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

ATTEMPTS TO FIND NEW ANTIMALARIALS. V. STUDIES IN THE ACRIDINE SERIES. 9-N-HETEROCYCLIC ACRIDINES AND 9-ACRIDYLSULFANILAMIDES[1]

LEWIS J. SARGENT AND LYNDON SMALL

Received November 15, 1945

With the synthesis of Atabrine and the demonstration of its high antimalarial activity a little over a decade ago (1), interest in compounds of related structure has expanded tremendously. Significantly, nearly all the effort expended in these researches was concerned with derivatives of 9-aminoacridine. This was principally due to the fact that only the 9-N-substituted aminoacridines exhibited plasmodicidal activity to any appreciable degree. By far, the bulk of the acridine compounds studied carried aminoalkamino groups of the type $-NH(CH_2)_nNR_2$ in the 9-position. Some notable exceptions were the heterocyclic substituted acridines recently described by Burckhalter (2). However, even in these latter cases the 9-amino nitrogen was part of an aliphatic and not a heterocyclic system. In view of this it was thought of interest to prepare certain substituted 9-aminoacridines in which the nitrogen atom of the amino group was an integral part of a heterocyclic system, *viz.* 6-methoxy-1,2,3,4-tetrahydroquinoline. In addition, the introduction of certain substituted sulfanilamido groups in the 9-position of the acridine molecule was carried out in order to determine the effect of these groups upon antimalarial activity.

With the exception of 9-chloroacridine, where anhydrous ether was employed as a solvent, 6-methoxytetrahydroquinoline was condensed with the variously substituted acridines in phenol at 90–100°. The condensation of 3,9-dichloro-7-methoxyacridine with sulfanilamide, sulfapyridine, and sulfathiazole gave best results in *n*-amyl alcohol at 120° yielding, in all cases, the corresponding hydrochlorides. With 2-aminothiazole, phenol proved to be the better solvent.

Antimalarial activity towards *P. gallinaceum* (chick infection) (3) was found present, in small degree, in compounds SN[2] 2762, 2667, and 2514 at the respective maximum tolerated doses. The remainder of the compounds were devoid of this property.

EXPERIMENTAL[3]

9-(6-Methoxytetrahydroquinolino)acridine (SN-2716). A solution of 5 g. of 9-chloroacridine (4) in 225 ml. of anhydrous ether was treated with 7.6 g. (2 moles) of 6-methoxytetrahydroquinoline[4] in 50 ml. of anhydrous ether and the mixture kept at room temperature

[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] The Survey Numbers (SN) are the identification numbers assigned by the Malaria Survey Office of the National Research Council.

[3] Analyses by Ass't Chemists L. R. Modlin and E. A. Garlock; m.p.'s are uncorrected.

[4] Prepared by high-pressure hydrogenation over copper chromite catalyst of 6-methoxyquinoline; for preparation of latter see Skraup, *Monatsh.*, **6**, 760 (1885).

for 60 hrs. The resulting orange solution was filtered from a small amount of insoluble matter, washed with water, dried over sodium sulfate and concentrated to small volume *in vacuo*. The residual, dark colored, oily crystals were covered with 40 ml. of ethanol and kept in the refrigerator for 12 hours, yielding a bright orange, crystalline product which was filtered, washed with a little cold ethanol, and dried; 5.2 g. (65%). Three recrystallizations from acetone afforded stout, orange prisms, m.p. 190–191.5°.

Anal. Calc'd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92.
Found: C, 81.35; H, 5.95.

3-Chloro-9-(6-methoxytetrahydroquinolino)acridine (SN-2637). A mixture of 8.1 g. of 3,9-dichloroacridine (5), 5.85 g. (1.1 moles) of 6-methoxytetrahydroquinoline, and 74 g. of phenol was heated in an oil-bath at 90–100° for 2 hours. After cooling, the melt was poured into 300 ml. of cold 10% sodium hydroxide and the resulting colored syrup taken up in ether. The latter solution was washed with water, dried over sodium sulfate, and concentrated to small volume *in vacuo*, yielding 2.6 g. (crop I) of dark red prisms, m.p. 192–194°. The concentrated mother liquor was freed of excess 6-methoxytetrahydroquinoline by steam distillation. The residual reddish-purple syrup, after trituration with ether and seeding, afforded 3.2 g. (crop II) of crystalline material. After one recrystallization from methanol 2.4 g. of dark red prisms, m.p. 191–193°, was recovered. Total yield of pure material 5 g. (42%).

Anal. Calc'd for $C_{23}H_{19}ClN_2O$: C, 73.69; H, 5.11.
Found: C, 73.43; H, 5.27.

7-Methoxy-9-(6-methoxytetrahydroquinolino)acridine (SN-2634). Twelve and seven-tenths grams of 7-methoxy-9-chloroacridine (4), 9.4 g. (1.1 moles) of 6-methoxytetrahydroquinoline, and 80 g. of phenol were heated together at 90–100° for 2 hours. The colored melt was poured into 350 ml. of cold 10% sodium hydroxide and the product extracted with ether. After washing the latter solution successively with dilute sodium hydroxide and water, concentration (*vacuo*) yielded a syrup from which the excess 6-methoxytetrahydroquinoline was removed by steam distillation. The resulting oil was taken up in ether and dried. From the ether a semi-crystalline mass was obtained which, after one trituration with 30–60° petroleum ether, followed by recrystallization from 50% methanol, yielded 8.5 g. of a bright orange powder of indefinite melting range 118–135°. Upon crystallization from absolute methanol the product separated as reddish-orange prisms which, however, were soon contaminated by the appearance of a by-product which crystallized in clusters of amber prisms. Owing to the marked difference in color as well as in crystalline form, the two substances were readily separated mechanically. Recrystallization of 6.6 g. of the orange prisms from methanol gave 5.7 g. of pure material, m.p. 138–140°.

Anal. Calc'd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99.
Found: C, 77.69; H, 6.03.

The amber colored by-product (1.1 g.) after recrystallization from methanol, melted at 151–153° and was identified as the intermediate 7-methoxy-9-phenoxyacridine by mixed m.p. with an authentic specimen, as well as by analysis.

3-Chloro-7-methoxy-9-(6-methoxytetrahydroquinolino)acridine (SN-2762). Seven and one-tenth grams of 3,9-dichloro-7-methoxyacridine (5) was condensed with 4.6 g. (1.1 moles) of 6-methoxytetrahydroquinoline in 45 g. of phenol as described above. The cooled, colored reaction mixture was poured into 200 ml. of 10% sodium hydroxide and the precipitated gum taken up in ether. From the dried ethereal solution there separated, on concentration *in vacuo*, a dark orange, crystalline powder which was recrystallized from ethanol, yielding 4.3 g. (crop I) of bright orange plates, m.p. 168–170°. The alcoholic mother liquor yielded, upon further concentration, 3.5 g. of less pure product which was recrystallized from acetone affording 2.5 g. (crop II) of relatively pure material, m.p. 161–164° (total yield, 6.8 g. or 65%). Crops I and II were combined and recrystallized from ethanol yielding 5.7 g. of pure product, m.p. 172–174°.

Anal. Calc'd for $C_{24}H_{21}ClN_2O_2$: C, 71.20; H, 5.23.
Found: C, 71.35; H, 5.45.

3-Chloro-7-methoxy-9-(8-amino-6-methoxyquinolino)acridine (SN-2667). The condensation of 7 g. of 3,9-dichloro-7-methoxyacridine with 4.4 g. (1 mole) of 6-methoxy-8-aminoquinoline[5] in 45 g. of phenol was carried out as previously described. The cooled melt was poured into 250 ml. of 10% sodium hydroxide and the yellow precipitate collected. It was successively washed by decantation with 5% sodium hydroxide then with water and finally air-dried. The crude material was purified by dissolving in 450 ml. of a hot mixture of chloroform-methanol (60:40) and concentrating to the point of incipient crystallization. After 24 hours (room temperature), 6.3 g. (60%) of bright yellow needles was collected; m.p. 244–245°.

Anal. Calc'd for $C_{24}H_{18}ClN_3O_2$: C, 69.16; H, 4.35.
Found: C, 69.43; H, 4.29.

3-Chloro-7-methoxy-9-(2-aminothiazolyl)acridine (SN-1440). Five grams of 3,9-dichloro-7-methoxyacridine was heated with 1.8 g. (1 mole) of 2-aminothiazole in 32 g. of phenol at 90–100° for 2 hours. The dark red melt was cooled, poured into 250 ml. of cold 10% sodium hydroxide and the red precipitate collected and washed several times with water by decantation. The yield of crude, air-dried product was 5.5 g. (86%). Recrystallization from ethanol afforded 2.3 g. of dark red microprisms, m.p. 246–247° (decomp.).

Anal. Calc'd for $C_{17}H_{12}ClN_3OS$: C, 59.73; H, 3.54.
Found: C, 59.41; H, 3.99.

N^4-[9-(3-Chloro-7-methoxyacridyl)]sulfanilamide hydrochloride (SN-188). A mechanically stirred mixture of 7 g. of 3,9-dichloro-7-methoxyacridine and 4.35 g. (1 mole) of sulfanilamide in 50 ml. of *n*-amyl alcohol was heated at 120° (oil-bath) for 2.25 hours. The bright orange, microcrystalline precipitate was filtered, triturated with hot (100°) amyl alcohol, washed with ether, and dried; the yield was 9.2 g. (80%). Recrystallization from a large volume of ethanol, in the presence of a few drops of alcoholic HCl to prevent hydrolysis of the salt, afforded minute, bright orange plates, m.p. 305–307° (decomp.).

Anal. Calc'd for $C_{20}H_{17}Cl_2N_3O_3S$: C, 53.34; H, 3.81.
Found: C, 53.00; H, 3.90.

N^1-(2-Thiazolyl)-N^4[9-(3-chloro-7-methoxyacridyl)]sulfanilamide hydrochloride (SN-2514). The condensation of 7 g. of 3,9-dichloro-7-methoxyacridine with 6.42 g. (1 mole) of sulfathiazole in 50 ml. of *n*-amyl alcohol was carried out as described in the preceding preparation. The washed and dried product consisted of a yellow-orange powder, 11 g. (81%). It was recrystallized from a large volume of ethanol, in the presence of a little alcoholic HCl and recovered as golden-yellow leaves, m.p. 301–303°.

Anal. Calc'd for $C_{23}H_{18}Cl_2N_4O_3S_2$: C, 51.78; H, 3.40.
Found: C, 51.71; H, 3.46.

N^1-(2-Pyridyl)-N^4[9-(3-chloro-7-methoxyacridyl)]sulfanilamide hydrochloride (SN-2515). Seven grams of 3,9-dichloro-7-methoxyacridine and 6.27 g. (1 mole) of sulfapyridine were condensed in 50 ml. of *n*-amyl alcohol in the above manner. The bright yellow, crystalline product, 10 g. (75%) crystallized from ethanol in minute, yellow, rhombic plates, m.p. 302–303° (decomp.).

Anal. Calc'd for $C_{25}H_{20}Cl_2N_4O_3S$: C, 56.93; H, 3.82.
Found: C, 56.99; H, 3.96.

SUMMARY

The synthesis of several N-substituted heterocyclic as well as certain 9-acridylsulfanilamides is described. A few of these compounds showed slight antimalarial activity.

BETHESDA 14, MD.

[5] Prepared by reduction ($SnCl_2$+HCl) of 6-methoxy-8-nitroquinoline; for latter see *Chem. Absts.*, **22**, 1216 (1928).

REFERENCES

(1) MIETSZCH AND MAUSS, *Klin. Woch.*, **12**, 1276 (1933); *Angew. Chem.* **47**, 633 (1934).
(2) BURCKHALTER AND CO-WORKERS, *J. Am. Chem. Soc.*, **65**, 2012 (1943); see also QUINN AND ROBINSON, *J. Chem. Soc.*, 555 (1943).
(3) COATNEY AND COOPER; EDDY, This laboratory, private communication.
(4) MAGIDSON AND GRIGOROWSKII, *Ber.*, **66**, 866 (1933).
(5) MAGIDSON, GRIGOROWSKII, AND GALPERIN, *J. Gen. Chem. (U.S.S.R.)*, **8**, 56 (1938); see *Chem. Absts.*, **32**, 5405 (1938).