chloroform afforded 2.1 g. of a resinous residue, which was dissolved in methanol (20 ml.) and 2*N* sulfuric acid (15 ml.). The brown solution was diazotized at 0° with the calculated amount of sodium nitrite (0.445 g.) in water (10 ml.), and the resultant red-brown solution maintained at 0° for 15 min. and then at room temperature for 30 min. Copper powder (2 g.) was then added, (nitrogen was evolved at this stage), the mixture was stirred for 1 hr., then kept at room temperature for 16 hr., and finally refluxed for 30 min. Concentrated hydrochloric acid (5 ml.) and zinc dust (3 g.) were added to the hot filtrate and the mixture refluxed for 50 min. The yellow solution was filtered hot, cooled, basified with dilute ammonia, and exhaustively extracted with ether. The dark brown material obtained from the extract was dissolved in a 7:1 mixture of benzene and petroleum ether (50–60°) and chromatographed on alumina. The column was eluted with 7:1 benzene:petroleum ether (50–60°). Upon removal of the solvent a yellow viscous oil (0.1 g.), which could not be induced to crystallize remained. This was dissolved in dilute hydrochloric acid and a saturated solution of potassium iodide was added. The yellow gummy precipitate was triturated with methanol when *4:6-dimethoxy-5-ethoxyaporphine hydroiodide* crystallized. Recrystallization from ethanol yielded prisms, m.p. 232–233° (charred).

Anal. Calcd. for $C_{21}H_{25}O_3N.HI.H_2O$: C, 51.9; H, 5.8; I, 26.2. Found: C, 51.6, 51.4; H, 5.6, 5.7; I, 26.0, 25.8.

Even after intensive drying (4 hr. at 120° *in vacuo*) the infrared spectrum, in chloroform solution still showed a diffuse band at 3600–3250 cm.$^{-1}$

Iso*thebaine ethyl ether hydroiodide.* A small specimen of isothebaine, in absolute ethanol, was treated with an ethereal solution of diazoethane. The nonphenolic base was purified by chromatographing upon alumina, and elution of the column with 60:40 benzene:petroleum ether (50–60°). Two distinct fluorescent bands were observed, the first yielding only a trace of material. The second larger band gave a pale yellow viscous oil upon evaporation of the solvent. This was dissolved in dilute hydrochloric acid and treated with a saturated solution of potassium iodide. The precipitated *iso*thebaine ethyl ether hydroiodide was crystallized from ethanol, and obtained as prisms, m.p. 236–237° (charred).

ABERDEEN, SCOTLAND

[CONTRIBUTION FROM THE DIVISION OF ONCOLOGY, CHICAGO MEDICAL SCHOOL]

Synthesis of C^{14} Labeled Anthracene, 9-Methylanthracene and 1,2-Benzanthracene[1]

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The synthesis of anthracene, 9-methylanthracene, and 1,2-benzanthracene labeled with C^{14} in the 9,10 positions is described.

The noncarcinogenic hydrocarbons, anthracene and 9-methylanthracene, and the weakly carcinogenic hydrocarbon, 1,2-benzanthracene, were labeled with C^{14} in the 9,10-positions in order to compare their metabolism with that of the potent carcinogen, 9,10-dimethyl-1,2-benzanthracene,[3,4] a hydrocarbon already labeled[5] with C^{14}. The four members of this structurally related series of compounds were conveniently prepared from the same labeled intermediate, *viz.*, phthalic anhydride -7-C^{14}.[5] Thus, syntheses utilizing C^{14} labeled phthalic anhydride constitute a general and practical method for the preparation of C^{14} labeled polycyclic hydrocarbons.

The anhydride, I, was condensed with benzene using ethylene chloride as the solvent according to Baddeley's general procedure for the Friedel-Crafts reaction.[6] The most satisfactory cyclization of the resultant ketoacid utilized fuming sulfuric acid rather than concentrated sulfuric acid. Fieser[7] made the same observations for the ring closure of *p*-toluyl-*o*-benzoic acid. Anthraquinone, II, was reduced to anthrone, III, with tin, hydrochloric and acetic acids according to Meyer.[8] The simultaneous addition of stannous chloride (which Badger and Cook substituted for tin in the reduction of 1,2-benzanthraquinone[9]) hastened the solution of anthraquinone. It was necessary to control carefully the amount of acidic reagents and the period of heating in order to avoid resinous products.

The addition of methylmagnesium iodide to anthrone and subsequent *in situ* dehydration to 9-methylanthracene, IV, had been reported without details.[10,11] This sequence was developed to give purified 9-methylanthracene in 63% yield.[12] While the ultraviolet absorption spectrum of this material was identical with that reported,[13] the m.p. was

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[1] This work was supported by Grant C-2399 and Cancer Control Grant CS-9212, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

[2] Bertha Gerber Memorial Cancer Foundation Fellow.

[3] V. Darchun and H. I. Hadler, *Cancer Research*, 16, 316 (1956).

[4] H. I. Hadler, V. Darchun, and K. Lee, *Science*, **125**, 72 (1957).

[5] H. I. Hadler, *J. Am. Chem. Soc.*, **27**, 1052 (1955).

[6] G. Baddeley, *J. Chem. Soc.*, S 99 (1949).

[7] L. F. Fieser, *Org. Syntheses*, **Col. Vol. 1**, 353 (1941).

[8] K. H. Meyer, *Org. Syntheses*, **Col. Vol. 1**, 60 (1941).

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

[10] F. Krollpfeiffer and F. Braunsheid, *Ber.*, **56**, 1617 (1923).

[11] A. Sieglitz and R. Marx, *Ber.*, **56**, 1619 (1923).

[12] A. L. Beckwith and W. A. Waters, *J. Chem. Soc.*, 1108 (1956), have recently reported that this reaction gave 9-methylanthracene in 80% yield.

[13] D. D. Phillips and J. Cason, *J. Am. Chem. Soc.*, **74**, 2934 (1952).

significantly lower than the literature values.[10–16] The methyl group was shown to be on C (9) in the low melting sample, as this methylanthracene (from analysis) was oxidized in high yield to 9,10-anthraquinone by potassium dichromate in acetic acid. The deviation in the m.p. may be due to polymorphism.

Anthrone was reduced to anthracene, V, with zinc and alkali. New conditions which required the addition of dioxane during the course of the reaction were developed. The yield was 82% of purified anthracene. The substitution of *n*-propyl alcohol (a solvent miscible with water and boiling at almost the same temperature as dioxane) for dioxane reduced the yield to 62%. Without any addition of solvent the yield was 55%. The efficiency of the dioxane procedure approached that of Martin's[17] which utilized toluene and gave anthracene in 93% yield.

C^{14} labeled 1,2-benzanthracene, VII, was obtained from 1,2-benzanthraquinone-9,10-C^{14},[5] VI, in 69% yield by a modification of the method of Badger and Cook.[9] The dioxane procedure was used to convert the intermediate anthrone-anthranol mixture to 1,2-benzanthracene.[18]

EXPERIMENTAL[19]

o-Benzoylbenzoic acid-13,14-C^{14}. The general conditions of Baddeley[6] for the Friedel-Crafts reaction were used. To a solution of 0.157 g. (0.00106 mole) of phthalic anhydride-7-C^{14} [5] m.p. 128–129 (m) (freshly sublimed at 250° at 35 mm. of Hg) in 2 ml. of ethylene chloride (dried over $CaCl_2$ and distilled) under an atmosphere of nitrogen there was added portionwise 0.203 g. (0.0022 mole) of granular aluminum chloride over a 10 min. period with constant stirring at room temperature. An additional 1.15 ml. of ethylene chloride and 0.4 ml. of methylene chloride were added to the almost clear solution and the flask cooled in an ice water bath. Dry benzene (3.9 ml. 0.044 mole) was added with constant stirring over a period of 30 min. The stirring was continued at 0° for 30 min., the cooling bath was removed and stirring continued for 20 hr. more. The flask was cooled to 0° and 6 ml. of 6*N* hydrochloric acid was cautiously added. The solvents were removed by steam distillation and the organic material taken up in ether. The ether extract was washed in succession with water and 1*N* aqueous sodium hydroxide. The alkaline wash was run into 6*N* hydrochloric acid and the acidic material taken up in ether. The extract was washed with water and the solvent evaporated. Residual water was removed by co-distillation with benzene. After subliming the residue at 230–240° at 0.3 mm. there was obtained 0.230 g. of white solid m.p. 127–128° (m) in 95% yield. The reported melting point of anhydrous *o*-benzoylbenzoic acid is 127°.[20] The anhydride test[21] was negative.

9,10-Anthraquinone-9,10-C^{14}. II. The procedure for the cyclization of *p*-toluyl-*o*-benzoic acid was applied.[7] To a dry flask fitted with a calcium chloride tube there was added 0.160 g. (0.0007 mole) of freshly sublimed *o*-benzoylbenzoic acid-13,14-C^{14} m.p. 127–128° followed by 0.8 ml. of fuming sulfuric acid (20% anhydride). After obtaining a clear red solution at room temperature the flask was warmed on the steam bath for 15 min. with occasional swirling. The flask was cooled to 0°, ice chips were added, and the sparingly soluble organic material taken up in chloroform. The extract was washed in succession with water, 1% aqueous sodium bicarbonate, and water and dried with sodium sulfate. The solvent was evaporated and the residue eluted from Florisil (60/100 mesh) with chloroform and sublimed at 250° at 35 mm. to yield 0.121 g. of yellow solid m.p. 282.1–284.3° in 84% yield. The reported m.p. of anthraquinone is 286°.[22]

Anthrone-9,10-C^{14}, III. The procedures of Meyer[8] and Badger and Cook[9] were combined. A mixture of 0.062 g. (0.0003 mole) of anthraquinone-9,10-C^{14} m.p. 282.7–284.9°, 0.160 g. (0.007 mole) of stannous chloride dihydrate, 0.121 g. (0.001 mole) of granulated tin, 3 ml. of glacial acetic acid were refluxed for 1 hr. with constant stirring. The cooled solution was diluted with 25 ml. of water and the organic material taken up in benzene. The extract was washed in succession with water, 1% aqueous sodium hydroxide to which sodium hydrosulfite had been freshly added, and water. After drying with sodium sulfate the solvent was evaporated. The residue was sublimed at 190° at 0.15 mm. to give 0.051 g. of pale yellow solid m.p. 150.4–152.7° in 88% yield. The reported m.p. of anthrone is 154–155°.[8]

9-Methylanthracene-9,10-C^{14}. IV. The previous procedures were extended.[10,11] In an atmosphere of dry nitrogen, during a period of 45 min. a solution of 0.051 g. (0.000263 mole) of anthrone-9,10-C^{14} m.p. 150.4–152.7° in 25 ml. of benzene was added at ice water temperature to a stirred Grignard reagent prepared from 0.030 g. (0.0012 mole) of magnesium, 10 ml. of ether, and 1.0 ml. (0.0162 mole) of methyl iodide. After stirring in the cold for 3 more hr. the mixture was refluxed for 1 hr. and left at room temperature for 16 hr. Twenty-five ml. of water were added, the mixture was well shaken, and the two phases were separated. The remaining organic material was taken up in benzene. The combined extracts were washed in succession with water, fresh aqueous sodium thiosulfate, water, 5% aqueous sodium hydroxide to which sodium hydrosulfite had been freshly added, and water. After drying with sodium sulfate the solvents were evaporated and the residue sublimed at 140° at 0.15 mm. of Hg. The solid was eluted from Florisil (60/100 mesh) with cyclohexane, crystallized from dilute ethanol, and sub-

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(14) W. G. Dauben, C. F. Hiskey, and M. A. Muhs, *J. Am. Chem. Soc.*, **74**, 2082 (1952).

(15) L. F. Fieser and J. L. Hartwell, *J. Am. Chem. Soc.*, **60**, 2555 (1938).

(16) W. E. Bachman and M. C. Kloetzal, *J. Org. Chem.*, **3**, 55 (1938).

(17) E. L. Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

(18) C. Heidelberger and M. G. Moldenhauer, *Cancer Research*, **16**, 442 (1956) independently reported the preparation of phthalic anhydride-7-C^{14} and 1,2-benz-9,10-anthraquinone-9,10-C^{14} by the sequence previously outlined.[5] These workers used the method of Badger and Cook[9] for the reduction of 1,2-benzanthraquinone and obtained 1,2-benzanthracene in 58% yield. In our hands this reduction was capricious until the dioxane modification was used. Since the transformation of 1,2-benz-9,10-anthraquinone to the hydrocarbon was a reaction of more than one step, the efficacy of the addition of dioxane was established for the reduction of anthrone to anthracene; a single transformation.

(19) Melting points were corrected and were taken on a hot stage when followed by (m). Ultraviolet absorption spectra were determined on Beckman spectrophotometers models DU or DK 1, 95% alcohol was employed as the solvent. All C^{14} labeled compounds had a specific activity of 2.77 millicuries per millimole. Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss, Oxford, England. Evaporations were conducted on a steam bath under a stream of nitrogen.

(20) W. Hemilian, *Ber.*, **11**, 837 (1878).

(21) F. Feigl, *Spot Tests*, Fourth edition, Vol. 2, p. 174, Elsevier Publishing Co., New York, N. Y., 1954.

(22) R. Kempf, *J. Pract. Chem.*, **78**, 257 (1908).

limed as above to give 0.032 g. of yellow solid m.p. 61–63° in 63% yield. From a cold run an analytical sample m.p. 61–63 (m) was obtained λ_{max} (log ϵ); 249 (5.05); 256 (5.39); 315 (3.10); 332 (3.49); 347 (3.83); 367 (4.05); 380 (3.77); 385 (4.05).

Anal. Calcd. for $C_{15}H_{12}$: C, 93.76; H, 6.29. Found: C, 93.88; H, 6.24.

The melting point of 9-methylanthracene has been reported as 75–77°,[14] 76.3–77.8°,[15] 78–79°,[16] 79.2–79.7°,[13] 79–80°,[10] 80°,[12] 81.5°.[11] The reported spectrum[13] is λ_{max} (log ϵ); 252 (5.18); 256 (5.33); 318 (3.04); 331 (3.44); 348 (3.76); 366 (3.96); 386 (3.95).

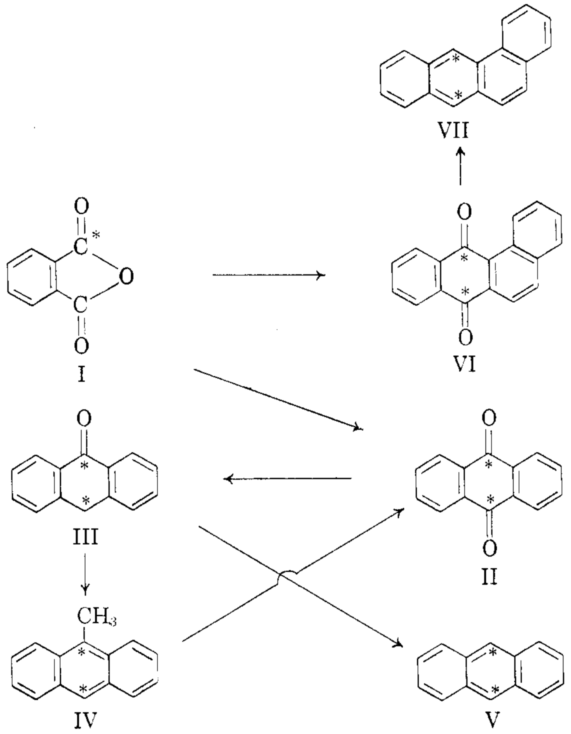
9,10-Anthraquinone from 9-methylanthracene. The procedure for the oxidation of 1,2,5,6-dibenzanthracene to 1,2,5,6-dibenz-9,10-anthraquinone was used.[23] A mixture of 0.165 g. (0.00085 mole) of 9-methylanthracene m.p. 62–63°, 0.4 g. (0.0013 mole) of powdered sodium dichromate dihydrate and 6 ml. of glacial acetic acid were refluxed for 30 min., cooled to room temperature and 25 ml. of water added. The organic material was taken up in chloroform and the extract was washed in succession with dilute sulfuric acid, water, aqueous sodium bicarbonate, and water and dried with sodium sulfate. The solvent was evaporated and the residue sublimed at 175° at 0.4 mm. of Hg to give 0.170 g. of yellow solid m.p. 274.3–275.5° in 97% yield. After elution from Florisil (60/100 mesh) with chloroform and sublimation as above there was obtained 0.157 g. of yellow solid m.p. 283.8–285.8° in 88% yield. On admixture with authentic anthraquinone m.p. 283.8–285.8°, the m.p. was unchanged.

Anthracene-9,10-C^{14}, V. The procedure of Badger and Cook[9] describing the conversion of 1,2-benz-9,10-anthraquinone to 1,2-benzanthracene was modified. A mixture of 0.058 g. (0.0003 mole) of anthrone[24] m.p. 149.1–151.9°, 3 ml. of 3*N* sodium hydroxide and 0.88 g. (0.013 mole) of activated zinc[25] were refluxed for 90 min. under nitrogen with stirring. Peroxide free dioxane (1.1 ml.) was added and the reaction continued 1 more hr. After cooling to room temperature 25 ml. of water was added and the organic material taken up in benzene. The extract was washed in succession with 5% aqueous sodium hydroxide to which sodium hydrosulfite had been freshly added, water, fresh aqueous sodium bisulfite, water, 1% hydrochloric acid, and water. After drying with sodium sulfate the solvent was evaporated and the residue was sublimed at 215° at 35 mm. of Hg. Elution from Florisil (60/100 mesh) with cyclohexane gave 0.044 g. of colorless, violet fluorescent crystals m.p. 210.2–212.1° in 82% yield.

Without dioxane the yield was 55% (m.p. 209.3–211.4°) and with *n*-propyl alcohol replacing dioxane the yield was 62% (m.p. 210.2–212.1). The melting point of anthracene has been reported as 211–213°,[16] 216–216.5°.[17] The analytical sample melted at 209.3–211.4°.

Anal. Calcd. for $C_{14}H_{10}$: C, 94.34; H, 5.66. Found: C, 93.96; H, 5.62.

1,2-Benzanthracene-9,10-C^{14}, VII. The previous procedure was modified.[9] To a solution of 0.086 g. (0.000327 mole) of 1,2-benz-9,10-anthraquinone-9,10-C^{14}[5] m.p. 167.5–168° in 4 ml. of glacial acetic acid there was added slowly a solution composed of 0.3375 g. (0.0015 mole) of stannous chloride dihydrate and 2 ml. of 12*N* hydrochloric acid. The clear solution was refluxed for 2 hr. After the first hour of refluxing the above amounts of stannous chloride dihydrate, 12*N* hydrochloric acid, and glacial acetic acid were again added. The flask was cooled and the reaction mixture diluted with water. The organic material was taken up in chloroform. The extract was washed with water, dried with sodium sulfate and the solvent evaporated. The residue was reduced by the procedure described above for the conversion of anthrone to anthracene. After removing the extraction solvent the residue was eluted from Florisil (60/100 mesh) with cyclohexane to give 0.052 g. (69%) of colorless solid m.p. 157.5–158° (m). The reported m.p. is 158–159°.[9]



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[24] The cold runs demonstrating the efficacy of dioxane are described.

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