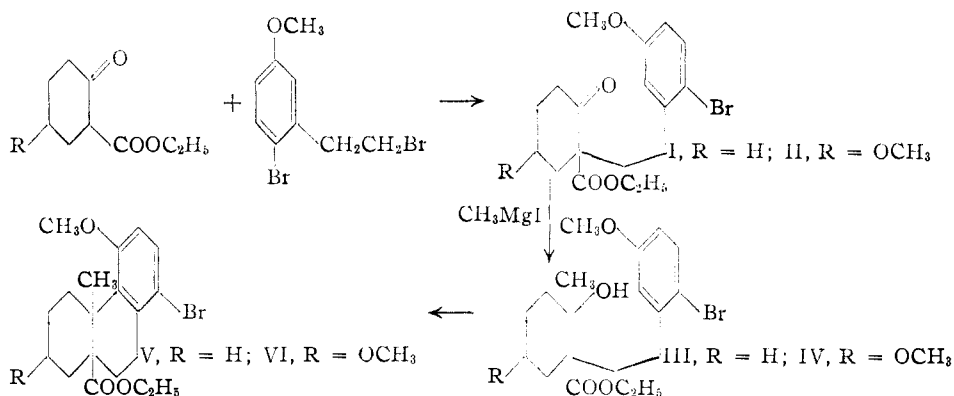# Synthesis of Phenanthrenes. I. Octahydrophenanthrenes with an Angular Carboxyl Substituent[1]

BY RODERICK A. BARNES, H. PETER HIRSCHLER AND BERNARD R. BLUESTEIN

By alkylation of 2-carbethoxycyclohexanone and 4-methoxy-2-carbethoxycyclohexanone with β-arylethyl bromides and reaction of the substituted ketoesters first with methylmagnesium iodide and then with sulfuric acid it has been possible to synthesize octahydrophenanthrenes having an angular carboxyl group. This modification of the Bardhan–Sengupta phenanthrene synthesis eliminated the troublesome hydrolysis of the alkylated ketoesters and also prevented the possibility of spirane-formation at the cyclization step. The aromatization of these octahydrophenanthrenes proceeded with loss of the angular carboxyl group.

One of the drawbacks of either the Bardhan–Sengupta or the Bogert–Cook phenanthrene synthesis is the uncertainty at the cyclization step. This uncertainty arises because of the fact that spiranes have also been obtained from cyclization of several alcohols[2] prepared by the Bogert–Cook procedure. Although it has not as yet been definitely proved it seems likely that the cyclization of alcohols obtained by *both* synthetic procedures proceeds by way of a common intermediate carbonium ion. Therefore, there is a possibility that spiranes may be formed in both methods.

One way to prevent the possibility of forming spiranes was to retain the carbethoxyl group until after the cyclization.[3] The addition of methylmagnesium iodide to ketoesters I and II was a smooth reaction. There was no evidence that the Grignard reagent reacted to any appreciable extent with the carbethoxyl group even though at the beginning of the addition it was present in large excess in relation to the amount of ketoester. This result might have been anticipated from the previously known fact that rather dilute aqueous bases attack the ketone group of substances similar to I and II more readily than the ester group.[3,4]
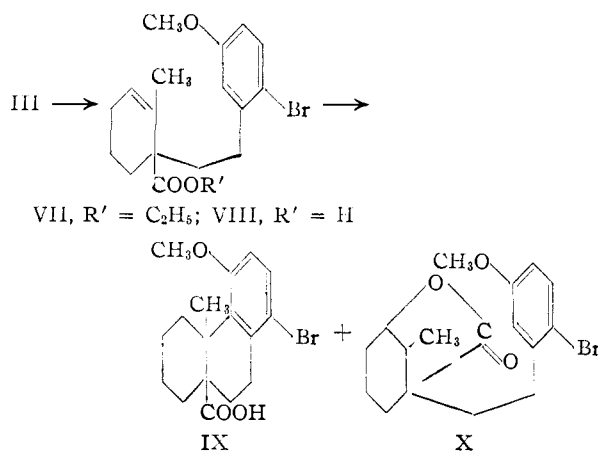
The cyclization of III and IV proved to be more difficult than had been expected. The first attempts to cyclize III (85% H_2SO_4) led only to dehydration. The unsaturated ester VII was

III →   → Br →

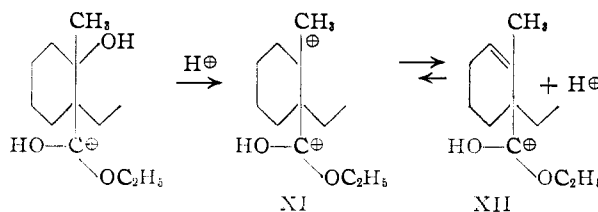VII, R′ = C_2H_5; VIII, R′ = H

IX   X

readily hydrolyzed to produce a crystalline acid VIII. By reaction of VIII with 90% sulfuric acid the desired phenanthrenecarboxylic acid IX was formed but a large amount of lactone X was also produced.

The difficulty in achieving cyclization in spite of the favorably located methoxyl group in the benzene nucleus is believed to be due to the presence of the carboxyl or carbethoxyl group. In sulfuric acid solution these groups can act as proton acceptors.[5] Such a proton transfer would bring a positive charge close to the carbon atom which must be converted to a carbonium ion in order for cyclization to take place. The carbonium ion, XI being of higher energy than the usual cyclization intermediate, is present in very low concentration; the equilibrium favors the unsaturated compound XII.

V, R = H; VI, R = OCH₃

I, R = H; II, R = OCH₃

III, R = H; IV, R = OCH₃

XI   XII

(1) Presented in part at the Meeting-in-Miniature of the North Jersey Section of the A. C. S., January 9, 1951.

(2) D. Perlman, D. Davidson and M. T. Bogert, *J. Org. Chem.*, **1**, 288, 300 (1936); J. W. Cook, C. L. Hewett and A. M. Robinson, *J. Chem. Soc.*, 168 (1939); R. A. Barnes and L. Gordon, THIS JOURNAL, **71**, 2644 (1949).

(3) J. C. Bardhan and S. C. Sengupta, *J. Chem. Soc.*, 2520, 2798 (1932), have cyclized secondary alcohols in which the carbethoxyl group was still present. The octahydrophenanthrenes were not isolated but directly dehydrogenated.

(4) G. A. R. Kon, *ibid.*, 1081 (1933)

(5) A. Hantzsch, *Z. physik. Chem.*, **61**, 257 (1908).

The Bardhan–Sengupta procedure requires a ketonic hydrolysis of ketoesters similar to I and II. This is almost impossible to effect in good yield with aqueous bases[6]; large amounts of acid cleavage products are always formed.

A number of ketoesters have been hydrolyzed in acid solution,[7] but we have found that a ketoester having a methoxyl substituent (XIII) was rapidly cyclized by dilute aqueous acid when such a hydrolysis was attempted.

XIII → XIV
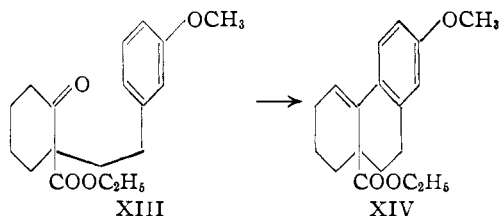
Structure XIV for the cyclization product is supported by the very great similarity of the ultraviolet absorption curve of this substance and methyl *cis*-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-1,2-dicarboxylate.[8]

Acknowledgment.—We wish to express our appreciation to the Research Corporation for a Frederick Gardner Cottrell Grant which made this work possible. We also wish to acknowledge the assistance of Doris E. Barnes in preparing many of the compounds used in this research.

Experimental[9]

β-(2-Bromo-5-methoxyphenyl)-ethyl Bromide.[10]—A solution of bromine (112 g.) in carbon tetrachloride (100 ml.) was added dropwise to a well-stirred mixture of β-(3-methoxyphenyl)-ethyl bromide[11] (150 g.) and carbon tetrachloride (400 ml.) maintained at −10°. The solution was stirred for 30 minutes after the addition was complete and then poured into ice-water. The organic layer was separated, washed with sodium bicarbonate solution and the solvent removed. There was obtained 190 g. (92%) of product which boiled at 100–103°[12] at 0.2 mm., n^{20}D 1.5872.

The structure of the bromide was proved by treating a sample with alcoholic potassium hydroxide and then oxidizng with potassium dichromate and sulfuric acid. 2-Bromo-5-methoxybenzoic acid was obtained; it melted at 158–159.5° alone or when mixed with an authentic sample.

Alkylation of 2-Carbethoxycyclohexanone and 2-Carbethoxy-4-methoxycyclohexanone.—The procedure used is a modification of that of Bardhan and Sengupta.[3] Powdered potassium (39 g.) was prepared by melting the metal under toluene (1200 ml.) and stirring vigorously. The ketoester (1.2 moles) was added slowly with stirring to the suspension which was initially at 50°. As the potassium enolate was generated the solution became thick and finally it was necessary to raise the temperature to keep the mixture fluid enough to stir. At the end of the addition the solution was at reflux temperature. When all of the potassium had dissolved the bromide (1 mole) was added in one portion and

the solution refluxed for 80 hours.[13] The reaction mixture was processed by washing with water, distilling the solvents and finally removing the unreacted starting materials by heating in an oil-bath to 180° at *ca*. 1 mm. Several of the alkylated ketoesters could be distilled in small portions without decomposition. Evaporative distillation in a modified "molecular still" was the most successful method of purification. In several alkylations considerable amounts of a polymer were formed, presumably by polymerization of a styrene generated when hydrogen bromide was eliminated from the β-arylethyl bromides. The polymer was removed by pouring the crude ketoester into warm 95% ethanol, stirring for several minutes and finally allowing the mixture to stand until the polymer had solidified and coagulated.

2-Carbethoxy-4-methoxy-2-β-phenylethylcyclohexanone was produced in 55% yield. It distilled at 181–185° at 0.3 mm., n^{16}D 1.5137.

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.01; H, 7.96. Found: C, 70.77; H, 7.87.

The 2,4-dinitrophenylhydrazone melted at 176–179° after several recrystallizations from benzene–petroleum ether.

Anal. Calcd. for $C_{24}H_{28}O_7N_4$: C, 59.48; H, 5.82. Found: C, 59.12; H, 5.68.

The pyrazolone was obtained as a mixture of the two possible racemates which melted mainly at 106–109° but a small amount of solid remained in the melt until the temperature reached 160°. An attempt to separate the mixture by chromatography on alumina was not successful.

Anal. Calcd. for $C_{18}H_{20}O_2N_2$: C, 70.56; H, 7.40. Found: C, 70.31; H, 7.28.

2-Carbethoxy-4-methoxy-2-β-(2'-bromo-5'-methoxyphenyl)-ethylcyclohexanone was obtained in 45% yield. It was evaporatively distilled at 170–178° (0.2 mm.), n^{24}D 1.5332.

Anal. Calcd. for $C_{19}H_{25}O_5Br$: C, 55.21; H, 6.10. Found: C, 55.25; H, 6.10.

The 2,4-dinitrophenylhydrazone melted mostly at 114–117° (clear at 125°).

Anal. Calcd. for $C_{25}H_{29}O_8N_4Br$: C, 50.6; H, 4.93. Found: C, 50.4; H, 4.76.

2-Carbethoxy-2-β-(2'-bromo-5'-methoxyphenyl)-ethylcyclohexanone was prepared in 75% yield (crude product). Attempted vacuum distillation resulted in decomposition (rapid drop in vacuum as temperature was raised). Small samples of the ketoester could be evaporatively distilled at 160–170° (n^{27}D 1.5352) but an analytically pure sample was not obtained by this procedure.

The 2,4-dinitrophenylhydrazone melted at 123–124°.

Anal. Calcd. for $C_{24}H_{27}O_7N_4Br$: C, 51.15; H, 4.83; N, 9.94. Found: C, 51.27; H, 4.98; N, 10.0.

2-Carbethoxy-2-β-(3'-methoxyphenyl)-ethylcyclohexanone (XIII) was obtained in 61% yield (crude). A small sample was evaporatively distilled at 150–160° (0.1 mm.), n^{25}D 1.5140, but was not obtained analytically pure.

The 2,4-dinitrophenylhydrazone melted at 120–121°.

Anal. Calcd. for $C_{24}H_{28}O_7N_4$: C, 59.48; H, 5.82. Found: C, 59.46; H, 5.84.

Addition of Methylmagnesium Iodide to the Ketoesters.—A solution of methylmagnesium iodide was prepared from magnesium (1 mole), methyl iodide (1.2 moles) and dry ether (1 liter). This solution was cooled to −10° and the ketoester (1 mole) dissolved in dry ether (250 ml.) was added during about one hour. The mixture was stirred at −10° for two additional hours and finally allowed to stand overnight. The reaction mixture was decomposed by adding excess ammonium chloride solution and separating the ether layer. The solution was washed with water, dried and the ether distilled to leave as a residue the crude tertiary alcohol.

2-Methyl-3-carbethoxy-3-β-(2'-bromo-5'-methoxyphenyl)-ethyl-1-cyclohexene (VII).—This olefin was obtained by dropping the corresponding crude tertiary alcohol (III) prepared from 232 g. of ketoester I as in the previous procedure into 85% sulfuric acid (2 liters) at 0°. The reaction mixture was stirred rapidly for 30 minutes and then poured onto

(6) W. B. Renfrow, A. Renfrow, E. Shoun and C. A. Sears, THIS JOURNAL, **73**, 317 (1951), have worked out a convenient procedure for obtaining ketones from alkylated ketoesters. This method involves ring-opening and recyclization to an unsubstituted ketoester which then can be hydrolyzed with aqueous alkali.

(7) H. Adkins and G. F. Hager, *ibid.*, **71**, 2965 (1949).

(8) W. E. Bachmann and J. Controulis, *ibid.*, **73**, 2636 (1951).

(9) Analyses by W. Manser, Zurich, Switzerland.

(10) The first preparation and permanganate oxidation of this compound in our laboratory was carried out by M. A. Manganelli.

(11) W. E. Bachmann and D. G. Thomas, THIS JOURNAL, **64**, 94 (1942).

(12) J. B. Shoesmith and R. J. Connor, *J. Chem. Soc.*, 2230 (1927), have reported the boiling point as 163–165° at 13 mm. They obtained this substance as a by-product in the reaction of phosphorus pentabromide with β-(3-methoxyphenyl)-ethanol.

(13) In experiments with β-(2-bromo-5-methoxyphenyl)-ethyl bromide the yield was nearly doubled by increasing the reflux time from 24 to 80 hours.

ice. The olefin was extracted with ether, the ether solution washed with water and sodium bicarbonate solution and concentrated. The product boiled at 170–175° at 0.03 mm., n^{22}D 1.5460. There was obtained 148 g. (64% based on ketoester).

Anal. Calcd. for $C_{19}H_{25}O_3Br$: C, 59.8; H, 6.6. Found: C, 59.77; H, 6.62.

Hydrolysis of this substance (130 g.) by boiling with potassium hydroxide (160 g.), alcohol (2400 ml.) and water (160 ml.) for 48 hours produced the corresponding acid (VIII). After recrystallization from benzene–ligroin there was obtained 104 g. (86%) of material which melted at 120–121°.

Anal. Calcd. for $C_{17}H_{21}O_3Br$: C, 57.8; H, 6.0; Br, 22.6. Found: C, 57.89; H, 6.13; Br, 22.72.

Permanganate oxidation of this acid produced 2-bromo-5-methoxybenzoic acid which melted at 158–159° alone or when mixed with an authentic sample.

2,5-Dimethoxy-8-bromo-4a-methyl-10a-carbethoxy-1,2,-3,4,4a,9,10,10a-octahydrophenanthrene (VI).—The crude tertiary alcohol IV (5 g.) was dissolved in 50 ml. of benzene and added to 90% sulfuric acid (107 g.). The reaction mixture was stirred for one hour at 0–2° and then poured onto ice. After processing and evaporatively distilling at 150–155° (0.15 mm.) there was obtained 1 g. of product, n^{22}D 1.5478.

Anal. Calcd. for $C_{20}H_{27}O_4Br$: C, 58.4; H, 6.6. Found: C, 58.62; H, 6.56.

5-Methoxy-8-bromo-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-10a-carboxylic Acid (IX).—The unsaturated acid VIII (1 g.) and benzene (3 ml.) were stirred with sulfuric acid (30 ml.) and water (4 ml.) for two hours at 25°. The reaction mixture was poured onto ice and extracted with ether. Extraction of the ether solution with 5% potassium hydroxide solution removed the acid (0.3 g.). After recrystallization from ethanol it melted at 190–191°.

Anal. Calcd. for $C_{17}H_{21}O_3Br$: C, 57.8; H, 6.0; Br, 22.6. Found: C, 57.71; H, 6.05; Br, 22.48.

From the ether solution there was obtained by evaporation a neutral product (0.4 g.) which melted at 119–120°. The melting point of a mixture of this substance (lactone X) and acid VIII (m.p. 120–121°) was 86–100°. This product slowly dissolved when heated with alcoholic aqueous potassium hydroxide. Acidification and heating of the acidic solution regenerated X.

Anal. Calcd. for $C_{17}H_{21}O_3Br$: C, 57.8; H, 6.0. Found: C, 57.57; H, 6.05.

4-Methoxyphenanthrene. A.—Acid IX was shaken with hydrogen and Raney nickel to remove the bromine atom and then dehydrogenated with palladium-on-charcoal at 270–300° for six hours. The crude dehydrogenation product was treated with picric acid in ethanol solution to yield an

orange picrate which melted at 186–187.5°[14] after recrystallization from ethanol. The melting point of a mixture of authentic 4-methoxyphenanthrene picrate[15] and that of the dehydrogenated product was also 185–187°. Also both samples when heated under the microscope sublimed (170–180°) to give the same characteristic stubby yellow-orange needles before melting.

The picrate was dissolved in ether and decomposed with dilute ammonia. The residue remaining after evaporation of the ether was recrystallized from aqueous methanol to yield 4-methoxyphenanthrene which melted at 61–63°.[16] A mixture of this sample with an authentic sample (m.p. 63–65°)[15] melted at 61.5–64°.

The trinitrobenzene adduct was prepared from both samples of 4-methoxyphenanthrene. The derivative separated readily from alcohol in long yellow needles which melted at 202–204.5° in a sealed capillary. Under the microscope it sublimed at about 150–170° and the sublimate melted at 207–209°.

Anal. Calcd. for $C_{15}H_{12}O \cdot C_6H_3O_6N_3$: C, 59.86; H, 3.59. Found: C, 59.35; H, 4.13.

B.—Ester VI could also be converted to 4-methoxyphenanthrene by first hydrolyzing it to a viscous liquid acid. This was debrominated and dehydrogenated to yield 4-methoxyphenanthrene which was identified by preparing both the trinitrobenzene and picric acid addition compounds and comparing them with authentic samples.

7-Methoxy-10a-carbethoxy-1,2,3,9,10,10a-hexahydrophenanthrene (XIV).—A mixture of crude 2-carbethoxy-2-β-(3'-methoxyphenyl)-ethylcyclohexanone (XIII) (8 g.), acetic acid (67 ml.), concd. hydrochloric acid (50 ml.) and water (16 ml.) was refluxed for one hour. On cooling a crystalline precipitate separated (6.5 g.). This substance melted at 87–88° after recrystallization from ethanol.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74; CH_3O, 21.67. Found: C, 75.01; H, 7.75; CH_3O, 21.27.

The ultraviolet absorption curve of XIV was determined in 95% ethanol solution. The following data were observed: λ_{max} 261 mμ (log ε 4.26); λ_{max} mμ (log ε 3.47); λ_{min} 233 mμ (log ε 3.67); λ_{min} 288 mμ (log ε 3.44). These maxima and minima occur at wave lengths 2–5 mμ lower and have values of ε which are practically the same as those estimated from the published curve[12] for methyl *cis*-7-methoxy-1,2,3,9,-10,10a-hexahydrophenanthrene-1,2-dicarboxylate. The most important maximum for this substance is reported to be at 264 mμ (log ε 4.28).

New Brunswick, New Jersey   Received April 30, 1951

(14) R. Pschorr and B. Jaeckel, *Ber.*, **33**, 1826 (1900), report the m.p. as 187–188°.

(15) Prepared from 4-ketotetrahydrophenanthrene by M. A. Manganelli.

(16) J. W. Krueger and E. Mosettig, *J. Org. Chem.*, **3**, 340 (1938), report that 4-methoxyphenanthrene sinters at 60° and melts at 64.5–66°; R. Pschorr and B. Jaeckel, ref. 14, give the melting point as 68°