 3,4-dihydrodiol Ia than with the 3,4,7,8-tetrahydrotetrol IIa. In order to resolve this point the acetate IIIa was treated with osmium tetroxide and converted to the 3-acetoxy-7,8-diacetoxydihydro derivative Va. After deacetylation with lithium aluminum hydride and dehydration of the resulting 3-hydroxy-7,8-dihydrodiol with acid, 3,7-dihydroxydibenzanthracene again was obtained, oxidized to the 9,10-quinone, and identified as described above. The same product resulted from the methoxy derivative IIIb as starting material. This finding proved that IIIc was actually 3-hydroxydibenzanthracene, as Cook and Schoental[15] had stated, and indicated that a different approach was required for the synthesis of 4,8-dihydroxydibenzanthracene.

In an earlier attempt to prepare 4,8-dihydroxydibenzanthracene, Heidelberger and Schoental[16] devised a new synthesis aimed at the dibenzanthracene ring system by visualizing the molecule as a derivative of terphenyl. However, cyclization of 2′,2″-bis-carboxymethylterphenyl under a variety of conditions invariably gave 7,8-dihydroxypicene

(10) J. Cason and L. F. Fieser, THIS JOURNAL, **63**, 1256 (1941).

(11) L. S. Hornig, *ibid.*, **74**, 4572 (1952).

(12) E. Boyland, A. A. Levi, E. H. Mawson and E. Roe, *Biochem. J.*, **35**, 184 (1941).

(13) J. W. Cook, *J. Chem. Soc.*, 2529 (1931).

(14) We are grateful to Professor Louis F. Fieser for a sample of 3,7-diacetoxydibenz-9,10-anthraquinone. It was converted to the 3,7-dihydroxy derivative as described in the Experimental for the preparation of VIIb.

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

(16) Unpublished experiments.

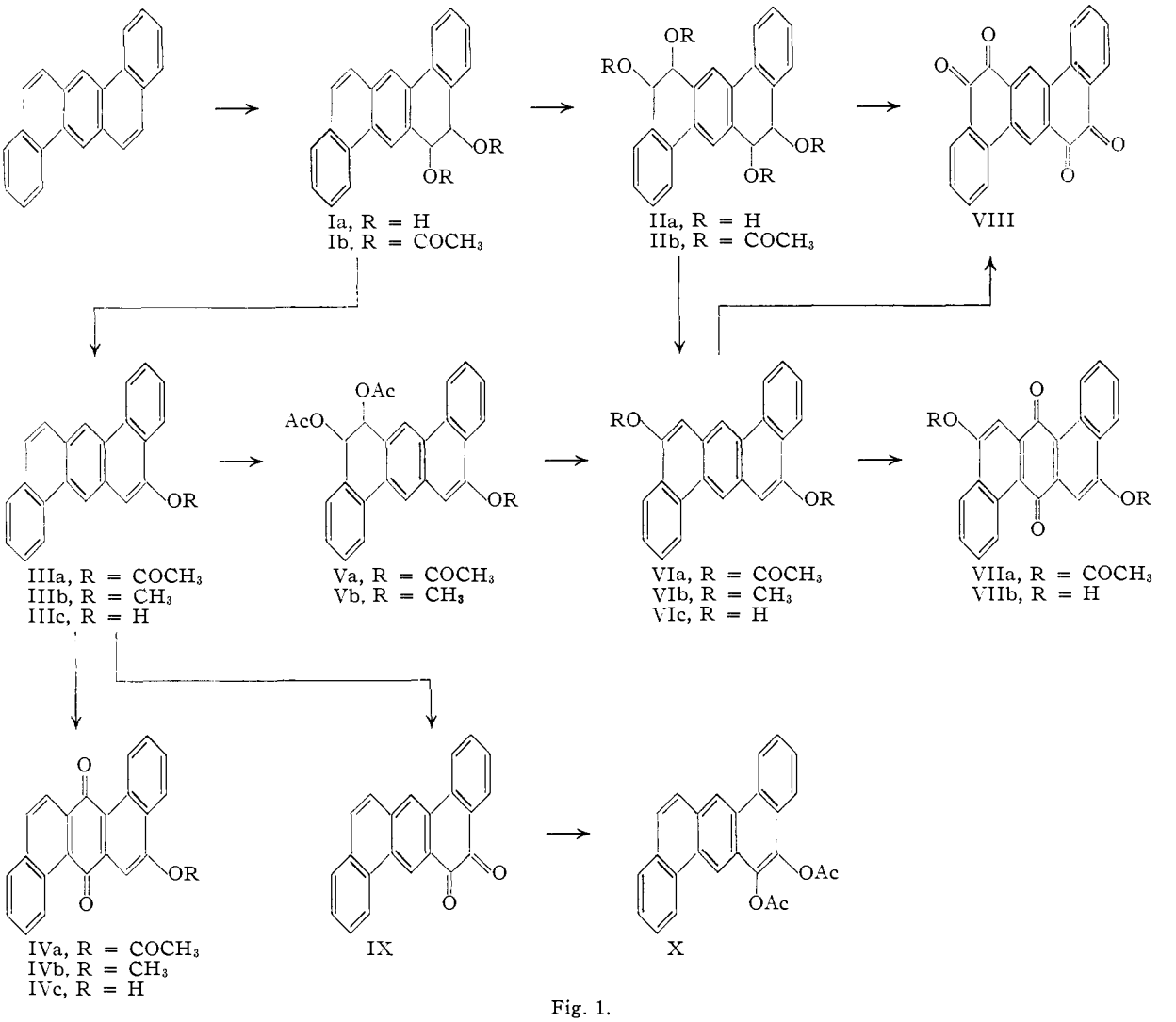
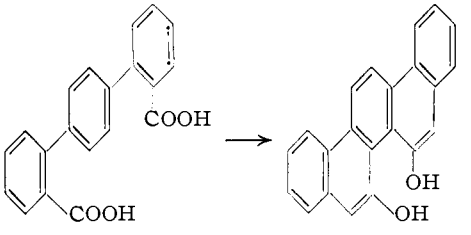


Fig. 1.

instead of the desired dibenzanthracene derivative.



If this approach were to yield a dibenzanthracene derivative, it was evident that two of the open positions on the central ring of the terphenyl nucleus, *para* to each other, would have to be blocked, and in the present work a synthesis of this type was carried out (Fig. 2).

In 1934, Kvalnes[17] described the reaction of *p*-benzoquinone with diazotized aromatic amines and stated that 2,5-disubstituted quinones could be obtained by using an excess of the diazonium salt. We reinvestigated this reaction in an effort to prepare the required terphenyl derivative XV. When two moles of diazotized *o*-toluidine were allowed to react with one mole of *p*-benzoquinone, the product which precipitated from the reaction mixture was the tetrasubstituted quinone XI, and the corresponding hydroquinone XIIa, hydroquinone diacetate XIIb and an octabromo derivative XIII were prepared. From the reaction mixture which had yielded XI the 2,6-disubstituted quinone XIV previously prepared by Jones and Kenner[18] also was isolated, but none of the 2,5-isomer XVI could be obtained. However, when the reaction was carried out with equimolar quantities of diazotized *o*-toluidine and *p*-benzoquinone, the desired product was obtained in poor yield in the form of the hydroquinone XV. Acetylation of XV and bromination with two molar equivalents of N-bromosuccinimide gave a dibromo derivative XVIIb, whereas treatment with four molar equivalents of N-bromosuccinimide resulted in a tetrabromo derivative of XVIIa, probably similar in structure to the octabromide XIII. Treatment of the dibromide XVIIb with sodium cyanide gave a neutral product containing neither bromine nor nitrogen which was probably a dialcohol rather than the desired dinitrile. However, the corresponding methoxy derivative XVIIIb was con-

(17) D. E. Kvalnes, THIS JOURNAL, **56**, 2478 (1934).

(18) E. S. J. Jones and J. Kenner, *J. Chem. Soc.*, 1842 (1931).

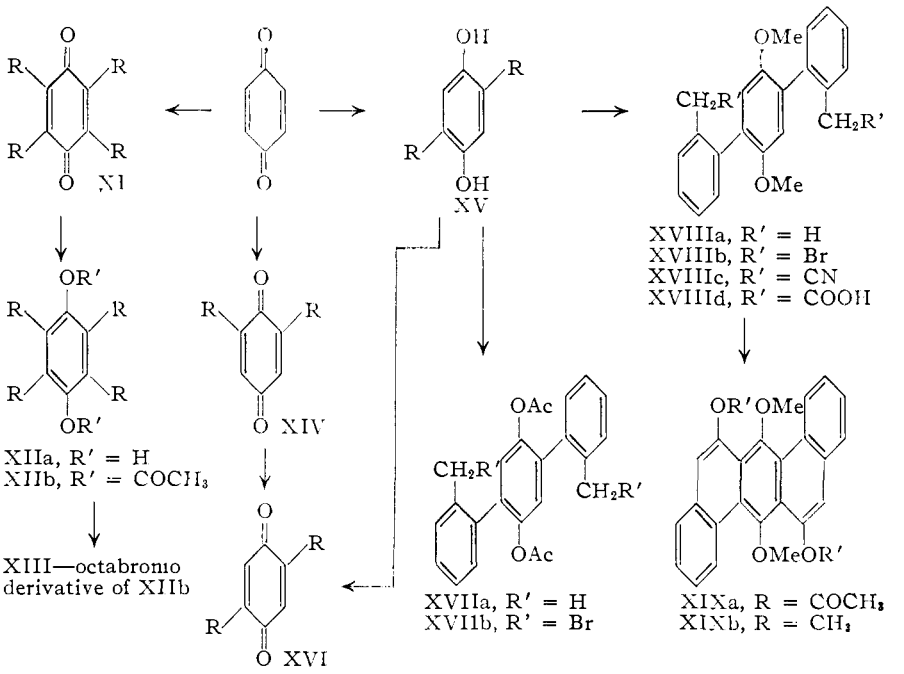
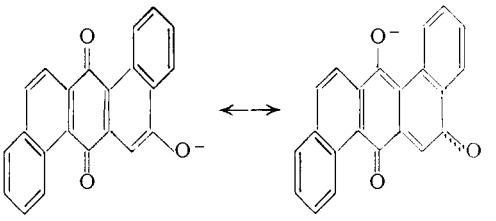


Fig. 2.—R = *o*-tolyl.

verted to the dinitrile XVIIIc in good yield, and subsequent alkaline hydrolysis gave the diacid XVIIId. Double ring closure of XVIIId to the 1,2,5,6-dibenzanthracene derivative XIXa was accomplished with zinc chloride in acetic anhydride and acetic acid. Methylation of the product gave 4,8,9,10 - tetramethoxy - 1,2,5,6 - dibenzanthracene (XIXb), m.p. 246–249°. A mixed m.p. of XIXb with the tetramethoxydibenzanthracene derivative, m.p. 230–232°, obtained by reduction and methylation of the 9,10-quinone of an authentic sample of the dihydroxy metabolite, gave a distinct depression. It was therefore established that the metabolite was not 4,8-dihydroxydibenzanthracene.

Although the ultraviolet absorption spectrum of the metabolite provided strong evidence, as outlined above, that one of the hydroxyl groups in the dihydroxy metabolite was in the 4-position, the finding that 3-hydroxydibenz-9,10-anthraquinone gave the same blue color in alkali as the anthraquinone of the metabolite suggested that one of the hydroxyl groups in the metabolite was in the 7-position; the blue color probably resulted from resonance of the anion of the quinone between the indicated structures



For these reasons it seemed likely that the metabolite was 4,7-dihydroxydibenzanthracene rather than a symmetrical derivative. Oxidation of the metabolite to dibenz-3,4,7,8-anthraquinone VIII would have proved its identity as the 4,7-dihydroxy derivative because the three other dihydroxy dibenzanthracene isomers which could theoretically be oxidized to the 3,4,7,8-quinone had all been shown to be different from the metabolite. Treatment of 3-hydroxydibenzanthracene (IIIc) with potassium nitrosodisulfonate[19] gave the 3,4-quinone IX, but 3,7-dihydroxydibenzanthracene (VIc) did not react with this reagent. Conversion of both IIIc and VIc to the 3,4,7,8-quinone VIII was accomplished by coupling the hydroxy derivatives with diazotized sulfanilic acid, reducing the resulting azo dyes to amino phenols and oxidizing the latter with chromic acid. However, similar treatment of the dihydroxy rabbit metabolite gave no recognizable product. The synthesis of 4,7-dihydroxydibenzanthracene was therefore carried out (Fig. 3). The method used was based on the addition of the Grignard reagent prepared from 4-methoxy-1-bromonaphthalene to 3-methoxy-1,2-naphthalic anhydride and cyclization of the resulting methoxy keto acid. By application of this method, utilizing the appropriate methoxy naphthalic anhydrides and methoxy naphthyl halides, all of the hydroxydibenzanthracene derivatives subsequently described in this paper were prepared.

The previously unknown 3-methoxy-1,2-naphthalic anhydride (XXII) was prepared by a modification of the von Auwers and Möller method for the synthesis of 1,2-naphthalic anhydride.[20] The sodium enolate of ethyl β-keto-γ-phenylbutyrate was acylated with ethyl oxalyl chloride and the crude product XX cyclized with concentrated sulfuric acid at −20°. Spontaneous enolization of the resulting diethyl 3-keto-3,4-dihydro-1,2-naphthalic acid yielded the diethyl ester XXI which was simultaneously methylated and hydrolyzed to give 3-methoxy-1,2-naphthalic acid which spontaneously formed the anhydride XXII.

(19) H. J. Teuber and G. Jellinek, *Ber.*, **85**, 95 (1952).
(20) K. von Auwers and K. Möller, *J. prakt. Chem.*, **217**, 124 (1925).

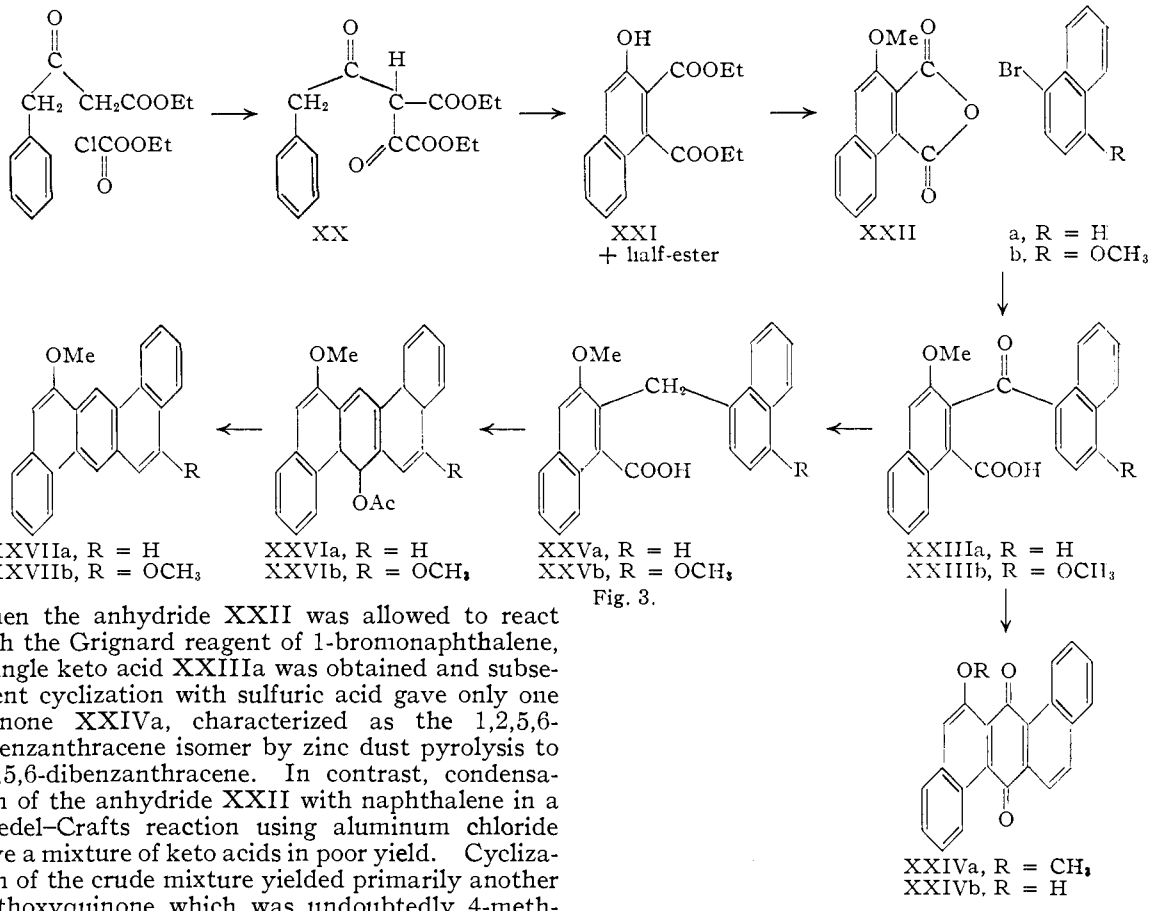


Fig. 3.

When the anhydride XXII was allowed to react with the Grignard reagent of 1-bromonaphthalene, a single keto acid XXIIIa was obtained and subsequent cyclization with sulfuric acid gave only one quinone XXIVa, characterized as the 1,2,5,6-dibenzanthracene isomer by zinc dust pyrolysis to 1,2,5,6-dibenzanthracene. In contrast, condensation of the anhydride XXII with naphthalene in a Friedel–Crafts reaction using aluminum chloride gave a mixture of keto acids in poor yield. Cyclization of the crude mixture yielded primarily another methoxyquinone which was undoubtedly 4-methoxy-1,2,7,8-dibenz-9,10-anthraquinone, and only a small amount of the desired 1,2,5,6-isomer XXIVa. Reduction of XXIVa to 4-methoxydibenzanthracene (XXVIIa) and a comparison of the latter compound, m.p. 235–237°, λ_{max} 395.5 mμ, with the methyl ether of the monohydroxy metabolite,[5] m.p. 214°, λ_{max} 400.5 mμ, demonstrated their non-identity. It was concluded that the monohydroxy metabolite was not 4-hydroxy-1,2,5,6-dibenzanthracene. The ultraviolet absorption spectrum of 4-hydroxydibenz-9,10-anthraquinone (XXIVb), prepared by demethylation of XXIVa with aluminum chloride, was similar to the spectrum of the 9,10-quinone of the dihydroxy metabolite in that the characteristic absorption maximum of the metabolite quinone at 454 mμ was at 448 mμ for the 4-hydroxy derivative. This finding led us to continue the synthesis of the 4,7-dihydroxy compound. Addition of the Grignard reagent of 1-bromo-4-methoxynaphthalene to the anhydride XXII gave a single keto acid XXIIIb, but attempted cyclization with sulfuric acid under a variety of conditions resulted in either sulfonated by-products or no reaction. Cyclization of the keto acid XXIIIb with hydrogen fluoride or phosphorus pentoxide and the acid chloride with stannic chloride or aluminum chloride also failed. The keto group was therefore reduced and the resulting acid XXVb was cyclized with zinc chloride in acetic anhydride and acetic acid to yield 4,7-dimethoxy-9-acetoxydibenzanthracene (XXVIb). Deacetylation of XXVIb and reduction of the anthranol gave the 4,7-dimethoxy derivative XXVIIb, m.p. 285–287°. A mixed m.p. of XXVIIb with the dimethyl ether of the dihydroxy metabolite, m.p. 256–260°, showed a large depression. This result demonstrated that the metabolite was not 4,7-dihydroxydibenzanthracene, and since all dihydroxy derivatives of dibenzanthracene having both hydroxyl groups in the anthracene portion of the molecule had now been shown to be different from the metabolite, it was evident that at least one of the hydroxyl groups in the dihydroxy metabolite was in a side ring.

We now turned our attention more closely to the characterization of the monohydroxy metabolite which we assumed might be a metabolic intermediate in the formation of the dihydroxy metabolite and thereby provide a clue to the structure of the latter compound. Cook and Schoental[5] had shown that the monohydroxy metabolite was not 3-hydroxy-, 9-hydroxy- or 1′-hydroxy-1,2,5,6-dibenzanthracene, and we had found that it was not the 4-hydroxy derivative. Since the syntheses of XXVIIa and XXVIIb provided a general method for the preparation of hydroxylated dibenzanthracene derivatives, the syntheses of 2′-hydroxy-, 3′-hydroxy- and 4′-hydroxy-1,2,5,6-dibenzanthracene were undertaken as described in Tables I and II. This work completed the preparation of all the monohydroxy isomers of 1,2,5,6-dibenzanthracene.

It was found that 2′-methoxy-1,2,5,6-dibenz-9,10-anthraquinone (XXXIV), m.p. 210–212°

TABLE I

METHOXY-2(1')-NAPHTHOYL-1-NAPHTHOIC ACIDS

No.	Starting materials	Isomer	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
XXVIII	1,2-Naphthalic anhydride,[a] 1-bromo-5-methoxy-naphthalene[b]	5'	213–215	24	$C_{23}H_{16}O_4$	77.51	77.42	4.53	4.60
XXXI	1,2-Naphthalic anhydride, 1-iodo-6-methoxy-naphthalene[c]	6'	228–229	19	$C_{23}H_{16}O_4$	77.51	77.59	4.53	4.44
XXXIII	6-Methoxy-1,2-naphthalic anhydride,[d] 1-bromo-naphthalene	7	201–202	72	$C_{23}H_{16}O_4$	77.51	77.52	4.53	4.74

[a] We thank Prof. L. Fieser for a generous sample of this compound. [b] Prepared from 1-nitronaphthalene by the method of P. Hill, W. F. Short and H. Stromberg, *J. Chem. Soc.*, 1619 (1937). [c] Prepared from 1-aminonaphthalene-6-sulfonic acid by the method of A. Butenandt and G. Schramm, *Ber.*, **68**, 2083 (1935). [d] Prepared by the method of L. F. Fieser and E. B. Hershberg, THIS JOURNAL, **58**, 2314 (1936).

TABLE II

DIBENZANTHRACENE DERIVATIVES

No.	Starting material	Substituents	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
XXIX	XXVIII[a]	4'-Methoxy-10-acetoxy	245–246	$C_{25}O_{18}O_3$	81.95	82.26	4.95	5.19
XXX[e]	XXIX[b]	4'-Methoxy	220–222	$C_{23}H_{16}O$	89.58	89.39	5.23	5.37
XXXII[e]	XXXI[c]	3'-Methoxy-9,10-anthraquinone	244–245	$C_{23}H_{14}O_3$	81.64	81.59	4.17	4.34
XXXIV[e]	XXXIII[c]	2'-Methoxy-9,10-anthraquinone	210–212	$C_{23}H_{14}O_3$	81.64	81.23	4.17	4.23
XXXV	XXXIV[d]	2'-Methoxy	205–207	$C_{23}H_{16}O$	89.58	89.38	5.23	5.36

[a] Reduced and cyclized as described in Experimental for preparation of XXVIb. [b] Reduced as described in Experimental for 4-methoxydibenzanthracene. [c] Cyclized as described in Experimental for 4-methoxydibenz-9,10-anthraquinone. [d] See Experimental for details of reduction. [e] Gave 1,2,5,6-dibenzanthracene when submitted to zinc dust pyrolysis.

did not depress the m.p. of the corresponding quinone of the monohydroxy metabolite, m.p. 210–212°. The ultraviolet absorption spectra (Table III) of the two compounds were identical as were the infrared spectra; λ_{max}^{KBr} 6.10, 6.20, 6.30, 6.64, 6.86, 7.28, 7.52, 7.84, 8.10, 8.25, 8.62, 8.78, 9.40, 9.65, 9.90, 11.56, 11.90, 12.56, 12.90, 13.16 and 14.28 μ. When 2'-hydroxy-1,2,5,6-dibenz-9,10-anthraquinone was dissolved in dilute alkali a blue-green color was obtained, identical with the color in alkali of the 9,10-quinone of the monohydroxy metabolite. The 2'-hydroxyquinone and the monohydroxy quinone metabolite had an absorption maximum furthest in the visible at 412 mμ. Reduction of the methoxyquinone XXXIV gave 2'-methoxy-1,2,5,6-dibenzanthracene (XXXV) which melted 7° below the reported m.p. of 214° (uncor.) of the methyl ether of the monohydroxy metabolite,[5] but the absorption maximum of XXXV at 400.5 mμ was identical with the reported absorption maximum of the methyl ether of the metabolite.[5] It is concluded that the monohydroxy rabbit metabolite is 2'-methoxy-1,2,5,6-dibenzanthracene.

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA OF METHOXY-1,2,5,6-DIBENZ-9,10-ANTHRAQUINONES[a]

Position of methoxy group(s)	Absorption maxima, mμ ($\epsilon \times 10^3$)			
3	392 (9.15)	327 (10.6)	298 (63.8)	.....
4	418 (6.14)	332 (5.88)	293 (37.8)	242 (34.9)
2'	414 (2.85)	335 (1.69)	300 (18.3)	246 (18.7)
3'	395 (5.68)	330 (4.87)	299 (56.8)	240 (23.1)
3,7[b]	397 (9.97)	335 (11.3)	299 (55.8)	247 (18.1)
2',6'	440 (7.46)	333 (5.95)	303 (40.7)	249 (48.8)

[a] Absorption spectra in absolute ethanol. [b] Absorption spectrum in acetonitrile.

On the assumption that the monohydroxy metabolite was an intermediate in the formation of the dihydroxy metabolite and that the dihydroxy metabolite was symmetrical, a synthesis of the 2',6'-dihydroxy derivative of dibenzanthracene was carried out. Addition of the Grignard reagent of either 1-bromo- or 1-iodo-7-methoxy-naphthalene to 6-methoxy-1,2-naphthalic anhydride resulted in a dimethoxy keto acid which we were unable to purify. However, cyclization of the crude keto acid with sulfuric acid gave a dimethoxyquinone with the same m.p. of 310–312° as the dimethoxy-1,2,5,6-dibenz-9,10-anthraquinone derivative of the dihydroxy metabolite. A mixed m.p. of the two compounds showed no depression and the infrared spectra, λ_{max}^{KBr} 6.10, 6.20, 6.28, 6.63, 6.89, 7.27, 7.55, 7.90, 8.27, 8.63, 8.81, 9.44, 9.65, 9.87, 11.52, 11.82, 12.34, 13.10, 13.42 and 14.50 μ, as well as the ultraviolet absorption spectra (Table III) were identical. The dihydroxy rabbit metabolite has therefore been characterized as 2',6'-dihydroxy-1,2,5,6-dibenzanthracene.

Discussion

The present work demonstrating the conversion of 1,2,5,6-dibenzanthracene in rabbits to the 2'-hydroxy- and 2',6'-dihydroxy derivatives is analogous to the finding of Berenblum, *et al.*,[21,22] on the metabolism of 3,4-benzpyrene. They showed that 3,4-benzpyrene is metabolized in both rats and rabbits to the 8-hydroxy and 10-hydroxy derivatives, but that the 10-hydroxy isomer, sterically analogous to 2'-hydroxydibenzanthracene, is excreted in relatively greater amounts by rabbits than by rats. Apparently the species difference in the metabolism of the two polycyclic hydrocarbons is more marked in the case of 1,2,5,6-dibenzanthracene than with 3,4-benzpyrene, since the 4',8'-dihydroxy metabolite of dibenzanthracene excreted by rats and mice is not produced by rabbits and the rabbit metabolites have not been demon-

(21) I. Berenblum and R. Schoental, *Cancer Research*, **6**, 699 (1946).

(22) I. Berenblum, D. Crowfoot, E. R. Holiday and R. Schoental, *ibid.*, **3**, 151 (1943).

strated to be excreted by rats or mice. The significance of these different routes of metabolism of dibenzanthracene in relation to the fact that rabbits are relatively resistant to hydrocarbon carcinogenesis is obscure, since it is likely that excreted metabolites of carcinogenic hydrocarbons result from detoxification mechanisms unrelated to the process of carcinogenesis. The 2'- and 6'-positions of dibenzanthracene hydroxylated by the rabbit are relatively unreactive sites in the molecule and are not part of the "M regions" (3',4'- and 7',8'-double bonds in 1,2,5,6-dibenzanthracene) which Pullman and Pullman[23] have designated as the regions most susceptible to hydroxylation after interaction of a polycyclic hydrocarbon with cellular components. The fact that the monohydroxy rabbit metabolite is 2'-hydroxydibenzanthracene suggests that it may be a metabolic intermediate in the formation of the 2',6'-dihydroxy derivative.

Experimental

All melting points were taken on a micro hot-stage apparatus and are uncorrected. Microanalyses are by Clark Microanalytical Laboratory, Urbana, Ill., or by Drs. Weiler and Strauss, Oxford, England.

Isolation of Metabolites.—A 5-kg. rabbit was maintained for 4 days on a diet containing 0.05% of 1,2,5,6-dibenzanthracene (total ingestion of dibenzanthracene was 1 g.). The feces were collected, dried and ground, acidified with hydrochloric acid, and extracted with 2 l. of ether in a Soxhlet apparatus for 24 hr. The ether was removed and the residue was refluxed for 2 hr. with 90 ml. of acetic anhydride and 10 ml. of pyridine. After removal of the solvents *in vacuo*, the tarry mass was dissolved in benzene, filtered and placed on a Florisil column (4 × 100 cm.). The material eluted with 2% ethyl acetate in benzene was heated for 2 hr. on the steam-bath with 1 g. of sodium dichromate in 50 ml. of glacial acetic acid. Water was added to the cooled reaction mixture, and the metabolite quinones were extracted into ether, which was dried over sodium sulfate and distilled. Chromatography of the product on Florisil gave two yellow bands which were worked up as follows:

A. The first band, eluted with benzene, yielded the monohydroxy metabolite in the form of the acetoxydibenz-9,10-anthraquinone. When dissolved in 2 *N* ethanolic potassium hydroxide it gave a blue-green solution which was refluxed with dimethyl sulfate to yield 1 mg. of the corresponding methyl ether, m.p. 200–204°. After chromatography on Florisil (elution with benzene) and crystallization from ethanol and benzene, orange needles, m.p. 211–212°, were obtained.

B. The second band, eluted with 2% ethyl acetate in benzene, gave a yellow solid that was crystallized from acetic acid as yellow needles, m.p. 292–295°, alone or mixed with an authentic sample[9] of the diacetoxy dibenz-9,10-anthraquinone derivative of the dihydroxy metabolite, m.p. 293–296°. The diacetate was dissolved in 2 *N* potassium hydroxide (deep blue solution) and treatment with dimethyl sulfate yielded 30 mg. of the corresponding dimethyl ether, m.p. 310–312°, as long orange needles after crystallization from acetic acid.

3,4-Diacetoxy-3,4-dihydro-1,2,5,6-dibenzanthracene (Ib).—The addition product of osmium tetroxide, 1,2,5,6-dibenzanthracene, and pyridine was prepared by the method of Cook and Schoental[15] in 96% yield. To a solution of 100 mg. of adduct in 5 ml. of chloroform, 5 ml. of acetic anhydride and 1 ml. of pyridine was added 0.05 ml. of concentrated hydrochloric acid. The mixture was refluxed for 10 minutes, and after cooling was filtered to remove a crystalline derivative of osmic acid, m.p. >370°. The solvents were removed *in vacuo*, and the residue was chromatographed on Florisil. Elution with 2% ethyl acetate in benzene yielded 50 mg. (87%) of the diacetate Ib which crystallized from benzene and ethanol as colorless prisms, m.p. 177–178° (lit. m.p. 176.5–177.5°).

(23) A. Pullman and B. Pullman, "Advances in Cancer Research," Vol. 3, Academic Press, Inc., New York, N. Y., 1955, pp. 156–158.

3-Acetoxy-1,2,5,6-dibenzanthracene (IIIa).—The following reactions were run under nitrogen using solvents previously flushed with nitrogen. Dibenzanthracene-3,4-dihydrodiol was obtained by refluxing a solution of 300 mg. of the diacetate Ib in 10 ml. of tetrahydrofuran with 3 mmoles of lithium aluminum hydride in 12 ml. of ether for 30 minutes. Five ml. of water was added dropwise to the reaction mixture and the solvents were removed *in vacuo*. To effect dehydration the residue was refluxed for 30 minutes with 20 ml. of glacial acetic acid and 1 ml. of concentrated hydrochloric acid. The solvents were removed at the water-pump and the residue was acetylated by refluxing with 15 ml. of acetic anhydride and 1 ml. of pyridine for 1 hr. After removal of the solvents *in vacuo*, water was added and the product was extracted into benzene. Evaporation of the benzene gave a yellow oil that was dissolved in benzene and chromatographed on Florisil. The product was eluted with 1% ethyl acetate in benzene and after crystallization from benzene and ethanol yielded 144 mg. (56%) of the 3-acetoxy derivative IIIa as colorless plates, m.p. 215–220°. Recrystallization from ethanol and benzene gave an analytical sample melting at 223–224°.

Anal. Calcd. for $C_{24}H_{16}O_2$: C, 85.69; H, 4.80. Found: C, 85.62; H, 4.55.

A solution of 250 mg. of IIIa in 30 ml. of dioxane was refluxed under nitrogen for 5 minutes with 30 ml. of 20% potassium hydroxide. The resulting phenol was methylated by the dropwise addition of 5 g. of dimethyl sulfate while the reaction mixture was stirred and refluxed for 1 hr. After cooling and dilution with water, the methylated product crystallized from solution as colorless plates of **3-methoxy-1,2,5,6-dibenzanthracene (IIIb)** which were collected, washed with water and melted at 199–201°, lit.[15] m.p. 200–201°. The yield was 219 mg. (95%).

3-Acetoxy-1,2,5,6-dibenz-9,10-anthraquinone (IVa).—A suspension of 60 mg. of IIIa in 5 ml. of glacial acetic acid was heated with 80 mg. of sodium dichromate on the steam-bath for 1 hr. The reaction mixture was diluted with water and the precipitated quinone filtered and washed with water. Crystallization from glacial acetic acid gave 35 mg. (53%) of yellow needles, m.p. 229–233°. After several recrystallizations from acetic acid, an analytical sample, m.p. 234–235°, was obtained.

Anal. Calcd. for $C_{24}H_{14}O_4$: C, 78.68; H, 3.85. Found: C, 79.02; H, 4.10.

Ten mg. of 3-acetoxydibenzanthraquinone was dissolved in 3 ml. of 1 *N* alcoholic potassium hydroxide to give a deep blue solution of the potassium salt. Acidification with hydrochloric acid gave an orange precipitate (8 mg.) of **3-hydroxy-1,2,5,6-dibenz-9,10-anthraquinone (IVc)** that was collected, washed with water and crystallized from acetic acid as red needles, m.p. 293–295°. The product was not analyzed.

3-Methoxy-1,2,5,6-dibenz-9,10-anthraquinone (IVb).—Saponification of 25 mg. of the acetate IVa with potassium hydroxide solution and methylation of the resulting phenol with dimethyl sulfate gave 22 mg. (96%) of the methyl ether, m.p. 221–222°. Deep orange needles, m.p. 221.5–222.5° were obtained after crystallization from ethanol and benzene.

Anal. Calcd. for $C_{23}H_{14}O_3$: C, 81.64; H, 4.17. Found: C, 81.81; H, 4.45.

3,4,7,8-Tetrahydrotetraacetoxy-1,2,5,6-dibenzanthracene (IIb).—A suspension of 1.2 g. of Ib in 200 ml. of benzene was treated with 1 g. of osmium tetroxide and 0.65 ml. of pyridine. The mixture was kept at 45° for 24 hr., refluxed for 6 hr. and cooled. The adduct was hydrolyzed under nitrogen by stirring with 50 ml. of an aqueous solution of 1% potassium hydroxide and 10% mannitol for 2 hr. The aqueous layer was separated and the precipitate was collected and added to the benzene layer which was refluxed for 1 hr. with 50 ml. of acetic anhydride and 5 ml. of pyridine. After removal of the solvents *in vacuo*, the residue was taken up in benzene and chromatographed on Florisil. Elution with 2% ethyl acetate in benzene gave 950 mg. of unchanged Ib, and subsequent elution with 4% ethyl acetate yielded 200 mg. of crude tetraacetate IIb, which was crystallized from acetic acid and then from benzene to give an analytical sample, m.p. 344–346° dec.

Anal. Calcd. for $C_{30}H_{26}O_8$: C, 70.03; H, 5.12. Found: C, 69.60; H, 4.78.

When IIb was heated with alcoholic potassium hydroxide in the presence of air, the resulting tetrahydrotetrol IIa was oxidized instantaneously to **1,2,5,6-dibenz-3,4,7,8-anthraquinone (VIII)**.

To a suspension of 10 mg. of the tetraacetate IIb in 10 ml. of ethanol was added 0.5 ml. of 20% potassium hydroxide. The mixture was boiled for 10 minutes while nitrogen was bubbled through, the ethanol was removed by evaporation in a stream of nitrogen, and 5 ml. of acetic acid and 0.1 ml. of concentrated hydrochloric acid were added. After heating on the steam-bath for 10 minutes, the solvents were removed and the resulting phenol was acetylated with acetic anhydride and pyridine. After removal of the solvents, the residue was dissolved in benzene and chromatographed on Florisil. The fluorescent product (6 mg.) was eluted with 3% ethyl acetate in benzene and identified as **3,7-diacetoxy-1,2,5,6-dibenzanthracene** VIa by oxidation to the corresponding 9,10-quinone as described below for the preparation of VIIa.

3-Acetoxy-7,8-diacetoxy-7,8-dihydro-1,2,5,6-dibenzanthracene (Va).—A suspension of 288 mg. (0.86 mmole) of 3-acetoxydibenzanthracene in 10 ml. of benzene was treated with 296 mg. (0.86 mmole) of osmium tetroxide and 0.2 ml. of pyridine. The reaction mixture was allowed to stand at 37° for 2 weeks, and the resulting light tan precipitate (405 mg.) was collected by filtration and washed with benzene. The filtrate, after 1 week at 37°, yielded an additional 158 mg. of adduct; total yield 563 mg. (87%). The osmic acid addition product was converted to Va by refluxing for 3 hr. under nitrogen with 25 ml. of chloroform, 25 ml. of acetic anhydride, 5 ml. of pyridine and 1 ml. of water. The solvents were removed *in vacuo* and the residue was taken up in benzene and chromatographed on Florisil. Elution with 2% ethyl acetate in benzene removed a small amount of fluorescent by-product and the product was eluted with 4% ethyl acetate in benzene. The resulting colorless oil was dissolved in a small amount of benzene and crystallized by addition of a large amount of ethanol, yielding 260 mg. (76%) of fine white needles, m.p. 205–208°. Recrystallization from ethanol and benzene gave an analytical sample, m.p. 210–212°.

Anal. Calcd. for $C_{28}H_{23}O_6$: C, 74.00; H, 4.88. Found: C, 74.37; H, 5.10.

3,7-Diacetoxy-1,2,5,6-dibenzanthracene (VIa).—Deacetylation and dehydration of 260 mg. of Va and acetylation of the resulting 3,7-dihydroxy derivative, as described above for the preparation of 3-acetoxydibenzanthracene, resulted in a yellowish solid that was eluted from a Florisil column with 3% ethyl acetate in benzene and was crystallized from benzene to give 75 mg. (33%) of the diacetate VIa, m.p. 300–305°. Recrystallization from ethanol and benzene resulted in colorless needles, m.p. 304–306°.

Anal. Calcd. for $C_{26}H_{18}O_4$: C, 79.17; H, 4.60. Found: C, 79.38; H, 4.67.

The above conversion was also carried out by heating 50 mg. of Va at 300° for 1 hr. in a nitrogen atmosphere. The melt was cooled and reacetylated by refluxing with acetic anhydride and pyridine. After removal of the solvents *in vacuo* the product was chromatographed on Florisil and eluted with 3% ethyl acetate in benzene. Crystallization from benzene and ethanol gave 6 mg. (14%) of white needles, m.p. 298–303° which did not depress the m.p. of the 3,7-diacetate VIa prepared by acid dehydration of Va.

3-Methoxy-7,8-diacetoxy-7,8-dihydro-1,2,5,6-dibenzanthracene (Vb).—Treatment of 200 mg. of 3-methoxydibenzanthracene with osmium tetroxide and pyridine according to the procedure described for the preparation of the adduct of IIIa gave 455 mg. (97%) of product. Conversion to the diacetate Vb was carried out by the same method used for the preparation of Va and yielded 150 mg. (56% based on adduct) of poorly crystalline material, m.p. 204–206°. Repeated crystallization from ethanol and benzene gave an analytical sample of Vb as large prisms, m.p. 207–208°.

Anal. Calcd. for $C_{27}H_{22}O_5$: C, 76.04; H, 5.20. Found: C, 75.85; H, 5.37.

Deacetylation of Vb to the 3-methoxy-7,8-dihydrodiol derivative, acid dehydration and acetylation by the method described above again resulted in 3,7-diacetoxydibenzanthracene.

3,7-Dimethoxy-1,2,5,6-dibenzanthracene (VIb).—A solution of 28 mg. of 3,7-diacetoxydibenzanthracene in 5 ml. of dioxane was hydrolyzed by boiling for a few minutes under nitrogen with 5 ml. of 20% potassium hydroxide. The resulting phenol was methylated by dropwise addition of dimethyl sulfate, the product was extracted into benzene and chromatographed on Florisil. Elution of the dimethyl ether with benzene and crystallization from benzene and petroleum ether yielded 22 mg. (91%) of white plates, m.p. 300–305°. Three recrystallizations from benzene and petroleum ether gave an analytical sample melting at 304–305°.

Anal. Calcd. for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 85.37; H, 5.28.

3,7-Diacetoxy-1,2,5,6-dibenz-9,10-anthraquinone (VIIa).—A suspension of 30 mg. of 3,7-diacetoxydibenzanthracene in 5 ml. of glacial acetic acid was heated on the steam-bath for 1 hr. with 40 mg. of sodium dichromate. After cooling and dilution of the reaction mixture with water, the orange precipitate was collected, washed with water, dried, dissolved in benzene, and chromatographed on Florisil. The diacetoxydibenzanthraquinone was eluted with 2% ethyl acetate in benzene and crystallized from acetic acid as 20 mg. (62%) of yellow needles, m.p. 309–311°. When mixed with an authentic sample[14] of 3,7-diacetoxydibenz-9,10-anthraquinone, m.p. 310–312°, there was no depression of the melting point.

Anal. Calcd. for $C_{26}H_{16}O_6$: C, 73.58; H, 3.80. Found: C, 73.55; H, 4.02.

Ten mg. of the diacetoxy quinone VIIa was hydrolyzed by boiling with 1 ml. of 1 *N* alcoholic potassium hydroxide until the solution became clear. The reaction mixture was diluted with water and neutralized by passing a stream of carbon dioxide into the hot solution. The red crystals of 3,7-dihydroxy-dibenz-9,10-anthraquinone (VIIb) which formed were collected and dried. The infrared spectrum of the product was identical to the spectrum of the dihydroxyquinone prepared as above from authentic 3,7-diacetoxydibenz-9,10-anthraquinone.

3,4-Diacetoxy-1,2,5,6-dibenzanthracene (X).—A suspension of 100 mg. of 1,2,5,6-dibenz-3,4-anthraquinone in 10 ml. of glacial acetic acid was refluxed under nitrogen for 30 minutes with 200 mg. of zinc dust. The solution gradually changed to a light green and after addition of 10 ml. of acetic anhydride and 1 ml. of pyridine, the reaction mixture was refluxed for 1 hr. and filtered while hot. The filtrate was diluted with sufficient water to decompose the acetic anhydride and the product crystallized from the cooled solution as fine white needles, m.p. 229–230°, which were collected and washed with water; yield 100 mg. (78%). When air was admitted to the reaction mixture before acetylation, the hydroquinone was rapidly re-oxidized to the starting material.

Anal. Calcd. for $C_{26}H_{18}O_4$: C, 79.17; H, 4.60. Found: C, 78.62; H, 4.58.

9,10-Dimethoxy-1,2,5,6-dibenzanthracene.—A solution of 200 mg. of sodium hydrosulfite in 5 ml. of water was added to a suspension of 90 mg. of 1,2,5,6-dibenz-9,10-anthraquinone in 10 ml. of 1 *N* alcoholic potassium hydroxide. The mixture was refluxed until all the solid material dissolved and the deep red solution was treated with 5 ml. of 20% potassium hydroxide and dimethyl sulfate until the red color was discharged. The product crystallized from the cooled reaction mixture as light green prisms which were collected and washed with water. Crystallization from ethanol and benzene gave 91 mg. (92.5%) of the dimethyl ether, m.p. 241–245°. A colorless analytical sample, m.p. 244–245°, was obtained by recrystallization from benzene and petroleum ether.

Anal. Calcd. for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 85.56; H, 5.43.

Oxidation of 3-Hydroxy-1,2,5,6-dibenzanthracene to 1,2,-5,6-Dibenz-3,4-anthraquinone (IX).—A suspension of 5 mg. of 3-acetoxydibenzanthracene in 2 ml. of 1 *N* alcoholic potassium hydroxide was boiled under nitrogen until a clear solution was obtained. The phenol was precipitated with hydrochloric acid, collected, washed with water and dissolved in 1 ml. of acetone. Fifteen mg. of potassium nitroso disulfonate[19] in 1 ml. of water was added and when the mixture was heated briefly on the steam-bath a red color gradually developed. After about 15 minutes, the product crystallized from solution and was collected, washed with water and dried, yielding 4.5 mg. of red needles, m.p. 351–353°,

alone or mixed with an authentic sample of 1,2,5,6-dibenz-3,4-anthraquinone.

Oxidation of 3-Hydroxy-1,2,5,6-dibenzanthracene to 1,2-5,6-Dibenz-3,4,7,8-anthraquinone (VIII).—A suspension of 20 mg. of diazotized sulfanilic acid in 0.5 ml. of water was added at 5° to a solution of 3-hydroxydibenzanthracene prepared by dissolving 4 mg. of 3-acetoxydibenzanthracene in 0.5 ml. of ethanol and 0.5 ml. of 10% sodium hydroxide. The bright red precipitate of azo dye that immediately formed was centrifuged, washed with water and dissolved in 1 ml. of ethanol and 2 ml. of 10% sodium hydroxide. Ten mg. of sodium hydrosulfite was added, and after heating on the steam-bath for a few minutes, the yellow solution was neutralized and the aminophenol extracted into ethyl acetate. After removal of the ethyl acetate, the residue was oxidized by heating briefly with chromic anhydride in glacial acetic acid. Red needles of 1,2,5,6-dibenz-3,4,7,8-anthraquinone which did not melt below 370° crystallized from the reaction mixture. Exactly the same procedure was followed for the oxidation of 3,7-dihydroxydibenzanthracene to the quinone VIII. The intermediate 3,7-dihydroxy-4,8-diaminodibenzanthracene was blue in color.

2,3,5,6-Tetra-*o*-tolyl-1,4-benzoquinone (XI).—One-tenth mole (10.7 g.) of *o*-toluidine was dissolved in 25 ml. of concentrated hydrochloric acid, cooled to −5° and diazotized at −5° with 7 g. of sodium nitrite in 16 ml. of water. The diazonium salt solution was added dropwise with stirring to a mixture of 6 g. (0.05 mole) of *p*-benzoquinone and 17 g. of sodium acetate in 125 ml. of ethanol. The temperature was maintained at 30° by external cooling, nitrogen was evolved, and after 1 hr. the yellow precipitate which formed was collected by filtration, washed with water and dried. Crystallization from benzene and ethanol yielded 1.6 g. (14%) of orange prisms, m.p. 262–265°. Recrystallization from benzene afforded an analytical sample, m.p. 271–272°.

Anal. Calcd. for $C_{34}H_{28}O_2$: C, 86.40; H, 6.82. Found: C, 86.96; H, 6.82.

2,6-Di-*o*-tolyl-1,4-benzoquinone (XIV).—The filtrate from the preceding reaction mixture was extracted with ether. The extract was washed with dilute hydrochloric acid and water, dried over sodium sulfate, and the ether removed to give a red oil which was dissolved in benzene and chromatographed on a Florisil column. Elution with a 1:1 mixture of benzene and petroleum ether gave a yellow oil which was crystallized from ethanol to yield 1.9 g. (13%) of orange, crystalline quinone, m.p. 120–123°. After recrystallization from ethanol, yellow needles were obtained, m.p. 123.5–124° (lit.[18] m.p. 124°).

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.16; H, 5.71.

2,3,5,6-Tetra-*o*-tolyl-1,4-benzohydroquinone (XIIa).—One gram of the quinone XI was dissolved in 60 ml. of glacial acetic acid and refluxed for 1 hr. with 0.5 g. of zinc dust. The reaction mixture was filtered while hot and the product which crystallized from the cooled filtrate was collected and washed with hot water to give 948 mg. (94%) of white plates, m.p. 274–280°. Three recrystallizations from benzene and ethanol gave an analytical sample, m.p. 279–282°.

Anal. Calcd. for $C_{34}H_{30}O_2$: C, 86.77; H, 6.42. Found: C, 87.02; H, 6.29.

3,6-Diacetoxy-2,5-di-*o*-tolyl-2′,2″-dimethylterphenyl (XIIb).—A solution of 900 mg. of the hydroquinone XIIa in 23 ml. of acetic anhydride and 2 ml. of pyridine was refluxed under nitrogen for 2 hr. The solvents were removed *in vacuo*, and the colorless residue was crystallized from benzene and ethanol to yield 860 mg. (89%) of the diacetate XIIb, m.p. 286–288°. Colorless prisms, m.p. 288–289°, were obtained after repeated crystallization from the same solvents.

Anal. Calcd. for $C_{38}H_{34}O_4$: C, 82.28; H, 6.17. Found: C, 82.82; H, 6.19.

3,6-Diacetoxy-2,5-di-*o*-tolyl-2′,2″-dimethylterphenyl octabromide (XIII).—A mixture of 720 mg. (4 mmoles of N-bromosuccinimide, 500 mg. (0.98 mmole) of XIIb and 10 mg. of benzoyl peroxide in 16 ml. of carbon tetrachloride was refluxed for 8 hr. The reaction mixture was diluted with chloroform and after filtration was washed with sodium bicarbonate solution and water. Evaporation of solvents left a yellow oil that was crystallized from benzene and ethanol to yield 700 mg. of white crystals, m.p. 298–306°. Three recrystallizations from benzene and ethanol gave an analytically pure octabromo derivative melting at 309–311° dec.

Anal. Calcd. for $C_{38}H_{26}Br_8O_4$: C, 38.48; H, 2.21. Found: C, 38.79; H, 2.46.

2,5-Di-*o*-tolyl-1,4-benzohydroquinone (XV).—A solution of 0.5 mole of diazotized *o*-toluidine, prepared as described above, was stirred rapidly into a mixture of 60 g. (0.5 mole) of *p*-benzoquinone and 85 g. of sodium acetate in 1250 ml. of absolute ethanol. Sufficient ice was added to maintain the temperature below 35° and the reaction appeared to be complete after about 30 minutes. No precipitate appeared either before or after addition of water. Five-hundred ml. of water was added and the reaction mixture was steam distilled to remove unreacted benzoquinone. The residue in the flask separated as a heavy black tar which was collected, dried on the steam-bath, and dissolved in 1 l. of benzene. Addition of 200 ml. of petroleum ether gave a black precipitate that was removed by filtration and discarded. The filtrate was chromatographed on a 5 × 70 cm. column of 100/200 mesh Florisil. Elution with a 2:1 mixture of benzene and petroleum ether gave an orange oil which crystallized upon trituration with ethanol to yield 4 g. (5.5%) of colorless hydroquinone. Recrystallization of a sample from ethanol and benzene afforded colorless prisms, m.p. 264–266°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.16; H, 6.21. Found: C, 82.55; H, 5.78.

2,5-Di-*o*-tolyl-1,4-benzoquinone (XVI).—Fifty mg. of the hydroquinone XV was dissolved in 5 ml. of glacial acetic acid and heated on the steam-bath for 1 hr. with 50 mg. of sodium dichromate. Dilution with water precipitated 41 mg. (83%) of quinone, m.p. 148–152°. Crystallization from ethanol gave long yellow needles, m.p. 155–156°.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.34; H, 5.81.

2,5-Diacetoxy-2′,2″-dimethylterphenyl (XVIIa).—One gram of XV was refluxed for 1 hr. with 40 ml. of acetic anhydride and 5 ml. of pyridine. The solvents were removed with the water-pump and the yellow residue was crystallized from benzene and ethanol, yielding 990 mg. (76%) of colorless prisms, m.p. 133–136°. An analytical sample melting at 135–136° was prepared by recrystallization from ethanol.

Anal. Calcd. for $C_{24}H_{22}O_4$: C, 76.98; H, 5.92. Found: C, 76.94; H, 5.91.

2,5-Diacetoxy-2′,2″-bis-bromomethylterphenyl (XVIIb).—Bromination of 250 mg. of XVIIa with 2 molar equivalents of N-bromosuccinimide under conditions described for the preparation of XIII resulted in 260 mg. of the crude dibromo derivative, m.p. 184–194°. White prisms which melted at 189–194° were obtained after crystallization from carbon tetrachloride and from benzene.

Anal. Calcd. for $C_{24}H_{20}Br_2O_4$: C, 54.16; H, 3.79. Found: C, 54.50; H, 3.74.

Treatment of 50 mg. of XVIIa with 4 molar equivalents of N-bromosuccinimide under the above conditions gave 84 mg. (91%) of a tetrabromo derivative, which probably has a structure analogous to that of the octabromide XIII. Recrystallization of the **2,5-diacetoxy-2′,2″-dimethylterphenyl tetrabromide** from benzene and petroleum ether gave an analytical sample consisting of colorless prisms, m.p. 254–256°.

Anal. Calcd. for $C_{24}H_{18}Br_4O_4$: C, 41.77; H, 2.63. Found: C, 41.46; H, 2.75.

In an attempt to convert the dibromo derivative XVIIb to the corresponding dinitrile, 50 mg. of XVIIb was heated with 2 ml. of ethanol, 0.5 ml. of water and 100 mg. of sodium cyanide for 30 minutes on the steam-bath. The reaction mixture was extracted with benzene and the extract, after washing with water, was evaporated to dryness to give 35 mg. of white prisms, m.p. 200–205°. The product was neutral, did not contain nitrogen or bromine, and could also be obtained by heating XVIIb with 1 *N* alcoholic potassium hydroxide for 2 minutes. The compound was not analyzed but was probably the 2′,2″-bis-hydroxymethyl derivative.

2,5-Dimethoxy-2′,2″-dimethylterphenyl (XVIIIa).—A solution of 1.3 g. of the hydroquinone XV in 20 ml. of dioxane was refluxed for 5 minutes under nitrogen with 20 ml. of 20% potassium hydroxide. The red solution was treated

dropwise with dimethyl sulfate until the color faded to light yellow and the dimethyl ether crystallized from the reaction mixture as colorless plates, m.p. 234–237°, which were collected and washed with water; yield 1.23 g. (86%). Three recrystallizations from ethanol and benzene gave an analytical sample, m.p. 236–237°.

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 82.98; H, 6.96. Found: C, 83.03; H, 6.71.

2,5-Dimethoxy-2′,2″-bis-bromomethylterphenyl (XVIIIb).—The bromination was carried out on 1.29 g. (4.95 mmoles) of XVIIIa with 1.46 g. (8.20 mmoles) of N-bromosuccinimide as described for the preparation of XIII. After crystallization of the product from ethanol and benzene, 1.34 g. (69%) of the dibromo derivative was obtained as white prisms, m.p. 160–170°. One recrystallization from carbon tetrachloride and two from benzene and petroleum ether gave colorless needles, m.p. 169–172°.

Anal. Calcd. for $C_{22}H_{20}Br_2O_2$: C, 55.48; H, 4.23. Found: C, 56.12; H, 4.31.

2,5-Dimethoxy-2′,2″-bis-cyanomethylterphenyl (XVIIIc).—A solution of 1.6 g. of the dibromo compound XVIIIb in 20 ml. of 2-methoxyethanol and 20 ml. of ethanol was refluxed with 1.6 g. of sodium cyanide in 2 ml. of water for 6 hr. After cooling, the product was precipitated with water, collected by filtration and washed with water to give 0.98 g. (78%) of the dinitrile as fine needle-like crystals, m.p. 193–198°. Three recrystallizations from benzene and ethanol raised the m.p. to 198–199°.

Anal. Calcd. for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47. Found: C, 78.24; H, 5.49.

2,5-Dimethoxy-2′,2″-bis-carboxymethylterphenyl (XVIIId).—The dinitrile XVIIIc (700 mg.) was refluxed with 10 ml. of 2-methoxyethanol, 10 ml. of ethanol and 10 ml. of 50% potassium hydroxide for 12 hr. The reaction mixture was diluted with water, filtered and acidified with hydrochloric acid to give a precipitate that was collected by filtration and redissolved in 5% sodium bicarbonate solution. After washing the bicarbonate solution with benzene, the acid was again precipitated with hydrochloric acid, collected and washed with water. The yield was 640 mg. (83%) of amorphous product, m.p. 260–280°. After four crystallizations from acetic acid the m.p. was 265–280° and recrystallization from various other solvents did not raise the melting point.

Anal. Calcd. for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46. Found: C, 70.03; H, 5.35.

4,8-Diacetoxy-9,10-dimethoxy-1,2,5,6-dibenzanthracene (XIXa).—A mixture of 300 mg. of the diacid XVIIId and 300 mg. of freshly fused zinc chloride in 6 ml. of glacial acetic acid and 9 ml. of acetic anhydride was refluxed for 1 hr. The cooled reaction mixture was poured into water to give a precipitate which was collected, dried, dissolved in benzene and chromatographed on a Florisil column. The product was eluted slowly with 2% ethyl acetate in benzene and was crystallized from benzene and ethanol to yield 30 mg. (9%) of yellow prisms, m.p. 292–300°. Further chromatography on Florisil and recrystallization from ethanol and benzene gave an analytical sample, m.p. 300–302°.

Anal. Calcd. for $C_{28}H_{22}O_6$: C, 74.00; H, 4.88. Found: C, 73.83; H, 4.81.

4,8,9,10-Tetramethoxy-1,2,5,6-dibenzanthracene (XIXb).—The tetramethyl ether was prepared by refluxing 30 mg. of XIXa with 2 *N* alcoholic potassium hydroxide under nitrogen and methylating the resulting phenol with 20% potassium hydroxide and dimethyl sulfate. The product was extracted into benzene and chromatographed on Florisil. Elution with benzene and repeated crystallization from benzene yielded an analytical sample consisting of square prisms, m.p. 246–249°.

Anal. Calcd. for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57. Found: C, 78.12; H, 5.63.

An authentic 5-mg. sample of the diacetate of the dihydroxy rabbit metabolite,[9] m.p. 296–298° after chromatography on Florisil and crystallization from ethanol and benzene, was converted to the dibenz-9,10-anthraquinone by heating with chromic anhydride in glacial acetic acid. The quinone was dissolved in 1 ml. of 1 *N* ethanolic potassium hydroxide and the characteristic blue color was discharged upon addition of 10 mg. of sodium hydrosulfite in a few drops of water. The orange colored dihydroxyhydroquinone was methylated with dimethyl sulfate in the usual manner, and the colorless reaction mixture was extracted with benzene. The extract was washed with water, concentrated and chromatographed on a small Florisil column. The product was eluted with benzene and evaporation of the solvent deposited crystals of the tetramethyl ether, m.p. 230–232°. When this compound was mixed with XIXb the m.p. was depressed to 210–215°.

Diethyl-3-hydroxy-1,2-naphthalic Acid (XXI).—Ethyl β-oxo-γ-phenylbutyrate (b.p. 130–132° (4 mm.)) was prepared by the method of Anderson, *et al.*[24] Thirty-one grams (0.15 mole) of the ester was added rapidly with shaking to a suspension of 3.5 g. (0.15 mole) of sodium hydride in 150 ml. of ether, and the reaction mixture was allowed to stand for 12 hr. at room temperature with occasional shaking. The flocculent mass of sodium enolate was stirred vigorously while 25 g. (0.18 mole) of ethyl oxalyl chloride in 30 ml. of ether was added dropwise. After being stirred for 6 hours at room temperature, the ether solution was refluxed for 1 hr., neutralized with 5% sodium bicarbonate solution, washed with water and dried over sodium sulfate. Removal of the ether yielded the crude acylated ester XX as a light orange oil which was cooled to −20° and mixed with 250 ml. of concentrated sulfuric acid at −20°. After standing at this temperature for 1 hr., the mixture was poured onto ice and the cyclized product was immediately extracted into ether. The ether solution was washed with water and upon subsequent extraction with 5% sodium bicarbonate solution, a crystalline sodium salt formed in the aqueous layer. This by-product was filtered and its purification is described below. The desired hydroxy ester was then extracted from the ether solution with cold 1 *N* sodium hydroxide, acidified and re-extracted into ether. The ether extract was washed with water, dried with sodium sulfate and the ether was removed. The residual yellow oil crystallized on standing, giving 10.8 g. (25%) of yellow ester, XXI m.p. 72–75°. Colorless prisms, m.p. 73–75°, were obtained by recrystallization from petroleum ether.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.69; H, 5.51.

The by-product isolated above as its sodium salt was taken up in dilute hydrochloric acid and the resulting precipitate was collected, washed with water and dried. Crystallization from alcohol yielded long yellow needles, m.p. 146–147°. The analysis indicated that this compound might be the half-ethyl ester of 3-hydroxy-1,2-naphthalic acid.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.20; H, 4.62. Found: C, 64.50; H, 4.44.

3-Methoxy-1,2-naphthalic Anhydride (XXII).—A solution of 10 g. of the ester XXI in 80 ml. of 20% potassium hydroxide was treated with 14 ml. of dimethyl sulfate and heated at 100° for 1 hr. Sufficient methanol was added to give a homogeneous reaction mixture which was refluxed for 8 hr., cooled, washed with ether, acidified with hydrochloric acid, and the resulting oil extracted into ether. The ether solution was extracted with 5% sodium bicarbonate, and acidification yielded a light yellow precipitate of the methoxynaphthalic acid that became deep yellow upon standing due to spontaneous conversion to the stable anhydride XXII. The product was collected by filtration and crystallized from ethanol giving 6.5 g. (83%) of yellow needles, m.p. 200–205°. An analytical sample melting at 211–212° was obtained by recrystallization from benzene.

Anal. Calcd. for $C_{13}H_8O_4$: C, 68.42; H, 3.53. Found: C, 68.34; H, 3.49.

2(1′)-Naphthoyl-3-methoxy-1-naphthoic Acid (XXIIIa).—The following procedure was used for the preparation of all naphthoylnaphthoic acids described in the present work. A mixture of 60 ml. of ether, 600 mg. of magnesium turnings, 5.05 g. of 1-bromonaphthalene and a drop of ether containing methyl iodide was stirred and refluxed for 10 hours. The solution was filtered through glass wool and added over the course of 1 hr. to 5.55 g. of the anhydride XXII in 300 ml. of boiling benzene, whereupon an orange complex precipitated from solution. After refluxing for an additional hour, the reaction mixture was cooled, decomposed with dilute sulfuric acid and extracted with a mixture of ether and

(24) Prepared by the method of G. W. Anderson, I. F. Halverstadt, W. H. Miller and R. O. Roblin, Jr., THIS JOURNAL, **67**, 2197 (1945).

benzene from which the product was extracted with sodium bicarbonate solution. Acidification gave a yellowish, oily precipitate that was extracted into ether; the ether phase was dried over sodium sulfate and the ether was removed. When the resulting oil was triturated with benzene, 4.95 g. (56%) of the keto acid XXIIIa crystallized, and after filtration unchanged anhydride XXII (0.6 g.) was recovered from the filtrate by precipitation with ethanol. The keto acid, m.p. 225–235°, was recrystallized from acetic acid, acetone and from ethanol and benzene, but its m.p. did not appreciably improve. For analysis the methyl ester of XXIIIa was prepared by treatment with methanol and concentrated sulfuric acid. It was crystallized from methanol giving long, white prisms, m.p. 148–149°.

Anal. Calcd. for $C_{24}H_{18}O_4$: C, 77.82; H, 4.90. Found: C, 77.90; H, 4.99.

4-Methoxy-1,2,5,6-dibenz-9,10-anthraquinone (XXIVa).—One gram of the keto acid XXIIIa was added to 40 ml. of 80% sulfuric acid and heated at 80° for 1 hr. The deep purple reaction mixture was poured onto ice, the precipitate was extracted into benzene and ether, and after washing with dilute alkali to recover unchanged acid, the organic layer was dried over sodium sulfate and the solvents were removed. Chromatography of the residue on Florisil gave a single orange band that was eluted from the column with 2% ethyl acetate in benzene and crystallized from benzene and ethanol, yielding 10 mg. of the quinone XXIVa as orange plates, m.p. 188–190°.

Anal. Calcd. for $C_{23}H_{14}O_3$: C, 81.64; H, 4.17. Found: C, 81.48; H, 4.37.

Various other concentrations of sulfuric acid and reaction temperatures and times were tried, but the conditions described were found to be optimal. Other standard methods of cyclization such as treatment of the keto acid XXIIIa with hydrogen fluoride or phosphorus pentoxide and treatment of the acid chloride of XXIIIa with aluminum chloride gave none of the desired product.

The methoxyquinone (3 mg.) was demethylated by refluxing for 1 hr. with 20 mg. of aluminum chloride in 3 ml. of benzene. The dark blue reaction mixture was decomposed with 2 *N* hydrochloric acid and ice. The product was extracted into benzene and extracted from the benzene solution with 1 *N* sodium hydroxide to give a dark blue solution. Acidification yielded a red precipitate of the 4-hydroxyquinone XXIVb, m.p. 258–260°; λ_{max} 448, 347 and 297 mμ (ε 4,080, 7,650 and 25,500).

4-Methoxy-1,2,5,6-dibenzanthracene (XXVIIa).—To a mixture of 3 ml. of 2 *N* potassium hydroxide, 500 mg. of zinc dust and 0.5 ml. of toluene was added 20 mg. of the quinone XXIVa. After refluxing the reaction mixture under nitrogen for 12 hr., the product was extracted into benzene and purified by chromatography on Florisil from which it was eluted with a 1:1 mixture of benzene and petroleum ether. Crystallization from benzene and petroleum ether gave 7 mg. of white needles, m.p. 235–236°.

Anal. Calcd. for $C_{23}H_{16}O$: C, 89.58; H, 5.23. Found: C, 89.92; H, 5.13.

The keto acid XXIIIa was also converted to 4-methoxydibenzanthracene by the route described below for the conversion of XXIIIb to XXVIIb. The methoxyanthranol acetate XXVIa obtained by cyclization of the reduced acid XXVa melted at 249–251°.

Anal. Calcd. for $C_{25}H_{18}O_3$: C, 81.95; H, 4.95. Found: C, 82.10; H, 4.92.

Hydrolysis and reduction of XXVIa gave a monomethoxy derivative identical with XXVIIa.

Zinc dust pyrolysis of XXVIIa demonstrated its identity as the 1,2,5,6-dibenzanthracene isomer. An intimate mixture of 5 mg. of XXVIIa and 500 mg. of zinc dust was heated in a sealed tube at 480–500° for 1 hr. The contents of the tube were removed with benzene, and after filtration and concentration, the benzene solution was chromatographed on Florisil. The product was eluted with 10:1 petroleum ether and benzene and three crystallizations from benzene and petroleum ether yielded colorless plates, m.p. 265–267°, alone or mixed with an authentic sample of 1,2,-5,6-dibenzanthracene.

2(1'-Naphthoyl-3,4'-dimethoxy-1-naphthoic Acid (XXIIIb).—The dimethoxy keto acid XXIIIb was prepared in 36% yield from 1-bromo-4-methoxynaphthalene[25] and the anhydride XXII by the method described for the preparation of XXIIIa. It was crystallized from acetic acid to give white prisms, m.p. 254–258°.

Anal. Calcd. for $C_{24}H_{18}O_5$: C, 74.60; H, 4.70. Found: C, 74.56; H, 4.75.

4,7-Dimethoxy-9-acetoxy-1,2,5,6-dibenzanthracene (XXVIb).—Two grams of the keto acid XXIIIb was dissolved in 90 ml. of 1 *N* sodium hydroxide and 3 g. of zinc dust was added. After refluxing the reaction mixture overnight, an additional 2 g. of zinc dust and 10 ml. of 10 *N* sodium hydroxide was added, refluxing was continued for 24 hr., and the reaction mixture was filtered while hot. The residual zinc dust was repeatedly leached with several portions of boiling water which were also filtered, and the combined filtrates were acidified with hydrochloric acid. The resulting light tan precipitate (1.8 g.) was collected and dried. Attempts to purify the reduced acid were unrewarding, and the crude product was therefore cyclized by refluxing it for 1 hr. with 12 ml. of acetic anhydride, 24 ml. of acetic acid and 200 mg. of freshly fused zinc chloride. After the solvents were removed *in vacuo*, the residue was taken up in ether, washed with sodium bicarbonate solution, water, and was taken to dryness. The crude product after being chromatographed several times on Florisil columns with benzene as the eluent gave 80 mg. of anthranol acetate XXVIb, m.p. 223–226°. Recrystallization from benzene and petroleum ether yielded long white needles, m.p. 227–228°.

Anal. Calcd. for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09. Found: C, 78.45; H, 5.17.

4,7-Dimethoxy-1,2,5,6-dibenzanthracene (XXVIIb).—A mixture of 40 mg. of XXVIb, 1 ml. of ethanol and 8 ml. of 2 *N* potassium hydroxide was refluxed until a clear, light green solution of dimethoxydibenzanthranol was obtained. After addition of 500 mg. of zinc dust and 1 ml. of toluene, the mixture was refluxed for 12 hr., benzene was added, and the organic layer was separated and evaporated to dryness. The residue was chromatographed on Florisil and eluted with a 1:1 mixture of benzene and petroleum ether to give 7 mg. of the 4,7-dimethoxy derivative, m.p. 282–286°. An analytical sample of white needles melting at 285–287° was obtained after crystallization from benzene and ethanol.

Anal. Calcd. for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 85.43; H, 5.41.

A mixture of 4,7-dimethoxydibenzanthracene and an authentic sample[9] of the dimethyl ether of the dihydroxy rabbit metabolite, m.p. 256–260°, melted at 250–275°.

When the 3,7-dimethoxy-9-acetoxy derivative XXVIb was submitted to zinc dust pyrolysis as described above for 4-methoxydibenzanthracene, 1,2,5,6-dibenzanthracene was obtained.

2'-Methoxy-1,2,5,6-dibenzanthracene (XXXV).—Although attempts to reduce the dibenzanthraquinone XXXIV by the method described for reduction of XXIV failed, the conversion was accomplished by the Clemmensen method. Twenty mg. of XXXIV was refluxed for 8 hr. with 1 g. of zinc dust (previously treated with 100 mg. of mercuric chloride, 1.5 ml. of water and 0.05 ml. of concentrated hydrochloric acid), 5 ml. of 6 *N* hydrochloric acid and 1 ml. of glacial acetic acid. After extraction of the reaction mixture with benzene, the benzene extract was taken to dryness and the residue was chromatographed on Florisil. Elution with a 1:1 mixture of benzene and petroleum ether gave 15 mg. of a white solid, m.p. 170–185°. Recrystallization from methanol and from benzene and petroleum ether gave 5 mg. of 2'-methoxydibenzanthracene as white needles, m.p. 205–207°. See Table II for analyses.

2-Methoxy-7-acetylaminonaphthalene.—The starting material, 2-hydroxy-7-acetylaminonaphthalene, prepared by alkaline fusion of 1-aminonaphthalene-7-sulfonic acid[26] and subsequent acetylation by the method of Kehrmann,[27] melted at 163–165° (lit. m.p. 165°). Conversion to the methyl ether was carried out by dissolving the hydroxy derivative in 1 *N* sodium hydroxide and treating with 1.1 moles of dimethyl sulfate at room temperature for 3 hr. The crude product, m.p. 160–170°, was obtained in almost quantitative yield and recrystallization from ethanol yielded colorless needles, m.p. 175–176°.

(25) Prepared by the method of N. P. Buu-Hoï, *Ann.*, **556**, 1 (1944).

(26) W. F. Brown, J. C. Hebden and J. R. Withrow, THIS JOURNAL, **51**, 1766 (1929).

(27) F. Kehrmann and E. F. Engelke, *Ber.*, **42**, 350 (1909).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.74; H, 5.90.

The methoxynaphthylamine acetate (8 g.) was deacetylated by heating with 60 ml. of ethanol and 16 ml. of concentrated hydrochloric acid for 2 hr. on the steam-bath. After evaporation of most of the alcohol and cooling, the crystalline mass was filtered off and washed with 2 *N* hydrochloric acid to yield 7.5 g. of amine hydrochloride melting at 185–190°, which was used for subsequent reactions without further purification.

1-Bromo-7-methoxynaphthalene.—Although treatment of diazotized 2-methoxy-7-naphthylamine with cuprous bromide and copper according to the usual Sandmeyer–Gattermann procedure resulted in a very poor yield of the bromo derivative, the conversion was satisfactorily carried out by application of the Schwechten procedure.[28]

A solution of 5 g. of the amine hydrochloride in 40 ml. of 2 *N* sulfuric acid was cooled to 0° and diazotized with 1.8 g. of sodium nitrite in 9 ml. of water. The clear solution was diluted with 50 ml. of ice-water and a solution of 26 g. of mercuric bromide and 26 g. of potassium bromide in 100 ml. of water was added. After standing for 1 hr. at 0°, the double salt was filtered and dried *in vacuo* at room temperature. It was then mixed with an equal weight of potassium bromide and heated gradually to a temperature of 140° whereupon rapid decomposition of the salt occurred. The entire reaction mixture was sublimed at 150° (1 mm.) to give a white solid which was dissolved in petroleum ether and passed through a Florisil column with the same solvent. A yield of 2.6 g. (46%) of 1-bromo-7-methoxynaphthalene (m.p. 64–67°) was obtained. Recrystallization from ethanol and then petroleum ether gave white prisms, m.p. 68–69°.

Anal. Calcd. for $C_{11}H_9BrO$: C, 55.72; H, 3.83. Found: C, 55.68; H, 3.89.

1-Iodo-7-methoxynaphthalene.—A solution of 10 g. of diazotized 2-methoxy-7-naphthylamine, prepared as above, was slowly added to 14 g. of potassium iodide in 65 ml. of 2 *N* sulfuric acid. The reaction mixture was kept at room temperature for 1 hr., heated on the steam-bath for 15 min., cooled and extracted with ether. The ether extract, after washing with sodium bisulfite solution, dilute alkali and water, was dried over sodium sulfate and evaporated to dryness. The residue was taken up in petroleum ether and, after passage through a Florisil column, 1.1 g. (6.8%) of the iodo derivative was obtained as a white solid, m.p. 74–77°. Several crystallizations from ethanol gave an analytical sample melting at 76–77°.

Anal. Calcd. for $C_{11}H_9IO$: C, 46.83; H, 3.22. Found: C, 46.86; H, 3.19.

2′,6′-Dimethoxy-1,2,5,6-dibenz-9,10-anthraquinone (XXXVI).—Addition of the Grignard reagent prepared from either 1-bromo- or 1-iodo-7-methoxynaphthalene to 6-methoxy-1,2-naphthalic anhydride under conditions described above for the preparation of the keto acid XXIIIa gave an amorphous product which we were unable to appreciably purify. Two grams of the crude material was treated with sulfuric acid as described for the preparation of the quinone XXIVa. Elution of the cyclized product from a Florisil column with 1% ethyl acetate in benzene, and crystallization from ethanol and benzene gave 2 mg. of orange needles, m.p. 310–312° alone or mixed with an authentic sample of the dimethyl ether of the 9,10-anthraquinone of the dihydroxy rabbit metabolite, m.p. 310–312°.

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.25; H, 4.38. Found: C, 78.11; H, 4.21.

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MADISON, WISCONSIN

(28) W. E. Bachmann and J. Boutner, THIS JOURNAL, **58**, 2194 (1936).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Terpenoids. XXXII.[1] The Structure of the Cactus Triterpene Treleasegenic Acid. Ring Conformational Alterations in a Pentacyclic Triterpene[2]

BY CARL DJERASSI AND JOHN S. MILLS

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Treleasegenic acid, a new triterpene isolated from the cactus *Lemaireocereus treleasei*, has been shown to be 21β,30-dihydroxyoleanolic acid (Ia). The structure proof, proceeding *via* the 30-trityl ether VI, involved multistage interconversions with the methyl esters of the cactus triterpenes machaerinic acid (XVIIa) and queretaroic acid (IXa) and thus led also to a rigorous definition of the stereochemistry. The formation of transient as well as stable lactones between the C-17 carboxyl group and the 21β-hydroxyl function in a D/E *cis* fused pentacyclic triterpene can only be reconciled by conformational alterations (chair to boat) in ring E and probably also ring D. As a consequence, methyl esters of certain ring E substituted oleanolic acids can be saponified with surprising ease.

The Mexican cactus *Lemaireocereus treleasei* has been shown[3] to be a good source of oleanolic acid and stellatogenin.[4] During a renewed extraction of this cactus in order to accumulate larger amounts of stellatogenin for its eventual conversion[5] to betulinic acid, Dr. Richard Hodges observed the presence of a neutral triterpene. A sufficient quantity of this substance has now been obtained so as to permit its structure elucidation.

Although encountered in the neutral fraction after methanolic hydrochloric acid hydrolysis of the glycosides, it was soon recognized that the substance represented a methyl ester and the probable form in which it occurs in the plant will be discussed below. Saponification with 10% methanolic potassium hydroxide furnished the free parent acid ($C_{30}H_{48}O_5$)—now named treleasegenic acid—and the nature of its functional groups was determined readily by the formation of a methyl ester (Ib), a methyl ester triacetate (Ic) and a triacetoxy acid (Id). Treleasegenic acid is thus a trihydroxy triterpenic acid and the ease of acetylation and saponification (of the triacetate) suggested that the hydroxyl

(1) Paper XXXI, C. Djerassi, D. B. Thomas, A. L. Livingston and C. R. Thompson, THIS JOURNAL, **79**, 5292 (1957).

(2) This investigation was supported by the Division of Research Grants (grant No. RG-3863) of the National Institutes of Health, U. S. Public Health Service.

(3) C. Djerassi, A. Bowers, S. Burstein, H. Estrada, J. Grossman, J. Herran, A. J. Lemin, A. Manjarrez and S. C. Pakrashi, THIS JOURNAL, **78**, 2312 (1956).

(4) C. Djerassi, E. Farkas, L. H. Liu and G. H. Thomas, *ibid.*, **77**, 5330 (1955).

(5) C. Djerassi and R. Hodges, *ibid.*, **78**, 3534 (1956).