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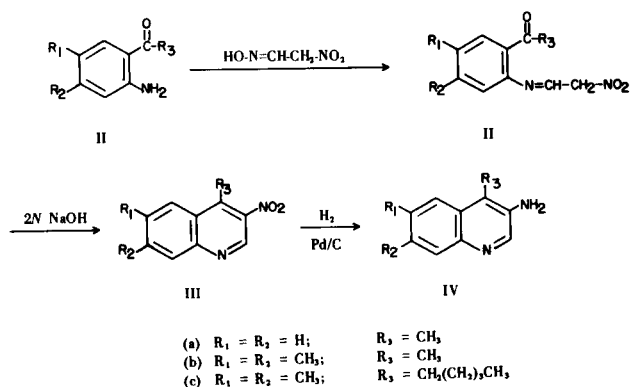
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A general method for the synthesis of 10-alkyl-substituted 10-deazaalloxazines (VIII) and the related chemistry are described. 4-Alkyl-substituted 3-aminoquinolines (IV) were reacted with benzoyl chloride and potassium cyanide in methylene chloride-water mixture to obtain Reissert compounds (V) which were hydrolyzed with a mixture of hydrobromic acid and acetic acid, and subsequently with 20% potassium hydroxide to give the corresponding 3-aminoquinaldic acids (VII). Cyclization with urea gave the 10-deazaalloxazines (VIII). Oxidation, hydroxylation and alkylation reactions of the 10-methyl derivatives (VIIIa,b) and of their quinaldic acid precursors are also reported.

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Previous attempts in this laboratory directed toward the synthesis of "9-deaza" analogs (2) of riboflavin by the introduction of side-chains into the 10 position of appropriately substituted pyrimido[5,4-*b*]quinolines (3) were unsuccessful because of the lack of reactivity of the functional groups (chloro, or oxo) at C<sub>10</sub> of this ring system (4). Therefore, a different synthetic approach was undertaken in the present work, using the 4-alkyl-substituted 3-aminoquinolines (IV) as starting materials. These compounds were obtained in excellent yields by catalytic reduction of the corresponding 3-nitroquinolines (III) which in turn, were synthesized according to the method of Schofield and Theobald (5) by reacting methazonic acid with the appropriate alkyl-*o*-amino-phenylketones (I) followed by cyclization of the nitroethylidene derivatives (II) (see Scheme 1).

Scheme 1

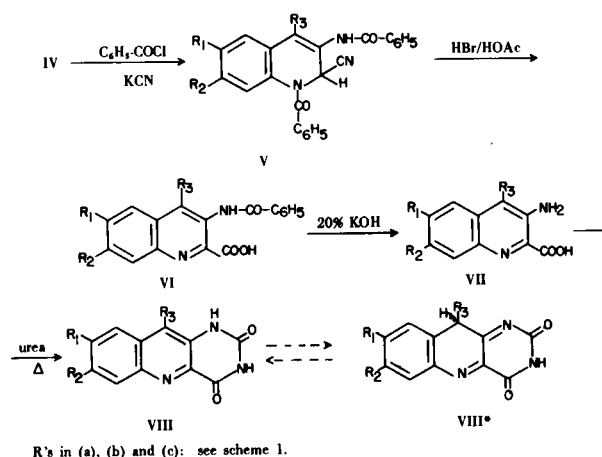


Reaction of the 3-aminoquinolines (IVa-c) with two molar equivalents of benzoyl chloride and an excess of potassium cyanide in methylene chloride-water mixture (6) gave excellent yields of the corresponding Reissert compounds with simultaneous benzoylation of the 3-amino group (Va-c). The advantages of the heterogeneous methylene chloride-water solvent system for the preparation of various Reissert compounds were previously

discussed by Popp and coworkers (who also found that quinolines with electron-donating substituents generally gave higher yields) (6). In agreement with the observation of Cobb and McEwen (7), the infrared spectra of the Reissert compounds did not show the characteristic absorption band of the nitrile group in the 2200-2400 cm<sup>-1</sup> range.

The hydrolysis of the Reissert compounds presented considerable difficulties. Finally a 1:1 mixture of 48% aqueous hydrobromic acid and acetic acid (8) gave satisfactory yields of the corresponding 3-benzamido-2-quinaldic acids (VIa-c) which were further hydrolyzed with 20% aqueous potassium hydroxide-ethanol to the free 3-amino derivatives (VIIa-c). Cyclization of the 3-amino-2-quinaldic acids with urea under fusion conditions (9) gave the "9-deazaflavins" (VIIIa-c) (see Scheme 2).

Scheme 2



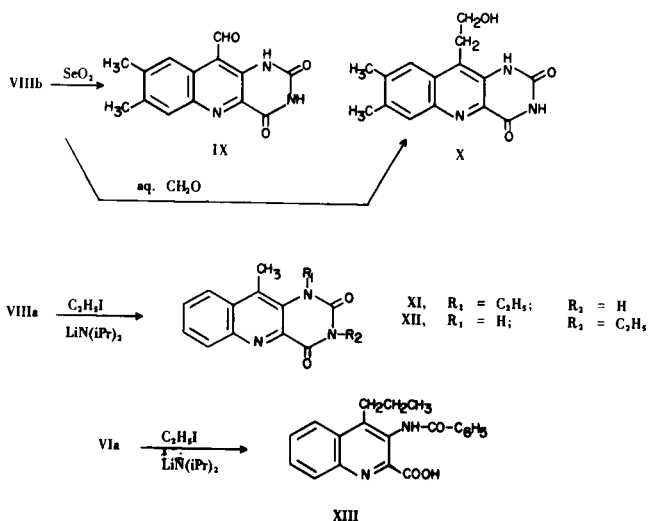
R's in (a), (b) and (c): see scheme 1.

The infrared spectra of these products showed characteristic absorption bands for the NH groups, and the nmr spectra contained the expected signals for the xylene and side-chain protons. In the case of VIIIa and VIIIb,

the 10-methyl protons appeared as a singlet at  $\delta$  2.72, indicating that the central ring had the aromatic structure shown in VIII and that the "flavin-type" tautomeric form (VIII\*) was absent. This might have been expected, particularly in view of the synthetic scheme. Also the ultraviolet and visible spectra failed to show the characteristic long-wave absorption peaks of the "transannular"-conjugated system (see VIII\*) of flavins. Thus, the heterocyclic ring system of the 10-alkyl-substituted pyrimido[5,4-*b*]quinolines appears to be analogous to the alloxazines rather than to that of the isoalloxazines (or flavins) with respect to its electronic configuration.

The 10-methyl group of VIIIb showed the expected reactivity of the  $\gamma$ -methyl substituent of a pyrimidine ring in that it could be selectively oxidized with selenium dioxide to the aldehyde IX, or hydroxymethylated with 38% aqueous formaldehyde (10) to the "9-deazahydroxyethylflavin" X, in very good yields. However, attempts to carry out an aldol-type condensation reaction with other aliphatic or aromatic aldehydes, using various solvents with or without base catalysts, were unsuccessful, probably due in part to the poor solubility of VIIIb and in part to the delocalization of the negative charge of its anionic species. Attempts to extend the 10-methyl "side-chain" of a VIIIa by alkylation with ethyl iodide in the presence of *n*-butyllithium or lithium diisopropylamide (generated *in situ*) led only to the N<sub>1</sub>- or N<sub>3</sub>-ethyl derivative (XI or XII). When the same reaction was applied to the quinaldic acid intermediate VIa, the 4-propyl derivative XIII was obtained. Although this method could be used for the lengthening of the side-chain of VIIIa or b, the introduction of the desired 10-alkyl moieties at an earlier stage of the synthetic scheme (see synthesis of Ic, Experimental) was found to give better results.

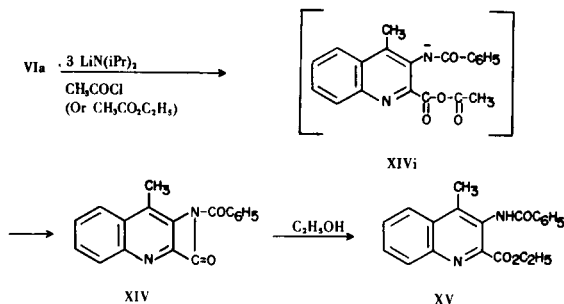
Scheme 3



It is interesting to note that when 3-benzamido-4-methyl-2-quinaldic acid (VIa) was treated with three molar equivalents of lithium diisopropylamide followed

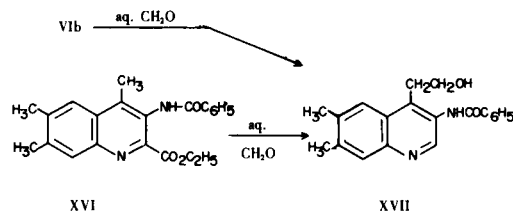
by an excess of either acetyl chloride or ethyl acetate, the  $\beta$ -lactam derivative XIV was obtained. The structural assignment of this compound was based on its nmr and ir spectra (11) and on its facile ring opening reaction with ethanol to give XV. It is conceivable that the formation of XIV proceeded *via* the intermediate XIVi.

Scheme 4



Another unexpected reaction, decarboxylation, occurred when either VIb or its ethyl ester (XVI) was heated with aqueous formaldehyde solution to give the 4-hydroxyethyl derivative XVII as the only crystalline product. It is possible that the decarboxylation of XVI was preceded by ester hydrolysis caused by the presence of formic acid in the formaldehyde reagent. Attempts to react VIb with other aldehydes were unsuccessful. The 4-methyl group of the ethyl ester XVI as well as that of the nitroquinoline precursor IIIb could be oxidized with selenium dioxide to the corresponding aldehydes (in a similar manner as the 10-methyl group of VIIIb).

Scheme 5



## EXPERIMENTAL

All melting points were recorded by the capillary tube method on a Mel-Temp and are uncorrected. Ultraviolet spectra were recorded on Gilford 2400 and Beckman DB-G Spectrophotometer in compressed potassium bromide discs. Pmr spectra were recorded on a Varian A-60 Spectrophotometer and the chemical shifts are expressed as parts per million from tetramethylsilane as an internal standard in the solvent indicated except with trifluoroacetic acid solvent for which tetramethylsilane in chloroform was used as an external standard. The detailed experimental procedures are described only for one representative of the three series of derivatives; the data for the other new compounds synthesized by analogous procedures are given in Table 1.

1-(2-Acetamido-4,5-dimethylphenyl)-1-hexanone.

Anhydrous aluminum chloride (14.4 g., 0.1 mole) was added portionwise to a mixture of 3,4-dimethylacetanilide (8.15 g., 0.05 mole) and hexanoyl chloride (7.37 g., 0.055 mole) in 150 ml.

Table I

Data for Preparation and Properties of Other New Compounds Synthesized by Procedures Analogous to Those Described in the Experimental

Compound No.	Yield %	Crystallizing solvent	M.p. °C	Formula	Anal. Calcd./Found		
					%C	%H	%N
IVa	known compound	(see reference 5)					
IVb		Methanol-water	155-157	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub>	77.38 77.35	7.58 7.62	15.04 15.00
Va	92	Ethanol-water	122-125	C <sub>25</sub> H <sub>18</sub> N <sub>3</sub> O <sub>2</sub>	76.52 76.15	4.69 4.69	10.71 10.47
Vc	(used without purification for further reaction step)						
VIa	78	Methanol	192-193	C <sub>18</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	70.50 70.28	4.60 4.76	9.15 8.99
VIc	74	Methanol-water	132-133	C <sub>23</sub> H <sub>26</sub> N <sub>2</sub> O <sub>3</sub>	70.88 70.59	6.81 6.37	6.74 6.86
VIIa	66	Methanol	212-213	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	65.34 65.35	4.99 5.03	13.85 13.92
VIIc	68	Ethanol	215-217	C <sub>17</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub>	71.33 71.39	7.69 7.79	9.79 9.33
VIIIa	71	Methanol	385 dec.	C <sub>12</sub> H <sub>9</sub> N <sub>3</sub> O	63.43 63.28	4.00 4.07	18.49 18.49
VIIIc	75	Acetic Acid	360-365	C <sub>18</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub>	69.45 69.12	6.75 6.87	13.50 13.32

of dry carbon disulfide and then the reaction mixture was refluxed on a steam-bath for one hour. After cooling, the solvent was decanted, and the residue poured into an ice-water mixture, and extracted with 300 ml. of chloroform. The solvent was evaporated *in vacuo*. Recrystallization from ethanol gave 10.0 g. (77%) of white leaflet crystals, m.p. 80-81°; *uv*  $\lambda$  max (ethanol): 240 nm ( $\epsilon$ , 34,250), 265 (16,420), 273 (15,140); *ir* (potassium bromide): 3225 (NH), 1695 (C=O), and 1640 cm<sup>-1</sup> (NHCO); *nmr* (deuteriochloroform):  $\delta$  0.93 (3H, t, J = 7, CH<sub>3</sub>), 1.17-2.00 (6H, m, CH<sub>2</sub>), 2.22 (3H, s, CH<sub>3</sub>), 2.28 (3H, s, CH<sub>3</sub>), 2.31 (3H, s, CH<sub>3</sub>), 3.33 (2H, t, CH<sub>2</sub>), 7.90 (1H, s, Ar-H), 8.60 (1H, s, Ar-H), and 11.80 (1H, broad, NHCO).

*Anal.* Calcd. for C<sub>16</sub>H<sub>23</sub>NO<sub>2</sub>: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.39; H, 8.98; N, 5.32.

#### 1-(2-Amino-4,5-dimethylphenyl)-1-hexanone (Ic).

A mixture of 1-(2-acetamido-4,5-dimethylphenyl)-1-hexanone (2.16 g., 0.01 mole) and 30 ml. of hydrochloric acid-acetic acid-water (1:1:1) was heated for one hour at 110° and poured into an ice-water mixture. The white precipitate formed was collected and recrystallized from a methanol-water mixture to yield 1.5 g. (68%) of white crystals, m.p. 65-67°; *uv*  $\lambda$  max (ethanol): 232 nm ( $\epsilon$ , 27,180) and 263 (16,390); *ir* (potassium bromide): 3480 and 3360 (NH<sub>2</sub>) and 1622 cm<sup>-1</sup> (C=O); *nmr* (deuteriochloroform):  $\delta$  0.92 (3H, t, J = 7, CH<sub>3</sub>), 1.17-2.00 (6H, m, CH<sub>2</sub>), 2.20 (6H, s, CH<sub>3</sub>), 2.94 (2H, t, J = 7, CH<sub>2</sub>), 5.97 (2H, b, NH<sub>2</sub>), 6.52 (1H, s, Ar-H), and 7.56 (1H, s, Ar-H).

*Anal.* Calcd. for C<sub>14</sub>H<sub>21</sub>NO: C, 76.71; H, 9.59; N, 6.39. Found: C, 76.36; H, 9.63; N, 6.28.

#### 1-[2-(2-Nitroethylideneamino)-4,5-dimethylphenyl]-1-hexanone (IIc).

Methazonic acid (2.08 g., 0.01 mole) (prepared from 2.44 g. of nitromethane and 2.44 g. of sodium hydroxide in 15 ml. of water) was added rapidly to a mixture of 2.1 g. (0.01 mole) of

Ic, 30 ml. of acetone, 50 ml. of water, and 6 ml. of concentrated hydrochloric acid. The reaction mixture was stirred for 15 hours and the resulting yellow precipitate was collected. After recrystallization from ethanol, 2.3 g. (79%) of yellow crystals were obtained, m.p. 146-148°; *uv*  $\lambda$  max (ethanol): 266 nm ( $\epsilon$ , 13,900) and 234 (16,570); *ir* (potassium bromide): 1622 (C=O), and 1365 cm<sup>-1</sup> (NO<sub>2</sub>); *nmr* (DMSO-d<sub>6</sub>):  $\delta$  0.75 (3H, t, J = 7, CH<sub>3</sub>), 0.90-1.70 (6H, m, CH<sub>2</sub>), 2.00 (3H, s, CH<sub>3</sub>), 2.01 (3H, s, CH<sub>3</sub>), 2.87 (2H, t, CH<sub>2</sub>), 6.52 (2H, d, J = 6.5, N=CH-CH<sub>2</sub>), 7.58 (1H, s, Ar-H), 7.66 (1H, s, Ar-H), 7.86 (1H, t, J = 6.5, N=CH).

*Anal.* Calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C, 66.21; H, 7.59; N, 9.66. Found: C, 66.22; H, 7.73; N, 9.53.

#### 3-Nitro-4-pentyl-6,7-dimethylquinoline (IIIc).

A mixture of 2.9 g. (0.01 mole) IIc and 20 ml. of 2*N* sodium hydroxide was heated for 5 minutes at 100-110° and then cooled to room temperature. The oily compound solidified; recrystallization from methanol gave 2.45 g. (84%) of pale yellow crystals, m.p. 108-110°; *uv*  $\lambda$  max (ethanol): 360 nm ( $\epsilon$ , 22,590); *ir* (potassium bromide): 1340 cm<sup>-1</sup> (NO<sub>2</sub>); *nmr* (deuteriochloroform):  $\delta$  0.93 (3H, b, CH<sub>3</sub>), 1.20-2.00 (6H, m, CH<sub>2</sub>), 2.52 (6H, s, CH<sub>3</sub>), 3.28 (2H, b, CH<sub>2</sub>), 7.99 (2H, s, Ar-H), and 9.22 (1H, s, Ar-H).

*Anal.* Calcd. for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>: C, 70.59; H, 7.35; N, 10.29. Found: C, 70.30; H, 7.49; N, 10.18.

#### 3-Amino-4-pentyl-6,7-dimethylquinoline (IVc).

A mixture of 15 g. (0.055 mole) of IIIc and 750 mg. of palladium-on-carbon (10%) in 200 ml. of absolute methanol was hydrogenated for 1.5 hours and after filtration, the filtrate was evaporated under reduced pressure to yield 13.4 g. (quantitative) of yellowish crystals, m.p. 130-131°; *uv*  $\lambda$  max (ethanol): 234 nm ( $\epsilon$  42,010); *ir* (potassium bromide): 3464 and 3342 cm<sup>-1</sup> (NH<sub>2</sub>); *nmr* (deuteriochloroform):  $\delta$  0.93 (3H, b, CH<sub>3</sub>), 1.20-2.00 (6H, m, CH<sub>2</sub>), 2.90 (2H, b, CH<sub>2</sub>), 3.92 (2H, b, NH<sub>2</sub>), 7.77

(1H, s, Ar-H), 7.95 (1H, s, Ar-H), and 8.61 (1H, s, Ar-H).

*Anal.* Calcd. for  $C_{16}H_{22}N_2$ : C, 79.35; H, 9.09; N, 11.57. Found: C, 79.21; H, 9.16; N, 11.52.

#### 1-Benzoyl-3-benzamido-4,6,7-trimethyl-1,2-dihydroquinoline (Vb).

Benzoyl chloride (2.81 g., 0.02 mole) was added to a stirred mixture of IVb (1.72 g., 0.01 mole) in 20 ml. of methylene chloride and potassium cyanide (1.95 g., 0.03 mole) in 8 ml. of water. After an additional 6-8 hours stirring, the two layers were separated and the water layer was extracted with 10 ml. of methylene chloride. The combined methylene chloride extract was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide and then finally with water. The methylene chloride solution was dried over anhydrous sodium sulfate and the solvent evaporated *in vacuo* to yield 3.4 g. (80%) of brownish amorphous crystals, m.p. 135-138° (ethanol-water); *uv*  $\lambda$  max (ethanol): 230 nm ( $\epsilon$ , 29,370), 270 (sh) (17,660); *ir* (potassium bromide) 3280  $cm^{-1}$  (NH) and 1640 (C=O); *nmr* (deuteriochloroform):  $\delta$  1.98 (3H, s, CH<sub>3</sub>), 2.12 (3H, s, CH<sub>3</sub>), 2.23 (3H, s, CH<sub>3</sub>), 6.56 (1H, s, Ar-H), 6.90 (1H, s, Ar-H), 7.16-8.35 (10H, m, Ar-H), and 8.56 (1H, s, CH-CN).

*Anal.* Calcd. for  $C_{27}H_{23}N_3O_2$ : C, 76.94; H, 5.50; N, 9.97. Found: C, 77.03; H, 5.66; N, 9.87.

#### 3-Benzamido-4,6,7-trimethyl-2-quinaldic Acid (VIb).

A mixture of Vb (6.0 g.) and 80 ml. of 46% hydrogen bromide-acetic acid (1:1) was heated at 95-100° for one hour and poured into an ice-water mixture, and then adjusted to pH 2-3 with sodium hydroxide solution. The brownish crystals formed were collected and recrystallized from methanol to yield 4.0 g. (84%), m.p. 187-189° dec.; *uv*  $\lambda$  max (ethanol): 235 nm ( $\epsilon$ , 35,840), 250 (sh) (31,230); *ir* (potassium bromide): 3100-2500 (CO<sub>2</sub>H) and 1665  $cm^{-1}$ ; *nmr* (DMSO-*d*<sub>6</sub>):  $\delta$  2.44 (3H, s, CH<sub>3</sub>), 2.46 (3H, s, CH<sub>3</sub>), 7.09 (1H, b, NHCO), 7.50-8.20 (7H, m, Ar-H), and 10.50 (1H, s, CO<sub>2</sub>H).

*Anal.* Calcd. for  $C_{26}H_{18}N_2O_3$ : C, 71.84; H, 5.43; N, 8.38. Found: C, 71.92; H, 5.52; N, 8.29.

#### 3-Amino-4,6,7-trimethyl-2-quinaldic Acid (VIIb).

A mixture of VIb (1.0 g., 0.003 mole), ethanol (10 ml.), and 20 ml. of 20% aqueous potassium hydroxide was refluxed for 24 hours. After cooling to room temperature, the above mixture was neutralized with concentrated hydrochloric acid (pH 6-7). The resulting orange-yellow precipitate was collected and recrystallized from methanol to yield 0.6 g. (87%), m.p. 238-239° dec.; *uv*  $\delta$  (ethanol): 233 nm ( $\epsilon$ , 22,700) and 256 (35,040); *ir* (potassium bromide): 3400 and 3300 (NH<sub>2</sub>), 2900-2500 (CO<sub>2</sub>H), and 1660  $cm^{-1}$  (C=O); *nmr* (TFA)  $\delta$  2.25 (6H, s, CH<sub>3</sub>), 2.65 (3H, s, CH<sub>3</sub>), 7.85 (2H, s, Ar-H).

*Anal.* Calcd. for  $C_{13}H_{14}N_2O_2$ : C, 67.81; H, 6.13; N, 12.17. Found: C, 67.70; H, 6.21; N, 12.09.

#### 7,8,10-Trimethylpyrimido[5,4-*b*]quinoline-2,4(1*H*,3*H*)dione ("9-Deazalumiflavin") (VIIIb).

A mixture of VIIb (230 mg., 0.001 mole) and urea (500 mg.) was ground in a mortar and heated at 180-190° for 30 minutes. The reaction mixture started to melt at 150-160°. After cooling the mixture to room temperature, 10 ml. of 2*N* sodium hydroxide solution was added to break the lumps and dissolve by-products of urea. The resulting yellow precipitate was filtered, washed with 2*N* sodium hydroxide solution, and then recrystallized from methanol to yield 236 mg. (93%) of yellow crystals, m.p. ca. 418 dec.; *uv*  $\lambda$  max (ethanol): 258 nm ( $\epsilon$ , 158,000), 327 (sh) (42,700); *ir* (potassium bromide): 3430, 3195, and 3070 (NH), 1725 (NHCO), and 1690  $cm^{-1}$  (NHCO); *nmr* (TFA)  $\delta$  2.50 (6H, s, CH<sub>3</sub>), 2.72 (3H, s, CH<sub>3</sub>), 7.90 (2H, s, Ar-H).

*Anal.* Calcd. for  $C_{14}H_{13}N_3O_2 \cdot H_2O$ : C, 61.54; H, 5.40; N, 15.38. Found: C, 61.50; H, 5.58; N, 15.18.

#### 7,8-Dimethylpyrimido[5,4-*b*]quinolin-2,4(1*H*,3*H*)dione-10-aldehyde (IX).

Selenium dioxide (222 mg., 0.002 mole) was added to a hot acetic acid (100 ml.) solution of VIIIb (255 mg., 0.001 mole), and the reaction mixture heated for 4 hours at 110-120°. After filtering the black precipitate (metallic selenium), acetic acid was evaporated to yield 250 mg. (93%) of IX, as brown leaflet crystals, m.p. 350-353°; *uv*  $\lambda$  max (ethanol): 228 nm ( $\epsilon$ , 24,630), 254 (46,180), 260 (44,700); *ir* (potassium bromide): 3220 and 3100 (NH), 2810 (CHO), 1720 (NHCO), 1700 (CHO), and 1660  $cm^{-1}$  (NHCO); *nmr* (DMSO-*d*<sub>6</sub>):  $\delta$  2.44 (6H, s, CH<sub>3</sub>), 7.86 (1H, s, Ar-H), 8.52 (1H, s, Ar-H), 10.97 (1H, s, CHO), 11.92 (1H, b, CONH).

*Anal.* Calcd. for  $C_{14}H_{11}N_3O_3$ : C, 62.45; H, 4.09; N, 15.61. Found: C, 62.22; H, 4.14; N, 15.46.

#### 7,8-Dimethyl-10-(2-hydroxyethyl)pyrimido[5,4-*b*]quinolin-2,4(1*H*,3*H*)dione (X).

A mixture of VIIIb (255 mg., 0.001 mole) and 25 ml. of formaldehyde solution (36% aqueous) was heated for 24 hours at 110-120°, and then the solvent was removed *in vacuo*. Water was added to the residue in order to induce precipitation and the resulting grey solid was recrystallized from acetic acid to yield 220 mg. (77%), m.p. > 400; *uv*  $\lambda$  max (ethanol): 255 nm ( $\epsilon$ , 54,100); *ir* (potassium bromide): 3375 and 3206 (NH), 1710 (NHCO) and 1660  $cm^{-1}$  (NHCO); *nmr* (TFA):  $\delta$  2.25 (6H, s, CH<sub>3</sub>), 3.63 (2H, broad t, CH<sub>2</sub>), 3.97 (2H, broad t, CH<sub>2</sub>), 7.92 (2H, s, Ar-H).

*Anal.* Calcd. for  $C_{15}H_{15}N_3O_3 \cdot 1.5/H_2O$ : C, 61.64; H, 5.48; N, 14.38. Found: C, 61.91; H, 5.43; N, 14.18.

#### 1-Ethyl (or, 3-Ethyl)-10-methylpyrimido[5,4-*b*]quinolin-2,4(1*H*,3*H*)dione (XI or XII).

Diisopropylamine (0.6 g., 0.006 mole) was dissolved in 20 ml. of dry THF and cooled to 0°. *n*-Butyllithium (2.8 ml., 0.006 mole in 2.38 *M* hexane solution) was added to the above solution and then stirred for 10 minutes under nitrogen atmosphere. To the resulting solution of lithium diisopropylamide a suspension of VIIIa (0.454 g., 0.002 mole) in 10 ml. of dry THF, and 5 ml. of hexamethylphosphoramide was added slowly. After stirring for 15 minutes, 0.312 g. (0.002 mole) of ethyl iodide in 5 ml. of THF was added. The reaction mixture was stirred overnight and neutralized with concentrated hydrochloric acid. The mixture was evaporated to dryness, water was added to give a precipitate, which was filtered and washed with ether. Recrystallization from THF gave 0.4 g. (60%), m.p. ca. 237°; *uv*  $\lambda$  max (ethanol): 227 nm ( $\epsilon$ , 26,200) and 248 (61,100); *nmr* (TFA)  $\delta$  1.22 (3H, t, CH<sub>3</sub>), 3.0 (3H, s, CH<sub>3</sub>), 4.16 (2H, b, CH<sub>2</sub>), and 7.8-8.4 (4H, m, Ar-H).

*Anal.* Calcd. for  $C_{14}H_{13}N_3O_2$ : C, 65.87; H, 5.13; N, 16.46. Found: C, 65.95; H, 5.32; N, 16.35.

#### 3-Benzamido-4-propyl-2-quinaldic Acid (XIII).

Diisopropylamine (0.6 g., 0.006 mole) was dissolved in 20 ml. of dry THF and cooled to 0°. *n*-Butyllithium (2.8 ml., 0.006 mole in 2.38 *M* hexane solution) was added, and the mixture stirred for 10 minutes under nitrogen atmosphere. To the resulting solution of lithium diisopropylamide a suspension of VIa (0.612 g., 0.002 mole) in 20 ml. of dry THF, was added slowly, at ca. 0°. During the addition, the reaction mixture turned red. Hexamethylphosphoramide (5 ml.) and ethyl iodide (0.311 g., 0.002 mole) were added to the solution, and the mixture stirred for 2 hours at 0°, and then for 18 hours at room temperature. The

solvent was evaporated *in vacuo*, cold water added to the residue and the precipitate collected. Recrystallization from chloroform yielded 0.5 g. (94%), m.p. 179-180.5° dec.;  $\text{uv } \lambda \text{ max}$  (ethanol): 234 nm ( $\epsilon$ , 36,400) and 237 (sh) (24,300); ir (potassium bromide): 3230 (NH) and 1665  $\text{cm}^{-1}$  (C=O); nmr (deuteriochloroform):  $\delta$  0.93 (3H, t, J = 7, CH<sub>3</sub>), 1.62 (2H, m, CH<sub>2</sub>), 3.25 (2H, m, CH<sub>2</sub>), and 7.25-8.4 (4H, m, Ar-H).

*Anal.* Calcd. for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C, 70.69; H, 5.63; N, 8.69. Found: C, 70.15; H, 5.43; N, 8.44.

#### 1-Benzoyl-2-oxo-8-methylazetidino[3,4-*b*]quinoline (XIV).

Compound VIa (306 mg., 0.001 mole) was dissolved in 20 ml. of a mixture of THF/HMPA (1:1) and in a dry box under nitrogen atmosphere lithium diisopropylamide (Aldrich) was added until the solution became red. The above solution was stirred for 10 minutes and then 1 ml. of acetyl chloride (or ethyl acetate) was added at -10° to 0°. After stirring for 2 hours, the mixture was allowed to warm to room temperature and the precipitate (white needles) formed was filtered. Recrystallization (below 40°) from a mixture of ethanol/chloroform gave 0.2 g. (60%) of white micro-needle crystals, m.p. 253-255°;  $\text{uv } \lambda \text{ max}$  (ethanol): 240 nm ( $\epsilon$ , 69,000); ir (potassium bromide): 1765 ( $\beta$ -lactam) and 1628  $\text{cm}^{-1}$  (NCOAr); nmr (deuteriochloroform):  $\delta$  3.0 (3H, s, CH<sub>3</sub>) and 7.26-8.40 (9H, m, Ar-H).

*Anal.* Calcd. for C<sub>18</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>: C, 74.99; H, 4.20; N, 9.71. Found: C, 74.87; H, 4.42; N, 9.68.

#### 3-Benzamido-4-methyl-2-quinaldic Acid Ethylester (XV).

Compound XIV was recrystallized with boiling ethanol to yield white crystals, m.p. 185-187°;  $\text{uv } \lambda \text{ max}$  (ethanol): 242 nm ( $\epsilon$ , 34,900); ir (potassium bromide): 3370 (NHCO), and 1695  $\text{cm}^{-1}$  (ester); nmr:  $\delta$  1.40 (3H, t, J = 6.5, Et), 8.55 (3H, s, CH<sub>3</sub>), 6.42 (2H, b, J = 6.5, Et) and 7.12-8.12 (9H, m, Ar-H).

*Anal.* Calcd. for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.60; H, 5.50; N, 8.39.

#### 3-Benzamido-4,6,7-trimethyl-2-quinaldic Acid Ethylester (XVI).

A mixture of 3-benzamido-4,6,7-trimethyl-2-quinaldic acid (VIb) (1.0 g., 0.003 mole), 150 ml. of absolute ethanol and 0.2 ml. of concentrated sulfuric acid was refluxed for 15 hours in a Soxhlet apparatus with 3 Å molecular sieves, cooled to room temperature and the mixture evaporated to dryness *in vacuo*. Water was added in order to induce crystal formation. After recrystallization from ethanol, 0.75 g. (81%) of colorless crystals were obtained, m.p. 198-200°;  $\text{uv } \lambda \text{ max}$  (ethanol): 244 nm ( $\epsilon$ , 51,450); ir (potassium bromide): 3370 (NH), 1700 (CO<sub>2</sub>Et), and 1675  $\text{cm}^{-1}$  (NHCO); nmr (deuteriochloroform):  $\delta$  1.40 (3H, t, J = 7, CH<sub>3</sub>), 2.43 (6H, s, CH<sub>3</sub>), 2.53 (3H, s, CH<sub>3</sub>), 4.42 (2H, q, J = 7, CH<sub>2</sub>), 7.20-8.00 (7H, m, Ar-H), and 9.73 (1H, b, NH).

*Anal.* Calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C, 72.93; H, 6.08; N, 7.73. Found: C, 72.88; H, 6.13; N, 7.74.

#### 3-Benzamido-4-(2-hydroxyethyl)-6,7-dimethylquinoline (XVII).

A mixture of the quinaldic acid ethyl ester XVI (722 mg., 0.002 mole), formaldehyde solution (20 ml., 36% aqueous) and 10 ml. of ethanol was heated at 115-120° for 38 hours. The reaction mixture was cooled in a refrigerator overnight and the white crystals formed were collected. A second crop of crystals was obtained by adding water to the filtrate. The combined crystals were recrystallized from methanol to yield 0.52 g. (80%), m.p. 221-222°. This compound was also obtained by treating quinaldic acid VIb with formaldehyde (46% of yield) under similar conditions;  $\text{uv } \lambda \text{ max}$  (ethanol): 240 nm ( $\epsilon$ , 40,180) and 260 (26,320); ir (potassium bromide): 3600-3400 (broad, OH) 1670  $\text{cm}^{-1}$  (NHCO); nmr (DMSO-d<sub>6</sub>):  $\delta$  2.42 (6H, s, CH<sub>3</sub>), 3.10-3.30 (2H, b, CH<sub>2</sub>), 3.55-3.88 (2H, b, CH<sub>2</sub>), 5.28 (1H, b, OH), 7.40-8.07 (7H, m, Ar-H), 8.78 (1H, s, Ar-H), and 10.20 (1H, s, NH).

*Anal.* Calcd. for C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>·1/2H<sub>2</sub>O: C, 72.95; H, 6.38. Found: C, 72.94; H, 6.43; N, 8.48.

#### REFERENCES AND NOTES

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(2) While Chemical Abstracts lists riboflavin as 7,8-dimethyl-10-*D*-ribitylisoalloxazine, and other isoalloxazines are numbered similarly, the majority of the riboflavin literature uses an alternative system of nomenclature wherein riboflavin is named 6,7-dimethyl-9-*D*-ribitylisoalloxazine. The term "9-deazaflavin" is used in this paper to avoid confusion with the "10-deazariboflavin" of Cheng *J. Heterocyclic Chem.*, 7, 99 (1970) which by Chemical Abstracts nomenclature is 5-deazariboflavin.

(3) E. M. Levine, C. K. Chu, and T. J. Bardos, *J. Heterocyclic Chem.*, 14, 611 (1977).

(4) E. M. Levine and T. J. Bardos, *ibid.*, 9, 91 (1972).

(5) K. Schofield and R. S. Theobald, *J. Chem. Soc.*, 395 (1950).

(6) F. D. Popp, W. Blount, and P. McIvin, *J. Org. Chem.*, 26, 4930 (1961).

(7) L. Cobb and W. E. McEwen, *J. Am. Chem. Soc.*, 77, 5042 (1955).

(8) J. W. Davis, Jr., *J. Org. Chem.*, 24, 1691 (1959).

(9) G. H. Hitchings and R. K. Robins, U.S. Patent No., 833015 (1960).

(10) J. Heisenheimer, O. Finn and W. Schneider, *Ann. Chem.*, 420, 190 (1920).

(11) J. A. Moore in "The Chemistry of Heterocyclic Compounds", Vol. 19, Part 2, A. Weissberger, Ed., John Wiley and Sons, Inc., New York, N.Y., 1962, p. 117.