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

REACTIONS OF 1,2,3,4-TETRAHYDROPHENANTHRENE AND DERIVATIVES. VI. COMPOUNDS DERIVED FROM 1-METHYLTETRAHYDROPHENANTHRENE

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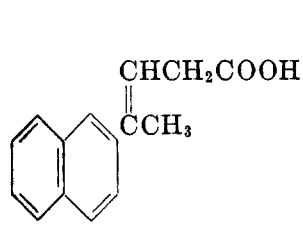
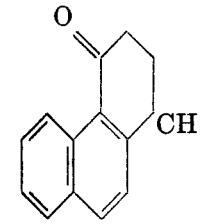
In continuation of the work on the reactions of 1,2,3,4-tetrahydrophenanthrene and its derivatives (1), 1-methyl-1,2,3,4-tetrahydrophenanthrene (III, R = H) and 1-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene (III, R = CH_2CH_3) have been prepared and subjected to Friedel-Crafts condensations with acetyl chloride. 1-Methyl-1,2,3,4-tetrahydrophenanthrene was prepared by two methods, which utilized both isomeric naphthoylpropionic acids formed on succinoylation of naphthalene. In one, 1-methyl-3,4-dihydrophenanthrene, which can be prepared in quantitative yield by acetic anhydride dehydration of the carbinol formed from 1-keto-1,2,3,4-tetrahydrophenanthrene by the Grignard reaction (2), was hydrogenated in the presence of Adams' catalyst to the tetrahydro compound. In the second method 4-(2-naphthyl)-3-pentenoic acid (I), prepared from methyl β-(2-naphthoyl)propionate and methylmagnesium iodide (3), was reduced catalytically to γ-(2-naphthyl)valeric acid. Cyclization of the acid chloride by anhydrous stannic chloride yielded 1-methyl-4-keto-1,2,3,4-tetrahydrophenanthrene (II), which was reduced by the Clemmensen method to 1-methyl-1,2,3,4-tetrahydrophenanthrene. The hydrocarbon has now been obtained in crystalline form, and the picrate derivative has been prepared. Palladium dehydrogenation of a sample of the hydrocarbon proceeded without migration of the methyl group and yielded 1-methylphenanthrene.



I



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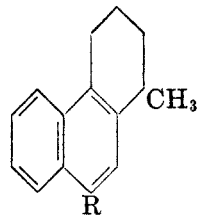
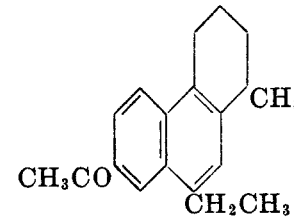


III



IV

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Acetylation of 1-methyl-1,2,3,4-tetrahydrophenanthrene in a carbon disulfide—*sym*-tetrachloroethane solution of acetyl chloride and aluminum chloride gave 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene (III, R = $COCH_3$) in high yield. In agreement with the results of Bachmann and Cronyn (4) on the parent hydrocarbon, only the 9-isomer was formed by this procedure. That the acetyl group was located in the 9-position was established by Clemmensen reduction of the ketone to 1-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene, which was dehydrorgenated by palladium on charcoal to 1-methyl-9-ethylphenanthrene. The latter hydrocarbon was found to be identical with that prepared from the known 1-keto-9-ethyl-1,2,3,4-tetrahydrophenanthrene (5) by reaction with methylmagnesium iodide, followed by dehydration and dehydrogenation of the carbinol with palladium.

By oxidation of 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene with sodium hypochlorite 1-methyl-1,2,3,4-tetrahydrophenanthrene-9-carboxylic acid (III, R = COOH) was produced. By the Willgerodt reaction with ammonium polysulfide the acetyl compound was converted into 1-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetamide, which was hydrolyzed to the corresponding acid. Decarboxylation and dehydrogenation of the substituted acetic acid yielded 1,9-dimethylphenanthrene. Beckmann rearrangement of the oxime of the acetyl compound gave the 9-acetylamino compound, which was hydrolyzed to 1-methyl-9-amino-1,2,3,4-tetrahydrophenanthrene.

Acetylation of 1-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene gave a crystalline ketone in good yield. Although the position of the acetyl group was not proved, by analogy with the acetylation of 9-ethyl-1,2,3,4-tetrahydrophenanthrene (6) the ketone is undoubtedly 1-methyl-7-acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene (IV).

The antimalarial activities of a number of compounds which were prepared from the two acetyl derivatives are reported in the survey of antimalarial drugs of the Committee on Medical Research (7).

EXPERIMENTAL

1-Methyl-1,2,3,4-tetrahydrophenanthrene. (*a*) *From 1-keto-1,2,3,4-tetrahydrophenanthrene.* A solution of 60 g. of the ketone (m.p. 95–96°) in 300 cc. of dry benzene was added with stirring to the Grignard reagent which had been prepared from 45 cc. of methyl iodide, 15 g. of magnesium, and 600 cc. of ether; throughout the addition the temperature was kept at 0°. After having been stirred for 36 hours at 0–10° the mixture was added slowly to a vigorously stirred (to prevent local superheating which causes a decrease in the yield of carbinol) mixture of ice and ammonium chloride solution. The 1-methyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrene, which was obtained by evaporation of the solution at room temperature, crystallized from benzene-ligroin in clusters of colorless needles; yield, 58.7 g. (90%); m.p. 84–86° [reported (2), 86–86.5°].

A solution of 60 g. of the carbinol in 400 cc. of acetic anhydride was heated on a steam-cone for 45 minutes and poured while hot into 1600 cc. of cold water. The colorless precipitate of the unsaturated hydrocarbon, which remained after the cooled mixture had been stirred until the acetic anhydride was hydrolyzed, was washed repeatedly with a dilute acetone-water solution until the filtrate was neutral to litmus; yield, 55 g.; m.p. 81–83.5°. After one recrystallization from methanol, the 1-methyl-3,4-dihydrophenanthrene formed colorless nacreous platelets; m.p. 85.5–86.5° [reported (2) 86–86.5°].

Five 10-g. portions of the crude unsaturated hydrocarbon, each with 0.1 g. of Adams' catalyst in 125 cc. of acetic acid, were shaken with hydrogen at 25 pounds pressure for 4–7 hours. The combined filtered solutions were diluted with water, and the product, which was extracted with benzene, was distilled at 130–133°/0.05 mm. The *1-methyl-1,2,3,4-tetrahydrophenanthrene* gradually crystallized in a refrigerator; m.p. 28-29°. The *picrate* crystallized from absolute alcohol in yellow needles; m.p. 100.5–101.5°.

Anal. Calc'd for $C_{21}H_{19}N_3O_7$: N, 9.9. Found: N, 9.8.

A mixture of 0.42 g. of 1-methyl-1,2,3,4-tetrahydrophenanthrene and 0.05 g. of palladium-charcoal catalyst was heated at 300–320° in a nitrogen atmosphere for 45 minutes. From a solution of the product in hot alcohol 1-methylphenanthrene crystallized in colorless leaflets; yield 0.31 g. (75%); m.p. 119.5–120.5° [reported (2) 120–121°].

(*b*). *From 1-methyl-4-keto-1,2,3,4-tetrahydrophenanthrene.* Refluxing a mixture of 45 g. of β-2-naphthoylpropionic acid, 150 cc. of methanol, and 4.5 cc. of sulfuric acid for 12 hours yielded 45.6 g. (96%) of the methyl ester; m.p. 74–77°. Following Robinson and Slater (3) and Kloetzel (8) for a similar reaction 18.4 g. of crude 4-(β-naphthyl)-3-pentenoic acid (m.p. 124–126°) was obtained from 30 g. of methyl β-2-naphthoylpropionate in 100 cc. of benzene and methylmagnesium iodide (from 4.2 g. of magnesium and 11 cc. of methyl iodide in 80 cc. of ether); after the addition of water and dilute hydrochloric acid the acid was extracted from the organic layer with aqueous sodium carbonate; 3.8 g. of unchanged methyl ester was recovered from the organic layer. After one recrystallization from dilute acetic acid, the compound formed colorless platelets, m.p. 133–135°. Two further recrystallizations from chloroform raised the melting point to 139–140.5° [reported (3) 141–142°].

A solution of 7.1 g. of 4-(β-naphthyl)-3-pentenoic acid (m.p. 133–135°) in 150 cc. of glacial acetic acid and 0.1 g. of Adams' catalyst was shaken with hydrogen for seven hours at 25 pounds pressure. The reaction mixture was diluted with water and the product was distilled at 0.05 mm. A solution of the distillate in hot 30–60° petroleum ether deposited 6.1 g. (85%) of *4-(β-naphthyl)valeric acid* as colorless prisms on cooling; m.p. 69.5–70.5°. Two recrystallizations from ether-petroleum ether gave m.p. 70–70.5°.

Anal. Calc'd for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1.
Found: C, 78.4; H, 7.9.

To a stirred solution of 5 g. of the substituted valeric acid in 20 cc. of benzene, 4.8 g. of pulverized phosphorus pentachloride was added portionwise. Stirring was continued for one hour at room temperature and for five minutes on a steam-cone. To the mixture which was chilled to 0°, a solution of 5 cc. of stannic chloride in 5 cc. of dry benzene was added rapidly; stirring was continued for 15 minutes. Evaporative distillation under reduced pressure of the product obtained on hydrolysis gave 4 g. of 1-methyl-4-keto-tetrahydrophenanthrene as a liquid. The *semicarbazone* crystallized from absolute alcohol in colorless needles; m.p. 206.5–207.5°.

Anal. Calc'd for $C_{16}H_{17}N_3O$: C, 71.9; H, 6.4.
Found: C, 72.6; H, 6.3.

To 20 g. of amalgamated zinc covered with a mixture of 25 cc. each of glacial acetic acid and concentrated hydrochloric acid was added 3 g. of the above ketone dissolved in 15 cc. of toluene. The mixture was refluxed for 24 hours, during which time 25 cc. of concentrated hydrochloric acid was added in portions. The 1-methyl-1,2,3,4-tetrahydrophenanthrene (2.4 g.) after purification by evaporative distillation formed a picrate which melted at 100–101° alone and when mixed with the picrate prepared in (a).

Acetylation of 1-methyl-1,2,3,4-tetrahydrophenanthrene. Following the procedure of Bachmann and Cronyn (4), a clear solution of the acetylating agent and catalyst was prepared by stirring a mixture of 32.3 g. of aluminum chloride, 350 cc. of carbon disulfide and 17.2 cc. of acetyl chloride for 15 minutes, then adding 250 cc. of *sym*-tetrachloroethane and stirring for half an hour with slight warming. To the stirred and chilled (0°) solution 21.6 g. of 1-methyl-1,2,3,4-tetrahydrophenanthrene in 40 cc. of carbon disulfide was added dropwise; stirring was continued for 15 minutes at 0° and for one-half hour at room temperature, and finally the mixture was kept in a refrigerator for 16 hours. The crystalline

complex which had precipitated was washed with carbon disulfide and hydrolyzed with ice and hydrochloric acid. The filtrate was hydrolyzed separately. The ketone after distillation at 173–175° and 0.1 mm. solidified after several days in a refrigerator; m.p. 23–25°; yield, 15.7 g. (from the solid complex) + 8.2 g. (from the filtrate) (91%). When the *1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene* was regenerated from its picrate, a higher-melting polymorphic form was obtained, which crystallized from methanol in colorless needles; m.p. 41–42°. The liquid ketone originally obtained on distillation crystallized in the higher-melting form when seeded with crystals of the latter.

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

Found: C, 85.6; H, 7.9.

Proof of structure of 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. 1-Methyl-9-ethylphenanthrene. (*a*) *From the acetyl compound.* To 220 g. of amalgamated zinc and 300 cc. each of concentrated hydrochloric acid and glacial acetic acid was added a solution of 36.5 g. of 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene in 200 cc. of toluene. The mixture was refluxed for 30 hours, during which time an additional 300 cc. of hydrochloric acid was added in portions. The organic layer was washed with dilute hydrochloric acid, water, and sodium bicarbonate. Distillation of the product at 125–127°/0.01–0.05 mm. gave 32.7 g. of 1-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene as a colorless liquid (*trinitrobenzene complex*, orange needles; m.p. 106.5–107°).

Heating 0.79 g. of the hydrocarbon with 0.05 g. of palladium-charcoal catalyst at 300–320° in a nitrogen atmosphere for one-half hour gave *1-methyl-9-ethylphenanthrene*, which crystallized from acetone-methanol solution in fine colorless needles; yield, 0.54 g. (70%); m.p. 69.5–70.5°. Two more recrystallizations raised the melting point to 70.5–71°.

Anal. Calc'd for $C_{17}H_{16}$: C, 92.7; H, 7.4.

Found: C, 92.8; H, 7.3.

The *picrate* formed orange-yellow needles from absolute alcohol; m.p. 132.5–133°.

Anal. Calc'd for $C_{23}H_{19}N_3O_7$: N, 9.3. Found: N, 9.2.

(*b*) *From 1-keto-9-ethyl-1,2,3,4-tetrahydrophenanthrene.* A solution of 0.19 g. of 1-keto-9-ethyl-1,2,3,4-tetrahydrophenanthrene (5) in 10 cc. of benzene was added dropwise with swirling to the Grignard reagent made from 0.39 g. of magnesium and 1.16 cc. of methyl iodide in 20 cc. of dry ether. The solution was kept at 0° throughout the addition of the ketone and then in a refrigerator for 48 hours. The product obtained on hydrolysis with ice-cold ammonium chloride solution was heated with 40 mg. of palladium-charcoal catalyst at 300–315° in a nitrogen atmosphere for one-half hour. The 1-methyl-9-ethylphenanthrene and its picrate proved to be identical with the compounds prepared in (a).

Reactions of 1-Methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. (*a*) *Haloform reaction.* A mixture of 2 g. of 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene, 50 cc. of sodium hypochlorite solution prepared according to Newman and Holmes (9), and 25 cc. of dioxane was stirred for two hours at 60–65°. The cooled solution was poured slowly into a mixture of hydrochloric acid, sodium bisulfite, and ice; yield of colorless acid, 1.94 g. (96%); m.p. 168–170.5°. Recrystallized once from dilute acetic acid and twice more from ethyl acetate, a sample of *1-methyl-1,2,3,4-tetrahydrophenanthrene-9-carboxylic acid* formed colorless plates; m.p. 173.5–174.5°.

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

Found: C, 79.5; H, 6.7.

(*b*) *Willgerodt reaction.* By the method of Fieser and Kilmer (10), except that the mixture was heated for 48 hours at 170°, 1.55 g. (54%) of *1-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetamide* was obtained from 2.68 g. of 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene; m.p. 173–174.5°. Recrystallized twice from acetone, a sample formed colorless needles; m.p. 175–176°.

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

A solution of 1 g. of the amide in 20 cc. of acetic acid and 10 cc. of hydrochloric acid was refluxed for 24 hours. After the addition of 50 cc. of concentrated hydrochloric acid the

mixture was cooled; yield of *1-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid* as colorless needles, 0.94 g. (93%); m.p. 160–161.5°. A sample formed colorless needles when recrystallized twice from ethyl acetate; m.p. 165.5–166.5°.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1.
Found: C, 80.6; H, 7.2.

A solution of 0.51 g. of crude 1-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid in 10 cc. of methanol was treated with an equivalent of methanolic sodium methoxide, the solvent was removed, and the salt was triturated with ether and filtered. A mixture of the dry salt and 2 g. of soda-lime was heated for four hours at 300–340°/0.01–0.05 mm. in a subliming-tube and the distillate was heated with palladium-charcoal at 310° for 45 minutes. The picrate of the resulting 1,9-dimethylphenanthrene formed orange needles after two recrystallizations from ethanol; m.p. 160–160.5°. Regenerated from the picrate and recrystallized from methanol, the hydrocarbon formed colorless needles; m.p. 86–87° [reported (11) 163.5° and 88° respectively].

(*c*) *Oximation and rearrangement.* A quantitative yield of the oxime was obtained by refluxing 29.1 g. of 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene, 20.5 g. of hydroxylamine hydrochloride, 100 cc. of absolute ethanol, and 35 cc. of pyridine for four hours. Recrystallized three times from ether-petroleum ether, a sample of *1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene oxime* formed colorless prisms; m.p. 129.5–131.5°.

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

A Beckmann rearrangement of 3.8 g. of the crude oxime in 80 cc. of benzene by heating with 4 g. of phosphorus pentachloride for 15 minutes on a steam-cone followed by treatment with water yielded *1-methyl-9-acetylamino-1,2,3,4-tetrahydrophenanthrene;* weight, 2.14 g. and m.p. 171–176° after recrystallization from ethanol. After evaporative distillation under reduced pressure and two recrystallizations from ethanol the amide formed colorless needles; m.p. 183–184.5°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.6.

The amide was hydrolyzed with alcoholic hydrochloric acid (4) to the amine, a solid which discolored rapidly. The *picrate* of *1-methyl-9-amino-1,2,3,4-tetrahydrophenanthrene* formed golden platelets from ethyl acetate; m.p. 178–180°.

Anal. Calc'd for $C_{21}H_{20}N_4O_7$: N, 12.7. Found: N, 13.4.

Acetylation of *1-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene.* From the crystalline complex which was formed by the reaction of 27.1 g. of the hydrocarbon with a solution of 19 cc. of acetyl chloride, 32.3 g. of aluminum chloride, 375 cc. of carbon disulfide, and 275 cc. of *sym*-tetrachloroethane carried out as described for the previous acetylation, 22.5 g. (70%) of colorless needles, presumably *1-methyl-7-acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene*, was obtained after distillation at 170–173° and 0.01–0.05 mm. and crystallization from methanol; m.p. 83–84°. Recrystallized twice from methanol, a sample melted at 84.5–85°.

Anal. Calc'd for $C_{19}H_{22}O$: C, 85.6; H, 8.3.
Found: C, 85.3; H, 8.1.

SUMMARY

1-Methyl-1,2,3,4-tetrahydrophenanthrene has been prepared by two different methods, and a number of reactions of it and its derivatives are described.

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