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

The Synthesis of Polynuclear Aromatic Hydrocarbons. II. Methylbenzo(c)phenanthrenes[1]

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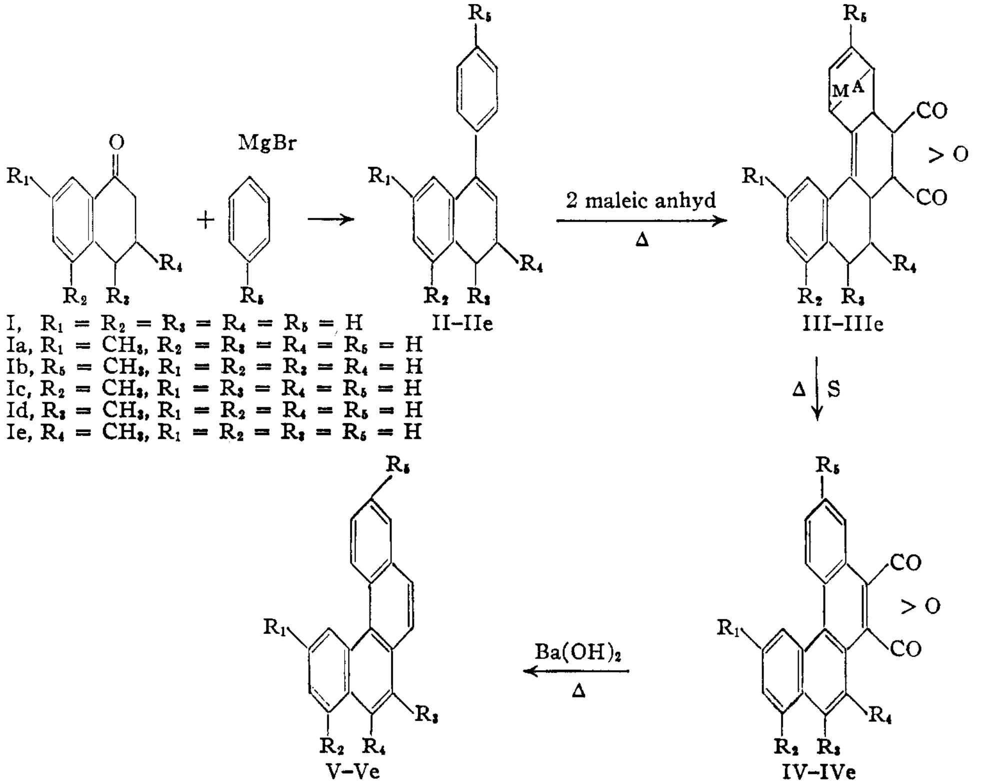
The syntheses of benzo(c)phenanthrene and the six monomethyl derivatives thereof are reported. These compounds have been prepared in quantity and are available for distribution for evaluation of chemical, physical and physiological properties.

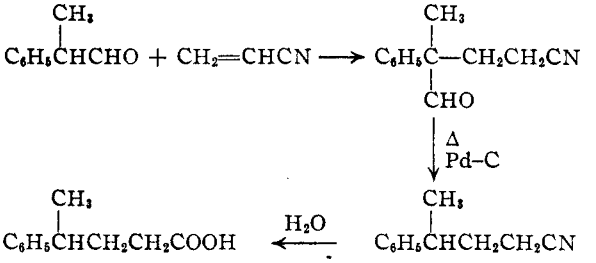
The reasons for preparing relatively large amounts of hydrocarbons for testing in connection with cancer research have been outlined in a previous paper[2] concerned with the syntheses of methyl-1,2-benzanthracenes. In this paper are described the methods used for the preparation of benzo(c)-phenanthrene and the six monomethylbenzo(c)-phenanthrenes as illustrated in the chart.

All of the compounds were prepared by the general benzo(c)phenanthrene synthesis recently developed[3] with the exception of the 1-methyl derivative which was prepared as previously described.[4] 3-Methyl- and 4-methylbenzo(c)phenanthrenes and the parent hydrocarbon had been prepared previously by similar methods on a small scale.[3] Our preparation of the 4-compound involved intermediates different from those used before.[3] The reactions are summarized in the chart.



I, $R_1 = R_2 = R_3 = R_4 = R_5 = H$
Ia, $R_1 = CH_3, R_2 = R_3 = R_4 = R_5 = H$
Ib, $R_5 = CH_3, R_1 = R_2 = R_3 = R_4 = H$
Ic, $R_2 = CH_3, R_1 = R_3 = R_4 = R_5 = H$
Id, $R_3 = CH_3, R_1 = R_2 = R_4 = R_5 = H$
Ie, $R_4 = CH_3, R_1 = R_2 = R_3 = R_5 = H$

The substituted butyric acids needed for cyclization to tetralones, I, were prepared by conventional methods except for γ-phenylvaleric acid. For this a new method was developed. The aldehyde produced by cyanoethylation[5] of hydratropaldehyde was decarbonylated by heating over palladized charcoal to yield[6] γ-phenylvaleronitrile which was hydrolyzed to yield γ-phenylvaleric acid in good over-all yield.



$$C_6H_5\overset{CH_3}{C}HCHO + CH_2{=}CHCN \longrightarrow C_6H_5\overset{CH_3}{\underset{CHO}{C}}{-}CH_2CH_2CN$$

$$\xrightarrow[\text{Pd-C}]{\Delta} C_6H_5\overset{CH_3}{C}HCH_2CH_2CN$$

$$C_6H_5\overset{CH_3}{C}HCH_2CH_2COOH \xleftarrow{H_2O} C_6H_5\overset{CH_3}{C}HCH_2CH_2CN$$

The cyclization of the butyric acids to tetralones proceeded easily in good yields with only one notable feature. The acids were converted into acid chlorides with the aid of phosphorus pentachloride. When the phosphorus oxychloride was removed, the cyclization brought about by stannic chloride went more slowly and in poorer yield than when the

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[1] The work herein reported was supported by grants C-483-C2, C-483-C3 from the U. S. Public Health Service, to whom grateful acknowledgment is made.

[2] M. S. Newman and R. Gaertner, THIS JOURNAL, **72**, 264 (1950).

[3] J. Szmuszkovicz and E. J. Modest, *ibid.*, **70**, 2542 (1948); **72**, 566 (1950).

[4] M. S. Newman and M. Wolf, *ibid.*, **74**, 3225 (1952).

[5] H. A. Bruson and T. W. Riener, *ibid.*, **66**, 56 (1944).

[6] M. S. Newman and H. V. Zahm, *ibid.*, **65**, 1097 (1943).

oxychloride was left in the reaction mixture. For the most striking example, when γ-phenylbutyryl chloride in benzene solution containing the phosphorus oxychloride from the reaction of the acid with pentachloride was treated with an excess of anhydrous stannic chloride and the mixture poured on ice after 1.5 minutes there was obtained 61% of tetralone and 20% of recovered γ-phenylbutyric acid. In an exactly comparable experiment (in which the oxychloride and benzene were removed and pure benzene was replaced) after 6.5 minutes of reaction with stannic chloride there was obtained 21% of tetralone and 67% of acid. In the other cases described herein the crude reaction mixtures resulting from treatment of the acids with phosphorus pentachloride in benzene were treated directly with stannic chloride and high yields were the rule. This observation concerning phosphorus oxychloride stands in marked contrast to the situation obtaining when aluminum chloride is the cyclizing reagent. In these cases the phosphorus oxychloride usually exerts a detrimental effect.[7]

Experimental[8]

γ-Phenylvaleric Acid.—A commercial sample of hydratropic aldehyde[9] was cyanoethylated[6] by adding 332 g. (6.2 moles) of acrylonitrile dropwise with stirring to a cooled flask containing 805 g. (6 moles) of aldehyde, 12 cc. of water and 12 g. of potassium hydroxide. The temperature was held near 55° during the addition. The exothermic reaction continued for 2 hours after addition of nitrile was complete during which time the temperature dropped to 40°. After heating to 58° for another hour the mixture was acidified. There was obtained γ-formyl-γ-phenylvaleronitrile, b.p. 130–133.5° at 0.4 mm., in 70.5% yield. Redistillation for analysis yielded a sample, b.p. 124.5° at 0.1 mm., $n^{20}{}_D$ 1.5289. The yellow 2,4-dinitrophenylhydrazone melted at 175.4–176.4° after crystallization from absolute alcohol.

Anal. Calcd. for $C_{12}H_{13}ON$: C, 77.1; H, 7.0. Found: C, 76.6; H, 6.7. Calcd. for $C_{18}H_{17}O_4N_5$: C, 58.9; H, 4.7. Found: C, 59.2; H, 5.0.

For further work it was not necessary to distil the crude aldehydonitrile; the alkali was washed out and the crude product processed as described below for a typical experiment.

A mixture of 187 g. (1 mole) of crude aldehydonitrile and 2.5 g. of 30% palladium-on-charcoal[10] was heated from about 190 to 240° at such a rate that the evolution of carbon monoxide was maintained at about 400 cc. per minute. When about the theoretical volume had been evolved the catalyst was removed and the product distilled to yield about 68% (from starting hydratropaldehyde) of crude γ-phenylvaleronitrile,[11] b.p. 93–113° at 0.7 mm. This was refluxed with 440 cc. of concd. hydrochloric acid and 660 cc. of acetic acid for 1.5 hours. An additional 100 cc. of hydrochloric acid was added and refluxing maintained for one hour. After washing and distillation there was obtained in 87.4% yield crude γ-phenylvaleric acid,[11,12] b.p. 110–117° at 0.04 mm., $n^{20}{}_D$ 1.5167, suitable for conversion to 4-methyl-1-tetralone (see below).

β-Methyl-γ-phenylbutyric Acid.—Ethyl β-hydroxy-β-methyl-γ-phenylbutyrate[13] was prepared by the condensation of ethyl bromoacetate with phenylacetone[9] and dehydrated by heating with an equivalent of phosphorus pentachloride to yield the unsaturated ester (position of double bond not established), b.p. 144–148° at 13–14 mm., $n^{20}{}_D$ 1.5160, in 58% yield over-all. This unsaturated ester was hydrogenated over Adams platinic oxide and then saponified to yield β-methyl-γ-phenylbutyric acid[13] in almost quantitative yield.

Tetralones, I.—The tetralones I, I_{a-e} were prepared by conversion of the requisite γ-arylbutyric acids to their acid chlorides using 1.1 equivalents of phosphorus pentachloride in sulfur-free benzene followed by treatment of the reaction mixture with about 2.4 equivalents of anhydrous stannic chloride in benzene. One of the better large runs is described. To a suspension of 230 g. (1.1 moles) of phosphorus pentachloride in 1 l. of benzene was added in portions 178 g. (1 mole) of γ-*o*-tolylbutyric acid.[14] After conversion to the acid chloride was complete the mixture was cooled until a quantity of benzene crystallized. A similarly cooled slurry from 625 g. (2.4 moles) of stannic chloride in 600 cc. of benzene was added rapidly with efficient stirring and cooling in an ice–salt bath. The reaction mixture set to a light yellow cake which was broken up rapidly with the aid of a spatula and transferred with the aid of additional benzene onto a mixture of about 2 kg. of crushed ice containing 200 cc. of concd. hydrochloric acid. The total time from addition of the stannic chloride was about 12 minutes. After suitable work-up there was obtained 152 g. (95%) of 5-methyl-1-tetralone,[14,15] b.p. 97–102° at 0.5 mm., m.p. 49.5–51.0°.

Other yields were as follows: γ-phenylbutyric acid to tetralone I, 84%; γ-phenylvaleric acid to 4-methyl-1-tetralone I_d, 82% (in this case no solid complex separated when the stannic chloride was added—the reaction mixture darkened after two minutes and was then immediately poured on ice); β-methyl-γ-phenylbutyric acid to 3-methyl-1-tetralone I_e, 80.5% (reaction conditions the same as for Id, but 9.7% of starting acid was recovered). 7-Methyl-1-tetralone was a student preparation, m.p. 29–30°.

Aryldihydronaphthalenes, II.—These olefins were prepared by slowly adding a solution of the requisite tetralone I, in ether to a cooled (about −30°) solution containing an excess (about 20%) of the Grignard reagent. After allowing the reaction mixture to come to room temperature, it was hydrolyzed with saturated ammonium chloride solution. The crude carbinol thus produced was isolated and dehydrated by refluxing in benzene to which 2 cc. of concd. hydrochloric acid was added. The olefins II were then isolated by vacuum distillation. The yields were as follows. From I and phenylmagnesium bromide, 1-phenyl-3,4-dihydronaphthalene (II),[3] b.p. 130.5–134.5° at 0.3 mm., was obtained in 68% yield. From I and *p*-tolylmagnesium bromide, crude 1-*p*-tolyl-3,4-dihydronaphthalene (II),[3] b.p. 107–135° at 0.1–0.2 mm., was obtained in 77% yield. From Ia and phenylmagnesium bromide, 1-phenyl-7-methyl-3,4-dihydronaphthalene (IIa), b.p. 157–159° at 3 mm., was obtained in 62% yield. From Ic and phenylmagnesium bromide, 1-phenyl-5-methyl-3,4-dihydronaphthalene (IId), b.p. 135–137.5° at 0.2 mm., was obtained in 79% yield. From Id and phenylmagnesium bromide, 1-phenyl-4-methyl-3,4-dihydronaphthalene (IId), b.p. 130–143° at 1.2 mm., was obtained in 73% yield. From Ie and phenylmagnesium bromide, 1-phenyl-3-methyl-3,4-dihydronaphthalene (IIe), b.p. 133–136° at 0.1 mm., m.p. 50.0–51.5°, was obtained in 84% yield.

Anal. Calcd. for $C_{17}H_{16}$: C, 92.7; H, 7.3. Found: C, 92.9; H, 7.4.

Double Diels–Alder Products, III.—In a typical experiment 1 mole of olefin IIc and 5 moles of maleic anhydride were heated to 150° with some agitation to effect homogeneity and held at this temperature for 24 hours. On slow cooling crystals separated. The mixture was then stirred with 300 cc. of acetic acid and left for several days. The crystalline adduct, IIIc, was collected, washed with acetic anhydride and petroleum ether, and air-dried to yield 35.8% of material, m.p. 305–308° with decomposition, suitable for the next step. An additional amount of crude cream colored adduct could be obtained by adding the acetic acid mother liquor in a thin stream to a large volume of well-stirred water. By processing this crude material a good yield of

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[7] W. S. Johnson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 136.

[8] All microanalyses by Clark Microanalytical Laboratories, Urbana, Illinois. All m.ps. under 240° are corrected; those above, uncorrected.

[9] Van Ameringen–Haebler, Inc., Elizabeth, New Jersey.

[10] N. D. Zelinsky and M. B. Turowa-Pollak, *Ber.*, **58**, 1292 (1925).

[11] J. V. Braun and A. Stuckenschmidt, *ibid.*, **56**, 1724 (1923), give b.p. 125–126° at 13 mm. for the nitrile and b.p. 165° at 12 mm. for the acid.

[12] See M. C. Kloetzel, THIS JOURNAL, **62**, 1708 (1940), for an alternate synthesis of this acid.

[13] F. Weygand and K. Schroder, *Ber.*, **74**, 1844 (1941).

[14] M. S. Newman and W. K. Cline, *J. Org. Chem.*, **16**, 934 (1951).

[15] L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1155 (1937).

aromatic type anhydride, IVc, was obtainable but this product did not yield enough good final hydrocarbon, Vc, to warrant the extra work involved. Accordingly, in the cases of all of the other adducts, III, no further work was done with the crude products. The properties of the purified adducts, III, yields, and their analyses are recorded in Table I.

TABLE I

YIELDS AND PROPERTIES OF INTERMEDIATES

			Analyses, found	
Compound	Yield, %	M.p.,[b,c] °C.	Carbon, %	Hydrogen, %
III	61[a]	314		
III^a	41[a]	307	72.1	5.1[d]
III^b	55[a]	330	72.1	4.9[d]
III^c	36[a]	317	71.7	5.0[d]
III^d	79[a]	342	72.1	4.9[d]
III^e	45[a]	328	71.9	4.9[d]
IV	[e]			
IV^a	[e]	236–238	80.8	3.9[f]
IV^b	[e]	288–290	80.8	3.7[f]
IV^c	[e]	235–236	80.8	3.9[f]
IV^d	[e]	267–269	80.0	3.9[f]
IV^e	[e]	216–217	80.5	3.6[f]

[a] This represents pure compound. Considerably more crude product was obtained but only in the case of the c series was this crude adduct further studied. The yields in the following steps are based on purified adduct except as noted. [b] The melting points represented by a single value are approximate and varied with the rate of heating. [c] Recrystallized from acetone except IIIa which was recrystallized from acetic acid containing 5% of acetic anhydride. [d] Calcd. for $C_{25}H_{20}O_6$: C, 72.1; H, 4.8. [e] Yields essentially quantitative from pure adduct but not determined from crude adducts. [f] Calcd. for $C_{21}H_{12}O_3$: C, 80.8; H, 3.9.

Aromatic Anhydrides, IV.—In a typical experiment 205 g. (0.49 mole) of crystalline adduct, IIIc, and 48 g. (1.5 moles) of sulfur were mixed and heated to 230° whereupon the evolution of hydrogen sulfide started. The temperature was raised gradually over one hour to 280° after which the reaction mixture was cooled and triturated with 3 l. of 4% potassium hydroxide solution. The filtered extract was treated with charcoal and acidified. The dark brown solid weighed 162 g. (100%). This material was used without further purification for the decarboxylation. The crude acid was converted into the anhydride by pyrolysis and vacuum sublimation. Recrystallization from dimethylformamide afforded yellow needles, m.p. 234.8–235.8°. Essentially quantitative yields of aromatic anhydrides, type IV, were obtained in every case. The properties and analyses are listed in Table I. It would surely be possible to obtain more pure aromatic anhydrides, type IV, from the crude adducts, type III, isolated from the mother liquors of crystallization. However, we have not studied this except in the one case mentioned (c series).

Aromatic Hydrocarbons, V.—In a typical run, an intimate mixture of 30 g. of crude IVc (obtained as described above and not recrystallized), 150 g. of anhydrous barium hydroxide, 180 g. of iron filings and 10 g. of copper–bronze was heated under reduced pressure in a flask provided with an efficient all metal stirrer made air tight in a glass bearing by graphite lubrication. The temperature was raised slowly to 170° when all the water was off and was then raised to 350° for 45 minutes. After cooling, the organic matter was extracted with several portions of boiling benzene. On removal of the solvent the residue was distilled to yield crude hydrocarbon which was converted directly to the picrate for purification. The yield of picrate,[3] m.p. 109.5–111.0° after one recrystallization from methanol, was 58%. The pure 4-methylbenzo[c]phenanthrene obtained from this picrate melted at 64.6–65.6°.[16] When the crude adduct, IIIc, obtained from the mother liquors as above described was processed, an over-all yield of only 7.3% of pure V, was obtained. For this reason none of the other crude adducts were processed further.

By similar processes of preparation and purification, the following benzo[c]phenanthrenes were obtained in the following yields from the double Diels–Alder adducts, III: benzo[c]phenanthrene, m.p. 66.4–67.0°,[17] 28.5%; 2-methylbenzo[c]phenanthrene (Va), m.p. 80.6–81.4°,[17] 36.7%; 3-methylbenzo[c]phenanthrene (Vb), m.p. 54.4–55.4°,[17] 40%; 5-methylbenzo[c]phenanthrene (Vd), m.p. 70.6–71.6°,[18] 20%; and 6-methylbenzo[c]phenanthrene (Ve), m.p. 76.8–77.6°,[19] 31%.

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(16) C. L. Hewett, *J. Chem. Soc.*, 1286 (1938).

(17) Compare m.p. with those listed by W. E. Bachmann and R. O. Edgerton, THIS JOURNAL, **62**, 2970 (1940).

(18) See M. S. Newman and L. M. Joshel, *ibid.*, **62**, 972 (1940), and C. L. Hewett, *J. Chem. Soc.*, 596 (1936), for other melting points.

(19) When we first prepared Ve, the melting point was 65.1–66.1°. However, this was a polymorphic form inasmuch as it melted at the higher temperature when mixed with a crystal of Ve of the higher melting point kindly sent to us by Dr. Hewett. See C. L. Hewett, *J. Chem. Soc.*, 293 (1940).

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[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Synthesis of Hydroaromatic Compounds Containing Angular Methyl Groups. III. 1,2-Cyclopentanonaphthalene Series[1]

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Methods which may be suitable for the synthesis of aromatic steroids containing oxygen at positions 11 and 12 are described. Model compounds thus prepared are 4-keto-2-methyl-1,2,3,4-tetrahydro-1,2-cyclopentanonaphthalene (VI) and 3-keto-2-methyl-1,2,3,4-tetrahydro-1,2-cyclopentanonaphthalene (VII). Characteristic infrared absorption bands have been noted for the diazomethyl ketone ($-COCHN_2$) function.

As early as 1943, experiments designed toward the synthesis of steroids isomeric with estrone and equilenin but containing oxygen in ring C were begun.[4] Because of certain poorly understood features of this and later work[3] publication of results has been postponed. However, we have now discovered the source of the trouble and in this paper is reported the synthesis of one isomer of 4-keto-2-methyl-1,2,3,4-tetrahydro-1,2-cyclopentanonaphthalene (VI) and of 3-keto-2-methyl-1,2,3,4-tetrahydro-1,2-cyclopentanonaphthalene (VII). The stereochemistry of the fusion of the rings bearing the angular methyl group is not known, but is the same for VI and VII. The syntheses are outlined in the chart.

The condensation of phenylmagnesium bromide with 2-carbethoxy-2-methylcyclopentanone yields 2-carbethoxy-2-methyl-1-phenylcyclopentanol (I)

(1) I and II, THIS JOURNAL, **66**, 1550, 1553 (1944).

(2) Postdoctoral Fellow, U. S. Public Health Service.

(3) Taken in part from the Ph.D. thesis of H. M. G., Ohio State, 1950.

(4) R. D. Closson, Ph.D. Thesis, Ohio State, 1944.