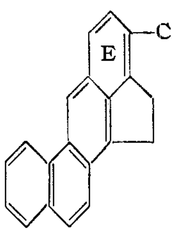
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Synthesis of 3-Alkyl-1,2-cyclopentenophenanthrenes

BY BYRON RIEGEL, SAMUEL SIEGEL[1] AND DAVID KRITCHEVSKY

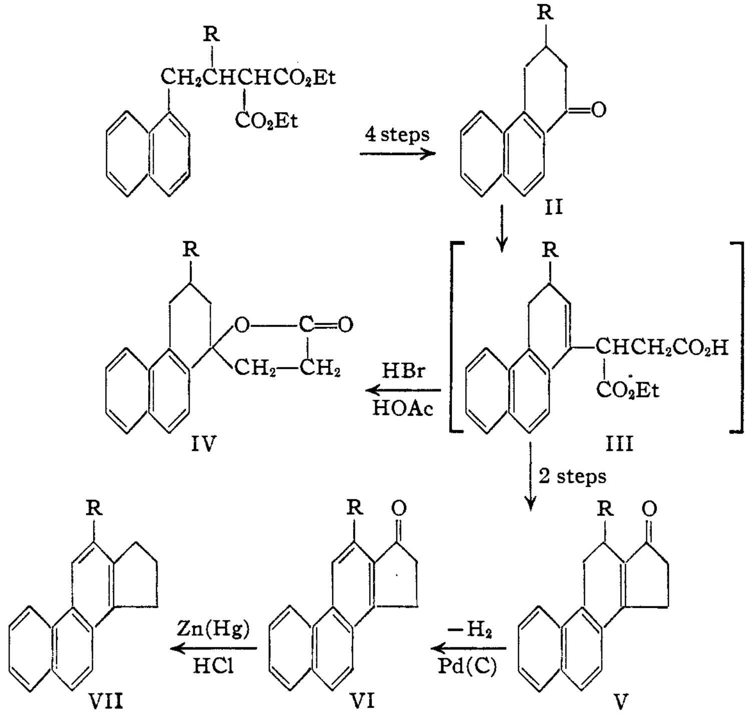
In certain carcinogenic hydrocarbons, a benzenoid ring may be replaced by two alkyl groups at the points of attachment of that ring[2] without serious diminution of potency. In methylcholanthrene (I), ring E was originally formed by cyclization of the side chain of cholanic acid to the 12-keto position. The two points of attachment of ring E in 1,2-cyclopentenophenanthrene are the 3 and 3′ positions. The preparation of compounds with alkyl groups in the 3′ position has been reported.[3] This paper describes the preparation of the 3-alkyl substituted 1,2-cyclopentenophenanthrenes, and the preparation of the 3,3′-dialkyl substituted hydrocarbons is in progress.



I

After exploring several methods for the preparation of this type of compound, the following proved to be the most convenient. The addition of 1-naphthylmethylmagnesium chloride to ethylidene-, propylidene- and isobutylidenemalonic esters[4] yielded the ethyl esters of the 2-carbethoxy-3-alkyl-4-(1-naphthyl)-butyric acids, where the alkyl group was methyl, ethyl and isopropyl, respectively. These diesters were hydrolyzed with methanolic potassium hydroxide and the resulting acids decarboxylated by heating above their melting points. The 3-alkyl-4-(1-naphthyl)-butyric acids thus obtained were cyclized with phosphorus pentachloride and stannic chloride[5] to yield the respective 1-keto-3-alkyl-1,2,3,4-tetrahydrophenanthrenes (II).

These ketones were condensed with diethyl succinate in a modified Stobbe condensation.[6] In every case the half ester (III) was obtained as an uncrystallizable oil. However, the crystalline lactones (IV) were obtained quite readily. Cyclization of the half esters yielded the desired 3′-keto-3-alkyl-4,5-dihydrocyclopentenophenanthrene (V). When these compounds were obtained as oils, chromatographic purification using alumina yielded the crystalline product. Dehydrogenation by the liquid phase method[7] over palladium-charcoal gave the 3′-keto-3-alkyl-1,2-cyclopentenophenanthrenes (VI). A Clemmensen type reduction[8] of the 3′-keto group gave the desired 3-alkyl-1,2-cyclopentenophenanthrenes (VII), where the alkyl group is ethyl, methyl and isopropyl, respectively.



R = CH_3, C_2H_5 and $i\text{-}C_3H_7$

An example of another method which proved to be almost as convenient as that described above involved the following reactions. Isobutyraldehyde was allowed to condense with diethyl β-ketoadipate[9] in the presence of piperidinium acetate and acetic acid[10] to give diethyl α-isobutylidene-β-ketoadipate (VIII). This compound upon treatment with 1-naphthylmethylmag-

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[1] Anna Fuller Fund Research Associate, 1942–1943. Present address: Department of Chemistry, Illinois Institute of Technology, Chicago 16, Illinois.

[2] W. E. Bachmann, J. W. Cook, A. Dansi, C. G. M. deWorms, G. A. D. Haslewood, C. L. Hewett and A. M. Robinson, *Proc. Roy. Soc. (London)*, **123B**, 343 (1937); M. J. Shear, *Am. J. Cancer*, **28**, 334 (1936).

[3] B. Riegel, M. H. Gold and M. A. Kubico, THIS JOURNAL, **65**, 1772 (1943).

[4] B. Riegel, S. Siegel and W. M. Lilienfeld, *ibid.*, **68**, 984 (1946).

[5] W. E. Bachmann and G. D. Cortes, *ibid.*, **65**, 1329 (1943).

[6] W. S. Johnson and J. W. Petersen, *ibid.*, **67**, 1366 (1945); W. S. Johnson, C. E. Johnson and J. W. Petersen, *ibid.*, **67**, 1360 (1945).

[7] R. P. Linstead, A. F. Millidge, S. L. S. Thomas and A. L. Walpole, *J. Chem. Soc.*, 1146 (1937).

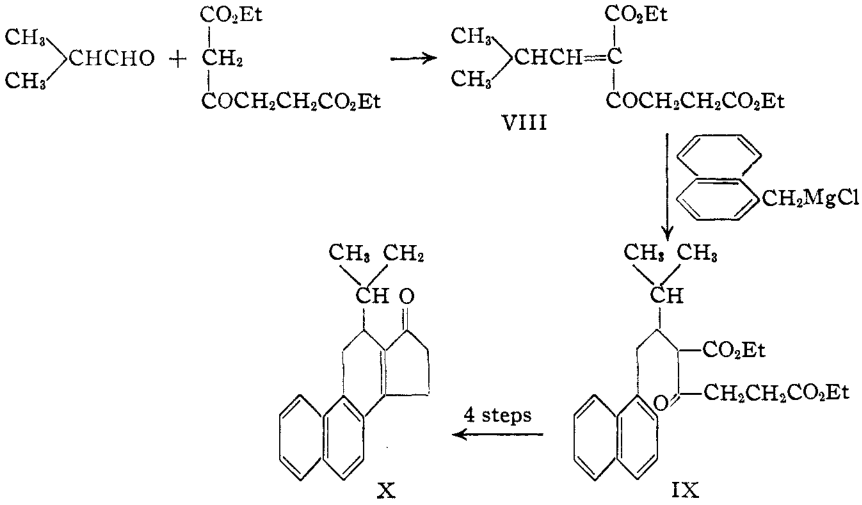
[8] E. L. Martin, THIS JOURNAL, **58**, 1438 (1936).

[9] B. Riegel and W. M. Lilienfeld, *ibid.*, **67**, 1273 (1945).

[10] A. C. Cope, C. M. Hoffman, C. Wyckoff and E. Hardenburgh, *ibid.*, **63**, 3452 (1941).

nesium or cadmium chloride gives rise to a product (IX), which contains all the skeletal elements required for the formation of 3′-keto-3-alkyl-3,4-dehydro-1,2-cyclopentenophenanthrene (X) by successive ring closures, the first acid catalyzed and the second base catalyzed.

This scheme differs from that of Bardhan[11] in the synthesis of the compound of type IX and in the acid catalyzed ring closure. Another improvement makes use of the Dieckmann condensation as described by Bachmann and co-workers[12] for the formation of the five-membered ring. Compound X was dehydrogenated and reduced as in the other preparative method described.



Attempts to synthesize 3-methyl and 3-ethyl-1,2-cyclopentenophenanthrenes *via* the reaction of the esters of α-ethylidene (or α-propylidene)-β-ketoadipic acid with 1-naphthylmethylmagnesium or cadmium chlorides were not successful. The source of the difficulty has not been established.

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Experimental[13]

1-Keto-3-alkyl-1,2,3,4-tetrahydrophenanthrenes (II).—Cyclizations of 1 mole of the appropriate 3-alkyl-4-(1-naphthyl)-butyric acids were carried out using 1.5 moles of phosphorus pentachloride and 2.2 moles of stannic chloride. Pure products were obtained by distillation at reduced pressure; yields 68–85%. The carbonyl derivatives were prepared according to standard procedures.

R	M. p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
Methyl	103–104^a	$C_{15}H_{14}O$	85.68	6.71	Not analyzed	
Ethyl	Oil^b	$C_{16}H_{16}O$	85.67^c	7.19	84.65	7.24
Isopropyl	68.5–69	$C_{17}H_{18}O$	85.68	7.61	85.95	7.86

R	Derivative	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	2,4-Dinitrophenylhydrazone	272–273	$C_{21}H_{18}N_4O_4$	14.35	13.85
Ethyl	2,4-Dinitrophenylhydrazone	245–247	$C_{22}H_{20}N_4O_4$	13.85	13.49
	Semicarbazone^d	214–215	$C_{17}H_{19}N_3O$	14.94	14.96
Isopropyl	2,4-Dinitrophenylhydrazone	247–248	$C_{23}H_{22}N_4O_4 \cdot {}^1/_2 \cdot C_2H_5OH$	12.69	12.71 12.60
	Semicarbazone	206–207	$C_{18}H_{21}N_3O$	14.23	14.05

^{a} Lit., 103–104°. ^{b} B. p. 184–187° (4 mm.), n^{20}_D 1.6250. ^{c} This material oxidized very rapidly in air. ^{d} Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.82. Found: C, 72.98; H, 6.88.

Lactone of β-(1-Hydroxy-3-alkyl-1,2,3,4-tetrahydro-1-phenanthryl)-propionic Acid (IV).—Stobbe condensation of 1 mole of 1-keto-3-alkyl-1,2,3,4-tetrahydrophenanthrenes with 1.5 moles of diethyl succinate in the presence of 1.45 moles of potassium dissolved in *t*-butyl alcohol gave the half ester as a non-crystallizable oil in every case. Average yields were 55, 48 and 60% using the methyl, ethyl and isopropyl homologs, respectively. The half ester was converted to the lactone on refluxing with a solution of 3 volumes of 48% hydrobromic acid, 2 volumes of glacial acetic acid and 1 volume of water. The lactones were obtained as needles from petroleum ether-benzene; yields 65–80%.

R	M. p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
Methyl	179–180	$C_{18}H_{18}O_2$	81.17	6.82	81.22	6.55
Ethyl^a	128.5–129	$C_{19}H_{20}O_2$	81.40	7.22	81.33	7.19
Isopropyl	119.5–120	$C_{20}H_{22}O_2$	81.60	7.53	81.83	7.55

^{a} The acid of this compound was obtained, m. p. 154–155°. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.22. Found: C, 81.31; H, 6.91.

3′-Keto-3-alkyl-3,4-dihydro-1,2-cyclopentenophenanthrene (V).—The Stobbe half ester (1 mole) was cyclized by refluxing with 22 moles of acetic anhydride and a solution of 0.28 mole of zinc chloride in glacial acetic acid (20 mg. per ml.). After the decomposition of the acetic anhydride, acidification with hydrochloric acid and distillation of volatile acids, the residue was extracted with ether to remove the zinc salts which complicate subsequent operations. The ether was evaporated and the residue heated with 100 ml. of a 5% potassium hydroxide solution for one hour at steam-bath temperatures. The product thus obtained was extracted with ether and, after drying, the ether was evaporated. The residue was dissolved in a 70:30 mixture of benzene-petroleum ether and absorbed on an alumina column. It was eluted with the same solvent. The product was present in the first 300 ml. of eluent. Products were recrystallized from benzene-methanol; yields 45–60%.

R	M. p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
Methyl	156.5–157	$C_{18}H_{16}O$	87.06	6.50	87.23	6.79
Ethyl	102–103	$C_{19}H_{18}O$	86.98	6.92	87.11	7.01
Isopropyl	115–116	$C_{20}H_{20}O$	86.91	7.30	86.88	7.67

3′-Keto-3-alkyl-1,2-cyclopentenophenanthrene (VI).—A solution of the above ketone dissolved in 30 ml. of *p*-

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[11] J. C. Bardhan, *J. Chem. Soc.*, 1848 (1936).

[12] W. E. Bachmann, W. Cole and A. L. Wilds, THIS JOURNAL, **62**, 824 (1940).

[13] All melting points on Fisher–Johns apparatus. Microanalyses performed by Margaret Ledyard, Patricia Craig, Nelda Mold, June Anderson and Margaret Hines of Northwestern University.

cymene was dehydrogenated in the presence of 0.10 g. of 5% palladium-charcoal at the boiling point of the mixture. A stream of dry carbon dioxide swept out the evolved hydrogen which was collected in a nitrometer. The dehydrogenation was completed in one hour. The yields were quantitative in all cases where pure starting products were used.

R	M. p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
Methyl	231–232	$C_{18}H_{14}O$	87.77	5.73	87.72	5.63
Ethyl[a]	206.5–207	$C_{19}H_{16}O$	87.66	6.19	87.41	6.15
Isopropyl	183.5–184	$C_{20}H_{18}O$	87.55	6.61	87.90	6.56

[a] The semicarbazone of this compound charred at 285° and did not melt even at 315°. Calcd. for $C_{20}H_{19}ON_3$: N, 13.24. Found: N, 12.80.

3-Alkyl-1,2-cyclopentenophenanthrene (VII).—The ketone was reduced by vigorous refluxing with amalgamated zinc, acetic acid, hydrochloric acid, water and toluene over a period of forty-eight hours. More concentrated hydrochloric acid was added periodically during the reaction. Products were purified by chromatography over alumina; yields 85–95%. The 2,4,7-trinitrofluorenates of these hydrocarbons were prepared after the method of Orchin and Woolfolk.[14]

R	M. p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
Methyl[15]	77.5–78	$C_{18}H_{16}$	93.06	6.94	92.69	7.18
Ethyl	64.5–65	$C_{19}H_{18}$	92.63	7.37	92.66	7.64
Isopropyl	88.5–89	$C_{20}H_{20}$	92.26	7.74	92.13	7.60

Trinitrofluorenates

R	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	196–197	$C_{31}H_{21}N_3O_7$	7.68	7.67
Ethyl	176–177	$C_{32}H_{23}N_3O_7$	7.48	7.47
Isopropyl	198–199	$C_{33}H_{25}N_3O_7$	7.30	7.08

Diethyl α-Isobutylidene-β-ketoadipate (VIII).—From 90 g. (0.42 mole) of diethyl β-ketoadipate, 37 g. (0.52 mole) of isobutyraldehyde, 7.5 ml. of acetic acid, 125 ml. of benzene and 2.5 ml. of piperidine, following the procedure of Cope and co-workers,[10] there was obtained 87 g. (74%) of material boiling at 129–140° (0.5 mm.), n^{21}D 1.4594. This was redistilled from a modified Claisen flask. An analytical sample was obtained from the middle cut, b. p. 118–120° (0.3 mm.), n^{21}D 1.4590.

Anal. Calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.21. Found: C, 62.21; H, 8.38.

Addition of 1-Naphthylmethylcadmium Chloride to Ethyl α-Isobutylidene-β-ketoadipate.—The Grignard reagent formed by reaction of 35.3 g. (0.21 mole) of 1-chloromethylnaphthalene and 15 g. (0.63 mole) of magnesium was treated with 36 g. (0.20 mole) of anhydrous cadmium chloride to give the cadmium reagent. To this was added 40 g. (0.15 mole) of ethyl α-isobutylidene-β-ketoadipate. The product (IX) was obtained as a light yellow, viscous oil, b. p. 207–217° (0.5 mm.); yield, 20.5 g. (33%).

β-(2-Carboxy-3-isopropyl-3,4-dihydro-1-phenanthryl)-propionic Acid.—To 50 ml. of concentrated sulfuric acid, stirred mechanically in a 100-ml. flask and cooled to −10°, was added a solution of the crude ester (4.0 g.) dissolved in 5 ml. of acetic acid and 5 ml. of acetic anhydride. The reaction flask was externally cooled and the rate of addition controlled so as to keep the temperature below 8°. The ester was added over a period of five minutes. The mixture was stirred five minutes longer at a temperature below 4° then poured, in a thin stream, into a mixture of ice and water. The resultant gum was quickly dissolved in ether. The ether was washed successively with water, dilute sodium bicarbonate and water. The solvent was removed in a stream of air and the residue oil hydrolyzed by heating for five hours with methanolic potassium hydroxide. The methanol was removed in a stream of air, and 50 ml. of water was added. The alkaline solution was chilled and acidified with 6 *N* hydrochloric acid. whereupon a stiff gum, which slowly hardened, precipitated. The crude acid, on drying, gave 1.7 g. of a crumbly, microcrystalline mass, m. p. 225–238°. The crude acid was wet with a few drops of acetic acid and filtered to remove most of the remaining dark impurities, leaving crystals (0.95 g., 28%), m. p. 230–245°. Repeated crystallizations from dilute ethanol yielded hard, prismatic crystals, m. p. 246–248°.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.53; H, 6.55. Found: C, 74.11; H, 7.00.

Methyl β-(2-Carbomethoxy-3-isopropyl-3,4-dihydro-1-phenanthryl)-propionate.—Esterification of β-(2-carboxy-3-isopropyl-1-phenanthryl)-propionic acid (2.6 g.) was accomplished by passing dry hydrogen chloride through a methanol solution of the acid for twenty minutes, followed by six hours of refluxing. The solution was cooled, diluted with water, and crystallization was induced. There was obtained 2.7 g. of a solid, m. p. 84–90°. The solid was dissolved in ether. The ether solution was washed with dilute aqueous ammonia and water. Evaporation of the solvent gave the desired ester; colorless needles (1.6 g.) from methanol, m. p. 94–95°.

Anal. Calcd. for $C_{23}H_{26}O_4$: C, 75.39; H, 7.15. Found: C, 75.44; H, 7.19.

Acidification of the alkaline extract gave 0.8 g. of a solid, m. p. 180–185°; colorless needles from methanol, m. p. 187–188°. This was probably **methyl β-(2-carboxy-3-isopropyl-3,4-dihydro-1-phenanthryl)-propionate.** It was converted to the dimethyl ester upon treatment with diazomethane. Of the two possible acid esters, that with the carboxyl group in the 2-position is most probable, since that is in the more hindered position.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.79; H, 7.13.

3'-Keto-3-isopropyl-3,4-dihydro-1,2-cyclopentenophenanthrene (X).—Methyl β-(2-carbomethoxy-3-isopropyl-3,4-dihydro-1-phenanthryl)-propionate (2.0 g.) was cyclized and decarbomethoxylated by heating with methanol-free sodium methoxide (1.2 g.) after the method of Bachmann, Cole and Wilds.[12] There was obtained 1.2 g. (80%) of a product, m. p. 100–105°. Sublimation at 0.2 mm. followed by four recrystallizations from methanol yielded large, flat, diamond-shaped, colorless crystals, m. p. 115–116°. The melting point of this ketone was not depressed by admixture with the ketone obtained *via* the Stobbe condensation.

Summary

1. Two convenient methods for the preparation of 3-alkyl-1,2-cyclopentenophenanthrenes have been described.

2. The synthesis involving the Stobbe reaction has been applied to the compounds in which the alkyl group is methyl, ethyl and isopropyl.

3. The synthesis involving a modified Bardhan reaction has been applied to the isopropyl homolog.

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[14] M. Orchin and E. O. Woolfolk, THIS JOURNAL, **68**, 1727 (1946).

[15] After completion of this work we found that A. Butenandt, H. Dannenberg and D. von Dresler, *Z. Naturforsch.*, **1**, 151 (1946), had prepared this compound in a different manner and had obtained white plates from ethanol, m. p. 86–87°; trinitrobenzene derivative m. p. 172–173°. Crystallization from ethanol of the sample which gave the constants reported above yielded white plates, m. p. 85–86°; trinitrobenzene derivative, m. p. 163–171°. Calcd. for $C_{24}H_{19}N_3O_6$: N, 9.44. Found: N, 9.67. Crystallization of the other hydrocarbons from ethanol gave no change in melting points.