and precipitating with ammonium hydroxide. This material proved to be difficult to purify, however, because of its sparing solubility in organic solvents and its tendency to decompose slowly in high boiling solvents such as dimethylformamide. It is best purified and characterized as its dihydrochloride as described above.

4,4'-Diamino-3,3'-dipicolyl (X).—To a suspension of 6.12 g. of 4,4'-dinitro-1,1'-dioxy-3,3'-dipicolyl in 200 ml. of glacial acid was added 4.5 g. of 5% palladium-on-carbon catalyst, and the mixture was hydrogenated at 3 atmospheres pressure and at 50° until hydrogen absorption ceased (about 5 hr.). The hydrogenation mixture was heated to 70° and filtered from the catalyst, and the filtrate was cooled and diluted with ether. The voluminous white solid which separated was collected by filtration and recrystallized from acetic acid to give 6.68 g. (100%) of 4,4'-diamino-3,3'-dipicolyl diacetate as colorless crystals, m.p. 115–116°.

Anal. Calcd. for $C_{16}H_{22}N_4O_4$: C, 57.5; H, 6.6; N, 16.8. Found: C, 57.2; H, 6.8; N, 16.9.

The free base was prepared in 75% yield by addition of aqueous sodium hydroxide to a saturated aqueous solution of the above diacetate. Recrystallization of the precipitated solid from ethanol–acetone yielded colorless prisms, m.p. 250–251°.

Anal. Calcd. for $C_{12}H_{14}N_4$: C, 67.3; H, 6.6; N, 26.2. Found: C, 67.2; H, 6.5; N, 26.3.

PRINCETON, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TULANE UNIVERSITY]

Azaquinones. I. Oxidation of Certain Hydroxy- and Aminopyridones[1]

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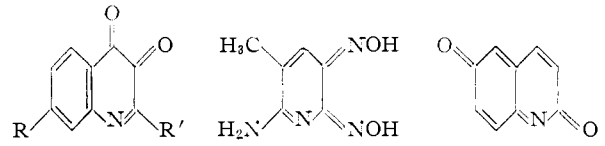
Hydroxylation at unsubstituted α-positions during oxidation of aminopyridones, V and VI (R = H, CH_3), or 3-hydroxypyridone-2 with manganese dioxide, chromium trioxide or potassium bromate (preferred) brought about the formation of tautomeric hydroxyazaquinones (VII ⇄ VIII, R = H, CH_3), isolated as quinhydrones. Reductive acetylation produced 2,3,6-triacetoxypyridine (X, R = H). Attempts to prepare 4-azabenzoquinone were unsuccessful.

Kudernatsch introduced azaquinones to the chemical literature by an oxidation of 2,3-dihydroxypyridine.[2] More recently 4-azanaphthquinone-1,2 (I)[3] as an impure yellow powder, its 3-hydroxy-6-methyl- derivative (II)[4] as light yellow needles and the dioxime (III) of 3-aza-4-amino-5-methylbenzquinone-1,2[5] as red needles have been reported. Derivatives of 1-azanaphthquinone-2,6 (IV) were considered as intermediates in the oxidation of derivatives of 6-hydroxycarbostyril into red carbostyril-5,6-quinones.[6]



I, R = R' = H
II, R = CH_3, R' = OH

III IV

Two general methods for the preparation of azaquinones were selected for preliminary investigations. The oxidation of certain aminopyridones is reported here; the transformation of azaquinone dioximes into quinones is under investigation.

Satisfactory oxidations of aminopyridones (V, VI, R = H, CH_3) were carried out in cold sulfuric acid with deficient amounts of manganese dioxide, chromium trioxide or potassium bromate (preferred). Bromate oxidation of 5-aminopyridone-2 (VI, R = H) occurred at a convenient rate at 0° whereas 3-aminopyridone-2 (V, R = H) required cooling to −20° for control of the reaction. Attempts to oxidize 3-aminopyridone-4 with deficient amounts of bromate even at −50° led to the formation of intractable tars. From each of 3- and 5-aminopyridone-2 and from 3-hydroxypyridone-2, a deep purple solid was obtained and was separated into two fractions by Soxhlet extraction with ethanol.

Oxidation of V (R = CH_3) and VI (R = CH_3) was successful at higher temperatures (*ca.* 25°); however, to avoid decomposition a deficient amount of bromate again was necessary. The deeply colored products appeared to be quinhydrones (VIII · VI and VII · V, R = CH_3). A condensation product from VII · V (R = CH_3) and phenylhydrazine was identified with a reported product from phenylhydrazine and XI.[7] This established the occurrence of hydroxylation at unsubstituted α-positions during the oxidation of V, VI (R = CH_3). Hydroxylation of a pyridine ring had previously been observed in the oxidation of 2-hydroxy-7-methylquinoline,[4] in the oxidation of 1,4-dihydroxyisoquinoline into yellow phthalonimide (X)[8a] and in the permanganate oxidation of 3,4-dihydroxypyridine-6-carboxylic acid into 2,3,4-trihydroxypyridine-6-carboxylic acid.[8b]

Elemental analyses and reductive acetylation demonstrated that hydroxylation, presumably at an α-position, had also occurred during the oxidation of V, VI (R = H) into hydroxyazabenzquinones (VII ⇄ VIII, R = H) and their quinhydrones with 2,3,6-trihydroxypyridine. The trihydroxypyridine was an expected product of the reversible oxidation–reduction between an aminopyridone and an hydroxyazaquinone. Impure quinhydrones, VII·V or VIII·VI (R = H), were apparently obtained in certain experiments. At-

(1) Partial support of this work under a National Institutes of Health Grant No. RG-4210 is gratefully acknowledged. Presented at the 129th American Chemical Society National Convention, Dallas, Texas, April, 1956.

(2) R. Kudernatsch, *Monatsh.*, **18**, 613 (1897); O. v. Schickh, A. Binz and A. Schulz, *Ber.*, **69**, 2593 (1936). In the present series, azaquinone designates nitrogen as a member of the quinone ring.

(3) M. Passerini, T. Bonciani and N. Di Gioia, *Gazz. chim. ital.*, **61**, 959 (1931).

(4) O. Kruber and L. Rappen, *Ber.*, **81**, 483 (1949).

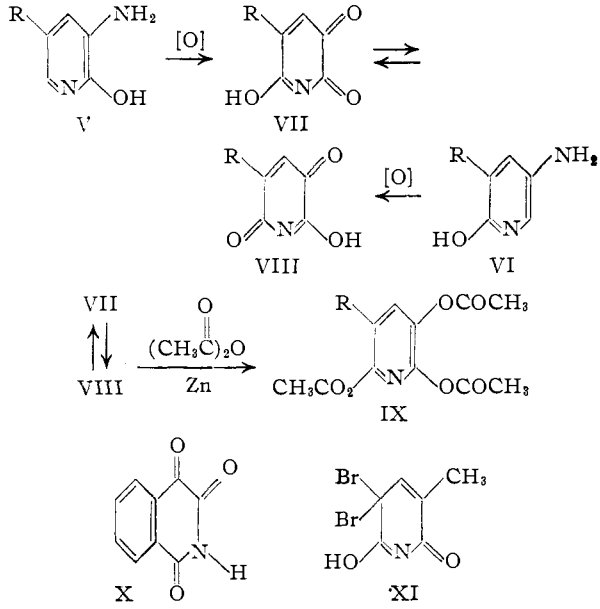
(5) J. H. Boyer and W. Schoen, THIS JOURNAL, **78**, 423 (1956).

(6) R. R. Holmes, J. Conrady, J. Guthrie and R. McKay, *ibid.*, **76**, 2400 (1954).

(7) S. Ruhemann, *Ber.*, **27**, 1272 (1894).

(8) (a) S. Gabriel and J. Colman, *ibid.*, **35**, 2421 (1902); (b) T. Reibstein, *J. prakt. Chem.*, [2] **24**, 286 (1881); *Ber.*, **14**, 2692 (1881).

tempts to repeat Kudernatsch's preparation of 3-azabenzquinone-1,2, a brown-violet powder, from 3-hydroxypyridone-2 and manganese dioxide[2] resulted, instead, in the formation of hydroxyazaquinones or their quinhydrones, identical with the oxidation products from the corresponding aminopyridone. Unidentified material was obtained upon refluxing samples of the oxidation product in acetic anhydride; however, reductive acetylation produced the previously unknown, 2,3,6-triacetoxypyridine (IX, R = H) in good yield.



Experimental[9]

Reduction of Nitropyridones.—According to a method described by Crowe for the reduction of 3-nitro-4-hydroxypyridine,[10] 3-nitropyridone-2[11] and 5-nitropyridone-2[11] were reduced by tin and hydrochloric acid to 3-aminopyridone-2 hydrochloride and 5-aminopyridone-2 hydrochloride in 85–90% yields.

Oxidation of 2-Hydroxy-5-aminopyridine.—A suspension of 3.0 g. (0.02 mole) of the amine hydrochloride in 25 ml. of concentrated sulfuric acid was warmed gently until hydrogen chloride evolution had ceased. The mixture was cooled and poured onto 50 g. of ice. A solution of 1.1 g. (0.0066 mole; 0.010 mole required for oxidation to the hydroquinone, $C_{10}H_8N_2O_6$; 0.0134 mole for the quinone, $C_5H_3NO_3$) of potassium bromate in 25 ml. of water was then rapidly added with stirring. The temperature of the reaction was not allowed to rise above 5°. The reaction mixture remained for several hours at 3–5° as a purple precipitate slowly separated. This was isolated by filtration, washed with ice-water and dried. A Soxhlet extraction of the dried solid with absolute ethanol was extended over a one-week period; however, several hours were sufficient for the extracting liquid portions to become colorless. After several recrystallizations from N,N-dimethylformamide and from molten acetanilide, the Soxhlet insoluble fraction separated as purple-brown micro-crystals with a metallic green sheen, 0.80 g. (47%).[12] It was very insoluble in all common organic solvents and had an indefinite decomposition range above 300°.

Anal. Calcd. for $C_5H_3NO_3$: C, 47.99; H, 2.42; N, 11.20. Calcd. for $C_{10}H_8N_2O_6$: C, 47.62; H, 3.20; N, 11.11. Found: C, 48.14, 48.16; H, 2.83, 2.70; N, 11.61, 11.99.

Upon concentration and cooling, the alcohol solution obtained from the Soxhlet extraction afforded red-brown leaflets, 0.40 g. (23%, total yield 70%).[12] This fraction was slightly soluble in common solvents and recrystallized from ethanol or methanol as purple-brown rhombs with indefinite decomposition above 300°. With the exception of ethanol solubility these two fractions appeared to be identical.

Anal. Calcd. for $C_5H_3NO_3$: C, 47.99; H, 2.42; N, 11.20. Calcd. for $C_{10}H_8N_2O_6$: C, 47.62; H, 3.20; N, 11.11. Found: C, 47.86, 47.65; H, 2.72, 3.31; N, 11.50, 11.15.

Attempts to carry out the oxidation with the theoretical amount of potassium bromate (at least 0.50 mole per mole of aminopyridone) led to excessive decomposition of organic material. The oxidation was also carried out with chromium trioxide in sulfuric acid.

Both the soluble and insoluble fractions of oxidation product dissolved in alkali. The formation of an intense blue color faded rapidly as decomposition progressed with the absorption of oxygen and evolution of ammonia. The alkaline solutions finally became red-yellow and fluoresced in ultraviolet light.

Oxidation of 2-Hydroxy-3-aminopyridine.—A suspension of 1.0 g. (0.0066 mole) of 2-hydroxy-3-aminopyridine hydrochloride in 10 ml. of concentrated sulfuric acid was warmed until evolution of hydrogen chloride gas had ceased. The solution was then maintained at −20° as 0.3 g. (0.003 mole; 0.0066 mole required for oxidation to the hydroquinone $C_{10}H_8N_2O_6$; 0.010 mole for the quinone, $C_5H_3NO_3$) of chromium trioxide in 5 ml. of concentrated sulfuric acid was added with stirring. The mixture was held at −20° for an additional 2 hr., slowly warmed to room temperature, poured onto ice and filtered. The purple precipitate (0.25 g., 62%)[12] was identical with the oxidation product obtained from 2-hydroxy-5-aminopyridine and separated into soluble and insoluble fractions upon Soxhlet extraction with absolute ethanol.

Reductive Acetylation.—A mixture of 0.1 g. (0.8 mmole) of either the ethanol-soluble or the ethanol-insoluble fraction of the above oxidation product obtained from the oxidation of either 2-hydroxy-3-aminopyridine or 2-hydroxy-5-aminopyridine and 0.5 g. zinc dust in 3 ml. of acetic anhydride was heated at water-bath temperature until all solid material had dissolved and the solution became pale yellow. A pale blue fluorescence to ultraviolet light developed during the reaction. The hot solution was filtered and excess solvent was removed *in vacuo*. Upon recrystallization from ethanol the residue separated as pale yellow crystals, 0.15 g. (75%), m.p. 135–140°. Further purification of a chloroform solution of the product by chromatographic separation on an alumina column easily was followed by the compound's characteristic blue fluorescence to ultraviolet light. The product upon additional recrystallization from ethanol produced pale cream platelets, m.p. 159°, of 2,3,6-triacetoxypyridine (X, R = H).

Anal. Calcd. for $C_{11}H_{11}NO_6$: C, 52.15; H, 4.38; N, 5.53; O, 37.94. Found: C, 52.58; H, 4.30; N, 5.78; O, 36.90.

Samples of 2,3,6-triacetoxypyridine obtained from each hydroxyazaquinone fraction obtained from each of the isomeric aminopyridones were identical as established by m.p. and mixture m.p. determinations.

Oxidation of 2,3-dihydroxypyridine by either Kudernatsch's procedure using manganese dioxide or by the present method using potassium bromate led to the formation of the ethanol-soluble and -insoluble fractions obtained above. A trace amount of an unidentified light yellow solid, m.p. >300° dec., was slowly collected over a period of two days upon attempted sublimation of a sample of the insoluble fraction at 250–280° (10^{-4} mm.) (*Anal.* Found: C, 47.62; H, 3.20; N, 11.11). In agreement with the previous results both fractions were transformed by reductive acetylation into 2,3,6-triacetoxypyridine, m.p. 159°.

Attempts to oxidize **3-amino-4-hydroxypyridine hydrochloride**[13] were unsuccessful and led to the formation of intractable red tars even with insufficient amounts of oxidizing agent at −50°.

(9) Analyses by Micro-tech Laboratories, Skokie, Ill.; Alfred Bernhardt, Mikroanalytisches Laboratorium, Max-Planck Institute, Mulheim (Ruhr), Germany; Midwest Microlab Inc., Indianapolis, Ind. Melting points are uncorrected.

(10) W. M. Crowe, *J. Chem. Soc.*, **127**, 2028 (1925).

(11) W. T. Caldwell and E. O. Kornfeld, THIS JOURNAL, **64**, 1695 (1942).

(12) The yield is based upon the oxidizing agent ($KBrO_3$ or CrO_3) and assumes the product to be a quinhydrone, $C_{10}H_8N_2O_6$.

(13) S. Kruger and F. G. Mann, *J. Chem. Soc.*, 2755 (1955).

Preparation of 3-Nitro-4-azidopyridine.—A solution of 3.2 g. (0.02 mole) of 3-nitro-4-chloropyridine and 2.6 g. (0.04 mole) of sodium azide in 23 ml. of methanol and 2 ml. of water was warmed to 35–40° for 10 minutes. The solution was filtered and concentrated to half its volume. Upon cooling, the azide separated as pale yellow crystalline rods, 2.55 g. (76.5%), m.p. 89° dec.

Anal. Calcd. for $C_5H_3N_5O_2$: C, 36.36; H, 1.83; N, 42.42. Found: C, 36.28; H, 2.03; N, 41.94.

Upon warming slightly above 90° for a few seconds decomposition occurred with a violent evolution of gas and formation of a yellow oil which changed rapidly into a dark-colored insoluble solid residue which neither melted nor decomposed under 300°.

Aminomethylpyridones.—Nitration of 2-amino-5-methylpyridine[14] followed by diazotization and hydrolysis afforded 2-hydroxy-3-nitro-5-methylpyridine, m.p. 253–255°, in 38% yield. To a suspension of 30.8 g. (0.2 mole) of this nitro compound in 400 ml. of 2% acetic acid, an excess of iron filings was added. The mixture was warmed on the water-bath with occasional stirring until the yellow color of the nitro compound had disappeared. The mixture was then neutralized with calcium carbonate, filtered while hot and the precipitate was washed several times with hot water. An excess of acetic anhydride was added with stirring to the filtrate, externally cooled in an ice-bath. The isolated precipitate was recrystallized from ethanol from which 2-hydroxy-3-acetamido-5-methylpyridine separated as rhombic leaflets, m.p. 253° (with slight sublimation), 22.2 g. (67%). A change in crystalline form from rhombic leaflets into needles occurred around 220°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.03; N, 16.87. Found: C, 57.89; H, 6.05; N, 17.14.

Nitration of 2-amino-3-methylpyridine[14] followed by diazotization and hydrolysis brought about the formation of 2-hydroxy-3-methyl-5-nitropyridine in 71% yield.[15] According to the above directions it was reduced and acetylated in 69% yield. Upon recrystallization from ethanol, 2-hydroxy-3-methyl-5-acetamidopyridine separated as colorless needles, m.p. 247°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.03; N, 16.87. Found: C, 57.44; H, 6.36; N, 16.45.

Oxidation of 2-Hydroxy-3-acetamido-5-methylpyridine.—A suspension of 3.0 g. (0.018 mole) of 2-hydroxy-3-acetamido-5-methylpyridine in 50 ml. of 16% (by volume) sulfuric acid was heated at 95–100° for 5 minutes. Longer heating at this stage diminished the final yield. The pale yellow solution was cooled to 25°, and 1.0 g. (0.006 mole) of potassium bromate in 25 ml. of water was added in one portion. The solution turned purple immediately and was cooled externally so that the temperature was held under 40°. A marked decrease in yield was observed if the temperature at this stage was allowed to reach 50–55°. A violet-brown precipitate separated from a blue solution upon standing at room temperature for 2 hr. and in the refrigerator for 24 hr. The crude product, 0.7 to 1.0 g. (29 to 42%), was washed with cold water and dried. An increase in the molar ratio of bromate resulted in nearly complete destruction of this product. Recrystallization from methanol allowed the separation of thin birefringent green-gray leaflets of impure quinhydrone, V·VII (R = CH_3), indefinite decomposition above 300°, from a deep purple supernatant liquid.

Anal. Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.73; H, 4.98; N, 15.96; O, 24.32. Found: C, 54.56; H, 4.94; N, 14.99; O, 25.49.

The product dissolved in alkali with the formation of an intense blue color which faded after a few hours and changed to a yellow-red. During the course of this alkaline decomposition a green-blue fluorescence under ultraviolet light was noted.

A suspension of 2.0 g. (0.008 mole) of the quinhydrone, V·VII (R = CH_3), in a solution of 5.0 ml. (0.05 mole) of phenylhydrazine in the minimum amount of 10% acetic acid was heated on the water-bath for 6 hr. as the color of the suspended solid slowly changed from purple to brown. From the cooled mixture a monophenylhydrazone of VII ⇄ VIII (R = CH_3) separated, 1.2 g. (67%), and recrystallized from methanol (less soluble) or ethanol as brown-red needles, m.p. 254° dec., whose color changed to yellow-red upon heating to 210°; lit.[7] reports yellow-red needles, m.p. 240° dec. It dissolved in dilute alkali with the formation of a yellow color.

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.88; H, 4.85; N, 18.38; O, 13.89. Found: C, 62.69; H, 4.90; N, 18.11; O, 14.15.

Oxidation of 2-Hydroxy-3-methyl-5-acetamidopyridine.—The conditions used above for the oxidation of isomeric 2-hydroxy-3-acetamido-5-methylpyridine were used. The final oxidation product, quinhydrone VI·VIII (R = CH_3), recrystallized from dioxane as green-gray platelets and decomposed above 300°. The deep purple dioxane solutions of this product were stable for short times only and soon became red-yellow in color with the simultaneous formation of a green-blue fluorescence to ultraviolet light. It was also soluble in alkali with decomposition and with the development of a green-blue fluorescence.

Anal. Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.73; H, 4.98; N, 15.96; O, 24.32. Found: C, 55.02; H, 4.88; N, 15.07; O, 24.63.

NEW ORLEANS, LOUISIANA

(14) Obtained from Reilly Tar and Chemical Co., Indianapolis, Ind.

(15) G. F. Hawkins and A. Roe, *J. Org. Chem.*, **14**, 328 (1949).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO.]

The Pyridylethylation of Indole and Related Reactions

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Pyridylethylation of indole and 1-substituted indoles in refluxing glacial acetic acid smoothly yielded 3-indolylethylpyridine derivatives. In ethanol containing a catalytic amount of sodium ethoxide, indole added to 4-vinylpyridine to provide 4-(1-indolylethyl)-pyridine. Under alkaline conditions indene yielded monopyridylethylated products which are tentatively formulated as 3-indenyl derivatives. Indole and 1-methylindole readily condensed with pyridinecarboxaldehydes in glacial acetic acid at room temperature to give relatively unstable di-indolylmethylpyridine products. Fischer cyclization in polyphosphoric acid of the phenylhydrazones of 3- and 4-acetylpyridine afforded the corresponding 2-indolylpyridines. The methobromide of 4-(2-indolyl)-pyridine gave no evidence of anhydronium base formation. Catalytic hydrogenation of the methobromides of many of the indolyl-substituted pyridines yielded the 1-methylpiperidine derivatives.

A general interest in pyridine derivatives with relatively large substituents[1] prompted this investigation. Although primary concern in the present paper is with a study of the reactions of indole and its 1-substituted derivatives with vinylpyridines and pyridinecarboxaldehydes, preparations of some related bases also are discussed.

Pyridylethylation.—The experiments of Doering and Weil[2] established 2- and 4-vinylpyridine as

(1) *E.g.*, A. P. Gray, W. L. Archer, E. E. Spinner and C. J. Cavallito THIS JOURNAL, **79**, July 20 (1957).

(2) W. E. Doering and R. A. N. Weil, *ibid.*, **69**, 2461 (1947).