# Synthesis of 10-Deazariboflavin and Related 2,4-Dioxopyrimido[4,5-*b*]quinolines (1a)

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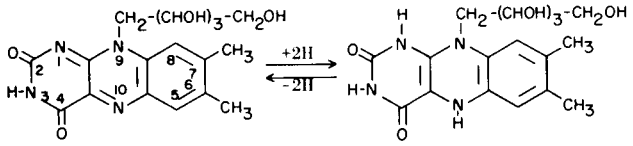
Condensation of substituted anthranilaldehydes with barbituric acid results in the formation of 2,4-dioxopyrimido[4,5-*b*]quinolines. Using this general synthetic approach, 7,8-dimethyl-2,4-dioxo-10-ribityl-2,3,4,10-tetrahydropyrimido[4,5-*b*]quinoline(10-deazariboflavin) was prepared by the condensation of barbituric acid with 4,5-dimethyl-*N*-ribitylanthranilaldehyde. The latter was obtained *in situ* by the treatment of 1-[4,5-dimethyl-*N*-(ribityl)anthraniloyl]-2-(*p*-toluenesulfonyl)hydrazine, prepared from 4,5-dimethylanthranilic acid with anhydrous sodium carbonate.

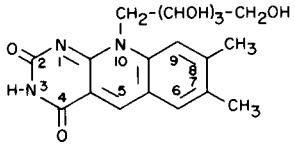
Riboflavin (I) is the active component of the oxidation-reduction enzyme flavin-adenine dinucleotide (FAD). Compounds possessing antiriboflavin activity are therefore expected to interfere with cellular metabolism wherein biological oxidation-reduction reactions are involved. This is reflected in the fact that many riboflavin antagonists were found to possess growth-inhibitory activity against a variety of biological systems (2-14). Systems with riboflavin deficiency also produced analogous results (15-20).

Although a number of acridine derivatives, such as mepacrine and acriflavine, have exhibited interesting biological activity, the activity is not due to acridine-riboflavin antagonism, as has been suggested (21-23). The arguments against the original thinking that acridine derivatives and riboflavin might be attracted by the same type of biological receptor are based on (a) $pK_a$ measurements and (b) the acridine ring system is flat because of its complete conjugation, whereas riboflavin is not (in the riboflavin molecule, the pyrimidine portion makes almost a right angle with the benzene portion) (24). The reported metabolic reversal of riboflavin by acridines is also by no means conclusive (24).

It therefore appears that in searching for more effective riboflavin antagonists as potential chemotherapeutic agents, the structure should be designed in such a way that conformation of molecules must also be considered. The synthesis of 10-deazariboflavin (II), wherein the $N_{10}$ of riboflavin is replaced by a -CH= linkage, was therefore initiated in our laboratory (25). Since biological activities of riboflavin are attributed to its *in vivo* oxidation-reduction reactions involving reversible 1,4-addition of hydrogen atoms to the conjugated system (between $N_1$ and $N_{10}$) of the isoalloxazine ring, similar reaction might be expected to occur with 10-deazariboflavin.




I

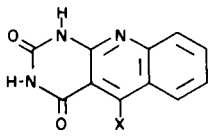



II

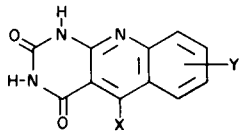
The redox potential for riboflavin is -0.185*v* at *p*H 7. Relative minor structural changes of riboflavin often significantly alter the redox potential. It has been suggested that the change in redox potential is mainly responsible for the antiriboflavin action of some analogs of riboflavin (26). Compound II, therefore, might be expected to be a potential riboflavin antagonist with interesting biological activities.

The parent compound of II, 2,4-dioxopyrimido[4,5-*b*]-quinoline (IIIa), has been synthesized by several groups of investigators (23,27-30) by the condensation of *o*-aminobenzaldehyde (anthranilaldehyde) and barbituric acid. The inaccessibility and instability of substituted anthranilaldehydes has limited the scope of this preparation. King, King and Thompson (31) used isatin in place of anthranilaldehyde and prepared a number of 5-substituted 2,4-dioxotetrahydropyrimido[4,5-*b*]quinolines (IIIb-IIIe), but these authors were unable to either decarboxylate the carboxylic acid IIIc (to give IIIa) or to deaminate IIIe (to give IIIf). In our laboratory several analogous 5,7-disubstituted compounds (IV, Y = 7-$CH_3$, 7-Br) were prepared

and similar difficulties in decarboxylation and deamination were encountered.



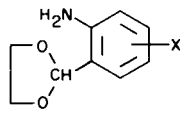
III



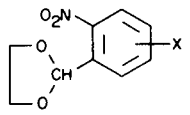
IV

a) X = H
b) X = COOR
c) X = COOH
d) X = $CONH_2$
e) X = $NH_2$
f) X = OH

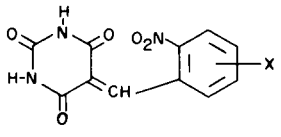
Baumgarten *et.al.* (32) have successfully utilized the acetal (V, X = H) of anthranilaldehyde in their cinnoline synthesis. This acetal, prepared by the treatment of *o*-nitrobenzaldehyde with ethylene glycol followed by reduction, was readily condensed with barbituric acid to yield IIIa. This reaction can be achieved with or without the use of mineral acid. The success of this synthetic route encouraged us to examine the possibility of preparing the substituted 2,4-dioxopyrimido[4,5-*b*]quinolines (IV, X = H). Accordingly, 5-chloro-2-nitrobenzaldehyde (33) was converted to the corresponding ethylene glycol acetal (VI, X = 5-Cl) in good yield. However, catalytic reduction of the acetal gave only highly colored, polymeric material rather than the desired amino derivative (V, X = 5-Cl) even though a theoretical amount of hydrogen was rapidly absorbed during hydrogenation. Apparently in this case the aldehyde group was not well protected by the acetal formation and underwent further undesired reactions during the reduction. Thus it negates the possible use of this approach as a general synthetic procedure of substituted 2,4-dioxopyrimido[4,5-*b*]quinolines.



V



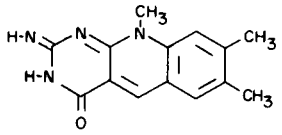
VI



VII

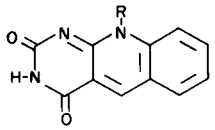
Speer and Dabovich (34) reported that 5-benzalbarbituric acid was formed by the condensation of benzaldehyde and barbituric acid. When substituted 2-nitrobenzaldehyde was refluxed with barbituric acid, an 80-90% yield of 5-(5-substituted-2-nitrobenzal)barbituric acid (VII) was obtained. Reductive cyclization of VII by means of sodium hydrosulfite yielded a crude product which contained the desired substituted 2,4-dioxopyrimido[4,5-*b*]-quinoline (IV, X = H). The tedious purification and consequently low yield of the final product, again, prevented this method from becoming a practical synthesis of compounds of this type.

Synthesis of 2-imino-4-oxo-7,8,10-trimethyl-2,3,4,10-tetrahydropyrimido[4,5-*b*]quinoline (VIII), a compound closely related to 10-deazariboflavin (II), was accomplished by Reist *et.al.* (35) by a multi-step synthesis. However, these investigators were unable to convert VIII to the corresponding dioxo derivative with either nitrous acid and/or mineral acid.



VIII

In 1962, Barlin (36) reported a modified McFayden and Stevens' procedure (37) for converting anthranilic acids to the corresponding anthranilaldehydes *via* the tosylated hydrazide intermediates. Utilizing this method, *N*-methyl anthranilaldehyde (35) and 4,5-dimethylanthranilaldehyde were prepared and condensed with barbituric acid to yield 2,4-dioxo-10-methyl-2,3,4,10-tetrahydropyrimido[4,5-*b*]quinoline (IXa) and 7,8-dimethyl-2,4-dioxotetrahydropyrimido[4,5-*b*]quinoline, (IV, X = H, Y = 7,8-$(CH_3)_2$), respectively. By an analogous procedure, 2,4-dioxo-10-(β-hydroxyethyl)-2,3,4,10-tetrahydropyrimido[4,5-*b*]quinoline (IXb) was readily synthesized from methyl *N*-(β-hydroxymethyl)anthranilate (38).

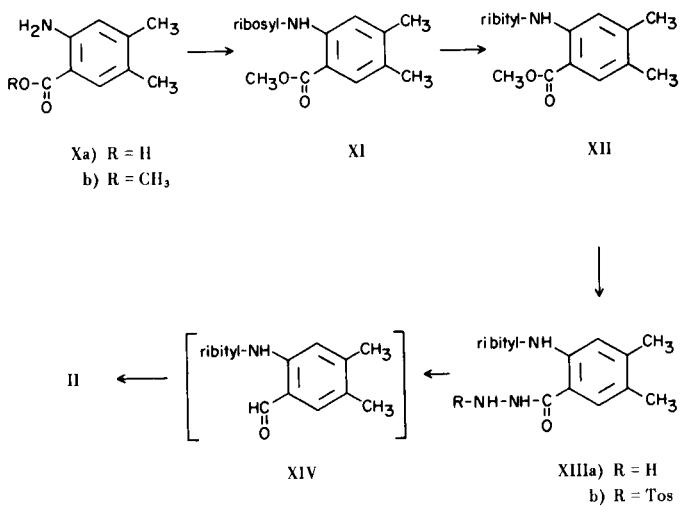


IXa) R = $CH_3$
b) R = $CH_2CH_2OH$
c) R = ribityl

4,5-Dimethylanthranilic acid (Xa), originally prepared by Baker *et.al.* (39), was used for the synthesis of 7,8-dimethyl-2,4-dioxo-10-ribityl-2,3,4,10-tetrahydropyrimido-[4,5-*b*]quinoline (10-deazariboflavin, II). Esterification of Xa in anhydrous methanolic hydrogen chloride gave an 85% yield of the methyl ester Xb. Condensation of Xb with one equivalent of D-ribose yielded methyl 4,5-dimethyl-*N*-ribosylanthranilate, XI. Catalytic reduction

of the ribosyl derivative, as in the case of riboflavin synthesis (40-42), smoothly yielded the corresponding *N*-ribityl derivative XII. Subsequent conversion of XII into the corresponding hydrazide XIIIa was readily accomplished by the treatment of XII with boiling aqueous hydrazine. *p*-Toluenesulfonyl chloride in pyridine converted XIIIa to the tosylated derivative XIIIb. The latter was treated with anhydrous sodium carbonate to give 4,5-dimethyl-*N*-ribitylanthranilaldehyde XIV, which was condensed, without purification, with barbituric acid under acidic conditions (23,27) to yield the desired 10-deazariboflavin (II).

2,4-Dioxo-10-ribityl-2,3,4,10-tetrahydropyrimido[4,5-*b*]quinoline (IXc) was synthesized from anthranilic acid by a similar procedure.




## EXPERIMENTAL

All melting points were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2-spectrophotomer.

2,4-Dioxo-7-methyl-1,2,3,4-tetrahydropyrimido[4,5-*b*]quinoline-5-carboxylic Acid (IV, X = COOH, Y = $CH_3$).

The procedure of King *et.al.* (31) was adapted for this preparation. A suspension of 32 g. (0.25 mole) of barbituric acid and 20.2 g. (0.125 mole) of 5-methylisatin in 200 ml. of 2*N* hydrochloric acid was refluxed while stirring for 30 minutes. During this time the initial red coloration faded and a tan solid separated. The reaction mixture was chilled and the intermediate 3-bis-(barbityl)-5-methyl-2-oxoindole was collected by filtration. This was placed in an evaporating dish, covered with 200 ml. of concentrated hydrochloric acid and heated on a steam bath for 3 hours. It was then added to 750 ml. of water and the precipitated material was collected by filtration and washed with water, ethanol and ether. The product was purified by dissolving the solid in dilute potassium hydroxide and reprecipitated with hydrochloric acid to give 22 g. (65% yield) of product, m.p. 323-324° dec. An analytical sample was prepared by recrystallization from glacial acetic acid, m.p. 336-338° dec.; λ max (*p*H 1) 222 (ε 26,000), 259 (ε 41,000), 314 (ε 8,700) and 365 mμ (ε 4,300); λ max (*p*H 11) 250 (ε 38,200), 298 (ε 7,800), 310 (ε 7,100) and 378 mμ (ε 4,300).

*Anal.* Calcd. for $C_{13}H_9N_3O_4 \cdot H_2O$: C, 54.0; H, 3.83; N, 14.5. Found: C, 54.1; H, 3.62; N, 14.6.

7-Bromo-2,4-dioxo-1,2,3,4-tetrahydropyrimido[4,5-*b*]quinoline-5-carboxylic Acid (IV, X = COOH, Y = Br).

This compound was prepared by a procedure analogous to the foregoing from barbituric acid and 5-bromoisatin, m.p. >360°. Yield, 37%; λ sh (*p*H 1) 225 mμ (ε 23,600); λ max (*p*H 1) 256 (ε 56,000), 308 (ε 6,100) and 366 mμ (ε 5,000); λ max (*p*H 11) 253 (ε 57,000) and 380 mμ (ε 6,100).

*Anal.* Calcd. for $C_{12}H_6BrN_3O_4$: C, 42.9; H, 1.80; N, 12.5. Found: C, 42.9; H, 2.13; N, 12.5.

2,4-Dioxo-7-methyl-1,2,3,4-tetrahydropyrimido[4,5-*b*]quinoline-5-carboxamide (IV, X = $CONH_2$, Y = $CH_3$).

The procedure of King *et.al.* (31) was adapted for this preparation. A suspension of 10 g. of 2,4-dioxo-7-methyl-1,2,3,4-tetrahydropyrimido[4,5-*b*]quinoline-5-carboxylic acid in 250 ml. of thionyl chloride was heated under reflux for 3.5 hours. During this time the crystalline form of the solids in suspension changed. At the end of the reflux period excess thionyl chloride was removed under pressure and the tan residue was collected, washed with ethyl acetate and air dried. This was then added to 750 ml. of concentrated aqueous ammonia and the resulting mixture was heated on a steam bath overnight. The light yellow crystalline product was collected by filtration and recrystallized from water to give 9.8 g. (65% yield) of yellow crystals, m.p. > 360°; λ max (*p*H 1) 221 (ε 33,800), 244 (ε 34,900), 260 (ε 28,700), 317 (ε 8,700) and 368 mμ (ε 5,400); λ max (*p*H 11) 252 (ε 47,000), 315 (ε 7,300) and 380 mμ (ε 5,400).

*Anal.* Calcd. for $C_{13}H_{10}N_4O_3$: C, 57.8; H, 3.73; N, 20.7. Found: C, 57.9; H, 3.49; N, 20.9.

7-Bromo-2,4-dioxo-1,2,3,4-tetrahydropyrimido[4,5-*b*]quinoline-5-carboxamide (IV, X = $CONH_2$, Y = Br).

This compound was prepared by a procedure analogous to the foregoing from the corresponding carboxylic acid in 50% yield, m.p. > 360°; λ max (*p*H 1) 223 (ε 24,400), 258 (ε 51,300), 310 (ε 6,100) and 368 mμ (ε 5,500); λ max (*p*H 11) 254 (ε 47,500), 368 (ε 5,400) and 388 mμ (ε 5,400).

*Anal.* Calcd. for $C_{12}H_7BrN_4O_3$; C, 43.0; H, 2.11; N, 16.7. Found: C, 43.3; H, 2.32; N, 16.4.

5-Amino-2,4-dioxo-7-methyl-1,2,3,4-tetrahydropyrimido[4,5-*b*]-quinoline (IV, X = $NH_2$, Y = $CH_3$).

The procedure of King *et.al.* (31) was adapted for this preparation. A mixture of 5.4 g. (0.02 mole) of 2,4-dioxo-7-methyl-1,2,3,4-tetrahydropyrimido[4,5-*b*]quinoline-5-carboxamide and 50 ml. of 2*N* sodium hydroxide in 200 ml. of water was stirred at room temperature for 30 minutes. To the suspension at 0°, was added a solution of sodium hypobromide (prepared by dissolving 3.2 g. (0.02 mole) of bromine in 50 ml. of 2*N* sodium hydroxide). The temperature during the addition was maintained at 0-2°. After the addition was complete (which required *ca.* 45 minutes). the resulting solution was stirred at the same temperature for 2.5 hours. Sodium hydroxide (20 g.) was added slowly to the cold solution and the resulting mixture was first stirred at 0-2° for 2 hours, then allowed to warm to room temperature and finally heated at 80° for 1.5 hours. The yellow sodium salt of the desired product, which gradually precipitated, was collected by filtration and dissolved in 1 l. of boiling water. The solution was decolorized with charcoal, filtered and the filtrate acidified with hot acetic

acid. A jel-like precipitate was formed. It was filtered and the solid recrystallized from a large volume of acetic acid. The product was isolated as a hydrate, m.p. $>360°$. The yield was 2.5 g. (48% yield). λ max (*p*H 1) 254 (ε 47,800), 288 (ε 10,200), 298 (ε 9,400) and 330 mμ (ε 4,100); λ max (*p*H 11) 255 (ε 36,400), 265 (ε 36,400), 296 (ε 8,200), 308 (ε 8,100), 354 (ε 4,100) and 368 m μ (ε 3,700).

*Anal.* Calcd. for $C_{12}H_{10}N_4O_2 \cdot H_2O$: C, 55.4; H, 4.65; N, 21.5. Found: C, 55.5; H, 4.40; N, 21.6.

2-Aminobenzaldehyde Ethylene Glycol Acetal (V, X = H).

A solution of 19.5 g. (0.1 mole) of 2-nitrobenzaldehyde ethylene glycol acetal (32) (VI, X = H) in 200 ml. of absolute ethanol was hydrogenated at 40 pounds per square inch in a Parr hydrogenator in the presence of 1 g. of Raney nickel. The theoretical amount of hydrogen was absorbed within 1 hour. The catalyst was removed by filtration and the filtrate evaporated to yield a straw colored oil. The product was purified by distillation, b.p. 81-82°/0.04 mm., yielding 10.8 g. (65% yield).

*Anal.* Calcd. for $C_9H_{11}NO_2$: C, 65.4; H, 6.71; N, 8.48. Found: C, 65.7; H, 6.96; N, 8.71.

5-Chloro-2-nitrobenzaldehyde Ethylene Glycol Acetal (VI, X = 5-Cl).

A mixture of 38 g. (0.2 mole) of 5-chloro-2-nitrobenzaldehyde, 100 ml. of ethylene glycol and 1 g. of *p*-toluenesulfonic acid in 1 l. of anhydrous benzene was refluxed while gently stirring for 30 hours. Water liberated during the reaction was collected in a Dean-Stark trap. The reaction mixture was then evaporated to dryness. To the residue was added 250 ml. of water and the *p*H of the resulting mixture was adjusted to 7-8 with dilute sodium hydroxide. The alkaline mixture was extracted with 3 x 200 ml. of ether. The combined ethereal extract was washed with 2 x 100 ml. of water and dried over anhydrous sodium sulfate. The dried ethereal extract was filtered, and the filtrate evaporated to dryness. The resulting light yellow oil was distilled at 123-127°/0.5 mm. to give 35.1 g. (75% yield) of product. An additional distillation at 104-106°/0.06 mm. yielded the product of analytical purity, which solidified on cooling, m.p. 41-44°.

*Anal.* Calcd. for $C_9H_8ClNO_4$: C, 47.1; H, 3.51; N, 6.10. Found: C, 47.0; H, 3.39; N, 6.35.

Attempted hydrogenation of this compound gave only polymeric material.

5-(5-Bromo-2-nitrobenzal)barbituric Acid (VII, X = 5-Br).

A mixture of 11.5 g. (0.05 mole) of 5-bromo-2-nitrobenzaldehyde (43) and 6.4 g. (0.05 mole) of barbituric acid in 100 ml. of water was refluxed with stirring for 1 hour. During that time the oily material slowly disappeared and an off-white crystalline material gradually separated. The reaction mixture was cooled and the solid was collected by filtration and washed with cold water and ethanol to give 14.5 g. (85% yield) of the product, m.p. 245-248° dec. An analytical sample was prepared by recrystallizing 1 g. of the product from 50 ml. of water, m.p. 248-250° dec. λ max (*p*H 1) 233 mμ (ε 14,600); λ max (*p*H 11) 257 mμ (ε 24,200).

*Anal.* Calcd. for $C_{11}H_6BrN_3O_5$: C, 38.9; H, 1.78; N, 12.4. Found: C, 39.2; H, 2.13; N, 12.3.

5-(2-Nitrobenzal)barbituric Acid (VII, X = H).

This compound was prepared from 6.4 g. (0.05 mole) of barbituric acid and 7.6 g. (0.05 mole) of 2-nitrobenzaldehyde in a manner analogous to the foregoing to give 12.3 g. (94% yield) of the product, m.p. 260-262° dec. λ max (*p*H 1) 233 mμ (ε 17,000); λ max (*p*H 11) 257 mμ (ε 20,700).

*Anal.* Calcd. for $C_{11}H_7N_3O_5$: C, 50.6; H, 2.70; N, 16.1. Found: C, 50.7; H, 2.89; N, 16.4.

2,4-Dioxo-1,2,3,4-tetrahydropyrimido[4,5-*b*]quinoline (IIIa).

Method A.

To a boiling solution of 6.4 g. (0.05 mole) of barbituric acid in 250 ml. of water was added, in one portion, 8.25 g. (0.05 mole) of 2-aminobenzaldehyde ethylene glycol acetal. The resulting mixture was stirred vigorously while heating at reflux temperature for 2 hours. A crystalline, light yellow product, which graduately precipitated during the reaction, was collected by filtration, washed with boiling water and absolute ethanol and dried. The product weighed 7.5 g. (71% yield), m.p. $>360°$. An analytical sample was prepared by recrystallization from glacial acetic acid, m.p. $>360°$. λ max (*p*H 1) 258 (ε 46,000) and 313 mμ (ε 9,800); λ max (*p*H 11) 223 (ε 27,300), 244 (ε 44,300), 310 (ε 7,700) and 356 mμ (ε 5,300). The product was found to be identical with that prepared by other methods (23,27-30).

Method B.

To a stirred, boiling suspension of 7.4 g. (0.03 mole) of 5-(2-nitrobenzal)barbituric acid in 500 ml. of water was added portionwise 31.2 g. (0.18 mole) of sodium hydrosulfite. After the addition was complete the mixture was refluxed for 15 minutes and the resulting light yellow solid collected by filtration. The product was washed successively with boiling water, ethanol and ether, and dried to give 2.3 g. (37% yield) of product, m.p. $>360°$. The product was found to be identical with that prepared by Method A.

7-Bromo-2,4-dioxo-1,2,3,4-tetrahydropyrimido[4,5-*b*]quinoline (IV, X = H, Y = 7-Br).

This compound was prepared by a procedure analogous to the foregoing from 10 g. (0.03 mole) of 5-(5-bromo-2-nitrobenzal)-barbituric acid and 31.2 g. of sodium hydrosulfite. It was recrystallized from glacial acetic acid to give 1.9 g. (22% yield) of the product, isolated as a monohydrate, m.p. 301-303° dec. λ max (*p*H 1) 240 (ε 32,400), 294 (ε 8,200) and 364 mμ (ε 4,100); λ max (*p*H 11) 242 (ε 31,500) and 340 mμ (ε 4,400).

*Anal.* Calcd. for $C_{11}H_6BrN_3O_2 \cdot H_2O$: C, 42.6; H, 2.60; N, 13.6. Found: C, 42.3; H, 2.56; N, 13.6.

Methyl 4,5-Dimethylanthranilate (Xb).

A stirred mixture of 4,5-dimethylanthranilic acid (39) (Xa) and 400 ml. of anhydrous methanol was heated under reflux while a stream of dry hydrogen chloride was passed through for 8 hours. The resulting reaction mixture was evaporated to dryness and the residue was covered with 150 ml. of water. The *p*H of the mixture was adjusted to 9 with alkali and the resulting buff-colored solid was collected by filtration, washed with water and dried to give 15.2 g. (85% yield) of Xb, m.p. 68-72°. An analytical sample was prepared by recrystallization from heptane, m.p. 75-78°.

*Anal.* Calcd. for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.31; N, 7.82. Found: C, 67.2; H, 7.24; N, 7.82.

4,5-Dimethylanthranilic Acid Hydrazide.

A mixture of 17.9 g. (0.1 mole) of methyl 4,5-dimethylanthranilate (Xb) and 100 ml. of 50% hydrazine hydrate was refluxed with stirring for three hours. On cooling, 17 g. (95% yield) of the product was obtained, m.p. 166-170°. An analytical sample was prepared by recrystallization from water, m.p. 170-172°.

*Anal.* Calcd. for $C_9H_{13}N_3O$: C, 60.3; H, 7.31; N, 23.5. Found: C, 60.7; H, 6.92; N, 23.5.

1-(4,5-Dimethylanthraniloyl)-2-(*p*-toluenesulfonyl)hydrazine.

To a solution of 17.9 g. (0.1 mole) of 4,5-dimethylanthranilic acid hydrazide in 300 ml. of reagent grade pyridine cooled to −3° was added portionwise, with stirring, 19.0 g. (0.1 mole) of *p*-toluenesulfonyl chloride. The temperature during the addition was maintained between −2° and +2°. After the addition was complete, the solution was allowed to stir at the same temperature for 45 minutes and then evaporated to dryness under reduced pressure. The resulting yellow-orange glass was covered with 200 ml. of water and the mixture was stirred at room temperature for 1 hour. The solidified product was collected by filtration, washed with cold water and air dired to give 25.0 g. (75% yield) of yellow solid, m.p. 172-176°. An analytical sample was obtained by recrystallization from benzene, m.p. 177-180°.

*Anal.* Calcd. for $C_{16}H_{19}N_3O_3S$: C, 57.6; H, 5.74; N, 12.6. Found: C, 57.8; H, 5.60; N, 12.8.

7,8-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimido[4,5-*b*]-quinoline (IV, X = H, Y = 7,8-$(CH_3)_2$).

To a solution of 33.3 g. (0.1 mole) of 1-(4,5-dimethylanthraniloyl)-2-(*p*-toluenesulfonyl)hydrazine in 500 ml. of ethylene glycol heated at 160° was added portionwise 32 g. (0.3 formula wt.) of anhydrous sodium carbonate. After the addition was complete, the mixture was heated at the same temperature for 30 minutes. It was then evaporated under reduced pressure. The residue was dissolved in 400 ml. of water and the solution decolorized with charcoal and filtered. The *p*H of the filtrate was adjusted to 3 with concentrated hydrochloric acid. To the acidic solution was added 12.8 g. (0.1 mole) of barbituric acid, and the resulting mixture was refluxed for 4 hours. On cooling, 10 g. (41% yield) of solid product was isolated, m.p. > 360°. An analytical sample was prepared by recrystallization from dimethylformamide, m.p. > 360°. λ max (*p*H 1) 259 (ε 17,600) and 340 mμ (ε 5,300); λ max (*p*H 11) 225 (ε 29,600), 247 (ε 40,400), 320 (ε 8,800) and 360 mμ (ε 5,400).

*Anal.* Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.7; H, 4.60; N, 17.4. Found: C, 64.9; H, 4.48; N, 17.7.

2,4-Dioxo-10-methyl-2,3,4,10-tetrahydropyrimido[4,5-*b*]quinoline (IXa).

To a boiling solution of 12.8 g. (0.1 mole) of barbituric acid in 250 ml. of water was added 13.5 g. (0.1 mole) of *N*-methylanthranilaldehyde (36) in one portion. A yellow crystalline solid started to precipitate immediately. The mixture was refluxed for 3 hours while gently stirring and then filtered. The solid was washed successively with boiling water, ethanol and ether to give, after drying, 21.5 g. (95% yield), m.p. 356-360° dec. Recrystallization from dimethylformamide gave 16.2 g. (72% yield) of analytically pure IXa, m.p. 354-356°. λ max (*p*H 1) 256 (ε 34,400) and 328 mμ (ε 14,500); λ max (*p*H 11) 261 (ε 43,500), 320 (ε 11,100) and 392 mμ (ε 11,800).

*Anal.* Calcd. for $C_{12}H_9N_3O_2$: C, 63.4; H, 3.99; N, 18.5. Found: C, 63.7; H, 4.13; N, 18.5.

*N*-(β-Hydroxyethyl)anthranilic Acid Hydrazide.

A mixture of 39.0 g. (0.2 mole) of methyl *N*-(β-hydroxyethyl)-anthranilate (38) and 200 ml. of 50% hydrazine hydrate was refluxed with stirring for three hours and cooled. The solid was collected by filtration to give 26.5 g. (68% yield) of product, m.p. 133-135°. An analytical sample was prepared by recrystallization from water, m.p. 135-136°.

*Anal.* Calcd. for $C_9H_{13}N_3O_2$: C, 55.4; H, 6.71; N, 21.5. Found: C, 55.1; H, 6.48; N, 21.3.

1-[*N*-(β-hydroxyethyl)anthraniloyl]-2-(*p*-toluenesulfonyl)hydrazine.

Treatment of 19.5 g. (0.1 mole) of *N*-(β-hydroxyethyl)anthranilic acid hydrazide with 19.0 g. (0.1 mole) of *p*-toluenesulfonyl chloride gave 28 g. (80% yield) of product, m.p. 153-155°. Recrystallization from 50% methanol yielded material of analytical purity having the same melting point.

*Anal.* Calcd. for $C_{16}H_{19}N_3O_4S$: C, 55.0; H, 5.48; N, 12.0. Found: C, 55.2; H, 5.12; N, 12.0.

2,4-Dioxo-10-(β-hydroxyethyl)-2,3,4,10-tetrahydropyrimido[4,5-*b*]-quinoline (IXb).

An aqueous mixture of 6.4 g. (0.05 mole) of barbituric acid and *N*-(β-hydroxyethyl)anthranilaldehyde (prepared by treatment of 17.5 g. (0.05 mole) of 1-[*N*-(β-hydroxyethyl)anthraniloyl]-2-(*p*-toluenesulfonyl)hydrazine with three equivalents of anhydrous sodium carbonate) was refluxed for 3 hours and the product was isolated in the usual manner. The yield of IXb was 7.3 g. (59% yield), m.p. 315-320° dec. An analytical sample was prepared by recrystallization from dimethylformamide, m.p. 322-324° dec. λ max (*p*H 1) 256 (ε 29,300) and 314 mμ (ε 10,100); λ max (*p*H 11) 262 (ε 35,100), 329 (ε 13,000) and 394 mμ (ε 9,900).

*Anal.* Calcd. for $C_{13}H_{11}N_3O_3 \cdot \frac{1}{2}H_2O$: C, 58.6; H, 4.54; N, 15.8. Found: C, 58.4; H, 4.66; N, 16.0.

Methyl *N*-Ribosyl-4,5-dimethylanthranilate (XI).

A solution containing 1.72 g. (0.01 mole) of methyl 4,5-dimethylanthranilate, 1.50 g. (0.01 mole) of D-ribose, 20 ml. of 95% methanol and two drops of concentrated hydrochloric acid was stirred at room temperature. After 1 hour a large portion of product had precipitated. The mixture was allowed to stir for another two hours at room temperature and then chilled. The resulting solid product was collected by filtration, washed with cold ethanol and ether, and dried in air. It weighed 2.0 g. (65% yield), m.p. 165-167°. Recrystallization from anhydrous methanol gave an analytically pure product, m.p. 175-176°.

*Anal.* Calcd. for $C_{15}H_{21}NO_6$: C, 57.9; H, 6.80; N, 4.50. Found: C, 58.0; H, 6.99; N, 4.25.

Methyl *N*-Ribosylanthranilate.

This compound was prepared from 1.51 g. (0.01 mole) of methyl anthranilate and 1.50 g. of D-ribose in a similar manner to give 1.75 g. (62% yield) of the product, m.p. 162-163°.

*Anal.* Calcd. for $C_{13}H_{17}NO_6$: C, 55.1; H, 6.05; N, 4.94. Found: C, 55.1; H, 5.98; N, 4.91.

Methyl 4,5-Dimethyl-*N*-(ribo-2,3,4,5-tetrahydroxypentyl)anthranilate (XII).

A solution of 15.6 g. (0.05 mole) of methyl 4,5-dimethyl-*N*-ribosylanthranilate in 150 ml. of reagent grade dimethylformamide was hydrogenated at 60 pounds per square inch in a Parr hydrogenator in the presence of 5 g. of 10% palladium-on-charcoal. The theoretical amount of hydrogen was absorbed in 2 hours. The catalyst was removed by filtration and the highly colored dimethylformamide solution was evaporated to dryness under reduced pressure on a steam bath. The resulting dark glass was dissolved in 100 ml. of boiling isopropyl alcohol, treated with charcoal and filtered. The filtrate, on cooling, deposited 12.5 g. (80% yield) of analytically pure product, m.p. 135-137°.

*Anal.* Calcd. for $C_{15}H_{23}NO_6$: C, 57.5; H, 7.40; N, 4.47. Found: C, 57.6; H, 7.26; N, 4.33.

Methyl *N*-(Ribo-2,3,4,5-tetrahydroxypentyl)anthranilate.

This compound was prepared in a similar manner from 14.2 g.

(0.05 mole) of methyl *N*-ribosylanthranilate. The yield of the ribityl derivative was 12.3 g. (86% yield), m.p. 134-136°.

*Anal.* Calcd. for $C_{13}H_{19}NO_6$: C, 54.7; H, 6.71; N, 4.91. Found: C, 54.7; H, 7.00; N, 4.97.

4,5-Dimethyl-*N*-(ribo-2,3,4,5-tetrahydroxypentyl)anthranilic Acid Hydrazide (XIIIa).

A solution of 15.6 g. (0.05 mole) of XII in 200 ml. of 50% hydrazine hydrate was refluxed for 3 hours with gentle stirring. The reaction mixture was then evaporated under reduced pressure on a steam bath and the resulting glass residue was crystallized from butanol to give 11.7 g. (75% yield) of XIIIa, m.p. 134-136°. An additional recrystallization from butanol yielded analytically pure product, m.p. 135-136°.

*Anal.* Calcd. for $C_{14}H_{23}N_3O_5$: C, 53.7; H, 7.40; N, 13.4. Found: C, 53.5; H, 7.27; N, 13.2.

*N*-(Ribo-2,3,4,5-tetrahydroxypentyl)anthranilic Acid Hydrazide.

Following the preceding procedure, 14.3 g. (0.05 mole) of methyl *N*-ribitylanthranilate and 200 ml. of 50% hydrazine hydrate gave 10.5 g. (74% yield) of the title compound, m.p. 92-94°.

*Anal.* Calcd. for $C_{12}H_{19}N_3O_5$: C, 50.5; H, 6.71; N, 14.7. Found: C, 50.4; H, 6.95; N, 14.4.

1-[4,5-Dimethyl-*N*-(ribo-2,3,4,5-tetrahydroxypentyl)anthraniloyl]-2-(*p*-toluenesulfonyl)hydrazine (XIIIb).

To a solution of 6.3 g. (0.02 mole) of XIIIa in 100 ml. of reagent grade pyridine cooled at −3° was added portionwise, with stirring, 3.8 g. (0.02 mole) of *p*-toluenesulfonyl chloride. The temperature throughout the addition was maintained at 0 ± 2°. After the addition was complete, the solution was stirred at the same temperature for 45 minutes and then allowed to slowly warm to room temperature. The solution was stirred at room temperature for 45 minutes and then evaporated to dryness under reduced pressure. To the yellow-orange glass residue was added 200 ml. of water and the mixture was stirred at room temperature for 1 hour. The resulting yellow solid was collected by filtration, washed with cold water and dried in air. It was then recrystallized from 20% aqueous ethanol to give 8.1 g. (87% yield) of XIIIb, m.p. 191-193°. An analytical sample was prepared by recrystallization once more from the same solvent, m.p. 193-195°.

*Anal.* Calcd. for $C_{21}H_{29}N_3O_7S$: C, 54.0; H, 6.25; N, 8.99. Found: C, 53.9; H, 6.29; N, 8.71.

1-[*N*-(Ribo-2,3,4,5-tetrahydroxypentyl)anthraniloyl]2-(*p*-tolysulfonyl)hydrazine.

Following the preceding procedure, treatment of 5.7 g. (0.02 mole) of *N*-ribitylanthranilic acid hydrazide with 3.8 g. of *p*-toluenesulfonyl chloride gave 7.6 g. (86% yield) of the desired product, m.p. 170-173°. Recrystallization from aqueous ethanol yielded an analytically pure product, m.p. 171-173°.

*Anal.* Calcd. for $C_{19}H_{25}N_3O_7S$: C, 51.9; H, 5.73; N, 9.56. Found: C, 51.9; H, 5.55; N, 9.66.

7,8-Dimethyl-2,4-dioxo-10-(ribo-2,3,4,5-tetrahydroxypentyl)-2,3,4,10-tetrahydropyrimido[4,5-*b*]quinoline (II, 10-Deazariboflavin).

To a solution of 4.7 g. (0.01 mole) of XIIIb in 100 ml. of ethylene glycol heated at 160° was added portionwise, with stirring, 3.2 g. (0.03 formula wts.) of anhydrous sodium carbonate. After the addition was complete the mixture was heated at the same temperature for 30 minutes and then evaporated *in vacuo*. The red glass residue was dissolved in 100 ml. of water, treated with decolorizing charcoal and filtered. The *p*H of the filtrate was adjusted to 3 with concentrated hydrochloric acid. To the acidic solution was added 1.3 g. (0.01 mole) of barbituric acid and the mixture was refluxed for 4 hours. The resulting orange solution was then allowed to cool gradually, during which time there was deposited 1.8 g. (48% yield) of II, m.p. 283-285° dec. Recrystallization from 400 ml. of water followed by another recrystallization from anhydrous methanol yielded 10-deazariboflavin of analytical purity, m.p. 286-288° dec. λ max (water) 226 (ε 30,800), 254 (ε 23,000), 271 (ε 25,200), 336 (ε 11,000) and 394 mμ (ε 12,000); λ max (*p*H 1) 225 (ε 28,900), 262 (ε 34,200) and 348 mμ (ε 16,500); λ max (*p*H 11) 263 (ε 32,000), 335 (ε 12,000) and 397 mμ (ε 11,000).

*Anal.* Calcd. for $C_{18}H_{21}N_3O_6$: C, 57.6; H, 5.64; N, 11.2. Found: C, 57.7; H, 5.54; N, 11.2.

2,4-Dioxo-10-(ribo-2,3,4,5-tetrahydroxypentyl)-2,3,4,10-tetrahydropyrimido[4,5-*b*]quinoline.

In an analogous manner, treatment of 4.4 g. (0.01 mole) of 1-[*N*-(ribo-2,3,4,5-tetrahydroxypentyl)anthraniloyl-2-(*p*-toluenesulfonyl)hydrazine with 3.2 g. of anhydrous sodium carbonate followed by refluxing of the resulting *N*-ribitylanthranilaldehyde with 1.3 g. (0.01 mole) of barbituric acid gave 1.6 g. (46% yield) of the product, m.p. 260-263° dec. An analytical sample was prepared by recrystallization of the product from water, m.p. 263-265° dec.; λ max (*p*H 1) 256 (ε 11,500) and 330 mμ (ε 5,300); λ max (*p*H 11) 261 (ε 15,000), 320 (ε 4,200) and 393 mμ (ε 4,300).

*Anal.* Calcd. for $C_{16}H_{17}N_3O_6$: C, 55.3; H, 4.93; N, 12.1. Found: C, 55.6; H, 5.21; N, 12.3.

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