

## Synthesis of 3-Amino-2,6-pyridinediol

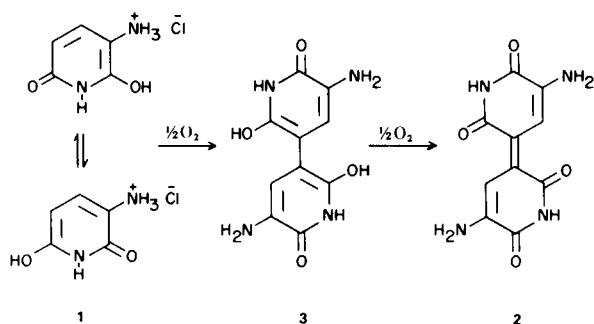
H. J. Knackmuss

Max-Planck-Institut für Medizinische Forschung

In a recent paper by Pathak, Dutta and Bardos (1) unsuccessful attempts to prepare 3-amino-2,6-pyridinediol were described. During our investigations (2) on the bacterial pigment indigoidine (2) 3-amino-2,6-pyridinediol hydrochloride (1) has been synthesized. Our results are briefly reported here.

3-Nitroso- or 3-benzeneazo-2,6-pyridinediol, which in accordance with Bardos and coworkers could not be hydrogenated catalytically, was easily reduced to 3-amino-2,6-pyridinediol by metallic tin in hydrochloric acid. The product was fairly stable in acidic solution and could be isolated as the hydrochloride 1. The N.M.R. spectrum of 1 agreed with the hydroxypyridone structures. Acetylation of 1 gave a tetraacetyl derivative, which was identical with an authentic sample (3), prepared by hydrogenation of 3-benzeneazo-2,6-pyridinediol in acetic anhydride.

The free 3-amino-2,6-pyridinediol could not be isolated, because it was readily autoxidized in solution. When 1 was dissolved in sodium bicarbonate solution a deep blue color was formed spontaneously, which disappeared after a few seconds. On further autoxidation the colorless solution turned blue again and slowly deposited indigoidine (2) in quantitative yield. The short-lived blue color could be explained by the formation of a semiquinoid intermediate, which readily dimerized to the colorless leuco-indigoidine 3, which was autoxidized to the diazadiphenoquinone 2.



## EXPERIMENTAL

## 3-Benzeneazo-2,6-pyridinediol.

2,6-Pyridinediol (3.33 g., 0.03 mole) was dissolved in water (200 ml.) by the addition of a minimum amount of 2 N sodium hydroxide. The pH (about 8.5) of the solution was lowered by

acidification with 2 N acetic acid without precipitating the pyridinediol. While the temperature was maintained below 10°, a solution of benzenediazonium chloride (from 0.03 mole of aniline in 7.5 ml. of concentrated hydrochloric acid) was slowly added to the vigorously stirred solution. The yellow precipitate was collected and washed with water and dried. Recrystallization from acetic acid gave 5.1 g. (yield 79%) 3-benzeneazo-2,6-pyridinediol as yellow-brown crystals, m.p. 219°; U.V. (methanol),  $\lambda$  max  $m\mu$  412 (log  $\epsilon$  4.56), 257 (log  $\epsilon$  4.15); I.R.  $cm^{-1}$  (potassium bromide) 3130, 3080 (NH), 1720, 1690, 1665 (CO), 1590, 1525.

*Anal.* Calcd. for  $C_{11}H_9N_3O_2$ : C, 61.40; H, 4.19; N, 19.53. Found: C, 61.32; H, 4.40; N, 19.72.

## 3-Diacetylamino-2,6-diacetoxypyridine.

3-Benzeneazo-2,6-pyridinediol (1.3 g., 6 mmoles) was hydrogenated in the presence of Raney Nickel in acetic anhydride. After 15 hours the catalyst was removed by filtration and the solution kept for two hours at 100° under an atmosphere of hydrogen. The solvent was evaporated and traces removed by repeated evaporation with toluene. The product crystallized when ether was added (900 mg.). Recrystallization from methanol or ether yielded colorless crystals, m.p. 89°; U.V. (methanol),  $\lambda$  max  $m\mu$  271 (log  $\epsilon$  3.69), 211 (log  $\epsilon$  4.11); N.M.R. (deuteriochloroform),  $\tau$  2.32 and 2.79 (1 H each, d; I = 8 Hz; pyridine), 7.65, 7.67 and 7.72 (3 H; s; 6 H, s; 3 H, s; 4  $CH_3CO$ ).

*Anal.* Calcd. for  $C_{13}H_{14}N_2O_6$ : C, 53.06; H, 4.80; N, 9.52;  $CH_3CO$ , 58.50. Found: C, 53.08; H, 4.61; N, 9.52;  $CH_3CO$ , 58.24.

## 3-Amino-2,6-pyridinediol Hydrochloride (1).

Powdered 3-benzeneazo- or 3-nitroso-2,6-pyridinediol (4.3 or 2.8 g. respectively, 20 mmoles) was suspended in concentrated hydrochloric acid (20 ml.) and cooled. Tin (about 3 g., tin coarse powder from E. Merck A. G., Darmstadt) was slowly added to the vigorously stirred solution, the temperature being kept between 10-15°. The clear colorless solution was decanted from the excess of tin and evaporated *in vacuo* to a small volume. Water was added, so that the crystals redissolved and the tin ions could be precipitated with hydrogen sulfide. 3-Amino-2,6-pyridinediol hydrochloride crystallized as colorless silky needles, when the solution was concentrated *in vacuo*. The collected material was washed with a methanol-acetone mixture, finally with dry acetone (yield 70-72%). Recrystallization was effected by dissolving in concentrated hydrochloric acid and addition of an equal volume of water under cooling. Apart from the weathering of the crystals the product is stable when protected from moisture and oxygen; U.V. (methanol),  $\lambda$  max  $m\mu$  317 (log  $\epsilon$  3.95); N.M.R. (deuterio-dimethylsulfoxide),  $\tau$  2.27 and 2.68 (1H each, d; I = 7Hz; pyridine), 0.12 (5H, broad; NH and OH). For analysis, a sample was dried at 90° for 15 hours. When dehydrated at higher temperatures decomposition was observed.

*Anal.* Calcd. for  $C_5H_7ClN_2O_2$ : C, 36.93; H, 4.32; N, 17.23; Cl, 21.81. Found: C, 36.55; H, 4.69; N, 16.88; Cl, 21.45.

#### Acetylation of 1.

In a nitrogen atmosphere 3-amino-2,6-pyridinediol hydrochloride (200 mg.) was heated at 100° for 2 hours in acetic anhydride (10 ml.) containing a small amount of perchloric acid. The colorless oil obtained after evaporation crystallized when ether was added. Colorless crystals (120 mg.) were obtained from methanol, which were identical with authentic 3-diacetylamino-2,6-diacetoxypyridine, mixture m.p. 89°.

#### Autoxidation of 3-Amino-2,6-pyridinediol.

When 1 (200 mg.) was dissolved in sodium bicarbonate solution (3.5%) a deep blue color was observed, which faded rapidly. Further autoxidation deposited indigoidine. The pigment was separated by filtration and washed with water and methanol (yield 98%). The product was identical with an authentic sample (visible spectrum, IR-spectrum).

For further identification the product (150 mg.) was hydrogenated in the presence of Raney Nickel in acetic anhydride at 50-60°. The colorless solution was separated from the catalyst

and heated for 2 hours at 100° in an atmosphere of hydrogen. After evaporation of the solvent, 5,5'-bis-diacetylamino-2,6,2',6'-tetraacetoxy-3,3'-bipyridyl crystallized on addition of methanol. Colorless crystals (110 mg.) from methanol were identical (mixed m.p. 163-164°) with a sample prepared analogously from authentic pigment, m.p. 164-165°; U.V. (methanol),  $\lambda$  max  $m\mu$  275 ( $\log \epsilon$  4.10); N.M.R. (deuteriochloroform),  $\tau$  2.30 (1H, s; pyridine); 7.64 (6H;  $NAc_2$ ); 7.68, 7.82 (3H each, s; 2 Ac).

*Anal.* Calcd. for  $C_{26}H_{26}N_4O_{12}$ : C, 53.24; H, 4.47; N, 9.55. Found: C, 53.19; H, 4.68; N, 9.43.

#### REFERENCES

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- (3) H.-J. Knackmuss, *ibid.*, **101**, 2679 (1968).

Received November 18, 1969

Heidelberg, Germany