[CONTRIBUTION FROM THE RESEARCH LABORATORY OF LADY ESTHER, INC.]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XII. DERIVATIVES OF PHENANTHRENE, IV. 1 (OR 8)-ACETYL-9-HALOPHENANTHRENE

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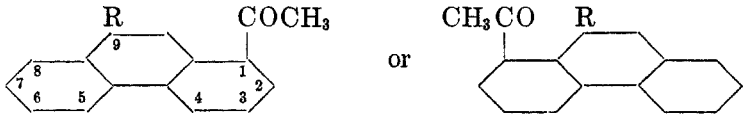
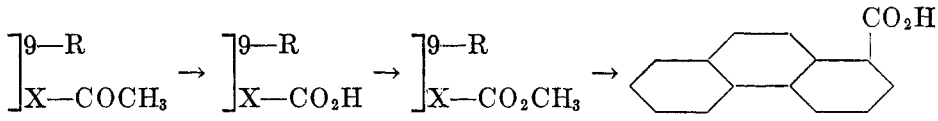
Received August 17, 1945

The acetylation of 9-bromo- and 9-chloro-phenanthrenes with acetyl chloride in the presence of aluminum chloride yields principally 3-acetyl derivatives (1, 2, 3,). We have succeeded, however, in isolating from these reaction mixtures smaller amounts of another isomer which we have identified as 1 (or 8)-acetyl-9-halophenanthrene:



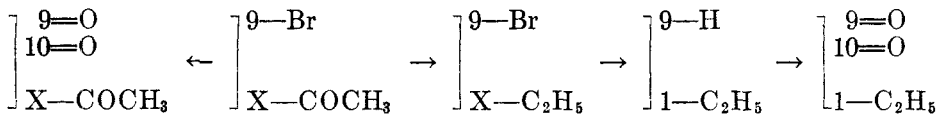
(R = Cl or Br)

The structure of these 1 (or 8)-ketones was elucidated in the following manner:



Oxidation with hypochlorite yielded the carboxylic acids which were esterified with methanol. The esters were then dehalogenated with hydrogen in the presence of palladium charcoal and the dehalogenated products saponified to the known 1-phenanthroic acid.

For 1 (or 8)-acetyl-9-bromophenanthrene, further proof of structure was obtained by the following reactions:



V I II III IV

The ketone (I) was converted to 9-bromo-1 (or 8)-ethylphenanthrene (II) by Clemmensen reduction. Debromination of (II) by hydrogen in the presence of palladium yielded the known 1-ethylphenanthrene (III) which was further identified by formation of its known picrate and by chromic acid oxidation to the previously described quinone (IV) (4). Ketone (I) was also oxidized by chromic acid to the bromine-free acetyl quinone (V).

From 1 (or 8)-acetyl-9-bromophenanthrene was prepared by methods de-

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scribed previously (2, 3) 1 (or 8)-(2-diamylamino-1-oxoethyl)-9-bromophenanthrene and the corresponding amino alcohol. The latter, SN 13456, showed a relatively low toxicity (5) and a high effectiveness towards *Plasmodium gallinaceum* (Q 1). The compound is inactive towards sporozoite-induced *gallinaceum* malaria (6).

EXPERIMENTAL

1(or 8)-Acetyl-9-bromophenanthrene. The mother liquors from the recrystallization of the crude 3-acetyl-9-bromophenanthrene (2) (three successive crops of 3-acetyl derivative had been removed) were concentrated to a thin syrup. After standing for several weeks a further quantity of crystalline material separated and was filtered off and washed with methanol. This material was dissolved in chloroform and allowed to crystallize very slowly. A small quantity of a new ketone, 1 (or 8)-acetyl-9-bromophenanthrene separated in the form of large colorless cubes. On repeated crystallization from chloroform the melting point became constant at 185.6°. This ketone is extremely insoluble in methanol and in ethanol, somewhat more soluble in benzene and toluene, and fairly soluble in hot dioxane and chloroform.

Anal. Calc'd for $C_{16}H_{11}BrO$: C, 64.2; H, 3.68.
Found: C, 63.8; H, 3.72.

1 (or 8)-Acetyl-9-bromophenanthrene oxime. The oxime was prepared in dioxane-alcohol-water and recrystallized from methanol; colorless needles, m.p. 183–184°.

Anal. Calc'd for $C_{16}H_{12}BrNO$: N, 4.46. Found: N, 4.43.

1 (or 8)-Acetyl-9-bromophenanthrene semicarbazone. The semicarbazone was prepared by treatment with semicarbazide hydrochloride in pyridine. Fine, colorless needles were obtained by recrystallization from alcohol; m.p. 220–221°.

Anal. Calc'd for $C_{17}H_{14}BrN_3O$: N, 11.8. Found: N, 12.1.

1-Acetyl-9,10-phenanthrenequinone. The 1 (or 8)-acetyl-9-bromophenanthrene was oxidized in the usual way with chromic acid (7). Recrystallization from glacial acetic acid yielded deep orange needles which did not melt but decomposed over a wide temperature range. A qualitative test (sodium fusion) showed no halogen.

Anal. Calc'd for $C_{16}H_{10}O_3 \cdot H_2O$: C, 71.6; H, 4.48.
Found: C, 71.54; H, 4.52.

9-Bromophenanthrene-(1 or 8)-carboxylic acid. To a solution of 2 g. of 1 (or 8)-acetyl-9-bromophenanthrene in 20 cc. of pyridine was added 7.5 cc. of 5.5 *N* sodium hypochlorite solution and 3 cc. of water. The mixture was refluxed for 30 minutes, poured into a large volume of water, and acidified with hydrochloric acid. The precipitate was filtered and washed with water, extracted with 300 cc. of 1% sodium hydroxide solution by heating to boiling. The solution of crude acid, which contained some insoluble material in suspension, was treated with carbon, filtered, and the acid precipitated with hydrochloric acid. The precipitated acid weighed 1.1 g. (55%). After crystallization from glacial acetic acid, it melted at 291–292°.

Anal. Calc'd for $C_{15}H_9BrO$: C, 59.8; H, 3.01.
Found: C, 59.51; H, 3.34.

9-Bromophenanthrene-1 (or 8)-carboxylic acid methyl ester. The 9-bromophenanthrene-1 (or 8)-carboxylic acid was esterified in the usual way with methanol in the presence of sulfuric acid. The ester was isolated by allowing the reaction mixture to cool and filtering off the crystallized product. The yield was almost quantitative. By recrystallization from methanol, colorless needles were obtained, m.p. 135.5–136°.

Anal. Calc'd for $C_{16}H_{11}BrO_2$: C, 61.00; H, 3.50.
Found: C, 61.02; H, 3.85.

Debromination of 9-bromophenanthrene-1 (or 8)-carboxylic acid methyl ester. To a solution of 0.1 g. of 9-bromophenanthrene-1 (or 8)-carboxylic acid methyl ester in 20 cc. of

methanol was added 50 mg. of 1% palladium on activated charcoal. A stream of hydrogen was passed through the suspension for 20 minutes at 50°. The catalyst was filtered off and the solution poured into a large volume of water. The ester was extracted with ether and the extract evaporated to dryness. The ester which remained was obtained as an oil and was saponified with methanolic potassium hydroxide. The saponification was complete in 15 minutes and the product was isolated by diluting the reaction mixture with water and acidifying with hydrochloric acid. After crystallization from glacial acetic acid, the acid was obtained as colorless crystals, m.p. 228.5–229.5°.

Calc'd for $C_{15}H_{10}O_2$: Neut. equiv., 222. Found: 225.

This acid when mixed with an authentic sample of 1-phenanthroic acid[5] showed no depresssion in melting point.

1 (or 8)-Ethyl-9-bromophenanthrene. A mixture of 1.0 g. of 1 (or 8)-acetyl-9-bromophenanthrene, 5 g. of amalgamated zinc, 10 cc. of glacial acetic acid, 10 cc. of concentrated hydrochloric acid, and 4 cc. of toluene was refluxed for 24 hours during which an additional 6 cc. of concentrated hydrochloric acid was added in small portions. The toluene layer was separated, evaporated to dryness, and the residue recrystallized from acetone-methanol. Colorless crystals, m.p. 72.5–73.5° were obtained.

Anal. Calc'd for $C_{16}H_{13}Br$: Br, 28.1. Found: Br, 27.8.

1-Ethylphenanthrene. To a solution of 0.5 g. of 1 (or 8)-ethyl-9-bromophenanthrene in 5 cc. of pyridine and 15 cc. of methanol was added 0.1 g. of palladium charcoal. A stream of hydrogen was passed through the solution at the boiling point for 30 minutes. The catalyst was then filtered off and the solution poured into water and acidified with hydrochloric acid. The debrominated product was extracted with ether and the ethereal solution evaporated to dryness. The residual ethylphenanthrene was crystallized from alcohol in the form of colorless needles, m.p. 61.5–63°; picrate, light orange, m.p. 109–110° [lit. (4), 62.5°; picrate, 108–109°].

1-Ethylphenanthrene-9,10-quinone. To a solution of 0.1 g. of 1-ethylphenanthrene in 2 cc. of glacial acetic acid was added a solution of 0.1 g. of chromic anhydride in 0.2 cc. of water and 0.5 cc. of glacial acetic acid. The solution was warmed to 70–80° for ten minutes and the quinone precipitated by the addition of water. Recrystallization from acetic acid yielded orange-red needles, m.p. 153–154° [lit. (4), 155°].

1 (or 8)-Acetyl-9-chlorophenanthrene. The mother liquors from the acetylation of 9-chlorophenanthrene (3) contained principally a mixture of the 3-acetyl- with 1 (or 8)-acetyl-9-chlorophenanthrene. By fractional crystallization from isopropanol and then chloroform, a small quantity of crystalline material was isolated, m.p. 159–160°.

Anal. Calc'd for $C_{16}H_{11}ClO$: C, 75.5; H, 4.36.
Found: C, 75.6; H, 4.57.

1 (or 8)-Acetyl-9-chlorophenanthrene oxime. The oxime was prepared by the method employed for 1 (or 8)-acetyl-9-bromophenanthrene oxime. After recrystallization from methanol it melted at 171–173°.

Anal. Calc'd for $C_{16}H_{12}ClNO$: N, 5.20. Found: N, 5.58.

9-Chlorophenanthrene-1 (or 8)-carboxylic acid. This acid was prepared by oxidation of the 1 (or 8)-acetyl-9-chlorophenanthrene with hypochlorite in exactly the same way as was used for the corresponding bromo derivative. After recrystallization from glacial acetic acid it was obtained in the form of colorless needles, m.p. 293–294°.

Calc'd for $C_{15}H_9ClO_2$: Neut. equiv. 256.5. Found: 258.

9-Chlorophenanthrene-1 (or 8)-carboxylic acid methyl ester. The methyl ester was prepared in the usual way with methanol in the presence of sulfuric acid. Recrystallization from methanol gave colorless crystals, m.p. 129.5–130°.

Anal. Calc'd for $C_{16}H_{11}ClO_2$: C, 70.9; H, 4.09.
Found: C, 70.8; H, 4.11.

Dechlorination of 9-chlorophenanthrene-1 (or 8)-carboxylic acid methyl ester. The ester

[5] The authentic 1-phenanthroic acid was furnished by Dr. Erich Mosettig.

was dehalogenated with hydrogen in the presence of palladium charcoal using the same procedure employed for the corresponding bromo compound. The dehalogenated product was isolated as 1-phenanthroic acid which did not depress the melting point of 1-phenanthroic acid obtained from the corresponding bromo compound.

1 (or 8)-(α-Bromoacetyl)-9-bromophenanthrene. To a suspension of 30 g. of 1 (or 8)-acetyl-9-bromophenanthrene in 400 cc. of absolute ether at 35° was added a few drops of bromine in chloroform. After decolorization was complete the temperature was lowered to 5–8° and 16 g. of bromine in 75 cc. of chloroform added slowly with stirring. After all the bromine had been absorbed, 200 cc. of hexane was added and the mixture chilled. The precipitate was filtered off and washed with hexane, then with petroleum ether. After one recrystallization from benzene-hexane the yield was 32.4 g., m.p. 117–128°. Recrystallization from dioxane-methanol gave colorless needles, m.p. 126–127°.

Anal. Calc'd for $C_{16}H_{10}Br_2O$: Br, 42.3. Found: Br, 42.1.

1 (or 8)-(2-Diamylamino-1-oxoethyl)-9-bromophenanthrene hydrochloride. To a solution of 16 g. (0.1 m.) of diamylamine in 70 cc. of benzene was added 19.7 g. (0.05 m.) of 1 (or 8)-α-bromoacetyl-9-bromophenanthrene. The mixture was shaken mechanically for one hour, 125 cc. of dry ether was added and the whole chilled overnight. The diamylamine hydrochloride which separated was filtered off and the filtrate evaporated to dryness. The residue was shaken with a mixture of dilute sodium carbonate solution and ether, the ethereal extract separated, washed with water, and dried over sodium sulfate. The remaining diamylamine was precipitated by adding alcoholic hydrogen chloride until *p*H 6 was indicated by a drop of the solution on "Hydrion A" paper. The precipitated amine hydrochloride was filtered off and the filtrate made strongly acid with alcoholic hydrogen chloride.

The amino ketone hydrochloride separated as long colorless needles, m.p. 154–156°. The yield was 16.0 g. (64%). After recrystallization from methanol-acetone-ether, the melting point became constant at 156–157.5°.

Anal. Calc'd for $C_{26}H_{43}BrClNO$: N, 2.85; Cl, 7.23.
Found: N, 2.71; Cl, 7.15.

1 (or 8)-(2-Diamylamino-1-hydroxyethyl)-9-bromophenanthrene hydrochloride, (SN-13456). To a solution of 14.9 g. (0.073 m.) of aluminum isopropoxide in 450 cc. of isopropanol was added 12 g. (0.0245 m.) of 1 (or 8)-(2-diamylamino-1-oxoethyl)-9-bromophenanthrene. Isopropanol containing acetone was slowly distilled from the solution through a 10-ball Snyder column. After 3.5 hours of distillation, the remaining isopropanol was evaporated *in vacuo*. The residue was diluted with ether, an aqueous solution of citric acid added and made alkaline to Phenol Red with sodium hydroxide solution. The ethereal phase was separated, dried over sodium sulfate, and acidified with alcoholic hydrogen chloride. After standing overnight, the separated crude amino carbinol hydrochloride was filtered and washed with ether. The yield was 7.3 g. (61%), m.p. 178–180°. After recrystallization from methanol-acetone-ether, the pure amino carbinol hydrochloride was obtained as colorless needles, m.p. 178.5–179°.

Anal. Calc'd for $C_{26}H_{45}BrClNO$: Cl, 7.20. Found: Cl, 7.19.

SUMMARY

1. 1(or 8)-Acetyl-9-bromophenanthrene and 1 (or 8)-acetyl-9-chlorophenanthrene have been prepared.

2. The structure of these ketones has been elucidated.

3. 1(or 8)-(2-Diamylamino-1-oxoethyl)-9-bromophenanthrene has been prepared and reduced to the corresponding carbinol.

4. The evaluation of this amino alcohol as an antimalarial is discussed.

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