[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XX.[1,2] AMINO ALCOHOLS OF THE TYPE—$CH_2CHOHCH_2NR_2$ DERIVED FROM PHENANTHRENE AND TETRAHYDROPHENANTHRENE

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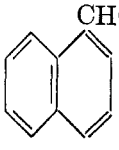
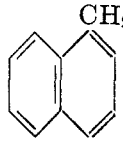
We have shown in previous communications (1,2) that amino alcohols of the type—$CHOHCH_2NR_2$, carrying this side chain in position 9 of tetrahydrophenanthrene and phenanthrene, exhibit considerable antimalarial activity, in some instances equal to that of quinine. Furthermore, Fry and Mosettig (3)[3] have found that some naphthyl alkamines (I) with the side chain in position 1, also have a definite, though rather weak plasmodicidal effect (*P. gallinaceum*)(5).

In 1930 Fourneau and associates (6) reported that the amino alcohol II shows a slight activity in avian malaria.

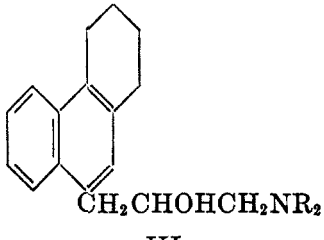


I

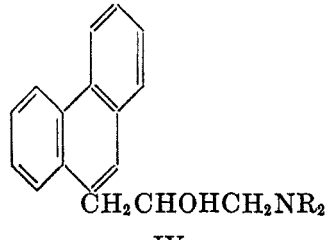


II

We had suspected from the beginning of our investigations, that in the vast group of amino alcohols studied, antimalarial activity is linked with the structural arrangement Ar—CHOH—. In other words the secondary carbinol group of the alkamine chain should be directly attached to an aromatic ring (or hetero ring with aromatic character). In order to test this hypothesis we synthesized, of each of III and IV, two characteristic representatives.



III



IV

[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2] Studies in the Phenanthrene Series XXXVI.

[3] See also Jacobs and associates (4).

Starting from phenanthryl-9-acetic acid and its tetrahydro analog we prepared compounds of types III and IV as follows:

$$—CH_2COOH \rightarrow —CH_2COCl \rightarrow —CH_2COCHN_2 \rightarrow$$

$$—CH_2COCH_2Br \rightarrow —CH_2COCH_2NR_2 \rightarrow —CH_2CHOHCH_2NR_2 .$$

In neither series were any particular difficulties encountered. Although not needed in the present synthesis we prepared in both series the acetone derivatives $—CH_2COCH_3$ by catalytic dehalogenation of the corresponding ω-bromo ketones. When we were able to isolate crystalline amino ketone hydrochlorides, we reduced them catalytically, otherwise the oily amino ketone bases were reduced with aluminum isopropoxide.

The amino alcohols (SN 12984, SN 12986, SN 13666, SN 13669)[4] submitted to biological tests (5, 7) are, as a whole, slightly more toxic than the corresponding lower homologs of the tetrahydrophenanthrene series (1) and phenanthrene series (2). They are, as we expected, ineffective against *P. gallinaceum*. On the other hand the new amino alcohols are much more effective inhibitors of plasma cholinesterase than their lower homologs (8, 1, 2). They did not show any activity against sporozoite-induced *gallinaceum* malaria (5).

Acknowledgment. We wish to thank Mr. Edward A. Garlock, Jr. for carrying out the microanalyses.

EXPERIMENTAL[5]

1,2,3,4-Tetrahydrophenanthrene-9-acetyl chloride. A mixture of 24 g. of 1,2,3,4-tetrahydrophenanthrene-9-acetic acid (9), 25 cc.of thionyl chloride, and 25 cc. of dry benzene was refluxed for one hour. Solvent and excess reagent were evaporated *in vacuo*, and the residue was recrystallized from dry ligroin (90–100°); yield 19 g., m.p. 65.5–67°. Another recrystallization followed by high vacuum sublimation gave the constant m.p. 66.5–67.5°; prisms.

Anal. Calc'd for $C_{16}H_{15}ClO$: C, 74.28; H, 5.84.
Found: C, 74.48; H, 6.04.

9-(3-Bromo-2-oxopropyl)-1,2,3,4-tetrahydrophenanthrene (*V*). A solution of 19 g. of the preceding chloride in 100 cc. of dry ether was added during forty-five minutes to 400 cc. of a stirred ether solution of diazomethane (from 40 g. of nitrosomethylurea) at 5° to 17°. The mixture was stirred for 5–6 hours at room temperature and left in the ice-box overnight. The precipitated diazo ketone (VI) (16 g., m.p. 126–128° to a frothy melt) was stirred in suspension with 50 cc. of benzene and 100 cc. of dry ether, while 18 cc. of 40% HBr in 18 cc. of U.S.P. ether was added (25–35 minutes). The resulting solution was washed with water, filtered, washed with sodium bicarbonate solution and dried (Na_2SO_4). It was concentrated *in vacuo* to about 60 cc., diluted with an equal volume of ligroin (30–60°), and cooled in the ice-box; yield of bromo ketone 16.5 g., m.p. 105–106.5°. Two recrystallizations from ethyl acetate-ether gave large needles of m.p. 107–108°.

Anal. Calc'd for $C_{17}H_{17}BrO$: C, 64.37; H, 5.40.
Found: C, 65.10; H, 5.44.

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[4] The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. Activities of drugs so listed will be published in a forthcoming monograph.

[5] All melting points given are uncorrected.

9-(2-Oxopropyl)-1,2,3,4-tetrahydrophenanthrene. (a) By the method of Wolfrom and Brown (10), 0.5 g. of VI was converted to 0.2 g. of this ketone, m.p. 58–60°. After two recrystallizations from methanol and a high vacuum sublimation, the m.p. was 63–64°; prisms.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.70; H, 7.61.
Found: C, 85.60; H, 7.70.

(b) A mixture of 0.5 g. of V, 0.2 g. of palladium-charcoal (5% Pd) and 14 cc. of absolute ethanol absorbed one mole of hydrogen in forty minutes. After removal of catalyst, the filtrate was concentrated to about 3 cc. to give 0.3 g. of the ketone identical with that obtained by method (a).

Occasionally this ketone crystallized in broad, flat needles of m.p. 58–60°. After solidification it remelted at 62–63.5°.

9-(3-Diethylamino-2-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (SN 12,984). Two grams of V, 1.5 cc. of diethylamine, and 10 cc. of dry ether were shaken together for one hour. The cooled, filtered mixture was washed four times with water and dried (Na_2SO_4). After evaporation, almost to dryness, acetone, 2 cc. of 15% alcoholic HCl, and ether were added in succession. The amino ketone hydrochloride which crystallized was recrystallized from absolute ethanol-ether to give 1.7 g. of needles, m.p. 75–87°. With 0.05 g. of platinum oxide and 17 cc. of methanol, it absorbed one mole of hydrogen in one hour. The catalyst was removed and the filtrate evaporated to dryness, leaving a syrup which crystallized from acetone-ether in a yield of 1.2 g., m.p. 126–129°; large needles from acetone-ether; m.p. 129–131°. The somewhat hygroscopic compound was dried in a desiccator.

Anal. Calc'd for $C_{21}H_{30}ClNO$: C, 72.49; H, 8.69.
Found: C, 72.28; H, 8.72.

The picrate crystallized from 95% ethanol in yellow needles of m.p. 125–126.5°.

Anal. Calc'd for $C_{27}H_{32}N_4O_8$: C, 59.99; H, 5.97.
Found: C, 60.33; H, 5.75.

9-(3-Diheptylamino-2-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (SN 12,986). A mixture of 5.0 g. of V. 6.0 g. of diheptylamine and 25 cc. of dry ether was shaken for 5–10 hours, cooled, and filtered from 4.0 g. of diheptylamine hydrobromide. The filtrate was evaporated to dryness *in vacuo* and the residue reduced with 25 cc. of 3 *N* aluminum isopropoxide (1). After two hours the isopropanol was distilled *in vacuo*. The residue was partitioned between ether and an excess of 10% sodium hydroxide, the ether layer washed twice with water, dried and acidified to Congo Red with 15% alcoholic HCl. On seeding[6] the salt separated in a yield of 3.6 g., m.p. 133–136°. It crystallized from acetone in fine needles of m.p. 136.5–137.5°.

Anal. Calc'd for $C_{31}H_{50}ClNO$: C, 76.26; H, 10.32.
Found: C, 75.85; H, 10.15.

Phenanthrene-9-acetyl chloride. A mixture of 17. g of phenanthrene-9-acetic acid (11) and 35 cc. of thionyl chloride was refluxed for 1–2 hours and excess reagent removed *in vacuo*. The residue crystallized from dry ligroin (90–100°) in a yield of 16.5 g., m.p. 90–93°. After another recrystallization followed by sublimation in a high vacuum, the chloride melted at 92–93°; broad needles.

Anal. Calc'd for $C_{16}H_{11}ClO$: C, 75.42; H, 4.35
Found: C, 75.09; H, 4.39.

9-(3-Bromo-2-oxopropyl)phenanthrene (VII). The foregoing acid chloride (16 g.) was added during forty minuutes to a stirred ether solution of diazomethane (from 32 g. of nitrosomethylurea), cooled to 4–7°. The mixture was stirred at 0–5° for one hour and for five hours without cooling, chilled in ice and filtered. The 14.5 g. of diazo ketone resulting (m.p. 157–158°, gas evolution) was stirred in suspension with 70 cc. of benzene and 50 cc. of dioxane, while 15 cc. of 40% HBr in 15 cc. of dioxane was added (fifteen minutes, 20–25°).

[6] The hydrochloride could be obtained crystalline (for the first time) only from an amino alcohol base that had been distilled in high vacuum.

After an additional thirty minutes, 150–200 cc. of benzene was added and the solution shaken successively with water, dilute sodium bicarbonate, and water, dried (Na_2SO_4) and concentrated to 70–80 cc. On slight dilution with ligroin (30–60°), the bromo ketone separated in a yield of 15.8 g., m.p. 127–129°. It crystallized from benzene in long needles of m.p. 128.5–129.5°.

Anal. Calc'd for $C_{17}H_{13}BrO$: C, 65.20; H, 4.18.
Found: C, 65.13; H, 4.38.

9-(2-Oxopropyl)phenanthrene. A mixture of 0.5 g. of VII, 0.2 g. of palladium-charcoal (5% Pd), and 25 cc. of absolute ethanol absorbed one mole of hydrogen in twenty-five minutes. The ketone crystallized from methanol in long needles of m.p. 98.5–99°; yield 0.25 g.

Anal. Calc'd for $C_{17}H_{14}O$: C, 87.15; H, 6.02.
Found: C, 86.42; H, 5.98.

9-(3-Dibutylamino-2-hydroxypropyl)phenanthrene hydrochloride (SN 13,666). Dibutylamine (5.7 g.), 7 g. of VII, 30 cc. of dry ether, and 5 cc. of acetone were shaken together for 1–2 hours. After cooling in ice, filtering, and evaporating the filtrate to dryness *in vacuo*, the residue was reduced with 35 cc. of 3 *N* aluminum isopropoxide (1) as described for SN 12,986. On diluting the alcoholic HCl-acidified ether solution with ligroin (30–60°) and seeding,[6] the hydrochloride separated in a yield of 2.5 g., m.p. 169–171.5°. A second fraction (0.9 g.) was obtained from the filtrate; prisms from absolute ethanol-ether, m.p. 173–174°.

Anal. Calc'd for $C_{25}H_{34}ClNO$: C, 75.06; H, 8.57.
Found: C, 75.18; H, 8.64.

9-(3-Diamylamino-2-oxopropyl)phenanthrene hydrochloride. A mixture of 5 g. of VII, 5 g. of diamylamine, 20 cc. of dry ether, and 5 cc. of acetone was shaken for three hours, cooled in ice, and diamylamine hydrobromide filtered. The filtrate was acidified to Congo Red with 15% alcoholic HCl. Upon cooling in the ice-box, 5.0 g. of amino ketone salt, m.p. 168–170.5°, crystallized; thin prisms from absolute ethanol-ether, m.p. 172–173°.

Anal. Calc'd for $C_{27}H_{38}ClNO$: C, 76.13; H, 8.52.
Found: C, 76.08; H, 8.63.

9-(3-Diamylamino-2-hydroxypropyl)phenanthrene hydrochloride. A mixture of 6.0 g. of the preceding compound, 0.1 g. of platinum oxide, and 50 cc. of methanol absorbed one mole of hydrogen in 1.5–2 hours. After removal of the catalyst, the filtrate was evaporated to dryness *in vacuo*. The syrupy residue crystallized from acetone in a yield of 5.8 g., m.p. 112–115°. Another recrystallization gave the m.p. 113–115°; thin prisms.

Anal. Calc'd for $C_{27}H_{38}ClNO$: C, 75.77; H, 8.93.
Found: C, 76.01; H, 9.19.

If, instead of acetone, ethanol was used as the solvent, a compound melting at about 85–90° and giving erratic analytical results, was obtained.

The picrate crystallized from 95% ethanol in yellow prisms, m.p. 115–117°.

Anal. Calc'd for $C_{33}H_{40}N_4O_8$: C, 63.85; H, 6.50.
Found: C, 64.23; H, 6.53.

SUMMARY

Four amino alcohols, two derived from phenanthrene and two from tetrahydrophenanthrene, and carrying the side chain $—CH_2CHOHCH_2NR_2$ in position 9 have been described.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA, MD.

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