[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Polynuclear Hydrocarbon Derivatives. XI. Octadecanoylbenz[a]anthracenes and Their Derivatives[1]

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12-Methyl-7-octadecanoylbenz[a]anthracene and five isomeric octadecanoylbenz[a]anthracenes with side chains located at nuclear positions 4,5,7,9 and 10, respectively, have been synthesized. With the exception of those carrying substituents in the 7-position, these ketones readily afforded oximes. Neither the ketones nor the oximes proved to be effective for inhibition of Sarcoma 180 in mice.

The 4- and 5-acyl derivatives were obtained from the reaction of 4- and 5-cyanobenz[a]anthracene with *n*-heptadecylmagnesium bromide; 4- and 7-acyl derivatives were produced when 4- and 7-benz[a]anthrylmagnesium bromide reacted with octadecanoyl chloride; and the 9- and 10-acyl derivatives were the major products when octadecanoyl chloride reacted with benz[a]anthracene under Friedel-Crafts conditions. When 7-benz[a]anthrylmagnesium bromide and 12-methyl-7-benz[a]anthrylmagnesium bromide reacted with aliphatic nitriles, the products were 7-cyanobenz[a]anthracene and 12-methyl-7-cyanobenz[a]anthracene together with dialkyl ketone and unidentified substances.

The possibility that two or more structural features, each of which is known to impart biological activity to simple molecules, can be combined to produce a molecule exhibiting enhanced activity is a concept that has been employed frequently to devise new substances for specific pharmacological purposes.[4] There have also been recorded several instances of a remarkable coincidence of carcinogenic and carcinostatic properties within the same polycyclic nucleus.[5-8]

These observations have led us to explore the feasibility of producing a useful carcinostat by combining the benz[a]anthracene nucleus, common to many carcinogenic compounds, with a characteristic structural feature of a known tumor inhibitory substance. As our first example of the latter we have chosen the 1-hydroxyliminooctadecyl group which is the functional feature of stearophenone oxime, a compound of consistent "intermediate" tumor inhibitory activity.[3]

Five isomeric octadecanoylbenz[a]anthracenes have been synthesized, in which the side chains were located at nuclear positions 4, 5, 7, 9, and 10, respectively. With the exception of the 7- isomer, all of these ketones were converted readily, by conventional methods, to the corresponding oximes which were desired for *in vivo* screening.

The choice of nuclear positions to be substituted was guided for the most part by the previously observed biological behavior of benz[a]anthracene derivatives. Side chains were placed in, or near, the "K region," which is implicated in carcinogenic activity and in which benz[a]anthracene appears to be attacked metabolically.[9-20]

Of particlar interest is the report[15] that 7-acetylbenz[a]anthracene is slightly active as a tumor inhibitor and inactive as a carcinogen, while the 7-alkylbenz[a]anthracenes show decreasing carcinogenic activity with increasing chain length. These observations indicated that 7-octadecanoylbenz[a]anthracene (XXXII) might be expected to exhibit tumor inhibition and suggested the screening of the isomeric octadecanoylbenz[a]anthracenes as well as their oximes.

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(2) We are indebted to John B. Field, M.D., in whose screening program (see reference 3) the compounds described in this paper were tested for tumor inhibitory activity. Present address of Dr. Field is Mount Sinai Hospital, Los Angeles 48, Calif.

(3) J. B. Field, M. C. Kloetzel, C. H. Thienes, L. T. Bascoy, R. Jersawitz, D. A. Filler, A. Boryczka, F. Costa, and E. Perez, *Cancer Research*, **18**, No. 8, Pt. 2, 365 (1958).

(4) H. Beckman, *Drugs, Their Nature, Action and Use*, W. B. Saunders Co., Philadelphia and London, 1958, p. 11.

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(6) G. M. Badger, L. A. Elson, A. Haddow, C. L. Hewett, and A. M. Robinson, *Proc. Roy. Soc.*, **130B**, 255 (1941-42).

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(11) N. V. Svartholm, *Arkiv Kemi, Mineral., Geol.*, **15A**, No. 13, 1 (1942); *Chem. Abstr.*, **36**, 6414 (1942).

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(13) A. Pullman, *Compt. rend.*, **226**, 486 (1948).

(14) A. Pullman, *Chem. Abstr.*, **42**, 5890 (1948).

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(19) M. J. Shear and J. Leiter, *J. Natl. Cancer Inst.*, 2, 241 (1941-42).

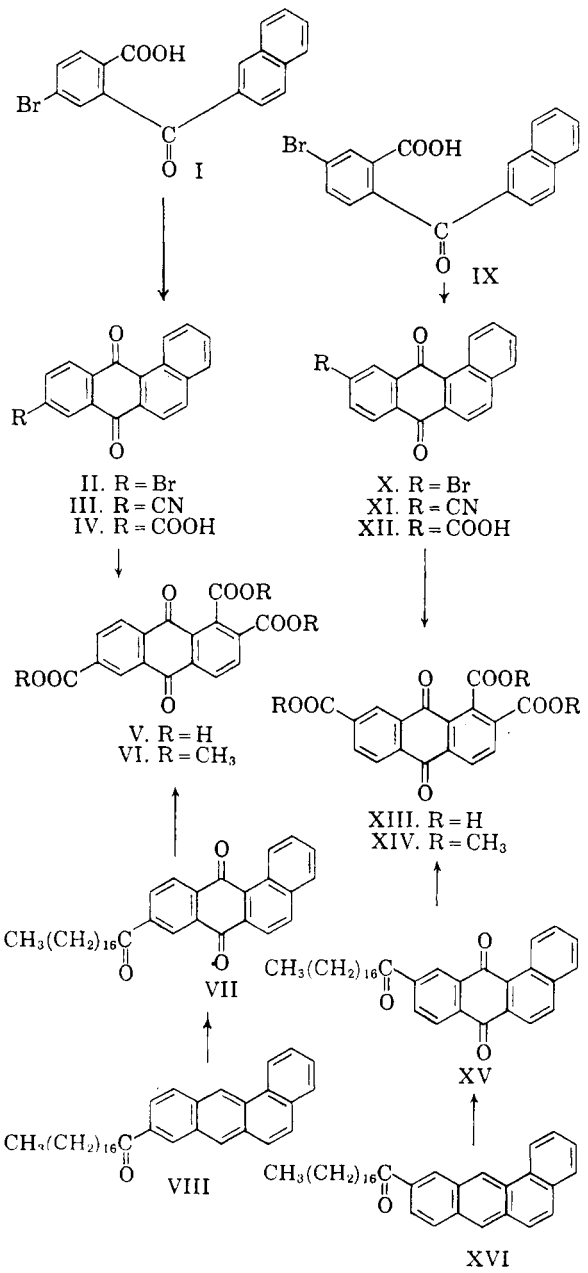
(20) A. Haddow and A. M. Robinson, *Proc. Roy. Soc.*, **127B**, 277 (1939).

A Friedel-Crafts reaction of benz[a]anthracene with octadecanoyl chloride conveniently provided reasonable yields of both 9- and 10-octadecanoylbenz[a]anthracene (VIII and XVI), in which the side chains are in positions far removed from the important meso positions.

Acetylation of benz[a]anthracene has been observed to yield primarily the 7-acetyl derivative at low temperatures[21,22] and the more thermodynamically stable 9- and 10-isomers when the reaction was effected at room temperature.[21,23] In our acylation studies, in which octadecanoyl chloride was employed in the presence of nitrobenzene as solvent and aluminum chloride as catalyst, at temperatures from 2° to 15°, the major products isolated were always the 9- and 10-acyl derivatives. 4- and 7-octadecanoylbenz[a]anthracene (XXIII and XXXII) also could be isolated in smaller amounts. Separation of isomers was difficult and was best accomplished with the aid of chromatography.

The structures of VIII and XVI were ascertained by oxidative degradation of these ketones to the corresponding anthraquinonetricarboxylic acids (V and XIII, respectively) in a manner similar to that used by Cook and Hewett[21] for the corresponding acetylbenz[a]anthracenes. However, we have synthesized the requisite acids V and XIII through a new sequence. For this purpose, the mixture of keto acids I and IX, obtained from the condensation of naphthalene with 4-bromophthalic anhydride, was cyclized with a mixture of sulfuric acid and boric acid,[24] but not successfully with a mixture of sulfuric acid and benzoyl chloride,[25] to afford a mixture of bromoquinones II and X. These were converted to the corresponding nitriles (III and XI) which subsequently were hydrolyzed to yield carboxylic acids IV and XII. Oxidation with acidified potassium permanganate then produced anthraquinonetricarboxylic acids V and XIII whose methyl esters proved to have the melting points recorded by Cook and Hewett[21] for these same compounds which they prepared by oxidative degradation of 9- and 10-methylbenz[a]anthracenes. These esters (VI and XIV) also were found to be identical with those produced by oxidative degradation of VIII and XVI (sequences VIII → VII → VI and XVI → XV → XIV), thereby establishing the positions of the side chains in XIII and XVI.

The synthesis of 4-octadecanoylbenz[a]anthracene (XXIII) was accomplished by two different routes from potassium benz[a]anthraquinone-4-sulfonate (XVII). Treatment of XVII with potassium bromate and hydrobromic acid yielded 4-bromobenz[a]anthraquinone (XVIII), a compound which has been prepared previously[26] from *o*-(5-bromo-2-naphthoyl)benzoic acid. Reduction of XVIII first with a mixture of stannous chloride and hydrochloric acid and subsequently with a mixture of zinc and aqueous sodium hydroxide, afforded 4-bromobenz[a]anthracene (XX). This reaction was accompanied by partial loss of halogen from the nucleus. The consequent difficulty encountered in purification resulted in depressed yields (45%) of XX.



(21) J. W. Cook and C. L. Hewett, *J. Chem. Soc.*, 1408 (1933).

(22) A. Dansi and C. Ferri, *Gazz. chim. ital.*, **69**, 195 (1939).

(23) P. H. Gore, *Chem. Revs.*, **55**, 266 (1955).

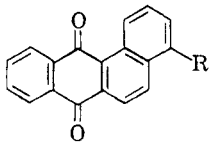
(24) E. Barnett and N. R. Campbell, *J. Chem. Soc.*, 1031 (1935).

(25) G. M. Badger and J. W. Cook, *J. Chem. Soc.*, 802 (1939).

(26) E. H. Johnson, V. Weinmayr, and R. Adams, *J. Am. Chem. Soc.*, **54**, 3289 (1932).

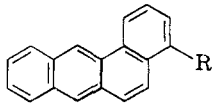
Preparation of a Grignard reagent from XX in a mixture of benzene and tetrahydrofuran was accompanied by coupling to yield approximately 40% of a hydrocarbon presumed to be 4,4-bibenz[a]anthryl. Coupling was enhanced in tetrahydrofuran alone, while the substitution of ethyl ether for tetrahydrofuran prevented the formation of Grignard reagent entirely. Nevertheless the reaction of 4-benz[a]anthrylmagnesium bromide with octadecanoyl chloride afforded a 27% yield of purified 4-octadecanoylbenz[a]anthracene (XXIII).

In the alternate synthesis, 4-chlorobenz[a]-anthraquinone[27] was reduced to 4-chlorobenz[a]-anthracene (XXI) in 87% yield, in the manner previously described for the bromo analog, apparently without loss of nuclear halogen. Subsequent conversion of XXI to 4-cyanobenz[a]-anthracene (XXII), by means of cuprous cyanide and pyridine, proceeded smoothly in 71% yield. In a trial experiment, nitrile XXII was allowed to react with *n*-hexadecylmagnesium bromide in a refluxing mixture of toluene and ethyl ether (4:1) for twenty-four hours, whereupon 14% of 4-heptadecanoylbenz[a]anthracene (XXIV) was obtained. Finally, the reaction of XXII with *n*-heptadecylmagnesium bromide, effected in refluxing toluene alone for twenty-four hours, afforded a 71% yield of 4-octadecanoylbenz[a]-anthracene (XXIII).



XVII. R = SO_3K

XVIII. R = Br
XIX. R = Cl

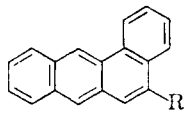


XX. R = Br
XXI. R = Cl
XXII. R = CN
XXIII. R = $CO(CH_2)_{16}CH_3$
XXIV. R = $CO(CH_2)_{15}CH_3$

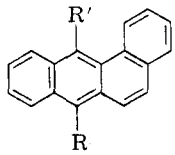
5-Octadecanoylbenz[a]anthracene (XXVII) was prepared in a manner similar to that used for the 4-isomer, through conversion of 5-chlorobenz[a]-anthracene (XXV) to the corresponding nitrile (XXVI) which subsequently was made to react with *n*-heptadecylmagnesium bromide. It was anticipated that XXVII might be obtained also from a reaction of *n*-heptadecylmagnesium bromide with 5-benz[a]anthroyl chloride (XXVIII) but an attempt to effect this synthesis was blocked when hydrolysis of nitrile XXVI could not be made to proceed beyond formation of the amide (XXIX).

Although small quantities of 7-octadecanoylbenz[a]anthracene (XXXII) were produced in the condensation of octadecanoyl chloride with benz[a]anthracene under Friedel-Crafts conditions, it proved to be more practical to prepare XXXII by allowing octadecanoyl chloride to react with 7-benz[a]anthrylmagnesium bromide. 12-Methyl-7-octadecanoylbenz[a]anthracene (XXXV), a derivative of the powerfully carcinogenic hydrocarbons 12-methylbenz[a]anthracene and 7,12-dimethylbenz[a]anthracene,[28] was prepared similarly from 12-methyl-7-benz[a]anthrylmagnesium bromide.

The polycyclic Grignard reagents derived from 7-bromobenz[a]anthracene derivatives XXX and XXXIII failed, however, to yield ketones XXXII and XXXV when allowed to react with octadecanonitrile. Instead there were produced small yields (13% and 3%, respectively) of the corresponding aromatic nitriles XXXI and XXXIV,[29] together with substantial quantities (25% and 15%, respectively) of diheptadecyl ketone and other complex products which displayed no evidence of containing an imine linkage despite intensive chromatographic and infrared spectroscopic examination. The reaction of 7-benz[a]anthrylmagnesium bromide took this unusual course even with propionitrile and a 25% yield of 7-cyanobenz[a]-



XXV. R = Cl
XXVI. R = CN
XXVII. R = $CO(CH_2)_{16}CH_3$
XXVIII. R = COCl
XXIX. R = $CONH_2$

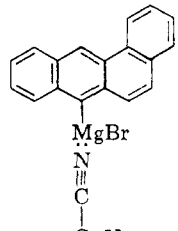


XXX. R = Br; R^1 = H
XXXI. R = CN; R^1 = H
XXXII. R = CO $(CH_2)_{16}CH_3$; R^1 = H
XXXIII. R = Br; R^1 = CH_3
XXXIV. R = CN; R^1 = CH_3
XXXV. R = $CO(CH_2)_{16}CH_3$; R^1 = CH_3

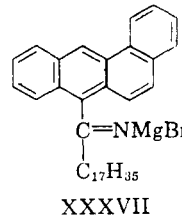
(27) A. Sempronj, *Gazz. chim. ital.*, 69, 448 (1939); *Chem. Abstr.*, 34, 416 (1940).

(28) M. J. Shear, *Am. J. Cancer*, 33, 499 (1938).

(29) Whether the initial product is a complex (*i.e.*, XXXVI) which then undergoes a radical rearrangement, as has been suggested[30] for a possibly analogous instance, or the expected imine derivative XXXVII which then dissociates to give the aromatic nitrile, is not known at this time. In any event, the presence of an incipient aliphatic Grignard reagent is suggested by the formation of dialkyl ketone.



XXXVI



XXXVII

(30) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, 1954, p. 779.

anthracene (XXXI) was produced. 9-Anthrylmagnesium bromide reacted similarly with octadecanonitrile, to afford small yields of 9-cyanoanthracene, diheptadecyl ketone and other unidentified products.

4-, 5-, 9- and 10-octadecanoylbenz[a]anthracene were converted readily to the corresponding oximes by treatment with hydroxylamine hydrochloride in refluxing dry pyridine for twenty-four hours. However neither 7-octadecanoylbenz[a]anthracene (XXXII) nor 12-methyl-7-octadecanoylbenz[a]-anthracene (XXXV) formed oximes, even under the most vigorous conditions.

The oximes (of ketones VIII, XVI, XXIII, and XXVII), isomeric octadecanoylbenz[a]anthracenes (VIII, XVI, XXIII, XXVII, and XXXII) and 12 - methyl - 7 - octadecanoylbenz[a]anthracene (XXXV) all proved to be ineffective for inhibition of Sarcoma 180 in mice, when tested by a previously reported method.[31]

EXPERIMENTAL[32]

Condensation of benz[a]anthracene with octadecanoyl chloride. A solution of benz[a]anthracene[33] (15 g.) in nitrobenzene (500 ml.) was added dropwise, over a period of 5 hr., to a stirred mixture of octadecanoyl chloride[34] (21.8 g.), anhydrous aluminum chloride (9.7 g.), and nitrobenzene (150 ml.) kept at 15°. After standing at 15° for 7 hr. the mixture was hydrolyzed and subjected to steam distillation to remove nitrobenzene. A benzene solution of the residue was shaken with 5% aqueous sodium carbonate, then filtered through Celite and finally evaporated. A hot ethanol solution of the resulting residue was treated with charcoal and then yielded, upon evaporation, 29.5 g. of yellow-brown solid. Crystallization of this material from 1 l. of petroleum ether (b.p. 60–70°) yielded 5.5 g. of crude 9-octadecanoylbenz[a]anthracene.

The mother liquor was passed through a column of silica gel (300 g.) which had been prepared in petroleum ether (b.p. 60–70°). Elution with a 10% solution of benzene in petroleum ether (b.p. 60–70°) yielded 4.4 g. of benz[a]-anthracene. Subsequent elution of the column with a 50% solution of benzene in petroleum ether (b.p. 60–70°) afforded 16 g. of crude 10-octadecanoylbenz[a]anthracene.

The crude 9- isomer, in a 10% solution of benzene in petroleum ether (b.p. 60–70°), was subjected to chromatography on a silica gel column (100 g.). Elution with a 50% solution of benzene in petroleum ether (b.p. 60–70°) gave a product which, when crystallized from 50 ml. of ethyl acetate, afforded 3.5 g. of *9-octadecanoylbenz[a]anthracene* (VIII), m.p. 105–115°. (The residue from the ethyl acetate mother liquor was the 10- isomer and was purified as described later.) Final purification of VIII was effected by one more chromatographic treatment, as previously described, and subsequent crystallization from a mixture of benzene and petroleum ether (b.p. 60–70°); yield, 2.8 g. (9%), m.p. 121–122°.

Anal. Calcd. for $C_{36}H_{46}O$: C, 87.39; H, 9.37. Found: C, 87.38; H, 9.50.

The crude *10-octadecanoylbenz[a]anthracene* (XVI), including that obtained during purification of the 9- isomer, was crystallized once from petroleum ether (b.p. 60–70°) and then from acetone; yield of pure ketone, 4.05 g. (12%), m.p. 84–85°.

Anal. Calcd. for $C_{36}H_{46}O$: C, 87.39; H, 9.37. Found: C, 87.17; H, 9.23.

Synthesis of 9-bromobenz[a]anthraquione (II) *and 10-bromobenz[a]anthraquinone* (X). A solution of aluminum chloride (9.4 g.) in nitrobenzene (40 ml.) was added dropwise to a stirred mixture of naphthalene (6.13 g.), 4-bromophthalic anhydride[35] (7.25 g.), and nitrobenzene (40 ml.). After being stirred for 24 hr. at room temperature the mixture was hydrolyzed and subjected to steam distillation. The nonvolatile residue was extracted with aqueous sodium hydroxide which, upon acidification, deposited 5.6 g. of an oily mixture of keto acids I and IX.

The dried mixture of keto acids was added slowly with continuous stirring to a solution of 5.6 g. of boric acid in 36 ml. of concd. sulfuric acid and the mixture was then warmed to 60° for 3 hr. After being allowed to stand at room temperature overnight the mixture was poured into water and the resulting precipitate was thoroughly extracted with hot, aqueous sodium hydroxide. Crystallization of the residue from acetone yielded alternate crops of crude crystalline isomeric quinones; these separated as needles, m.p. 205–215°, and as scales, m.p. 185–200°.

The higher melting fraction crystallized from acetic acid to afford *10-bromobenz[a]anthraquinone* (X) in the form of yellow needles, m.p. 228–229°.

Anal. Calcd. for $C_{18}H_9BrO_2$: C, 64.11; H, 2.69. Found: C, 64.00; H, 2.89.

9-Bromobenz[a]anthraquinone (II) separated from acetone in thin yellow blades, m.p. 204–205°.

Anal. Calcd. for $C_{18}H_9BrO_2$: C, 64.11; H, 2.69. Found: C, 64.07; H, 2.92.

Synthesis of 1,2,6-tricarbomethoxyanthraquinone (VI). The dark residue obtained by heating a mixture of II (500 mg.) and anhydrous cuprous cyanide (500 mg.) in a sealed tube for 15 hr. at 240–250° was extracted with acetic acid in a Soxhlet extractor. Evaporation of the solvent left a residue (220 mg.) which was dissolved in benzene (50 ml.) and passed through an alumina column (150 g.) which was wet with petroleum ether (b.p. 60–70°). Elution with a mixture of petroleum ether (b.p. 60–70°), and benzene (4:1) yielded 45 mg. of II and subsequent elution with benzene afforded 125 mg. of *9-cyanobenz[a]anthraquinone* (III), which separated in yellow needles from acetone, m.p. 269–270°.

Hydrolysis of III (125 mg.) was effected by heating to reflux for 20 hr. with a mixture of acetic acid (20 ml.) and 65% sulfuric acid (1.3 ml.).

9-Carboxybenz[a]anthraquinone (IV; 170 mg., m.p. above 300°) precipitated when the cooled reaction mixture was poured into water.

A solution of this material (IV) in 2 ml. of concd. sulfuric acid was poured slowly into 10 ml. of water and to the boiling mixture 350 mg. of potassium permanganate was added cautiously. After being heated for 5 min. the dark mixture was treated with oxalic acid to destroy excess permanganate and the solid residue obtained by filtration was digested with dilute aqueous sodium hydroxide. Acidification of the filtered solution yielded 75 mg. of dried solid *1,2,6-tricarboxyanthraquinone* (V).

(31) J. B. Field, M. C. Kloetzel, C. H. Thienes, L. T. Bascoy, R. Jersawitz, D. A. Filler, A. Boryczka, F. Costa, and E. Perez, *Cancer Research*, 18, No. 8, Pt. 2, 467 (1958).

(32) Melting points are uncorrected. Microanalyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles.

(33) Commercially available material (Fluka A.G. Chemische Fabrik, Buchs SG Switzerland) in benzene solution was passed through an alumina column and crystallized from petroleum ether (b.p. 60–70°) to a m.p. of 158–159°.

(34) Stearic acid (The Matheson Co., Inc., East Rutherford, N. J.) recrystallized to m.p. 69–70°, was heated for 3 hr. with excess thionyl chloride which had been purified according to L. F. Fieser, *Experiments in Organic Chemistry*, 3rd Ed., D. C. Heath and Co., Boston, 1955, p. 345. The product distilled at 168–170° at 3 mm.

(35) F. F. Blicke and F. D. Smith, *J. Am. Chem. Soc.*, 51, 1865 (1929).

This acid (50 mg.), in absolute methanol, was esterified with cold ethereal diazomethane.[36] Evaporation of the solvents left 52 mg. of *1,2,6-tricarbomethoxyanthraquinone* (VI) which separated from a mixture of chloroform and methanol in yellow crystals, m.p. 233–234°, as reported by Cook and Hewett.[21]

Oxidation of 9-octadecanoylbenz[a]anthracene was accomplished by heating to reflux for 30 min. a mixture of the ketone (VIII, 125 mg.), sodium dichromate (375 mg.), and acetic acid (20 ml.). The residue (303 mg.) obtained by pouring the solution into water was dissolved in benzene and chromatographed on a 10 g. column of alumina. Elution with benzene afforded 100 mg. of yellow *9-octadecanoylbenz[a]-anthraquinone* (VII), m.p. 110–112° after one crystallization from 20 ml. of ethanol. This ketone (90 mg.) was dissolved in 10 ml. of concd. sulfuric acid, the resulting solution was poured into 50 ml. of water and to the boiling mixture was added 270 mg. of potassium permanganate. 1,2,6-Tricarboxyanthraquinone (22 mg.) was isolated as described for oxidation of IV. Esterification with diazomethane, as previously described, yielded 15 mg. of *1,2,6-tricarbomethoxy-anthraquinone* (VI), m.p. 233–234° alone and also when mixed with ester VI, of the same melting point, obtained from oxidation of 9-carboxybenz[a]anthraquinone (IV).

Synthesis of 1,2,7-tricarbomethoxyanthraquinone (XIV). 10-Bromobenz[a]anthraquinone (X, 220 mg.) was converted to *10-cyanobenz[a]anthraquinone* (XI, 40 mg.), m.p. 242–243°, in the manner previously described for the 9-isomer. Hydrolysis of the nitrile (35 mg.) afforded a quantitative yield of *10-carboxybenz[a]anthraquinone* (XII), which crystallized in needles, m.p. above 290°. When this acid (42 mg.) was oxidized as described for the 9- isomer, there was obtained 20 mg. of *1,2,7-tricarboxyanthraquinone* (XIII) which subsequently afforded 25 mg. of the *trimethyl ester* XIV, m.p. 198–199° as reported by Cook and Hewett.[21]

Oxidation of 10-octadecanoylbenz[a]anthracene (XVI, 150 mg.) with sodium dichromate, as described for the 9- isomer, yielded 75 mg. of *10-octadecanoylbenz[a]anthraquinone* (XV) which subsequently was oxidized with potassium permanganate to yield 20 mg. of 1,2,7-tricarboxyanthraquinone (XIII). Esterification then afforded the trimethyl ester (XIV), m.p. 197–199°. Admixture with the ester obtained by oxidation of XII did not change this melting point.

4-Bromobenz[a]anthraquinone (XVIII) was prepared by a method based upon that described by Sempronj[27] for synthesis of the chloro analog. During a period of 3 hr., a solution of 60 g. of potassium bromate in 1 l. of water was added dropwise to a boiling solution of 27.5 g. of potassium 4-benz-[a]anthraquinonesulfonate[37] and 400 ml. of 48% hydrobromic acid in 1 l. of water. After being heated for 2 hr. the mixture was cooled and filtered. A benzene solution of the residue was subjected to chromatography on alumina and afforded 8.10 g. of XVIII, m.p. 232–233°, as yellow needles from benzene. The filtered reaction solution yielded 9.0 g. of unchanged XVII upon being made basic with potassium hydroxide.

4-Bromobenz[a]anthracene (XX). To a warm solution of stannous chloride (20 g.) in hydrochloric acid (50 ml.) was added, in portions, 6.1 g. of 4-bromobenz[a]anthraquinone (XVIII), followed by 200 ml. of acetic acid. The mixture was heated to reflux for 12 hr., cooled, and poured into a large volume of water. After 2 hr., filtration yielded 6.6 g. of solid residue. A benzene (100 ml.) solution of the latter, together with 300 ml. of 2*N* sodium hydroxide and 30 g. of activated zinc (swirled with dilute aqueous copper sulfate and decanted) was stirred and warmed on a steam bath for 15 hr. After addition of more benzene, the mixture was acidified with hydrochloric acid and filtered. The benzene layer was washed with water, dried and evaporated to yield a residue (5.4 g.) which was subjected to chromatography in petroleum ether (b.p. 60–70°) on 200 g. of alumina. Elution of the column with a 5% solution of benzene in petroleum ether (b.p. 60–70°) yielded a colorless residue (5.0 g.) which crystallized from acetone (100 ml.) to yield 2.45 g. of 4-bromobenz[a]anthracene in colorless plates, m.p. 210–212°. Further crystallization from acetone raised the m.p. to 212–213°.

Anal. Calcd. for $C_{18}H_{11}Br$: C, 70.37; H, 3.61. Found: C, 70.60; H, 3.64.

Concentration of the acetone mother liquors yielded benz[a]anthracene. Elution of the alumina column with a 20% solution of benzene in petroleum ether allowed recovery of a small quantity of quinone XVIII.

4-Chlorobenz[a]anthracene (XXI, 9.3 g.) was obtained in a similar manner from 12 g. of 4-chlorobenz[a]anthraquinone (XIX),[27] 12 g. of stannous chloride, 75 ml. of hydrochloric acid, and 150 ml. of acetic acid, followed by further reduction with 500 ml. of 2*N* sodium hydroxide and 30 g. of activated zinc. Crystallization from acetone afforded colorless platelets, m.p. 202–203°.

Anal. Calcd. for $C_{18}H_{11}Cl$: C, 82.28; H, 4.22. Found: C, 82.47; H, 4.41.

4-Cyanobenz[a]anthracene (XXII). A mixture of 4-chlorobenz[a]anthracene (1.9 g.), anhydrous cuprous cyanide (2.0 g.), and pyridine (1.5 ml.) was heated to 200–210° for 15 hr. and was then extracted with benzene for 20 hr. in a Soxhlet extractor. After being washed with dilute acid and then with water, the benzene extract was evaporated. The residue, in a mixture of petroleum ether (b.p. 60–70°) and benzene (2:1), was subjected to chromatography on an alumina (200 g.) column. Elution with the same solvent gave 160 mg. of unchanged halide (XXI). Subsequent elution with a 50% solution of benzene in petroleum ether (b.p. 60–70°) yielded 1.3 g. of 4-cyanobenz[a]anthracene which separated from benzene in platelets or from ethanol or acetone in needles, m.p. 181–182°.

Anal. Calcd. for $C_{19}H_{11}N$: C, 90.09; H, 4.37. Found: C, 90.01; H, 4.42.

4-Heptadecanoylbenz[a]anthracene (XXIV). To the Grignard reagent prepared from 1.4 g. of 1-bromohexadecane 0.15 g. of magnesium and 30 ml. of ether was added a solution of 1.1 g. of nitrile XXII in 125 ml. of toluene and the mixture was heated to reflux for 24 hr. Hydrolysis with dilute hydrochloric acid and subsequent chromatography of the product in 400 ml. of 30% benzene in petroleum ether (b.p. 60–70°) on alumina (200 g.) afforded first a hydrocarbon fraction (probably hexadecane), easily eluted with a 10% solution of benzene in petroleum ether, and then a ketone fraction, eluted with a 50% solution of benzene in petroleum ether. Crystallization of the ketone fraction from acetone yielded 300 mg. of ketone XXIV in colorless needles, m.p. 103–104°.

Anal. Calcd. for $C_{35}H_{44}O$: C, 87.44; H, 9.22. Found: C, 87.90; H, 9.45.

Elution of the alumina column with benzene yielded 720 mg. of unchanged nitrile.

4-Octadecanoylbenz[a]anthracene (XXIII); (*a*) *From 4-cyanobenz[a]anthracene.* To the Grignard reagent prepared from 1.4 g. of 1-bromoheptadecane, 200 mg. of magnesium, and 30 ml. of ether was added a solution of 560 mg. of nitrile XXII in 100 ml. of toluene. Ether was removed by distillation of 40 ml. of solvent and the toluene solution then was heated to reflux for 72 hr. Ketone XXIII, isolated as described for the heptadecanoyl homolog, melted at 103–104° after crystallization from acetone; yield, 780 mg. (71%).

(*b*) *From 4-benz[a]anthrylmagnesium bromide.* To the Grignard reagent prepared by heating 2.4 g. of 4-bromobenz[a]anthracene (XX), 1.8 g. of magnesium, 40 ml. of benzene and 50 ml. of tetrahydrofuran for 20 hr. in an atmosphere of nitrogen was added a solution of 3.0 g. of octadecanoyl chloride in 20 ml. of benzene. After being heated to reflux for 20 hr., the mixture was hydrolyzed with dilute hydrochloric acid. The benzene layer was shaken with 5% aqueous sodium carbonate and then filtered through Celite.

(36) F. Arndt, *Org. Syntheses*, **Coll. Vol. II**, 165 (1943).

(37) J. Cason and L. F. Fieser, *J. Am. Chem. Soc.*, 62, 2681 (1940).

Evaporation left a residue (4.7 g.) which was subjected to chromatography in petroleum ether (b.p. 60–70°) on a column of silica gel (100 g.). Elution of the column with a 10% solution of benzene in petroleum ether yielded 1.3 g. of a mixture of hydrocarbons. Subsequent elution of the column with a 50% solution of benzene in petroleum ether afforded 2.7 g. of crude ketonic fraction. *4-Octadecanoylbenz[a]anthracene* (XXIII, 1.07 g.) separated in colorless needles when the latter was crystallized from acetone; m.p. 103–104° alone and also when mixed with ketone prepared by method (a).

Anal. Calcd. for $C_{36}H_{46}O$: C, 87.39; H, 9.37. Found: C, 87.10; H, 9.32.

The mixture of hydrocarbons (1.3 g.) was dissolved in 200 ml. of petrolum ether (b.p. 60–70°) and the solution was passed through a silica gel column (100 g.). Elution of the column with a 10% solution of benzene in petroleum ether (b.p. 30–35°) yielded 480 mg. of benz[a]anthracene. Subsequent elution with benzene afforded 780 mg. of a hydrocarbon presumed to be 4,4-bibenz[a]anthryl, which separated from a mixture of benzene and ethanol in colorless needles, m.p. 335–336°.

Anal. Calcd. for $C_{36}H_{22}$: C, 95.12; H, 4.87. Found: C, 95.23; H, 4.80

5-Chlorobenz[a]anthracene (XXV). The following conditions for preparation of *o*-(4-chloro-1-naphthoyl)benzoic acid were found superior to those reported by Heller.[38] Aluminum chloride (300 g.) was added in portions, with stirring, to a mixture of α-chloronaphthalene (245 g.), phthalic anhydride (148 g.), and carbon disulfide (500 ml.) cooled to 0°. The mixture was allowed to warm to room temperature and after 6 hr. was hydrolyzed with ice and hydrochloric acid. Extraction of the organic product with aqueous sodium carbonate, followed by precipitation with hydrochloric acid, yielded a mixture of solid acids from which the desired product was extracted with ether (leaving behind phthalic acid). Evaporation of the ether gave a residue (68.4 g.) which, upon one crystallization from benzene, yielded 43.8 g. of *o*-(4-chloro-1-naphthoyl)benzoic acid, m.p. 173–174°. This material was suitable for cyclization, which was best accomplished by adding the solid acid in portions, with continuous stirring, to concentrated sulfuric acid (10 g. per g. of organic acid). When the dark mixture was warmed to 100° for 1 hr. and then poured into water, there was obtained a residue from which acidic components were removed by extraction with dilute aqueous sodium hydroxide. Chromatographic purification, in benzene solution on an alumina column, afforded an 85% yield of *5-chlorobenz[a]anthraquinone*, which separated from acetone in yellow needles, m.p. 180–181° (substantially the melting point reported by Heller[38]).

5-Chlorobenz[a]anthraquinone (9 g.) was reduced with stannous chloride (27 g.), hydrochloric acid (100 ml.), and acetic acid (700 ml.), followed by treatment with zinc (40 g.) and 2*N* sodium hydroxide solution (600 ml.), as described for the 4-chloro isomer; yield, 6.6 g. (82%) of *5-chlorobenz[a]anthracene* (XXV), m.p. 146–147°. One crystallization from acetone afforded long colorless needles, m.p. 148–149°.

Anal. Calcd. for $C_{18}H_{11}Cl$: C, 82.28; H, 4.22. Found: C, 82.17; H, 4.25.

5-Cyanobenz[a]anthracene (XXVI) was prepared in 60% yield from XXV in the manner described for the 4- isomer; m.p. 172–175°. Crystallization from acetone afforded straw-colored needles, m.p. 175–176°.

Anal. Calcd. for $C_{19}H_{11}N$: C, 90.09; H, 4.37. Found: C, 90.03; H, 4.39.

Hydrolysis of nitrile XXVI (4 g.) was effected by heating to reflux for 48 hr. with acetic acid (300 ml.) and 65% sulfuric acid (40 ml.). The precipitate (3 g.) obtained by pouring the reaction mixture into water contained essentially no alkali-soluble material. Crystallization from acetic acid yielded cream-colored needles, m.p. 280–281°. That this was *5-benz[a]anthramide* (XXIX) became evident when a sample was reconverted quantitatively to nitrile XXVI upon being heated to reflux for 2 hr. with thionyl chloride.

The same amide was obtained when 200 mg. of nitrile XXVI was heated to reflux for 72 hr. with 20 ml. of 25% methanolic potassium hydroxide.[39]

5-Octadecanoylbenz[a]anthracene (XXVII) was prepared in a manner similar to that described for the 4- isomer, by the reaction of nitrile XXVI with 1-heptadecylmagnesium bromide in refluxing toluene for 96 hr. The product was purified by chromatography in petroleum ether (b.p. 60–70°) on silica gel. Elution of the column with a mixture of petroleum ether (b.p. 60–70°) and benzene (2:1) afforded an 80% yield of nearly pure ketone which separated from a mixture of benzene and ethanol in straw-colored needles, m.p. 86–87°.

Anal. Calcd. for $C_{36}H_{46}O$: C, 87.39; H, 9.37. Found: C, 87.18; H, 9.36.

Oximes of the aforedescribed isomeric octadecanoylbenz[a]anthracenes formed readily when the ketones (500–900 mg.) were heated to reflux for 24 hr. with a mixture of hydroxylamine hydrochloride (1 g.) and anhydrous pyridine (10–20 ml.). Most of the solvent was removed and a benzene extract of the residue was then washed with dilute hydrochloric acid and subsequently with water. Evaporation of the benzene and crystallization from ethanol or petroleum ether (b.p. 60–70°) afforded 50–72% yields of pure colorless oximes.

The oxime of 4-octadecanoylbenz[a]anthracene (XXIII) melted at 125–126°.

Anal. Calcd. for $C_{36}H_{47}NO$: C, 84.82; H, 9.29; N, 2.75. Found: C, 85.00; H, 9.25; N, 3.26.

Oxime of the 5- isomer (XXVII), m.p. 112–113°.

Anal. Calcd. for $C_{36}H_{47}NO$: C, 84.82; H, 9.29; N, 2.75. Found: C, 84.82; H, 9.29; N, 3.21.

Oxime of the 9- isomer (VIII), m.p. 122–123°.

Anal. Calcd. for $C_{36}H_{47}NO$: C, 84.82; H, 9.29; N, 2.75. Found: C, 85.06; H, 9.05; N, 3.19.

Oxime of the 10- isomer (XVI) m.p. 103–104°.

Anal. Calcd. for $C_{36}H_{47}NO$: C, 84.82; H, 9.29; N, 2.75. Found: C, 85.12; H, 9.10; N, 2.86.

7-Octadecanoylbenz[a]anthracene (XXXII) was formed when a solution of 3.6 g. of octadecanoyl chloride in 10 ml. of benzene was allowed to react for 20 hr. at reflux temperature with the Grignard reagent prepared from 4 g. of 7-bromobenz[a]anthracene (XXX),[40] 1 g. of magnesium, 25 ml. of ether, and 75 ml. of benzene. The ketone was isolated as described for the 4- isomer; yield, 2.7 g. (42%), m.p. 88–89°.

Anal. Calcd. for $C_{36}H_{46}O$: C, 87.39; H, 9.37. Found: C, 86.91; H, 9.45.

A Grignard reagent was prepared similarly when a mixture of 4.3 g. of 7-bromo-12-methylbenz[a]anthracene (XXXIII),[40] 7 g. of magnesium, 25 ml. of ether, 75 ml. of benzene, and a trace of methylmagnesium iodide was stirred for 18 hr. at reflux temperature. After removal of excess magnesium a solution of 4 g. of octadecanoyl chloride in 50 ml. of benzene was added and heating and stirring were continued for 24 hr. *7-Octadecanoyl-12-methylbenz[a]anthracene* (XXXV) was isolated as described for ketone XXIII; yield, 3.25 g. of pale yellow needles, m.p. 82–88°. Further recrystallization from acetone or from a mixture of benzene and petroleum ether (b.p. 60–70°) raised the m.p. to 90–91°.

Anal. Calcd. for $C_{37}H_{48}O$: C, 87.34; H, 9.51. Found: C, 87.11; H, 9.54.

General procedure for reactions of aliphatic nitriles with Grignard reagents from meso-bromoanthracenes. A mixture

(38) G. Heller, *Ber.*, **45**, 665 (1912).

(39) Compare E. Mosettig and J. Van De Kamp, *J. Am. Chem. Soc.*, **54**, 3328 (1932).

(40) G. M. Badger and J. W. Cook, *J. Chem. Soc.*, 409 (1940).

of 0.013 mole of aromatic bromide (XXX, XXXIII, or 9-bromoanthracene), 6 g. of magnesium, 25 ml. of ether, 75 ml. of benzene, and a small crystal of iodine was stirred for 20 hr. at reflux temperature in an atmosphere of nitrogen. After removal of excess magnesium, the ether was removed by distillation and a solution of 0.013 mole of the aliphatic nitrile (octadecanonitrile or propionitrile) in 25 ml. of benzene was added. The resulting mixture was heated to reflux, with stirring, for 24 hr. and was then hydrolyzed with 70 ml. of 10% acetic acid. The organic layer was washed successively with 36% hydrochloric acid, water, 10% aqueous sodium carbonate, and water. Evaporation of the solvents left a residue which was dissolved in a mixture of petroleum ether (b.p. 60–70°) and benzene (2:1) and the solution then was poured onto a column (40 × 4.5 cm.) of alumina. Development of the resulting chromatogram was effected with a mixture of petroleum ether and benzene (3:1) and its progress was followed by visible coloration and ultraviolet fluorescence of bands. Elution of the column with mixtures of benzene and petroleum ether of increasing benzene concentration allowed the separation of crystalline products. Aromatic nitriles XXXI[40] and XXXIV,[40] 9-cyanoanthracene,[41] and diheptadecyl ketone[42] were isolated in yields already mentioned and were identified by the method of mixed melting points with authentic samples of these known compounds. Considerable quantities (up to 36%) of the aromatic hydrocarbons (anthracene, benz[a]anthracene and 12-methylbenz[a]anthracene) also were isolated but none of the expected ketones (XXXII or XXXV, for example).

LOS ANGELES, CALIF.

(41) W. E. Bachmann and M. C. Kloetzel, *J. Org. Chem.*, **3**, 55 (1938).

(42) F. S. Kipping, *J. Chem. Soc.*, **57**, 532 (1890).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Studies in the Tetrahydronaphthalene Series: Synthesis of 1-Methyl-1-ethyl-2-*n*-propyl-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene

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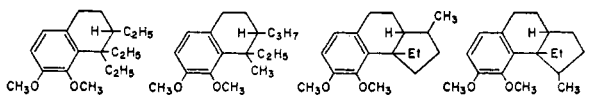
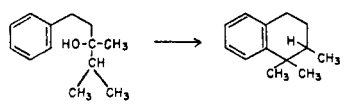
The synthesis of the above-titled naphthalene derivative is described.

The degradation of dihydrothebaine to a novel nitrogen-free end product was reported from this laboratory, and four plausible structures (A–D)



A B C D



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were proposed for the substance.[1] Because the analytical data, at the time, appeared to favor a tetralin system exemplified by structures A or B, attempts to synthesize these highly substituted species were initiated. It should be mentioned at the outset, however, that recent NMR studies[2] of the degradation product have necessitated altering our former views in favor of structures C or D. In the light of these new findings, we are prompted to report on the earlier synthetic approaches at this time. Experiments directed toward the synthesis of structures C and D, along with a detailed account of the NMR data, will form the body of a later communication.

Of the several possible routes to structures A or B that were considered, the first was patterned after the work of Bogert *et. al.*[3] who prepared 1,1,2-trimethyltetralin (II) through cyclodehydration of the pentanol (I). Regarding the present problem it is evident that, to arrive at structure A, for example, a logical intermediate would be 1-(3,4-dimethoxy-6-bromophenyl)-3,4-diethylpentanol-3, in which the halogen serves as a blocking group in order to direct the subsequent cyclization to the desired position on the aromatic ring. This involved synthesizing 1-(3,4-dimethoxy-6-bromophenyl)pentanone-3 and treating it with the Grignard reagent prepared from 3-bromopentane. The route to the pentanone originated with methyl homoveratrate[4] which was reduced to the corresponding phenethanol and the latter converted, in turn, *via* the chloride, iodide and nitrile to 3,4-dimethoxyhydrocinnamic acid. Bromination of the latter to the 6-bromo derivative (bromine position established) was followed by conversion to the acid chloride which, on treatment with diethylcadmium,[5] afforded the required pentanone in

(1) L. J. Sargent and L. F. Small, *J. Org. Chem.*, **16**, 1031 (1951).

(2) We are indebted to Dr. E. D. Becker and Mr. R. B. Bradley, Laboratory of Physical Biology, NIAMD for these data.

(3) D. Price, D. Davidson, and M. T. Bogert, *J. Org. Chem.*, **2**, 540 (1938).

(4) H. R. Snyder, J. S. Buck, and W. S. Ide, *Org. Syntheses*, **Coll. Vol. II**, 333 (1943).

(5)(a) J. Cason, *Chem. Revs.* **40**, 15 (1947); (b) D. A. Shirley, *Org. Reactions*, **8**, 26 (1954).