[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Methyl Homologs of Triphenylene

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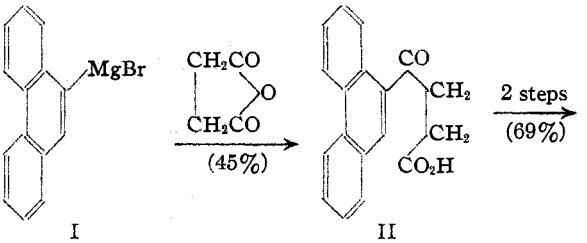
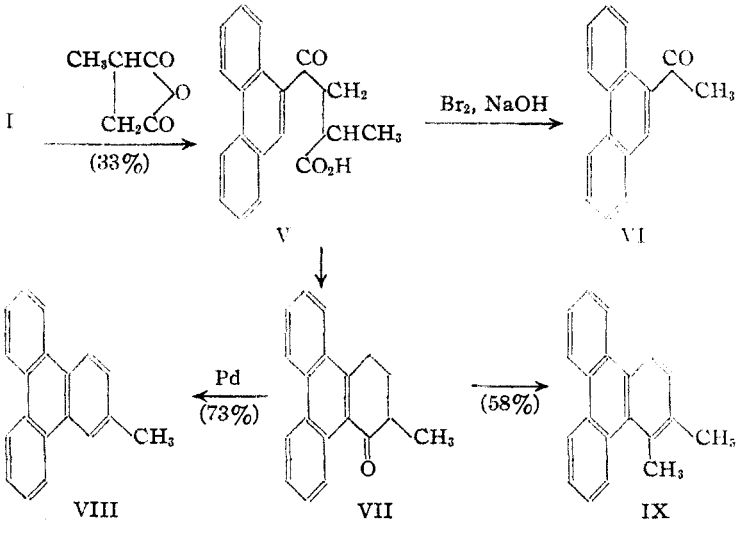
This work is an extension of investigations undertaken by the junior author in collaboration with Dr. M. S. Newman. Newman and Joshel[2] pointed out that, since the introduction of methyl groups in certain positions into the biologically



inactive 1,2-benzanthracene gives rise to powerfully carcinogenic hydrocarbons, it would be of interest to study the methyl homologs of all four of the tetracyclic aromatic hydrocarbons isomeric with 1,2-benzanthracene. The present research is devoted to a synthesis of the two monomethyl triphenylenes and of two of the fourteen possible dimethyl compounds of this series.

Since but little is known concerning the substitution reactions of triphenylene, and since the structures of homologs obtained in this way probably could be established most readily by synthesis, the choice in the present work fell on methods involving the synthetic construction of the tetracyclic system. A convenient approach to 1-methyltriphenylene (IV) already has been worked out by Bergmann and Blum-Bergmann,[3] who synthesized 1-keto-1,2,3,4-tetrahydrotriphenylene (III) by the condensation of 9-phenanthrylmagnesium bromide with succinic anhydride, reduction of the keto acid II and cyclization with phosphorus pentoxide in toluene. By introducing some modifications in these steps, for example by using anhydrous hydrogen fluoride for ring closure (87% yield), the ketone has been obtained in over-all yield of 31%. The ketone reacted readily with methylmagnesium chloride, and the crude carbinol on dehydration followed by dehydrogenation with sulfur was converted into 1-methyltriphenylene, which was purified through the picrate.

The 2-isomer was obtained in an analogous manner starting with methylsuccinic anhydride. The chief acidic product of the Grignard reaction was obtained in 33% yield and identified as having the structure V by a convenient method which was applied recently to an unmethylated product of the general succinoylation reaction.[4] The keto acid was brominated and the crude bromo derivative treated with alcoholic alkali, whereupon it underwent fission to 9-acetophenanthrene (VI). If the methyl group were in the alternate position adjacent to the carbonyl group the cleavage product would be 9-propiophenanthrene. The ketone



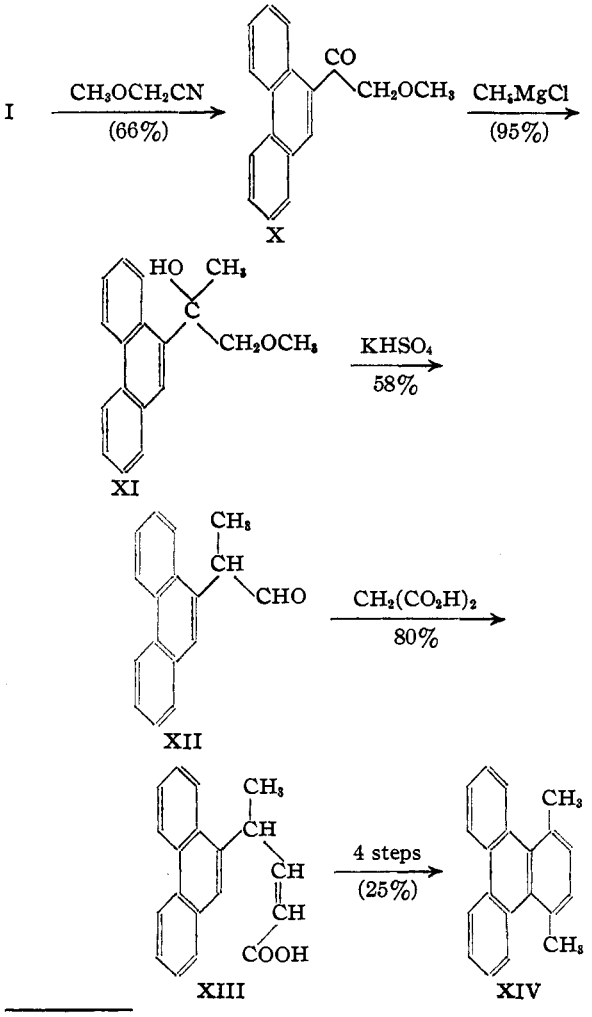
VII, obtained by reduction and cyclization with HF (92% yield), afforded 2-methyltriphenylene (VIII) by Clemmensen reduction followed by dehydrogenation with palladium charcoal. A more

(1) Fellow of the Finney-Howell Research Foundation.
(2) Newman and Joshel, THIS JOURNAL, 60, 485 (1938).
(3) Bergmann and Blum-Bergmann, *ibid.*, 59, 1441 (1937).
(4) Fieser and Hershberg, *ibid.*, 61, 1279 (1939).

novel method of accomplishing this transformation was found in heating the ketone with palladium charcoal at 310°, whereby the aromatic hydrocarbon VIII was produced in excellent yield. By the Grignard process the ketone VII was also converted into 1,2-dimethyltriphenylene (IX), which bears some structural resemblance to 1,2,3,4-dibenzphenanthrene,[5] an active agent for the production of skin tumors.

In the triphenylene series the nearest approach to a structure analogous to that of the carcinogenic 10-methyl-1,2-benzanthracene is met with in the 1-derivative, and the 1,4-dimethyl derivative (XIV) would correspond to the potent 9,10-dimethyl-1,2-benzanthracene. In one attempt to obtain this hydrocarbon we tried to add the methyl Grignard reagent to the carbonyl group of β-(9-phenanthroyl)-propionic acid or its ester, but the experiments were all unsuccessful. Trial was also made of the reaction between 9-phenanthrylmagnesium bromide and the ethyl ester of levulinic acid, in analogy with a condensation reported by Grignard,[6] but the chief product was phenanthrene. A very satisfactory route to the desired hydrocarbon was then found in the utilization of the recently described method of preparing arylacetaldehydes.[7] α-(9-Phenanthryl)-propionaldehyde (XII) was obtained readily by the sequence of Grignard reactions indicated in the chart and dehydration of the resulting carbinol XI. Condensation with malonic acid gave an acid side chain of the required length, and the second methyl group was introduced after reduction and cyclization and the remainder of the process completed by the usual methods.

Tests for carcinogenic properties are being conducted in part by Dr. M. J. Shear and in part by Dr. Shields Warren.



(5) Hewett, *J. Chem. Soc.*, 193, 1286 (1936).

Experimental Part[8]

β-(9-Phenanthroyl)-propionic acid was prepared according to Bergmann and Blum-Bergmann[3] by the action of the Grignard reagent from 81 g. of 9-bromophenanthrene on 25 g. of succinic anhydride. On decomposition with acid part of the product separated in a crystalline condition and was collected by filtration; the rest was extracted from the organic layer with soda. The yield of material of m. p. 179.5–180.5° was 45%.

Treatment of the acid with methylmagnesium chloride in refluxing benzene–ether resulted only in the production of dark oils in the neutral fraction with invariable recovery of starting material.

The **methyl ester** was prepared by adding 21 g. of acid to 500 cc. of methanol containing dissolved hydrogen chloride, refluxing the suspension for four hours, during which time the solid dissolved, distilling about half of the solvent, and adding water. It crystallized from benzene–ligroin in colorless needles, m. p. 88.6–89.4° (21.5 g., 0.6 g. of good material from the mother liquor). Bergmann and Blum-Bergmann[3] report the m. p. 88°, using diazomethane.

Condensation of the ester with methylmagnesium chloride or iodide by the procedure found satisfactory in an analogous case[9] proved unsuccessful; about half of the ester was always recovered unchanged.

γ-(9-Phenanthryl)-butyric Acid.—The keto acid (10.5 g.) was refluxed for twenty-four hours with 30 g. of amalgamated zinc, 100 cc. of toluene, and 100 cc. of concentrated hydrochloric acid, added in portions; fresh zinc and acid were added and boiling continued for another day. On cooling, the product separated in a hard cake and this was collected together with the zinc and the

(6) Grignard, *Ann. chim.*, [7] **27**, 548 (1902); *Compt. rend.*, **135**, 627 (1902).

(7) Fieser, Joshel and Seligman, THIS JOURNAL, **61**, 2134 (1939).

(8) All melting points are corrected. Microanalyses by Lyon Southworth.

(9) Fieser and Johnson, THIS JOURNAL, **61**, 1647 (1939).

reduction product extracted with acetone (very little material was found in the toluene layer), giving 6.85 g. of acid, m. p. 172.8–174°, and 1.05 g. of slightly lower m. p.; yield 79% (compare 53–56% by the Wolff–Kishner method[3]).

1-Keto-1,2,3,4-tetrahydrotriphenylene (III) was prepared by treating 2.6 g. of the above acid with 25 g. of hydrogen fluoride at 0° for forty-five minutes, pouring the mixture onto ice and extracting with ether. Extraction with soda removed a small amount of starting material, and crystallization of the neutral fraction afforded 1.6 g. of ketone, m. p. 97–99°, and 0.5 g., m. p. 95–98° (87%, compare 68% with phosphorus pentoxide[3]). The m. p. of the first crop was not changed appreciably by two recrystallizations from methanol.

1-Methyltriphenylene (IV).—A benzene solution of 5.5 g. of the ketone III was added to the Grignard reagent from 1 g. of magnesium and excess methyl chloride, and after stirring at room temperature for one-half hour, refluxing for a like period, and standing overnight the mixture was worked up as usual. The neutral portion was heated with a crystal of iodine at 200–220° for one-half hour to effect dehydration, 0.75 g. of sulfur was added, and the oil was heated at 230° for one hour and at 230–250° for one-half hour. The distilled product was treated in benzene with 5 g. of picric acid and the once recrystallized picrate dissolved in benzene and passed through a tower of alumina. The hydrocarbon was obtained from benzene–alcohol as almost colorless needles, m. p. 92–93.5°; yield 2.3 g. (42.5%). Recrystallization gave a colorless product, m. p. 93.4–94.2°.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.18; H, 5.82. Found: C, 94.19; H, 5.83.

The **picrate** crystallized from benzene as orange needles, m. p. 177.2–178.2°.

Anal. Calcd. for $C_{25}H_{17}O_7N_3$: N, 8.91. Found: N, 8.80.

α-Methyl-β-(9-phenanthroyl)-propionic Acid (V).—The Grignard reagent from 93.5 g. of 9-bromophenanthrene and 10 g. of magnesium in 250 cc. each of benzene and ether was added in the course of seventy-five minutes to a boiling solution of 37 g. of methylsuccinic anhydride in 250 cc. of ether; refluxing was continued for one-half hour and the mixture worked up the next day. Two crystallizations of the acid fraction from acetone–benzene gave 26 g. of small, colorless needles, m. p. 155–156°, and 4.8 g. of slightly lower melting material; yield 33%. The acidic material in the mother liquor was not investigated.

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.98; H, 5.75.

For proof of structure, 2.9 g. of V was treated in chloroform solution (50 cc.) with 0.5 cc. of bromine. The reaction seemed slow, but decoloration took place immediately on irradiation for a few seconds with ultraviolet light. The chloroform was evaporated and the remaining viscous oil was dissolved in 30 cc. of alcohol and treated with 5 g. of sodium hydroxide in 15 cc. of water. After twenty-four hours at room temperature the mixture was diluted with water and extracted with ether. The neutral fraction was distilled in vacuum and the 9-acetophenanthrene (0.5 g.) then crystallized from alcohol in long needles, m. p. 73–74°. Mosettig and van de Kamp[10] found the m. p. 74–74.5°; 9-propiophenanthrene[11] melts at 55–57°.

α-Methyl-γ-(9-phenanthryl)-butyric Acid.—The keto acid V (3.0 g.) was reduced by refluxing for twenty-four hours with amalgamated zinc (30 g.), toluene (40 cc.), and concentrated hydrochloric acid (100 cc.), added in portions. Crystallized from toluene–ligroin and then from benzene–ligroin the acid was obtained as colorless needles, m. p. 136.6–137.4°; yield 2.2 g. (77%).

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 81.84; H, 6.57.

2-Methyl-1-keto-1,2,3,4-tetrahydrotriphenylene (VII).—The above acid (20.7 g.) was cyclized with hydrogen fluoride (150 g.) and obtained as colorless needles, m. p. 85–86.5° (unchanged on recrystallization) from benzene–ligroin; yield 17.9 g. (92.5%).

Anal. Calcd. for $C_{19}H_{16}O$: C, 87.66; H, 6.20. Found: C, 87.69; H, 6.33.

2-Methyltriphenylene (VIII).—A mixture of 1 g. of the ketone VII and 0.1 g. of palladium charcoal was heated under nitrogen in a sealed tube at 300–310° for seven hours. The product was extracted with benzene and crystallized from benzene–alcohol, giving 0.68 g. (73%) of colorless needles, m. p. 102.6–103.6°.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.18; H, 5.82. Found: C, 94.23; H, 5.88.

The **picrate** formed light orange needles from benzene–alcohol, m. p. 192.4–193°.

Anal. Calcd. for $C_{25}H_{17}O_7N_3$: C, 8.91. Found: N, 9.09.

4′-Keto-1,2,3,4-tetrahydro-3,4-benzpyrene gave no satisfactory reaction product when similarly treated.

2-Methyl-1,2,3,4-tetrahydrotriphenylene was prepared by Clemmensen–Martin reduction of VII (3 g.) as above; it crystallized from benzene–alcohol as colorless needles, m. p. 114–116° (2.2 g., 77.5%). A recrystallized sample melted at 116.2–116.8°.

Anal. Calcd. for $C_{19}H_{18}$: C, 92.63; H, 7.37. Found: C, 92.45; H, 7.42.

A 1.6-g. portion of the tetrahydride was heated with 0.16 g. of palladium charcoal under nitrogen at 215–230° for one-half hour and the temperature was then raised to 310° in the course of one and one-half hours, when nearly the calculated amount of hydrogen had been evolved. The product crystallized from benzene–alcohol as colorless needles, m. p. 104–105°, and gave no depression with the above sample of 2-methyltriphenylene; yield 1.3 g. (83%).

1,2-Dimethyltriphenylene (IX) was prepared from 1.4 g. of the ketone VII and excess methylmagnesium chloride, refluxing for three hours in benzene–ether and using ammonium chloride for decomposition. Following the procedure of Bachmann and Wilds,[12] the crude carbinol was heated under nitrogen with 150 mg. of palladium charcoal at 290–315° for one and one-quarter hours (80% of theoretical hydrogen evolution). The hydrocarbon was extracted with benzene and crystallized from benzene–alcohol, giving 0.8 g. (58%) of colorless needles, m. p. 86.8–87.4°.

(10) Mosettig and van de Kamp, THIS JOURNAL, **55**, 3442 (1933).
(11) Bachmann and Struve, *ibid.*, **58**, 1659 (1936).
(12) Bachmann and Wilds, *ibid.*, **60**, 624 (1938).

Anal. Calcd. for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.58; H, 6.37.

The **picrate** formed orange needles, m. p. 154–155°, from benzene–alcohol.

Anal. Calcd. for $C_{26}H_{19}O_7N_3$: C, 64.33; H, 3.95. Found: C, 64.58; H, 3.97.

Methoxymethyl 9-Phenanthryl Ketone (X).—The Grignard reagent from 15.5 g. of 9-bromophenanthrene and 1.6 g. of magnesium was treated with 3.6 g. of methoxyacetonitrile in benzene and the mixture refluxed for one hour and decomposed with hydrochloric acid the next day. After steam distillation for one hour the product was taken up in ether and distilled, b. p. 220–225° (3 mm.). Two crystallizations from ether afforded 7.9 g. of colorless prisms, m. p. 67.2–68°, and 2.0 g. of material of m. p. 66.5–67.8° (66%).

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.57; H, 5.64. Found: C, 81.94; H, 5.75.

Methylmethoxymethyl-9-phenanthrylcarbinol (XI) was prepared from 7.5 g. of X, treated in benzene with a solution of methylmagnesium chloride from 1.2 g. of magnesium. After one hour at room temperature and refluxing for three hours, decomposition was accomplished with ammonium chloride. The product distilled as a yellow glass, b. p. 192–195° (1 mm.), which solidified when rubbed with petroleum ether at −70° but melted below 0°; yield 7.6 g. (95%).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.23; H, 7.23.

α-(9-Phenanthryl)-propionaldehyde (XII).—On heating 31.5 g. of the carbinol XI with 3.5 g. of potassium bisulfate at 180° in a Claisen flask a vigorous reaction ensued and was over in about five minutes. The product was then distilled in vacuum and the resulting dark oil dissolved in 100 cc. of benzene and stirred overnight with 100 cc. of saturated sodium bisulfite solution. The crystalline addition compound was collected, washed with benzene, and decomposed by shaking with aqueous sodium carbonate solution and ether. Crystallization of the aldehyde from ether–petroleum ether gave 13.9 g. of colorless needles, m. p. 65.6–67.6°, and a second crop of 2.1 g., m. p. 65–67° (58%). A recrystallized sample melted at 66.2–67.2°.

Anal. Calcd. for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.23; H, 6.08.

γ-Methyl-γ-(9-phenanthryl)-crotonic Acid (XIII).—A solution of 15.6 g. of the aldehyde in 15 cc. of pyridine was treated with 10.4 g. of malonic acid and 5 drops of piperidine; on heating on the steam-bath the mixture rapidly turned yellow and evolved carbon dioxide, and after ten hours it was poured cautiously into dilute hydrochloric acid. The precipitated reaction product was washed with dilute acid and crystallized from acetone–benzene, giving 11.8 g. of colorless plates, m. p. 172–174°, and 3 g. of slightly less pure material (80.5%). Further purification raised the m. p. to 178.8–179.4° (softening at 173°).

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.67; H, 5.91.

γ-(9-Phenanthryl)-valeric Acid.—A suspension of 11.8 g. of the unsaturated acid XIII in 150 cc. of glacial acetic acid readily absorbed the calculated amount of hydrogen in the presence of 100 mg. of Adams catalyst. The reduced acid crystallized from benzene–ligroin to give 10.4 g. (87.5%) of colorless prisms, m. p. 83–85° (unchanged by further purification).

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 81.92; H, 6.61.

4-Methyl-1-keto-1,2,3,4-tetrahydrotriphenylene was prepared by cyclizing the acid (9.9 g.) with hydrogen fluoride (150 g.) at room temperature. After two hours the solution was poured onto ice and the precipitate coagulated by heating for a few minutes and then collected. Very little acid was removed by digestion with soda, and the neutral product on crystallization from benzene–ligroin gave 6.6 g. of the ketone as colorless prisms, m. p. 99–100.5°, and 1 g., 98.6–101° (82%).

Anal. Calcd. for $C_{19}H_{16}O$: C, 87.66; H, 6.20. Found: C, 87.74; H, 6.26.

1,4-Dimethyltriphenylene (XIV) was prepared from the ketone in 35% yield by the procedure described for the 1-methyl compound. The hydrocarbon crystallized from benzene–alcohol as colorless prisms, m. p. 108.4–109.2°.

Anal.[13] Calcd. for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.62; H, 6.35.

The **picrate** crystallized from benzene in orange-red needles, m. p. 148.4–149.4°.

Anal. Calcd. for $C_{26}H_{19}O_7N_3$: N, 8.66. Found: N, 8.78.

Summary

In order to investigate the possibility that the introduction into triphenylene of suitably located alkyl groups might lead to carcinogenically active hydrocarbons, methods have been developed for the synthesis of the 1- and 2-methyl and the 1,2- and 1,4-dimethyl derivatives of this hydrocarbon. These homologs were obtained from the condensation products of 9-phenanthrylmagnesium bromide with succinic anhydride, methylsuccinic anhydride, or methoxyacetonitrile.

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(13) Analysis by Herbert S. Wight.