[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

REACTIONS OF 1,2,3,4-TETRAHYDROPHENANTHRENE AND DERIVATIVES. IV. ALKYL DERIVATIVES AND ANTIMALARIAL DRUGS[1, 2]

W. E. BACHMANN AND J. R. DICE[3]

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An investigation has been made of the acetylation, succinoylation, and sulfonation of 4-methyl-1,2,3,4-tetrahydrophenanthrene. In continuation of the program on antimalarial drugs outlined previously (1, 2), some amino alcohol derivatives of 4-methyl-1,2,3,4-tetrahydrophenanthrene and some derivatives of 9-methyl-1,2,3,4-tetrahydrophenanthrene and 7-ethyl-1,2,3,4-tetrahydrophenanthrene were prepared.

Acetylation of 4-methyl-1,2,3,4-tetrahydrophenanthrene by means of a Perrier modification of the Friedel-Crafts reaction gave 4-methyl-9-acetyl-1,2,-3,4-tetrahydrophenanthrene (I). In agreement with Bachmann and Cronyn (3) this method gives only the 9 isomer, uncontaminated by any of the 7 isomer. The position of the acetyl group was proved by Clemmensen reduction to 4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene which was identical with the compound prepared by the following different method. 4-Ethyl-1-acetylnaphthalene (4) was allowed to react with methyl bromoacetate and zinc to yield the methyl ester of β-(4-ethyl-1-naphthyl)-β-hydroxybutyric acid. The hydroxy ester was converted to the chloro ester which was dehydrohalogenated and hydrolyzed with alcoholic potassium hydroxide. The resulting β-4-ethyl-1-naphthylcrotonic acid (II) was reduced to the butyric acid with 2% sodium amalgam. γ-4-Ethyl-1-naphthylvaleric acid (III) was formed by means of an Arndt-Eistert synthesis and was cyclized to 1-keto-4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene (IV) with thionyl chloride and stannic chloride. Clemmensen reduction gave 4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene identical with the hydrocarbon prepared previously. Dehydrogenation of samples with palladium-charcoal yielded 4-methyl-9-ethylphenanthrene in both cases.

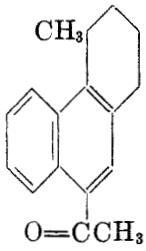
4-Methyl-1,2,3,4-tetrahydro-9-phenanthroic acid was formed by sodium hypochlorite oxidation of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. A Willgerodt reaction on the acetyl compound yielded the amide of 4-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid which was hydrolyzed to the free acid. 4-Methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene was obtained by bromination of the acetyl compound. Beckmann rearrangement of the oxime of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene gave 4-methyl-9-acetylamino-1,2,3,4-tetrahydrophenanthrene which was hydrolyzed to 4-methyl-9-amino-1,2,3,4-tetrahydrophenanthrene.

[1] The work on antimalarials was done in cooperation with the Committee on Medical Research.

[2] From the Ph.D. dissertation of J. R. Dice, 1946.

[3] Present address: The University of Texas, Austin, Texas.

Sulfonation of 4-methyl-1,2,3,4-tetrahydrophenanthrene with chlorosulfonic acid gave 4-methyl-1,2,3,4-tetrahydrophenanthrene-9-sulfonic acid. By treating an aqueous solution of the potassium salt of the acid with aqueous bromine-sodium bromide solution (5), 4-methyl-9-bromo-1,2,3,4-tetrahydrophenanthrene was formed. The position of the groups was determined by adding the



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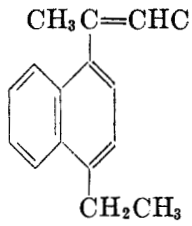

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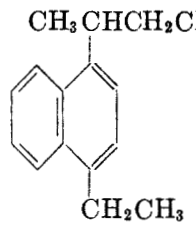

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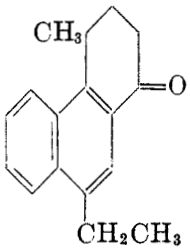

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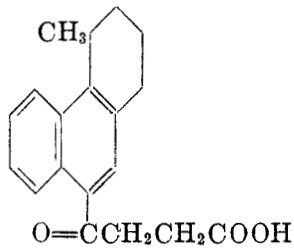

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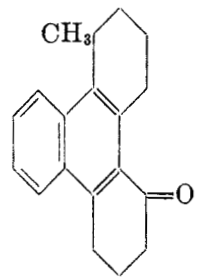

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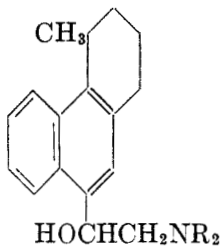

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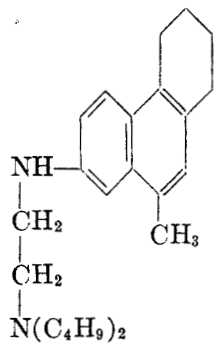

VIII

Grignard reagent prepared from the bromo compound to Dry Ice. The 4-methyl-1,2,3,4-tetrahydro-9-phenanthroic acid so obtained was identical with that prepared previously by oxidation. The homogeneity of the bromo derivative proved that sulfonation occurred only at the 9 position. Sulfonation in the 9 position is of interest since treatment of 1,2,3,4-tetrahydrophenanthrene with concentrated sulfuric acid yielded only the 7-sulfonic acid (6).

Succinoylation of 4-methyl-1,2,3,4-tetrahydrophenanthrene formed β-4-methyl-1,2,3,4-tetrahydro-9-phenanthroylpropionic acid (V) which was subjected to a Clemmensen reaction to give γ-4-methyl-1,2,3,4-tetrahydro-9-phenanthrylbutyric acid. Cyclization of the acid chloride by stannic chloride resulted in the formation of 1-methyl-5-keto-1,2,3,4,5,6,7,8-octahydrotriphenylene (VI), which was reduced to 1-methyl-1-2,3,4,5,6,7,8-octahydrotriphenylene. 1-Methyltriphenylene [identical with the material prepared by Bachmann and Struve (7) by another method] was formed by dehydrogenation with palladium-charcoal. The position at which succinoylation occurred was proved by preparing β-4-methyl-1,2,3,4-tetrahydro-9-phenanthroylpropionic acid from 4-methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene by a malonic ester synthesis.

Amino alcohol derivatives (VII) of 4-methyl-1,2,3,4-tetrahydrophenanthrene were prepared by coupling 4-methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene with a secondary amine and reducing the amino ketone with aluminum isopropoxide. 4-Methyl-9-β-di-*n*-butylamino-α-hydroxyethyl-1,2,3,4-tetrahydrophenanthrene, 4-methyl-9-β-N-piperidino-α-hydroxyethyl-1,2,3,4-tetrahydrophenanthrene, and 4-methyl-9-β-N-morpholino-α-hydroxyethyl-1,2,3,4-tetrahydrophenanthrene were prepared in this way.

Beckmann rearrangement of the oximes of 9-methyl-7-acetyl-1,2,3,4-tetrahydrophenanthrene and 7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene (1) and hydrolysis of the resulting acetylamines gave 9-methyl-7-amino-1,2,3,4-tetrahydrophenanthrene and 7-ethyl-9-amino-1,2,3,4-tetrahydrophenanthrene respectively. The 9-methyl-7-amino-1,2,3,4-tetrahydrophenanthrene was coupled with β-di-*n*-butylaminoethylbromide hydrobromide in the presence of sodium acetate and copper to yield 9-methyl-7-β-di-*n*-butylaminoethylamino-1,2,3,4-tetrahydrophenanthrene (VIII).

Complete pharmacological results are reported in the Survey of Antimalarial Drugs of the Committee on Medical Research.

Acknowledgment. We wish to thank the Abbott Laboratories for a fellowship to one of us (J. R. D.). We are grateful to Dr. R. C. Elderfield for generous gifts of amines and for information on the preparation of the amino alcohols by aluminum isopropoxide reduction.

EXPERIMENTAL[4]

4-Methyl-1,2,3,4-tetrahydrophenanthrene. 4-Methyl-1,2,3,4-tetrahydrophenanthrene (8, 9) was prepared by known methods: over-all yield from naphthalene, 60–65%. Evaporative distillation gave a colorless solid; m.p. 30–32° [reported as a colorless oil (9)]. The picrate melted at 116–117° [reported 117–119° (9)] and 4-methylphenanthrene prepared by dehydrogenation (9) melted at 52.0–52.5° [reported, 49° (8), 49–50° (9)].

Acetylation of 4-methyl-1,2,3,4-tetrahydrophenanthrene. 4-Methyl-1,2,3,4-tetrahydrophenanthrene was acetylated in 98% yield following the procedure given by Bachmann and Cronyn (3). Vacuum distillation at 0.02 mm. and 170–180° followed by several crystallizations from methanol-water yielded *4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene* as colorless, fluffy needles; m.p. 78.0–78.5°.

[4] Micro-analyses by Micro-Tech Laboratories, Skokie, Illinois.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.7; H, 7.6.
Found: C, 85.3; H, 7.7.

No 4-methyl-7-acetyl-1,2,3,4-tetrahydrophenanthrene could be isolated from the reaction mixture.

Structure proof of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene; 4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene. (a) *From 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene.* A mixture of 14 g. of amalgamated zinc, 18 ml. of hydrochloric acid, 18 ml. of glacial acetic acid, 2 g. of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene, and 15 ml. of toluene was refluxed for 24 hours with the addition of 5 ml. of hydrochloric acid every 6 hours. The toluene layer was washed with 10% hydrochloric acid, water, 10% sodium hydroxide, and water. Evaporative distillation of the solvent-free residue gave 1.6 g. (87%) of *4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene* as a colorless oil. The *trinitrobenzene derivative* formed yellow needles after three crystallizations from absolute alcohol; m.p. 97–98°.

Anal. Calc'd for $C_{23}H_{23}N_3O_6$: C, 63.2; H, 5.3; N, 9.6.
Found: C, 63.3; H, 5.2; N, 9.6.

Dehydrogenation of 240 mg. of 4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene occurred readily upon heating to 200–210° in the presence of palladium-charcoal catalyst for 30 minutes (10) to give 210 mg. (88%) of *4-methyl-9-ethylphenanthrene* as a colorless oil. The *trinitrobenzene complex* formed yellow needles after several crystallizations from absolute alcohol; m.p. 143–144°.

Anal. Calc'd for $C_{23}H_{19}N_3O_6$: C, 63.7; H, 4.4; N, 9.7.
Found: C, 64.1; H, 4.2; N, 9.5.

(b) *From 1-ethylnaphthalene.* 1-Ethyl-4-acetylnaphthalene (1.98 g.), prepared by acetylation of 1-ethylnaphthalene according to Froschl and Horlass (4), was subjected to a Reformatsky reaction following the method of Bachmann, Cole, and Wilds (11), to give 2.73 g. of crude *methyl β-hydroxy-β-4-ethyl-1-naphthylpropionate* as a slightly yellow oil. The crude material was converted to the chloro ester and the latter was dehydrohalogenated and saponified (11) to *β-4-ethyl-1-naphthylcrotonic acid*, a colorless oil. *β-4-Ethyl-1-naphthylbutyric acid* was prepared from the above acid by reduction (11) with 2% sodium amalgam and was evaporatively distilled at 0.02 mm. and 160–180°; yield 1.75 g. of a colorless oil (73% over-all from 4-ethyl-1-acetylnaphthalene). By means of an Arndt-Eistert synthesis with oxalyl chloride (12), the side chain was extended by one carbon with the formation of *γ-4-ethyl-1-naphthylvaleric acid* in 60% yield. The *anilide* formed short colorless needles and melted at 109.5–110.5° after several recrystallizations from methanol.

Anal. Calc'd for $C_{23}H_{25}NO$: N, 4.8. Found: N, 4.5.

To a cooled solution of 0.95 g. of γ-4-ethyl-1-naphthylvaleric acid in 10 ml. of dry ether and 1 drop of pyridine was added 1.5 ml. of thionyl chloride. The mixture was allowed to stand at room temperature for 30 minutes and at 35° for 10 minutes, and the solvents were removed under reduced pressure. After two portions of dry benzene were added and then removed under reduced pressure, the *γ-4-ethyl-1-naphthylvaleryl chloride* was dissolved in 10 ml. of benzene and cooled to 0°, and a solution of 1.5 ml. of stannic chloride in 10 ml. of benzene was added rapidly. After standing at 0° for 30 minutes, the mixture was poured on ice, hydrochloric acid, and ether. The water layer was extracted with benzene, and the combined organic layers were washed with 10% hydrochloric acid, water, 10% sodium hydroxide, and water. *1-Keto-4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene* was a colorless oil after evaporative distillation at 0.01 mm. and 180–200°; yield 0.69 g. (76%). Its *oxime* after several recrystallizations from methanol-ethanol with Norit formed colorless needles; m.p. 174.5–175.5°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.8.

A mixture of 240 mg. of 1-keto-4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene, 10 ml. of toluene, 1.7 g. of amalgamated zinc, 2.2 ml. of hydrochloric acid, and 2.2 ml. of glacial acetic acid was refluxed for 30 hours with the addition of 0.7-ml. portions of hydrochloric acid at approximately 6 hour intervals. The organic layer was washed with 10% hydro-

chloric acid, water, 10% sodium hydroxide, and water. Evaporative distillation yielded 210 mg. (93%) of 4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene as a colorless oil. The trinitrobenzene derivative (m.p. 97–98°) melted at 97-98° when mixed with a sample prepared by method (a). The trinitrobenzene derivative of 4-methyl-9-ethylphenanthrene synthesized from the above material melted at 143–144° and showed no depression when mixed with the material from method (a).

Reactions of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. (a) *Haloform reaction.* A solution of 2 g. of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene in 25 ml. of distilled dioxane was added to 50 ml. of sodium hypochlorite solution, prepared as described by Newman and Holmes (13), at 50–55°. After initial cooling the mixture was maintained at 60–70° with vigorous stirring for 2 hours. The cooled solution was poured on 100 ml. of hydrochloric acid, 2.0 g. sodium bisulfite, and ice. The *4-methyl-1,2,3,4-tetrahydro-9-phenanthroic acid* was collected and crystallized from acetone with Norit; m.p. 191–194°; yield, 1.9 g. (95%). After two recrystallizations from acetone and sublimation *in vacuo*, a sample melted at 202.0–202.5°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.
Found: C, 80.0; H, 6.9.

(b) *Willgerodt reaction.* Using the method of Fieser and Kilmer (14) except that the time of heating was 24 hours and the temperature 175°, 1.1 g. (50%) of *4-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid amide* (m.p. 180.0–181.5°) was obtained from 2 g. of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. After two recrystallizations from acetone and sublimation *in vacuo*, the amide was obtained as colorless needles; m.p. 186.0–186.5°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.5.

A mixture of 0.4 g. of the amide, 8.0 ml. of glacial acetic acid, 3.6 ml. of concentrated hydrochloric acid, and 0.8 ml. of water was refluxed for 24 hours. The hot solution was poured into 12 ml. of boiling hydrochloric acid. The colorless needles were treated with Norit in acetone, and sublimed *in vacuo;* m.p. 135–138°; yield, 0.32 g. (80%). A sample of *4-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid* crystallized several times from 90–100° petroleum ether and resublimed melted at 142.5–143.5°.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1.
Found: C, 80.2; H, 7.3.

(c) *Bromination.* Bromination in the manner of Bachmann and Cronyn (3) gave 14.7 g. (74%) of *4-methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene* from 15.0 g. of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. The product, a light yellow oil, was washed with 2% sodium bisulfite, 5% sodium bicarbonate, and water, and was used directly in subsequent reactions.

The *quaternary pyridine salt*, formed by adding a slight excess of pyridine and triturating with ether, was a colorless powder which was recrystallized five times from absolute alcohol with Norit; m.p. 230–231°.

Anal. Calc'd for $C_{22}H_{21}BrNO$: Br, 20.2. Found: Br, 19.5.

(d) *Oximation and rearrangement.* Following the procedure described by Bachmann and Cronyn (3), 10.0 g. of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene was converted to the oxime. A sample of *4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene oxime* which had been recrystallized several times from methanol with Norit formed colorless needles; m.p. 137–138°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.0.

The crude oxime was subjected to a Beckmann rearrangement (3). A sample of *4-methyl-9-acetylamino-1,2,3,4-tetrahydrophenanthrene* crystallized from ethanol with Norit, sublimed *in vacuo*, and recrystallized three times from methanol, formed bright, colorless leaflets; m.p. 190–191°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.3.

The acetyl amine was hydrolyzed in the manner suggested (3), and the liquid amine was extracted with benzene. The *4-methyl-9-amino-1,2,3,4-tetrahydrophenanthrene* weighed

6.0 g. (68% over-all yield from 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene) after removing the solvents, and darkened rapidly on exposure to air.

The *hydrochloride* was formed by passing dry hydrogen chloride into a benzene solution of the amine. The precipitate was recrystallized from methanol-ether, sublimed *in vacuo*, and recrystallized four times from methanol-ether as colorless needles; m.p. 259–261°.

Anal. Calc'd for $C_{15}H_{18}ClN$: N, 5.7. Found: N, 5.7.

The *picrate* crystallized from absolute alcohol in yellow needles; m.p. 203–205° dec.

Anal. Calc'd for $C_{21}H_{20}N_4O_7$: N, 12.7. Found: N, 12.3

Succinoylation of 4-methyl-1,2,3,4-tetrahydrophenanthrene. A solution of 10 g. of 4-methyl-1,2,3,4-tetrahydrophenanthrene in 30 ml. of nitrobenzene was added slowly to a mixture of 18.6 g. of anhydrous aluminum chloride and 6.0 g. of succinic anhydride in 50 ml. of nitrobenzene cooled in an ice-salt bath. The mixture was stirred at −5° for 3 hours, placed in a refrigerator for 36 hours, and was poured on ice and hydrochloric acid. The nitrobenzene was removed with steam, the precipitated acid was dissolved in hot sodium bicarbonate solution, and the solution was filtered. Acidification with hydrochloric acid reprecipitated *β-4-methyl-1,2,3,4-tetrahydro-9-phenanthroylpropionic acid* as a gum which was dissolved in toluene, treated with Norit, and used in the next reaction.

γ-4-Methyl-1,2,3,4-tetrahydro-9-phenanthrylbutyric acid. A mixture of the above crude acid, 25 ml. of toluene, 65 g. of amalgamated zinc, 80 ml. of hydrochloric acid, and 80 ml. of glacial acetic acid was refluxed for 36 hours with the addition of three 26-ml. portions of hydrochloric acid at 6 hour intervals during the first part of the reaction. After the toluene layer had been washed with 10% hydrochloric acid and water, the solvents were flash-distilled and the residue was evaporatively distilled at 0.02 mm. The butyric acid formed an almost colorless glass on cooling but could not be crystallized; yield, 12.2 g. (85% from 4-methyl-1,2,3,4-tetrahydrophenanthrene).

1-Methyl-5-keto-1,2,3,4,5,6,7,8-octahydrotriphenylene. To a solution of 5.3 g. of the above acid in 50 ml. of dry benzene was added 4.1 g. of powdered phosphorous pentachloride in portions with vigorous stirring. After 1 hour at room temperature and 5 minutes at 85°, the solution was cooled in an ice-salt bath, and 10 g. of stannic chloride in 12 ml. of dry benzene was added in one portion. The mixture was stirred at 0° for 25 minutes and was poured on ice, 10% hydrochloric acid, and ether. The aqueous layer was extracted with ether and the combined organic layers were washed with 10% hydrochloric acid, 10% sodium hydroxide, and water. The alkaline wash removed most of the color and gave a slight precipitate on acidification. The solvents were removed from the organic layer by a current of air and the residue was evaporatively distilled at 0.01 mm.; 1-methyl-5-keto-1,2,3,4,5,6,7,8-octahydrotriphenylene solidified on standing; yield, 4.49 g. A sample recrystallized five times from methanol gave colorless prisms; m.p. 130–131°.

Anal. Calc'd for $C_{19}H_{20}O$: C, 86.3; H, 7.6.
Found: C, 85.5; H, 7.5.

The *oxime* crystallized from ethanol in tiny, colorless prisms; m.p. 173–175°.

Anal. Calc'd for $C_{19}H_{21}NO$: N, 5.0. Found: N, 5.2.

1-Methyl-1,2,3,4,5,6,7,8-octahydrotriphenylene. A mixture of 1.64 g. of the ketone, 15 ml. of toluene, 20 ml. of hydrochloric acid, 20 ml. of glacial acetic acid, and 16.5 g. of amalgamated zinc was refluxed for 24 hours with the addition of 6.5 ml. of hydrochloric acid every 6 hours. The toluene layer was washed as previously described, and the residue was evaporatively distilled at 0.01 mm. The colorless distillate (1.52 g.) crystallized slowly. In some cases it was necessary to purify the product *via* the picrate in order to obtain a satisfactory solid. Several crystallizations from acetone-absolute alcohol yielded 1-methyl-1,2,3,4,5,6,7,8-octahydrotriphenylene as colorless prisms; m.p. 91–92°.

Anal. Calc'd for $C_{19}H_{22}$: C, 91.1; H, 8.9.
Found: C, 90.4; H, 8.8.

The *picrate* crystallized from absolute alcohol as orange needles; m.p. 164–165°.

Anal. Calc'd for $C_{25}H_{25}N_3O_7$: N, 8.8. Found: N, 8.4.

A sample of 105 mg. of the octahydro compound was dehydrogenated to 1-methyltri-

phenylene by the method of Bachmann and Struve (7); yield, 70 mg. (70%); m.p. 87–89°. Three recrystallizations from alcohol-acetone gave colorless needles; m.p. 93–94°. A mixture with an authentic sample (7) melted at 93–94°. The picrate melted at 176–178° alone and when mixed with an authentic sample (7).

β-4-Methyl-1,2,3,4-tetrahydro-9-phenanthroylpropionic acid. Diethyl malonate (5.1 g.) was added to the sodium ethoxide prepared from 0.54 g. of sodium, 5 ml. of absolute alcohol, and 5 ml. of benzene, and the mixture was refluxed until homogeneous. Excess solvents were removed under reduced pressure until a small amount of solid formed, and 5 g. of 4-methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene in 40 ml. of dry benzene was added with vigorous stirring. The mixture was allowed to stand for 24 hours and then refluxed for 2 hours. The solvents were removed in a current of air, and the residue was refluxed with 40 ml. of 45% potassium hydroxide and 25 ml. of alcohol for 1 hour. The solution was diluted with water and washed with ether-benzene. Acidification of the alkaline layer precipitated an oil which was extracted with two portions of ether. The ether was removed with a current of air, and the residue was heated at 170–180° for 15 minutes, with the evolution of carbon dioxide. The crude β-4-methyl-1,2,3,4-tetrahydro-9-phenanthroylpropionic acid was reduced by a Clemmensen reaction and cyclized to 1-methyl-5-keto-1,2,3,4,5,6,7,8-octahydrotriphenylene by the methods previously described; over-all yield from 4-methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene, 1.0 g. (24%); m.p. 130–131° alone and when mixed with the ketone prepared by the first method.

Sulfonation of 4-methyl-1,2,3,4-tetrahydrophenanthrene. To a stirred, ice-cold solution of 10 g. of 4-methyl-1,2,3,4-tetrahydrophenanthrene in 25 ml. of dry carbon tetrachloride was added dropwise 6.42 g. of technical chlorosulfonic acid over a period of 30 minutes. The chlorosulfonic acid was covered with a layer of carbon tetrachloride to protect it from atmospheric moisture. After an additional 30 minutes of stirring at 0°, the solution was allowed to warm to room temperature, and 25 ml. of water was added. The carbon tetrachloride layer was washed with water, and the combined aqueous layers were neutralized with 25% potassium hydroxide until just basic to litmus. On cooling, 12.8 g. of the potassium salt of *4-methyl-1,2,3,4-tetrahydrophenanthrene-9-sulfonic acid* crystallized as colorless needles. A second crop raised the yield to 14.9 g.

To a vigorously stirred solution of 5.0 g. of the above potassium salt in 100 ml. of water at 70° was added rapidly a solution of 2.91 g. of bromine and 4.3 g. of sodium bromide in 15 ml. of water at 55° (5). Excess sodium bisulfite was added after 30 seconds, and the precipitated oil was extracted with two portions of carbon tetrachloride. Removal of the solvent by a current of air yielded 2.7 g. (62%) of *4-methyl-9-bromo-1,2,3,4-tetrahydrophenanthrene* as a colorless oil which crystallized slowly on standing; m.p. 58–60°.

The product was evaporatively distilled at 0.05 mm. and 100–120°, dissolved in benzene and passed through a 4-cm. column of alumina. After removal of the solvent in a current of air, two recrystallizations from absolute alcohol-acetone gave colorless prisms; m.p. 61–62°.

Anal. Calc'd for $C_{15}H_{15}Br$: C, 65.5; H, 5.5.
Found: C, 66.0; H, 5.7.

4-Methyl-1,2,3,4-tetrahydro-9-phenanthroic acid. A mixture of 0.5 g. of 4-methyl-9-bromo-1,2,3,4-tetrahydrophenanthrene, 0.05 g. of magnesium, 10 ml. of anhydrous ether, and a small crystal of iodine was refluxed for 5 hours. A small amount of ethylmagnesium bromide was added to start the reaction. The Grignard reagent was diluted with 50 ml. of ether and added dropwise to Dry Ice. After standing 16–24 hours the mixture was poured on ice and 10% hydrochloric acid. The aqueous layer was extracted with ether, and the combined organic layers were treated with three portions of 10% sodium hydroxide. Acidification of the basic extracts gave 0.31 g. of 4-methyl-1,2,3,4-tetrahydro-9-phenanthroic acid; m.p. 195–198°. Several recrystallizations from acetone with Norit gave colorless needles; m.p. 201.5–202.5°. When mixed with a sample of the tetrahydrophenanthroic acid obtained previously it melted at 201.5–202.5°.

Synthesis of antimalarial derivatives of 4-methyl-1,2,3,4-tetrahydrophenanthrene. (a)

4-Methyl-9-β-di-n-butylamino-α-hydroxyethyl-1,2,3,4-tetrahydrophenanthrene (SN. 12740). The method outlined in the preceding paper in this series (3) was used in the following condensations. The condensation of 4.9 g. of 4-methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene with 4.0 g. of di-*n*-butylamine yielded the amino ketone, which was reduced directly to the amino alcohol with aluminum isopropoxide. Slow addition of dilute ethereal hydrochloric acid to the ether solution of the amino alcohol yielded the *hydrochloride* which formed tiny, colorless needles after four recrystallizations from acetone-ether; m.p. 197–198°.

Anal. Calc'd for $C_{25}H_{38}ClNO$: C, 74.3; H, 9.5; N, 3.5.
Found: C, 74.3; H, 9.8; N, 3.9.

(b) *4-Methyl-9-β-N-piperidino-α-hydroxyethyl-1,2,3,4-tetrahydrophenanthrene* (SN. 12129). The condensation of 4.9 g. of the bromo ketone and 2.7 g. of piperdine and reduction of the amino ketone were carried out as above. The *picrate* of the amino alcohol was prepared in absolute alcohol by adding 3.5 g. of picric acid. The solvent was removed in a current of air and the residue was triturated with ether in the cold. The crude picrate, recrystallized twice from absolute alcohol-acetone and triturated with ether, gave yellow needles; m.p. 160–162° dec.

Anal. Calc'd for $C_{28}H_{32}N_4O_8$: C, 60.9; H, 5.9; N, 10.1.
Found: C, 60.6; H, 5.9; N, 9.9.

(c) *4-Methyl-9-β-N-morpholino-α-hydroxyethyl-1,2,3,4-tetrahydrophenanthrene* (SN. 12130). The condensation of 4.9 g. of the bromo compound and 2.7 g. of morpholine, and reduction of the amino ketone were carried out as above. The yellow *picrate* melted at 180–182° dec.

Anal. Calc'd for $C_{27}H_{31}N_4O_9$: C, 58.4; H. 5.6; N. 10.1.
Found: C, 58.2; H, 5.6; N, 9.7.

Derivatives of 9-methyl-7-acetyl-1,2,3,4-tetrahydrophenanthrene. The oxime of 30 g. of 9-methyl-7-acetyl-1,2,3,4-tetrahydrophenanthrene (1) was prepared by the method of Bachmann and Cronyn (3). A sample of *9-methyl-7-acetyl-1,2,3,4-tetrahydrophenanthrene oxime* which was recrystallized four times from ethanol formed colorless leaflets; m.p. 174–175°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.0.

The oxime when subjected to a Beckmann rearrangement (3) gave *9-methyl-7-acetylamino-1,2,3,4-tetrahydrophenanthrene* as colorless leaflets after several recrystallizations from absolute alcohol; m.p. 233.5–234.5°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5. 6.

Hydrolysis of the acetylamine (3) formed a solid amine; crude yield, 15.6 g. (59% over-all from the acetyl compound); m.p. 88–91°. A sample of *9-methyl-7-amino-1,2,3,4-tetrahydrophenanthrene* recrystallized five times from ethanol gave colorless needles; m.p. 98.5–99.5°.

Anal. Calc'd for $C_{15}H_{17}N$: C, 85.3; H, 8.1; N, 6.6.
Found: C, 85.6; H, 8.2; N, 6.2.

The yellow *picrate* crystallized from absolute alcohol-ethyl acetate; m.p. 200–202° dec.

Anal. Calc'd for $C_{21}H_{20}N_4O_7$: N, 12.7. Found: N, 12.6.

The *hydrochloride* prepared by passing hydrogen chloride into a benzene solution of the amine melted at 258–260° dec. after two recrystallizations from absolute alcohol with Norit and sublimation at 0.01 mm.

Anal. Calc'd for $C_{15}H_{18}ClN$: Cl, 14.3. Found: Cl, 14.3.

9-Methyl-7-β-di-n-butylaminoethylamino-1,2,3,4-tetrahydrophenanthrene (SN. 12131). Using the method of Barnum and Hamilton (15), 5.0. g. of 9-methyl-7-amino-1,2,3,4-tetrahydrophenanthrene was coupled with 13.1 g. of β-di-*n*-butylaminoethylbromide hydrobromide, and the product was distilled several times at 0.02 mm. and 210–220°; yield of yellow oil, 2.7 g. The *oxalic acid salt* formed fine, colorless needles after several recrystallizations from absolute alcohol; m.p. 125–127°.

Anal. Calc'd for $C_{27}H_{40}N_2O_4$: C, 71.0;H, 8.8; N, 6. 1.
Found: C, 70.6; H, 8.7; N, 5.8.

Derivatives of 7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. The oximation of 14.0 g. of 7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene (3) was carried out as above. A sample of *7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene oxime* crystallized several times from methanol as fine, colorless needles; m.p. 143–144°.

Anal. Calc'd for $C_{18}H_{21}NO$: N, 5.2. Found: N, 5.2.

The crude oxime was subjected to a Beckmann rearrangement (3) to give *7-ethyl-9-acetylamino-1,2,3,4-tetrahydrophenanthrene* which was crystallized several times from ethanol as colorless needles; m.p. 219–220°.

Anal. Calc'd for $C_{18}H_{21}NO$: N, 5.2. Found: N, 5.0.

Only 2.6 g. of the *7-ethyl-9-amino-1,2,3,4-tetrahydrophenanthrene* could be isolated after hydrolysis (3). It was an unstable solid which decomposed during all attempts to purify it.

The *picrate* crystallized from absolute alcohol as greenish-yellow needles; m.p. 184–185° dec.

Anal. Calc'd for $C_{22}H_{22}N_4O_7$: N, 12.3. Found: N, 12.5.

The *hydrochloride* was prepated by dissolving the amine in an excess of boiling 2% hydrochloric acid. The hot solution was filtered through Norit and was cooled for 12 hours. The long, colorless needles were crystallized from absolute alcohol and sublimed at 110–120° and 0.01 mm. as a colorless powder; m.p. 230–232° dec.

Anal. Calc'd for $C_{16}H_{20}ClN$: Cl, 13.6. Found: Cl, 14.1.

SUMMARY

1. Several new derivatives of 4-methyl-1,2,3,4-tetrahydrophenanthrene were prepared.

2. 1-Methyltriphenylene was synthesized by a new method.

3. New compounds derived from 9-methyl-7-acetyl-1,2,3,4-tetrahydrophenanthrene and 7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene are described.

4. Some compounds with antimalarial properties were prepared from the parent compounds.

ANN ARBOR, MICH.

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