[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

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

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In certain carcinogenic hydrocarbons, a benzenoid ring may be replaced by two alkyl groups at the points of attachment of that ring² without serious diminution of potency. In methylcholanthrene (I), ring E was originally formed by cycli-



zation 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.⁸ This paper describes the prepara-

tion of the 3-alkyl substituted 1,2-cyclopentenophenanthrenes, and the preparation of the 3,3'dialkyl substituted hydrocarbons is in progress.

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-, propylideneand isobutylidenemalonic esters⁴ yielded the ethyl esters of the 2carbethoxy-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 chloride⁵ 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

(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). 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' over palladiumcharcoal gave the 3'-keto-3-alkyl-1,2-cyclopentenophenanthrenes (VI). A Clemmensen type reduction⁸ of the 3'-keto group gave the desired 3 - alkyl - 1,2 - cyclopentenophenanthrenes (VII), where the alkyl group is ethyl, methyl and isopropyl, respectively.

An example of another method which proved to be almost as convenient as that described above involved the following reactions. Isobutyralde-



hyde was allowed to condense with diethyl β ketoadipate⁹ in the presence of piperidinium acetate and acetic acid¹⁰ to give diethyl α -isobutylidene- β -ketoadipate (VIII). This compound upon treatment with 1-naphthylmethylmag-(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-3,4dehydro-1,2-cyclopentenophenanthrene (X) by successive ring closures, the first acid catalyzed and the second base catalyzed.

This scheme differs from that of Bardhan¹¹ 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-workers¹² for the formation of the five-membered ring. Compound X was dehydrogenated and reduced



		M. p.,		Nitro	gen, %
R	Derivative	°C.	Formula	Calcd.	Found
Methyl	2,4-Dinitro- phenylhydi	272-273 azone	C21H18N4O4	14,35	13,85
Ethyl	2,4-Dinitro- phenylhydi	245-247 azone	C22H20N4O4	13.85	13.49
	Semicar- bazone ^d	214-215	C ₁₇ H ₁₉ N ₈ O	14.94	14.96
Isopropyl	2,4-Dinitro- phenylhydr	247-248 azone	C28H22N4O4 · 1/2· C2H5OH	12.69	$\frac{12.71}{12.60}$
	Semicar- bazone	206-207	$C_{18}H_{21}N_{3}O$	14.23	14,05

^a Lit., 103-104[°]. ^b B. p. 184-187[°] (4 mm.), n²⁰ D 1.6250. ^c This material oxidized very rapidly in air. ⁴ Calcd. for C₁₇H₁₉N₃O: 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, respec-tively. 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

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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Experimental¹³

1-Keto-3-alkyl-1,2,3,4-tetrahydrophenanthrenes (II). —Cyclizations of 1 mole of the appropriate 3-alkyl-4-(1naphthyl)-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.

	M. p.,		Calcd	%	Foun	d. %
R	°C.	Formula	С	H	С	Ĥ
Methyl	103-104 ^a	C15H14O	85.68	6.71	Not an	alyzed
Ethyl	Oil ^b	C16H16O	85.67°	7.19	84.65	7,24
Isopropyl	68.5 - 69	$C_{17}H_{18}O$	85.68	7.61	85.95	7.86

(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. petroleum ether-benzene; yields 65-80%.

R	M. p., °C.	Formula	Caled C	., % H	Found C	1, % 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 a	cid of this	compound	was ol	btained	l, m. p.	154-
C, 81.31;	H, 6.91.	9112002, C	, 01.10	,, /	.22. 14	Juna.

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 benzenemethanol; yields 45-60%.

R	M. p., °C.	Formula	Calcd C	l., % H	Foun	d, %
Methyl	156.5-157	C18H16O	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 pcymene 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.

	M. p.,		Calcd	1., %	Found	d, %
R	°Ĉ.	Formula	С	H	С	н
Methyl	231-232	C18H14O	87.77	5.73	87.72	5.63
Ethyl	206.5 - 207	C19H16O	87.66	6,19	87.41	6.15
Isopropyl	183.5-184	C20H18O	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

	M. p.,		Calcd	., %	Found	, %
R	°C.	Formula	С	H	С	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

			Nitrogen, %		
R	M. p., °C.	Formula	Caled.	Found	
Methyl	196-197	$C_{31}H_{21}N_{3}O_{7}$	7.68	7.67	
Ethyl	176 - 177	C32H23N3O7	7.48	7.47	
Isopropyl	198 - 199	C33H25N3O7	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 1chloromethylnaphthalene 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-isoproyl-3,4-dihydro-1-phenanthryl)propionic Acid.—To 50 ml. of concentrated sulfuric

 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

(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. $86-87^\circ$; trinitrobenzene derivative m. p. 172-173°. Crystallization from ethanol of the sample which gave the constants reported above yielded white plates, m. p. $85-86^\circ$; trinitrobenzene derivative, m. p. $163-171^\circ$. Calcd. for C₂₄H₁₉N₄O₄: N, 9.44. Found: N, 9.67. Crystallization of the other hydrocarbons from ethanol gave no change in melting points. 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 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 Nhydrochloric 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 . 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-1phenanthryl)-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; coloriess 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 C₂₂H₂₄O₄: 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 methanolfree 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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