[Contribution from the Chemistry Laboratory
of the University of Michigan]

REACTIONS OF 1,2,3,4-TETRAHYDROPHENANTHRENE AND DERIVATIVES. III. ALKYL DERIVATIVES AND ANTIMALARIALS

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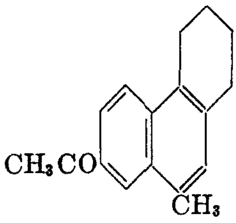
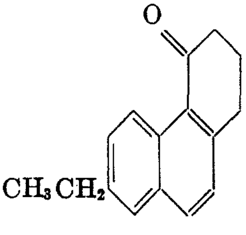
In continuing the study of 1,2,3,4-tetrahydrophenanthrene (1), 9-methyl-, 9-ethyl-, and 7-ethyl-1,2,3,4-tetrahydrophenanthrene were acetylated and succinoylated by means of the Friedel-Crafts reaction. Since tetrahydrophenanthrene acylates (1) and succinoylates (2, 3) in the 7 and 9 positions in the ratio of about 1:2 and 1:3 respectively, it was expected that the 9-alkyl derivatives would be attacked in the 7 position and the 7-alkyl compound in the 9 position. This was found to be the case.

The reaction of acetyl chloride with 9-methyl-1,2,3,4-tetrahydrophenanthrene gave 7-acetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene (I). This ketone was reduced by the Clemmensen method to 7-ethyl-9-methyl-1,2,3,4-tetrahydrophenanthrene, which was dehydrogenated by palladium on charcoal to 7-ethyl-9-methylphenanthrene. The structure of this compound was established by its synthesis from β-ethylnaphthalene. This hydrocarbon was succinoylated and the resulting β-6-ethyl-2-naphthoylpropionic acid was reduced by the Clemmensen method. Cyclization of the acid chloride of the reduced acid with stannic chloride yielded 4-keto-7-ethyl-1,2,3,4-tetrahydrophenanthrene (II), which on Clemmensen reduction gave 7-ethyl-1,2,3,4-tetrahydrophenanthrene. The hydrocarbon was identical with that obtained by Clemmensen reduction of 7-acetyl-1,2,3,4-tetrahydrophenanthrene, which is formed to some extent by acetylation of tetrahydrophenanthrene (1).



I



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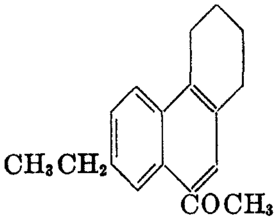

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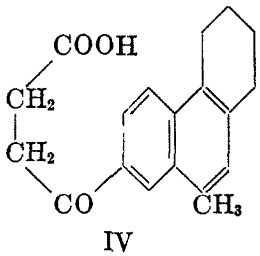

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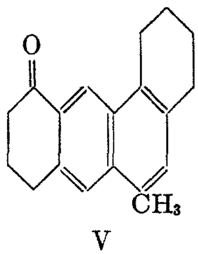

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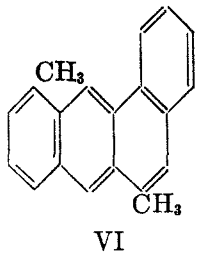

VI

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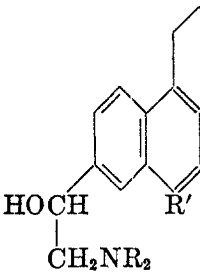

VII

Acetylation of 7-ethyl-1,2,3,4-tetrahydrophenanthrene in carbon disulfide and *sym.*-tetrachloroethane gave 7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene (III) in good yield. A Willgerodt reaction on III, followed by hydrolysis and a soda-lime fusion on the sodium salt of the resulting acid yielded 7-ethyl-9-methyl-1,2,3,4-tetrahydrophenanthrene, which was dehydrogenaged to 7-ethyl-9-methylphenanthrene.

Similarly, acetylation of 9-ethyl-1,2,3,4-tetrahydrophenanthrene gave 7-acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene, as was shown by the formation of the same hydrocarbon, 7,9-diethyl-1,2,3,4-tetrahydrophenanthrene, by Clemmensen reduction of the acetyl compound and by Clemmensen reduction of the semicarbazone of the ketone III. Of novel interest is the use of the semicarbazone in the Clemmensen reduction; it yielded the hydrocarbon in good yield. Sulfur dehydrogenation of the diethyltetrahydrophenanthrene gave 7,9-diethylphenanthrene.

Condensation of 9-methyltetrahydrophenanthrene with succinic anhydride and $AlCl_3$ gave only one product, β-9-methyl-1,2,3,4-tetrahydro-7-phenanthroylpropionic acid IV. Its structure was proved in two ways: (a) by synthesis from 7-bromoacetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene by the malonic ester synthesis; and (b) by alkali cleavage to 9-methyl-1,2,3,4-tetrahydro-7-phenanthroic acid, which was identical with the acid obtained by the haloform reaction on 7-acetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene.

Clemmensen reduction of the keto acid IV gave γ-9-methyl-1,2,3,4-tetrahydro-7-phenanthrylbutyric acid whose acid chloride was cyclized with stannic chloride to 4-methyl-8-keto-1′,2′,3′,4′,5,6,7,8-octahydro-1,2-benzanthracene (V). This result differs markedly from that obtained with the acid not bearing a methyl group in the 9-position, which cyclizes from the 7 to the 8 position with formation of a chrysene derivative (3). It is, however, in agreement with the cyclization of γ-8-methyl-2-naphthylbutyric acid (4) and of γ-5,6,7,8-tetramethyl-2-naphthylbutyric acid (5) to the 3 position rather than to the 1 position, results that have been explained on the basis of the steric effect of the methyl group. Clemmensen reduction of the cyclic ketone gave 4-methyl-1′,2′,3′,4′,5,6,7,8-octahydro-1,2-benzanthracene which was dehydrogenated by palladium on charcoal to 4-methyl-1,2-benzanthracene. Interaction of the

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4-methyl-8-ketooctahydro-1,2-benzanthracene with methylmagnesium iodide gave 8-hydroxy-4,8-dimethyl-1′,2′,3′,4′,5,6,7,8-octahydro-1,2-benzanthracene which on simultaneous dehydration and dehydrogenation with palladium-charcoal at 300–320° was converted into 4,8-dimethyl-1,2-benzanthracene (VI).

While the work on derivatives of 1,2,3,4-tetrahydrophenanthrene was in progress, the possible importance of tetrahydrophenanthrene derivatives as antimalarials became known to us through the work of the National Institute of Health group (6). By arrangement with Dr. L. F. Small a number of 7-α-hydroxy-β-dialkylaminoethyl-9-alkyl-1,2,3,4-tetrahydrophenanthrenes VII were synthesized to supplement their work. These compounds were obtained by condensing dialkyl amines with 7-bromoacetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene and then reducing the amino ketones with aluminum isopropoxide. The products, most of which are oils, are listed in Table I. The activities of the compounds are reported in a monograph of the Survey of Antimalarial Drugs (12).

EXPERIMENTAL

α-4-Methyl-1-naphthylbutyric acid. A mixture of 18.5 g. of β-4-methyl-1-naphthoylpropionic acid (6), 50 g. of amalgamated zinc, 75 cc. of concentrated hydrochloric acid, 75 cc. of acetic acid, and 50 cc. of toluene was refluxed for twenty-four hours, an additional 75 cc. of concentrated hydrochloric acid being added in portions over this time. The toluene layer was separated and evaporated. The residue crystallized from benzene in colorless needles; m.p. 158.5–159.5°; weight, 16.1 g. (93%). The melting point was unchanged after two more recrystallizations from benzene.

Anal. Calc'd for $C_{15}H_{16}O_2$: C, 79.0; H, 7.0.
Found: C, 78.6; H, 7.0.

1-Keto-9-methyl-1,2,3,4-tetrahydrophenanthrene. To a solution of 11.2 g. of the aforementioned acid in 100 cc. of dry ether and 10 drops of pyridine was added 20 cc. of thionyl chloride. After the mixture had stood at room temperature for one-half hour, the ether and thionyl chloride were evaporated under reduced pressure. To a solution of the acid chloride in 100 cc. of dry benzene cooled in ice-water, 15 cc. of stannic chloride was added with swirling. After five minutes the complex was decomposed with ice and hydrochloric acid. The benzene layer was washed with dilute ammonium hydroxide, and the benzene was evaporated. The residue crystallized from petroleum ether in colorless needles; weight, 9.64 g. (94%); m.p. 75.5–76°. After two more recrystallizations from petroleum ether the ketone melted at 76–77° [reported (7), 74–75°].

9-Methyl-1,2,3,4-tetrahydrophenanthrene. A mixture of 5.82 g. of 1-keto-9-methyl-1,2,3,4-tetrahydrophenanthrene, 30 g. of amalgamated zinc, 45 cc. of concentrated hydrochloric acid, 45 cc. of acetic acid, and 25 cc. of toluene was refluxed for twenty-four hours. An additional 45 cc. of concentrated hydrochloric acid was added in portions over this period. The toluene layer was separated, the toluene was evaporated, and the residue was distilled at 0.4 mm. The colorless distillate was dissolved in hot alcohol and 5.8 g. of picric acid was added. On cooling, the solution deposited 10 g. of picrate; yield, 85%; m.p. 114–115°. In further experiments the liquid hydrocarbon was used without purification through the picrate.

The pure *picrate* crystallized from alcohol in reddish-orange needles; m.p. 114–115.5°.

Anal. Calc'd for $C_{21}H_{19}N_3O_7$: N, 9.9. Found: N, 9.7.

A mixture of 0.42 g. of 9-methyl-1,2,3,4-tetrahydrophenanthrene and 0.04 g. of palladium-charcoal catalyst (8) was heated at 300–320° for one hour. The mixture was taken up in hot acetone and filtered. The hydrocarbon obtained by evaporation crystallized from alcohol in colorless needles; yield, 0.34 g. (83%); m.p. 91.5–92.5°. A mixture of the hydro-

TABLE I

SUBSTITUTED AMINO ALCOHOLS REPRESENTED BY FORMULA VII

SN	R′	R	DERIVATIVE ANALYZED	CRYST. FORM[a]	M.P. °C.	ANAL.					
						Calc'd			Found		
						C	H	N	C	H	N
7953-S_1	CH_3	n-C_4H_9	Picrate	Yellow platelets	170.5–171.5	62.40	6.76	9.39	62.30	6.63	9.20
7956-S_1	CH_3	n-C_5H_{11}	Picrate	Yellow prisms	140–141	63.44	7.10	8.97	63.18	7.00	9.20
7957	CH_3	iso-C_5H_{11}	Picrate	Yellow prisms	139–140	63.44	7.10	8.97	63.16	6.98	9.20
7959-S_1	CH_3	n-C_6H_{13}	Picrate	Yellow prisms	136–138	64.40	7.44	8.58	64.25	7.36	8.60
7958-S_1	CH_3	iso-C_6H_{13}	Picrate	Orange prisms	118.5–120	64.40 60.12	7.44 6.57	8.58[b] 9.85[c]	59.88	6.61	10.06
7954-S_1	CH_3	cyclohexyl	Picrate	Yellow needles	192–193	64.80	6.84	8.80	64.13	6.93	8.80
7955	CH_3	NR_2 = Tetrahydroquinoline	Free base	Colorless needles	131–132	84.05	7.87	3.77	83.57	7.99	3.82

[a] All compounds were recrystallized from ethanol.

[b] Calc'd for monopicrate.

[c] Calc'd for sesquipicrate.

carbon and authentic 9-methylphenanthrene (m.p. 90–91°) prepared from 9-phenanthrylmagnesium bromide and methyl iodide (9) melted at 90–91°.

7-Acetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene. Five grams of 9-methyltetrahydrophenanthrene was added to an ice-cold solution of 6.6 g. of aluminum chloride and 2 cc. of acetyl chloride in 20 cc. of nitrobenzene and the mixture was kept in a refrigerator for twenty hours. The nitrobenzene was removed by steam distillation from the hydrolyzed mixture, the residue was dissolved in benzene, the filtered benzene solution was evaporated, and the acetyl compound was crystallized from alcohol; weight, 4.14 g. (68%); m.p. 96–97.5°. After two recrystallizations from alcohol, the colorless prisms melted at 98–100°.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.7; H, 7.6. Found: C, 85.7; H, 7.6.

7-Ethyl-9-methyl-1,2,3,4-tetrahydrophenanthrene. A mixture of 1 g. of 7-acetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene, 10 g. of amalgamated zinc, 20 cc. of acetic acid, 12 cc. of concentrated hydrochloric acid, and 5 cc. of toluene was refluxed for twenty-four hours. An additional 30 cc. of a 1:1 mixture of acetic acid and concentrated hydrochloric acid was added in portions over this time. The toluene layer was separated, the toluene was evaporated, and the hydrocarbon was evaporatively distilled at 220° and 0.4 mm. A solution of the colorless oily distillate and 0.9 g. of picric acid in hot absolute alcohol deposited 1.55 g. of the (82%) picrate; m.p. 119–120°. For the subsequent dehydrogenation the hydrocarbon was obtained by decomposition of the picrate with dilute ammonium hydroxide.

The *picrate* crystallized from acetone-alcohol in red needles; m.p. 119.5–120°.

Anal. Calc'd for $C_{23}H_{23}N_3O_7$: N, 9.3. Found: N, 9.1.

7-Ethyl-9-methylphenanthrene. A mixture of 0.69 g. of 7-ethyl-9-methyl-1,2,3,4-tetrahydrophenanthrene and 0.08 g. of palladium-charcoal catalyst (8) was heated for one hour at 300–320°. The mixture was taken up in hot acetone and filtered. The acetone was evaporated, and the colorless oily residue was dissolved in hot alcohol and treated with 0.75 g. of picric acid. The solution deposited 1.29 g. of picrate; yield, 93%; m.p. 106–108°.

The *picrate* crystallized from alcohol-acetone in bright orange prisms; m.p. 107–108°.

Anal. Calc'd for $C_{23}H_{19}N_3O_7$: N, 9.4.
Found: N, 9.2.

β-6-Ethyl-2-naphthoylpropionic acid. β-Ethylnaphthalene was prepared by refluxing a mixture of 100 g. of β-acetylnaphthalene, 400 g. of amalgamated zinc, 600 cc. of concentrated hydrochloric acid, 600 cc. of glacial acetic acid, and 400 cc. of toluene for twenty-four hours with the addition of 600 cc. of hydrochloric acid over this time. After separation of the toluene layer, washing with water, and removal of the toluene, the β-ethylnaphthalene was distilled under reduced pressure; b.p. 100–102° at 2 mm.; yield, 78 g. (85%).

To an ice-cooled solution of 146 g. of aluminum chloride and 110 g. of succinic anhydride in 500 cc. of *sym.*-tetrachloroethane was added 78 g. of β-ethylnaphthalene dropwise with good stirring. After the addition of the hydrocarbon the mixture was stirred for an hour and a half in the ice-bath, kept in a refrigerator for twenty-four hours, and then hydrolyzed with ice and hydrochloric acid. After a recrystallization from benzene, the acid weighed 85 g. and melted at 152–155°. After two recrystallizations from acetone a sample formed colorless prisms; m.p. 171–172°.

Anal. Calc'd for $C_{16}H_{16}O_3$: C, 75.0; H, 6.3.
Found: C, 74.7; H, 6.3.

α-6-Ethyl-2-naphthylbutyric acid. A mixture of 73 g. of the aforementioned acid, 400 g. of amalgamated zinc, 600 cc. of concentrated hydrochloric acid, 600 cc. of glacial acetic acid, and 400 cc. of toluene was refluxed for twenty-four hours with the addition of 600 cc. of hydrochloric acid over this time. The warm toluene layer was separated, the aqueous layer was shaken with benzene and the combined organic solutions were concentrated; yield, 54 g. (78%); m.p. 114–118°. After two recrystallizations from benzene the nacreous leaflets melted at 120.5–121.5°.

Anal. Calc'd for $C_{16}H_{18}O_2$: C, 79.3; H, 7.5.
Found: C, 79.2; H, 7.3.

4-Keto-7-ethyl-1,2,3,4-tetrahydrophenanthrene. A mixture of 45 g. of the aforementioned butyric acid, 42.5 g. of phosphorus pentachloride, and 175 cc. of dry benzene was allowed to stand for one hour with occasional swirling, was warmed for five minutes on a steam cone, and was then cooled in ice until the benzene started to crystallize. To this solution was added rapidly 48 cc. of stannic chloride in 50 cc. of benzene, the mixture was swirled intermittently for seven minutes and was then hydrolyzed in crushed ice and concentrated hydrochloric acid. After the mixture had been washed with concentrated hydrochloric, dilute hydrochloric, water, and dilute ammonium hydroxide, the benzene was evaporated; yield of ketone, 38 g. (91%); m.p. 46–48°. A sample of the ketone formed colorless prisms after two recrystallizations from benzene-petroleum ether; m.p. 48.5–50°.

Anal. Calc'd for $C_{16}H_{16}O$: C, 85.7; H, 7.2.
Found: C, 85.6; H, 7.2.

7-Ethyl-1,2,3,4-tetrahydrophenanthrene. A mixture of 36 g. of 4-keto-7-ethyl-1,2,3,4-tetrahydrophenanthrene, 200 g. of amalgamated zinc, 300 cc. of concentrated hydrochloric acid, 300 cc. of glacial acetic acid, and 200 cc. of toluene was refluxed for twenty-four hours with the addition of 300 cc. of concentrated hydrochloric acid over this time. The product isolated from the toluene layer was distilled under reduced pressure; b.p. 140° at 0.1 mm.; yield, 33 g. (98%). The picrate was obtained as yellow needles from ethanol; m.p. 90–91°. A mixed melting point with the picrate of 7-ethyl-1,2,3,4-tetrahydrophenanthrene (1) obtained by reduction of the 7-acetyl derivative gave no depression.

7-Ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. To a mixture of 32 g. of aluminum chloride and 19 g. of acetyl chloride in 340 cc. of carbon disulfide which had been stirred at room temperature for fifteen minutes was added 230 cc. of *sym.*-tetrachloroethane and then a solution of 23.5 g. of 7-ethyl-1,2,3,4-tetrahydrophenanthrene in 40 cc. of carbon disulfide. After being stirred for half an hour at room temperature the mixture was placed in a refrigerator overnight. The product which was isolated in the usual manner was distilled under reduced pressure; b.p. 180° at 0.05 mm.; yield, 26 g. (92%). The ketone crystallized from methanol in colorless plates; yield, 21 g. (74%); m.p. 43–45°. After two more recrystallizations a sample melted at 45.5–47°.

Anal. Calc'd for $C_{18}H_{20}O$: C, 85.6; H, 8.0.
Found: C, 85.8; H, 8.0.

The *semicarbazone* after several recrystallizations from ethyl acetate formed colorless needles; m.p. 223.5–224.5° dec.

Anal. Calc'd for $C_{19}H_{23}N_3O$: N, 13.6. Found: N, 13.3.

7-Ethyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid amide. 7-Ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene (2 g.) was heated in a sealed tube at 170–175° for twenty-four hours with 10 g. of concentrated ammonium hydroxide saturated with hydrogen sulfide, 2 g. of sulfur, and 8 cc. of dioxane. The amide (0.8 g.; m.p. 188–192°) obtained by recrystallization of the crude reaction product from chlorobenzene was recrystallized twice from ethyl acetate; the colorless needles melted at 192.5–193.5°.

Anal. Calc'd for $C_{18}H_{21}NO$: C, 80.76; H, 7.92; N, 5.2.
Found: C, 80.79; H, 7.63; N, 5.1.

7-Ethyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid. A mixture of 1.3 g. of the aforementioned acid amide, 25 cc. of glacial acetic acid, 11 cc. of concentrated hydrochloric acid, and 25 cc. of water was refluxed for twenty-four hours. Dilution of the product with 50 cc. of concentrated hydrochloric acid precipitated 1.1 g. (85%) of the desired acid; m.p. 171–173°. After two recrystallizations from acetone a sample formed colorless needles; m.p. 173–174.5°.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5.
Found: C, 80.6; H, 7.5.

A mixture of the dry sodium salt from 0.16 g. of the acid and 0.5 g. of soda-lime was heated in a sublimation tube under 0.05 to 0.1 mm. pressure at 300–320° for four to five hours. A colorless oil (0.075 g.) was obtained. Since previous experiments had shown this to be a mixture containing some dehydrogenated product it was dehydrogenated directly by heating with palladium-charcoal catalyst (8) at 300–320° for one hour. After filtration of the catalyst and evaporation of the benzene, an alcoholic solution of the resulting oil with picric acid deposited 0.13 g. of bright orange prisms; m.p. 103–106°. After recrystallization from absolute alcohol the picrate melted at 108–109° alone and when mixed with a sample of the picrate of 7-ethyl-9-methylphenanthrene prepared as described previously.

7-Bromoacetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene. To an ice-cold solution of 1 g. of 7-acetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene in 40 cc. of dry ether was added a cold solution of 0.72 g. of bromine in 20 cc. of ether, and the mixture was allowed to stand in the cold for one-half hour. The precipitated bromide was filtered off and the filtrate was evaporated to obtain a second crop; total weight, 1.1 g. (83%); m.p. 120–121.5°. After two recrystallizations from acetone-methanol the colorless needles melted at 123.5–124°.

Anal. Calc'd for $C_{17}H_{17}BrO$: Br, 25.2. Found: Br, 26.0.

β-9-Methyl-1,2,3,4-tetrahydro-7-phenanthroylpropionic acid. (a) A mixture of 0.08 g. of powdered sodium, 0.75 cc. of malonic ester, and 10 cc. of benzene was refluxed until all of the sodium had reacted and then 0.59 g. of 7-bromoacetyl-9-methyltetrahydrophenanthrene was added. The mixture was allowed to stand at room temperature overnight and was then heated on a steam-bath for six hours. Dilute hydrochloric acid was added, the benzene layer was washed with water, and the benzene was evaporated. The residue was hydrolyzed with hot 40% potassium hydroxide solution, water was added to dissolve the potassium salt formed, and the solution was filtered and acidified. The precipitated acid was heated at 180° for one-half hour and the product was recrystallized from acetic acid; weight, 0.46 g. (84%); m.p. 212–215°. After two further recrystallizations from acetic acid-toluene it melted at 215.5–217°.

(b) To an ice-cold solution of 11.8 g. of aluminum chloride and 4.8 g. of succinic anhydride in 50 cc. of nitrobenzene was added 8.5 g. of 9-methyltetrahydrophenanthrene. The mixture was allowed to stand in a refrigerator for twelve hours, ice and hydrochloric acid were added to hydrolyze the complex, and the nitrobenzene layer was steam distilled. The residue was taken up in hot dilute sodium hydroxide solution and the filtered solution was acidified. The precipitated acid (12 g.; m.p. 183–193°) was recrystallized from toluene-acetic acid; weight, 7.9 g.; m.p. 211–214°. After two more recrystallizations the acid formed colorless needles; m.p. 215.5–217° alone and when mixed with the acid prepared in part (a).

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8.
Found: C, 76.9; H, 6.7.

γ-9-Methyl-1,2,3,4-tetrahydro-7-phenanthrylbutyric acid. A mixture of 3 g. of the aforementioned keto acid, 15 g. of amalgamated zinc, 23 cc. of concentrated hydrochloric acid, 23 cc. of acetic acid, and 10 cc. of toluene was refluxed for twenty-four hours, an additional 20 cc. of concentrated hydrochloric acid being added in portions over this time. The acid isolated from the toluene layer crystallized from benzene in clusters of colorless needles; weight, 2.55 g. (89%); m.p. 141–143°. After two recrystallizations from benzene the acid melted at 142.5–144°.

Anal. Calc'd for $C_{19}H_{22}O_2$: C, 80.9; H, 7.8.
Found: C, 80.7; H, 7.8.

4-Methyl-8-keto-1′,2′,3′,4′,5,6,7,8-octahydro-1,2-benzanthracene. To a mixture of 2.55 g. of the aforementioned butyric acid, 25 cc. of dry ether, and 2 drops of pyridine, was added 5 cc. of thionyl chloride. The mixture was allowed to stand at toom temperature for one-half hour after the acid had dissolved, the ether and thionyl chloride were removed under reduced pressure, and the acid chloride was dissolved in 25 cc. of dry benzene. To the cooled solution was added 4 cc. of stannic chloride, and the mixture was allowed to stand at room temperature for fifteen minutes. Ice and dilute hydrochloric acid were added to decompose the complex, the benzene layer was washed with dilute ammonium hydroxide and with water, and the benzene was evaporated. The residue crystallized from alcohol in colorless prisms; yield, 2.16 g. (91%); m.p. 109–110.5°. After two recrystallizations from alcohol the ketone melted at 111–112°.

Anal. Calc'd for $C_{19}H_{20}O$: C, 86.4; H, 7.6.
Found: C, 86.2; H, 7.6.

4-Methyl-1′,2′,3′,4′,5,6,7,8-octahydro-1,2-benzanthracene. A mixture of 1 g. of 4-methyl-8-ketooctahydro-1,2-benzanthracene, 10 g. of amalgamated zinc, 20 cc. of acetic acid, 12 cc. of concentrated hydrochloric acid, and 5 cc. of toluene was refluxed for twenty-four hours, an additional 20 cc. of a 1:1 mixture of acetic and concentrated hydrochloric acids being added in portions over this period. The product isolated from the toluene layer was evaporatively distilled at 220° and 0.4 mm. The distillate crystallized from acetone-alcohol in colorless prisms; weight, 0.74 g. (78%); m.p. 70–72°. After two recrystallizations from acetone-alcohol the hydrocarbon melted at 71–72.5°.

Anal. Calc'd for $C_{19}H_{22}$: C, 91.2; H, 8.8.
Found: C, 90.8; H, 8.6.

The *picrate* crystallized from alcohol in deep red needles; m.p. 183–184°.

Anal. Calc'd for $C_{25}H_{25}N_3O_7$: N, 8.8. Found: N, 8.7.

4-Methyl-1,2-benzanthracene. A mixture of 0.31 g. of 4-methyloctahydro-1,2-benzanthracene and 0.05 g. of palladium-charcoal catalyst (8) was heated at 300–320° for one hour. The mixture was taken up in benzene and the filtered benzene solution was evaporated. The hydrocarbon crystallized from acetone-alcohol in colorless needles; weight, 0.26 g. (87%); m.p. 122–124°. After several crystallizations from acetone-alcohol the hydrocarbon melted at 124.5–125°. The picrate melted at 149–150° and the quinone at 164–165°. These values are in agreement with those reported by Cook (10) and by Fieser and Jones (11).

4,8-Dimethyl-8-hydroxy-1′,2′,3′,4′,5,6,7,8-octahydro-1,2-benzanthracene. To an ice-cold solution of a Grignard reagent made from 1.2 cc. of methyl iodide in 15 cc. of dry ether was added a cooled solution of 1.57 g. of 4-methyl-8-ketooctahydro-1,2-benzanthracene in 15 cc. of dry benzene. After standing cold for ten hours, the solution was shaken with ice and ammonium chloride solution, the organic layer was separated, and the ether and benzene were evaporated in the cold. The residue crystallized from benzene-petroleum ether in colorless, diamond-shaped prisms; yield, 1.5 g. (87%); m.p. 131–133°. After two recrystallizations from benzene-petroleum ether the carbinol melted at 133–134°. It gives a brown color with sulfuric acid.

Anal. Calc'd for $C_{20}H_{24}O$: C, 85.7; H, 8.6.
Found: C, 85.6; H, 8.5.

4,8-Dimethyl-1,2-benzanthracene. A mixture of 0.5 g. of the aforementioned carbinol and 0.08 g. of palladium-charcoal catalyst was heated in a nitrogen atmosphere at 300–320° for one hour. The mixture was taken up in benzene, and the filtered benzene solution was evaporated. The hydrocarbon crystallized from benzene-alcohol in colorless needles; weight, 0.41 g. (90%); m.p. 142.5–144°. After two recrystallizations from benzene-alcohol the hydrocarbon melted at 144°.

Anal. Calc'd for $C_{20}H_{16}$: C, 93.8; H, 6.3.
Found: C, 93.8; H, 6.4.

The *picrate* crystallized from alcohol-acetone in deep red needles; m.p. 175–176°.

Anal. Calc'd for $C_{26}H_{19}N_3O_7$: N, 8.7. Found: N, 8.6.

9-Methyl-1,2,3,4-tetrahydro-7-phenanthroic acid. (a) A suspension of 2.18 g. of 7-acetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene in 110 cc. of 3% sodium hypochlorite solution and 2 cc. of 45% potassium hydroxide solution was refluxed for one hour. The solution was filtered, sodium bisulfite was added to destroy the remaining hypochlorite, and the solution was acidified; weight of product, 1.95 g. (89%); m.p. 264–266.5°. After two recrystallizations from acetic acid-toluene, colorless prisms were obtained; m.p. 269–270°.

(b) A mixture of 0.5 g. of β-9-methyl-1,2,3,4-tetrahydro-7-phenanthroylpropionic acid and 0.8 g. of powdered potassium hydroxide was heated over a free flame for about three minutes. Water was added and the aqueous solution was extracted with benzene and acidified; weight, 0.12 g. (30%); m.p. 230—240°. The acid was recrystallized from toluene-acetic acid, sublimed at 250° and 0.4 mm. and recrystallized again; m.p. 268–269° alone and when mixed with the acid prepared in part (a).

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 79.98; H, 6.71.
Found: C, 79.60; H, 6.80.

7-Acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene. To a well stirred, cooled solution of 97 g. of aluminum chloride and 59 g. of acetyl chloride in 1100 cc. of carbon disulfide which had been stirred for fifteen minutes at room temperature was added 700 cc. of *sym.*-tetrachloroethane followed by 68 g. of 9-ethyl-1,2,3,4-tetrahydrophenanthrene dissolved in 140 cc. of carbon disulfide. The mixture was stirred for thirty minutes in the cold and forty-five minutes at room temperature and then placed in a refrigerator overnight. The mixture was hydrolyzed, the solvent was removed, and the product was distilled under reduced pressure; b.p. 202–204° at 0.3–0.4 mm. Crystallization of the distillate from alcohol gave 63 g. (77%) of ketone; m.p. 82–83.5°. Two more recrystallizations of a sample from ethanol gave colorless needles with the melting point 82–83°.

Anal. Calc'd for $C_{18}H_{20}O$: C, 85.6; H, 8.0.
Found: C, 85.3; H, 7.9.

7,9-Diethyl-1,2,3,4-tetrahydrophenanthrene. (a) A mixture of 0.76 g. of 7-acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene, 10 g. of amalgamated zinc, 20 cc. of acetic acid, 12 cc. of concentrated hydrochloric acid, and 6 cc. of toluene was refluxed for twenty-four hours with the addition of 30 cc. of a 1:1 mixture of hydrochloric acid and acetic acid during this time. Separation of the toluene, followed by washing with water, drying, evaporation, and sublimation of the residue gave 0.68 g. (95%) of an oil. A solution of the hydrocarbon in alcohol with 0.8 g. of picric acid gave 0.9 g. of a picrate. Two recrystallizations of a sample from ethanol gave long red needles; m.p. 120.5–122°.

(b) Clemmensen reduction, using the same proportions as above, on 0.37 g. of the semicarbazone of the isomeric 7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene gave 0.25 g. of hydrocarbon sublimate which deposited 0.4 g. of a *picrate* from alcohol. Recrystallization from alcohol gave long red needles; m.p. 120.5–122° alone and when mixed with the picrate of part (a).

Anal. Calc'd for $C_{24}H_{25}N_3O_7$: C, 61.66; H, 5.39; N, 8.98.
Found: C, 61.46; H, 5.18; N, 8.77.

7,9-Diethylphenanthrene. A mixture of 0.3 g. of 7,9-diethyl-1,2,3,4-tetrahydrophenanthrene regenerated from the crude picrate and 80 mg. of sulfur was heated at 200–220° for one hour in a carbon dioxide atmosphere. Sublimation of the product gave 0.24 g. of hydrocarbon which deposited 0.26 g. of *picrate* when mixed with 0.25 g. of picric acid in alcohol; m.p. 100–103°. Two recrystallizations from ethanol gave golden needles with the m.p. 104–105°. The same results were obtained from the hydrocarbon prepared in (b) above.

Anal. Calc'd for $C_{24}H_{21}N_3O_7$: C, 62.19; H, 4.57; N, 9.06.
Found: C, 62.41; H, 4.48; N, 8.89.

7-Bromoacetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene. To a suspension of 61 g. of 7-acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene in 800 cc. of ether cooled to 5–10°, 40 g. of bromine was added dropwise at such a rate that each drop was decolorized before the next drop was added. The orange-red addition complex soon broke up to give a flocculent white precipitate of the bromo ketone. After the mixture had come to room temperature, the first crop of bromo ketone was collected and washed with ether. The ether solutions were combined and washed with dilute sodium bicarbonate and water, and the ether was removed by distillation. The total yield of the brominated product was 68 g. (85%); m.p. 90–92°. After two recrystallizations from ethanol a sample formed colorless prisms; m.p. 92–93.5°.

Anal. Calc'd for $C_{18}H_{19}BrO$: C, 65.26; H, 5.78; Br, 24.1.
Found: C, 65.31; H, 5.92; Br, 24.3.

7-α-Hydroxy-β-dibutylaminoethyl-9-methyl-1,2,3,4-tetrahydrophenanthrene. To a solution of 5.7 g. of di-*n*-butylamine[3] in 15 cc. of dry benzene at room temperature was added in portions, with stirring, 7.0 g. of 7-bromoacetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene. The mixture was warmed on a steam cone for ten minutes, cooled in refrigerator,

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[3] We are grateful to Dr. R. C. Elderfield for generous supplies of the amines and for information on the preparation of the amino alcohols.

and the precipitated dibutylamine hydrobromide filtered and washed well with cold ether. The ether-benzene solution was washed several times with water, once with 5% sodium hydroxide, and with water. Acidification of the alkaline solution gave 0.2–0.7 g. of an acid, identical with 9-methyl-1,2,3,4-tetrahydro-7-phenanthroic acid, as shown by a mixed melting point. The amount of acid seemed to depend on how long the mixture had stood before being treated with the alkali. The ether-benzene solution was dried over magnesium sulfate and was transfered to the reduction flask. The solvents were removed in a current of air, since heating caused formation of more acid. The residue was refluxed for three hours with 75 cc. of 1.5 *M* aluminum isopropoxide, the mixture was poured into 100 cc. of 10% sodium hydroxide, benzene was added, and the alkaline solution was extracted twice with portions of benzene. The benzene was washed twice with water and dried, and the solvent was removed. To the residue (4.7 g.) was added the theoretical amount (2.9 g.) of picric acid in 25 cc. of absolute alcohol. The mixture was heated on a steam-bath until a clear solution was obtained and then cooled; the alcohol was removed and the residue was triturated with ether. The crude picrate was recrystallized from absolute ethanol; yield, 6.4 g. (49%); m.p. 170–171.5°. Two recrystallizations from absolute ethanol gave yellow platelets melting at 170.5–171.5°.

This same procedure with minor modifications was used for the other amine condensations and reductions, except for the tetrahydroquinolino derivative which separated as the hydrobromide and was reduced as such.

SUMMARY

The Friedel-Crafts reaction with 9-methyl- and 9-ethyl-tetrahydrophenanthrenes gives predominantly the 7 derivative. Several 7-β-hydroxy-β-dialkylaminoethyl-9-methyl-1,2,3,4-tetrahydrophenanthrenes have been made and tested for antimalarial activity.

4-Methyl- and 4,8-dimethyl-1,2-benzanthracene have been synthesized.

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