Pyrimido[5,4-*b*]quinolines. I. Synthesis of Substituted Tricyclic Systems Related to Riboflavin (1a).

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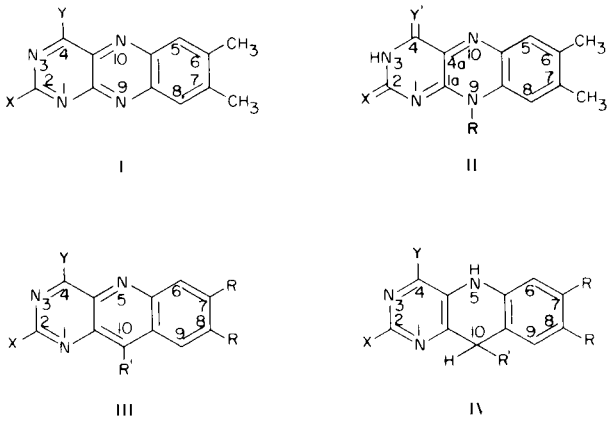
Two alternative synthetic routes were investigated for the synthesis of 2,4,10-substituted-7,8-dimethylpyrimido[5,4-*b*]quinolines: (1) cyclization of 5-(3,4-xylidino)-2,4-disubstituted-pyrimidine-6-carboxylic acids, and (2) cyclization of *N*-5-(2,4-disubstituted-pyrimidinyl)-4,5-dimethylanthranilic acids. Route (1) invariably led to isomeric mixtures of the corresponding 7,8- and 8,9-dimethylpyrimido[5,4-*b*]quinolines which were difficult to separate, while route (2) yielded only the desired 7,8-dimethyl derivatives. The required intermediates were synthesized by Ullman-type condensation of the appropriate pyrimidine and benzene derivatives. Cyclization with polyphosphoric acid, or phosphorus oxychloride (under various conditions) led to a number of new pyrimido[5,4-*b*]quinoline derivatives, with oxo, methoxy and/or chloro substituents in the 2,4 and 10 positions. A mild, but effective chlorination procedure was developed for the chlorination of the 10-(oxo) position without the cleavage of methoxyl groups at positions 2 and 4.

Earlier work in this laboratory directed toward the synthesis of riboflavin antagonists as potential antineoplastic agents (2a,b) or antimalarials (3a-c), included the syntheses of a group of deoxyalloxazines (benzo[*g*]pteridines) (4) and of a series of "open-chain" analogs (5). One of the deoxyalloxazines, 2,4-diamino-6,7-dimethyl-2,4-dideoxyalloxazine (I: X = Y = amino), was a potent "dual antagonist" of riboflavin (II: X′ = Y′ = O, R = ribityl) as well as of folinic acid in at least two bacterial systems (4,6), and it inhibited the growth of transplanted tumors in mice (7a,b). However, various attempts to synthesize the corresponding deoxy*iso*alloxazines (deoxyflavins) (II: X′ and Y′ = NH or S, R = alkyl or hydroxyalkyl) by the same general method (4), or by alkylation of I (8) with the purpose of introducing a side-chain in the N_9-position, were unsuccessful. Therefore, further work was directed toward the synthesis of the 9-deaza analogs of both the *iso*alloxazines, and deoxy*iso*alloxazines, *i.e.*, compounds of the types III and IV (X and Y = hydroxyl or amino, R = CH_3 [9], and R′ = alkyl or hydroxyalkyl). Compounds of the type III are substituted pyrimido[5,4-*b*]quinolines, while compounds of the type IV are derived from 5,10-dihydropyrimido[5,4-*b*]quinoline and have a π electron distribution similar to that of the reduced form of riboflavin. It should be noted that in IV, when X = Y = hydroxyl, the pyrimidine ring would be expected to be in the 2,4(1*H*,3*H*)dione tautomeric form (as in uracil).

CHART I



I II

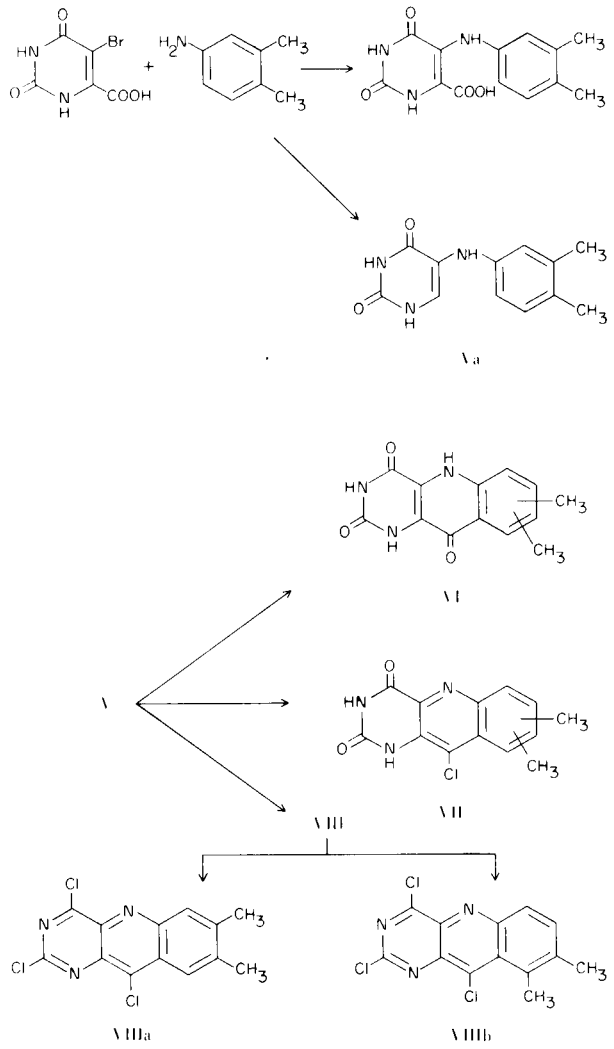
III IV

It may be noted that the characteristic transnuclear N_1-C_{1a}-C_{4a}-N_{10} sequence of the riboflavin ring system (II), which is the "functional" portion of the molecule in the flavin co-enzymes, has been maintained in the proposed 9-deaza analogs of II, *i.e.*, III and IV (see ref. 10 for the change in the numbering of the ring positions). This is not so in the case of the recently synthesized 10-deazariboflavin (11a,b) which is derived from the pyrimido[4,5-*b*]quinoline ring system and where the isosteric replacement involves the N_{10} nitrogen of II. The present paper describes the synthesis of 2,4,10-substituted-7,8-dimethylpyrimido[5,4-*b*]quinolines (III), a series of com-

pounds containing the substituted ring system of 9-deazariboflavin (12).

It was thought that 5-(3,4-xylidino)orotic acid (V) might be an appropriate starting material for the desired compounds. Although the possibility of obtaining two isomers, through ring closure of V on either the 2- or the 6-position of the 3,4-xylidine ring, was recognized, there was also some precedent in the literature (13) to suggest that closure on the 6-position would be sterically favored. Initial attempts to synthesize V by condensing 5-bromoorotic acid with 3,4-xylidine in homogenous solutions (*e.g.*, in dimethyl sulfoxide), or under fusion conditions, were unsuccessful and usually led to the isolation of 5-bromouracil, or the corresponding decarboxylated product Va. However, V was obtained in good yield by a modified Ullman-type condensation (14) of the two reactants (see Chart II).

CHART II



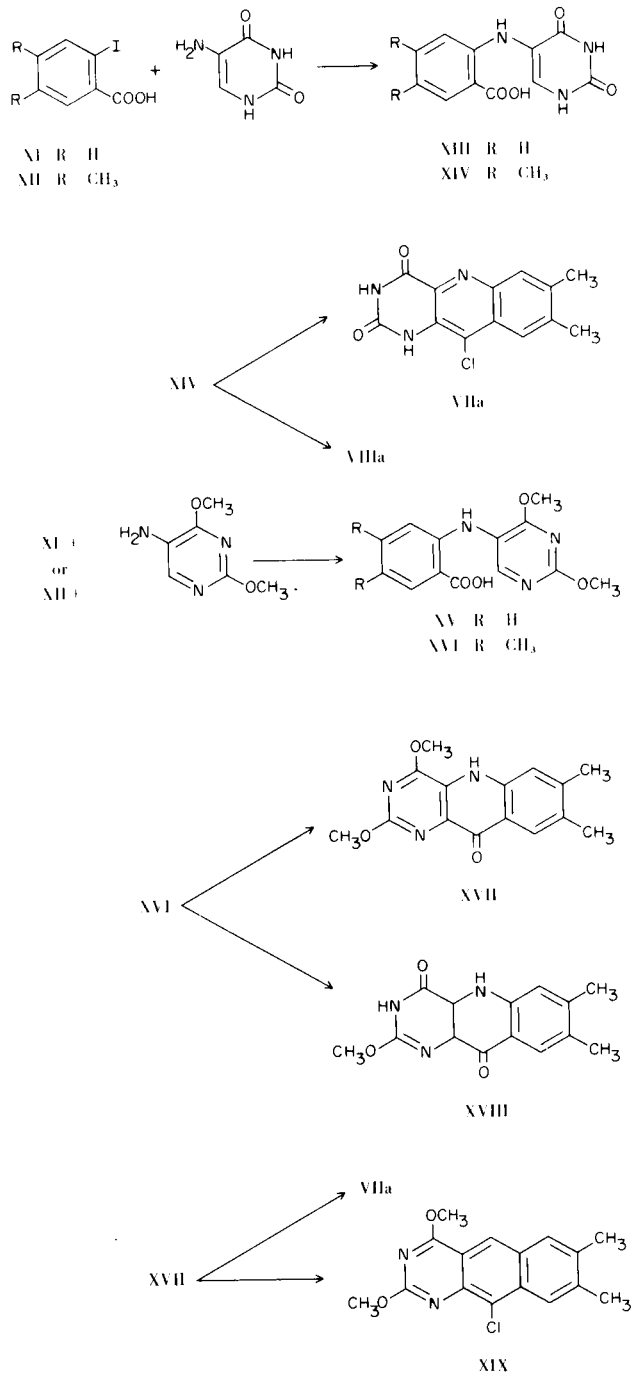
Ring closure was effected by treatment of V with polyphosphoric acid, to give a product identified by elemental analysis and infrared spectrum as 7,8(8,9)dimethylpyrimido[5,4-*b*]quinolin-2,4,10(1*H*,3*H*,5*H*)trione (VI). Due to the insolubility of this material, its nmr spectrum could not be taken. The same product was also obtained by the treatment of V with a 10:1 ratio of phosphorus oxychloride, in addition to a minor side product which gave correct elemental analysis for 7,8(8,9)-dimethyl-10-chloropyrimido[5,4-*b*]quinolin-2,4(1*H*,3*H*)-dione (VII). The latter was the only product isolated when 25:1 ratio of phosphorus oxychloride to V was employed. Although VII was obtained as a crystalline, apparently homogenous material (tlc, m.p.), its nmr spectrum indicated that it was a mixture of the 7,8- and 8,9-dimethyl isomers which could not be resolved by tlc. (The pure 7,8-dimethyl isomer, VIIa, was subsequently obtained *via* two different, unambigous routes, see below). When the ratio of phosphorus oxychloride to V was further increased to 50:1, and also the reaction time was lengthened, a crystalline product, 7,8(8,9)dimethyl-2,4,10-trichloropyrimido[5,4-*b*]quinoline (VIII) was obtained. This product was soluble in chloroform, and its nmr spectrum clearly showed that it was a 1:1 mixture of the 7,8- and 8,9-dimethyl isomers, VIIIa and VIIIb, respectively. Separation of these isomers was eventually accomplished, and their structures could be assigned on the basis of the characteristic nmr patterns of their benzene and methyl protons.

In a preliminary study, the unresolved isomeric mixture of the trichloro derivatives (VIII) was reacted with phenol and with *n*-butylamine, in the hope that the displacement of the 10-chloro substituent by these "bulky" nucleophiles might show some selectivity in favor of the sterically less hindered 7,8-dimethyl isomer, or, that the separation of the two isomers might be better achieved with the resulting phenoxy or *n*-butylamino derivatives than in the case of VIII. Both reactions yielded multicomponent mixtures from which the 2,4,10-triphenoxy derivative(s) IX and the 4-butylamino-2,10-dichloro derivative(s) X, respectively (see Experimental), were isolated analytically pure but in the form of isomeric mixtures of the corresponding 7,8- and 8,9-dimethyl isomers (nmr) which could not be separated by tlc or by column chromatography (15).

Since all cyclization reactions of V invariably led to isomeric mixtures of 7,8- and 8,9-dimethylpyrimido-[5,4-*b*]quinoline derivatives which were difficult to separate, an alternative synthetic route was explored, involving *N*-(5-pyrimidinyl)-4,5-dimethylanthranilic acids as synthetic intermediates; cyclization of the latter could give only 7,8-dimethylpyrimido[5,4-*b*]quinolines. Many different procedures were investigated for the synthesis of the

desired intermediates by the condensation of various uracil derivatives with appropriately substituted benzoic acids, but again only the modified Ullman reaction (14) led to satisfactory results. Under the latter conditions, either 2-iodobenzoic acid (XI) or 2-iodo-4,5-dimethylbenzoic acid (XII) reacted with 5-aminouracil to give the corresponding anthranilic acid derivatives XIII and XIV,

CHART III



respectively. Cyclization of XIV with phosphorus oxychloride under relatively mild conditions gave a good yield of 7,8-dimethyl-10-chloropyrimido[5,4-*b*]quinolin-2,4-(1*H*,3*H*)dione (VIIa). More drastic treatment of XIV with excess phosphorus oxychloride gave the trichloro derivative VIIIa.

Better yields of the corresponding anthranilic acid intermediates were obtained in the condensation of the iodobenzoic acids XI or XII with 2,4-dimethoxy-5-aminopyrimidine under the Ullman reaction conditions, to yield *N*-5-(2,4-dimethoxypyrimidinyl)anthranilic acid (XV) and its 4,5-dimethyl derivative XVI, respectively. Cyclization of XVI with polyphosphoric acid proceeded smoothly, to give 2,4-dimethoxy-7,8-dimethylpyrimido[5,4-*b*]quinolin-10(5*H*)one (XVII) in up to 76% yield. When the reaction was allowed to proceed longer, partial cleavage of the methoxyl groups occurred, and in addition to XVII, some 2-methoxy-7,8-dimethylpyrimido[5,4-*b*]quinolin-4,10(3*H*,5*H*)dione (XVIII) was also isolated (see Chart III).

Treatment of XVII with phosphorus oxychloride under mild conditions resulted in the chlorination of the 10-position, but with simultaneous cleavage of both methoxyl groups to give VIIa. However, the desired 2,4-dimethoxy-10-chloro-7,8-dimethylpyrimido[5,4-*b*]quinoline (XIX) could be prepared in poor yield by using phosphorus oxychloride together with triethylamine. Much better results were obtained by a subsequently developed procedure using phosphorus pentachloride in dimethylformamide as a selective chlorinating agent. When XVII was added to this system, the desired product precipitated in excellent yield; moreover, the collected precipitate was found to be essentially pure XIX.

EXPERIMENTAL

All melting points were taken by the capillary tube method on a Mel-Temp melting point apparatus and those below 230° are corrected. Ultraviolet spectra were determined on Perkin-Elmer Model 202 and Beckman DB-G spectrophotometers. Infrared spectra were taken on Perkin-Elmer Infracord and Beckman IR 8 spectrophotometers. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, and by Dr. Alfred Bernhard, 433 Mulheim (Ruhr), West Germany. The nuclear magnetic resonance spectra were determined on a Varian A-60 spectrophotometer, using tetramethylsilane as an internal standard in the solvents indicated, except with trifluoroacetic acid as solvent where *t*-butanol was used. Proton signals are reported in ppm downfield from tetramethylsilane and are corrected. The homogeneity and purity of the compounds was confirmed by thin layer chromatography (tlc) on Silica gel HF_{254} (or, in some cases, on cellulose), using the following solvent systems: dioxane/cyclohexane; dimethylformamide/water; benzene/ether; *n*-butanol/5 *N* acetic acid (7:3); acetone/chloroform; benzene/10% methanol; benzene/20% methanol; ethyl acetate.

5-(3,4-Xylidino)orotic Acid (V).

5-Bromoorotic acid (16) (50 g., 0.185 mole), potassium carbonate (55 g., 0.4 mole) and 3,4-dimethylaniline (157 g., 1.3 moles),

in 500 ml. of water and 50 ml. of *n*-propanol, with trace amounts of copper bronze powder and cuprous iodide added, were refluxed with continuous mechanical stirring for 7 days. After cooling, the reaction mixture was extracted several times with ether, the aqueous layer was treated with charcoal and filtered. The cooled filtrate was carefully acidified with concentrated hydrochloric acid, the precipitated solids were collected, washed with water, then suspended in hot water with the minimum amount of potassium carbonate necessary to effect solution. The filtrate was again acidified, filtered, and the filter-cake was washed with water, ether and air dried; 27.0 g. (53%); m.p. 340-342° dec. This was recrystallized from aqueous dimethyl sulfoxide to give yellow crystals, m.p. 340-342° dec.; uv λ max (0.1 *N* sodium hydroxide) 245 (ε, 13,200), 293 mμ (ε, 7,600); ir ν max (potassium bromide) 3400 (NH), 1740 and 1700 cm^{-1} (uracil-CONH, COOH).

Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.73; H, 4.76; N, 15.27. Found: C, 56.46; H, 4.72; N, 15.30.

5-(3,4-Xylidino)uracil (Va).

5-Bromoorotic acid (1.0 g., 0.0037 mole) and dimethylaniline (7.0 g., 0.058 mole) were fused at 150-160° (oil bath) for 20 hours. After cooling to room temperature, ether was added, and the mixture was extracted with dilute sodium hydroxide solution. The aqueous layer was treated with charcoal, filtered and cooled. The filtrate was acidified with concentrated hydrochloric acid, and the precipitated solids were filtered, washed with water and air-dried. Crystallization of the product from aqueous dimethylformamide yielded 0.165 g. (10%) of an off-white powder, m.p. 340-342° dec.; uv λ max (0.1 *N* sodium hydroxide) 250 (ε, 12,500) and 287 mμ (ε, 13,900); ir ν max (potassium bromide) 3420 (NH), 1750 and 1700 cm^{-1} (uracil).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.50; H, 5.68; N, 18.20. Found: C, 62.70; H, 5.99; N, 18.51.

7,8(8,9)-Dimethylpyrimido[5,4-*b*]quinolin-2,4,10(1*H*,3*H*,5*H*)trione (VI).

Method A.

A mixture of 5-(3,4-xylidino)orotic acid (V) (1.0 g., 0.0036 mole) and polyphosphoric acid (3.5 g.) was heated at 110° with stirring for 24 hours, and the reaction mixture was then poured into ice-water. The resulting mixture was stirred for 0.5 hour and then centrifuged, decanted and washed with water (3 times), 10% sodium bicarbonate (2 times), ethanol (2 times) and ether (2 times). The green residue was extracted with boiling dioxane and filtered. On cooling, a yellow solid precipitated which was filtered, washed with ether and air-dried, to yield 300 mg. (32%) of a bright yellow compound, m.p. > 400°. The solid was suspended in benzene and evaporated to dryness; uv λ max (methanol) 270 (ε, 28,400), 280 (ε, 30,700), 297 (ε, 1,800), 311 (ε, 2,300), 326 (ε, 1,900), 370 (sh) (ε, 4,400), 387 (ε, 6,800) and 408 mμ (ε, 6,600); ir ν max (potassium bromide) 3440, 3250, 3150 (NH); 1740 (sh), 1700, 1670 (C=O), 1630, 1600, 1570 cm^{-1} (C=C).

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.33. Found: C, 60.71; H, 4.70; N, 16.06.

Method B.

A mixture of V (2.75 g., 0.01 mole) and phosphorus oxychloride (28 ml., 10.3 moles) was refluxed for 24 hours. The excess phosphorus oxychloride was removed by evaporation under reduced pressure, the residue was triturated with acetone-ether and filtered, to yield 1.67 g. (65%) of dark solid. The solid was dissolved in a large volume of dioxane, treated with charcoal and filtered. From the filtrate on cooling a bright yellow solid crystallized; 550 mg., m.p. > 400°; uv and ir spectra identical with those of VI prepared by Method A.

Addition of water to the filtrate from VI caused the formation of another crop of yellow precipitate. Crystallization from dioxane-water gave 40 mg. of a yellow crystalline compound, m.p. 293-294° dec.; uv and ir spectra identical with those of VII (see below).

7,8(8,9)-Dimethyl-10-chloropyrimido[5,4-*b*]quinolin-2,4(1*H*,3*H*)-dione (VII).

A mixture of V (1.0 g., 0.0036 mole) and phosphorus oxychloride (25 ml.) was refluxed for 24 hours, then poured into ice-water. The precipitated solids were filtered, washed with water, ethanol and ether, then air-dried, to give 910 mg. of a dark residue. Two recrystallizations from dioxane-water (charcoal) yielded 130 mg. of a tan colored substance which could be recrystallized from dioxane to give 62 mg. of VII, as yellow crystals, m.p. 293-294° dec.; uv λ max (dioxane) 255 (broad; ε, 45,200), 330 (broad; ε, 5,380), and 375 mμ (ε, 3,900); ir ν max (potassium bromide) 3430 (NH), 1730 and 1710 cm^{-1} (uracil); nmr (trifluoroacetic acid) δ 8.10 and 7.95 (m, aromatic), 2.75 and 2.28 (s, Ar-CH_3).

Anal. Calcd. for $C_{13}H_{10}ClN_3O_2$: C, 56.64; H, 3.66; N, 15.24; Cl, 12.86. Found: C, 57.10; H, 3.68; N, 15.14; Cl, 12.78.

7,8- and 8,9-Dimethyl-2,4,10-trichloropyrimido[5,4-*b*]quinolines (VIII, VIIIa, and VIIIb).

A mixture of V (10 g., 0.036 mole) and 500 ml. of phosphorus oxychloride was refluxed 70 hours. The excess phosphorus oxychloride was removed by evaporation under reduced pressure, and to the residue cold ether was added. After filtration and washing with cold ether, the residue was extracted with boiling cyclohexane, the extract was concentrated to a small volume and allowed to cool to room temperature. The resulting precipitate was filtered and washed with cold cyclohexane to yield 6.3 g. (56%) of VIII as bright yellow crystals, m.p. 202-204° dec.; uv λ max (methanol) 275 (ε, 66,500), 355 (sh, ε, 5,300), 372 (ε, 10,500); nmr (deuteriochloroform) δ 8.10 (broad m, aromatic), 7.80 (s, aromatic), 3.05 (s, Ar-CH_3) and 2.60 (s, Ar-CH_3), the last two bands showed an integrated ratio of 1:2.

Anal. Calcd. for $C_{13}H_8Cl_3N_3$: N, 13.44; Cl, 34.03. Found: N, 13.09; Cl, 33.74.

Using a 25 cm long tlc plate (silica gel HF_{254}) with dioxane-cyclohexane solvent system, it was possible to resolve VIII into 2 partially overlapping spots. Subsequently, VIIIa and VIIIb were separated by column chromatography in the following manner:

The "analytically pure" isomeric mixture VIII (1.0 g.) was dissolved in chloroform-benzene and was eluted through 100 g. of neutral silica gel (Merck: 0.05-0.20 mm) with benzene as eluent. After 600 ml. of benzene had been passed through the column, 50 ml. fractions were collected, and the elution of the isomers was followed by tlc.

Fractions #11 through #18 were combined, evaporated to dryness, then crystallized from cyclohexane to yield 150 mg. (15%) of VIIIa, as pale yellow crystals, m.p. 256-258° dec.; uv λ max (methanol) 272 (ε, 69,500), 355 (sh), 373 mμ (ε, 11,300); nmr (deuteriochloroform) δ 8.20 (broad s, 2H, aromatic), 2.60 (s, 6H, Ar-CH_3).

Anal. Calcd. for $C_{13}H_8Cl_3N_3$: C, 49.95; H, 2.58; N, 13.44; Cl, 34.03. Found: C, 50.07; H, 2.71; N, 13.41; Cl, 33.89.

Fractions #2 through #8 were combined, evaporated to dryness, then crystallized from cyclohexane to yield 135 mg. (13.5%) of VIIIb as bright yellow crystals, m.p. 230-233° dec.; uv λ max (methanol) 277 (ε, 65,600), 355 (sh), and 372 mμ (ε, 10,900); nmr (deuteriochloroform); δ 7.95 (d of d, 2H, aromatic), 3.05 (s, 3H, Ar-CH_3) and 2.60 (s, 3H, Ar-CH_3).

Anal. Found: C, 50.06; H, 2.71; N, 13.26; Cl, 33.91.

On the basis of the nmr spectra, VIIIa was identified as 7,8-dimethyl-2,4,10-trichloropyrimido[5,4-*b*]quinoline, and VIIIb as 8,9-dimethyl-2,4,10-trichloropyrimido[5,4-*b*]quinoline. The structure of VIIIa was further confirmed by unambigous synthesis from XVI (see below).

7,8(8,9)-Dimethyl-2,4,10-triphenoxypyrimido[5,4-*b*]quinoline (IX).

The "analytically pure" isomeric mixture of 7,8- and 8,9-dimethyl-2,4,10-trichloropyrimido[5,4-*b*]quinolines (VIII) (1.0 g., 0.0032 mole) and 10 g. (0.106 mole) of phenol was heated in an oil bath, with stirring under nitrogen atmosphere, at 110-115° for 7 hours (until the evolution of hydrogen chloride gas ceased). The red solution was neutralized with 5% aqueous sodium hydroxide and filtered. The filter-cake was washed with water and air-dried, to yield 1.5 g. (97%) of an orange solid, which however, contained at least 4 different products (tlc). Since crystallization from methanol caused some reaction to take place (as shown by tlc and the appearance of a methoxyl group in the nmr), the mixture was chromatographed on silica gel using methylene chloride as eluent. The first few fractions appeared homogenous by tlc and were evaporated to dryness. The residue was recrystallized from cyclohexane-methylene chloride to give 113 mg. (8%) of yellow clusters of needles, m.p. 208-210°; nmr (deuteriochloroform); δ 7.2 (m, 17H, aromatic), 2.75 and 2.50 (s, 6H, Ar-CH_3). Although this material was presumably a mixture of the 7,8- and 8,9-dimethyl derivatives, a resolution of the single tlc spot could not be obtained with any of a variety of solvent systems.

Anal. Calcd. for $C_{31}H_{23}N_3O_3$: C, 76.69; H, 4.77; N, 8.65. Found: C, 76.88; H, 4.71; N, 8.69.

The other products from the reaction were not identified.

7,8(8,9)-Dimethyl-2,10-dichloro-4-*n*-butylaminopyrimido[5,4-*b*]-quinoline (X).

The "analytically pure" isomeric mixture of 7,8- and 8,9-dimethyl-2,4,10-trichloropyrimido[5,4-*b*]quinolines (VIII) (1.0 g., 0.0032 mole) was dissolved in 100 ml. of benzene (dried over sodium). To the solution was added 0.63 ml. (2 equiv.) of *n*-butylamine, all at once. The precipitate (*n*-butylamine hydrochloride) was filtered and washed with benzene. The filtrate and washings were evaporated to dryness, the residue was triturated with water and filtered, to yield 1.03 g. of a bright yellow solid, which gave 3-4 spots on tlc. Crystallization from cyclohexane gave 0.75 g. (67%) yellow crystals, m.p. 132.5-134°, homogenous by tlc; ir ν max (potassium bromide), 3420 cm^{-1} (NH); nmr (deuteriochloroform); δ 7.6 (m, 2H, aromatic), 3.7 (q, 2H, CH_2), 2.8 and 2.4 (s, 6H, Ar-CH_3), 1.68 (m, 4H, CH_2), 1.10 (t, 3H, CH_3).

Anal. Calcd. for $C_{17}H_{18}Cl_2N_4$: C, 58.46; H, 5.19; N, 16.04; Cl, 20.30. Found: C, 58.37; H, 5.40; N, 15.99; Cl, 20.17.

4,5-Dimethyl-2-iodobenzoic Acid (XII).

4,5-Dimethylanthranilic acid (17) (16.5 g., 0.1 mole) and sodium nitrite (7.0 g., 0.1 mole) were dissolved in 100 ml. of water containing 20 ml. of 6 *N* sodium hydroxide. The solution was cooled and added dropwise to a cold mixture of 50 ml. of concentrated hydrochloric acid and 50 g. of crushed ice. The reaction mixture was stirred for another 0.5 hour, and a cooled solution of potassium iodide (16.6 g., 0.1 mole) in 100 ml. of water was added. The mixture was warmed on the steam bath, until the evolution of nitrogen ceased, and then cooled. The precipitated product was filtered and washed with water. Crystallization from cyclohexane (charcoal) yielded 17.9 g. (65%) of bright yellow crystals, m.p. 201-204°; ir ν max (potassium bromide) 1695 cm^{-1} (COOH); nmr (deuteriochloroform); δ 7.85 (s, 2H, aromatic), 2.27 (s, 6H, Ar-CH_3).

Anal. Calcd. for $C_9H_9IO_2$: C, 39.16; H, 3.29; I, 45.97. Found: C, 39.20; H, 3.46; I, 45.87.

N-[5-Pyrimidin-2,4(1*H*,3*H*)dioneyl]anthranilic Acid (XIII).

o-Iodobenzoic acid (XI) (4.96 g., 0.02 mole) was dissolved in 50 ml. of water containing 1.38 g. (0.01 mole) of potassium carbonate. The *p*H was adjusted to 7 with acetic acid, and 2.54 g. (0.02 mole) of 5-aminouracil was added with trace amounts of copper bronze powder and cupric oxide. The mixture was refluxed for 5 days and filtered while hot. The filter cake was suspended in 0.05 *N* hydrochloric acid, filtered, and washed with water. The filtercake was suspended in hot water and sodium bicarbonate was added to effect solution. The solution was filtered, and to the filtrate sodium chloride was added to precipitate the sodium salt of XIII. The salt was filtered and dissolved in boiling water and acidified with acetic acid. The precipitate was filtered, washed and air-dried, to yield 2.0 g. of tan colored solid. Crystallization from aqueous dimethyl sulfoxide (charcoal) yielded 1.5 g. (30%) of cream colored crystals, m.p. 351-352° dec.; uv λ max (methanol) 255 (ε, 15,500), 340 mμ (ε, 9,900); ir ν max (potassium bromide), 1720 and 1670 cm^{-1} (uracil, COOH).

Anal. Calcd. for $C_{11}H_9N_3O_4$: C, 53.44; H, 3.67; N, 17.00. Found: C, 53.18; H, 3.94; N, 16.90.

N-[5-Pyrimidin-2,4(1*H*,3*H*)dioneyl]-4,5-dimethylanthranilic Acid (XIV).

4,5-Dimethyl-2-iodobenzoic acid (XIV) (2.76 g., 0.01 mole), potassium carbonate (1.38 g., 0.01 mole), 5-aminouracil (1.20 g., 0.01 mole), and 200 mg. of copper bronze powder, in 18 ml. of water, were refluxed for 4 days. After filtration of the hot mixture, the filtrate was acidified and filtered. The filter-cake was extracted with 400 ml. of boiling cyclohexane, filtered and dried, to yield 2.10 g. of the crude product. Two crystallizations from methanol (charcoal) yielded 1.10 g. (40%) of off-white crystals, m.p. 320° (effervescence); uv λ max (methanol) 250 (sh) (ε, 13,200), 348 mμ (ε, 7,050); ir ν max (potassium bromide) 1720 and 1670 cm^{-1} (uracil, COOH); nmr (DMSO-d_6) δ 7.63 (s, 1H, aromatic), 7.50 (d, 1H, aromatic, which changed on heating at 100° to a singlet at 7.36, indicating that the "doublet" was due to 2 rotomers), 6.65 (s, 1H, pyrimidine-C_6-H), 2.17 (s, 3H, Ar-CH_3), 2.13 (s, 3H, Ar-CH_3).

Anal. Calcd. for $C_{13}H_{13}N_3O_4 \cdot 0.5\ H_2O$: C, 54.93; H, 4.85; N, 14.78. Found: C, 55.14; H, 5.01; N, 14.75.

Unambigous Synthesis of 7,8-Dimethyl-2,4,10-trichloropyrimido-[5,4-*b*]quinoline (VIIIa).

A small sample of XIV (100 mg.) and 5 ml. of phosphorus oxychloride were refluxed for 3 days. After removal of the excess reagent by evaporation *in vacuo*, the dark residue was extracted several times with boiling cyclohexane. Evaporation of the extracts, yielded 40 mg. of a pale yellow crystalline solid. This material was identical to the isomer (VIIIa) crystallized from the "slower moving" chromatographic fractions of VIII (see above), by m.p., mixture m.p., tlc, ir and uv spectra.

N-[5-(2,4-Dimethoxypyrimidinyl]anthranilic Acid (XV).

5-Amino-2,4-dimethoxypyrimidine (14) (9.30 g., 0.06 mole), *o*-iodobenzoic acid (XI) (14.88 g., 0.06 mole), potassium carbonate (8.28 g., 0.06 mole), 90 ml. of water and 1.0 g. of copper bronze powder were refluxed for 2 days. The hot mixture was filtered, the orange filter-cake was extracted with 200 ml. of hot water, filtered and air-dried, to yield 13 g. of a crude product. Crystal-

lization from methanol (charcoal) gave 6.5 g. (39%) of off-white crystals, m.p. 199-202°. The methanol-insoluble material was crystallized first from aqueous dimethyl sulfoxide and then from methanol, to yield an additional 2.0 g. of product (total yield 8.5 g., 51%); uv λ max (methanol) 279 (ε, 11,400), 340 (ε, 7,800); ir ν max (potassium bromide) 3400 (NH), 1900, 1675 cm^{-1} (COOH); nmr (trifluoroacetic acid); δ 7.94 (s, 1H, pyrimidine-C_6-H), 6.82 (m, 4H, aromatic), 4.06 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3).

Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.73; H, 4.76; N, 15.27. Found: C, 56.72; H, 4.81; N, 15.08.

N-[5-(2,4-Dimethoxypyrimidinyl)]-4,5-dimethylanthranilic Acid (XVI).

Method A.

5-Amino-2,4-dimethoxypyrimidine (14) (0.846 g., 0.0055 mole), 4,5-dimethyl-2-iodobenzoic acid (XII) (1.50 g., 0.0054 mole), potassium carbonate (0.75 g., 0.0054 mole), and copper bronze powder (0.10 g.) in 8.2 ml. of water, were refluxed for 2 days. The mixture was filtered while hot, and the filtrate was acidified with concentrated hydrochloric acid. The precipitated crude product was collected, washed, dried and extracted with boiling cyclohexane. The residue was then extracted with hot benzene and filtered. The benzene filtrate was evaporated to dryness and the residue was crystallized (twice) from ethyl acetate (charcoal), to yield 150 mg. (9%) of XVI in the form of bright yellow crystals, m.p. 201-203°; uv λ max (methanol) 285 (ε, 12,800), 343 (ε, 8,350); ir ν max (potassium bromide) 3400 (NH), 1670 cm^{-1} (COOH); nmr (trifluoroacetic acid) δ 7.87 (s, 1H, pyrimidine-C_6-H), 7.64 (s, 1H, aromatic), 6.77 (s, 1H, aromatic), 4.08 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 1.98 (s, 3H, Ar-CH_3), 1.95 (s, 3H, Ar-CH_3).

Anal. Calcd. for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.24; H, 5.46; N, 13.64.

The benzene-insoluble residue was crystallized from aqueous dimethyl sulfoxide (charcoal) to yield 150 mg. of pale yellow solid, m.p. 249-251° dec.; uv λ max (methanol) 275 (sh) (ε, 9,000), 350 (ε, 7,800); ir ν max (potassium bromide) 1720 (sh) and 1675 cm^{-1} (CONH, COOH).

Anal. Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 58.27; H, 5.03; N, 14.49.

This compound was, therefore, presumably *N*-[5-(2-methoxy-4-hydroxypyrimidinyl)]-4,5-dimethylanthranilic acid.

Method B.

5-Amino-2,4-dimethoxypyrimidine (14) (4.65 g., 0.03 mole), 4,5-dimethyl-2-iodobenzoic acid (XII) (2.76 g., 0.01 mole), potassium carbonate (1.38 g., 0.01 mole) and copper bronze powder (0.20 g.), in 20 ml. of water were refluxed for 22 hours. The reaction mixture was worked up as above. After the extraction with boiling cyclohexane, the residue was crystallized from ethyl acetate, to yield 1.37 g. (45%, based on XII) of XVI, m.p. 202-204°, spectra identical to those of the analytical sample obtained by Method A.

The acidic filtrate obtained after separation of the precipitated crude product in the work-up of the reaction mixture above, was neutralized with 10% sodium hydroxide and evaporated to dryness. The residue was extracted with benzene, filtered, and the benzene filtrate was evaporated to dryness. The residue was crystallized from *n*-hexane to give 2.33 g. of 5-amino-2,4-dimethoxypyrimidine, *i.e.*, a 75% recovery of the "excess" (3.1 g., 0.02 mole) of this reactant over the molar equivalent of XIV used in this preparation.

Method C.

When the reaction was run as in Method A but on a 20-times larger scale (*i.e.*, using 0.1 mole of all reactants) and with copper bronze powder freshly pretreated (18) with 2% iodine in acetone, hydrochloric acid-acetone 1:1, and acetone, a 50% yield of pure XVI was obtained.

2,4-Dimethoxy-7,8-dimethylpyrimido[5,4-*b*]quinolin-10(5*H*)one (XVII).

N-[5-(2,4-Dimethoxypyrimidinyl)]-4,5-dimethylanthranilic acid (XVI) (3.0 g., 0.01 mole) and 60 g. of polyphosphoric acid were heated at 110-115° in an oil bath for 1.5 hours. The reaction was quenched by pouring the mixture into ice-water and adjusting the *p*H to 8 with 6 *N* sodium hydroxide solution. The mixture was warmed on a steam bath to allow coagulation of the precipitate, then cooled and filtered. After washing with a sodium bicarbonate solution followed by water, the filter-cake was dried at 50° under vacuum, to yield 2.4 g. of crude product. This was extracted with hot ethyl acetate and filtered; the pure, yellow product (XVII) crystallized from the filtrate; 1.24 g., m.p. > 400°. Concentration of the mother liquors gave another 0.275 g. of XIX (total yield 1.515 g., 54%). When prepared on a 10 g. scale, the yield was 76%. At high dilutions in methanol, the compound shows blue fluorescence; uv λ max (methanol) 267 (sh) (ε, 39,000), 276 (ε, 58,200), 309 (ε, 2,150), 327 (ε, 1,800), 370 (ε, 4,100), 390 (ε, 6,500), and 409 mμ (ε, 6,500); nmr (trifluoroacetic acid) δ 8.12 (s, 1H, aromatic), 7.61 (s, 1H, aromatic), 4.50 (s, 3H, OCH_3), 4.34 (s, 3H, OCH_3), 2.30 (broad s, 6H, Ar-CH_3).

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.91; H, 5.40; N, 14.50.

The ethyl acetate insoluble residue was crystallized from boiling dimethylformamide to yield a yellow product, m.p. >400°; uv λ max (dioxane) 272 (sh), 283, 298, 310, 325, 360 (sh), 380, and 400 mμ. This compound gave the correct analysis for 2-methoxy-7,8-dimethylpyrimido[5,4-*b*]quinolin-4,10(3*H*,5*H*)dione (XVIII).

Anal. Calcd. for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 62.03; H, 5.02; N, 15.17.

Unambigous Synthesis of 7,8-Dimethyl-10-chloropyrimido[5,4-*b*]-quinolin-2,4(1*H*,3*H*)dione (VIIa).

Method A.

A small (100 mg.) sample of 2,4-dimethoxy-7,8-dimethylpyrimido[5,4-*b*]quinolin-10-one (XVII) and 5 ml. of phosphorus oxychloride were stirred at room temperature for 6 hours. The excess of the reagent was evaporated *in vacuo*, the residue was washed with ether, triturated with cyclohexane and filtered. The product was recrystallized from acetone, to yield 31 mg. of bright yellow crystals, and an additional 13 mg. was recovered from the mother liquor (total yield 43 mg., 45%); m.p. 330° dec; uv λ max (methanol) 259 (ε, 66,500), 328 (ε, 6,300), 368 (ε, 3,900), 386 mμ (ε, 3,300 sh); ir ν max (potassium bromide) 3430 (NH), 1725 and 1705 cm^{-1} (uracil); nmr (trifluoroacetic acid) δ 8.10 (s, 1H, aromatic), 8.04 (s, 1H, aromatic), 2.40 (s, 6H, Ar-CH_3).

Anal. Calcd. for $C_{13}H_{10}ClN_3O_2$: C, 56.64; H, 3.66; N, 15.24; Cl, 12.86. Found: C, 56.65; H, 3.56; N, 14.95; Cl, 12.77.

Method B.

N-[5-Pyrimidin-2,4(1*H*,3*H*)dioneyl]-4,5-dimethylanthranilic acid (XIV) (3.45 g., 0.012 mole) and 170 ml. of phosphorus oxychloride were stirred at 50° (oil bath) for 2 days. The excess of the reagent was then evaporated *in vacuo*, and the residue was triturated with cold ether and filtered. Crystallization from

acetone (charcoal) yielded 1.92 g. (50%) of pure VIIa, in the form of bright yellow crystals, m.p. 326-328° dec., identical to the product obtained by Method A.

2,4-Dimethoxy-7,8-dimethyl-10-chloropyrimido[5,4-*b*]quinoline (XIX).

Method A.

A mixture of 2,4-dimethoxy-7,8-dimethylpyrimido[5,4-*b*]-quinolin-10(5*H*)one (XVII) (100 mg., 0.0003 mole), 5 ml. of phosphorus oxychloride (0.054 mole) and 1 ml. of triethylamine (0.0072 mole) were stirred at room temperature for 5 days. The dark mixture was evaporated *in vacuo*, triturated with ether and filtered. The residue was suspended in water and filtered. The solid was crystallized from acetone to yield 20 mg. of a bright yellow product, m.p. 251-253°; uv λ max (methanol) 258, 270 (sh), 344, 360, 378, and 400 mμ; nmr (deuteriochloroform); δ 8.00 (s, 2H, aromatic), 4.44 (s, 3H, OCH_3), 4.21 (s, 3H, OCH_3), 2.49 (s, 6H, Ar-CH_3).

Anal. Calcd. for $C_{15}H_{14}ClN_3O_2$: C, 59.31; H, 4.65; N, 13.83; Cl, 11.67. Found: C, 59.11; H, 4.50; N, 13.65; Cl, 11.61.

This reaction could not be applied on a larger scale since it led to mixtures of XIX with VIIa and XVII.

Method B.

2,4-Dimethoxy-7,8-dimethylpyrimido[5,4-*b*]quinolin-10(5*H*)-one (XVII) (1.0 g., 0.003 mole) was added to 20 ml. of dimethylformamide containing 0.73 g. (0.0035 mole) of phosphorus oxychloride. The mixture was stirred at room temperature for 0.5 hour and filtered. The precipitate was washed with cold ether and dried to yield 0.889 g. (84%) of XIX. Crystallization from 1,2-dimethoxyethane gave 0.813 g. (77%) of yellow crystals, m.p. 251-253°, identical to the material prepared by Method A.

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