g. (theoretical, 105 g.). The liquid layer was decanted from the calcium chloride sludge and neutralized by shaking with anhydrous potassium carbonate. Distillation yielded 108 g. (42%) of the dichloride (V), b. p. 65–70° (25 mm.). Purification was achieved by low temperature crystallization from ligroin followed by one fractionation: b. p. 62° (14 mm.), f. p. 22.5–22.0°, $n^{20}D$ 1.4605, d^{20} 1.009. Dupont[15] reported b. p. 62–63° (15 mm.); m. p. 29°.

Anal. Calcd. for $C_8H_{12}Cl_2$: Cl, 39.6; mol. wt., 179. Found: Cl, 39.2; mol. wt., 172.

Attempted Methylation of *bis*-2(-Chloroisopropyl)-acetylene.—Ninety-eight grams (0.57 mole) of *bis*-(2-chloroisopropyl)-acetylene (V) in ether was added dropwise to 1.68 moles of methylmagnesium bromide solution. An inflammable gas was evolved continuously from the reaction mixture, even when the flask was packed in crushed ice. After the addition of the halide the flask contents was stirred for six hours as the bath temperature was raised slowly to 50° When the product was poured into dilute iced hydrochloric acid, the ether layer was seen to contain considerable solid matter. After washing, drying and distillation of the ether, 66 g. of a white solid remained. This substance, somewhat waxy in appearance and feel, gave no test for halogen, decomposed without melting, and burned readily though incompletely.

(15) Dupont, *Compt. rend.*, **152**, 198 (1911).

Summary

1. Di-*t*-butylacetylene has been prepared and the structure proved. It was found to have physical properties consistent with its compact, symmetrical structure, and chemical properties influenced by the steric screening of the triple bond.

2. Di-*t*-butylacetylene was hydrogenated to *sym*-di-*t*-butylethylene and thence to *sym*-di-*t*-butylethane.

3. Oxidation of the acetylene gave di-*t*-butyldiketone rather than pivalic acid. Attempts to hydrate the triple bond catalytically were unsuccessful. The sodium in liquid ammonia reduction likewise failed. Bromine added slowly to give a dibromo derivative.

4. A synthesis of *bis*-(2-chloroisopropyl)-acetylene is given. On attempted coupling of this compound with methylmagnesium bromide, a polymer was formed.

NOTRE DAME, INDIANA RECEIVED MARCH 29, 1946

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

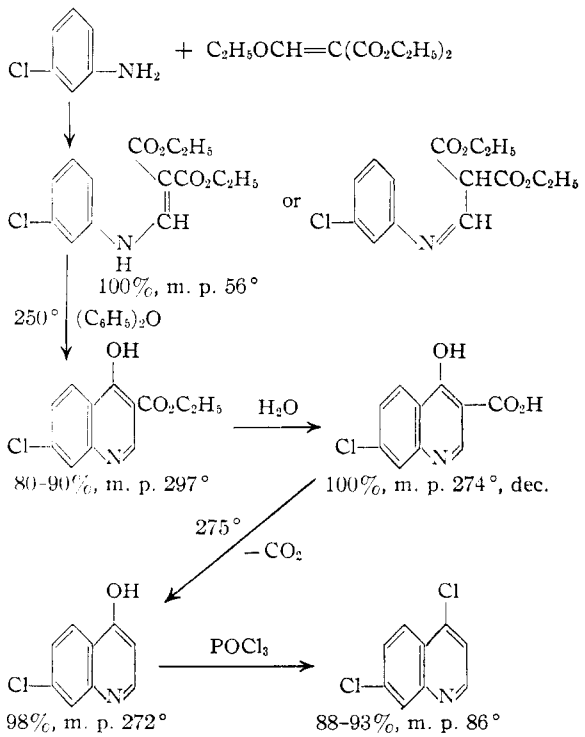
The Synthesis of 4-Hydroxyquinolines.[1] I. Through Ethoxymethylenemalonic Ester

BY CHARLES C. PRICE[2] AND ROYSTON M. ROBERTS[3]

The marked antimalarial activity of a number of quinoline derivatives having an alkylamino side chain attached in the 4-position[4] has led to an investigation of new procedures for the preparation of 4-hydroxyquinolines, which may be readily converted to the desired drugs. It has been found that the reaction reported by Gould and Jacobs,[5] the thermal cyclization of ethyl β-anilino-α-carbethoxyacrylate, is capable of very general application. Furthermore the 4-hydroxy-3-carboxyquinoline derivatives so formed may be readily decarboxylated, producing 4-hydroxyquinolines containing no other substituent in the pyridoring.

The procedure is illustrated by the reaction involved in the conversion of *m*-chloroaniline to 4-hydroxy-7-chloroquinoline.

The present paper also describes the preparation of 6-methoxy and 6,7-dimethyl-4-hydroxyquinoline from *p*-anisidine and 3,4-dimethylaniline, respectively. Further examples will be given in the following papers of this series.



The reaction of ethoxymethylenemalonic ester with aromatic amines to form anilinoacrylates takes place readily even at room temperature.

(1) The work reported in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

(2) Present address: University of Notre Dame, Notre Dame, Indiana.

(3) Present address: Merck and Company, Rahway, New Jersey.

(4) Andersag, Breitner and Jung, German Patent 683,792 (1939); C. A., **36**, 4973 (1942).

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

Claisen[6] carried out the reaction with aniline by heating the reactants for a short time on a water-bath. This was found to be very satisfactory on a small scale, but when large amounts were prepared the handling of acrylate can be conveniently circumvented by mixing the reactants in diphenyl ether at room temperature and then heating this solution directly to the cyclizing temperature of 250°. The anilinoacrylates prepared from *m*-chloroaniline and 3,4-dimethylaniline were low-melting crystalline solids, while that from *p*-anisidine was a liquid at room temperature. All were produced in essentially quantitative yields and could be cyclized without further purification.

The original Limpach cyclization, as utilized by Gould and Jacobs,[5] involved adding a β-arylaminocrotonate to from two to ten times its weight of mineral oil preheated to 250–290° and then heating the solution at 240–250° for fifteen or twenty minutes. It has been found that both diphenyl ether and "Dowtherm-A"[7] are far superior as a cyclization medium. These solvents boil at a temperature which is optimum for the cyclization, are much less viscous and more easily removed from the product by filtration, and, in general, the product is formed with much less darkening.

The volume of solvent required for cyclization of the various acrylates varied considerably. The *m*-chloroanilino compound could be cyclized in good yield by heating without any solvent, but 3-pyridylaminoacrylate, and other examples to be described later, required dilution with up to forty volumes of Dowtherm. Under proper conditions, the yields on the cyclizations averaged 80–85% and some large-scale experiments gave yields of over 95%.

In contrast to the oxaloacetic ester method[8] this cyclization proceeds to a remarkable degree in one direction. From *m*-chloroaniline, 3-carbethoxy-7-chloro-4-hydroxyquinoline was obtained in yields of over 90% and not more than minor amounts of the isomeric 3-carbethoxy-5-chloro-4-hydroxyquinoline were ever found. The product from 3,4-dimethylaniline evidently did contain some isomeric material, but the amount of pure, crystalline 4-chlorodimethylquinoline obtained corresponded to over 75% of the total product and was presumed to be the 6,7-dimethyl derivative.[9] The cyclization of the anilinoacrylate from 3-aminopyridine apparently took place in the α-position, for the hydroxy acid and the decarboxylated product corresponded well in physical and chemical properties with the 4-hydroxy-1,5-naphthyridine-3-carboxylic acid[10] and 4-hydroxy-1,5-naphthyridine prepared in a different manner by Klisiecki and Sucharda.[11] This would be the direction of closure predicted by analogy, since the Skraup, Doebner–von Miller, and Doebner reactions, when applied to 3-aminopyridine and its derivatives, lead to 1,5-naphthyridines.[12]

The use of the synthesis for the preparation of drugs is illustrated by the coupling of 4-amino-1-diethylaminopentane with 4-chloro-6,7-dimethylquinoline to produce 4-(4-diethylamino-1-methylbutylamino)-6,7-dimethylquinoline(SN-12,308).[12a] This compound was tested as a suppressive drug against avian malaria and found to be roughly equivalent to atabrine.

Experimental[13]

α-Carbethoxy-β-(*p*-anisidino)-acrylate.—A mixture of 24.6 g. (0.2 mole) of *p*-anisidine and 43.2 g. (0.2 mole) of ethoxymethylenemalonic ester[14] was heated at 130° until no more bubbles of alcohol could be detected coming from the mixture. The dark oil failed to solidify upon cooling to room temperature.

When the ester was cooled in a Dry-Ice–ethanol bath, it crystallized to a solid mass. Ether (40 cc.) was added to dissolve the solid and the solution was cooled again in the Dry-Ice mixture. The white crystals which separated were collected on a previously cooled Buchner funnel and transferred quickly to a beaker. A thermometer placed in the melting crystals indicated that the melting point was between −10 and −15°.

3-Carbethoxy-4-hydroxy-6-methoxyquinoline.—Forty-three grams (0.17 mole) of ethyl α-carbethoxy-β-(*p*-methoxyanilino)-acrylate was added to 500 cc. of boiling Dowtherm. The dark solution was heated under reflux for forty-five minutes, allowed to cool, and diluted with 500 cc. of high-boiling petroleum ether. The light-colored solid which separated was removed by filtration and washed twice with petroleum ether and twice with ethyl ether. When dry, the ester weighed 25 g. (65%) and melted with decomposition at 260–265°. After recrystallization from 50% ethanol, it melted at 274–277°. It was insoluble in water, but soluble in ethanol and in 10% aqueous sodium hydroxide and hydrochloric acid solutions.

(6) Claisen, *Ber.*, **36**, 2729 (1903); Claisen and Haase, *Ann.*, **297**, 75 (1897).

(7) A eutectic mixture of diphenyl ether and biphenyl. This is superior to pure diphenyl ether (m. p. 27°) because of its lower cost and lower freezing point (12°).

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

(9) 4-Chloro-5,6-dimethylquinoline is not reported in the literature. The only reference to 4-chloro-6,7-dimethylquinoline (I. G. Farbenind, A. G., Indian Patent 25,810, April 1, 1939; *Chem. Zentr.* **110**, II, 2446 (1939) gives the boiling point of an oil which probably contained both isomers, since the other isomer present in our mother liquors was apparently a liquid at room temperature. Moreover, the product obtained from this oil and 4-amino-1-diethylaminopentane is described by a boiling point, whereas our product crystallized spontaneously from the crude reaction mixture.

(10) No proof was given for the position of the carboxyl group in this acid, which was obtained by the stepwise decarboxylation of 4-hydroxy-1,5-naphthyridine-2,3-dicarboxylic acid. In view of the fact that many 4-hydroxyquinoline-3-carboxylic acids lose carbon dioxide more easily than the corresponding 2-acids it would appear to be more than possible that the mono-acid obtained was actually 4-hydroxy-1,5-naphthyridine-2-carboxylic acid.

(11) Klisiecki and Sucharda, *Roczniki Chem.*, **7**, 204 (1927); *C. A.*, **22**, 777 (1928).

(12) British Patent 259,973, Dec. 15, 1926; *Chem. Zentr.*, **99**, I, 2312 (1928); U. S. Patent 1,755,515, Apr. 22, 1930; *Chem. Zentr.*, **101**, II, 814 (1930); German Patent 507,637, Sept. 19, 1930; *Chem. Zentr.*, **101**, II, 3084 (1930).

(12a) The Survey Number, designated SN-, refers to the number assigned a drug by the Survey of Antimalarial Drugs. The activity of these compounds will be summarized in a forthcoming monograph.

(13) All melting points are uncorrected. Analyses by Howard Clark and Miss Theta Spoor.

(14) The ethoxymethylenemalonic ester should be of a high degree of purity. The use of impure ester led to deep coloration and low yields in cyclization steps. The refractive index is a good criterion of purity, $n^{20}D$ 1.4600 and above being satisfactory.

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30. Found: C, 63.06; H, 5.57.

The quinoline ester (0.5 g.) was hydrolyzed by boiling with 18% hydrochloric acid (30 cc.) for one hour. The hot solution was filtered through a fluted funnel and 4-hydroxy-6-methoxyquinoline-3-carboxylic acid crystallized as the filtrate cooled, m. p. 271–272° with effervescence.

The acid was decarboxylated by placing it in a small beaker immersed in a metal-bath and heating at 270–275° until the evolution of carbon dioxide ceased. The product was taken up in 10 cc. of hot water and treated with decolorizing charcoal. This hot mixture was filtered and 4-hydroxy-6-methoxyquinoline separated from the filtrate in the form of fine, white needles, m. p. 239–240° (lit., 244°).[15] When a drop of ferric chloride solution was added to an aqueous solution of this product a pink color was produced.

A 15-g. sample of the hydroxy compound was converted to the 4-chloro-compound in 67% yield by treatment with phosphorus oxychloride. The product, m. p. 74–75°, was much purer than that obtained from the N-oxide procedure.[15]

Ethyl α-Carbethoxy-β-*m*-chloroanilinoacrylate.—A mixture of 12.8 g. (0.100 mole) of *m*-chloroaniline and 23.3 g. (0.108 mole) of ethoxymethylenemalonic ester was stirred until homogeneous, a few boiling chips were added, and the flask was heated in an oil-bath at 100° for an hour. When working with larger amounts of material it was found advantageous to pass a stream of nitrogen through the mixture to aid in the removal of ethanol.

The condensation was also effected at lower temperatures by passing a fine stream of air from a capillary ebullator through the reactants contained in a filter flask evacuated by a water pump.

The reaction mixtures prepared in these ways were normally used directly in the next step without further purifying the acrylate. The compound crystallized in the form of slender white needles, m. p. 55–56°. It was very soluble in ether, alcohols, and other common organic solvents, but was recrystallized easily from low-boiling petroleum ether.

Anal. Calcd. for $C_{14}H_{16}O_4NCl$: C, 56.47; H, 5.42 Found: C, 56.63; H, 5.60.

3-Carbethoxy-7-chloro-4-hydroxyquinoline.—The molten acrylate above (0.100 mole at 100°) was poured slowly through the top of an air condenser into 100 cc. of boiling diphenyl ether. Thirty minutes after the addition the cyclized product began to crystallize on the walls of the flask, the crystals soon filling the boiling solution. The mixture was heated for a total of forty-five minutes and then allowed to cool to room temperature. To the semi-solid mass was added 50 cc. of high-boiling petroleum ether, the mixture was stirred well, the crystalline product was collected and washed on the filter with two 50-cc. portions of high-boiling petroleum ether. The remainder of the solvent was removed by means of high-boiling petroleum ether in a Soxhlet extractor to yield 21 g. (80%) of quinoline ester. The melting point of the extracted product was 295–297°. In subsequent experiments it was found that the cyclization solvent could be satisfactorily removed from the product by resuspending the filter cake in a large volume of petroleum ether, triturating well, and refiltering.

3-Carbethoxy-7-chloro-4-hydroxyquinoline was very insoluble in water, alcohols, benzene, petroleum ether, chloroform, nitromethane, and ethyl acetate; it was slightly soluble in acetic acid and more so in pyridine. It could be recrystallized from either of the latter solvents, preferably pyridine, m. p. 295–297°.

Anal. Calcd. for $C_{12}H_{10}O_3NCl$: C, 57.27; H, 4.01. Found: C, 57.17; H, 4.37.

When mineral oil was used as the cyclization solvent, the reaction mixture turned very dark and the yield was diminished.

(15) Magidson and Rubtsov, *J. Gen. Chem.* (U. S. S. R.), **1**, 1896 (1937).

7-Chloro-4-hydroxyquinoline-3-carboxylic Acid.—3-Carbethoxy-7-chloro-4-hydroxyquinoline (3.93 g., 0.0156 mole) was boiled under reflux with 10% sodium hydroxide solution (32 cc.) for one hour. A few grams of decolorizing charcoal was added and the mixture was boiled an additional five minutes, filtered, and washed with 20 cc. of hot water. The filtrate was acidified with 10% hydrochloric acid and the white 7-chloro-4-hydroxyquinoline-3-carboxylic acid was collected on a filter and washed. After drying thoroughly in a vacuum desiccator, the product weighed 3.48 g. (100% of the theoretical amount), m. p. 266°, with effervescence. The quinoline acid is practically insoluble in water (in contrast to 4-hydroxy-6-methoxyquinoline-3-carboxylic acid), but it is easily soluble in dilute alkali and moderately soluble in ethanol, crystallizing from the latter in the form of fine white needles, m. p. 273–274°, with frothing.

Anal. Calcd. for $C_{10}H_6O_3NCl$: C, 53.71; H, 2.71. Found: C, 53.37; H, 2.87.

The quinoline ester was also hydrolyzed satisfactorily with 18% hydrochloric acid.

7-Chloro-4-hydroxyquinoline.—The decarboxylation of small amounts (up to 5 g.) of 7-chloro-4-hydroxyquinoline-3-carboxylic acid was conveniently carried out in Pyrex test-tubes immersed in a Wood's metal-bath heated to 250–270°. For larger amounts the use of an electric heating unit designed to fit a 1-liter Pyrex beaker was found greatly superior to a metal-bath. In this apparatus, 200 to 300 g. of acid were decarboxylated by heating until effervescence ceased and then allowing the product to cool and solidify. The cake usually cracked away from this side of the beaker and was ground up in a mortar and used directly in the next step. The yield of crude 7-chloro-4-hydroxyquinoline was 98% of the theoretical amount.

When desired, the pure hydroxyquinoline was obtained by recrystallization of the crude decarboxylation product from a large amount of water after decolorization with charcoal, affording very fine white needles, m. p. 270–272° sintering from 260°

Anal. Calcd. for C_9H_6ONCl: C, 60.18; H, 3.37. Found: C, 60.10; H, 3.55.

Decarboxylations carried out in the presence of powdered glass and copper chromite catalyst indicated no favorable effect on lowering the temperature or increasing the rate at which loss of carbon dioxide occurred. The use of a high-boiling solvent to effect the reaction is described below.

4,7-Dichloroquinoline.—The crude hydroxyquinoline (478 g.) was converted to 4,7-dichloroquinoline by treatment with phosphorus oxychloride essentially as described by Surrey and Hammer.[8] The crude product, obtained in 88 to 93% yield, was very pale tan, melted at about 75–80°, and was strongly lachrymatory and irritating to the skin. One recrystallization from 80% ethanol gave beautiful cottony needles, m. p. 84.5–85° (lit.[8] 84.5°).

Anal. Calcd. for $C_9H_5NCl_2$: C, 54.57; H, 2.54. Found: C, 54.48; H, 2.43.

Decarboxylation and Chlorination in High-Boiling Solvent.—7-Chloro-4-hydroxyquinoline-3-carboxylic acid (20 g., 0.090 mole) and "Dowtherm-A" (100 cc.) were heated to boiling. The acid dissolved in the boiling solvent and the clear light brown solution was heated under reflux for one hour. The reaction mixture was allowed to cool to room temperature and 9 cc. (0.10 mole) of phosphorus oxychloride was added with practically no evolution of heat. The temperature was raised to 135–140° and the mixture stirred for one hour. The cool reaction mixture was transferred to a separatory funnel with the addition of ethyl ether to facilitate the transfer and to thin the mixture and the 4,7-dichloroquinoline was extracted with four 100-cc. portions of 10% hydrochloric acid. Ice was added and the combined acid extracts were neutralized with 10% sodium hydroxide. The precipitate was collected on a filter, resuspended in a liter of water and triturated, then collected again on a filter. After drying in a vacuum desiccator the crude product weighed 13.7 g (77.5%), m. p. 80–82°.

Simplified Procedure for Preparation of 4,7-Dichloroquinoline.—A mixture of 12.8 g. (0.100 mole) of *m*-chloroaniline and 22.0 g. (0.102 mole) of ethoxymethylenemalonic ester was warmed in an oil-bath heated to 70–80° for forty minutes. The molten acrylate was added to 80 cc. of boiling "Dowtherm-A" and washed in with an additional 20 cc. of hot solvent. It was later found that the separate preparation of the acrylate was unnecessary; the reactants may be dissolved in the solvent and heated directly to the cyclization temperature. The cyclization mixture was boiled for thirty minutes in the open flask, allowed to cool to 180°, and 100 cc. of 10% sodium hydroxide solution was added cautiously with stirring. A reflux condenser was attached and the heterogeneous mixture was boiled vigorously under reflux for half an hour (all the solid disappeared within fifteen minutes). The cool reaction mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was made acid to congo red with 10% sulfuric acid; the precipitated acid was collected on a filter and sucked as dry as possible. The pasty filter cake was then recombined with the "Dowtherm-A" layer, together with an additional 40 cc. of fresh solvent. The mixture was heated to boiling cautiously, so that the removal of occluded water was not too vigorous, and boiled for an hour. All the solid material went into solution as the decarboxylation proceeded. The reaction mixture was allowed to cool to room temperature, diluted with 25 cc. of petroleum ether, and the 7-chloro-4-hydroxyquinoline was collected on a filter. The product was resuspended in a small amount of petroleum ether, collected, and dried. It was converted to a 4,7-dichloroquinoline according to the procedure described above and a yield of 14.9 g. of this crude product was obtained. This corresponded to an over-all yield of 75% from *m*-chloroaniline to 4,7-dichloroquinoline.

Ethyl α-Carbethoxy-β-(3,4-dimethylanilino)-acrylate.—A fine stream of air was passed through a mixture of 121 g. (1 mole) of technical 3,4-dimethylaniline and 216 g. (1 mole) of ethoxymethylenemalonic ester evacuated by a water pump. Crystals of the product began to separate after about three hours and, at the end of twenty-four hours, the mass was almost completely solid. The ethyl α-carbethoxy-β-(3,4-dimethylanilino)-acrylate could be purified by recrystallization from low-boiling petroleum ether and was obtained in the form of white micro-crystals, m. p. 52–53.5°.

Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.97; H, 7.27. Found: C, 66.20; H, 7.22.

4-Chloro-6,7-dimethylquinoline.—The application of the ethoxymethylenemalonic ester synthesis to 3,4-dimethylaniline evidently resulted in the formation of appreciable amounts of isomers. The product of the cyclization had a wide melting-point range, the decomposition point of the acid is not a true melting point and was naturally not wide, but the decarboxylated product also melted over a wide range. None of these intermediates could be readily purified by fractional crystallization. It was therefore most satisfactory to carry the synthesis through to the preparation of 4-chlorodimethylquinoline before attempting any separation.

The acrylate prepared above was melted on the steam-bath and poured through the reflux condenser into 1 liter of boiling "Dowtherm-A" at such a rate that the addition was complete in three to four minutes. Crystals of the cyclized product began to separate after twenty-five minutes. After one hour, heating of the dark red mixture was discontinued. When the reaction mixture had cooled sufficiently, 1 liter of 10% sodium hydroxide solution was added and the mixture was boiled under reflux for three and one-half hours. All the lumps of cyclized product had not dissolved, so the liquid was decanted and these were broken up with a glass rod. After recombining, the mixture was boiled another two hours, the remaining solid having disappeared by the end of the first hour. The aqueous layer of the cool, two-phase mixture was separated, traces of solvent were removed by extraction with high-boiling petroleum ether, and 18% hydrochloric acid (*ca.* 500 cc.) was added until the solution was just acid to congo red. The precipitate was digested by heating to boiling, 500 cc. of water was added to thin the pasty mass, and it was allowed to cool to room temperature. The light tan precipitate was collected by vacuum filtration, pressed dry by a rubber dam, resuspended and stirred in 1.5 liters of water, and collected again on a filter. After sucking as dry as possible again under the rubber dam, the cake was broken up and dried to constant weight in an oven at 100° (about twenty-four hours). The tan powdery acid obtained weighed 172 g. (79% of the theoretical amount calculated from 3,4-dimethylaniline).

The acid was decarboxylated by heating at 270–280° for half an hour after the solid had all melted. This product apparently lost carbon dioxide more slowly than the corresponding 7-chloro analog—the loss in weight after this treatment was 5 g. short of the theoretical. After reheating for another thirty minutes an additional 3 g. was lost. The decarboxylation product was very dark brown so it was purified by conversion to the hydrochloride. The brown crystalline cake was broken up into small lumps and dissolved in 2.5 liters of water and 70 cc. of concentrated hydrochloric acid by heating to boiling and stirring. Thirty grams of decolorizing charcoal was added and the heating and stirring was continued for an hour, adding water occasionally to maintain the volume. The mixture was filtered and 2 liters of concentrated hydrochloric acid was added rapidly with stirring to the hot filtrate. The quinoline hydrochloride began to crystallize immediately, and, after the mixture had stood overnight in the refrigerator, it was collected by filtration and dried in a vacuum oven. The yield of tan crystals was 115 g. or 70% of the amount calculated from the acid; the loss involved in the crystallization of the hydrochloride was evidently a considerable factor in the low yield.

This hydrochloride (114 g., 0.55 mole) was added to 114 g. (0.55 mole) of phosphorus pentachloride and 175 cc. of phosphorus oxychloride in small portions. The temperature was kept at 110° by an oil-bath; the addition required twenty minutes. When it was completed, the oil-bath was heated to 135° and stirring and refluxing were maintained for another forty-five minutes. The excess phosphorus oxychloride was removed under reduced pressure and the hard solid cake was dissolved by stirring into a mixture of benzene (*ca.* 500 cc.) and dilute sodium hydroxide (*ca.* 500 cc.). Enough solid sodium carbonate was added to make the mixture slightly basic, and after stirring several hours, the benzene layer was separated. The aqueous layer was extracted with a 200- and a 100-cc. portion of benzene and the benzene extracts were combined, treated with charcoal, filtered, and evaporated. The residue, which crystallized immediately on cooling, melted at 70–83°. This product was purified by charcoal treatment followed by a thirteen-step fractional crystallization from low-boiling petroleum ether. This afforded 59.5 g. (a 31% yield from 3,4-dimethylaniline) of almost white plates, m. p. 86–88°, presumably 4-chloro-6,7-dimethylquinoline.[9]

Anal. Calcd. for $C_{11}H_{10}NCl$: C, 68.93; H, 5.26. Found: C, 68.78; H, 5.39.

The mixture of crystals and oil recovered from the mother liquors amounted to 19.5 g. and probably contained the isomeric 4-chloro-5,6-dimethylquinoline, which was not isolated in a pure state.

4-(4-Diethylamino-1-methylbutylamino)-6,7-dimethylquinoline, (SN-12,308).—A mixture of 18.4 g. (0.096) of 4-chloro-6,7-dimethylquinoline and 33.4 g. (0.211 mole) of purified 4-amino-1-diethylaminopentane was heated in an oil-bath to an inside temperature of 165–175° for five hours. At the end of this time, a 0.3-cc. sample of the reaction mixture dissolved in 3 cc. of 5% nitric acid no longer gave a precipitate of the chloroquinoline when about 5 cc. of 20% sodium acetate buffer solution was added, so the reaction was considered complete. To the cool reaction mixture was added 5.8 g. (0.144 mole) of sodium hydroxide in 55 cc. of water, and 100 cc. of ether. The mixture was transferred to a separatory funnel and, after shaking, the layers were separated and the aqueous solu-

tion was extracted twice more with 50-cc. portions of ether. The combined ether extracts were dried over magnesium sulfate and the ether was removed on the steam cone. Excess diamine was distilled under reduced pressure; 8.3 g. was collected at 81–82° (14 mm.) and 5.5 g. at 45–48° (0.5 mm.). The residue began to crystallize even before all the diamine had distilled so it was purified by recrystallization rather than by distillation. After treating with 3 g. of decolorizing charcoal in 200 cc. of boiling benzene, the benzene solution was concentrated to about 40 cc. and 300 cc. of low-boiling petroleum ether was added with stirring. The mixture was cooled and the light tan crystalline product was collected in a filter; 24.5 g. (82%), m. p. 113–119°. This product was recrystallized twice from Skellysolve B (b. p. 60–68°), yielding 20.0 g of white plates, m. p. 122–123°.

Anal. Calcd. for $C_{20}H_{31}N_3$: C, 76.63; H, 9.97. Found: C, 76.74; H, 9.99.

4-Hydroxy-1,5-naphthyridine.—In view of the parallel preparation reported concurrently by Hauser,[16] only the properties of our products will be described. **3-Aminopyridine** was prepared from (a) nicotinamide by the Hofmann method,[17] (b) nicotinamide and ethyl nicotinate by the Curtius method[18] and (c) 3-bromopyridine by amination.[19] The last method was found to be the most satisfactory. Vacuum distillation was found to be greatly superior to recrystallization as a means of purifying crude 3-aminopyridine. Ethyl β-(3-pyridylamino)-α-carbethoxyacrylate was isolated as white microneedles, m. p. 63–65°

(16) Hauser, THIS JOURNAL, **68**, 1317 (1946).

(17) Pollak, *Monatsh.*, **16**, 54 (1895).

(18) Curtius and Mohr, *Ber.*, **31**, 2493 (1898).

(19) Maier-Bode, *ibid.*, **69**, 1534 (1936).

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.07; H, 6.10. Found: C, 59.23; H, 6.27.

Cyclization at high dilution yielded tan powdery **3-carbethoxy-4-hydroxy-1,5-naphthyridine** (79%), m. p. 268°, dec., softening from 250°. **4-Hydroxy-1,5-naphthyridine-3-carboxylic acid,** obtained by hydrolysis in 85% yield, sublimed without melting at about 315°, losing carbon dioxide, to yield a sublimate of **4-hydroxy-1,5-naphthyridine.** The latter also sublimed without melting, but with no decomposition, at about 300–305°. These properties agree very well with the observations of Klisiecki and Sucharda.[11]

Anal. Calcd. for $C_8H_6ON_2$: C, 65.74; H, 4.14. Found: C, 65.53; H, 4.32.

Summary

A general method for the preparation of 4-hydroxyquinolines has been developed. This synthesis is illustrated by the conversion of *m*-chloroaniline, *p*-anisidine, and 3,4-dimethylaniline to 4-hydroxyquinoline derivatives and of 3-aminopyridine to 4-hydroxy-1,5-naphthyridine. The aromatic amines were condensed with ethoxymethylenemalonic ester and the resulting carbethoxyanilinoacrylates cyclized by heating in a high-boiling solvent to produce 4-hydroxyquinoline-3-carboxylic acid esters. Saponification yielded the corresponding acids which were converted readily to the desired 4-hydroxyquinolines by decarboxylation.

URBANA, ILLINOIS RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Synthetic Antimalarials. The Preparation of Certain 4-Aminoquinolines[1]

BY NATHAN L. DRAKE, HUGH J. CREECH, JOHN A. GARMAN, STUART T. HAYWOOD, RICHARD M. PECK, JOHN O. VAN HOOK AND EDWARD WALTON

Prior to 1942 little attention had been given in this country to quinolines bearing dialkylaminoalkylamino groups in the 4-position as possible antimalarials. A number of members of this class of compounds, however, had been prepared by the Germans[2,3] and by the Russians.[4] Some members of this class have been described recently in the American literature[5] and reported active.

The present paper describes the preparation of a number of substituted 4-aminoquinolines. These compounds fall into two well-defined groups. Those found in Part I of the experimental part are 4-(4-diethylamino-1-methylbutylamino)-quinolines variously substituted in the nucleus; those described in Part II are 7-chloro-4-(dialkylaminoalkylamino)-quinolines[6] with the exception of one 7-chloro-4-aminoalkylaminoquinoline. The present communication deals only with the chemistry of the drugs; their activity and pharmacology will be reported elsewhere.[7]

Substituted 4-aminoquinolines are conveniently synthesized by reaction of an appropriately substituted 4-chloroquinoline with a primary amine. It was found that the conditions necesssary for condensation vary widely as a function of substitution. 4-Chloroquinolines bearing a substituent in the 2 or 3-position require longer times and higher temperatures for complete reaction than do 4-chloroquinolines bearing their other substituents only in the benzene ring. In a few cases

(1) The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Maryland.

(2) H. Andersag, S. Breitner and H. Jung, German Patent 683,692 (Oct. 26, 1939); *C. A.*, **36**, 4973 (1942).

(3) H. Andersag, S. Breitner and H. Jung, U. S. Patent 2,233,970 (March 4, 1941); *C. A.*, **35**, 3771 (1941).

(4) E. P. Hal'perin, *Med. Parisitol. Parasitic Diseases* (U.S.S.R.), **9**, 44 (1940); *C. A.*, **36**, 1674 (1942); O. J. Magidson and M. V. Rubstov, *J. Gen. Chem.* (U.S.S.R.), **7**, 1896 (1937); *C. A.*, **32**, 564 (1938).

(5) Steck, Hallock and Holland, THIS JOURNAL, **68**, 129, 132 (1946).

(6) 7-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline (SN-7618) is omitted from this group. It will form the subject of a separate communication; *cf.* Drake, *et al.*, THIS JOURNAL, **68**, 1214 (1946).

(7) Synthetic Antimalarials 1941–1945. Published by the Survey of Antimalarial Drugs, in press. The various drugs will be assigned the same SN numbers in the monograph by which they were identified in the Survey Office. These same SN numbers will also be used to identify the drugs in our paper.