Antimalarial Agents VIII. Synthesis of Amopyroquine

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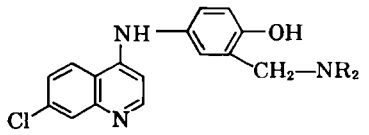
Synthesis of the new parenteral antimalarial amopyroquine and analogs is described.

A BRIEF chemical study was designed to provide analogs of the antimalarial agent amodiaquine (I) hydrochloride U.S.P. (1) in which the diethylamino group was replaced by pyrrolidino, hexamethylenimino, and 4-methylpiperazino (structures II, IV, and V, respectively). The piperidino



		—NR_2
I	(amodiaquine)	$-N(CH_2CH_3)_2$
II	(amopyroquine)	$-N$
III		$-N$
IV		$-N$
V		$-N\langle\rangle NCH_3$

analog III has been previously described (1). The ethyl groups of I are free to move, while the movements of the corresponding groups of II, III, IV, and V are restricted owing to the cyclic structures. Models readily show the three-dimensional nature of the cyclic amines piperidine, hexamethylenimino, and N-methylpiperazine, while all the carbon atoms of pyrrolidine occupy the same plane. Also, V contains an additional ionic center as seen in the second basic nitrogen. In view of these considerations, the compounds were desired for a study of relative antimalarial activity and usefulness.

In order to obtain amopyroquinone (II),[1] *p*-acetamidophenol, pyrrolidine, and aqueous formaldehyde were subjected to Mannich conditions (1). When the intermediate *p*-acetamido-α-pyrrolidino-*o*-cresol was not obtained in crystalline form, the oily substance was hydrolyzed by acid and the unisolated diamine condensed with 4,7-dichloroquinoline to give 4-(7-chloro-4-quinolylamino)-α-pyrrolidino-*o*-cresol (amopyroquine II) in 78% yield. Compounds IV and V were similarly prepared by substitution of hexamethylenimine and N-methylpiperazine for pyrrolidine. In the case of IV, intermediate *p*-acetamido-α-hexamethylenimino-*o*-cresol could be isolated as the crystalline monohydrochloride in 51% yield.

An acridine analog of amopyroquine was obtained by substitution of 6,9-dichloro-2-methoxyacridine for 4,7-dichloroquinoline in the preparative procedure of II.

Pharmacological Results.[2]—Compound II (amopyroquine) is 37 times as active as quinine (*Plasmodium lophurae* in chicks) or equiactive with amodiaquine (2). Toxicity studies reveal that amopyroquine is considerably less toxic than amodiaquine, suggesting the former as a potential antimalarial for parenteral use (2). It has been found to be effective in human malaria (3) and is especially recommended as an agent of choice for intramuscular administration (4).

Compound III is 10 times as active as quinine (*P. lophurae* in ducks) (6), while IV is 3.5 times as active as quinine, V is 1.5 and the 6-chloro-2-methoxy-9-acridyl analog of amopyroquine is 5 (*P. lophurae* in chicks).

Conclusions drawn from the limited biological data in animals are that a total of four carbon atoms in the NR_2 grouping of structures I to V affords optimum antimalarial effectiveness; and if the carbons are rigidly held in the same plane as in amopyroquine, systemic toxicity is low.

EXPERIMENTAL

4-(7-Chloro-4-quinolylamino)-α-pyrrolidino-*o*-cresol (II).—A mixture of 45.3 Gm. (0.3 mole) of *p*-acetamidophenol, 25 ml. (0.3 mole) of 37% formaldehyde solution, 21.3 Gm. (0.3 mole) of pyrrolidine, and 75 ml. of 95% ethyl alcohol was refluxed for 2½ hours. When a solid product was not isolated, the solvent was removed *in vacuo* to leave a thick, sirupy residue. One-third of the residue was refluxed for 1 hour with 50 ml. of 20% hydrochloric acid. The solution was cooled and treated with 6*N* sodium hydroxide until just acidic to Congo red. After the addition of 19.8 Gm. (0.1 mole) of 4,7-dichloroquinoline, the mixture was refluxed for 2 hours. The solution was cooled and made basic with 28% ammonium hydroxide to give 27.5 Gm. (78% yield) of light yellow product, m.p. 186–191° dec. A sample was prepared for analysis by repeated recrystallization from isopropyl alcohol-water, m.p. 196–198° dec.

Anal.—Calcd. for $C_{20}H_{20}ClN_3O$: C, 67.88; H, 5.69. Found: C, 67.60; H, 5.76.

Dihydrochloride of II.[3]—Crude II free base was dissolved in warm isopropyl alcohol, treated with charcoal and then with an excess of dry hydrogen chloride to precipitate a yellow crystalline dihydrochloride, m.p. 288–290° dec. Two recrystallizations from isopropyl alcohol elevated the melting point to 299–300° dec.

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[1] Marketed as Propoquin by Parke, Davis and Co., Detroit, Mich.

[2] Dr. P. E. Thompson, of Parke, Davis and Co., Research Department, Ann Arbor, Mich., has kindly furnished data on antimalarial studies in chicks.

[3] Data kindly furnished by Dr. Robert F. Meyer, Research Department, Parke, Davis and Co., Ann Arbor, Mich.

Anal.—Calcd. for $C_{20}H_{20}ClN_3O \cdot 2HCl$: C, 56.28; H, 5.20; Cl (ionic), 16.62. Found: C, 55.95; H, 5.36; Cl, 16.26.

4-(6-Chloro-2-methoxy-9-acridylamino)-α-pyrrolidino-o-cresol Dihydrochloride Sesquihydrate.—One-third of the residue from the preparation of II was treated as in that experiment except that 27.8 Gm. (0.1 mole) of 6,9-dichloro-2-methoxyacridine replaced 4,7-dichloroquinoline. The hot reaction mixture was filtered in order to remove insoluble 6-chloro-9-(4-hydroxyanilino)-2-methoxyacridine. Cooling the filtrate gave 30 Gm. (56% yield) of dihydrochloride, m.p. 245–249° dec. It was recrystallized from alcohol-acetone, m.p. 252–253° dec.

Anal.—Calcd. for $C_{25}H_{24}ClN_3O_2 \cdot 2HCl \cdot 1^1/_2H_2O$: C, 56.25; H, 5.47. Found: C, 56.54; H, 5.37.

p-Acetamido-α-hexamethylenimino-o-cresol Monohydrochloride.—A mixture of 15.1 Gm. (0.1 mole) of *p*-acetamidophenol, 9.9 Gm. (0.1 mole) of hexamethylenimine (5), 3 Gm. (0.1 mole) of paraformaldehyde, and 25 ml. of alcohol was heated to boiling for 4 hours. When cooling gave no precipitate, solvent was removed by distillation under reduced pressure. The residual dark oil was dissolved in ether, and excess alcoholic hydrogen chloride added to precipitate a yellow viscous oil. After decantation of the ether, solution in hot isopropyl alcohol and cooling gave 15.3 Gm. (51% yield) of product, m.p. 192–194°. Recrystallization from the same solvent elevated the melting point to 194.5 to 195°.

Anal.—Calcd. for $C_{15}H_{22}N_2O_2 \cdot HCl$: C, 60.29; H, 7.76. Found: C, 60.46; H, 7.96.

4-(7-Chloro-4-quinolylamino)-α-hexamethylenimino-o-cresol (IV).—A mixture of 14.3 Gm. (0.0478 mole) of *p*-acetamido-α-hexamethyleniminо-*o*-cresol monohydrochloride and 20 ml. of 20% hydrochloric acid was heated at reflux temperature for 1 hour. Sodium hydroxide solution was added to the cooled solution until it was barely acidic to Congo red. After the addition of 9.5 Gm. (0.048 mole) of 4,7-dichloroquinoline, the mixture was heated on a steam bath for 2 hours. Then, with cooling, it was made basic to litmus with 10% sodium hydroxide. The precipitated yellow solid was recrystallized twice from benzene to give 3.8 Gm. (21% yield) of IV, m.p. 212–214° dec.

Anal.—Calcd. for $C_{22}H_{24}ClN_3O$: C, 69.19; H, 6.33. Found: C, 69.31; H, 6.35.

It was found that following the procedure for II, which does not entail isolation of a purified acetamido Mannich phenolic base, actually led to a better yield of IV (45%).

4-(7-Chloro-4-quinolylamino)-α-(4-methyl-1-piperazinyl)-o-cresol (V) Trihydrochloride Dihydrate.—Procedure for II was followed; however, the free base was extracted with chloroform instead of being isolated. The extract was washed with water, dried over potassium carbonate, and treated with excess alcoholic hydrogen chloride. The addition of acetone completed precipitation of product. Recrystallization from alcohol gave 28 Gm. (53% yield) of bright yellow crystalline powder, m.p. 240–300° dec. It is very soluble in water.

Anal.—Calcd. for $C_{21}H_{23}ClN_4O \cdot 3HCl \cdot 2H_2O$: C, 47.73; H, 5.72. Found: C, 47.67; H, 5.93.

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Antifungal Properties of Perfume Oils

By JASPER C. MARUZZELLA

The antifungal properties of 30 perfume oils were tested by allowing the organisms to grow in varying concentrations of the oils *in vitro*. Fifteen of the perfume oils inhibited the growth of all test organisms at concentrations ranging from 1:500 to 1:13,000. The remaining 15 oils inhibited some of the test organisms at concentrations up to 1:11,000. Oil of rose no. 81412 otto type, crab apple blossom, and rose briar were found to possess marked antifungal properties. The dermatophytes were extremely susceptible to many of the perfume oils at minute concentrations.

PERFUME OILS were demonstrated to possess remarkable fungicidal properties when studied by the filter paper disk method (1). However, the oils were tested in the undiluted form at which strength they are rarely used in cosmetics and medicaments. Small amounts of perfumery materials are added to toilet articles and dermatological products in an attempt to render the item more fragrant and to mask unpleasant odors. Whether such minute concentrations possess germicidal properties has been suggested (2) but not experimentally established. This investigation was undertaken in order to determine the mimimal concentration of perfume oil needed to inhibit the growth of fungi *in vitro*.

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