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

ATTEMPTS TO FIND NEW ANTIMALARIALS. XVI.[1,2] AMINO ALCOHOLS OF THE TYPE —CHOHCH$_2$NR$_2$ DERIVED FROM 3-CHLORO-9-ACETYLPHENANTHRENE

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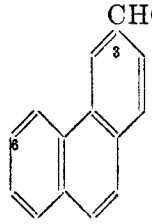
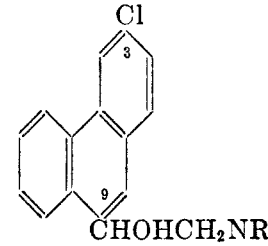
In the foregoing communication (1) we have shown that the introduction of a chlorine atom into the nucleus (position 6) of 3-phenanthrylamino alcohols (I) increases considerably the activity against *Plasmodium gallinaceum*.



I



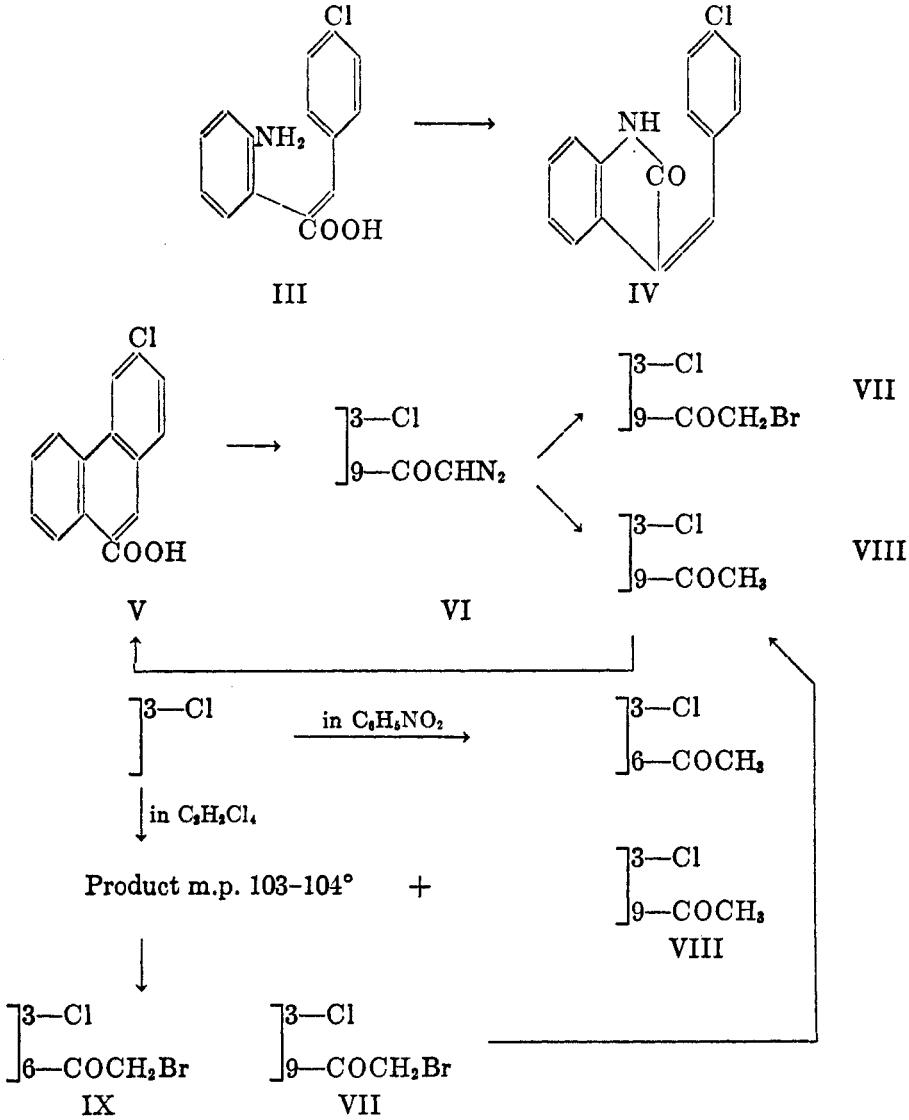
II

The synthesis of these amino alcohols (chlorine in position 6) was not planned originally. Rather, it was hoped that in the Friedel-Crafts reaction on 3-chlorophenanthrene, the acetyl group would enter position 9. Our previous investigations had shown that the phenanthrylalkamines carrying the alkamine side chain in position 9 are decidedly more active than the corresponding 3-isomers (2), and we expected that this would be true also with phenanthrylalkamines containing a nuclear chlorine. Thus, in order to arrive at compounds of formula II, it appeared necessary to prepare the starting material, the 3-chloro-9-acetylphenanthrene (VIII) by total synthesis. We prepared first 3-chloro-9-phenanthrenecarboxylic acid (V) by the Pschorr method, employing *o*-nitrophenylacetic acid and *p*-chlorobenzaldehyde. The yields of acid V were lower than generally observed in the Pschorr synthesis when the nitro group, instrumental in the ring closure, is located in the aromatic aldehyde. This corroborates the results obtained by Mayer and Balle (3) in the preparation of phenanthrene derivatives from *o*-nitrophenylacetic acid. The intermediate cinnamic acid derivative III loses water readily, even by recrystallization from ethanol, to form lactam IV which we also prepared by condensing *p*-chlorobenzaldehyde with oxindole, and which proved to be very resistant to hydrolyzing agents. Phenanthroic acid V was then converted by the method of Arndt and Eistert (4) *via* diazo ketone VI either to 3-chloro-9-ω-bromoacetylphenanthrene (VII) or according to Wolfrom and Brown (5) to 3-chloro-9-acetylphenanthrene (VIII).

[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 XXXII.

In the foregoing communication (1) we described the formation of 3-chloro-6-acetylphenanthrene in a yield of 60% in the Friedel-Crafts reaction with



acetyl chloride and 3-chlorophenanthrene in a nitrobenzene medium. No 9-acyl derivative could be found among the by-products. We find now that by employing *s*-tetrachloroethane as reaction medium, the course of this reaction is considerably altered.[3] We obtained in a 20–25% yield 3-chloro-9-acetylphenan-

[3] In the choice of this solvent we were influenced by similar experiments of Bachmann and Cronyn (6) in the tetrahydrophenanthrene series.

threne, and in about 30% yield a seemingly isomeric ketone which had after purification by crystallization and sublimation, the constant m.p. 103–104°. By bromination of this product it became apparent, however, that it is a double compound of the two ketones. The brominated substance could be separated by fractional crystallization into approximately equal amounts of two ω-bromoacetyl derivatives which yielded on catalytic debromination 3-chloro-6-acetylphenanthrene and 3-chloro-9-acetylphenanthrene. The structure of the latter was proved by oxidizing it with sodium hypochlorite to an acid identical with 3-chloro-9-phenanthrenecarboxylic acid prepared by the Pschorr method, and by direct comparison with the methyl ketone prepared therefrom.

Two amino alcohols of type II, the dihexylamino derivative (SN 10908)[4] and the diheptylamino derivative (SN 9161) were prepared from 3-chloro-9-ω-bromoacetylphenanthrene by treatment with the appropriate amine and subsequent reduction of the resulting amino ketone with aluminum isopropoxide.

SN 10908 (Q 2) and SN 9161 (Q 1) do not differ in their effectiveness towards *P. gallinaceum* from the corresponding chlorine-free 9-alkamines (2a) as much as the analogous pairs in the phenanthryl-3-alkamine series (1). They do not differ appreciably from the corresponding 3-chlorophenanthryl-6-alkamines (1). They are, however, four times as effective as the corresponding 9-chlorophenanthryl-3-alkamines (SN 13454, SN 10230) in which the positions of the alkamine side chain and the chlorine atom are reversed (7, 8, 9). The two amino alcohols described in this paper do not show any prophylactic activity against sporozoite induced *gallinaceum* malaria (9).

Acknowledgment. We are indebted to Mr. Edward A. Garlock, Jr. for carrying out the microanalyses, and to Dr. R. C. Elderfield for the supply of large quantities of 3-chlorophenanthrene. We wish to thank Heyden Chemical Corporation for furnishing us with *p*-chlorobenzaldehyde.

EXPERIMENTAL[5]

o-Nitrophenylacetic acid. The procedure of Mayer and Balle (3) with a few modifications, was used in this preparation. To a stirred solution of 51 g. of commercial sodium methoxide and 120 cc. of ethyl oxalate in 250 cc. of absolute ethanol was added during forty-five minutes, 110 cc. of *o*-nitrotoluene. The mixture was boiled under reflux for fifteen minutes, cooled somewhat, diluted with about 100 cc. of water, and steam passed in until all volatile material was removed. The almost clear solution (volume about 1000 cc.) was treated with 60 cc. of 30% hydrogen peroxide while keeping the temperature below 30°. After gas evolution had ceased the reaction mixture was filtered, the filtrate acidified with concentrated hydrochloric acid, and the precipitated material recrystallized from about 1200 cc. of water (Norit). The yield of acid melting at 136–139° was 60 g. The reported melting point is 141°.

α-(o-Nitrophenyl)-p-chlorocinnamic acid. To an ice-cooled solution of 7.1 g. of sodium in 100 cc. of absolute ethanol was added with stirring 55 g. of *o*-nitrophenylacetic acid.

[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.

After adding 250 cc. of dry ether, the sludge was stirred mechanically for one hour and left in the ice-box overnight. The sodium salt was collected, washed with absolute ethanol-ether, and dried in a vacuum desiccator (56.5 g. yield). A mixture of 28 g. of this sodium *o*-nitrophenylacetate, 19 g. of *p*-chlorobenzaldehyde, 2.5 g. of fused zinc chloride, and 100 cc. of acetic anhydride was heated on the steam-bath for fifteen to twenty hours. Excess acetic anhydride was decomposed with 100 cc. of water. Further dilution with water and cooling in ice yielded a semisolid product which, on recrystallization from glacial acetic acid, gave 14.9 g. of nitro acid melting at 196–199°. After one recrystallization from acetic acid and one from methanol, it melted at 199–200.5°; light yellow, prismatic rods.

Anal. Calc'd for $C_{15}H_{10}ClNO_4$: C, 59.32; H, 3.32.
Found: C, 59.56; H, 3.74.

p-Chlorobenzaloxindole (*IV*). A hot solution of 5.1 g. of the above nitro acid in 16 cc. of conc'd NH_4OH and 34 cc. of water was added to a mixture of 34 g. of ferrous sulfate, 102 cc. of water, and 85 cc. of conc'd NH_4OH heated to 80–90°. The mixture was then maintained at 85–90° for about ten minutes and filtered through Filter-Cel. Acidification of the filtrate with acetic acid yielded 3.4 g. (air-dried) of α-(*o*-aminophenyl)-*p*-chlorocinnamic acid (III) of m.p. 138–140° with effervescence. The melt solidified and remelted at 170–180°. The yield of III could be reproduced even in large scale runs. Upon recrystallization from ethanol, it underwent dehydration to IV of m.p. 188–190°; yellow needles.

Anal. Calc'd for $C_{15}H_{10}ClNO$: C, 70.45; H, 3.94.
Found: C, 70.30; H, 4.27.

The same compound was obtained in 60% yield when 0.5 g. of oxindole (10), 0.5 g. of *p*-chlorobenzaldehyde, two drops of piperidine, and 100 cc. of ethanol were refluxed together for fifteen hours. It melted at 185–188°. A mixture m.p. with the sample of m.p. 188–190° was 186–189°.

3-Chloro-9-phenanthrenecarboxylic acid (*V*). To 80 cc. of 5 *N* sulfuric acid, mechanically stirred, and cooled to −3° to 2°, was added a homogeneous suspension of 5 g. of III, 3 g. of sodium nitrite, 75 cc. of water, and 2 cc. of conc'd NH_4OH during twenty minutes. After an additional hour of stirring at 0° to 5°, 20–30 cc. of ethanol and 5 g. of copper-bronze were added, and the mixture was heated to 70–80° (stirring) for one-half hour. The precipitate was collected and alkali-soluble material leached from the copper with hot dilute sodium hydroxide. The alkaline filtrate yielded, on acidification, V (1.4 g. of m.p. 249–251° after one recrystallization from glacial acetic acid). Sublimation in a high vacuum followed by two recrystallizations from ethanol gave small needles of m.p. 250–252°.

Anal. Calc'd for $C_{15}H_9ClO_2$: C, 70.18; H, 3.53.
Found: C, 69.83; H, 3.95.

3-Chloro-9-phenanthroyl chloride. A mixture of 5 g. of V, 5 cc. of dry benzene, and 5 cc. of thionyl chloride was refluxed for two hours. Solvent and excess reagent were removed *in vacuo* and the residual acid chloride sublimed in a high vacuum; yield 5.1 g., m.p. 154–156°. Two recrystallizations from benzene gave the constant m.p. 153–154°; long needles.

Anal. Calc'd for $C_{15}H_8Cl_2O$: C, 65.49; H, 2.93.
Found: C, 65.34; H, 3.03.

3-Chloro-9-ω-bromoacetylphenanthrene (*VII*). To a stirred mixture (0° to 5°) of 100 cc. of an ether solution of diazomethane (from 10 g. of nitrosomethylurea) and 50 cc. of dry benzene, was added 5.0 g. of the above finely-divided acid chloride during forty-five minutes. The mixture was stirred for one hour at 0° to 5° and for five hours without cooling, and allowed to stand overnight. After cooling to 0°, the solid 3-chloro-9-phenanthroyldiazomethane (VI) was collected; 4.5 g. of m.p. 150–151.5° with gas evolution. It was stirred in suspension with 100 cc. of dioxane, while 4 cc. of 48% HBr in 4 cc. of dioxane was added during ten minutes (temperature 20–25°). After stirring for an additional one-half hour, 2.5 g. of potassium carbonate in about 5 cc. of water was added and the dioxane evaporated *in vacuo* at a bath temperature of 50–70°. The residue was partitioned between warm benzene and water, the benzene layer dried over sodium sulfate and concentrated to 15–20 cc. On addition of ligroin (30–60°), the bromo ketone separated in a yield of 4.7 g.,

m.p. 122–126°. Two recrystallizations from ethyl acetate (Norit) gave prismatic rods of m.p. 127–128°.

Anal. Calc'd for $C_{16}H_{10}BrClO$: C, 57.61; H, 3.02.
Found: C, 57.71; H, 3.42.

3-Chloro-9-acetylphenanthrene (VIII). (a) From VI and (b) from the Friedel-Crafts reaction on 3-chlorophenanthrene. (a) To a solution of 0.5 g. of VI in 15 cc. of chloroform was added dropwise with shaking, 1.5 cc. of 55% HI. After ten minutes the chloroform was washed with water, 10% sodium carbonate solution, and again with water, dried over sodium sulfate and evaporated to dryness. The residue, on sublimation in a high vacuum followed by two recrystallizations from methanol yielded 0.25 g. of ketone, m.p. 115–116°; blades.

Anal. Calc'd for $C_{16}H_{11}ClO$: C, 75.44; H, 4.35.
Found: C, 75.16; H, 4.50.

(b) A mixture of 16 g. of aluminum chloride, 70 cc. of *s*-tetrachloroethane, and 10 cc. of acetyl chloride was stirred at 10–15° while adding to it during twenty minutes, 12 g. of 3-chlorophenanthrene in 30 cc. of *s*-tetrachloroethane. Stirring was continued for one hour at 10° and for two hours at 0° to 5°. The complex was collected, washed with a little benzene, and decomposed in cold dilute HCl. The resulting material was dried in benzene (sodium sulfate) and the oil remaining after evaporation of solvent was dissolved in 75–100 cc. of hot methanol, yielding 4.9 g. of ketone of m.p. 110–113°. It was identical with the VIII synthesized as described above.

The methanol filtrate yielded 3.0 g. of product melting at 93–103°, which, when recrystallized had the constant m.p. 103–104°. By bromination (see below) it was found to consist of about equal quantities of 3-chloro-6- and 3-chloro-9-acetylphenanthrenes. On recrystallization or fusion of a 1:1 mixture of these ketones, a product melting at 103–104°, and giving no depression with the Friedel-Crafts product of m.p. 103–104°, was obtained. High vacuum sublimation did not alter the melting point.

The foregoing Friedel-Crafts experiment represents the best in a series of about twenty runs. The yields of VIII were quite variable and appeared to depend somewhat on the aluminum chloride used. In some runs only the fraction melting at 103–104° was obtained.

Bromination of the fraction melting at 103–104°. To 15 g. of crude double compound (m.p. 96–100°) in 125 cc. of dry ether was added 9.4 g. of bromine in about twenty minutes (stirring). After stirring an additional hour at room temperature and cooling in ice, 16 g. of precipitate was collected. It was dissolved in 300 cc. of boiling benzene and the solution allowed to stand at room temperature for five hours, then in the ice-box overnight. The product which separated (6 g. of m.p. 197–200°) was identical with 3-chloro-6-ω-bromoacetylphenanthrene (1). The benzene filtrate was concentrated to 40–50 cc., diluted with 95 cc. of ligroin (30–60°) and the mixture cooled thoroughly, yielding 7.0 g. of bromo ketone of m.p. 119–124°. After recrystallization from ethyl acetate the m.p. was 126–127° and was unchanged when mixed with 3-chloro-9-ω-bromoacetylphenanthrene, prepared by the Pschorr and Arndt-Eistert reactions. However, with 3-chloro-10-ω-bromoacetylphenanthrene (11) of m.p. 126.5–127°, it gave a 20–25° depression.

The same compound (VII) was prepared in a yield of 90% by the bromination of pure 3-chloro-9-acetylphenanthrene, isolated as the first fraction in the acetylation of 3-chlorophenanthrene above.

Debromination of 3-chloro-9-ω-bromoacetylphenanthrene. A mixture of 1.0 g. of VII, 0.5 g. of palladium-charcoal (5% Pd), and 50 cc. of absolute ethanol absorbed one mole of hydrogen in twenty-five minutes. After warming the mixture on the steam-bath, the catalyst was removed and the filtrate concentrated to about 10 cc., whereupon 0.5 g. of VIII of m.p. 114–115.5° separated. This ketone (0.5 g.) was oxidized by heating it under reflux for three hours with 35 cc. of potassium hypochlorite solution (prepared from 1.0 g. of "HTH"). The resulting 3-chloro-9-phenanthrenecarboxylic acid crystallized from acetic acid in needles of m.p. 251–253°. It was identical with a pure synthetic sample previously described.

3-Chloro-9-(2-dihexylamino-1-hydroxyethyl)phenanthrene hydrochloride (SN 10908). A mixture of 6.0 g. of VII, 7.0 g. of dihexylamine, 24 cc. of dry ether, and 6 cc. of acetone was shaken mechanically for one to two hours and left in the ice-box overnight. The precipitate of dihexylamine hydrobromide was filtered, the filtrate evaporated to dryness *in vacuo* and the residual amino ketone reduced with 25 cc. of 3 *N* aluminum isopropoxide (12). After 1.5–2 hours, the isopropanol was evaporated *in vacuo* and the reddish residue partitioned between ether and an excess of 10% sodium hydroxide. The ether layer was washed twice with water, dried over sodium sulfate, and made acidic to Congo Red with dry gaseous hydrogen chloride. The amino alcohol hydrochloride eventually crystallized in a yield of 4.0 g., m.p. 152–157°. An additional 0.4 g. was recovered from the filtrate. After one recrystallization from acetone-ether and one from acetone, it appeared as clusters of rods of m.p. 164–165.5°.

Anal. Calc'd for $C_{28}H_{39}Cl_2NO$: C, 70.57; H, 8.25.
Found: C, 70.81; H, 8.47.

3-Chloro-9-(2-diheptylamino-1-hydroxyethyl)phenanthrene hydrochloride (SN 9161). This compound was prepared like the foregoing one; yield from 5.6 g. of VII, 3.7 g., m.p. 135–139°. It crystallized from acetone-ether in rectangular plates of m.p. 137–138.5°.

Anal. Calc'd for $C_{30}H_{43}Cl_2NO$: C, 71.40; H, 8.59.
Found: C, 71.41; H, 8.93.

SUMMARY

Two amino alcohols derived from 3-chlorophenanthrene, and carrying the alkamine side chain in position 9 have been described.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA 14, MD.

REFERENCES

(1) MAY AND MOSETTIG, *J. Org. Chem.*, **11**, 429 (1946).
(2) (a) MAY AND MOSETTIG, *J. Org. Chem.*, **11**, 10 (1946).
(b) GARLOCK, MOSETTIG, AND SHAVER, Unpublished results.
(3) MAYER AND BALLE, *Ann.*, **403**, 167 (1914).
(4) "Organic Reactions", I, (John Wiley and Sons, Inc.) p. 38 (1942).
(5) WOLFROM AND BROWN, *J. Am. Chem. Soc.*, **65**, 1516 (1943).
(6) BACHMANN AND CRONYN, *J. Org. Chem.*, **8**, 456 (1943).
(7) SCHULTZ, GOLDBERG, ORDAS, AND CARSCH, *J. Org. Chem.*, **11**, 320 (1946).
(8) EDDY, Unpublished results.
(9) COATNEY AND COOPER, Unpublished results.
(10) DI CARLO, *J. Am. Chem. Soc.*, **66**, 1420 (1944).
(11) MAY AND MOSETTIG, *J. Org. Chem.*, **11**, 441 (1946).
(12) MAY AND MOSETTIG, *J. Org. Chem.*, **11**, 1 (1946).