Initial attempts to prepare 2,6-pyridinedicarboxylic acid *N*-oxide by peracetic or performic acid oxidation of 2,6-pyridinedicarboxylic acid led to recovery of unreacted dicarboxylic acid, even when large excesses of peracid at elevated temperatures were used.[8] 2,5-Pyridinedicarboxylic acid also was unreactive to *N*-oxide formation by peracetic acid, although a small yield of *N*-oxide was isolated in one experiment when a 40-fold excess of peracid was used at 80–100°. These results might have been anticipated in the light of patents[9] which describe the use of 2,5- and 2,6-pyridinedicarboxylic acids as stabilizers for hydrogen peroxide, persulfuric and peracetic acids, although it was not demonstrated whether the stabilizing action was due to the pyridine diacid or the *N*-oxide.

2,5- and 2,6-Pyridinedicarboxylic acid *N*-oxide were prepared in good yields by oxidizing the sodium salts of the dicarboxylic acid in water–acetic acid solution with peracetic acid. Structures of the *N*-oxides were indicated by analyses and by decarboxylation to the known nicotinic and picolinic acid *N*-oxides. Although excess acetic acid was present, the relatively high dissociation constant[10] of the first carboxylic acid group of the pyridine diacid ensures that the species being oxidized was the mono-salt, probably in equilibrium with the disalt.

The low reactivity of the pyridine diacids toward electrophilic attack on the nitrogen atom is at least in part due to steric hindrance and/or Zwitterion formation, but an additional effect is the accumulation of electron withdrawing substituents on the pyridine nucleus, a phenomenon observed also by Taylor and Crovetti.[7] It is suggested that all the above effects are removed or minimized by oxidizing the diacid as the mono- or disodium salt.

EXPERIMENTAL

2,6-Pyridinedicarboxylic acid, 2,5-pyridinedicarboxylic acid monohydrate and picolinic acid *N*-oxide were obtained from Aldrich Chemical Co.; melting points are uncorrected.

2,6-Pyridinedicarboxylic acid N-oxide. 2,6-Pyridinedicarboxylic acid (5.01 g., 0.03 mole) was dissolved in 45 g. of 6.67% aqueous sodium hydroxide, and to this was added 10 g. of 45% peracetic acid in acetic acid, concurrently with 20 g. 10% aqueous sodium hydroxide. After heating at 60° for 1 hr. an additional 5 g. peracetic acid solution was added and the solution was warmed on the steam bath for 1 hr. The solution was cooled, acidified with conc. HCl, and filtered, and the white crystals were dried to yield 4.0 g. (73% yield) of 2,6-pyridinedicarboxylic acid *N*-oxide, m.p. 155–157°. Mixed m.p.'s with 2,6-pyridinedicarboxylic acid and with picolinic acid *N*-oxide were depressed (146° and 116°, respectively).

Anal. Calcd. for $C_7H_7O_5N$: C, 45.91; H, 2.75; N, 7.65; acid equiv., 91.5. Found: C, 45.54; H, 3.06; N, 7.94; acid equiv., 93.

The decarboxylation of 2,6-pyridinedicarboxylic acid *N*-oxide was accomplished by immersing a test tube containing the *N*-oxide (4.0 g.) in a bath held at 155°; as the contents melted, vigorous gas evolution was observed and the temperature rose to 163°. After 4 min., the test tube was cooled. The resulting solid mass was dissolved in hot methanol and filtered while hot, and the filtrate was allowed to cool. The crystals obtained were recrystallized again from methanol, m.p. and mixed m.p. with authentic picolinc acid *N*-oxide, 153–154°.

2,5-Pyridinedicarboxylic acid N-oxide. Conditions similar to those for oxidation of 2,6-pyridinedicarboxylic acid were used; 15.0 g. of 2,5-pyridinedicarboxylic acid monohydrate gave 14 g. (86%) 2,5-pyridinedicarboxylic *N*-oxide as light tan crystals, m.p. 241–244°, mixed m.p. with starting material, 216–218°.

Anal. Calcd. for $C_7H_5O_5N$: C, 45.91; H, 2.75; N, 7.65; acid equiv. 91.5. Found: C, 46.08; H, 3.20; N, 7.73; acid equiv., 91.9.

The decarboxylation of 2,5-pyridinedicarboxylic acid *N*-oxide was accomplished by heating the above product in ethylene glycol at 150° for 30 min., to give nicotinic acid *N*-oxide, m.p. 246–248° (methanol). Mixed m.p.'s of this product with starting dicarboxylic acid *N*-oxide and with nicotinic acid (m.p. 234°) were depressed (199–208° and 187–230°, respectively). Acid equiv.: calcd. for $C_6H_5O_3N$: 139; found: 143.

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(8) We are indebted to Mr. P. S. Starcher of this department for these observations.

(9) F. P. Greenspan and D. G. MacKellar, U. S. Patent 2,609,391 (Sept. 2, 1952); F. P. Greenspan, U. S. Patent 2,624,655 (Jan. 6, 1953); F. P. Greenspan and D. G. MacKellar, U. S. Patent 2,663,621 (Dec. 22, 1953).

(10) V. D. Canic, *Ber. Chem. Ges. Belgrad*, **20**, 29 (1955), as reported in *Chem. Zentr.* **128**, 381 (1957).

Rearrangement of 4-Amino-6-chloro-1-methylpyrazolo(3,4-d)pyrimidine in Basic Solution[1]

C. C. CHENG[2] AND ROLAND K. ROBINS[3]

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When 4-amino-6-chloro-1-methylpyrazolo(3,4-d)-pyrimidine (I)[4] was refluxed in dilute alkaline solution, the expected 4-amino-6-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine (IV) was not obtained. Instead, the isomeric 6-amino-4-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine (II) was formed in 68% yield. The product was identified by comparison of ultraviolet absorption spectra, as well as by the R_f values of authentic samples of both 4-amino-6-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine[4] and 6-amino-4-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine[4] previously prepared.

(1) Presented in part before the Division of Medicinal Chemistry, 131st Meeting of the American Chemical Society, Miami, Fla., April 1957.

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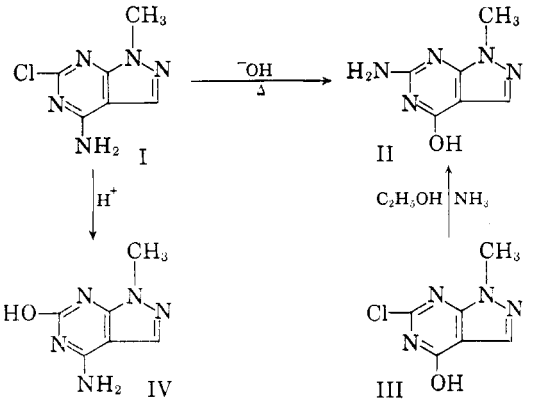
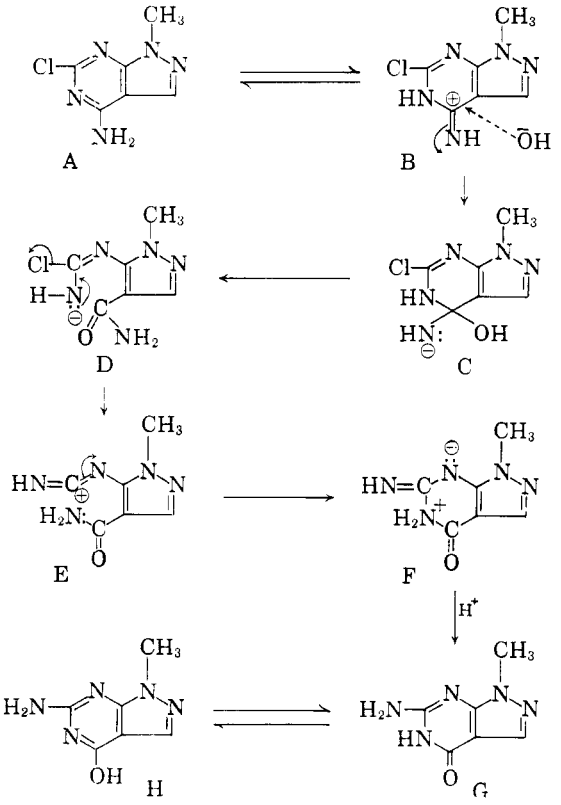
(4) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **23**, 852 (1958).



A theoretical mechanism for this rearrangement involves a ring opening followed by ring closure as follows:



This type of rearrangement has previously been noted in the purine series. Fischer[5] observed that 6-amino-2-chloro-7-methylpurine (isomeric to I) rearranged in basic medium to give 7-methylguanine. It is interesting to note that in Fischer's case, although the 7-methyl group exerts a steric interference to the nearby amino group, the rearrangement was not influenced since the initial nucleophilic attack was at the *carbon* atom in the 6 position.

No rearrangement was observed in acid medium. When 4 - amino - 6 - chloro - 1 - methylpyrazolo-(3,4-d)pyrimidine (I) was refluxed in hydrochloric acid, the expected 4-amino-6-hydroxy derivative (IV) was obtained.

(5) E. Fischer, *Ber.*, **31**, 542 (1898).

EXPERIMENTAL

4-Amino-6-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine (IV). This compound was prepared from 4-amino-6-chloro-1-methylpyrazolo(3,4-d)pyrimidine and concentrated hydrochloric acid as previously described.[4] The ultraviolet absorption spectra of this compound at *p*H 1 are 234 mμ (log ε = 4.10) and 251 mμ (log ε = 4.19); at *p*H 11.6, 247 mμ (log ε = 4.28) and 269 mμ (log ε = 4.11). The R_f value of the compound measured at 23° using *n*-propyl alcohol–1% ammonium hydroxide (2:1, volume ratio) is 0.55 (descending method). (Absorption spot was measured on Whatman #1 paper.)

6-Amino-4-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine (II). This compound was prepared from 6-chloro-4-hydroxy-1-methylpyrazolo(3,4-d)pyrimidine and ethanolic ammonia as indicated in a previous paper.[4] The ultraviolet absorption spectra of this compound at *p*H 1 is 251 mμ (log ε = 4.34); at *p*H 11.6, 267 mμ (log ε = 4.29). The R_f value of the compound measured under the same conditions as for IV is 0.64.

Action of sodium hydroxide on 4-amino-6-chloro-1-methylpyrazolo(3,4-d)pyrimidine. Five g. of finely powdered 4-amino-6-chloro-1-methylpyrazolo(3,4-d)pyrimidine was added to 400 ml. of boiling water. To this suspension was added 20 ml. of 30% sodium hydroxide. The mixture was vigorously refluxed for 1 hr. The hot, clear solution was acidified with acetic acid. The white precipitate was filtered and re-dissolved in dilute hydrochloric acid, followed by reprecipitation with ammonium hydroxide. It was recrystallized from dimethyl formamide to give 3.1 g. (68%) of a white solid, m.p. >300°. The R_f value of this compound, measured under the same conditions as for IV, was identical with that of 6-amino-4-hydroxy-1-methylpyrazolo-(3,4-d)pyrimidine (II) prepared by the above procedure. The ultraviolet absorption spectra measured at *p*H 1 and *p*H 11.6 are also identical.

Anal. Calcd. for $C_6H_7N_5O$: C, 43.6; H, 4.3; N, 42.4. Found: (dried at 135° *in vacuo* for 6 hr.) C 43.3; H, 4.5; N, 42.4.

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Amylsodium, Triethyl Amine, Sodium Hydroxide and the Metalation of Cumene[1]

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A previous paper[2] reported that the association of triethyl amine and sodium hydroxide (sodium chloride also was present) with amylsodium changed the polymerization of butadiene from a 1,2- to a

(1) This work was performed as part of a research project sponsored by the National Science Foundation.

(2) A. A. Morton and F. K. Ward, *J. Org. Chem.*, **24**, 929 (1959).