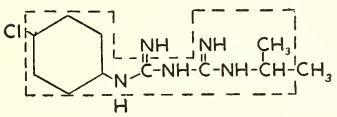
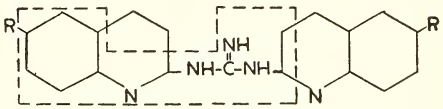
Synthesis of Symmetrical Diquinolylguanidines[1]

G. Bryant Bachman and Martin Hamer, Purdue University

The antimalarial activity of Paludrine (I) and, to a lesser extent, that of certain 2,8′-diquinolylamines (Cooper, 1) has suggested to us the desirability of preparing and testing 1,3-di-(2′-quinolyl)guanidine (II) and its 6,6′-dimethoxy derivative. The structural analogy between these molecules is rather close as may be seen from the following formulas in which similar parts are outlined.



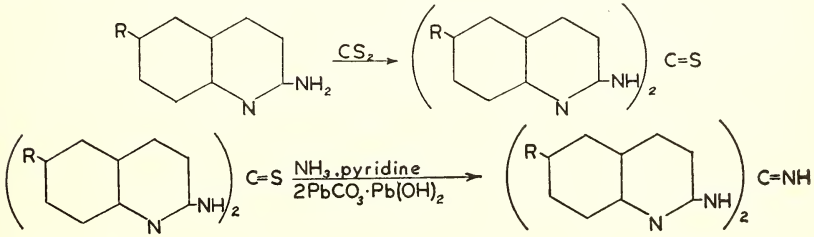
Paludrine I



Diquinolylguanidines
II, R is -H; III, R is -OCH_3

The first attempts to prepare diquinolylguanidine (II) involved reaction between 2-chloroquinoline and guanidine salts. With guanidine carbonate in phenol at 180°, the chief product of the reaction was 2-phenoxyquinoline; however, a small amount (0.2 g.) of a product was obtained which by mixed melting points seemed to be identical with II prepared in a subsequent reaction. With guanidine hydrochloride in moist hexanol, only 2-hydroxyquinoline was obtained. Fusion of 2-chloroquinoline with guanidine carbonate at 210-235° did not alter the chloro compound.

The above unsuccessful attempts to obtain direct arylation of guanidine in satisfactory yields were abandoned in favor of an indirect approach. Topchiev (4) obtained 1,3-di-(2′-pyridyl)guanidine from 2-aminopyridine by condensation with carbon disulfide followed by desulfurization and ammonolysis in the presence of basic lead carbonate. This method was applied successfully by us in the preparation of II and III.



[1] An abstract of a thesis submitted to the faculty of Purdue University by Martin Hamer in partial fulfillment of the requirements for the degree of Master of Science.

Reaction with carbon disulfide was much slower in the quinoline series (3 weeks) than that observed by Topchiev in the pyridine series (4 days). Morover, the yields were less satisfactory (35-37% compared to 65%). Ammonolysis of the thioureas may easily proceed too far (to 2-aminoquinolines) if conditions in the second step of the synthesis are too drastic. Under milder conditions, the yield in this step is good (64%).

Compounds II and III are almost completely insoluble in water, dilute mineral acids and the common organic solvents. This remarkable behavior precludes their testing as antimalarials.

Experimental

Condensation of 2-chloroquinoline with guanidine—(a) In phenol-2-Chloroquinoline, 29.4 g. (0.18 mole), and 8.1 g. (0.09 mole) of guanidine carbonate were heated in phenol, 177.0 g. (1.88 moles), at 180° for 21 hours. The dark reddish-brown mixture was allowed to cool and was then poured into 900 g. of 10% NaOH solution. A dark yellow oil separated which solidified upon cooling. The solid was filtered, washed with aqueous alkali and water, and then recrystallized from ethanol. The first product which separated was recrystallized from pyridine to m.p. 237° (yield 0.2 g.): picrate m.p. 288° d. (uncorr.). These m.p.'s were unchanged when the substances were mixed with authentic samples of 1,3-diquinolylguanidine and its picrate as prepared in later experiments. The second product obtained from the ethanol solution was recrystallized from methanol to m.p. 61.5-62.5°. This compound (10.6 g.) was found to be the known 2-phenoxyquinoline.

Anal. Calcd. for $C_{15}H_{11}ON$: C, 81.42; H, 5.02; N, 6.33. Found: C, 81.50; H, 4.94; N, 6.31.

(b) Without solvent—2-Chloroquinoline, 3.6 g., and guanidine carbonate, 1.0 g., were heated together in a tube to 210° by means of an oil bath. Complete melting did not occur, and upon cooling, most of the chloroquinoline was recovered. Direct fusion at 235° gave similar results.

(c) In hexanol—A mixture of guanidine hydrochloride, 9.6 g. (0.1 mole), and 2-chloroquinoline, 32.7 g. (0.2 mole) was heated in 100 ml. of hexanol under reflux for 48 hours. The tan solid which appeared upon cooling was washed well with aqueous alkali. Recrystallization of the free amine from an ethanol-water mixture yielded 11.2 g. of white crystals, m.p. 195-196°. Analysis showed it to be the known 2-hydroxyquinoline.

Anal. Calcd. for C_9H_7ON: N, 9.66. Found: N, 9.70, 9.76. The picrate melted at 134°; literature m.p. 132° (Kent, et al, 3).

2-Aminoquinoline—The 2-aminoquinoline used to prepare the 1,3-di(2′-quinolyl)thiourea was made by the method of Elderfield (2) for 4-aminoquinoline. Gaseous ammonia was bubbled for 11 hours through a refluxing solution of 39.6 g. (0.24 moles) of 2-chloroquinoline in 226 g. (2.4 moles) of phenol. A solid remained in the flask until the end of

this period. The reaction mixture was cooled and poured into 900 g. of 10% NaOH solution. The yellow solid which separated was washed with water and recrystallized from benzene. 2-Aminoquinoline, 13.0 g., m.p. 128-129°, was obtained (37% yield).

2-Amino-6-Methoxyquinoline—Essentially the same procedure was employed in preparing the 6-methoxy analogue; however, a longer reaction time (24 hours) was used. Gaseous ammonia was bubbled for 24 hours through a refluxing solution of 44.7 g. (0.23 mole) of 2-chloro-6-methoxyquinoline in 226.1 g. (2.41 moles) of phenol. At the end of this time, the reaction was stopped, allowed to cool, and the reaction mixture poured into a solution of 115 g. of NaOH in a liter of water. The product which separated was washed with NaOH solution and several times with water. After recrystallizing from benzene, 20.6 g. of the white, crystalline 2-amino-6-methoxyquinoline, m.p. 179.5-181° were obtained (51% yield).

1,3-Di-(2′-quinolyl)thiourea—A mixture of 2-aminoquinoline, 12.6 g. (0.087 mole), carbon disulfide, 30 ml., and sulfur, 0.2 g., was refluxed for 21 days. A gas (H_2S) was evolved slowly throughout this period of time. The reaction mixture was cooled and filtered. The solid product was shaken with ethanol to dissolve the unreacted 2-aminoquinoline. The residue, after recrystallization from pyridine, melted at 214° and gave a positive test for sulfur after Na fusion. The yield was 5.1 g. of a white crystalline solid (35% theory). Analysis showed it to be 1,3-di-(2′-quinolyl)thiourea.

Anal. Calcd. for $C_{19}H_{14}N_4S$: N, 17.01. Found: N, 17.00.

1,3-Di-(2′-quinolyl)guanidine—The above thiourea, 4.5 g., was dissolved in 60 ml. of pyridine which had been previously saturated with ammonia gas. Basic lead carbonate, $2PbCO_3 \cdot Pb(OH)_2$, 25 g., was added, and ammonia was bubbled through the refluxing mixture for 15 hours. A small amount of the clear liquid was withdrawn and heated with fresh basic lead carbonate to test for completeness of reaction. Since no PbS precipitated, the entire mixture was filtered and the filtrate evaporated to 20 ml. The solid which separated on cooling was recrystallized from pyridine. Yield 0.11 g. (2.6% theory) of white crystals, m.p. 236°. Analysis showed it to be the desired product, 1,3-di-(2′-quinolyl)guanidine.

Anal. Calcd. for $C_{19}H_{15}N_5$: N, 22.35. Found: N, 22.25. The picrate prepared from a nitrobenzene solution decomposed at 284° (uncor.).

1,3-Di-(6′methoxy-2′-quinolyl)thiourea—A mixture of 2-amino-6-methoxyquinoline, 20.3 g. (0.12 mole), toluene, 200 ml., carbon disulfide, 40 ml., and sulfur, 0.2 g., was refluxed for 25 days on the steam bath. The odor of H_2S was detected even at the end of this period of time. The reaction was not run continuously, but was stopped twice during the course of the reaction, and the insoluble thiourea which had precipitated was filtered off. Also small amounts of carbon disulfide were added frequently to replace that lost by evaporation. The solid product

was separated and washed with ethanol to remove the unreacted aminoquinoline. All of the batches of thiourea collected were combined and recrystallized from pyridine. Yield, 8.5 g. (37% theory) of yellow, fine needles, m.p. 241.5-242°.

Anal. Calcd. for $C_{21}H_{18}O_2N_4S$: N, 14.35. Found: N, 14.41.

1,3-Di-(6′-methoxy-2′-quinolyl)guanidine—A solution of the above thiourea, 8.4 g. (.022 mole), in 150 ml. of pyridine was saturated with ammonia gas. Basic lead carbonate, 50 g., was added, and the mixture was heated with stirring at 112° for 7 hours. The gas was not passed through continuously but only intermittently for short periods of time. The warm reaction mixture was filtered, evaporated to 25 ml. and cooled. Recrystallization of the precipitated solid from pyridine gave 5.0 g. (62% theory) of white crystalline 1,3-di-(6′-methoxy-2′-quinolyl)-guanidine, m.p. 240.5-241.5°.

Anal. Calcd. for $C_{21}H_{19}O_2N_5$: N, 18.76. Found: N, 18.63. The conditions used in the above desulfurization were less drastic than those employed for the unsubstituted thiourea; viz., less ammonia and a shorter reaction time. This probably accounts for the greatly improved yield.

Summary

1,3-Di-(2′-quinolyl)guanidine and its 6,6′-dimethoxy derivative have been prepared from the corresponding 2-quinolylamines via the diquinolylthioureas. The guanidines as well as their hydrochlorides and nitrates were too insoluble to permit testing as antimalarials.

Literature Cited

1. COOPER, D. E. 1943. Ph.D. Thesis, Purdue University.
2. ELDERFIELD, R. C., et al. 1946. Synthesis of certain simple 4-aminoquinoline derivatives. J. Am. Chem. Soc., **68**:1250.
3. KENT, A., MCNEIL, D., and COWPER, R. M. 1946. Compounds of polynitrosubstances with derivatives of carbostyril. J. Chem. Soc., **1946**:1860.
4. TOPCHIEV, K. S. 1934. Dipyridylguanidine and its derivatives. Arch. Pharm., **272**:775.