NEW COMPOUND

2-(4-Diethylamino-1-methylbutylamino)-4-hydroxyquinazoline[1]

2-Chloro-4-methoxyquinazoline[2] (3.0 g.) and 4.8 g. of purified noval diamine[3] were heated two and a half hours at 125–130°. The thick oil was dissolved in 40 cc. of 6 *N* hydrochloric acid and the solution heated six hours on the steam-bath. Then 20 cc. of concentrated hydrochloric acid was added and the solution allowed to stand overnight.

The solution was made strongly alkaline with sodium hydroxide, and was extracted with ether. Between the ether and aqueous layers there was a considerable layer of a thick red-brown oil. The aqueous layer was saturated with carbon dioxide gas; a gummy white solid separated. It was picked out and dissolved in acetone, while the carbonate solution was extracted with ether. The ether and acetone solutions were combined and evaporated to dryness, and the residue sublimed in a high vacuum with the temperature of the oil-bath surrounding the sublimation apparatus at 100–150°. The creamy-white crystalline sublimate of the quinazoline derivative melted at 165–167°; yield, 0.44 g. (9.5%).

The product from another run was purified by repeated sublimation. White crystals, m. p. 177.5–181°, were obtained.

Anal. Calcd. for $C_{17}H_{26}ON_4$: C, 67.51; H, 8.67. Found: C, 67.64; H, 8.69.

Samples of this compound melted as a rule at about 90°, then resolidified and melted again at the temperatures reported above.

(1) This work was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Rochester.

(2) Lange, Roush and Asbeck, THIS JOURNAL, **52**, 3699 (1930).

(3) Jones, *Ind. Eng. Chem., Anal. Ed.*, **16**, 431 (1944).

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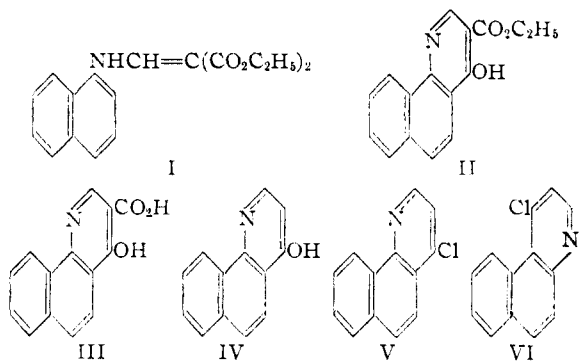
[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Some γ-Substituted Benzoquinoline Derivatives[1]

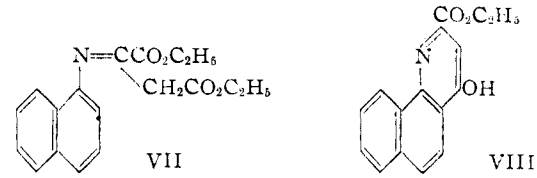
BY ROBERT E. FOSTER, ROBERT D. LIPSCOMB, THEOS. J. THOMPSON[2] AND CLIFF S. HAMILTON[3]

In a continuation of the study of derivatives of benzoquinolines which has been carried on in this Laboratory,[4] the syntheses of 4-chlorobenzo(h)-quinoline and 1-chlorobenzo(f)quinoline have been carried out by the method of Price and Roberts.[5] In addition, the former compound has been synthesized by an alternative method employing ethyl ethoxalylacetate, and derivatives of both chloro compounds have been prepared.

The synthesis of 4-chlorobenzo(h)quinoline involved initially the condensation of ethyl ethoxymethylenemalonate with 1-naphthylamine to give ethyl 2-naphthylaminomethylenemalonate (I). Cyclization of (I) in phenyl ether at 250° gave 3-carbethoxy-4-hydroxybenzo(h)quinoline (II) which yielded 3-carboxy-4-hydroxybenzo(h)quinoline (III) upon hydrolysis in alkaline solution. When the acid (III) was heated near its melting point, carbon dioxide was evolved and 4-hydroxybenzo(h)quinoline (IV) was obtained. Conversion of this product to 4-chlorobenzo(h)quinoline (V) was readily accomplished by treatment with a mixture of phosphorus oxychloride and phosphorus pentachloride. The synthesis of 1-chlorobenzo(f)quinoline (VI) was carried out in an exactly analogous manner starting with 2-naphthylamine.



In the synthesis involving ethyl ethoxalylacetate, the initial condensation with 1-naphthylamine yielded ethyl 1-naphthyliminosuccinate (VII). This compound was cyclized in mineral oil at 230° to yield an isomer of II, namely, 2-carbethoxy-4-hydroxybenzo(h)quinoline (VIII). This ester was converted to the corresponding acid by alkaline hydrolysis; subsequent decarboxylation yielded 4-hydroxybenzo(h)quinoline (IV).



The over-all yield of γ-chlorobenzoquinoline prepared by either method was above 35%. The method using ethyl ethoxymethylenemalonate

(1) A part of the work described in this manuscript was done under contract OEMsr-85, recommended by the National Defense Research Committee, between the Office of Scientific Research and Development and the Board of Regents of the University of Nebraska.

(2) Part of the work described in this paper was taken from a thesis submitted to the graduate faculty of the University of Nebraska by Theos. J. Thompson in partial fulfillment of the requirements for the degree of Master of Science.

(3) Responsible investigator.

(4) For preceding communications see Gobeil and Hamilton, THIS JOURNAL, **67**, 511 (1945).

(5) Price and Roberts, *ibid.*, **68**, 1208 (1946).

gave higher yields in the preparation of these particular compounds.[6]

Condensation of V was accomplished with ammonia, morpholine, piperidine, γ-N-morpholinopropylamine, γ-diethylaminopropylamine, δ-diethylaminobutylamine, and 4-amino-1-diethylaminopentane. In addition, VI was condensed with 4-amino-1-diethylaminopentane.[6]

The attempted condensation of V with 4-amino-1-diethylaminopentane in the presence of alcoholic alkali yielded only 4-ethoxybenzo(h)quinoline and the reaction of V with an acidified aqueous solution of 4-amino-1-diethylaminopentane, in a manner similar to that of Banks,[7] resulted in hydrolysis of V to 4-hydroxybenzo(h)quinoline (IV).

Experimental[8]

All melting points were corrected for exposed thermometer stem.

Ethyl 1-Naphthylaminomethylenemalonate (I).—A solution of 185.8 g. (0.6 mole) of 1-naphthylamine and 129.6 g. (0.6 mole) of ethyl ethoxymethylenemalonate was placed *in vacuo* and dry air bubbled through the reaction mixture overnight. The solidified material was melted and again placed *in vacuo* to remove more completely the ethanol generated. The dark gray solid could be utilized in the next step of the synthesis without purification. Crystallized twice from ethanol, the anil appeared as white tetragonal platelets; m. p. 87.5–88.0°.

Anal. Calcd. for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11. Found: C, 68.93; H, 6.35.

Ethyl 2-Naphthylaminomethylenemalonate.—This compound was prepared in an exactly analogous manner. The yield of colorless product which was crystallized from methanol was 90%; m. p. 78–78.5°.

Anal. Calcd. for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11. Found: C, 68.88; H, 6.11.

3-Carbethoxy-4-hydroxybenzo(h)quinoline (II).—The cyclization was carried out in a flask fitted with a steam-jacketed condenser which allowed the ethanol generated during the reaction to escape.

The crude ethyl 1-naphthylaminomethylenemalonate was melted and added to 350 ml. of boiling phenyl ether. The solution was refluxed for fifty minutes, during which time the temperature of the refluxing vapors rose from 200 to 257°. The solution was then allowed to cool. The crude product was separated from the phenyl ether by filtration, triturated three times with low-boiling petroleum ether to remove the phenyl ether, and dried. The yield of the brown, crude 3-carbethoxy-4-hydroxybenzo(h)-quinoline, m. p. 257–259°, was 150.7 g. or 94% based on 1-naphthylamine and ethyl ethoxymethylenemalonate.

This ester was soluble in dilute hydrochloric acid, and insoluble in dilute alkali; the material was very slightly soluble in alcohol, acetone, and toluene. Fine, fluffy, cream-colored needles were obtained by crystallization from acetic acid; m. p. 261–262°.

Anal. Calcd. for $C_{16}H_{13}O_3N$: C, 71.89; H, 4.90. Found: C, 72.15; H, 5.11.

2-Carbethoxy-1-hydroxybenzo(f)quinoline.—To 220 ml. of boiling phenyl ether in a round-bottomed flask fitted with an air-cooled condenser was added 131 g. (0.42 mole) of melted ethyl 2-naphthylaminomethylenemalonate and the temperature of the solution held at 245–252° for twenty minutes. Tan crystals separated when the solution was allowed to cool and were collected on a filter and washed several times with petroleum ether; yield, 92 g. (82%). A sample recrystallized from glacial acetic acid melted at 261–265°.

Anal. Calcd. for $C_{16}H_{13}O_3N$: C, 71.89; H, 4.90. Found: C, 71.91; H, 5.15.

3-Carboxy-4-hydroxybenzo(h)quinoline (III).—The crude 3-carbethoxy-4-hydroxybenzo(h)quinoline (150.7 g.) from the preceding step was refluxed with 1000 ml. of 5% sodium hydroxide solution for forty-five minutes. The hot solution was acidified with dilute hydrochloric acid, and the precipitated solid was isolated on a filter, washed with water, and dried. The yield of the crude acid was 127.5 g. (94.8%).

The acid could be purified by dissolving it in a boiling dilute solution of potassium bicarbonate, filtering hot, and reprecipitating with dilute hydrochloric acid; fine white, powdery crystals were thus obtained; m. p. 291–292° (d.)

Anal. Calcd. for $C_{14}H_9O_3N$: C, 70.29; H, 3.79. Found: C, 69.83; H, 3.75.

2-Carboxy-1-hydroxybenzo(f)quinoline.—The saponification was carried out in an analogous manner. Nearly quantitative yields of the acid were obtained. The crude acid was not analyzed but used directly in the next step of the synthesis. It melted about 260° with loss of carbon dioxide.

4-Hydroxybenzo(h)quinoline (IV).—The crude 3-carboxy-4-hydroxybenzo(h)quinoline (127.5 g.) was decarboxylated by introducing it portionwise into a 300-ml., taper-walled beaker which was maintained at a temperature slightly above the melting point of the acid. It was necessary to stir the mixture manually, and to add the acid gradually to avoid excessive foaming. When all the acid had been added, the mixture was heated and stirred until the evolution of carbon dioxide ceased, and then the liquid was allowed to cool and solidify. The stirrer was allowed to remain in the material; it facilitated the removal of the solid cake from the beaker. The hard cake was ground to a powder; the yield of light brown product satisfactory for use in the next step was 102.0 g. (98%).

The product could be purified readily by dissolving the material in dilute sodium hydroxide solution, and precipitating the 4-hydroxybenzo(h)quinoline by means of carbon dioxide. A white solid was obtained in this manner; m. p. 235–238° (d.).

This compound was prepared also by heating 2-carboxy-4-hydroxybenzo(h)quinoline (*q. v.*) at 280–290° for twenty minutes. The brown solid when cool was purified by reprecipitation from hot alcohol by the addition of water; m. p. 242–243°; yield, 85.8%. The 4-hydroxybenzo(h)-quinoline existed as a monohydrate below 100°.

Anal. Calcd. for $C_{13}H_9ON \cdot H_2O$: C, 73.22; H, 5.20; H_2O, 8.45. Found: C, 73.34, 73.41; H, 5.28, 5.39; H_2O, 8.55.

1-Hydroxybenzo(f)quinoline.—The decarboxylation of crude 2-carboxy-1-hydroxybenzo(f)quinoline was carried out in a similar manner. The yield of light tan powder was quantitative. Purification was effected by dissolving the product in 5% sodium hydroxide solution and reprecipitation with carbon dioxide or by recrystallization from ethanol in which it was sparingly soluble. The purified 1-hydroxybenzo(f)quinoline melted at 278–280°. This compound has been characterized by Mueller and Hamilton.[6]

4-Chlorobenzo(h)quinoline (V).—The crude 4-hydroxybenzo(h)quinoline (104.5 g.) was added portionwise, with stirring, to a boiling mixture of an equivalent amount of phosphorus pentachloride (111 g.) and 700 ml. of phosphorus oxychloride. The mixture became very "thick" by the time all of the hydroxy compound was added (two hours). The mixture was heated and stirred overnight; complete solution was thus effected. As much as possible of the phosphorus oxychloride was removed by distillation, and the residue was poured onto 1 kg. of crushed ice. Concentrated hydrochloric acid (500 ml.) was added and

(6) The preparation of 1-chlorobenzo(f)quinoline by the ethyl ethoxalylacetate method and the preparation of several derivatives of this compound have been described by Mueller and Hamilton, THIS JOURNAL, **65**, 1017 (1943).

(7) Banks, THIS JOURNAL, **66**, 1127 (1944).

(8) Most of the analyses reported were performed by Mr. H. S. Clark of the Illinois State Geological Survey, Champaign, Illinois, or by T. J. T.

the mixture stirred occasionally for several hours in order to dissolve the product. The solution of 4-chlorobenzo(h)quinoline hydrochloride was filtered through "celite," the filtrate cooled to below 15° and neutralized with 10% sodium hydroxide solution. The precipitated product was isolated on a Büchner funnel, sucked as dry as possible, and dried in an oven.

The cream-colored 4-chlorobenzo(h)quinoline weighed 100 g. (87.5%), m. p. 82–86°. This material was crystallized twice from 95% ethanol and once from petroleum ether (b. p. 60–70°); the yield of the pale yellow crystals, m. p. 87.5–89°, was 56.7 g. Concentration of the mother liquors provided an additional 12.2 g., m. p. 86–88°. The yield of purified material was 60.2%. Several recrystallizations of a small sample of the material from alcohol and from petroleum ether gave white needles; m. p. 88–89°. A melting point of 95° for this compound has been reported.[9]

The 4-chlorobenzo(h)quinoline was also prepared by the action of phosphorus oxychloride alone on the hydroxy compound.[10] Six grams of 4-hydroxybenzo(h)quinoline was refluxed for four hours with 40 ml. of phosphorus oxychloride. The product was isolated as described above; the yield of once-crystallized material was 5.5 g. (86%).

Anal. Calcd. for $C_{13}H_8NCl$: C, 73.07; H, 3.77. Found: C, 73.04, 72.95; H, 3.74, 3.89.

1-Chlorobenzo(f)quinoline (VI).—A solution of 37.8 g. (0.17 mole) of phosphorus pentachloride in 75 ml. of phosphorus oxychloride was heated to boiling and 31.2 g. (0.16 mole) of 1-hydroxybenzo(f)quinoline added in 2–3-g. portions with stirring. The addition required about fifteen minutes. Stirring and refluxing were continued for forty-five minutes longer.

Nearly all of the phosphorus oxychloride was removed by distillation under reduced pressure (twelve to fifteen minutes). The nearly dry, porous residue was added to 250 ml. of ice and water, the mixture stirred and allowed to stand two hours. A small amount of insoluble material was removed by filtration and the filtrate neutralized with 8% sodium hydroxide solution. The nearly white precipitate of 1-chlorobenzo(f)quinoline was collected on a filter, washed thoroughly, and dried in air; yield, 32 g. (93.5%).

Purification was best effected by recrystallization from petroleum ether. Eighty per cent. of the material can be recovered as small white crystals melting at 62.5–64°. An additional 10% melting about 59° can be obtained by working the mother liquors.

Ethyl 1-Naphthyliminosuccinate.—Twenty-two grams of 1-naphthylamine, 200 ml. of absolute methanol, 32 ml. of ethyl ethoxalylacetate, and 15 g. of anhydrous sodium sulfate were mixed and allowed to stand at room temperature in the absence of air for sixty hours. The mixture was shaken occasionally during this time. The sodium sulfate was separated by filtration, and the filtrate was concentrated to 35 ml. and cooled. A brown solid separated which crystallized from alcohol in light yellow crystals; m. p. 77.8–77.9°; yield, 37.2 g. (77.1%).

Anal. Calcd. for $C_{18}H_{19}O_4N$: C, 68.95; H, 6.11. Found: C, 68.72, 68.80; H, 6.31, 6.22.

2-Carbethoxy-4-hydroxybenzo(h)quinoline.—Three hundred milliliters of mineral oil was heated at 238°, and 25 g. of ethyl 1-naphthyliminosuccinate was added at such a rate that the temperature of the oil was maintained between 220 and 230°. After all the anil had been added, the solution was heated at 230° for an additional ten minutes. When the solution was cooled the product separated as a black cake. This was dissolved in alcohol, and the solution decolorized with charcoal and concentrated. Cooling the concentrate precipitated 2-carbethoxy-4-hydroxybenzo(h)quinoline; m. p. 126–127°; yield, 19 g. (89.1%).

Anal. Calcd. for $C_{16}H_{13}O_3N$: C, 71.89; H, 4.90. Found: C, 72.11, 71.99; H, 5.04, 5.05.

2-Carboxy-4-hydroxybenzo(h)quinoline.—Nineteen grams of the preceding ester was refluxed with 200 ml. of 5% aqueous sodium hydroxide solution for five hours. The solution was cooled, treated with decolorizing charcoal, and filtered. The 2-carboxy-4-hydroxybenzo(h)quinoline was precipitated by the addition of dilute hydrochloric acid, and purified by reprecipitation from sodium bicarbonate solution. The white crystalline solid melted with decomposition at 280°; yield 13 g. (76%).

Anal. Calcd. for $C_{14}H_9O_3N$: C, 70.29; H, 3.79; N, 5.85. Found: C, 70.02; H, 3.76; N, 5.57.

Condensations of the γ-Chlorobenzoquinolines

4-Aminobenzo(h)quinoline.—A mixture of 5 g. of 4-chlorobenzo(h)quinoline, 3 g. of cuprous hydroxide, 50 ml. of ethanol, and 40 ml. of water was treated with gaseous ammonia until the solution was saturated. The reaction mixture was then heated at 205° in an autoclave for six hours. Alcohol (50 ml.) was added to the mixture, which was then warmed and filtered; the filtrate was evaporated, and the residue dissolved in dilute hydrochloric acid. The solution was decolorized and the product was precipitated by alkali. The yield of the white crystalline solid was 2.95 g. (66.1%), m. p. 173–175°.

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19. Found: C, 80.64, 80.06; H, 4.95, 5.02.

Condensations with Amines.—The preparation of γ-aminobenzoquinolines was carried out by heating the γ-chlorobenzoquinoline with a one to two mole excess of the desired amine at, or just below, the boiling point of the amine for several hours. When a sample of the reaction solution dissolved in dilute nitric acid did not yield a precipitate when buffered with a saturated sodium acetate solution, the heating was halted. The product, if solid, was crystallized from alcohol. The procedure for the preparation of 4-(4-diethylamino-1-methylbutylamino)-benzo(h)quinoline illustrates conditions which give satisfactory results.

4-(4-Diethylamino-1-methylbutylamino)-benzo(h)quinoline.[9]—A mixture of 10.6 g. of 4-chlorobenzo(h)quinoline (0.05 mole) and 20 g. of 4-amino-1-diethylaminopentane[11] (0.125 mole) was heated for twenty-four hours. The temperature of the heating bath was carefully controlled to prevent excessive decomposition of the condensation product; the internal temperature was 168–178° during this period. About 0.5 ml. of a volatile amine was liberated from the reaction mixture, indicating slight decomposition. The solution was poured into water, and the viscous oil taken up in ether. The ether solution was washed with water, dried, and the solvent evaporated, and the product distilled *in vacuo* through a short-path still. The yield of the pure base distilling at 214–225° (0.3–0.45 mm.) was 10.62 g. (62%).

Anal. Calcd. for $C_{22}H_{29}N_3$: C, 78.76; H, 8.71; N, 12.53. Found: C, 78.95; H, 8.39; N, 12.49.

For convenience of manipulation, the free base was converted to a phosphate by the addition of exactly two moles of phosphoric acid in ether to a rapidly-stirred ethereal solution of the base.[12] The salt was a cream-colored, hygroscopic powder, insoluble in dry organic solvents. It could not be recrystallized. Analysis indicated the formation of hydrated salt.

Anal. Calcd. for $C_{22}H_{29}N_3 \cdot 2H_3PO_4 \cdot H_2O$: C, 48.08; H, 6.79; N, 7.65. Found: C, 48.12; H, 6.31; N, 7.31.

An attempt was made to prepare the condensation product by the method of Banks.[7]

The 4-chlorobenzo(h)quinoline, 2.13 g., was mixed with 3 ml. of 4-amino-1-diethylaminopentane, 50 ml. of 1 *N* hydrochloric acid, and 100 ml. of water. This mixture

(9) I. G. Farben, German Patent 669,806; U. S. Patent 2,231,844; *C. A.*, **32**, 6262 (1938).

(10) Ainley and King, *Proc. Roy. Soc.* (London), **B125**, 49 (1938).

(11) Commercial noval diamine was purified by the method of Jones, *Ind. Eng. Chem., Anal. Ed.*, **16**, 431 (1944).

(12) Excess phosphoric acid resulted in the formation of an intractable gum.

TABLE I

PREPARATION AND PROPERTIES OF 4-AMINOBENZO(h)QUINOLINES

Product Benzo(h)quinoline	Condensation conditions Time	Temp., °C.	Yield, %	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
4-Benzylamino-	5	165	81	154.5–155.5	84.47	84.29	5.67	5.46
4-(4-Diethylaminobutylamino)-	10	165	55	73–75[a]	78.46	78.41	8.47	8.37
4-(3-Diethylaminopropylamino)-	8	165	81.5	60.5–62.5[b]	78.13	78.02	8.20	8.19
4-N-Morpholino-	7	130	48	98–100	77.24	77.02	6.10	5.86
4-(3-N-Morpholinopropylamino)-	9	170	31	122–123	74.73	74.53	7.21	7.58
4-N-Piperidino-	10	105	61	85–86	82.40	82.62	6.92	6.66

[a] Crystallized from aqueous alcohol, probably as a hydrate. Drying *in vacuo* resulted in a 6.3% loss in weight. [b] Crystallized from aqueous alcohol, probably as a hydrate. Drying *in vacuo* resulted in a 5.1% loss in weight and the formation of an oil, which was analyzed.

was refluxed for forty-five hours. The insoluble material present at this time was crystallized from alcohol; it was only partially soluble in this solvent. Unchanged chloro compound, 1.25 g., m. p. 88.5–89.5°, was recovered from the alcohol. The insoluble residue, 0.27 g., was 4-hydroxybenzo(h)quinoline; m. p. 238–241°. The aqueous reaction medium, when made basic, yielded no condensation product.

An attempted condensation in alcoholic alkali yielded only 4-ethoxybenzo(h)quinoline.

The chloro compound, 2.13 g., was mixed with 3 ml. of the diamine, and 0.56 g. of potassium hydroxide in 60 ml. of absolute alcohol. The mixture was refluxed for ninety-six hours. By this time, 0.55 g. of potassium chloride had separated. More potassium hydroxide (0.2 g.) and amine (2 ml.) were added and the solution was refluxed for forty-eight hours; 0.1 g. of additional potassium chloride was isolated. The reaction mixture was poured into water, and the solid which separated was crystallized from alcohol, in which it was completely soluble. The 4-ethoxybenzo(h)quinoline crystallized as colorless needles, m. p. 119–120°; yield, 1.2 g., (54%).

Anal. Calcd. for $C_{15}H_{13}ON$: C, 80.69; H, 5.87. Found: C, 80.54; H, 5.93.

1-(4-Diethylamino-1-methylbutylamino)-benzo(f)quinoline.—In a similar manner, 1-chlorobenzo(f)quinoline was condensed with 4-amino-1-diethylaminopentane by heating their mixture at 175–185° for seven hours. The yield of pure base distilling at 187–188.5° (0.14 mm.) was 47.5%.

Anal. Calcd. for $C_{22}H_{29}N_3$: C, 78.76; H, 8.71; N, 12.53. Found: C, 78.42; H, 8.88; N, 12.23.

This product also was converted to a phosphate salt.

The preparation and properties of other 4-aminobenzo(h)quinolines obtained are summarized in the accompanying table.

Summary

4-Chlorobenzo(h)quinoline and 1-chlorobenzo(f)quinoline have been prepared by an extension of the Price-Roberts synthesis of quinolines, employing ethyl ethoxymethylenemalonate. The first compound was also prepared by the ethyl ethoxalylacetate method.

These active chloro compounds have been condensed with several amines to yield nine products of possible pharmaceutical value.

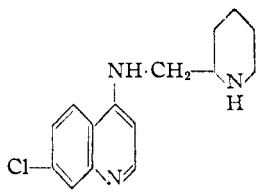
LINCOLN, NEBRASKA RECEIVED APRIL 19, 1946

NOTE

Preparation of 7-Chloro-4-(2-piperidylmethylamino)-quinoline[1]

BY T. R. NORTON, A. A. BENSON, R. A. SEIBERT AND F. W. BERGSTROM

Antimalarials having a 4-amino-7-chloroquinoline nucleus and a basic side chain attached to the 4-amino group have been extensively investigated of late. In this report the preparation of 7-chloro-4-(2-piperidylmethylamino)-quinoline (I) is reported and a description is included of an unsuccessful attempt to obtain 7-chloro-4-[1-methyl-2-(2-piperidyl)-ethylamino]-quinoline through the condensation of 7-chloroquinoline-4-sulfonic acid with 1-(N-acetyl-2-piperidyl)-2-aminopropane.



I

2-Aminomethylpiperidine was prepared in good yield by reduction of 2-cyanopyridine with chromous acetate by the method of Graf[2] followed by catalytic hydrogenation of the pyridine nucleus. The method of Reihlen, *et al.*,[3] for the complete catalytic hydrogenation of 2-cyanopyridine in acetic anhydride gave yields of less than twenty per cent.

The condensation of 2-aminomethylpiperidine with 4,7-dichloroquinoline was carried out by a modification of a procedure reported by Drake *et al.*,[4] to give I in excellent yield. That the condensation took place as indicated and not on

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

(2) Graf, *J. prakt. Chem.*, **140**, 39 (1934); **146**, 88 (1936).

(3) Reihlen, Hessling, Hühn, Weinbrenner, *Ann.*, **493**, 20 (1932).

(4) Drake, *et al.*, THIS JOURNAL, **68**, 1208 (1946).