An Unusual Arylation of 4-Oxo-3,4-dihydropyrimido[4,5-*b*]quinoline (1)

E. Campaigne and G. Randau

The Chemistry Laboratories of Indiana University, Bloomington, Indiana 47401

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Treatment of 4-oxo-3,4-dihydropyrimido[4,5-*b*]quinoline (II) with phosphorus oxychloride and a dialkylaniline resulted in the introduction of a *p*-dialkylaminophenyl group at position-5, and reduction of the central (pyridine) ring, as well as substitution of oxygen by chlorine at position-4, forming compounds considered to be 4-chloro-5-(*p*-dialkylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinolines (XV). Several 4-oxo-3,4-dihydropyrimido[4,5-*b*]quinolines having phenyl substituents at position-5 were synthesized unequivocally, and could be readily reduced to the corresponding 4-oxo-5-phenyl-3,4,5,10-tetrahydropyrimido[4,5-*b*]quinolines, and the 4-oxo group replaced by chlorine, in the usual manner, leading to compounds related structurally to XV. Comparison of the chemical and physical properties of these compounds established the structure of XV, and a mechanism which rationalizes the formation of XV from II is presented.

In connection with studies on antimalarial agents we were interested in preparing substituted pyrimido[4,5-*b*]-quinolines of type I (Chart I). As a route to these compounds we proposed the conversion of 4-oxo-3,4-dihydropyrimido[4,5-*b*]quinoline (IIa) to the chloro derivative III and subsequent reaction with the appropriate amines. Taylor and Kalenda (2) have developed a convenient method for the synthesis of IIa by reaction of 2-aminoquinoline-3-carboxamide (VIIa) with formamide. Chart I outlines the syntheses of VIIa and derivatives of this compound. Condensation of malononitrile with *o*-aminobenzaldehyde (IVa) gives 2-amino-3-cyanoquinoline (Va) (3) whereas 2-aminobenzophenone (IVb) and 2-amino-5-chlorobenzophenone (IVc) give 2-amino-3-cyano-4-phenylquinoline (Vb) and 2-amino-6-chloro-3-cyano-4-phenylquinoline (Vc) respectively. An alternate route to Va was found in the condensation of malononitrile with *o*-nitrobenzaldehyde and reductive cyclization of the intermediate α-cyano-β-(2-nitrophenyl) acrylonitrile (VI) with iron powder in acetic acid.

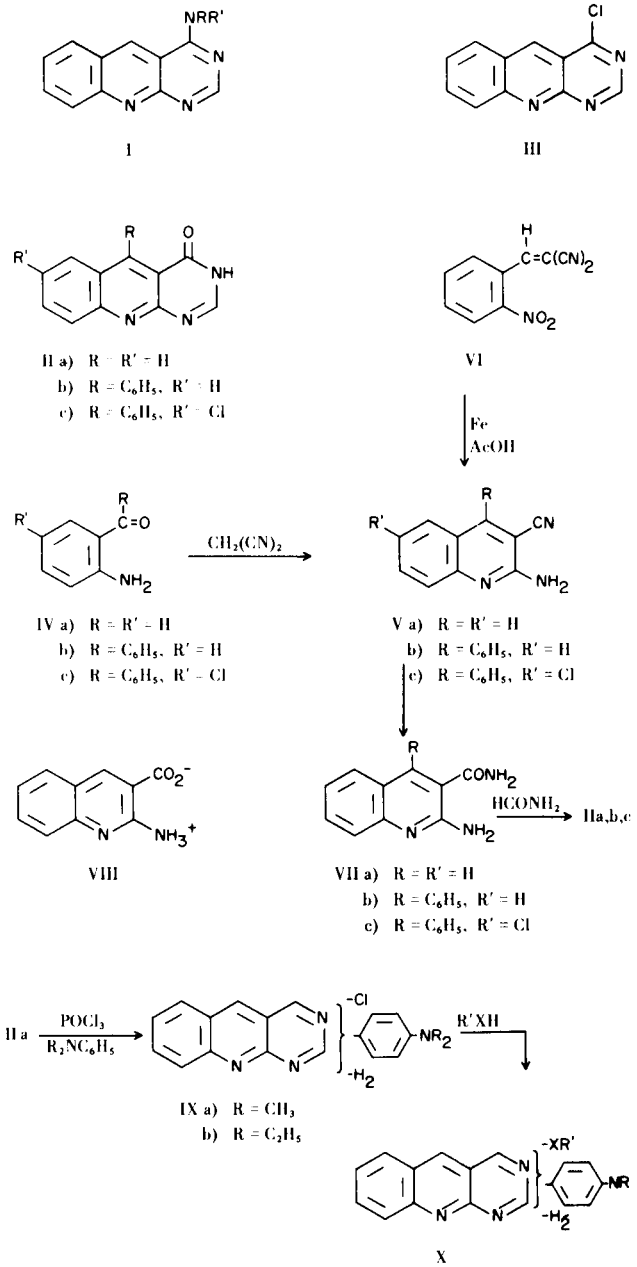
The hydrolysis of Va to VIIa can be achieved with potassium hydroxide-hydrogen peroxide in ethanol (3) but we found it advantageous to hydrolyze Va with 96% sulfuric acid, which gives predominantly VIIa and a small amount of 2-aminoquinoline-3-carboxylic acid (VIII). The acid hydrolysis is the method of choice for the preparation of the substituted quinoline-3-carboxamides VIIb and VIIc whereas the potassium hydroxide-hydrogen peroxide reaction gave only poor yields of these compounds.

Like VIIa, the substituted carboxamides VIIb and VIIc on reaction with formamide gave the substituted 4-oxo-3,4-dihydropyrimido[4,5-*b*]quinolines IIb and IIc in good yield.

Attempts to prepare III from IIa by conventional methods met with failure. Reaction of IIa with phosphorus oxychloride resulted in the formation of a brown amorphous solid from which no pure compound could be isolated. The reaction of IIa with phosphorus oxychloride in the presence of pyridine, triethylamine, or acetic acid (4) gave black tars from which only starting material IIa could be recovered. Phenylphosphoric dichloride and IIa gave a black, high melting solid which could not be purified (5).

There are several accounts in the literature reporting the catalytic effect of *N,N*-dimethylaniline on the chlorination reaction of oxopyrimidines with phosphorus oxychloride. For example, 2,4-dioxo-5-nitro-1,2,3,4-tetrahydropyrimidine was chlorinated with a mixture of *N,N*-dimethylaniline and phosphorus oxychloride (6) and the same reagent mixture was used for the preparation of 4-chloro-2-methylquinazoline (7) and 2,4-dichloroquinazolines (8). Consequently we attempted to chlorinate IIa with phosphorus oxychloride in the presence of two equivalents of *N,N*-dimethylaniline. The behavior of this mixture turned out to differ significantly from the above-mentioned reaction, as in a short time a reaction took place and a pure, easily characterized product was obtained. The resulting product, however, was not the expected III but elemental analysis showed it to be IXa, *i.e.* it contained chlorine and the dimethylaniline moiety. The NMR spectrum showed a singlet for the dimethylamino group (δ 2.83) and the upfield part of an A_2B_2 system at δ 6.63 was separated from the multiplet for the remaining aromatic protons, thus indi-

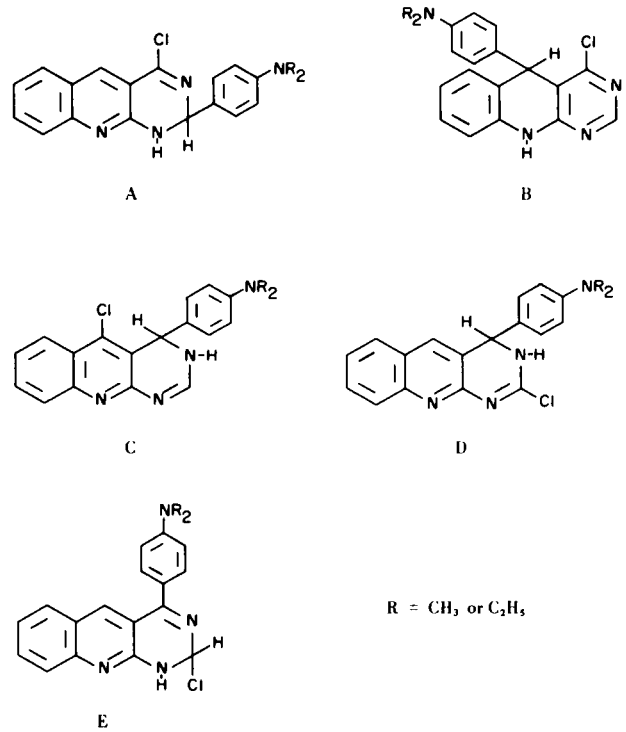
CHART I



cating the presence of a *p*-substituted dimethylaminophenyl group. Furthermore, the observation of singlets at δ 5.27 and 8.24, integrating for one proton each, indicated the presence of one hydrogen atom bonded to a saturated tertiary carbon atom and another on an aromatic pyrimidine or pyridine ring. Since the spectrum of IXa was measured in deuteriochloroform containing acetic acid, no NH signal was observed.

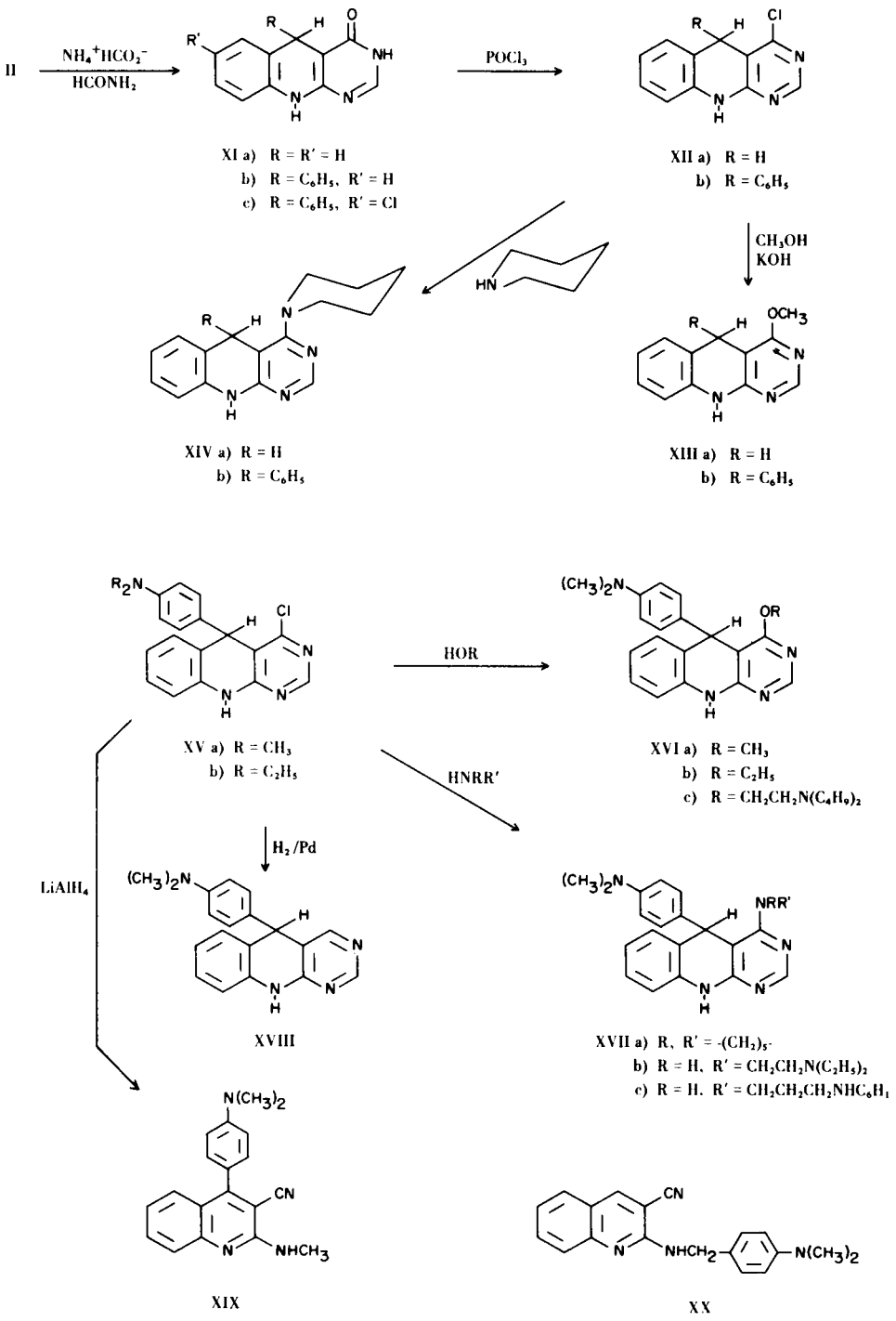
It is known that 9-oxo-9,10-dihydroacridine is converted to 9-(*p*-dimethylaminophenyl)acridine by reaction with phosphorus oxychloride and *N,N*-dimethylaniline (9) and that this reaction proceeds *via* 9-chloroacridine (10). The presence of chlorine in IXa, however, indicates that this type of reaction did not occur in the reaction of IIa with these reagents.

The compound IXb, obtained by reaction of IIa with phosphorus oxychloride and *N,N*-diethylaniline, gave an NMR spectrum similar to that of IXa, differing only in the presence of signals for the diethylamino group instead of the dimethylamino group. IXb was soluble in chloroform and in the NMR spectrum showed the presence of an NH group which was also found in derivatives of IXa described below. The analytical and spectroscopic evidence therefore suggested structures such as A - E for IXa and IXb.



The fact that IXa and IXb did not react with boiling aqueous sodium hydroxide and not even with sodium methoxide in boiling methanol ruled out structures like D and E, in which the chlorine atom is expected to be quite reactive (11). Under more vigorous conditions, however, the chlorine atom in IXa could be replaced by nucleophilic reagents giving compounds of type X as described below. Compounds of structures such as A, D, and E would probably be hydrolyzed by acids, but IXa was not affected by prolonged heating in concentrated hydrochloric acid. Considering possible pathways for the formation of IXa and IXb from IIa we therefore concluded structures of type B to be the most likely.

CHART II



We found that we were able to synthesize compounds of structure B unequivocally, utilizing the following observation. In order to obtain higher yields of IIa from VIIa with formamide we increased the reaction time. Instead of achieving this goal, however, we isolated an additional compound XIa (Chart II) which was shown by elemental analysis and NMR spectrum to be the dihydro derivative of IIa. Compound XIa could be obtained in almost quantitative yield by reaction of IIa with ammonium formate in formamide. The same reaction occurred with IIb and

IIc giving XIb and XIc respectively. The NMR spectra of these latter two compounds both showing a singlet at δ 5.25 integrating for one proton, established the structure of 4-oxo-5-phenyl-3,4,5,10-tetrahydropyrimido[4,5-*b*]-quinoline (XIb) and the corresponding 7-chloro derivative (XIc) (Chart II), and, by comparison of the very similar U.V. spectra, the structure of 4-oxo-3,4,5,10-tetrahydropyrimido[4,5-*b*]quinoline (XIa) as well.

Compounds XIa and XIb were chlorinated with phosphorus oxychloride to form 4-chloro-5,10-dihydropyrimido[4,5-*b*]quinoline (XIIa) and 4-chloro-5-phenyl-5,10-dihydropyrimido[4,5-*b*]quinoline (XIIb) respectively. In this case, the presence of *N*,*N*-dimethylaniline did not alter the course of the chlorination reaction. Compound XIIb showed striking similarity to IXa and b both spectroscopically and chemically. The NMR spectrum of XIIb shows singlets for H-5 at δ 5.46 and for H-2 at 8.36, compared with 5.27 and 8.24 for IXa and 5.32 and 8.42 for IXb. The U.V. and I.R. spectra of XIIb are very similar to those of IXa and b (see experimental part).

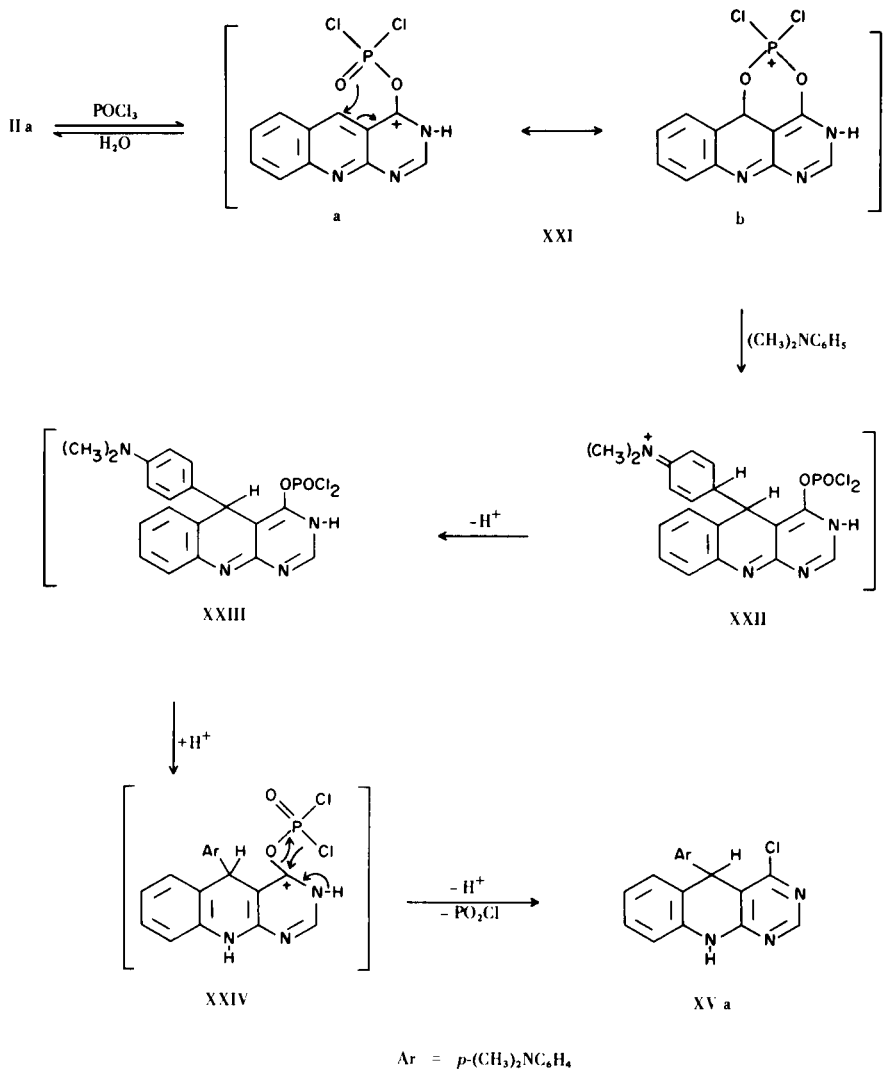
On prolonged heating with potassium hydroxide in methanol XIIb formed 4-methoxy-5-phenyl-5,10-dihydropyrimido[4,5-*b*]quinoline (XIIIb). 4-Methoxy-5,10-dihydropyrimido[4,5-*b*]quinoline (XIIIa) was obtained in the same manner from XIIa. Reaction with piperidine occurred more easily; XIIa and XIIb gave 4-piperidino-5,10-dihydropyrimido[4,5-*b*]quinoline (XIVa) and 4-piperidino-5-phenyl-5,10-dihydropyrimido[4,5-*b*]quinoline (XIVb) respectively after short heating with piperidine. Essentially under the same conditions the corresponding derivatives of IXa were formed. Taking these findings into account we concluded the structure of IXa to be 4-chloro-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinoline (XVa) and that of IXb to be the *p*-diethylamino derivative (XVb). The nucleophilic substitutions of XVa which we achieved are outlined in Chart II. Reaction with potassium hydroxide in methanol gave 4-methoxy-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinoline (XVIa), with potassium hydroxide in ethanol we obtained 4-ethoxy-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]-quinoline (XVIb), and with sodium β-dibutylaminoethoxide 4-(β-dibutylaminoethoxy)-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinoline (XVIc) was formed. The formation of the alkoxide derivatives XVIa and XVIb rather than of the oxo derivative under the described conditions may be explained by the deactivating effect of the NH and dimethylaminobenzyl groups on the chlorine atom in XVa and finds its parallel in the reaction of 2-amino-4-chloro-6-methylpyrimidine with potassium hydroxide in aqueous methanol to form 2-amino-4-methoxy-6-methylpyrimidine (12). Reaction of XVa with the appropriate primary and secondary amines gave rise to the formation of 4-piperidino-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinoline (XVIIa), 4-(β-diethylaminoethylamino)-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinoline (XVIIb), and 4-(3-cyclohexylaminopropylamino)-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinoline (XVIIc). The I.R. spectrum of XVIIc showed only one band in the region 2.8-3.2 μ and two bands at 6.60 and 7.72 (characteristic for aryl substituted secondary amines) besides one band at 7.42 μ (assigned to the C-N vibration of the dimethylaminophenyl group), thus indicating that XVIIc does not contain a primary amine, and was formed by reaction of XVa with the primary rather than the secondary amino group of *N*-(3-aminopropyl)cyclohexylamine.

The reductive removal of the chlorine atom in XVa was achieved by hydrogenation under low pressure in the presence of palladium on charcoal (13) giving 5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinoline (XVIII). The NMR spectrum of XVIII shows singlets for H-2 at δ 8.24, for H-4 at 8.70 and for H-5 at 5.72. This is in good agreement with the observation by Katritzky *et al.* (14) that H-4 in quinazoline is less shielded and its signal occurs further downfield than that of H-2. Furthermore, the formation of XVIII rules out structures such as E for IX. Compound XVIII was also obtained by reaction of XVa with lithium aluminum hydride. This reaction also gave an isomer of XVIII, although in very low yield, which by means of elemental analysis, I.R. and NMR spectra was shown to be 2-methylamino-3-cyano-4-(*p*-dimethylaminophenyl)quinoline (XIX). The formation of XIX from XVa may be envisioned in consequence of the fact that fused pyrimidin-4(3*H*)ones undergo reductive ring cleavage with lithium aluminum hydride at the 2-3 position (15) and the facile elimination of chloride anions from 4-chloropyrimidines with strong nucleophiles (16). The isolation of XIX is further proof for the structure XV, as formation of a nitrile is only conceivable from structures A or B. A compound of structure A, however, in a similar reaction would give 2-(*p*-dimethylaminobenzylamino)-3-cyanoquinoline (XX), which, when prepared unequivocally by condensation of Va with *p*-dimethylaminobenzaldehyde and reduction of the resulting Schiff-base, was found to be completely different from XIX.

As an explanation for the unusual reaction of IIa with phosphorus oxychloride and *N*,*N*-dialkylaniline we propose the following reaction mechanism (Chart III).

Very probably IIa reacts first with phosphorus oxychloride to form the dichlorophosphoric ester intermediate XXI. The assumption that the cation XXIa is not susceptible to the usual internal displacement reaction to form III seems reasonable in view of the fact that in XXI the actual positive charge on C-4 may be decreased due to resonance delocalization, especially participation of benzyl carbonium ion type formulas carrying the positive charge

CHART III



on C-5 (XXIb). The partial localization of the positive charge on C-5 may also be favored by some interaction with the oxygen of the dichlorophosphoryl group which may be geometrically close to this position permitting partial positive charge on phosphorus. Hydrolysis of XXIb leads to a 5-hydroxy dihydro derivative, which eliminates water to regenerate IIa, but attack by *N*,*N*-dimethylaniline on C-5, forms the intermediate of an electrophilic aromatic substitution, XXII, which after loss of a proton forms the partly saturated intermediate XXIII. This finally, probably after protonation of N-10 forming XXIV, should be capable of the internal displacement reaction that leads to the formation of XVa. It should be mentioned that chlorination of 2-methyl-4-oxo-3,4-dihydroquinazoline (7) and of 4-oxo-3,4-dihydropyrido[2,3-*d*]pyrimidine (17) occurs in the usual manner. In these cases the participation of benzyl type carbonium ions in the resonance of the initial intermediate of the chlorination reaction (such as XXI) is less favored than in case of IIa.

Compounds XVa, XVIb, XVIc, and XVIIb were screened for potential antimalarial activity by the Walter Reed Army Institute of Research, using the procedure described by Osdene, Russell, and Rane (18). 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 were considered active at the 640 mg./kg. dose level.

EXPERIMENTAL

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

Lomb Model 505 spectrophotometer. The NMR spectra were obtained on a Varian HA-100 instrument using tetramethylsilane as internal standard, by Dr. A. Dinner in our laboratory. The following abbreviations are used in reporting the NMR data: s = singlet, d = doublet, t = triplet, q = quartet.

2-Amino-3-cyanoquinoline (Va).

α-Cyano-β-(*o*-nitrophenyl)acrylonitrile (3b) (10.0 g., 0.05 mole) was placed in 225 ml. of acetic acid and heated on a steam-bath. Iron powder (12 g., 0.225 mole) was added in small portions during 30 minutes and the mixture was heated and occasionally shaken for another 1.5 hours. After filtering hot, the residue was washed with 25 ml. of hot acetic acid. Water (200 ml.) was added to the warm filtrate, which caused the precipitation of a yellow solid. After cooling, the precipitate was collected, thoroughly washed with water, and dried. The filtrate was extracted 3 times with ether (200 ml. and 2 x 100 ml.), the ether layers were combined and evaporated to dryness on a steam-bath. The residues were combined and recrystallized from ethanol, yielding yellow needles of Va (6.13 g., 73%), m.p. 229-231° (lit. (3a): 228.5-230°); NMR (DMSO-d_6) δ 6.95 (broad s, 2H, NH_2), 7.2-7.8 (m, 4H, H-5 - H-8), and 8.67 (s, 1H, H-4).

2-Amino-3-cyano-4-phenylquinoline (Vb).

2-Aminobenzophenone (19) (9.85 g., 0.05 mole) and malononitrile (6.60 g., 0.10 mole) were mixed in 60 ml. of pyridine and heated under reflux for 24 hours. The solution was cooled, concentrated *in vacuo*, and the precipitate collected and washed with ethanol. TLC showed the residue to be a mixture of 2-aminobenzophenone and Vb. Recrystallization from ethanol (300 ml.) yielded yellow needles of Vb (2.85 g., 23%), m.p. 243-246°. From the mother liquor a total of 6.39 g. (65%) of 2-aminobenzophenone, m.p. 104-108°, was recovered. Reaction of malononitrile and 2-aminobenzophenone in absolute ethanol or in benzene in the presence of pyridine (in the latter case with removal of water by a Dean-Stark trap) did not result in higher yields of Vb.

The spectral characteristics of Vb are as follows: I.R. λ max (potassium bromide), 3.92, 3.00 3.20 (NH_2), 4.50 (C≡N), 6.10, 6.20, 6.40 (C_6H_5 and C≡N), 13.28, and 14.36 μ (C_6H_5); U.V. λ max (ethanol), 221 (ε = 26,300), 252 (ε = 27,000), *ca.* 260 (sh), and 303 mμ (ε = 4,500); NMR (DMSO-d_6): δ 6.94 (broad s, 2H, NH_2), 7.2-7.7 (m, 9H).

Anal. Calcd. for $C_{16}H_{11}N_3$: C, 78.34; H, 4.52; N, 17.13. Found: C, 78.22; H, 4.75; N, 17.08.

2-Amino-6-chloro-3-cyano-4-phenylquinoline (Vc). (20)

2-Amino-5-chlorobenzophenone (Aldrich Chem. Co.) (6.93 g., 0.03 mole), malononitrile (1.98 g., 0.03 mole), and 40 ml. of pyridine were heated at reflux for 15 hours. The pyridine was removed under reduced pressure, leaving a black tar-like substance. After several extractions with benzene and evaporation of the solvent, a yellow product was obtained. Recrystallization from ethanol yielded yellow plates of Vc (1.70 g., 20%), m.p. 272-273.5°; I.R. λ max (potassium bromide), 2.82, 2.98 (NH_2), and 4.50 μ (C≡N); U.V. λ max (ethanol), 227 (ε = 37,000), 255 (ε = 45,500), and 305 mμ (sh) (ε = 4,400).

Anal. Calcd. for $C_{16}H_{10}ClN_3$: C, 68.69; H, 3.60; N, 15.02. Found: C, 68.62; H, 3.61; N, 15.17.

2-Aminoquinoline-3-carboxamide (VIIa).

(a) Hydrolysis of Va with hydrogen peroxide-potassium hydroxide, after the manner of Taylor and Kalenda (3a), gave yields of VIIa ranging from 55-75% when carried out on a small scale (1.2 g.), but much smaller yields when carried out on a larger scale.

(b) When Va (10.0 g., 0.059 mole) was dissolved in 80 ml. of 95% sulfuric acid, heated on a steam bath for 1.5 hours and poured into 2 l. of ice water, a yellow precipitate formed. It was collected, dissolved in boiling water, and made alkaline with 5*N* sodium hydroxide (*p*H 13). The precipitate was filtered after cooling, washed with water and dried, yielding yellow crystals of VIIa (6.73 g.), m.p. 243-245° (lit. (3a): 240-242°). The first filtrate was made alkaline with 5*N* sodium hydroxide and kept overnight at 0°, yielding another 1.60 g. of VIIa (total yield, 8.33 g., 75%) m.p. 239-240°. The I.R. spectra of these samples were identical with that of VIIa obtained by method a.

The alkaline filtrates were combined, neutralized with sulfuric acid (*p*H 8) and concentrated on a steam bath. After cooling, the precipitate was filtered, and washed with water, yielding yellow crystals of 2-aminoquinoline-3-carboxylic acid (VIII) (0.79 g., 6.3%), m.p. 328° after recrystallization from water (lit. (3a): 324-325°); I.R. λ max (potassium bromide), 3.1, 3.4, 5.1 (NH_2, NH_3^+), 5.9 (COOH) 6.2 and 7.5 μ ($-CO_2^-$).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.81; H, 4.29; N, 14.89. Found: C, 63.81; H, 4.38; N, 15.05.

2-Amino-4-phenylquinoline-3-carboxamide (VIIb).

A solution of Vb (2.0 g., 0.0041 mole) in 20 ml. of 95% sulfuric acid was heated for 3 hours on a steam bath, then poured into 500 ml. of ice water and filtered after standing overnight. The small amount of red residue was discarded and the filtrate made alkaline with 5*N* sodium hydroxide (*p*H 11.5). The precipitate was filtered, washed with water and dried, yielding light orange crystals of VIIb (0.96 g., 90%), m.p. 248-251°; I.R. λ max (potassium bromide), 2.90 (sh), 3.02, 3.24 (NH_2), 6.04 (sh), 6.15, 6.29 (sh) (C_6H_5 and $CONH_2$), 13.23, and 14.43 μ (C_6H_5).

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.12; H, 5.22; N, 16.02.

2-Amino-6-chloro-4-phenylquinoline-3-carboxamide (VIIc).

A sample of Vc (0.70 g., 0.00235 mole) was dissolved in 10 ml. of 95% sulfuric acid and heated in an open beaker on a steam bath for 2 hours. The solution was poured into 400 ml. of ice water, the precipitate filtered, washed with water, and dissolved in boiling water. The solution was made alkaline with 5*N* potassium hydroxide (*p*H 13) and the precipitate was filtered after cooling, washed with water and dried, yielding light orange crystals of VIIc (0.530 g.), m.p. 249-253°. The first filtrate was made alkaline with 5*N* potassium hydroxide, yielding another 150 mg. of VIIc (total yield, 0.68 g., 91%), m.p. 245-249°; I.R. λ max (potassium bromide), 2.98, 3.25 (NH_2), 6.04, and 6.16 μ ($CONH_2$).

Anal. Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.06; Cl, 11.91; N, 14.12. Found: C, 64.45; H, 4.23; Cl, 11.94; N, 14.10.

4-Oxo-3,4-dihydropyrimido[4,5-*b*]quinoline (IIa).

Following the procedure of Taylor and Kalenda (2), heating 6.95 g., (0.037 mole) of VIIa for 1.25 hours in 70 ml. of formamide at 160-170° gave IIa (5.46 g., 75%), m.p. 354° (dec.) (lit. (2): 355-356.5° (dec.); I.R. λ max (potassium bromide), 3.2 (NH) and 5.88 μ (CONH); U.V. λ max (ethanol), 221 (sh), 226 (ε = 24,600), 243 (ε = 34,000), 270 (sh), 277 (ε = 26,300), 314 (ε = 5,400), 344 (sh), 356 (ε = 8,100), and 373 mμ (sh).

The U.V. spectrum in 0.1*N* sodium hydroxide was identical with that reported (2).

From the filtrate of the above reaction after further heating for 2 hours at 160-170°, XIa (1.51 g., 20.4%) was obtained, identical in all respect with XIa obtained by reaction of IIa with ammonium formate, as described below.

5-Phenyl-4-oxo-3,4-dihydropyrimido[4,5-*b*]quinoline (IIb).

After heating VIIb (6.0 g., 0.0228 mole) in 50 ml. of freshly distilled formamide with stirring at 175-185° for 90 minutes, the mixture was cooled and the precipitate filtered and washed with acetone, yielding light yellow-gray crystals of IIb (5.2 g., 83.5%), m.p. > 360°; I.R. λ max (potassium bromide), 3.30 (NH), 5.90 and 6.20 (-CO-NH-), 13.1 and 14.4 μ (C_6H_5); U.V. λ max (ethanol) 232 (sh), 246 (ε = 39,200), 272 (sh), 280 (ε = 32,300), 316 (ε = 5,920), 345 (sh), 360 (ε = 9,100), and 375 mμ (sh).

Anal. Calcd. for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.59; H, 4.30; N, 15.45.

7-Chloro-5-phenyl-4-oxo-3,4-dihydropyrimido[4,5-*b*]quinoline (IIc).

After heating VIIc (0.76 g., 0.0025 mole) in 18 ml. of freshly distilled formamide at 165-175° for 1.5 hours, the mixture was cooled, and the precipitate filtered and thoroughly washed with acetone, yielding light orange crystals of IIc (0.60 g., 76.5%), m.p. > 360°; I.R. λ max (potassium bromide), 3.25, 3.50 (NH), 5.92, and 6.20 μ (CONH); U.V. λ max (ethanol) *ca.* 232 (sh), 253 (ε = 33,900), 260 (sh), 281 (ε = 24,600), 312 (sh), 351 (sh), 367 (ε = 5,400), and 385 mμ (ε = 4,500).

Anal. Calcd. for $C_{17}H_{10}ClN_3O$: C, 66.34; H, 3.28; Cl, 11.52; N, 13.66. Found: C, 66.10; H, 3.45; Cl, 11.67; N, 13.72.

4-Oxo-3,4,5,10-tetrahydropyrimido[4,5-*b*]quinoline (XIa).

A mixture of IIa (1.0 g., 0.005 mole) and 3.0 g. of ammonium formate were placed in 50 ml. of formamide and heated with stirring at 170-180° for 3.5 hours. After standing overnight at 0° the precipitate was filtered, washed with water and dried, yielding light yellow crystals of XIa (1.0 g., 99%), m.p. 309-311° (with sublimation and decomposition). An analytical sample was recrystallized from DMSO-acetone-water, yielding light yellow crystals, m.p. 310-313° (dec.); I.R. λ max (potassium bromide), 3.15, 3.60 (NH), and 6.10 μ (CONH); U.V. λ max (ethanol), 215 (ε = 26,200), 233 (sh), 239 (sh), 256 (ε = 19,900), and 328 mμ (ε = 8,950); NMR (DMSO-d_6): δ 3.78 (s, 2H, H-5), 6.75-7.10 (m, 5H, NH and aromatic H), 7.86 (s, 1H, H-2), and 9.27 (broad s, 1H, NH).

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.31; H, 4.55; N, 21.11. Found: C, 66.13; H, 4.71; N, 21.29.

5-Phenyl-4-oxo-3,4,5,10-tetrahydropyrimido[4,5-*b*]quinoline (XIb).

A mixture of IIb (5.0 g., 0.0183 mole) and 15 g. of ammonium formate were placed in 100 ml. of formamide and heated with stirring at 175-185° for 2.3 hours. After cooling, the precipitate was filtered, washed with water and acetone and dried, yielding light green crystals of XIb (4.26 g., 85%), m.p. 328-333° (dec.); I.R. λ max (potassium bromide), 3.1, 3.6 (NH), 6.15 (CONH), 13.45, and 14.42 μ (C_6H_5); U.V. λ max (ethanol), *ca.* 221 (ε = 19,700), 246 (15,700), *ca.* 258 (sh, ε *ca.* 14,000), and 332 mμ (ε = 6,050); NMR (DMSO-d_6) δ 5.25 (s, 1H, H-5), 6.8-7.3 (m, *ca.* 10H, aromatic H and NH), 7.94 (s, 1H, H-2), and 9.7 (broad s, 1H, NH).

Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.27. Found: C, 74.35; H, 4.91; N, 15.49.

7-Chloro-5-phenyl-4-oxo-3,4,5,10-tetrahydropyrimido[4,5-*b*]-quinoline (XIc).

A mixture of IIc (0.31 g., 0.001 mole) and 2.0 g. of ammonium formate were placed in 25 ml. of formamide and heated with stirring at 175-185° for 2 hours. The clear yellow solution was cooled and kept overnight at 0°, and the precipitate which had separated was filtered, washed with water and acetone and dried, yielding light brown crystals of XIc (0.21 g., 67.5%), m.p. 375°; I.R. λ max (potassium bromide), 3.25, 3.60 (NH), and 6.16 μ (CONH); U.V. λ max (ethanol), 217 (ε = 17,600), 251 (sh), 258 (ε = 14,200), and 317 mμ (ε = 5,700); NMR (DMSO-d_6): δ 5.25 (s, 1H, H-5), 6.95-7.25 (m, *ca.* 8H, aromatic H), 7.92 (s, 1H, H-2), and 9.80 (broad s, 1H, NH).

Anal. Calcd. for $C_{17}H_{12}ClN_3O$: C, 65.92; H, 3.91; Cl, 11.45; N, 13.57. Found: C, 65.82; H, 4.18; Cl, 11.56; N, 13.84.

4-Chloro-5,10-dihydropyrimido[4,5-*b*]quinoline (XIIa).

(a) A solution of XIa (1.4 g., 0.007 mole) in phosphorus oxychloride (20 ml.) was allowed to reflux with stirring for 1.5 hours. After cooling, the excess phosphorus oxychloride was removed under reduced pressure, the residue treated with ice water and after standing for some time filtered, yielding brown crystals of XIIa. Extraction of the aqueous solution with chloroform yielded another 0.16 g. of XIIa. Recrystallization from DMF-water and methanol (NORIT) gave yellow needles of XIIa (0.47 g., 31%), m.p. 223-224.5°.

(b) A mixture of XIa (1.99 g., 0.01 mole), *N,N*-dimethylaniline (2.42 g., 0.02 mole) and phosphorus oxychloride (25 ml.), which rapidly turned black, was refluxed with stirring for 70 minutes. After cooling, the excess of phosphorus oxychloride was removed *in vacuo*, the deep brown residue treated with ice water, filtered and washed with water. The filtrate was extracted with chloroform, washed with water, dried over sodium sulfate and evaporated, yielding a brown residue, which was combined with the first residue and recrystallized from methanol, yielding yellow crystals of XIIa (1.07 g., 49%), m.p. 223-225°; I.R. λ max (potassium bromide), 3.05 (NH), 3.30 (w) (CH_2), 6.20, 6.31, 6.43 (C=N), and 10.28 μ (pyrimidine-Cl); U.V. λ max (ethanol), 225 (ε = 15,800), 300 (8,600), and 320 mμ (sh); NMR (DMSO-d_6): δ 3.75 (s, 2H, H-5), 6.8-7.15 (m, 4H, aromatic H), 7.38 (s, 1H, H-2), 9.23 (broad s, 1H, NH).

Anal. Calcd. for $C_{11}H_8ClN_3$: C, 60.69; H, 3.71; Cl, 16.19; N, 19.31. Found: C, 60.51; H, 3.99; Cl, 16.30; N, 18.97.

4-Chloro-5-phenyl-5,10-dihydropyrimido[4,5-*b*]quinoline (XIIb).

A mixture of XIb (2.75 g., 0.010 mole) in phosphorus oxychloride (30 ml.) was gently heated under reflux with stirring for 17 hours. The clear dark brown solution was cooled, and excess phosphorus oxychloride removed under reduced pressure. After addition of 20 ml. of acetone, the mixture was again evaporated under reduced pressure and this procedure was repeated with 20 ml. of methylene chloride. The black sticky residue was treated with 50 ml. of water and heated on a steam bath. After cooling, the green residue was filtered (1.75 g., 60%) and recrystallized from absolute ethanol (NORIT), yielding light yellow crystals of XIIb (1.23 g., 42%), m.p. 252° (turns orange > 170°); I.R. λ max (potassium bromide), 3.08 (NH), 6.21, 6.35, 6.45 (C_6H_5 and C=N), 10.21 (pyrimidine-Cl), 13.35, and 14.36 μ (C_6H_5); U.V. λ max (ethanol), 214 (ε = 15,000), 228 (sh), 293 (ε = 5,860), and *ca.* 320 mμ (sh); NMR (DMSO-d_6-deuteriochloroform): δ 5.46 (s, 1H, H-5), 6.85-7.25 (m, 9H, aromatic H), 8.36 (s, 1H, H-2), 10.56 (broad s, 1H, NH).

Anal. Calcd. for $C_{17}H_{12}ClN_3$: C, 69.50; H, 4.12; Cl, 12.06; N, 14.31. Found: C, 69.29; H, 4.24; Cl, 12.05; N, 14.56.

4-Methoxy-5,10-dihydropyrimido[4,5-*b*]quinoline (XIIIa).

A solution of XIIa (0.22 g., 0.001 mole) and potassium hydroxide (0.50 g.) in 30 ml. of absolute methanol was heated with stirring under reflux for 6 hours. The clear, yellow brown solution was diluted with some water and concentrated under reduced pressure until crystallization began. After cooling, the red brown precipitate was filtered, washed thoroughly with water and recrystallized from methanol-water (NORIT), yielding light yellow needles

of XIIIa (0.11 g., 52%), m.p. 201-202°; I.R. λ max (potassium bromide), 3.10 (NH), 3.32 (CH_3), 6.18, 6.28 and 6.53 μ (C=N); U.V. λ max (ethanol), 216 (ε = 26,800) and 296 mμ (ε = 13,000).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.58; H, 5.20; N, 19.71. Found: C, 67.30; H, 5.34; N, 19.57.

4-Methoxy-5-phenyl-5,10-dihydropyrimido[4,5-*b*]quinoline (XIIIb).

A solution of XIIb (0.295 g., 0.001 mole) and potassium hydroxide (3.0 g., 0.065 mole) in 30 ml. of absolute methanol was heated under reflux with stirring. After 1 hour a clear solution had been formed, but subsequently a precipitate separated. After 6 hours of refluxing, the mixture was cooled overnight, the precipitate filtered, washed with water, cold methanol and ether, yielding light yellow crystals of XIIIb (0.250 g., 86.5%), m.p. 225-227°; I.R. λ max (potassium bromide), 3.1 (NH), 3.3 (CH_3), 6.21, 6.35 (C_6H_5 and C=N), 13.36, and 14.35 μ (C_6H_5); U.V. λ max (ethanol), 216 (sh), 222 (ε = 15,800), *ca.* 236 (sh), 286 (ε = 5,560), and *ca.* 310 mμ (sh); NMR (DMSO-d_6, deuteriochloroform): δ 3.83 (s, 3H, OCH_3), 5.33 (s, 1H, H-5), 6.85-7.20 (m, 9H, aromatic H), 8.23 (s, 1H, H-2), and 9.96 (broad s, 1H, NH).

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.73; H, 5.23; N, 14.52; M.W. 289.3. Found: C, 74.81; H, 5.30; N, 14.54; M.W. 289 (mass spec.)

4-Piperidino-5,10-dihydropyrimido[4,5-*b*]quinoline (XIVa).

A solution of XIIa (0.30 g., 0.0014 mole) in piperidine (4 ml.) was heated with stirring at 50°, and after short time a precipitate was formed. The mixture was allowed to reflux for 15 minutes and cooled, the colorless precipitate filtered and washed with ether and identified as piperidine hydrochloride by mixed m.p. (243-245°) and I.R. spectrum. The filtrate was evaporated under reduced pressure, the yellow residue solidified on standing overnight. Recrystallization from acetone-water yielded light yellow crystals of XIVa (0.27 g., 73.5%), m.p. 188-191°; I.R. λ max (potassium bromide), 3.12 (NH), 3.38 (CH_2), 6.28 and 6.44 μ (C=N).

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.16; H, 6.81; N, 21.04. Found: C, 72.07; H, 7.04; N, 20.88.

4-Piperidino-5-phenyl-5,10-dihydropyrimido[4,5-*b*]quinoline (XIVb).

In a similar manner, XIIb (0.295 g., 0.001 mole) was stirred with 6 ml. of piperidine and allowed to reflux for 2 hours. After cooling overnight, some methanol was added, causing dissolution of the precipitated piperidine hydrochloride, and the mixture was evaporated under reduced pressure to dryness. The yellow residue was treated with methanol-water, the precipitate filtered, washed with water and dried, yielding yellow crystals of XIVb (0.310 g., 202-206°. Recrystallization from methanol-acetone-water (NORIT) gave almost colorless crystals of XIVb (0.210 g., 62%), m.p. 215-217°; I.R. λ max (potassium bromide), 3.1 (NH), 3.4, 3.5 (CH_2), 6.22, 6.30, 6.46 (C_6H_5 and C=N), 13.2, and 14.45 μ (C_6H_5); U.V. λ max (ethanol), 212.5 (ε = 14,500), *ca.* 229 (sh), 281 (ε = 9,200), and *ca.* 320 mμ (sh).

Anal. Calcd. for $C_{22}H_{22}N_4$: C, 77.16; H, 6.48; N, 16.36. Found: C, 77.08; H, 6.65; N, 16.34.

4-Chloro-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*d*]-quinoline (XVa).

A mixture of IIa (4.93 g., 0.025 mole) and *N,N*-dimethylaniline (6.05 g., 0.05 mole) in phosphorus oxychloride (40 ml.) was heated under reflux with stirring for 1 hour, then the excess of phosphorus oxychloride removed under reduced pressure. The black residue was treated with water (100 ml.) and gently warmed until a black solution had been formed. The solution was brought to *p*H 1.5 with 10% sodium hydroxide, which caused the precipitation of a black residue. The residue was filtered by suction and discarded. The filtrate was extracted with chloroform (3 x 100 ml.) and methylene chloride (100 ml.). The organic layers were combined, washed with water (20 ml.) and dried over sodium sulfate. Evaporation under reduced pressure gave 4 g. of a dark residue, and recrystallization from DMF-ethanol 1:2 (NORIT) and ethanol-acetone 1:1 yielded light gray needles (3.43 g., 41%) of XVa, m.p. 253-255°. Repeated recrystallization from acetone (NORIT) gave almost colorless needles of m.p. 256-258° (dec.); I.R. λ max (potassium bromide), 3.09 (NH), 3.34 (CH_3), 6.20, 6.33, 6.44, 6.59 (C_6H_5 and C=N), 10.24 (pyrimidine-Cl), and 13.35 μ (*p*-subst. C_6H_4); U.V. λ max (ethanol), 210.5 (ε = 83,200), *ca.* 230 (sh), 290 (ε = 41,000), and *ca.* 319 mμ (sh); NMR (deuteriochloroform-acetic acid): δ 2.83 (s, 6H, $(CH_3)_2N$), 5.27 (s, 1H, H-5), 6.6-7.13 (m, 8H, aromatic H), and 8.24 (s, 1H, H-2).

Anal. Calcd. for $C_{19}H_{17}ClN_4$: C, 67.75; H, 5.09; Cl, 10.53; N, 16.63. Found: C, 68.01; H, 5.09; Cl, 10.54; N, 16.66.

4-Chloro-5-(*p*-diethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]-quinoline (XVb).

Using the same procedure as described for XVa, IIa (1.97 g., 0.01 mole) and *N,N*-diethylaniline (1.49 g., 0.01 mole) was treated with 20 ml. of phosphorus oxychloride. The crude material from the chloroform extracts (1.15 g., m.p. 220-223°) was recrystallized twice from methanol (NORIT), yielding colorless crystals of XVb (1.02 g., 28%), m.p. 238-239°; I.R. λ max (potassium bromide), 3.10 (NH), 3.38 (CH_2CH_3), 6.20, 6.33, 6.44, 6.60 (C_6H_5 and C=N), 10.25 (pyrimidine-Cl), and 13.40 μ (*p*-subst. C_6H_4); U.V. λ max (ethanol), 209 (ε = 28,700), 228 (sh), 294 (ε = 17,700) and 319 (sh); NMR (deuteriochloroform): δ 1.11 (t, J = 14Hz, 6H, CH_3), 3.27 (q, J = 14Hz, 4H, $-CH_2-$), 5.32 (s, 1H, H-5), 6.51-7.24 (m, 8H, aromatic H), 8.42 (broad s, 1H, NH), and 8.55 (s, 1H, H-2).

Anal. Calcd. for $C_{21}H_{21}ClN_4$: C, 69.12; H, 5.80; Cl, 9.72; N, 15.35; M.W. 364.5. Found: C, 69.02; H, 4.86; Cl, 9.85; N, 15.30; M.W. (osmometer, chloroform): 373.

4-Methoxy-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido-[4,5-*b*]quinoline (XVIa).

A solution of XVa (0.50 g., 0.0015 mole) and potassium hydroxide (4.0 g.) in absolute methanol (50 ml.) was heated under reflux with stirring for 4 hours. After standing overnight at room temperature, the precipitate was filtered and washed with methanol, then with hot water and recrystallized from ethanol-benzene, yielding colorless needles of XVIa (0.38 g., 76%), m.p. 254-256°; I.R. λ max (potassium bromide), 3.06, 3.16 (NH), 3.25, 3.35 (CH_3), 6.22, 6.37 (C=N), and 13.42 μ (*p*-subst. C_6H_4).

Anal. Calcd. for $C_{20}H_{20}N_4O$: C, 72.28; H, 6.07; N, 16.86; M.W. 332.4. Found: C, 72.44; H, 6.15; N, 16.77; M.W. (mass spectrometer) 332.

4-Ethoxy-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]-quinoline (XVIb).

In a similar manner, XVa (0.34 g., 0.001 mole) was treated in absolute ethanol (25 ml.) with potassium hydroxide (2.5 g.). The product was washed with hot water and recrystallized from ethanol, yielding almost colorless needles of XVIb (0.23 g., 67%), m.p. 236-238°; I.R. λ max (potassium bromide), 3.10, 3.20 (NH), 3.28, 3.37 (CH_3), 6.22, 6.37 (C=N), and 13.37 μ (*p*-subst. C_6H_4); U.V. λ max (ethanol), 213.5 (ε = 30,800), 234 (sh), 283 (ε = 29,000), and 308 μ (sh); NMR (perdeuterioacetic acid-deuterium oxide): δ 1.32 (t, J = 7Hz, 3H, CH_3-CH_2), 4.37 (q, J = 7Hz, 2H, CH_3-CH_2-), 3.30 (s, 6H, $(CH_3)_2N$), 5.44 (s, 1H, H-5), 7.0-7.9 (m, 8H, aromatic H), and 8.27 (s, 1H, H-2).

Anal. Calcd. for $C_{21}H_{22}N_4O$: C, 72.81; H, 6.40; N, 16.17. Found: C, 73.01; H, 6.42; N, 16.13.

4-(β-Dibutylaminoethoxy)-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinoline (XVIc).

Sodium hydride (2.4 g. of 50% oil dispersion, 0.05 mole) was triturated in dry THF (50 ml.), the solvent decanted, and β-dibutylaminoethanol (8.65 g., 0.05 mole) added. The mixture was heated at 120-140° for 1 hour with stirring, then XVa (0.84 g., 0.05 mole) was added and heating and stirring continued for 4.5 hours. To the cooled mixture ethanol was added, the precipitate which formed was filtered and washed with methanol and water. The residue was treated with hot water, filtered hot and recrystallized from methanol-acetone (5:1), yielding almost colorless needles of XVIc (0.78 g., 66%), m.p. 142-142.5°; I.R. λ max (potassium bromide), 3.10 (NH), 3.42 (CH), 6.12, 6.36 (C=N), and 13.52 μ (*p*-subst. C_6H_4).

Anal. Calcd. for $C_{29}H_{39}N_5O$: C, 73.52; N, 8.30; N, 14.79. Found: C, 73.58; H, 8.40; N, 15.03.

4-Piperidino-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido-[4,5-*b*]quinoline (XVIIa).

A mixture of XVa (1.0 g., 0.003 mole) in 10 ml. of piperidine was heated under reflux with stirring for 3 hours. After cooling, the mixture was filtered, the residue washed with acetone, yielding 0.28 g. of piperidine hydrochloride, m.p. 242-244°, identified by I.R. spectrum. The filtrate was diluted with water, and the precipitate which formed was filtered and recrystallized from acetone-methanol, yielding light yellow needles of XVIIa (0.85 g., 67.5%), m.p. 215-217°; I.R. λ max (potassium bromide), 3.15 (NH), 3.45 (CH_2), 6.22, 6.30, 6.54 (C=N), and 13.36 μ (*p*-subst. C_6H_4).

Anal. Calcd. for $C_{24}H_{27}N_5$: C, 74.77; H, 7.06; N, 18.17. Found: C, 74.60; H, 7.18; N, 18.09.

4-(β-Diethylaminoethylamino)-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinoline (XVIIb).

A mixture of XVa (2.5 g., 0.0075 mole) in 2-diethylaminoethylamine (30 ml., 0.21 mole) was heated under reflux with stirring for 3.5 hours. After standing overnight at room temperature the mixture was diluted with water, filtered, and the residue washed with water, dried, and recrystallized from methanol as colorless needles of XVIIb (2.98 g., 93%), m.p. 202-204.5°; I.R. λ max (potassium bromide), 3.00, 3.05 (NH), 3.38, 3.48, 3.58 (CH_2), 6.21, 6.38 (C=N), and 13.44 μ (*p*-subst. C_6H_4).

Anal. Calcd. for $C_{25}H_{32}N_6$: C, 72.09; H, 7.75; N, 20.18. Found: C, 72.11; H, 7.74; N, 20.14.

4-(3′-Cyclohexylaminopropylamino)-5-(*p*-dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinoline (XVIIc).

In a similar way, XVa (0.5 g., 0.0015 mole) in 15 ml. of *N*-(3-aminopropyl)cyclohexylamine heated at 140° with stirring for 1.5 hours, gave a product which recrystallized from methanol as colorless crystals of XVIIc (0.46 g., 68%), m.p. 206-207°; I.R. λ max (potassium bromide), 2.92 (NH), 3.43, 3.52 (CH_2), 6.22, 6.34 (C=N), 6.60 (ArNH), 7.42 ($(CH_3)_2NC_6H_4$), 7.22 (ArNH), and 13.45 μ (*p*-subst. C_6H_4).

Anal. Calcd. for $C_{28}H_{36}N_6$: C, 73.64; H, 7.95; N, 18.40. Found: C, 73.25; H, 8.06; N, 18.45.

5-(*p*-Dimethylaminophenyl)-5,10-dihydropyrimido[4,5-*b*]quinoline (XVIII).

A solution of XVa (1.3 g., 0.0039 mole) in a mixture of 50 ml. of water, 25 ml. of acetic acid, and 6 ml. of 2*N* hydrochloric acid, was placed in a PARR-hydrogenation bomb and hydrogenated under a starting pressure of 49.5 psi of hydrogen. After 2.5 hours the pressure remained steady, the reaction mixture was filtered, evaporated to about 5 ml. of a yellow oil. After dilution with water the solution was made basic with 10% sodium hydroxide. The yellow precipitate was filtered, washed with water and cold methanol, and recrystallized from methanol-DMF (1:1), yielding 0.74 g., (64%) of slight yellow crystals of XVIII, m.p. 242.5-245°; I.R. λ max (potassium bromide), 3.15 (NH), 6.28, 6.37 (C=N), and 13.35 μ (*p*-subst. C_6H_4); U.V. λ max (ethanol), 211 (ε = 13,500), *ca.* 270 (sh), 289 (ε = 7,300), and *ca.* 325 mμ (sh); NMR (perdeuterioacetic acid-deuterium oxide): δ 3.26 (s, 6H, CH_3), 5.72 (s, 1H, H-5), 7.1-7.7 (m, aromatic H), 8.24 (s, 1H, H-2), and 8.70 (s, 1H, H-4).

Anal. Calcd. for $C_{19}H_{18}N_4$: C, 75.46; H, 6.00; N, 18.53. Found: C, 75.21; H, 6.13; N, 18.35.

2-Methylamino-3-cyano-4-(*p*-dimethylaminophenyl)quinoline (XIX).

A mixture of XVa (0.50 g., 0.0015 mole) in dry THF (20 ml.) with lithium aluminum hydride (LAH) (0.40 g., 0.01 mole) was heated at reflux with stirring for 3 hours. The excess of LAH was destroyed with methanol and water (25 ml.) and the mixture was made strongly basic with sodium hydroxide until almost all aluminum hydroxide was dissolved. The solution was extracted with methylene chloride (400 ml.), the extracts washed with water (25 ml.), dried over sodium sulfate and evaporated under reduced pressure. A yellow brown oil remained which solidified after some time. Recrystallization from methanol yielded XVIII (0.12 g., 26%), m.p. 237-239°, identified by I.R. spectrum.

The mother liquor was evaporated to dryness and the brown solid residue recrystallized from a small amount of acetone-methanol, yielding yellow crystals of XIX (0.06 g., 13%), m.p. 287-290°; I.R. λ max (potassium bromide), 2.90 (NH), 3.45 (CH_3), 4.52 (C≡N), 6.22, 6.30 (C=N), 13.08 μ (*p*-subst. C_6H_4); U.V. λ max (ethanol), 222.5 (ε = 23,000), 261 (ε = 28,000), and 306 mμ (sh) (ε = 2,500); NMR ($CDCl_3$): δ 3.07 (s, $(CH_3)_2N$), 3.19 (d, NH-CH_3), 6.8-7.75 (m, aromatic H).

Anal. Calcd. for $C_{19}H_{18}N_4$: C, 75.46; H, 6.00; N, 18.53. Found: C, 75.13; H, 6.16; N, 18.30.

2-(*p*-Dimethylaminobenzylamino)-3-cyanoquinoline (XX).

A solution of Va (1.69 g., 0.01 mole) and *p*-dimethylaminobenzaldehyde (3.98 g., 0.02 mole) in toluene (100 ml.) to which 4 drops of pyridine and 4 drops of sulfuric acid were added was heated under reflux with stirring, using a Dean-Stark trap. After 24 hours, 0.12 ml. of water had separated, so the mixture was cooled and filtered, and the brown residue (dec. > 220°) washed with benzene and petrol ether. The filtrate was concentrated under reduced pressure until crystallization began. On cooling orange crystals separated which were filtered and washed with toluene-petroleum ether 1:1 and petroleum ether, yielding 2-(*p*-dimethylaminobenzylideneamino)-3-cyanoquinoline (1.98 g., 66%), m.p. 155-160°. The compound is very sensitive to hydrolysis; recrystallization from ethanol resulted in complete decomposition, yielding Va. A sample was recrystallized from benzene, yielding bright orange needles, m.p. 174-178°, (about 40% recovery); I.R. λ max (potassium bromide), 4.50 (C≡N), 6.20 (CH=N), and 13.15 μ (*p*-subst. C_6H_4). Attempts for further purification were unsuccessful.

Crude 2-(*p*-dimethylaminobenzylideneamino)-3-cyanoquinoline (m.p. 155-160°) (0.60 g., 0.002 mole) and sodium borohydride (0.15 g., 0.004 mole) were placed in absolute ethanol (75 ml.) and the mixture was stirred at room temperature. After 3 hours the orange color has dissappeared and an almost clear yellow solution had formed. The solution was warmed and filtered, the yellow filtrate was concentrated *in vacuo* and the yellow precipitate was

filtered, washed with water and methanol, and dried, yielding 0.18 g. of XX, m.p. 137-139°. A second crop of XX (0.070 g., total yield, 41.5%) m.p. 137-138°, was obtained by diluting the mother liquor with water and extraction with chloroform; I.R. λ max (potassium bromide), 2.92 (NH), 4.52 (C≡N), 6.20, 6.27, 6.43 (C=N), and 13.25 μ (*p*-subst. C_6H_4); U.V. λ max (ethanol), 219.5 (ε = 23,600), 262.5 (ε = 28,700), and 301 mμ (sh) (ε = 3,500); NMR (deuteriochloroform): δ 2.92 (s, 6H, $(CH_3)_2N$), 4.67 (d, J = 12Hz, 2H, $-CH_2-N$), 5.23 (broad s, 1H, NH), 6.68-7.70 (m, 8H, aromatic H), and 8.08 (s, 1H, H-4). The doublet at δ 4.67 changed to a broad singlet on radiation at the NH-signal.

Anal. Calcd. for $C_{19}H_{18}N_4$: C, 75.46; H, 6.00; N, 18.53. Found: C, 75.32; H, 6.03; N, 18.31.

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