[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY AND CHEMOTHERAPY, EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

FUNCTIONAL DERIVATIVES OF THE ANTIMALARIAL 9-(2-DIAMYLAMINO-1-HYDROXYETHYL)-1,2,3,4-TETRAHYDROPHENANTHRENE (SN 1796[1])

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Within the malaria research program carried out by the Section on Chemotherapy of this Laboratory it became advisable to synthesize two derivatives of the very active antimalarial 9-(2-diamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene (SN 1796) (1). The first compound, 9-(1-chloro-2-diamylaminoethyl)-1,2,3,4-tetrahydrophenanthrene (SN 8845), is distinguished from SN 1796 by having the hydroxyl group replaced by chlorine; it was prepared from the parent compound by the action of phosphorus pentachloride. The second compound, 9-(2-diamylaminoethyl)-1,2,3,4-tetrahydrophenanthrene (SN 11,580), is the desoxy derivative of SN 1796; it was prepared from the chloro compound by hydrogenation in the presence of a palladium catalyst.

While the chloro compound showed about the same antimalarial activity as SN 1796 (Q 0.3, *Plasmodium gallinaceum*), the desoxy compound was inactive. Neither compound showed any activity on sporozoite-induced *gallinaceum* malaria (2).

$C_{14}H_{13}$-9-$CHOHCH_2N(C_5H_{11})_2$	SN 1796
$C_{14}H_{13}$-9-$CHClCH_2N(C_5H_{11})_2$	SN 8845
$C_{14}H_{13}$-9-$CH_2CH_2N(C_5H_{11})_2$	SN 11,580

EXPERIMENTAL PART

9-(1-Chloro-2-diamylaminoethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (SN 8845). Although consistently high yields of this compound were not obtained, the most satisfactory procedure was as follows. To 8.4 g. of powdered phosphorous pentachloride suspended in 100 ml. of alcohol-free, dry chloroform was added gradually 8.4 g. of 9-(2-diamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (1). The flask containing the mixture was shaken gently in a bath of cold water until homogeneous, then left overnight at room temperature. If ether was added at this point, an oil precipitated and became crystalline spontaneously in the course of several hours. This material appeared to be an addition compound of the desired chloride with a phosphorus halide and was not investigated further. Instead, the original chloroform solution was concentrated *in vacuo* and the resulting oil was shaken for a few minutes with 100 ml. of absolute ether to extract as much of the phosphorus halides as possible. The mixture was left in the refrigerator overnight or longer until the oil had crystallized completely. The ethereal solution was then decanted, and the solid residue was decomposed carefully by shaking it with ice and ether to which small amounts of sodium carbonate were added from time to time until the aqueous layer remained slightly alkaline. The ethereal layer containing the free organic

[1] The Survey Numbers, designated SN, correspond to those listed in F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," J. W. Edwards, Ann Arbor, 1946.

base was separated, washed with water, dried with Drierite, and concentrated *in vacuo* to a sirup. An equivalent amount of methyl alcoholic hydrogen chloride was added, and the mixture was concentrated *in vacuo* to a sirup which could be crystallized with ether and isopentane. The yield was 8.0 g. For analysis the substance was recrystallized thrice from a small amount of methyl alcohol by the addition of ether and isopentane. The product, bundles of thin plates, sintered at about 82° and melted at 89–91° to a yellowish melt; after standing for several weeks in a desiccator, the crystals melted at about 95°; they became brownish yellow on continued exposure to light.

Anal.[2] Calc'd for $C_{26}H_{33}ClN \cdot HCl$: C, 71.54; H, 9.01; Cl, 16.25; N, 3.21.
Found: C, 71.09; H, 8.78; Cl, 16.40; N, 2.84.

9-(2-Diamylaminoethyl)-1,2,3,4-tetrahydrophenanthrene picrate. Removal of chlorine from the preceding compound was effected by catalytic hydrogenation in the presence of palladium hydroxide (with zinc and copper hydroxides) on calcium carbonate, prepared by the method of Kuhn and Ströbele (3). A mixture of 0.3 g. of catalyst, 2.7 g. of calcium carbonate, and 75 ml. of methyl alcohol was shaken with hydrogen to reduce the catalyst, then 2.2 g. of the chloro compound was added, and the mixture was shaken with hydrogen until no further change in volume occurred. The reaction was completed within forty-five minutes at 30°, with 95 ml. of hydrogen being absorbed; the theory for complete unimolecular reduction was 124 ml. The methyl alcohol solution was filtered, concentrated *in vacuo*, and the residue extracted with ether; a small amount of aqueous sodium hydroxide was added to ensure complete liberation of the organic base. The ethereal solution was washed with water, dried with Drierite, concentrated, and the residue subjected to evaporative distillation. A mobile, yellowish oil weighing 1.5 g. was obtained between 100° and 150° at 0.1 mm. It was dissolved in ether and mixed with 1.5 g. of picric acid in absolute ethyl alcohol. Upon concentration of this solution, 1.5 g. of crystalline picrate separated; recrystallized thrice from absolute alcohol, it formed clusters of large, elongated, yellow prisms melting at 110–111°.

Anal.[2] Calc'd for $C_{32}H_{42}N_4O_7$: C, 64.62; H, 7.12; N, 9.42.
Found: C, 64.67; H, 7.09; N, 9.41.

9-(2-Diamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene picrate. For comparison with the picrate just described, the picrate of the 2-diamylamino-1-hydroxyethyl derivative also was prepared. Four recrystallizations from absolute ethyl alcohol yielded clusters of yellow, elongated, somewhat flattened prisms which sintered at about 142°, and melted at 150–151°.

Anal.[2] Calc'd for $C_{32}H_{42}N_4O_8$: C, 62.93; H, 6.93; N, 9.17.
Found: C, 62.92; H, 7.01; N, 9.20.

9-(2-Diamylaminoethyl)-1,2,3,4-tetrahydrophenanthrene acid sulfate (SN 11,580). Preliminary experiments showed that the 2-diamylaminoethyl compound could be characterized also by the crystalline products which it formed with perchloric, *l*-malic, and sulfuric acids. For biological tests the sulfate was chosen. Accordingly, 11.4 g. of the purified picrate was dissolved in 1 liter of ether, and the solution was extracted with 10% aqueous sodium hydroxide until all the picric acid had been removed. The ethereal solution was washed with water, dried with Drierite, and concentrated to 200 ml.; an equivalent amount of concentrated sulfuric acid (1.1 ml.) was added, and the ether removed *in vacuo*. The residual sirup solidified, and was recrystallized four times from absolute ethyl alcohol by the addition of ether and isopentane. The product separated in clusters of small, thin plates which melted at 124–127° after preliminary sintering at 120°. The yield was practically quantitative. The sulfate appeared to hydrolyze to oily drops when added to water.

Anal.[2] Calc'd for $C_{26}H_{39}N \cdot H_2SO_4$: C, 67.35; H, 8.91; N, 3.02.
Found: C, 67.41; H, 8.86; N, 2.97.

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[2] The microanalyses were carried out by Dr. Arthur T. Ness of this Laboratory.

SUMMARY

The antimalarial 9-(2-diamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene (SN 1796) has been converted to a chloro derivative (SN 8845) and a desoxy derivative (SN 11,580). The therapeutic evaluation of these derivatives is given.

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REFERENCES

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(2) COATNEY AND COOPER, unpublished results.
(3) KUHN AND STRÖBELE, *Ber.*, **70**, 786 (1937).