[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

THE ORIENTATION OF BENZO[*c*]PHENANTHRENE[1]

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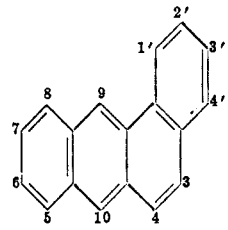
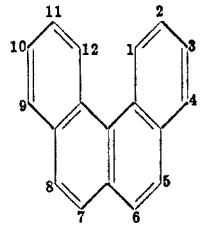
In surveying the information concerning the carcinogenic activity of the monomethyl derivatives of polycyclic aromatic hydrocarbons it appears that when a methyl group is substituted at a position of high chemical activity the resulting derivative is an active carcinogenic agent. Of the twelve monomethyl-1,2-benzanthracenes all of which have been synthesized (1) the most active are the 5-, 9-, and 10-derivatives (2). When the parent hydrocarbon, 1,2-benzanthracene (I), is reacted with various reagents, the substituent enters the 10-position preferentially (3).



I



II

The work herein reported was undertaken to find out which position in benzo[*c*]phenanthrene[3] (II), was most active chemically. We have prepared a quantity of II and subjected it successfully to nitration, bromination, and acetylation. In each case the substituent entered position 5 preferentially.[4] Although the testing of all of the monomethyl derivatives of II has not been completed,[5] the 5-methyl compound is the most potent carcinogen on the basis of available data.

In view of the present state of knowledge concerning the relative carcinogenic activity of the monomethyl derivatives of I, II, and chrysene[6] it appears unde-

[1] The material herein presented is taken from the Ph.D thesis of Alvin I. Kosak, The Ohio State University, June, 1948.

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[3] Chemical Abstracts numbering.

[4] It is of interest to note that the calculations of Pullman, *Ann. chim.*, **12,** 5 (1947) and Berthier, Coulson, Greenwood, and Pullman, *Compt. rend.*, **226,** 1906 (1948), place the position of maximum electron density at carbon 5.

[5] Data on the carcinogenic activity of 1-methylbenzo[*c*]phenanthrene, recently synthesized by Newman and Wheatley, *J. Am. Chem. Soc.*, **70,** 1913 (1948), has not yet been reported.

[6] Because of the general lack of carcinogenic activity in the chrysene series, comparisons are probably of little value. However, it is noteworthy that 5- and 6-methylchrysene have been reported to have cancer producing activity, Dunlap and Warren, *Cancer Research*, **3,** 606 (1943); *Cf.* (2) (a), pg. 87. Newman and Cathcart, *J. Org. Chem.*, **5,** 618 (1940), proved that chrysene is substituted in the 6-position.

sirable at this time to do more than point out the interesting fact that the substitution of a methyl group at (or adjacent to) a position of high chemical reactivity produces an active carcinogenic agent.

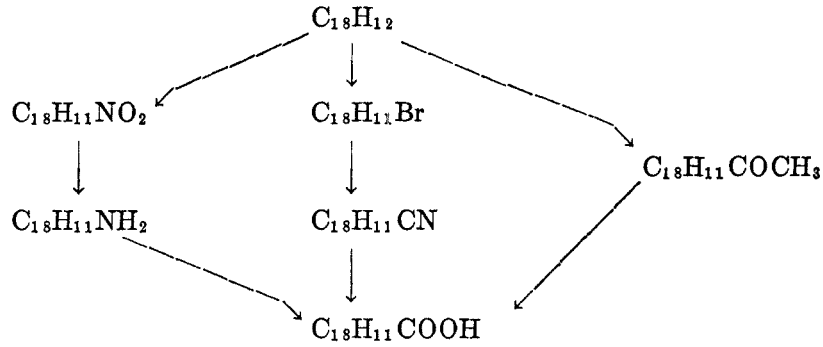
The required benzo[*c*]phenanthrene was prepared essentially by Hewett's method (4); the following observations seem worthy of comment. 1-Bromo-2-methylnaphthalene (5) is more completely and easily converted to 1-bromo-2-bromomethylnaphthalene by N-bromosuccinimide (6) than by the high temperature bromination procedure recommended (5). We were unable to attain the yield of α-(1-bromo-2-naphthyl)-β-phenylacrylic acid in the condensation of benzaldehyde with sodium 1-bromo-2-naphthylacetate reported by Hewett (4). However, we obtained the desired acid in 50% yield by a procedure patterned after that of Hauser and Patterson (7). We were able to obtain a good yield of α-(1-bromo-2-naphthyl)-β-phenylacrylonitrile by condensation of benzaldehyde with 1-bromo-2-naphthylacetonitrile but, in agreement with Hewett (4), hydrolysis to the corresponding acid could not be effected. The decarboxylation of 6-benzo[*c*]phenanthrenecarboxylic acid was accomplished in 79% yield by refluxing in quinoline with copper bronze (4) or better (88%) by heating with a copper chromite catalyst, 37KAF, (8) at 300°.

Bromination of II yielded a complex mixture of products from which a monobromo compound was isolated in 59% yield as its complex with 2,4,7-trinitrofluorenone, hereinafter designated TNF (9). Other polybromo compounds were also produced but were not identified. The pure bromo compound obtained from the TNF complex by chromatography melted at 76.6–77.6° and was converted into a cyanide by heating with cuprous cyanide and pyridine (10). This cyanide had the same melting point, 129°, as that reported by Hewett (11), and on hydrolysis was converted into the known 5-benzo[*c*]phenanthrenecarboxylic acid (12). Attempted bromination of II with N-bromosuccinimide in the presence of benzoyl peroxide or of aluminum chloride failed (12a), the hydrocarbon being recovered almost completely in the first case and an unpromising mixture being obtained in the second.

Nitration of II with mixed acid in acetic acid yielded a mononitro (54% yield) and two dinitro derivatives. The mononitro compound was proved to be the 5-nitro derivative by reduction to the amino compound and comparison of its TNF complex with that formed from 5-aminobenzo[*c*]phenanthrene prepared by a Curtius degradation of authentic 5-benzo[*c*]phenanthrenecarboxylic acid. Attempts to reduce 5-nitrobenzo[*c*]phenanthrene by several standard methods failed. The reduction was accomplished by heating with titanous chloride and hydrochloric acid (13). No attempts were made to determine the structure of the dinitro compounds.

Acetylation of II with acetic anhydride and aluminum chloride in chlorobenzene afforded an acetyl derivative which was proved to be 5-benzo[*c*]phenanthryl methyl ketone by hypochlorite oxidation to 5-benzo[*c*]phenanthrenecarboxylic acid. No pure acetyl derivative could be isolated when acetyl chloride was used.

The various interconversions of the 5-substituted benzo[*c*]phenanthrenes are shown in the chart.



We were unable to isolate any pure derivative of II after reaction with lead tetraacetate (14) and the hydrocarbon was recovered unchanged after treatment with N-methylformanilide (15).

Benzo[c]phenanthrene (II), and several of its alkyl derivatives couple with *p*-nitrobenzenediazonium chloride in acetic acid (16) quite rapidly. However, the highly carcinogenic 5-methyl derivative, weakly active parent hydrocarbon (II), inactive 5,8-dimethyl and 5,8-diethyl derivatives, and the 1-methyl compound of as yet unknown activity, all coupled at the same rate and gave solutions of the same color. The color was an orange-brown, which would place these compounds in the moderately active group, whereas the rapid rate of color formation would place them in the active group (16). It is thus seen that there is no correlation between carcinogenic activity and response to the diazo coupling test among the derivatives of benzo[c]phenanthrene.

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EXPERIMENTAL[7]

1-Bromo-2-methylnaphthalene (III). This compound prepared in 83% yield by bromination of 2-methylnaphthalene (5), boiled at 117–118° at 2 mm.; n_D^{20} 1.6484; *picrate*, m.p. 114.7–115.1° [literature (17) m.p. 113°].

1-Bromo-2-bromomethylnaphthalene (IV). In the best of several runs a mixture of 210 g. (0.95 mole) of 1-bromo-2-methyl-naphthalene, 160 g. (0.90 mole) of N-bromosuccinimide, 1 g. of benzoyl peroxide, and 250 ml. of carbon tetrachloride was refluxed for two and one-half hours. The warm product was filtered after the addition of 250 ml. of carbon tetrachloride, the residue being washed several times with solvent. There was obtained from the filtrate upon concentration and cooling 230 g. (85%) of IV, m.p. 103.5–105.5°. The high temperature (230–240°) bromination of III (5) yielded IV but in yields which never exceeded 59%.

1-Bromo-2-naphthylacetonitrile (V). A hot solution of 297 g. (4.57 mole) of potassium cyanide in 400 ml. of water was added to a warm slurry of 682 g. (2.27 mole) of IV in 2.2 l. of

[7] All melting points are corrected; most were taken on a calibrated Fisher-Johns block. All chromatograms were run on 80–200 mesh activated alumina and were of the flowing type. Analyses marked[p] were W. J. Polglase;[k] by E. Klotz;[c] by Clark Microanalytical Laboratories;[a] by Arlington Laboratories;[s] by Sadtler & Sons;[t] by Carl Tiedcke.

absolute alcohol. After heating and stirring for five minutes an exothermic reaction lasting for ten minutes ensued during which much potassium bromide separated. The mixture was further refluxed for 1½ hours and was then poured into 4.5 l of water. The precipitate was collected, washed, dried, and recrystallized from Skellysolve C to yield 400 g. (72%) of V, m.p. 126.2–127.2°, and 45.7 g. (8%) of a second crop, m.p. 119–122°, suitable for hydrolysis. When the reaction was run in the presence of added potassium iodide or at 185–200° in glycerol solution the main product was a substance, m.p. 205.4–205.6°, whose identity has not been established. It is evidently a coupled product, but is not a stilbene type.

1-Bromo-2-naphthylacetic acid, (VI). After refluxing a solution of 424 g. (1.72 mole) of V, 2.5 l. of acetic acid, 500 ml. of concentrated sulfuric acid, and 500 ml. of water for fourteen hours and quenching in 5 l. of ice water, there was obtained 459 g. (100%) of good acid, m.p. 190.0–192.8°. A sample, recrystallized from acetic acid, melted at 196.0–196.2° [lit. (5) m.p. 194°].

α-(1-Bromo-2-naphthyl)-β-phenylacrylic acid, (VII). When a mixture of 10.8 g. (0.038 mole) of the sodium salt of VI, 5.3 g. (0.05 mole) of benzaldehyde, 2.5 g. (0.018 mole) of potassium carbonate, 0.5 ml. of pyridine, and 14 g. (0.125 mole) of acetic anhydride was heated with stirring an exothermic reaction soon took place. After maintaining the mixture at 150–155° for three hours, it was poured into water. The organic residue was digested with hot concentrated sodium hydroxide solution. The insoluble sodium salt was then taken into a large volume of water and freed of neutral material by ether extraction. The acid obtained on acidification melted at 189–196°. Recrystallization from aqueous alcohol afforded 6.6 g. (50%) of VII, m.p. 205–206° [literature (4) m.p. 206–207°]. In large scale runs it is important to add the acetic anhydride to the other components slowly to prevent excessive foaming. By following Hewett's directions (4), we obtained only a 15% yield. Attempts to use acetamide or potassium *t*-butoxide as catalysts were not encouraging.

6-Benzo[c]phenanthrene carboxylic acid, (VIII). This acid was obtained in 54% yield by the reported procedure (4).

Benzo[c]phenanthrene(II). A mixture of 2 g. (7.3 mmoles) of VIII and 0.15 g. of catalyst 37KAF (8) was heated at 295–300° for one hour, during which time 61% of the theoretical amount of carbon dioxide was evolved. Vacuum distillation afforded 1.48 g. (88%) of crude II as a yellow oil, b.p. 175–180° at 0.3 mm., which crystallized on standing and melted at 64.5–67.3°. A sample, purified for biological testing, formed colorless needles, m.p. 67.4–68.0°. The *picrate* (19) was obtained in the form of dark red needles, m.p. 125.9–126.3°. The *TNF complex* formed orange needles, m.p. 170.8–171.1°, from alcohol-benzene.

Anal. Calc'd for $C_{31}H_{17}N_3O_7$: N, 7.8. Found[P]: N, 7.9, 7.8.

By following Hewett's procedure (4), a 79% yield of II was obtained (refluxed one half hour at 160–170° with copper-bronze and quinoline) from VIII.

5-Bromobenzo[c]phenanthrene(IX). A solution of 456 mg. (2 mmoles) of II and 320 mg. (2 mmoles) of bromine in 3 ml. of carbon tetrachloride was held at 40–50° until the evolution of hydrogen bromide ceased (3½ hours). The reaction solution was washed with alkali, dried over calcium sulfate (Drierite), diluted with one-half a volume of petroleum ether, b.p. 65–70° (Skellysolve B), and chromatographed over alumina. The most rapidly eluted fraction, A, yielded 562 mg. of a partly crystalline product which was followed by a smaller fraction, B, of 52 mg. Fraction A was treated with a benzene-alcoholic solution of trinitrofluorenone and the solid complex thus formed was fractionally recrystallized to yield 734 mg. (equivalent to a 59% yield of monobromobenzo[c]phenanthrene) of light orange micro-crystals, m.p. 167.4–170.5°.

A sample recrystallized from benzene-alcohol for analysis melted at 170.2–171.4°. A mixed m.p. with the *TNF complex* of II melted at 140–153°.

Anal. Calc'd for $C_{31}H_{16}BrN_3O_7$: N, 6.7. Found[k]: N, 6.5, 6.5.

Similar treatment of fraction B yielded 34 mg. of a *TNF complex*, m.p. 105–108°, which on recrystallization for analysis yielded fine orange needles, m.p. 116.0–117.0°.

Anal. Calc'd for $C_{31}H_{15}Br_2N_3O_7$: N, 6.0. Found[k]: N, 5.7, 5.5.

On chromatographic purification over alumina, the complex from A yielded pure 5-bromobenzo[c]phenanthrene as colorless rosettes, m.p. 76.6–77.6°.

Anal. Calc'd for $C_{18}H_{11}Br$: C, 70.4; H, 3.6. Found[k]: C, 70.0; H, 3.9.

Similar treatment of the complex from B yielded a few mg. of crystals, m.p. 169–173°, but too little was obtained for further study.

5-Cyanobenzo[c]phenanthrene(X). A mixture of 90 mg. (0.29 mmoles) of IX, 39 mg. (0.43 meq) of cuprous cyanide, a trace of anhydrous cupric sulfate, and 2 ml. of dry pyridine was heated in a sealed tube at 220–230° for 8½ hours. By chromatographing a benzene solution of the reaction products, there was isolated from the least strongly adsorbed material 56 mg. (76%) of X, m.p. 121–124°. Recrystallization from alcohol yielded colorless needles, m.p. 129.5–129.8° [literature (11) 128–129°].

5-Benzo[c]phenanthrene carboxylic acid(XI). A small amount of the above nitrile (15 mg.) was hydrolyzed by refluxing for twenty hours with 0.9 ml. of acetic acid, 0.2 ml. of sulfuric acid, and 0.2 ml. of water. The product was purified by crystallization of the sodium salt followed by conversion to the acid and sublimation. The m.p. and mixed m.p. with an authentic sample[8] of XI (12) were constant at 238.1–239.2°.

5-Nitrobenzo[c]phenanthrene(XII). A solution of 2.28 g. (10 mmoles) of II, 0.6 ml. of concentrated sulfuric acid, and 0.63 g. (10 mmoles) of nitric acid in 5 ml. of acetic acid was allowed to stand for one hour at room temperature and was then poured into water. The yellow precipitate was collected, dried, dissolved in Skellysolve B—benzene, 1:3, and chromatographed over alumina. The least strongly absorbed material was fractionally crystallized to yield 1.47 g. (54%) of XII as yellow crystals, m.p. 141.5–142.1°. From other eluates, two other compounds were obtained which proved to be dinitro derivatives. These melted at 249.2–251.3° and 212–217° respectively, the latter being isolated in only very small yield.

Anal. Calc'd for $C_{18}H_{11}NO_2$: C, 79.1; H, 4.1. Found[t]: C, 79.2, 79.4; H, 4.5, 4.3.
Calc'd for $C_{18}H_{10}N_2O_4$: C, 67.9; H, 3.2. Found[t]: (250° isomer) C, 67.2; 67.4; H, 3.6, 3.4. (215° isomer) C, 68.0; H, 4.4.

5-Aminobenzo[c]phenanthrene(XIII). (*a*). *By reduction of the 5-nitro derivative.* To a refluxing solution of 110 mg. (0.4 mmole) of XII in 100 ml. of absolute alcohol was added a solution of 2.04 g. (10% excess) of 20% aqueous titanous chloride and 2 ml. of concentrated hydrochloric acid. Decolorization was instantaneous. About 70 ml. of solvent was allowed to distil and the remaining solution made slightly alkaline with 2 *M* methanolic potassium hydroxide. After removing the precipitated oxide, the amine was isolated by ether extraction, taken into carbon tetrachloride—benzene, 5:1, and chromatographed on alumina. The fractions which ran through first, using the same solvent pair in ratio 5:1 and then 1:1 were small in weight and were discarded. On elution with benzene-methanol, 70:1 and then 1:1, 74 mg. of material was isolated. Since this would not crystallize or form a crystalline acetate, it was treated with TNF. A brown crystalline complex separated. This was recrystallized to a constant melting point of 195.8–196.2° and proved to be identical to the complex formed from the amine prepared by a Curtius degradation from XI.

Anal. Calc'd for $C_{31}H_{18}N_4O_7$: C, 66.7; H, 3.3; N, 10.0.
Found[c]: C, 66.8; H, 3.3; N, 10.2.

Attempts to reduce the nitro compound with sodium hydrosulfite, with activated iron (20), and catalytically (21) proved unsatisfactory.

(*b*) *By degradation of VIII.* To a cold solution of 500 mg. (1.7 mmoles) of the acid chloride of VIII (prepared in 95% yield with thionyl chloride) in 15 ml. of acetone was added in the cold with shaking, a solution of 150 mg. (2.3 mmoles) of sodium azide in 0.75 ml. of water. After standing in an ice-bath for twenty minutes, the reaction mixture was diluted with water and the precipitated azide was collected and dried to yield 445 mg. of a product which melted at 69–72° decomp. The azide was decomposed by boiling in toluene solution for 2½ hours. Since this solution still gave a positive test for undecomposed azide (22), the toluene was replaced by xylene and the solution refluxed for one hour. The reaction

[8] This sample was prepared by the procedure cited in (12) with the exception of the condensation between 1-bromo-2-naphthaldehyde and sodium phenylacetate which was effected in 59% yield by the method described for the preparation of VII.

mixture was heated with 10 ml. of 50% potassium hydroxide for fifteen minutes. A small amount (101 mg.) of tan solid, m.p. 240–249°, separated but was not further examined. The xylene layer was dried and treated with dry hydrogen chloride to yield 217 mg. of amine hydrochloride, m.p. 192–209°. Since this proved difficult to purify, it was converted to the free amine. The *TNF complex* prepared from this formed brown needles, m.p. 195.8–196.2°. The mixed melting point with the TNF complex prepared as under (a) above was not depressed.

5-Benzo[c]phenanthryl methyl ketone(XIV). To a stirred solution at room temperature of 228 mg. (1 mmole) of II and 102 mg. (1 mmole) of acetic anhydride in 2 ml. of chlorobenzene was added in six portions 280 mg. (2.1 mmoles) of aluminum chloride. After stirring for three hours, the mixture was hydrolyzed and the dried green chlorobenzene solution was poured on to an alumina column. Upon developing and eluting with first, carbon tetrachloride-benzene, 1:1; secondly, benzene; and finally, benzene-1% methanol, fractions A and C crystallized. From A was isolated a small amount of unchanged benzo[c]phenanthrene. From C was obtained 100 mg. of almost colorless prisms of XIV, m.p. 109.8–110.5°, after two recrystallizations from alcohol (literature (11) m.p. 111.5–112.5°). The *semicarbazone*, prepared by the Hopper method (23), melted at 234–234.5° with decomp. (literature (11) m.p. 235–236°).

Attempts to prepare an acetyl derivative of II using acetyl chloride produced only high melting compounds in complex mixture. No acetylation of II occurred on heating II, acetic anhydride, benzene, and 85% phosphoric acid (24) at reflux for 2½ hours.

To a boiling solution of 46 mg. of XIV in 1 ml. of pyridine was added during ten minutes 1.5 ml. of a potassium hypochlorite solution (25) containing a slight excess of oxidizing agent. The color of the solution darkened to deep cherry red and then lightened to yellow. After refluxing two minutes more, a saturated solution of sodium bisulfite was added to destroy excess hypochlorite. The acid fraction was taken into alkali and treated with decolorizing carbon (Dareo G-60). The crude acid thus obtained was recrystallized to a melting point of 238–239° and on mixing with an authentic sample (12) of XI, no depression was observed.

Reactions of II and homologs with diazotized p-nitraniline. Ten drops of a solution of *p*-nitrobenzenediazonium chloride (26) was added to a solution of 5 mg. of the compound to be tested in ten drops of acetic acid. The colors all formed within five seconds and were of approximately the same intensity. No change was noted after twelve hours. A blank test gave a light yellow color. The following alkyl derivatives of II and III all gave the same orange-brown color: 1-methyl-, 5-methyl-, 5,8-dimethyl-, and 5,8-diethyl- (19).

α-(1-Bromo-2-naphthyl)-β-phenylacrylonitrile(XV). To an agitated mixture of 1.8 g. (7.3 mmoles) of 1-bromo-2-naphthylacetonitrile, 5 ml. of dioxane, 0.2 g. (5.1 mmoles) of potassium, and 4 ml. of *t*-butyl alcohol was added 1.8 g. (17 mmoles) of benzaldehyde. The purple mixture was heated on the steam-bath for fifteen minutes, poured into water, acidified, and extracted with ether. After the ethereal layer had been washed with saturated sodium bisulfite and sodium chloride solutions, removal of the solvent left 1.17 g. (53%) of nitrile, m.p. 82–94°. Sodium ethoxide was an inferior catalyst (4) (27) and sodium amide (28) was inactive.

Attempted hydrolysis of XV. (*27b*) (*29*) A mixture of 15 ml. of 10% hydrogen peroxide, 1.2 g of XV, 8 ml. of 10% sodium carbonate solution, and 25 ml. of acetone was heated at 45–55° for fourteen hours, refluxed for 2½ hours, and then poured into water to yield XV unchanged. 1-Bromo-2-naphthylacetonitrile was hydrolyzed under the same conditions. A hydrolytic mixture of sulfuric acid, acetic acid, and water was also ineffectual.

SUMMARY

It is shown that the most reactive position of benzo[c]phenanthrene is position 5. A monobromo, mononitro, and monoacetyl derivative of benzo[c]phenanthrene have been prepared and each shown to be the 5-isomer.

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