[CONTRIBUTION FROM ABBOTT LABORATORIES]

Some Displacement Reactions of 4,7-Dichloro-1-methylquinolinium Ion

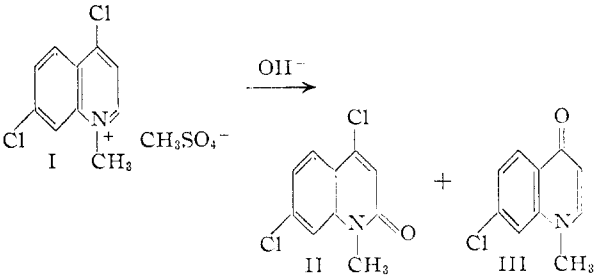
BY R. U. SCHOCK

RECEIVED JULY 23, 1956

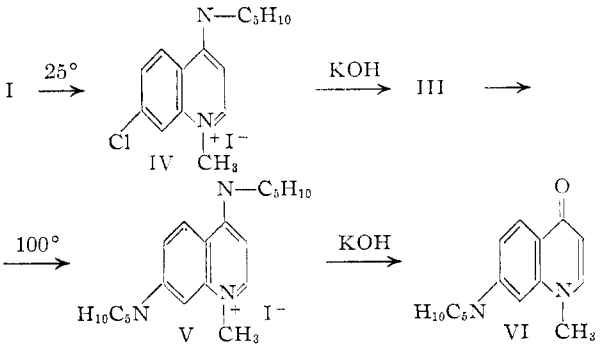
Hydrolysis of 4,7-dichloroquinoline methosulfate with aqueous alkali produces a mixture of 4,7-dichloro-1-methyl-2-quinolone and 7-chloro-1-methyl-4-quinolone. Displacement of the 4-chloro group by amine readily takes place at room temperature. At higher temperatures, the 7-chlorine substituent is also replaced. Aromatic amines as hydrochlorides react at the 4-position, also at room temperature. The synthesis of a nuclear quaternized version of the antimalarial drug amodiaquin is described.

Few references cite reactions of 1-methyl-4-haloquinolinium salts. An unsuccessful attempt to oxidize 4,7-dichloro-1-methylquinolinium iodide to the corresponding carbostyril has been reported.[1] 1-Methyl-4-chloroquinolinium iodide has been used to alkylate sodiomalonitrile.[2] The 4-haloquinolium salts also find utility in structure determination in isocyanine dyes.[3] As one would expect, there is a profound difference in activity between the two substituents in 4,7-dichloroquinoline, and, under ordinary circumstances, only the 4-chloro group is reactive. Under more vigorous conditions, the 7-chloro group may be displaced by the arylthio[4] substituent at 150–170° and by dimethylamino at 290°.[5] In this Laboratory it has been found that when 4,7-dichloroquinoline is quaternized, both chlorine substituents are rendered more amenable to reaction. The effect of inorganic and organic bases upon the halogens of this salt is the subject of this communication.

When aqueous solutions of 4,7-dichloroquinoline methosulfate (I) and alkali were mixed, the 2-quinolone II[1] and the 4-quinolone III were formed. The identity of II as 4,7-dichloro-1-methyl-2-quinolone[1] rests on the following considerations: elemental analysis, melting point and similarity in ultraviolet absorption spectrum to 1-methyl-2-quinolone.[6] Compound II also was converted with phosphorus pentachloride to 2,4,7-trichloroquinoline, as previously described.[1] The structure proposed for III follows from the resemblance of its ultraviolet absorption spectrum to that of 1-methyl-4-quinolone.[6,7] Typical bifurcation of the two peaks in the 326–339 mμ and 248–256 mμ regions clearly demonstrates the presence of the 4-quinolone function.[8] The formation of II may be rationalized by assuming that the intermediate pseudo base is oxidized by air or perhaps is the result of a disproportion.[9] The 4-quinolone III is formed through simple displacement by hydroxyl and, indeed, by warming with sodium bicarbonate instead of potassium hydroxide, an 84% yield of III may be obtained. These reactions are



The reaction of 4,7-dichloroquinoline with amines is usually carried out in molten phenol wherein the latter serves to create a reactive intermediate.[10] In the absence of phenol, higher temperatures may be required. In contrast to this behavior, compound I reacted exothermically with piperidine at room temperature to form the 4-piperidino derivative IV, isolated as the iodide salt. 2-Aminopyridine reacted in a similar fashion. Alkaline hydrolysis of the quaternary salt IV then led to the previously discussed quinolone III. By warming I with excess piperidine on the steam-bath, both halogens are displaced and the corresponding 4,7-dipiperidino compound V formed. Alkaline hydrolysis of V then produced the quinolone VI. *n*-Amylamine reacted with I in a similar fashion. These reactions are depicted in the diagram



Activation of both chlorine substituents is brought about by an electronic shift caused by the formal positive charge on the nitrogen atom.

(1) R. E. Lutz, *et al.*, THIS JOURNAL, **68**, 1810 (1946).

(2) N. J. Leonard and R. L. Foster, *ibid.*, **74**, 2110 (1952).

(3) F. M. Hamer, *J. Chem. Soc.*, 1008 (1939).

(4) G. Illuminati and H. Gilman, THIS JOURNAL, **71**, 3349 (1949); **72**, 4288 (1950); G. Illuminati and L. Santucci, *Gazz. chim. ital.*, **83**, 1107 (1953).

(5) L. Bradford, T. J. Eliot and F. M. Rowe, *J. Chem. Soc.*, 437 (1947).

(6) R. D. Brown and F. N. Lahey, *Australian J. Sci. Res.*, **A3**, 622 (1950).

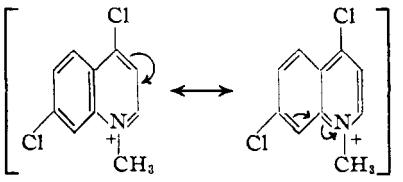
(7) An attempted oxidation of 1-methyl-4-methoxy-7-chloroquinolinium iodide as reported in ref. 1 yielded a compound of similar melting point and, in part, a similar analysis to III. Professor Lutz kindly supplied a sample for comparison and no melting point depression was observed on admixture. Thus the 4-methoxy group was displaced in the same manner as the corresponding chloro group.

(8) E. A. Steck, G. W. Ewing and F. C. Nachod, THIS JOURNAL, **71**, 238 (1949).

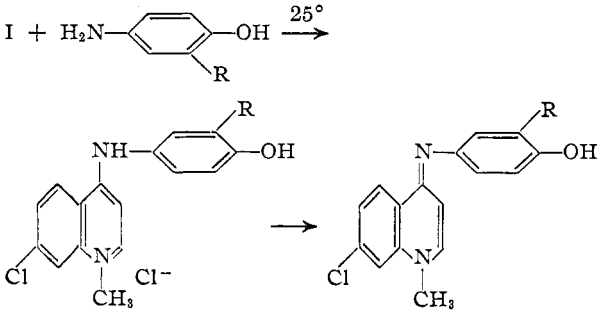
(9) Quinoline methiodide with alkali undergoes a disproportionating reaction to N-methylquinolone and N-methyl-1,2,3,4-tetrahydroquinoline; H. Decker, *Ber.*, **36**, 2568 (1903). However, no corresponding tetrahydroquinoline was isolated in experiments conducted in this Laboratory.

(10) A. R. Surrey and R. A. Cutler, THIS JOURNAL, **73**, 2623 (1951), demonstrate that the 4-phenoxyquinoline hydrochloride is the intermediate.

The electron deficiency at positions 4 and 7 renders these positions accessible to nucleophilic attack, *viz.*



It would thus be expected that facile replacement with anilino or substituted anilino groups would take place from considerations of similar electronic arrangement in mineral acid salts of 4-chloroquinolines. *p*-Aminophenol hydrochloride reacts with 4,7-dichloroquinoline in aqueous solution at 100° to produce the corresponding 4-(*p*-hydroxyanilino) derivative.[11] With I and *p*-aminophenol, within 20 minutes, the product VIIa began crystallizing from the solution at room temperature. With a view to preparing a nuclear quaternized version of the antimalarial drug amodiaquin, VIIa was condensed with formaldehyde and diethylamine. The precipitation of the highly insoluble imine VIIIa nullified the reaction. Reaction with 4-amino-2-diethylaminomethylphenol[11] led to the desired compound VIIa. The imine VIIb was formed by addition of ammonium hydroxide to its aqueous solution.



VIIa, R = H
VIIb, R = $CH_2N(C_2H_5)_2$

VIIIa
VIIIb

Experimental[12]

1-Methyl-4,7-dichloroquinolinium Methyl Sulfate (I).—A solution of 50 g. of 4,7-dichloroquinoline and 75 ml. of methyl sulfate in 400 ml. of dry benzene was stirred and heated under reflux for 5 hr. After the mixture cooled, the solid was filtered and washed with benzene. The product melted at 174–176° dec. and weighed 81.0 g. (99%). A sample recrystallized twice from acetone–methanol melted at 176–177°(dec.).

Anal. Calcd. for $C_{11}H_{11}Cl_2NO_4S$: C, 40.75; H, 3.42; N, 4.32. Found: C, 40.69; H, 3.57; N, 4.52.

Reaction of I with Aqueous Bases.—A solution of 3 g. of potassium hydroxide in 20 ml. of water was added to a solution of 6 g. of the methosulfate in 60 ml. of water. A colorless solid precipitated and turned to a dark oil. After standing, the oil solidified to a dark product which weighed 4.0 g. Recrystallization from dilute methanol (Darco) produced 0.81 g. of II, m.p. 159–160°.

In alcohol solution, three peaks were observed: 233 mμ (log ε 4.55), 278 mμ (log ε 3.92) and 336 mμ (log ε 3.92). Peaks in these ranges are characteristic of 2-quinolones.[13]

Anal. Calcd. for $C_{10}H_7Cl_2NO$: C, 52.66; H, 3.09; N, 6.14; Cl, 31.09. Found: C, 52.98; H, 3.18; N, 6.28; Cl, 30.83.

When this compound was heated with phosphorus pentachloride as in ref. 1, a product was isolated, m.p. 100–101° (reported m.p. 99–100°), which gave the correct analysis for 2,4,7-trichloroquinoline.

Anal. Calcd. for $C_9H_4Cl_3N$: C, 46.49; H, 1.73; N, 6.03; Cl, 45.74. Found: C, 46.17; H, 2.04; N, 6.44; Cl, 45.76.

The filtrate was concentrated to a small volume and allowed to crystallize. This produced 1.20 g. of III, m.p. 233–234°. An analytical sample recrystallized from dilute methanol melted at 235–236°.

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.02; H, 4.16; N, 7.23; Cl, 18.31. Found: C, 61.89; H, 4.46; N, 7.35; Cl, 18.24.

In alcohol solution, twin peaks at 248 mμ (log ε 4.36) and 256 mμ (log ε 4.38) and 326 mμ (log ε 4.06) and 3.39 mμ (log ε 4.08) were observed. The 4-quinolone III could be prepared in higher yield in the following manner. A solution of 5 g. of the methosulfate and 5 g. of sodium bicarbonate in 100 ml. of water was heated on the steam-bath for 4 hr. After the solution was cooled, the crystalline product was filtered and washed with water. The yield was 2.5 g. (84%), m.p. 233–234°, and unchanged on admixture with the product obtained in the potassium hydroxide experiment. Apparently no 2-quinolone was formed under these conditions.

Reaction Products of I with Amines. A. 4-Piperidyl-7-chloro-1-methylquinolinium Iodide (IV).—To a solution of 4.0 g. of I in 30 ml. of methanol was added 4 ml. of piperidine. A noticeable amount of heat was evolved. The solution was allowed to stand overnight; 4.0 g. of sodium iodide dissolved in a few ml. of water was added and the precipitated solid was filtered and washed with methanol. The yellow product weighed 3.8 g. and melted at 257–258°. Recrystallization did not change the melting point.

Anal. Calcd. for $C_{15}H_{18}ClIN_2$: C, 46.35; H, 4.67; N, 7.21. Found: C, 46.65; H, 4.86; N, 7.56.

A mixture of 3.0 g. of IV and 4.0 g. of potassium hydroxide in 75 ml. of water and 75 ml. of alcohol was boiled under reflux for 6 hr. Approximately half the solvent was distilled and the solid which separated on cooling was filtered and recrystallized from dilute methanol. The yield was 0.96 g.; the melting point of 231–232° was raised to 234–235° on admixture with III as prepared previously.

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.02; H, 4.16; N, 7.23. Found: C, 62.38; H, 4.10; N, 7.23.

B. 4,7-Dipiperidyl-1-methylquinolinium Iodide (V).—A mixture of 5.0 g. of I and 15 ml. of piperidine was heated for 5 hr. at 100°. The mixture was cooled and diluted with 100 ml. of ether and the precipitated semi-solid washed by decantation. A hot solution of 5 g. of sodium iodide in 100 ml. of water was then added and sufficient hot water to bring the oily material into solution. When the solution was cooled, yellow crystals accompanied by some oily material were obtained. This was recrystallized from hot water which yielded 3.0 g. of product, m.p. 237–238°. Further recrystallization did not raise the melting point.

Anal. Calcd. for $C_{20}H_{28}IN_3$: C, 54.92; H, 6.45; N, 9.61; I, 29.02. Found: C, 54.99; H, 6.63; N, 9.46; I, 28.47.

A mixture of 1.00 g. of V and 5 g. of potassium hydroxide in 125 ml. of water was heated for 16 hr. on the steam-bath. The solution was cooled and extracted with two 75-ml. portions of chloroform. Evaporation of the solvent left 0.51 g. of VI as a crystalline residue which was recrystallized twice from acetone–cyclohexane. It melted when pure at 166–167°.

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.12; H, 7.38; N, 11.67.

C. 4,7-Di-*n*-amylamino-1-methylquinolinium Iodide.—A mixture of 10 ml. of *n*-amylamine and 4.0 g. of I was treated as in B. A yield of 3.1 g. of product was obtained after recrystallization from methanol. The analytical sample melted at 216–218°.

Anal. Calcd. for $C_{20}H_{35}IN_3$: C, 54.42; H, 7.31; N, 9.52. Found: C, 54.38; H, 7.50; N, 9.34.

D. 7-Chloro-4-(α-pyridylamino)-1-methylquinolinium Iodide.—A solution of 3.24 g. of I and 5.0 g. of 2-amino-

(11) J. H. Burckhalter, *et al.*, THIS JOURNAL, **70**, 1363 (1948).

(12) Microanalyses by E. F. Shelberg and staff. All melting points are uncorrected.

(13) B. Witkop, J. P. Patrick and M. Rosenblum, THIS JOURNAL, **73**, 2644 (1951)

pyridine in 50 ml. of methanol was allowed to stand 16 hr. The solution was warmed to dissolve some precipitated material while 2–3 g. of sodium iodide was stirred in. When the solution was cooled, 3.1 g. of product was obtained. The analytical sample, which melted at 268–269°, was obtained by one crystallization from methanol.

Anal. Calcd. for $C_{15}H_{13}ClIN$: C, 45.30; H, 3.29; N, 10.57. Found: C, 45.31; H, 3.00; N, 10.55.

Reaction Products of I with Salts of Aromatic Amines. A. 7-Chloro-4-anilino-1-methylquinolinium Chloride.—A solution of 6.5 g. of I (0.02 mole) and 2.6 g. of aniline hydrochloride (0.02 mole) in 60 ml. of water was allowed to stand for 72 hr. The mixture was heated to boiling, made just neutral with ammonium hydroxide and a few grams of sodium chloride added. The yellow mat of needles was filtered and washed with cold 1:1 methanol–water. The product weighed 6.5 g. and melted at 285–286° (dec.) after two recrystallizations from acetone.

Anal. Calcd. for $C_{16}H_{14}Cl_2N_2$: C, 62.96; H, 4.62; N, 9.18. Found: C, 63.21; H, 4.80; N, 9.32.

B. 7-Chloro-4-*p*-hydroxyanilino-1-methylquinolinium chloride (VIIa).—A mixture of 16.2 g. of I (0.05 mole) and 8.0 g. of *p*-aminophenol hydrochloride (0.055 mole) was dissolved in 75 ml. of water. Within 20 minutes the product had begun to separate. After 16 hr., the solid was filtered and recrystallized from water. A yield of 10.6 g. was obtained, whose melting point was above 300°.

Anal. Calcd. for $C_{16}H_{14}Cl_2N_2O$: C, 59.82; H, 4.39; N, 8.72. Found: C, 59.57; H, 4.32; N, 8.66.

When a solution of 4.0 g. of the above salt in 350 ml. of water was made basic with concentrated ammonium hydroxide, a yellow solid (VIIIa) was precipitated. The product weighed 3.0 g. and, after two recrystallizations from dimethylformamide, the melting point was 275–277°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84; Cl, 12.45; O, 5.62. Found: C, 67.71; H, 4.70; N, 9.75; Cl, 12.36; O, 5.80.

C. 7-Chloro-4-(4′-hydroxy-5′-diethylaminomethylanilino)-1-methylquinolinium Chloride Hydrochloride (VIIb).—A solution of 12.8 g. of I (0.04 mole) and 10.6 g. of 4-amino-2-diethylaminomethylphenol dihydrochloride[11] in 75 ml. of water was allowed to stand 24 hr. The solution was then made basic with concentrated ammonium hydroxide and the precipitated solid was filtered and washed with water. The product was dissolved in 400 ml. of acetone and then 15 ml. of concentrated hydrochloric acid was added. On storage, the precipitated gum solidified and was recrystallized by dissolving in a minimum of warm methanol and adding seven volumes of acetone. The yield was 11.8 g., m.p. 132–134° (fused at 102° and resolidified).

Anal. Calcd. for $C_{21}H_{25}Cl_2N_3O_2 \cdot HCl \cdot 3H_2O$: C, 50.76; H, 6.49; N, 8.46; Cl, 21.41. Found: C, 50.64; H, 6.59; N, 8.28; Cl, 21.60.

When a solution of 4.0 g. of the salt was dissolved in 100 ml. of water and made basic with concentrated ammonium hydroxide, 3.1 g. of the imine VIIIb was precipitated. After two recrystallizations from dilute methanol, the melting point was 143–144°.

Anal. Calcd. for $C_{21}H_{24}ClN_3O$: C, 68.19; H, 6.54; N, 11.36; Cl, 9.59. Found: C, 68.66; H, 6.97; N, 11.30; Cl, 9.81.

NORTH CHICAGO, ILLINOIS

[CONTRIBUTION FROM ABBOTT LABORATORIES]

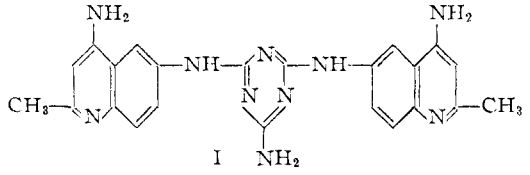
The Preparation of Some N,N′-Bis-(4-quinaldyl)-α,ω-diaminoalkanes as Potential Trypanocides[1]

BY R. U. SCHOCK

RECEIVED OCTOBER 8, 1956

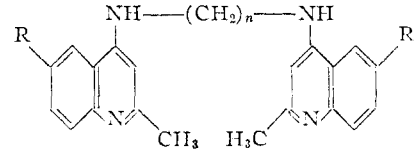
The preparation of the title compounds by reaction of substituted 4-chloro- or 4-methoxyquinaldines with α,ω-diaminoalkanes is described. Many are curative against *T. gambiense* in mice at doses comparable to standard trypanocides.

Although Suramin and Pentamidine, the two drugs used most commonly in human trypanosomiasis, are not quinoline derivatives, many 4-aminoquinaldines are active against various Trypanosoma.[2–4] A proper review of such compounds is beyond the scope of this publication; however, many fall into a general class: a bridging element combined at the 6- or 8-positions of two quinoline nuclei producing a symmetrical structure. An example of this is Surfen C (I), which found utility at one time in *T. congolense* infections.



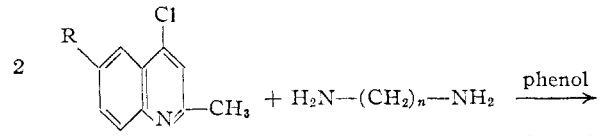
I

Since there are no recorded examples of analogous trypanocides wherein symmetry is achieved by attachment in the 4-positions, it was of interest to prepare a series of this type. The synthesis of compounds represented as II [R = NH_2, OCH_3, $N(CH_3)_2$] is the subject of this communication.



II

The preparation of this general type was accomplished according to the scheme



II·2HCl

The intermediate 4-chloroquinaldines were obtained by reaction of $POCl_3$ with the corresponding 4-hydroxyquinaldines readily available through the Conrad–Limpach reaction.[5] Reaction at 140–

(1) Presented before the Division of Medicinal Chemistry at the 129th National Meeting of the American Chemical Society, Dallas, Texas, April, 1956.

(2) H. Jensch, *Angew. Chem.*, **50**, 891 (1937); *Ann.*, **568**, 73 (1950).

(3) L. P. Walls, *Chemistry & Industry*, 606 (1951).

(4) M. G. Pratt and S. Archer, THIS JOURNAL, **70**, 4065 (1948).

(5) R. C. Elderfield, "Heterocyclic Compounds," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 32.