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1,5-Dideazariboflavin, an analog of riboflavin containing the original conjugated double bond system between positions 1 and 5, was synthesized by the condensation of 4,5-dimethyl-*N*-ribitylanthranilaldehyde and the sodium salt of 2,4,6-piperidinetrione.

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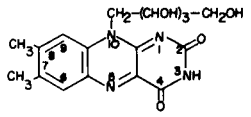
It is well known that biological activities of riboflavin (**1**) are closely associated with its *in vivo* oxidation-reduction reactions involving reversible 1,4-addition of hydrogen atoms to the conjugated double bond system between N_1 and N_5 (N_{10} in the older numbering system). Replacement of each of these nitrogen atoms by a -CH= linkage should provide analogs of riboflavin which still maintain this significant conjugated system [*e.g.*, 5(10)-deazariboflavin (**2**)].



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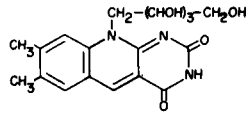
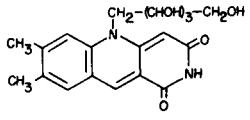


2

5-Deazariboflavin (**2**) and its FMN (flavin mononucleotide) analog were synthesized in this laboratory (1,2). These compounds have since prompted various biological studies by a number of investigators (3-14). It was found that the nitrogen atom at position 5 is important in flavin binding and that the reduced 5-deazaFMN is more resistant to oxidation than the reduced FMN. In addition, 5-deazariboflavin has frequently been used as a probe in the study of the mechanism of electron transfer of flavoproteins.

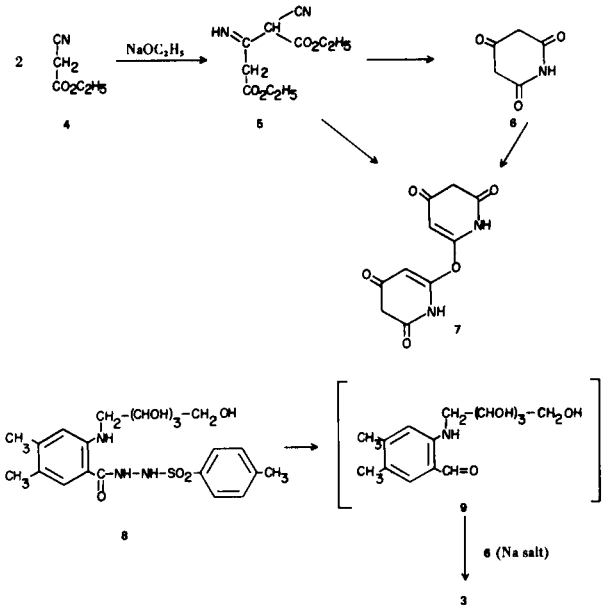
The intriguing biological activities displayed by 5-deazariboflavin suggested the synthesis of 1,5-dideazariboflavin (**3**) in which both the N_1 and N_5 atoms are replaced by -CH= units. Compound 3 can be considered as an ultimate deazariboflavin analog, wherein the aforementioned conjugated system is still retained.



3

Compound **3** was synthesized by the following route. Bimolecular condensation of ethyl cyanoacetate (**4**) in the presence of sodium ethoxide, according to the procedure of Baron, *et al.*, (15), yelded diethyl 2-cyano-3-iminoglutarate (**5**). These investigators also reported the preparation of 2,4,6-piperidinetrione (**6**) by the treatment of **5** with hydrochloric acid. Stokes and Pechmann (16) also reported the preparation of **6** from glutazine.

In our hands, none of these procedures proved satisfactory and often a different product was obtained. Based on analytical and mass spectrum information, a structure such as **7** can be assigned for that product. It is of interest to note that a similar product ($C_{10}H_8N_2O_5$) was also reported by Stokes and Pechmann (16) which they described as an "anhydride." Since **7** could not be utilized for the preparation of target compound **3**, a study of its detailed structural aspects was not conducted in the present work. The authentic 2,4,6-piperidinetrione (**6**) was eventually isolated from the reaction mixture at *p*H 7. Albert and Phillips (17) noted previously that **6** oxidizes in air and is therefore unstable. We found that **6** is rapidly converted to **7** in dilute aqueous solution at *p*H 4. Condensation of the sodium salt of **6** with 4,5-dimethyl-*N*-ribitylanthranilaldehyde (**9**) [prepared *in situ* from the corresponding tosylated hydrazide **8** (1,2)] readily afforded 1,5-dideazariboflavin (**3**).



EXPERIMENTAL

All melting points were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer and the mass spectrum data were obtained with a Varian Mat CH-4B mass spectrometer.

2,4,6-Piperidinetrione (**6**).

A mixture of 42 g. (0.186 mole) of diethyl 2-cyano-3-iminoglutarate (**5**) (15) in 150 ml. of concentrated hydrochloric

acid was refluxed for 3 hours and concentrated under reduced pressure. The residue was dissolved in 150 ml. of water and the *p*H of the solution was quickly adjusted to 13 by the addition of sodium hydroxide. The resulting dark solution was transferred to a large beaker and boiled for 2 hours until all the ammonia in the solution was evaporated. The solution was cooled and its *p*H was carefully adjusted to 7 with dilute hydrochloric acid. A yellow solid, which slowly precipitated on standing overnight, was collected by filtration to give 23 g. (82% yield) of the sodium salt of 2,4,6-piperidinetrione (**6**), m.p. >360°; λ max (*p*H 1): 267 nm (ε, 7,500); λ max (*p*H 11): 282 nm (ε, 10,000).

Anal. Calcd. for $C_5H_4NNaO_3$: C, 40.28; H, 2.70; N, 9.39. Found: C, 40.35; H, 2.93; N, 9.19.

When the *p*H of the reaction mixture was adjusted to 4, a yellow powder, m.p. >360°, rapidly separated from the solution, λ sh (*p*H 1): 278 nm (ε, 4,700); λ max (*p*H 1): 302 nm (ε, 5,800); λ sh (*p*H 11): 290 nm (ε, 6,600); λ max (*p*H 11): 324 nm (ε, 8,800); m/e: 236 (M^+, 62%).

Anal. Calcd. for $C_{10}H_8N_2O_5 \cdot H_2O$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.29; H, 4.11; N, 10.77.

1-Deoxy-1-(2,3-dihydro-7,8-dimethyl-1,3-dioxobenzo[*b*][1,6]-naphthyridin-5-[1*H*]yl)-D-ribitol (1,5-Dideazariboflavin, **3**).

To a solution of 4.7 g. (0.01 mole) of 1-[4,5-dimethyl-*N*-(ribo-2,3,4,5-tetrahydroxypentylanthraniloyl]-2-(*p*-toluenesulfonyl)hydrazine (**8**) (2) in 100 ml. of ethylene glycol heated at 160° was added portionwise, with stirring, 3.2 g. (0.03 formula weight) of anhydrous sodium carbonate. After the addition was complete, the reaction mixture was heated at the same temperature for 30 minutes and then evaporated *in vacuo*. The 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 1.5 g. (0.01 mole) of the sodium salt of 2,4,6-piperidinetrione (**6**) and the mixture was refluxed for 3 hours. The solid slowly dissolved on heating and an orange solid started to precipitate from the refluxing mixture. After cooling, the solid was collected by filtration to give 1.5 g. (43% yield) of **3**, m.p. 280-283° dec.; λ max (*p*H 1): 236 (ε, 22,300), 305 (ε, 17,600) and 450 nm (ε, 11,000); λ sh (*p*H 1): 262 (ε, 13,700) and 293 nm (ε, 16,900); λ nax (*p*H 11): 305 (ε, 12,500) and 475 nm (ε, 7,100); λ sh (*p*H 11): 235 (ε, 12,900) and 293 nm (ε, 11,800).

Anal. Calcd. for $C_{19}H_{22}N_2O_6 \cdot H_2O$: C, 58.15; H, 6.17; N, 7.14. Found: C, 58.11; H, 6.38; N, 6.99.

Acknowledgment.

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