Some *N*-Substituted 2-Amino- and 2-Methylquinoline-3,4-dicarboximides (1)

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The reaction of sodium 2-amino-3-cyanoquinoline-4-carboxylate and 2-methyl-3-cyanoquinoline-4-carboxylic acid in polyphosphoric acid led to 2-amino- and 2-methylquinoline-3,4-dicarboximide, respectively. Both of these compounds undergo imide *N*-alkylation reactions with methyl iodide and various chloroalkylaminodialkyl amines, while the latter also condenses with 3,4-dichlorobenzaldehyde to form styryl derivatives. Although some of these compounds may be considered structural analogs of the antimalarial 4-quinolinemethanols, none exhibited antimalarial activity.

We have prepared several quinoline-3,4-dicarboximide derivatives, having an amino, methyl or 3′,4′-dichlorostyryl group at the 2-position, for screening in the antimalarial program. The appropriate intermediate 2-substituted-3-cyanoquinoline-4-carboxylic acids were obtained by the condensation of isatin with malononitrile or 3-aminocrotononitrile. Pfitzinger (3) first carried out reactions involving the condensation of isatin with ketones having α-methyl or α-methylene groups to form quinoline-4-carboxylic acids. Walter (4) in 1902 condensed isatin with malononitrile to form 3-(dicyanomethenyl)oxindole, I. Later Zrike and Lindwall (5) repeated Walter's work and converted I to 2-quinolone-3,4-dicarboxylic acid (II) which was decarboxylated to form 2-quinolone-4-carboxylic acid, III (Scheme I). Walther (6) had reported in 1903 that from the condensation of the sodium salt of isatinic acid and 3-aminocrotononitrile he obtained 2-methyl-3-cyanoquinoline-4-carboxylic acid (XV).

After treating isatin with an equivalent amount of sodium hydroxide (forming sodium 2-aminobenzoyl formate), an excess of malononitrile, and evaporating the reaction mixture to dryness on the steam bath, the hydrated sodium salt of 2-amino-3-cyanoquinoline-4-carboxylic acid (V) was obtained in excellent yield. Treatment of V with methyl iodide converted it to its methyl ester VI. Acidification of an aqueous solution of V gave the free acid VII which was hydrolyzed to VIII and subsequently converted to its anhydride IX.

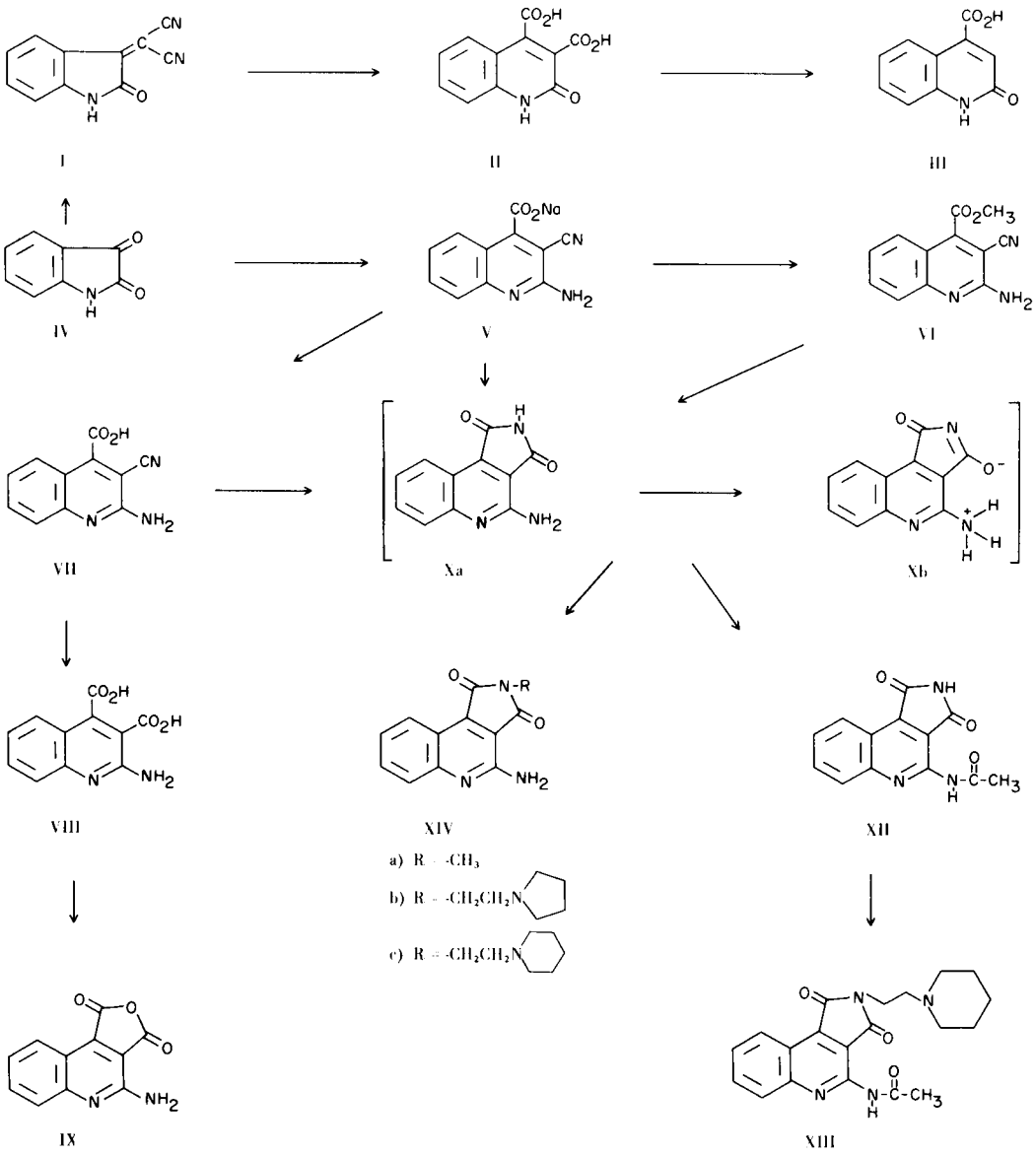
When either V, VI, or VII was heated in polyphosphoric acid, 2-aminoquinoline-3,4-dicarboximide (X) was obtained. It is interesting to note that in the I.R. spectrum of X there is only one carbonyl absorption at 5.74 μ. For imides with a 5-membered cyclic ring, two strong absorptions are expected at about 5.65 and 5.88 μ (7). However, when X was either alkylated or acetylated the resulting product exhibited the normal two carbonyl absorptions in the 5.5 to 6 μ region of the infrared. Possibly the reason for this is that X forms an enolate salt (Xb) between the amino group and the hydroxy protion of the enolized imide. This structure is supported by the fact that both ammonium and C=N absorptions were observed in the infrared. It should also be noted that X sublimes whereas both its alkylated or acetylated derivatives have melting points.

The only report found in the literature for the quinoline-3,4-dicarboximide ring system was for 2-methylquinoline-3,4-dicarboximide (XI) (Scheme 2) an intermediate in the synthesis of 2-methyl-3-aminoquinoline (8). Quinoline-3,4-dicarboximides having a dialkylaminoalkyl side chain attached to the imide nitrogen are structurally related to the active antimalarial 4-quinolylaminoalcohols. We therefore synthesized several examples of this class of compounds, having either amino or methyl groups at position-2 of the quinoline ring.

Syntheses of the 2-aminoquinoline series are outlined in Scheme I. The acetylation of the amino group of X proceeded smoothly in acetic acid-acetic anhydride to give XII, which was converted to XIII by treating it in dimethylformamide with sodium methoxide followed by *N*-(2-chloroethyl)piperidine hydrochloride. When a mixture of X and potassium carbonate in dimethylformamide was treated with methyl iodide the resulting *N*-methylimide, XIVa, was formed. However under these same conditions, dialkylaminoalkyl chloride hydrochlorides did not react. These reactions were accomplished from the reaction of X and sodium methoxide in dimethylformamide followed by the appropriate dialkylaminoalkyl chloride hydrochloride to produce XIVb and XIVc.

To synthesize a few 2-methylquinoline-3,4-dicarboximides the starting material, 2-methyl-3-cyanoquinoline-4-carboxylic acid (XV), prepared after the manner of

SCHEME I



Walther (6) was converted to its imide XI (Scheme II). After the reaction was completed the polyphosphoric acid solution was poured over ice. However, unlike X, XI did not precipitate from the aqueous acid solution, indicating that it is a stronger base than X. This may be interpreted as further evidence for structure Xb since a positively charged ammonium ion at position 2 would decrease the basicity of the quinoline nucleus. Also unlike X, both carbonyl absorptions, characteristic of a 5-membered cyclic imide, were observed in the infrared. *N*-Alkylation of XI was carried out in dimethylformamide using either potassium carbonate or sodium methoxide as the base and the appropriate dialkylaminoalkyl chloride of the hydrochloride to produce XVIa, XVIb, and XVIc.

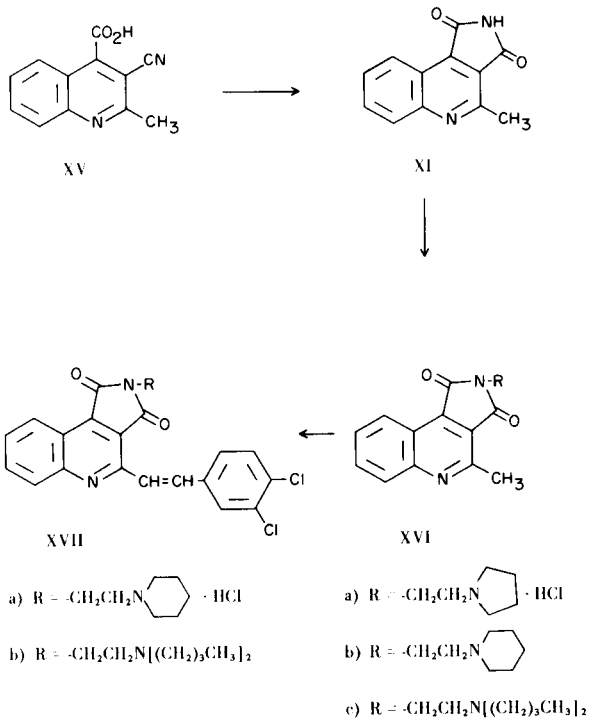
Although derivatives of 4-aminoquinaldine have no antimalarial activity, the styryl derivatives formed from this compound have activity against certain types of malaria (9). With this in mind the styryl derivatives of XVIb and XVIc were formed by condensation with 3,4-dichlorobenzaldehyde, forming XVIIa and XVIIb.

Pharmacology.

Most of the above described compounds were screened for potential antimalarial activity by the Walter Reed Army Institute of Research, using the procedure described by Osdene, Russell, and Rane (10). We are indebted to

Drs. Steck, Sweeney, and Jacobus, of the W.R.A.I.R., for the results of these tests. None of the compounds submitted (X, XI, XIVc, XVIb, c, and XVIIa, b) were considered active at the 640 mg./kg. dose level.

SCHEME II



EXPERIMENTAL

All melting points reported were obtained from a Mel-Temp capillary melting point apparatus and are corrected. The microanalyses were performed by either the Midwest Microlab, Inc., Indianapolis, Indiana or the Huffman Laboratories, Inc., Wheatridge, Colorado. I.R. spectra were recorded with a Perkin-Elmer Model 137 or 137A Infracord. The U.V. spectra were recorded using a Bausch and Lomb Model 505 spectrophotometer. All I.R. and U.V. spectra are in agreement with the assigned structures.

Sodium 2-Amino-3-cyanoquinoline-4-carboxylate (V).

Isatin (5.15 g., 0.035 mole) was treated with sodium hydroxide (1.4 g., 0.035 mole) dissolved in 85 ml. of water and the resulting solution was heated on the steam bath for ½ hour, removed, and malononitrile (1.0 g., 0.015 mole) was added. After stirring for 1 hour at room conditions, malononitrile (1.0 g., 0.015 mole) was again added and the solution was heated on the steam bath for 1 hour. After cooling, more malononitrile (0.5 g., 0.007 mole) was added and the solution was allowed to stir at ambient temperature overnight. After evaporation of the solution to dryness on the steam bath, the black residue was triturated under acetone and filtered, yielding a green-brown powder. The filtrate was evaporated to dryness and again triturated under acetone. The yield of yellow salt, recrystallized from water was 7.8 g. (94%), m.p. >340° dec.; I.R. λ max (potassium bromide), 2.85 and 2.95 (NH_2), 4.5 (CN), and 6.15 μ (CO_2^-).

Anal. Calcd. for $C_{11}H_6N_3O_2Na \cdot \frac{1}{2}H_2O$: C, 54.12; H, 2.47; N, 17.21. Found: C, 54.59; H, 2.53; N, 17.05.

Methyl 2-Amino-3-cyanoquinoline-4-carboxylate (VI) Picrate.

A suspension of V (6.7 g., 0.028 mole) in 50 ml. of DMF was added dropwise to a stirred solution of methyl iodide (4.05 g., 0.028 mole) in 10 ml. of DMF. The resulting solution was stirred at room temperature for 1 hour and a like amount of methyl iodide was added. The solution was heated on the steam bath for 2 hours, cooled, and poured over 100 g. of ice. The yield of the brown precipitate was 3.1 g. (47.3%). Recrystallization from ethanol yielded fine orange crystals, m.p. 197-198.5° dec.; I.R. λ max (potassium bromide) 2.88 and 2.96 (NH_2), 4.5 (CN), and 5.77 μ (CO of an ester). U.V. λ max (ethanol), 222 (ε = 43,400), 252 mμ (ε = 34,400).

Since several recrystallizations failed to give a product with satisfactory analyses, for the analytical sample a picrate was formed and when recrystallized from ethanol yielded brilliant yellow crystals, m.p. 233-235° dec. The analytical sample was sublimed at 150-160° at 0.5 torr.

Anal. Calcd. for $C_{18}H_{12}N_6O_9$: C, 47.37; H, 2.65; N, 18.41. Found: C, 47.74; H, 3.14; N, 18.36.

2-Amino-3-cyanoquinoline-4-carboxylic Acid (VII).

The synthesis of VII was accomplished by the acidification of an aqueous solution of its sodium salt, V. It was quite water soluble and difficult to crystallize, melting with decomposition at 255-260°, but could be used for further work in the crude state; I.R. λ max (potassium bromide), 4.48 (CN) and 5.95 μ (CO acid).

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.91; H, 3.30; N, 19.70. Found: C, 61.76; H, 3.36; N, 19.24.

2-Aminoquinoline-3,4-dicarboxylic Acid (VIII).

Crude VII (1.0 g., 0.004 mole) and 24 ml. of 10% hydrochloric acid were heated at reflux for 2 hours. The mixture was cooled and filtered yielding 1.0 g. of product. Recrystallization (charcoal) from a large quantity of hot water afforded fine pale green needles which sublimed above 220°; I.R. λ max (potassium bromide), 4.0 and 5.1 (NH_3^+), 5.96 (CO acid), and 6.18 μ (CO_2^-).

Anal. Calcd. for $C_{11}H_8N_2O_4$: C, 56.89; H, 3.47; N, 12.06. Found: C, 56.58; H, 3.98; N, 11.84.

2-Aminoquinoline-3,4-dicarboxylic Anhydride (IX).

A few milligrams of VIII were sublimed at 220° and 0.1 torr. yielding an orange sublimate. Recrystallization from a large volume of ethyl acetate afforded an orange crystalline powder, m.p. 290.5-292° with sublimation; I.R. λ max (potassium bromide), 2.91 (NH_2), 5.44 and 5.66 μ (5-membered anhydride).

Anal. Calcd. for $C_{11}H_6N_2O_3$: C, 61.68; H, 2.82; N, 13.08. Found: C, 61.33; H, 2.81; N, 13.02.

2-Aminoquinoline-3,4-dicarboximide (X).

A mixture of V (7.36 g., 0.031 mole) and 80 g. of polyphosphoric acid was heated with stirring on the steam bath for 45 minutes. The dark solution was poured over ice and the solid material was collected and dried yielding 6.4 g. (97%) of the crude dark green product. A yellow-green powder which sublimed above 260° was obtained when recrystallized from DMF; U.V. λ max (ethanol), 222 (ε = 24,500) and 256 mμ (ε = 14,200); I.R. λ max (potassium bromide), 2.88 and 3.02 (NH_2), 3.4 (CH), 3.66 (NH_3^+), 5.74 (CO), and 6.08 μ (C=N).

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71.

Found: C, 62.05; H, 3.46; N, 19.47.

2-Acetamidoquinoline-3,4-dicarboximide (XII).

A solution of X (0.25 g., 0.0011 mole), 3 ml. of acetic anhydride, and 5.55 ml. of glacial acetic acid was heated at reflux for 10 minutes. The product precipitated on cooling and was collected and dried, yielding 0.2 g. (66%). Recrystallization from acetic acid afforded yellow platelets, m.p. 296-298° dec.; I.R. λ max (potassium bromide), 2.86 (NH), 5.63 and 5.77 (5-membered cyclic imide), and 5.96 μ (CONH); U.V. λ max (ethanol), 225 (ε = 21,800) and 260 mμ (ε = 23,000).

Anal. Calcd. for $C_{13}H_9N_3O_3$: C, 61.17; H, 3.55; N, 16.46. Found: C, 60.88; H, 3.54; N, 16.04.

N'-(β-*N'''*-Piperidylethyl)-2-acetamidoquinoline-3,4-dicarboximide (XIII).

A mixture of XII (0.64 g., 0.0025 mole) in 7 ml. of DMF was treated with sodium methoxide (0.27 g., 0.005 mole) and to the resulting solution was added *N*-(2-chloroethyl)piperidine hydrochloride (0.46 g., 0.0025 mole). After stirring at room temperature for 3 hours a heavy precipitate had formed; the stirring was continued for an additional 17 hours. The product, 0.33 g. (36%), was collected, dried and recrystallized from ethyl acetate to yield fine yellow needles, m.p. 159-160°; I.R. λ max (potassium bromide), 288 (NH), 5.62 and 5.88 μ (5-membered cyclic imide); U.V. λ max (ethanol), 225 (ε = 28,600), 253 (ε = 38,500), and 330 mμ (ε = 3,140).

Anal. Calcd. for $C_{20}H_{22}N_4O_3$: C, 65.55; H, 6.04; N, 15.29. Found: C, 65.40; H, 6.37; N, 15.11.

N'-Methyl-2-aminoquinoline-3,4-dicarboximide (XIVa).

A mixture of X (0.53 g., 0.0025 mole) and potassium carbonate (0.345 g., 0.0025 mole) in 5 ml. of DMF was stirred with methyl iodide (0.35 g., 0.0025 mole) at room temperature for 24 hours. The product was collected and dried, yielding 0.58 g. (99%) of an orange powder, m.p. 240-245°. Recrystallization from methanol afforded fine yellow needles, m.p. 252-253°; I.R. λ max (potassium bromide), 2.75 (NH_2), and 5.65 and 5.85 μ (5-membered cyclic imide); U.V. λ max (ethanol), 224 (ε = 56,000), 257 (ε = 30,800), and 300 mμ (sh) (ε = 2,500).

Anal. Calcd. for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.26; H, 4.23; N, 18.45.

N'-(β-*N'''*-Pyrrolidinylethyl)-2-aminoquinoline-3,4-dicarboximide (XIVb).

A solution of X (0.53 g., 0.0025 mole) in 7 ml. of DMF and sodium methoxide (0.27 g., 0.005 mole) was stirred with *N*-(2-chloroethyl)pyrrolidine hydrochloride (0.43 g., 0.0025 mole) at room temperature for 20 hours. The yellow product when collected, washed with water and dried, weighed 0.42 g. (54%). Recrystallization from ethyl acetate afforded bright yellow needles which, on melting, became orange at 167-175° and then melted at 199-200°; I.R. λ max (potassium bromide), 2.86 (NH_2), 5.64 and 5.83 μ (5-membered cyclic imide); U.V. λ max (ethanol), 223 (ε = 37,400), 251 (ε = 23,000), and 299 mμ (sh) (ε = 2,500).

Anal. Calcd. for $C_{17}H_{18}N_4O_2$: C, 65.78; H, 5.84; N, 18.02. Found: C, 65.65; H, 6.09; N, 18.00.

N'-(β-*N'''*-Piperidylethyl)-2-aminoquinoline-3,4-dicarboximide (XIVc).

A solution of X (10.6 g., 0.05 mole) in 140 ml. of DMF containing sodium methoxide (5.4 g., 0.1 mole) was stirred with *N*-(2-chloroethyl)piperidine hydrochloride (9.29 g., 0.05 mole) at room temperature for 21 hours. The mixture was poured into 300 ml. of ice and water, the precipitate filtered, dried and recrystallized from ethyl acetate, yielding 12.5 g. (77.3%) of fine yellow-orange needles, m.p. 208.5-210°; I.R. λ max (potassium bromide) 2.85 and 2.98 (NH_2), 5.65 and 5.86 μ (5-membered cyclic imide); U.V. λ max (ethanol), 224 (ε = 48,200), 252 (ε = 34,200), and 300 (sh) mμ (ε = 2,900).

Anal. Calcd. for $C_{18}H_{29}N_4O_2$: C, 66.64; H, 6.21; N, 17.27. Found: C, 66.41; H, 6.20; N, 16.98.

2-Methylquinoline-3,4-dicarboximide (XI).

To a solution of isatin (9.0 g., 0.061 mole) and sodium hydroxide (2.5 g., 0.062 mole) dissolved in 150 ml. of water was added 3-aminocrotononitrile (5.0 g., 0.061 mole). The resulting solution was heated on the steam bath for 5 hours, cooled, and acidified with hydrochloric acid. The resulting precipitate was collected and dried yielding 6.85 g. (66.5% based on consumed isatin) of 2-methyl-3-cyanoquinoline-4-carboxylic acid (XV), m.p. 234-236° dec. (Lit. (6) 238° dec.)

A mixture of XV (3.8 g., 0.018 mole) and 40 g. of polyphosphoric acid was heated with stirring on the steam bath for 30 minutes, poured over 350 g. of ice and left to stand overnight. The solution was filtered and the *p*H of the filtrate was adjusted to 3 with sodium hydroxide, causing the product to precipitate. The product was collected, dried and recrystallized from ethyl acetate yielding 2.42 g. (63.3%) of yellow needles, m.p. 255-256° (Lit. (8) 257°); I.R. λ max (potassium bromide), 2.88 (NH) and 5.62 and 5.75 μ (5-membered cyclic imide); U.V. λ max (ethanol), 212 (ε = 36,000) and 254 mμ (ε = 30,200).

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.91; H, 3.79; N, 13.20. Found: C, 67.71; H, 3.66; N, 13.05.

N'-(β-*N'''*-Pyrrolidinylethyl)-2-methylquinoline-3,4-dicarboximide Hydrochloride (XVIa).

A mixture of XI (0.53 g., 0.0025 mole), potassium carbonate (0.51 g., 0.0037 mole), 7 ml. DMF, and *N*-(2-chloroethyl)pyrrolidine hydrochloride (0.43 g., 0.0025 mole) was stirred at room temperature for 20 hours. The solid was filtered, washed well with water, dried and recrystallized from isopropyl alcohol containing a few drops of hydrochloric acid. The resulting precipitate was collected as an off-white crystalline powder (0.40 g., 46%), m.p. 275-277° dec.; I.R. λ max (potassium bromide), 5.61 and 5.81 μ (5-membered cyclic imide).

Anal. Calcd. for $C_{18}H_{20}ClN_3O_2$: C, 62.51; H, 5.83; N, 12.15; Cl, 10.25. Found: C, 62.29; H, 5.92; N, 12.16; Cl, 10.33.

N'-(β-*N'''*-Piperidylethyl)-2-methylquinoline-3,4-dicarboximide (XVIb).

A solution of XI (10.6 g., 0.05 mole) and sodium methoxide (5.4 g., 0.10 mole) in 140 ml. of DMF was treated with *N*-(2-chloroethyl)piperidine hydrochloride (9.29 g., 0.05 mole), and stirred at room temperature for 24 hours. The mixture was poured into 350 ml. of ice and water, and the product was collected, dried and recrystallized from ethyl acetate yielding 12.8 g. (79.2%) of a white powder, m.p. 134.5-136°; I.R. λ max (potassium bromide) 5.63 and 5.83 μ (5-membered cyclic imide); U.V. λ max (ethanol) 214 (ε = 37,200), 234 (sh) (ε = 28,000), 257 (ε = 17,700), 312 (ε = 3,200), and 325 mμ (ε = 3,400).

Anal. Calcd. for $C_{19}H_{21}N_3O_2$: C, 70.56; H, 6.55; N, 12.99; Found: C, 70.56; H, 6.74; N, 12.79.

N'-(β-Dibutylaminoethyl)-2-methylquinoline-3,4-dicarboximide (XVIc).

A solution of XI (5.3 g., 0.025 mole) and sodium methoxide (2.7 g., 0.05 mole) in 60 ml. DMF was treated with 2-dibutyl-

aminoethyl chloride hydrochloride (5.7 g., 0.025 mole), and the mixture was allowed to stir at room temperature for 22 hours before pouring over 600 g. of ice. The yellow solid was collected and recrystallized from ethanol, yielding 8.0 g. (88%) of fine yellow crystals, m.p. 78-79°; I.R. λ max (potassium bromide) 5.63 and 5.81 μ (5-membered cyclic imide); U.V. λ max (ethanol), 214 (ϵ = 51,000) and 257 mμ (ϵ = 40,000).

Anal. Calcd. for $C_{22}H_{29}N_3O_2$: C, 71.90; H, 7.95; N, 11.43. Found: C, 71.83; H, 7.83; N, 11.49.

N'(β-*N'''*-Piperidylethyl)-2-(3',4'-dichlorostyryl)quinoline-3,4-dicarboximide Hydrochloride (XVIIa).

A mixture of XVIb (7.56 g., 0.023 mole), 3,4-dichlorobenzaldehyde (7.62 g., 0.043 mole), 0.3 ml. of piperidine, and 1 ml. of xylene was heated at 170-175° for 5 hours. At the end of the reaction period the solid mass was cooled, triturated under ether, filtered, and recrystallized from chloroform-ethanol mixture giving 8.05 g. of fine yellow needles (72%), m.p. 173.5-175°; I.R. λ max (potassium bromide), 5.61 and 5.85 μ (5-membered cyclic imide); U.V. λ max (ethanol), 212 (ϵ = 40,800), 234 (sh), 249 (sh), 294 (ϵ = 34,000), and 338 mμ (ϵ = 24,800).

Anal. Calcd. for $C_{26}H_{23}Cl_2N_3O_2$: C, 65.04; H, 4.82; N, 8.74; Cl, 14.76. Found: C, 64.67; H, 4.83; N, 8.68; Cl, 15.13.

The hydrochloride was formed by dissolving the yellow needles in hot isopropyl alcohol and adding a few drops of concentrated hydrochloric acid. On cooling the precipitate was collected, dried, and recrystallized (charcoal) from isopropyl alcohol, yielding a bright yellow powder, m.p. 253-256° dec.

Anal. Calcd. for $C_{26}H_{24}Cl_3N_3O_2$: C, 60.41; H, 4.67; N, 8.13; Cl, 20.57. Found: C, 60.45; H, 4.88; N, 8.12; Cl, 20.48.

N'-(β-Dibutylaminoethyl)-2-(3',4'-dichlorostyryl)quinoline-3,4-dicarboximide Hydrochloride (XVIIb).

A mixture of XVIc (6.0 g., 0.0163 mole), 3,4-dichlorobenzaldehyde (5.25 g., 0.03 mole), 0.2 ml. of piperidine, and 0.8 ml. of xylene were heated at 170-175° for 5 hours, while water was azeotroped with the xylene. The product was cooled, dissolved in 600 ml. of ether, and precipitated as the hydrochloride by passing dry hydrogen chloride gas into the solution. When recrystallized from methanol, 5.3 g. (58%) of a yellow-green powder, m.p. 240-241° dec., was obtained; I.R. λ max (potassium bromide), 4.1 (NH^+), 5.63 and 5.81 μ (5-membered cyclic imide); U.V. λ max (ethanol), 213 (ϵ = 46,500), 238 (sh) (ϵ = 32,700), 270 (ϵ = 29,500), and 334 mμ (ϵ = 47,500).

Anal. Calcd. for $C_{29}H_{32}Cl_3N_3O_2$: C, 62.09; H, 5.75; N, 7.49; Cl, 18.96. Found: C, 62.25; H, 5.80; N, 7.26; Cl, 19.01.

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