while the hindrance to addition in reaction I should be greater with *i*-propanol, the attractive force should also be greater. It was therefore to be predicted that the various influences at work would tend to compensate each other, although it could not have been predicted that the compensation would be so complete.

It is to be noted that although in all the systems studied unimolecular reaction kinetics should be observed, [R″OH] was not the same for the different alcohols and consequently the conditions are not strictly comparable. It is not apparent how this could be avoided without introducing other uncertainties, and with low hydrogen ion concentration there should be considerable compensation. Where a higher alcohol is used [R″-OH] in equation 1 is lower than with methanol. On the other hand [I] should be greater in nearly the same proportion. With high concentrations of hydrogen chloride the amount of protonated alcohol which is not available for reaction in the sense of equation 1 subtracts significantly from the total alcohol concentration. This subtraction is, of course, most serious when [R″OH] is initially low and the more so since this situation holds in the cases in which high hydrogen chloride concentrations had to be used.

Summary

The rates of hydrogen chloride-catalyzed alcoholysis have been determined for a series of β-naphthyl esters in methanol, ethanol, propanol and *i*-propanol.

A micro-method for the estimation of β-naphthol has been developed.

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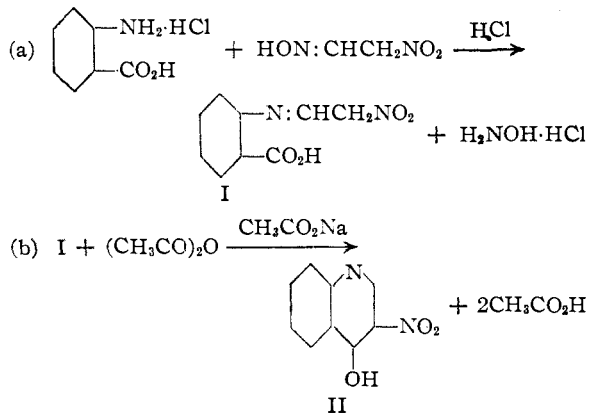
Quinoline Derivatives from 3-Nitro-4-hydroxyquinoline[1]

BY G. BRYANT BACHMAN, D. E. WELTON,[2] GLENN L. JENKINS AND JOHN E. CHRISTIAN

A search conducted in this Laboratory for new compounds suitable as antimalarial drugs has led to the preparation of a number of new 3,4-disubstituted quinolines from 3-nitro-4-hydroxyquinoline (II) as the primary intermediate. The synthesis of II itself was patented in 1922[3] and involves the condensation of anthranilic acid hydrochloride with methazonic acid to yield 2-β-nitroethylideneaminobenzoic acid (I), which is subsequently dehydrated to II by acetic anhydride in the presence of sodium acetate. The yields of II



obtained by the patented method leave much to be desired; although reaction (a) gives 80–90% yields of I, reaction (b) gives only 30–45% yields of difficultly purifiable II. Reaction (b) has been subjected to further study by Musajo,[4] who greatly simplified the experimental procedure for the isolation of II. Colonna[5] attempted to synthesize the latter from methyl anthranilate through reactions similar to (a) and (b) but was unable to cyclize the intermediate methyl ester of I. We made an extensive study of reaction (b) but could convert I to II only by the anhydride–acetate combination previously employed. The alkali acetate catalyst was found to be essential to the reaction. Other metal salts are ineffective as catalysts, as are organic bases.

The preparation of 3-amino-4-hydroxyquinoline hydrochloride (III-HCl) by chemical reduction of II with metallic tin or stannous chloride in concentrated hydrochloric acid has been reported by other investigators.[4,5] We have found that reduction of II may easily be effected by low-pressure catalytic hydrogenation of a suspension of II and Raney nickel in water or alcohols containing ammonia or organic amines. These bases greatly accelerate the reaction rate by increasing the solubility of II through salt formation. The resultant 3-amino-4-hydroxyquinoline (III) was not isolated as the free base, since it is rapidly oxidized by atmospheric oxygen, but was converted to its stable hydrochloride, III-HCl, consistently isolated in 95–98% of the theoretical yield.

The heretofore unreported 5-methoxy derivatives of I, II and III-HCl were also prepared by

(1) Delivered before the Symposium on Antimalarial Agents at the Atlantic City Meeting of the American Chemical Society, April, 1946.

(2) Present address: du Pont Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

(3) German Patent, 347,375 (to Badische Anilin- and Soda-Fabrik) Jan. 17, 1922.

(4) L. Musajo, *Gazz. chim. ital.*, **67**, 222-230 (1937).

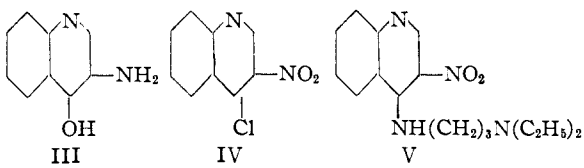
(5) M. Colonna, *ibid.*, **67**, 46-53 (1937).

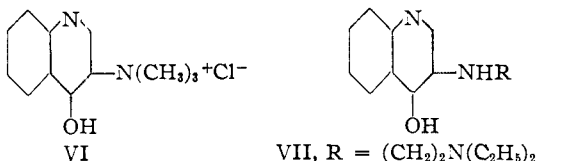
substituting 5-methoxyanthranilic acid[6] for anthranilic acid in the above reactions.

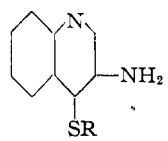
Refluxing II with phosphorus pentachloride in phosphorus oxychloride and evaporating the reaction mixture gives 3-nitro-4-chloroquinoline hydrochloride, which is easily dissociated into hydrogen chloride and the free base, 3-nitro-4-chloroquinoline (IV) by heat or hydroxylic solvents. Vacuum distillation of the reaction mixture yields the free base, IV, in 95–98% of the theoretical yield. It is a crystalline solid closely resembling an aromatic acid chloride in its reactivity with water or bases and is a powerful lachrymator and skin irritant.

Condensation of IV and 3-diethylamino-1-propylamine[7] gives 3-nitro-4-(3′-diethylamino-1′-propyl)-aminoquinoline (V). The free base is easily crystallized from moist alcohols as its hemihydrate which is stable in contact with the atmosphere at room temperature but is easily dehydrated by heat or application of a vacuum. With hydrogen chloride it forms a crystalline water-soluble dihydrochloride.

The 3-amino group of III-HCl is methylated by heating with excess methanol in a sealed tube to yield the quaternary salt (4-hydroxy-3-quinolyl)-trimethylammonium chloride (VI).







The properties of VI correspond to those expected for the proposed structure; it is readily soluble in water (neutral solution), aqueous acids and alkalies, but insoluble in organic solvents of all kinds.

Alkylation of III in alkaline or buffered acetic acid solution with diethylaminoethyl chloride[8] yields 3-(diethylaminoethylamino)-4-hydroxyquinoline (VII). The free base is insoluble in water but soluble in alkali by virtue of its phenolic group. It does not crystallize, hence it was isolated as its stable dihydrochloride. Alkylation of III with di-isobutylaminoethyl chloride,[8] gives a product whose properties contrast somewhat with those of VII. Analysis confirms its identity as the expected monosubstituted III, presumably 3-(di-isobutylaminoethylamino)-4-hydroxyquinoline (VIII), although it is completely insoluble in and unaffected by aqueous alkali, a surprising phenomenon in view of the free hydroxyl group. In addition, in contrast to VII, the free base is readily crystallizable, but gives no solid salts with acids in spite of the fact that the free base is very soluble in aqueous acetic or mineral acid solutions. However substitution on the amino group is indicated by the facts that both VII and VIII give similar blue-green colors with ferric chloride solution, whereas III gives a brown-red color. Furthermore, neither VII nor VIII can be diazotized and coupled with phenol or alpha-naphthol although III couples readily under similar conditions after treatment with nitrous acid. The insolubility in alkali exhibited by VIII is difficult to explain on the basis of the information available at present.

The synthesis of 3-amino-4-quinolinethiol (IX) from IV and excess sodium sulfide is easily accomplished in excellent yields. This compound alkylates readily on the thiol group, and with 3-diethylamino-1,2-epoxypropane[9] gives 3-amino-4-(3′-diethylamino-2′-hydroxy-1′-propylthio)-quinoline (X). The free base is a crystalline solid, insoluble in water or alkaline solutions but very soluble in dilute acids. With hydrogen chloride it forms a stable crystalline dihydrochloride.

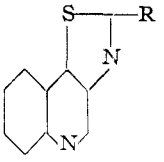
The reactions of IX with reagents capable of yielding thiazole derivatives from *o*-aminothiols yield 2-substituted thiazolo[4,5-c]quinolines with great ease. Thus IX with boiling acetic anhydride gives 2-methylthiazolo[4,5-c]quinoline (XI), which may also be obtained from the monoacetyl derivative of IX, 3-acetylamino-4-quinolinethiol, by the same procedure, or by warming with concentrated sulfuric acid, then diluting and neutralizing the resultant solution. Compound IX gives 2-mercaptothiazolo[4,5-c]quinoline (XII) with carbon disulfide in alkali or pyridine solution, and fusion of IX with excess urea gives 2-hydroxythiazolo[4,5-c]quinoline (XIII). Cyanogen bromide reacts vigorously with IX. By carrying out the reaction at or below room temperature, an unstable product (probably 3-amino-4-quinoline thiocyanate, since it is insoluble in alkali) is produced. It forms red water-soluble salts with acids. Warming either the free base or its salts in acidic, neutral or basic solutions readily yields 2-aminothiazolo[4,5-c]quinoline (XIV) or its salts, which are pale yellow and much less soluble than those of the unstable intermediate.

(6) G. B. Bachman and G. M. Picha, THIS JOURNAL, **68**, 1599 (1946).

(7) O. Y. Magidson and A. M. Grigorovskii, *Ber.*, **69B**, 396–412 (1936).

(8) G. B. Bachman and H. H. Szmant, THIS JOURNAL, **68**, 31–34 (1946).

(9) O. Eisleb, U. S. Patent, 1,790,042 (to Winthrop Chemical Co.), Jan. 27, 1931.



XI, R = CH_3
XII, R = SH
XIII, R = OH
XIV, R = NH_2
XV, R = $SCH_2CHOHCH_2N(C_2H_5)_2$

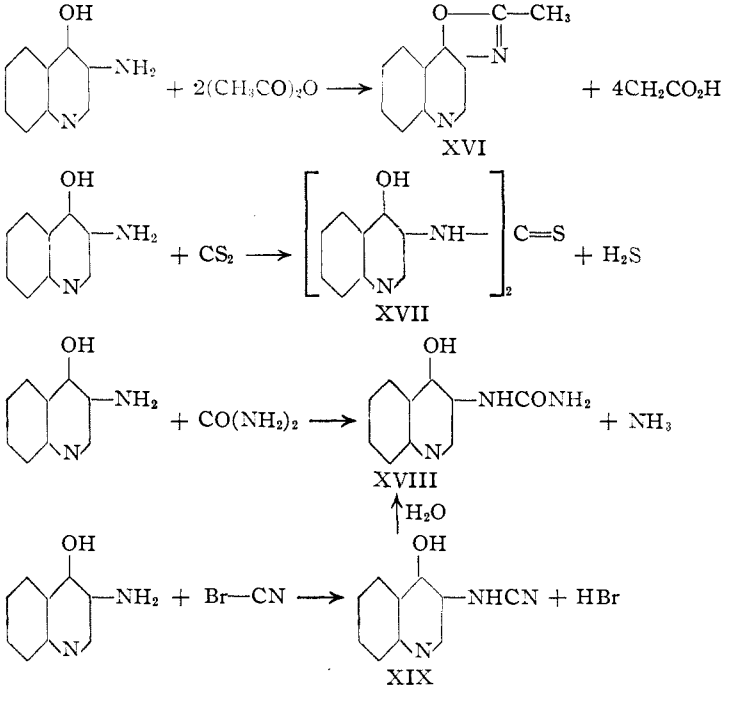
Of the thiazoloquinolines prepared by the preceding reactions only the methyl derivative shows any significant instability on long boiling with dilute acids or bases. It is stable to alkali but the thiazole ring is slowly opened by hot dilute acids to yield 3-acetylamino-4-quinolinethiol. The mercapto- and hydroxythiazoloquinolines, XII and XIII, are weakly amphoteric and are soluble in dilute aqueous ammonium or sodium hydroxide solutions but insoluble in aqueous acids, although they form salts with anhydrous acetic or mineral acids. Both XI and XIV are completely insoluble in alkali and react as mono-acid bases; with hydrogen chloride they yield monohydrochlorides which are only slightly soluble in cold water. The melting point of XI contrasts sharply with those of XII, XIII and XIV. Whereas XI melts below 100°, the latter three melt or decompose in the neighborhood of 300°, the high values probably resulting from strong hydrogen bonding.

Alkylation of XII in acetone or aqueous alkali solution with 3-diethylamino-1,2-epoxypropane gives 2-(3′-diethylamino-2′-hydroxy-1′-propylthio)-thiazolo[4,5-c]quinoline (XV), isolated as its dihydrochloride. The free base could not be crystallized. The alkyl group of XV was shown to be on the sulfur atom by subjecting it to alkaline hydrolysis, yielding XIII by hydrolytic splitting of the S-(2-thiazoloquinoline) bond. This phenomenon was unexpected, inasmuch as the sulfur–carbon bond in unsubstituted XII is stable to hot alkali.

All attempts to alkylate XIII and XIV with 3-diethylamino-1,2-epoxypropane and diethylaminoethyl chloride failed. The epoxide does not react with either, upon heating the reagents alone or in neutral organic solvents, pyridine, acetic acid or sodium hydroxide solutions. Similarly, the alkyl halide or its hydrochloride fails to produce any significant alkylation under the same conditions or in sodium ethoxide–absolute ethanol solution. In all cases the alkylating agent is decomposed without reacting with the thiazoloquinolines.

Attempts to prepare 2-substituted oxazolo[4,5-c]quinolines from 3-amino-4-hydroxyquinoline (III) and the reagents utilized for the synthesis of the aforementioned 2-substituted thiazolo[4,5-c]quinolines were successful only with acetic anhydride, which yielded 2-methyloxazolo[4,5-c]-quinoline (XVI). Its chemical and physical properties are similar to those of XI. Treatments of III with carbon disulfide, urea, or cyanogen bromide under conditions which produce thiazoloquinoline derivatives from IX result only in substitution on the 3-amino group. Thus III with carbon disulfide in pyridine yields N,N′-bis-(4-hydroxy-3-quinolyl)-thiourea (XVII), and fusion with excess urea gives mainly N-(4-hydroxy-3-quinolyl)-urea (XVIII), apparently contaminated with the corresponding bis-substituted urea which could not be removed because of the extreme insolubility of both. The synthesis of XVIII is better accomplished through partial hydrolysis of 3-cyanamino-4-hydroxyquinoline (XIX), obtained by the reaction of III with cyanogen bromide. Although XIX is readily soluble in both dilute acids and alkalies, XVII and XVIII are soluble only in the latter. All three compounds are very insoluble in organic solvents.

Pharmacological Testing.—The water-soluble hydrochlorides of V, VI, VII, VIII, X, XI, XIV, XV and XVI were tested as antimalarials but none was effective. The results of these tests will be reported in detail elsewhere.



Acknowledgment.—The authors are indebted to Eli Lilly and Company and to the Purdue Research Foundation for financial assistance and to the former for pharmacological testing.

Experimental

All melting points are corrected.

2-β-Nitroethylidenaminobenzoic Acid (I).—A solution of 268 g. of 96–98% sodium hydroxide in 536 ml. of water was cooled and stirred mechanically while 134 g. (2.2

moles) of nitromethane was added dropwise, keeping the temperature at 25–30°. The mixture was then warmed to 40° and again cooled and stirred while another 134 g. of nitromethane was added slowly at 40–45°. This temperature was maintained until all solids had dissolved and a clear red solution was obtained. The solution was then heated to 50–55° for two to five minutes and finally cooled to 30°, poured onto 600 g. of chipped ice, and acidified with 600 ml. of concentrated hydrochloric acid. The resultant solution of methazonic acid was immediately added to a filtered solution of 274 g. (2.0 moles) of anthranilic acid and 183 ml. of concentrated hydrochloric acid in 4 liters of water. The solution was allowed to stand at room temperature for twelve to eighteen hours, then filtered. The solid product was washed repeatedly with water. The cake was sliced into thin flakes and allowed to dry at room temperature until it could be ground to a dry powder, then heated to constant weight at 110°. Yield was 354–374 g. (85–90%) of bright yellow microneedles, m. p. 196–197° (German Patent 347,375 gives m. p. 197°[1], Musajo[2] reports m. p. 196°).

2-β-Nitroethylidenamino-5-methoxybenzoic Acid.—A solution of 29.8 g. (0.146 mole) of 5-methoxyanthranilic acid hydrochloride in 600 ml. of water was mixed with a methazonic acid solution prepared from 22 ml. of nitromethane (see preceding synthesis for experimental procedure) and allowed to stand for twelve hours. The product was filtered off, washed repeatedly with water, dried first at room temperature and then at 110°. Yield was 29.8 g. (86%) of minute yellow needles, m. p. 192–193° (dec.). Recrystallization from absolute alcohol produced no change in melting point.

Anal. Calcd. for $C_{10}H_{10}O_5N_2$: C, 50.40; H, 4.24; N, 11.76. Found: C, 50.40, 50.51; H, 4.28, 4.40; N, 11.79, 11.87.

3-Nitro-4-hydroxyquinoline (II).—A mixture of 104 g. (0.5 mole) of 2-β-nitroethylidenaminobenzoic acid and 500 ml. of technical acetic anhydride was placed in a 3-necked flask of at least 1000-ml. capacity fitted with thermometer, mechanical stirrer and reflux condenser. It was stirred and heated to 100–105° until a clear solution was obtained. Heating was then discontinued and 50 g. (0.51 mole) of anhydrous potassium acetate (freshly dried at 110°) was added rapidly with stirring. The temperature rose spontaneously to 134–138°. When it began to fall (five to ten minutes) external heat was applied and the mixture was refluxed an additional fifteen minutes with vigorous stirring, then allowed to cool slowly to room temperature. The product was filtered off and washed with glacial acetic acid until the washings were colorless, then suspended in 500 ml. of water, filtered again, washed repeatedly with water and dried at 110°. Yield was 41–43 g. (43–45%) of small tan needles, m. p. above 325° (German Patent 347,375 gives m. p. above 300°[1]).

3-Nitro-4-hydroxy-6-methoxyquinoline.—A mixture of 11.9 g. (0.05 mole) of 2-β-nitroethylidenamino-5-methoxybenzoic acid and 150 ml. of acetic anhydride was heated and stirred at 105–110° until a homogeneous solution was obtained. Then 4.1 g. (0.05 mole) of anhydrous sodium acetate was added and the solution was refluxed one hour, allowed to cool slowly to room temperature and then filtered. The solid product was washed repeatedly with glacial acetic acid, then suspended in water, filtered off, washed well with water and dried at 110°; yield 5.3 g. (48%) of pale yellow needles, m. p. above 325°.

Anal. Calcd. for $C_{10}H_8O_4N_2$: C, 54.52; H, 3.68; N, 12.72. Found: C, 54.50, 54.62; H, 3.70, 3.76; N, 12.70, 12.79.

3-Amino-4-hydroxyquinoline Hydrochloride (III·HCl).—A suspension of 19.0 g. (0.10 mole) of 3-nitro-4-hydroxyquinoline and 5–10 g. of Raney nickel catalyst in 200 ml. of methanol containing 5 ml. of concentrated ammonium hydroxide was shaken at room temperature with hydrogen under an initial gage pressure of 60 lb. per sq. in. until the absorption of hydrogen ceased (one-half to three hours). The solution was filtered and 0.5–1.0 g. of crystalline sodium sulfide was added to the filtrate, which was then evaporated under vacuum. The residue was dissolved in 150 ml. of boiling water and purified by treating the hot solution with charcoal, filtering, acidifying with 10 ml. of concentrated hydrochloric acid, again treating with charcoal and filtering. The filtrate was made strongly acid with another 10 ml. of concentrated hydrochloric acid and evaporated to incipient crystallization at the boiling point, then allowed to cool to room temperature. The product was filtered off, rinsed with alcohol and dried to constant weight at 110°. Yield was 18.7–19.3 g. (95–98%) of a white to light pink powder, m. p. 302–305° (dec.) (Musajo gives m. p. above 300°[4]).

Anal. Calcd. for $C_9H_8ON_2 \cdot HCl$: C, 54.93; N, 4.63; Cl, 18.06. Found: C, 54.89, 54.96; H, 4.61, 4.66; Cl, 18.03, 18.15.

2-Amino-4-hydroxy-6-methoxyquinoline Hydrochloride.—A suspension of 4.8 g. (0.022 mole) of 3-nitro-4-hydroxy-6-methoxyquinoline and 5 g. of Raney nickel catalyst in 50 ml. of methanol containing 3 ml. of concentrated ammonium hydroxide was reduced and the product isolated and purified as above for III·HCl. Yield was 4.3 g. (88%) of white needles, m. p. 295–296° (dec.).

Anal. Calcd. for $C_{10}H_{10}O_2N_2 \cdot HCl$: C, 52.96; H, 4.90; N, 12.36; Cl, 15.67. Found: C, 52.97, 53.08; H, 4.93, 5.02; N, 12.39, 12.50; Cl, 15.60, 15.71.

3-Nitro-4-chloroquinoline (IV).—A mixture of 38.0 g. (0.20 mole) of III, 41.6 g. (0.20 mole) of phosphorus pentachloride and 100 ml. of phosphorus-oxychloride was warmed in a 500-ml. flask fitted for reflux (all glass apparatus) to partial liquefaction and then refluxed until evolution of hydrogen chloride ceased (one to two hours). The product was distilled at 3–5 mm. pressure after removing excess phosphorus oxychloride. Yield was 39–40 g. (94–96%) of yellow solid, m. p. 121–122°.

Anal. Calcd. for $C_9H_5O_2N_2Cl$: C, 51.80; H, 2.40; N, 13.43; Cl, 17.03. Found: C, 51.78, 51.83; H, 2.39, 2.49; N, 13.47, 13.58; Cl, 17.00, 16.86.

3-Nitro-4-(3′-diethylamino-1′-propylamino)-quinoline (V).—A solution of 7.2 g. (0.055 mole) of 3-diethylamino-1-propylamine in 110 ml. of methanol was cooled and stirred while 10.4 g. (0.050 mole) of powdered 3-nitro-4-chloroquinoline was added in small portions, keeping the temperature below 20°. The mixture was stirred two hours at 15–20°, then heated to boiling and finally evaporated under vacuum. The residue was mixed with 100 ml. of hot water and carefully acidified to congo red indicator with concentrated hydrochloric acid. Charcoal was added and the solution was filtered, then made basic with a solution of 12 g. of sodium hydroxide in 50 ml. of water. The mixture was cooled in an ice-bath and stirred mechanically until the precipitated oil had crystallized. The solid was pulverized, filtered off, rinsed well with water, and dried to constant weight in air at room temperature. Yield was 15.2 g. (98%) of the hemihydrate, yellow in color, m. p. 51–53°. Recrystallization from aqueous methanol failed to cause any change in melting point.

Anal. Calcd. for $C_{16}H_{22}O_2N_4 \cdot {}^1/_2H_2O$: C, 61.70; H, 7.46; N, 18.00. Found: C, 61.83, 61.87; H, 7.45, 7.54; N, 18.00, 17.92.

A 5.0-g. sample was dissolved in excess dry ether and the solution was saturated with anhydrous hydrogen chloride. The precipitate was filtered off and dried under vacuum, then dissolved in 50 ml. of absolute alcohol and diluted at the boiling point with carbon tetrachloride until a faint permanent cloudiness appeared, cooled slowly to 0° with occasional scratching, and finally filtered. The product was rinsed with ether and dried at 60°. Yield was 5.5 g. (91%) of the dihydrochloride, m. p. 200–201° (dec.).

Anal. Calcd. for $C_{16}H_{22}O_2N_4 \cdot 2HCl$: N, 14.92; Cl, 18.92. Found: N, 14.84, 14.88; Cl, 18.72, 18.81.

(4-Hydroxy-3-quinolyl)-trimethylammonium Chloride (VI).—A mixture of 10.0 g. of 3-amino-4-hydroxyquinoline

hydrochloride and 15 ml. of methanol in a sealed tube was heated at 150° for twenty-four hours. The tube was finally cooled in a Dry-Ice-bath, opened carefully and allowed to warm slowly to room temperature. The product was suspended in methanol, filtered off and washed with methanol until the washings were colorless, yielding 8.6 g. of pink solid, m. p. 264–274° (depending on the rate of heating). It was dissolved in hot 75% acetic acid, boiled with charcoal and filtered. Evaporating the filtrate to incipient crystallization at the boiling point, then cooling to room temperature gave 6.0 g. of white needles. The filtrate was again evaporated to incipient crystallization and allowed to cool, giving an additional 1.7 g. of product. The two fractions were identical and melted at 264–275°, depending on the rate of heating.

Anal. Calcd. for $C_{12}H_{15}ON_2Cl$: C, 60.35; H, 6.33; Cl, 14.88. Found: C, 60.32, 60.21; H, 6.28, 6.26; Cl, 14.88, 14.95.

3-(Diethylaminoethylamino)-4-hydroxyquinoline (VII) Dihydrochloride.—A solution of 4.9 g. (0.025 mole) of 3-amino-4-hydroxyquinoline hydrochloride, 2.2 g. (0.025 mole) of sodium bicarbonate, 4.3 g. (0.027 mole) of 2-diethylaminoethyl chloride hydrochloride and 2.3 g. (0.027 mole) of sodium acetate in 30 ml. of 50% alcohol was refluxed for ten hours. The hot solution was then treated with charcoal, filtered, acidified with 3 ml. of concentrated hydrochloric acid and finally evaporated to dryness at 100° under vacuum. The residue was extracted with 75 ml. of boiling absolute alcohol and filtered. The filtrate was treated with charcoal, filtered, evaporated to incipient crystallization at the boiling point, and then diluted with 5 volumes of ether. The solid product which precipitated was filtered off, washed with ether and dried under vacuum, giving 6.8 g. of product, m. p. 195–200° (dec.). It was redissolved in 30 ml. of hot absolute alcohol, diluted at the boiling point with isopropyl ether until a faint permanent cloudiness appeared, then allowed to cool to room temperature. The product was filtered off, rinsed with isopropyl ether and dried under vacuum. Yield was 4.3 g. (52%) of white powder, m. p. 200–202° (dec.).

Anal. Calcd. for $C_{15}H_{21}ON_3 \cdot 2HCl$: C, 54.18; H, 6.98; N, 12.64; Cl, 20.89. Found: C, 54.12, 54.20; H, 6.95, 7.00; N, 12.54, 12.66; Cl, 20.80, 20.69.

3-(Di-isobutylaminoethylamino)-4-hydroxyquinoline (VIII).—A solution of 4.9 g. (0.025 mole) of 3-amino-4-hydroxyquinoline hydrochloride, 2.2 g. (0.025 mole) of sodium bicarbonate, 6.8 g. (0.030 mole) of diisobutylaminoethyl chloride hydrochloride and 2.5 g. (0.030 mole) of sodium acetate in 30 ml. of 50% alcohol was refluxed four hours. It was then treated with charcoal, filtered, acidified with 3 ml. of concentrated hydrochloric acid, evaporated to about half its original volume, cooled, diluted with twice its volume of water, and then made strongly basic with concentrated sodium hydroxide solution. The precipitated oil was extracted with benzene, which was separated, then carefully evaporated. The residue was allowed to crystallize, dried under vacuum, then dissolved in about 40 ml. of methanol. Water was added at room temperature until a faint permanent cloudiness appeared, and the product was allowed to crystallize at 0°. The product was filtered off, washed with water and dried under vacuum. Yield was 6.6 g. (83%) of greenish-yellow needles, m. p. 121–123°. Repeated crystallization failed to change the melting point.

Anal. Calcd. for $C_{19}H_{29}ON_3$: C, 72.33; H, 9.27; N, 13.33. Found: C, 72.53, 72.65; H, 9.57, 9.51; N, 13.41, 13.27.

3-Amino-4-quinolinethiol (IX).—A solution of 12.0 g. (0.050 mole) of $Na_2S \cdot 9H_2O$ in 30 ml. of water and 100 ml. of methanol was added dropwise over a fifteen-minute period to a well-stirred solution of 20.8 g. (0.1 mole) of freshly-distilled IV in 40 ml. of dry chloroform, keeping the temperature below 25°. After thirty minutes the solid product (17.0–18.0 g.) was filtered off, washed with methanol, and then suspended in water. Sodium hydroxide was added to strong alkalinity, the solid product again isolated, washed repeatedly with water, and finally dried at 60°. The orange powder so obtained was 3-nitro-4-(3′-nitro-4′-quinolylthio)-quinoline, m. p. darkens at 200°, decomposes at higher temperatures.

Anal. Calcd. for $C_{18}H_{10}O_4N_4S$: N, 14.80; S, 8.48. Found: N, 14.77, 14.92; S, 8.55, 8.63.

It was further reduced as follows: 18.9 g. (0.05 mole) mixed with 92.0 g. (0.375 mole) of $Na_2S \cdot 9H_2O$ and 300 ml. of 50% ethanol was stirred and refluxed for two hours, cooled, and acidified cautiously with 100 ml. of concentrated hydrochloric acid. The solid was filtered off, washed with 50% ethanol, suspended in water, and made strongly alkaline. A little sodium sulfite (2 g.) was added to prevent air oxidation, and the solution was filtered. The filtrate was decolorized (Norit), refiltered and then slowly acidified with acetic acid. After standing thirty minutes the precipitated 3-amino-4-quinolinethiol hydrate was filtered off, rinsed with water, then dried at least twenty-four hours over a drying agent *in vacuo*. Yield was 16.2 g. (92–100%) of anhydrous product, an orange powder which slowly darkens and carbonizes above 190°. It must be stored in a closed container, as exposure to moist air results in partial conversion to the yellow hydrate, accompanied by oxidation.

Anal. Calcd. for $C_9H_8N_2S$: N, 15.89; S, 17.80. Found: N, 15.73, 15.60; S, 18.02, 18.08.

The N-acetyl derivative m. p. 260–264° (dec.) was prepared by treating IX with acetic anhydride in pyridine solution.

3-Amino-4-(3′-diethylamino-2′-hydroxy-1′-propylthio)-quinoline (X).—A solution of 4.4 g. (0.025 mole) of 3-amino-4-quinolinethiol and 1.1 g. (0.028 mole) of sodium hydroxide in 50 ml. of water was stirred while a solution of 3.3 g. (0.025 mole) of 3-diethylamino-1,2-epoxypropane in 25 ml. of water was added dropwise. A yellow oil separated after a few minutes and crystallized readily on seeding. The mixture was stirred 3–4 hours, then filtered. The crystals were washed with water, then dried at 60°, yielding 7.3 g. of product m. p. 88–90°. It was dissolved in about 35 ml. of methanol, then diluted carefully at room temperature with water until a faint permanent cloudiness appeared, seeded and cooled to 0°. The product was filtered off, rinsed with 50% methanol and dried at 60°. Yield was 6.5 g. (85%) of colorless needles, m. p. 90–91°.

Anal. Calcd. for $C_{16}H_{23}ON_3S$: C, 62.89; H, 7.60; N, 13.76; S, 10.51. Found: C, 63.00, 63.02; H, 7.53, 7.64; N, 13.85, 13.90; S, 10.55, 10.43.

A 6.3-g. sample was dissolved in 35 ml. of methanol and anhydrous hydrogen chloride was led in until the solution was barely acid to congo red indicator. This solution was cooled to room temperature and diluted with acetone until a faint permanent cloudiness appeared. It was then warmed and scratched until crystallization began and finally cooled slowly to 0° and filtered. The product was rinsed with alcohol and dried at 60° giving 7.7 g. (98%) of yellow needles of 3-amino-4-(3′-diethylamino-2′-hydroxy-1′-propylthio)-quinoline dihydrochloride, m. p. 205–207° (dec.).

Anal. Calcd. for $C_{16}H_{23}ON_3S \cdot 2HCl$: Cl, 18.77. Found: Cl, 18.58, 18.44.

2-Methylthiazolo[4,5-c]quinoline (XI).—A mixture of 4.4 g. (0.025 mole) of 3-amino-4-quinolinethiol and 15 ml. of acetic anhydride was warmed slowly and refluxed cautiously for one hour after all solid had dissolved (one-half to one hour). The resultant solution was poured into 150 ml. of water containing 2–3 ml. of concentrated hydrochloric acid and stirred until the solution was homogeneous. It was then made strongly basic with concentrated sodium hydroxide solution and extracted twice with benzene. The benzene extract was dried over anhydrous potassium carbonate, filtered, then evaporated until the boiling point of the residue rose to 95–100°. The product crystallized on cooling. It was powdered and dried at 60°; yield 4.5 g., m. p. 98–99°. It was dissolved in 20 ml. of methanol, then diluted with water until a faint

permanent cloudiness appeared, and finally cooled to 0°. The white needles were filtered off, rinsed with water, and dried at 60°, during which time they disintegrated to a white powder. Yield was 4.3 g. (86%), m. p. 99–100°.

Anal. Calcd. for $C_{11}H_8N_2S$: S, 16.03. Found: S, 16.01, 16.13.

A 5.9-g. sample was dissolved in 50 ml. of absolute alcohol and carefully acidified to congo red indicator with concentrated hydrochloric acid. The mixture was cooled to 0°, then filtered. The yellow needles were washed with absolute alcohol, and dried under vacuum, during which time they disintegrated to a pale yellow powder. Yield was 5.9 g. (100%), of 2-methylthiazolo[4,5-c]quinoline monohydrochloride which slowly turned red above 200°, m. p. 240–245° (dec.).

Anal. Calcd. for $C_{11}H_8N_2S \cdot HCl$: N, 11.83, Cl, 15.00. Found: N, 11.97, 12.11; Cl, 15.22, 15.28.

2-Hydroxythiazolo[4,5-c]quinoline (XIII).—A mixture of 3.5 g. (0.02 mole) of 3-amino-4-quinolinethiol and 3.5 g. of urea was powdered and placed in a wide-mouth flask fitted with a gas outlet carrying a bubbler tube. The flask was immersed in an oil-bath at 150–160° until the evolution of gases was complete and the red liquid initially formed had changed to a yellow solid (one to two hours). The product was cooled, ground to a powder and dissolved in 100 ml. of hot 5% sodium hydroxide solution, which was then treated with charcoal, filtered, reheated to boiling and acidified slowly with dilute acetic acid. The product was filtered off, washed with hot water and dried at 110°, yielding 3.5 g. of light yellow powder, m. p. 320–323° (dec.). It was dissolved in 80–90 ml. of boiling glacial acetic acid, then cooled slowly to 15–20° and filtered. The yellow needles were washed repeatedly with water, during which time they disintegrated to a white powder which was dried at 110°. Yield was 3.0 g. (74%) of a product which darkened and became crystalline above 300° but did not melt below 325°.

Anal. Calcd. for $C_{10}H_6N_2OS$: S, 15.88. Found: S, 15.82, 15.95.

2-Aminothiazolo[4,5-c]quinoline (XIV).—A solution of 2.2 g. (0.02 mole) of cyanogen bromide in 100 ml. of water was stirred vigorously while 3.5 g. (0.02 mole) of powdered 3-amino-4-quinolinethiol was added slowly. The mixture was stirred for thirty minutes at room temperature, then refluxed for fifteen minutes. Charcoal was added, the hot solution was filtered, then made basic with concentrated sodium hydroxide solution and allowed to cool to room temperature. The product was filtered off, rinsed with hot water, then with methanol and finally dried at 60°. Yield was 3.7 g. (92%) of a pale yellow powder which slowly decomposed above 300° but did not melt below 325°.

Anal. Calcd. for $C_{10}H_7N_3S$: N, 20.87; S, 15.95. Found: N, 20.89, 20.98; S, 16.06, 16.16.

A 10.0-g. portion was boiled with 100 ml. of water containing 5 ml. of concentrated hydrochloric acid. The resultant solution was evaporated to incipient crystallization at the boiling point, then allowed to cool to room temperature, giving pale yellow needles of the monohydrochloride, which were filtered off, washed with alcohol and dried at 60°. Yield was 11.0 g. (93%), m. p. above 325° (darkens above 300°).

Anal. Calcd. for $C_{10}H_7N_3S \cdot HCl$: Cl, 14.91. Found: Cl, 14.72, 14.59.

2-(3′-Diethylamino-2′-hydroxy-1′-propylthio)-thiazolo[4,5-c]quinoline (XV) Dihydrochloride.—A mixture of 4.4 g. (0.020 mole) of 2-mercaptothiazolo[4,5-c]quinoline, 2.0 g. (0.022 mole) of 3-diethylamino-1,3-epoxypropane and 50 ml. of acetone was stirred mechanically and refluxed for one hour. The resultant solution was allowed to cool slightly, then acidified with 4.5 ml. of concentrated hydrochloric acid and stirred until the precipitated oil had crystallized. It was then allowed to cool to room temperature and filtered. The product was washed with acetone and dried at 110°. Yield was 8.3–8.4 g. (99%) of pale yellow needles, m. p. 220–221° (dec.). Recrystallization from a methanol–*i*-propyl ether solution produced no change in melting point.

Anal. Calcd. for $C_{17}H_{21}ON_3S_2 \cdot 2HCl$: S, 15.25; Cl, 16.87. Found: S, 15.32, 15.45; Cl, 16.98, 17.05.

2-Methyloxazolo[4,5-c]quinoline (XVI).—A mixture of 4.9 g. (0.025 mole) of 3-amino-4-hydroxyquinoline hydrochloride, 2.3 g. (0.027 mole) of anhydrous sodium acetate and 25 ml. of acetic anhydride was stirred and refluxed for four hours, then cooled and poured into 250 ml. of water and stirred until the solution was homogeneous. Excess concentrated sodium hydroxide solution was added and the precipitated oil was extracted with two 50-ml. portions of benzene. The benzene extracts were washed with a saturated sodium chloride solution, combined, dried over anhydrous potassium carbonate and finally evaporated until the boiling point of the residue rose to 95–100°. Cooling and scratching caused it to solidify, giving a white solid which was powdered and dried at 60°. Yield was 3.7 g. (80%), m. p. 90–91°. Recrystallization from ligroin or aqueous methanol produced no change in melting point.

Anal. Calcd. for $C_{11}H_8ON_2$: C, 71.72; H, 4.40; N, 15.20. Found: C, 71.75, 71.83; H, 4.39, 4.47; N, 15.16, 15.10.

A 3.5-g. sample was dissolved in 35 ml. of absolute alcohol and carefully acidified to congo red indicator with concentrated hydrochloric acid. The mixture was cooled to 0°, then filtered. The precipitate was washed with absolute alcohol, then dried under vacuum. Yield was 3.8 g. (90%) of the monohydrochloride, which slowly turned red above 200°, m. p. 252–253° (dec.).

Anal. Calcd. for $C_{11}H_8ON_2 \cdot HCl$: N, 12.69; Cl, 16.09. Found: N, 12.89, 12.99; Cl, 16.22, 16.30.

N,N′-bis-(4-Hydroxy-3-quinolyl)-thiourea (XVII).—A mixture of 4.9 g. (0.025 mole) of 3-amino-4-hydroxyquinoline hydrochloride, 3.3 g. (0.04 mole) of anhydrous sodium acetate and 50 ml. of water was stirred until the solids dissolved completely. Then a solution of 2.3 g. (0.022 mole) of cyanogen bromide in 50 ml. of water was added slowly with stirring. The mixture was stirred fifteen minutes, then acidified to congo red indicator with concentrated hydrochloric acid and refluxed two hours. The hot solution was treated with charcoal, filtered, and made basic with dilute ammonium hydroxide solution. The precipitate was filtered off, washed with hot water and dried at 110°. Yield was 2.3 g. (56–57%), of light pink crystals which did not melt at 325°.

Anal. Calcd. for $C_{10}H_9O_2N_3$: C, 59.10; H, 4.48; N, 20.67. Found: C, 59.39, 59.58; H, 4.47, 4.56; N, 20.60, 20.51.

3-Cyanamino-4-hydroxyquinoline (XIX).—A mixture of 5.9 g. (0.030 mole) of 3-amino-4-hydroxyquinoline hydrochloride and 5.5 g. (0.065 mole) of sodium bicarbonate was stirred with 100 ml. of water until the solids dissolved. Then a solution of 3.5 g. (0.033 mole) of cyanogen bromide in 50 ml. of water was added dropwise with vigorous stirring. The mixture was stirred thirty minutes and finally filtered. The solid product was washed with water, suspended in 150 ml. of water and slowly acidified with concentrated hydrochloric acid until it dissolved. The cold solution was stirred with charcoal, filtered and neutralized with dilute ammonium hydroxide solution. The white precipitate was filtered off, washed with water and dried under vacuum. Yield was 5.1 g. (93%) of white powder which slowly darkened above 250°, turned red and partly melted at 270–280°.

Anal. Calcd. for $C_{10}H_7ON_3$: C, 64.85; H, 3.83; N, 22.68. Found: C, 64.74, 64.79; H, 3.70, 3.59; N, 22.60, 22.68.

Summary

1. A number of compounds derived from 3-nitro-4-hydroxyquinoline have been prepared for testing as antimalarials.

2. The syntheses of aminoalkyl derivatives of 3-nitro-4-aminoquinoline, 3-amino-4-hydroxyquinoline and 3-amino-4-quinolinethiol are described.

3. The preparations of various 2-substituted derivatives of the previously undescribed thiazolo[4,5-c]quinoline are reported.

4. Several derivatives of (4-hydroxy-3-quinolyl)-urea have been prepared.

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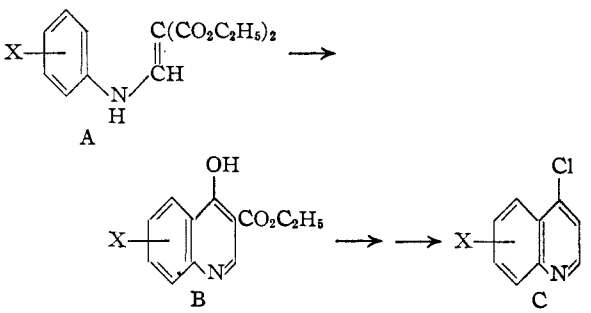
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Synthesis of 4-Hydroxyquinolines. VIII. Some Halogen Containing 4-Aminoquinoline Derivatives[1]

BY H. R. SNYDER, HERBERT E. FREIER,[2] PETER KOVACIC[3] AND EARLE M. VAN HEYNINGEN[4]

In connection with the development of antimalarial drugs it was desirable to have available for testing certain substances similar to SN-7618[5] but with a methoxyl group in the 5- or 6-position and other substances having a fluorine atom or a trifluoromethyl group in or near the position occupied by the chlorine atom of SN-7618.[5] This paper reports the synthesis of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-5-methoxyquinoline (SN-11,630)[5] (I), 7-chloro-4-(1-ethyl-4-piperidylamino)-6-methoxyquinoline (II), 4-(3-diethylaminopropylamino)-6-fluoroquinoline (SN-14,884)[5] (III), 4-(4-diethylamino-1-methylbutylamino)-7-fluoroquinoline (SN-13,986)[5] (IV), and 4-(4-diethylamino-1-methylbutylamino)-7-trifluoromethylquinoline (SN-11,524)[5] (V). The last of these compounds has been mentioned in the patent literature[6] and substances of the type represented by IV evidently have been studied[7] in Germany. A compound having the nucleus of II but with a different side chain was announced[8] while the present work was in progress.

The compounds reported herein were prepared by the condensation of a primary aromatic amine with ethoxymethylenemalonic ester, yielding an ethyl α-carbethoxy-β-arylaminoacrylate (A) which was converted to a 4-chloroquinoline (C) by cyclization, saponification, decarboxylation, and reaction with a mixture of phosphorus pentachloride and oxychloride.[9,10] The principal steps in the process are shown in the accompanying scheme.



The basic side chain was introduced by treatment of the 4-chloroquinoline with the appropriate diamine.

It was expected that the cyclization of each arylaminoacrylic ester (A) derived from a *meta*-substituted aniline would yield ultimately the 7-substituted 4-chloroquinoline as the major product, in analogy to the cyclization of the intermediate obtained from *m*-chloroaniline.[10] Of the *meta*-substituted esters studied in the present work, only the one derived from *m*-fluoroaniline gave a detectable amount of the 5-substituted quinoline; the pure 7-fluoro-4-hydroxyquinoline could be obtained by recrystallization from water. This structure, rather than that of 5-fluoro-4-hydroxyquinoline, is assumed for the isomer formed in larger quantity; the relationships of relative abundance in the cyclization mixture, of solubility of the 4-hydroxyhaloquinolines, and of activity of the final drugs in the 5- and 7-fluoro series then are the same as in the 5- and 7-chloro series. In an experiment in which the isomers were not separated, the mixture of 5- and 7-fluoro-4-chloroquinolines was treated with 1-diethylamino-4-aminopentane. Along with the expected mixture of the two fluorine-containing bases there was isolated a substance which contained no halogen and which, from its analysis, appeared to have been formed by replacement of

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(5) The Survey Number, designated SN-, refers to the number assigned a drug by the Survey of Antimalarial Drugs. The activities of these compounds will be tabulated in a forthcoming monograph.

(6) Andersag, Breitner and Jung, German Patent 683,692 (1939); *C. A.*, **36**, 4973 (1942).

(7) Curtis, Davis, Smadel, Southworth and Volwiler, "Pharmaceuticals and Insecticides at I. G. Farben Plants, Elberfeld and Leverkusen," Report No. 237, Office of the Publication Board, Department of Commerce, Washington, D. C.

(8) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(9) Gould and Jacobs, THIS JOURNAL, **61**, 2890 (1939).

(10) Price and Roberts, *ibid.*, **68**, 1204 (1946).