(OH^- cycle) ($^3/_4'' \times 18''$). The column was washed with 500 ml. of water, and the effluent was concentrated to dryness to determine the amount of β-alanine that came through the column (residue = 0 g.). The resin was washed with 1000 ml. of absolute ethanol followed by dry ether. A vacuum was then applied to the column to dry the resin. The dried resin was transferred to a 1-l. erlenmeyer flask, and 32.5 g. (0.25 mole) of D(−)-pantolactone in 200 ml. of absolute ethanol was added. The flask was gently shaken for 67 hr. at 25°. The resin was removed by filtration and washed well with absolute ethanol followed by dry ether. The filtrate was concentrated to dryness yielding 9.0 g. (50% recovery of the theoretical excess) of pantolactone. Calcium chloride (6.2 g., 0.56 mole) in 200 ml. of water was passed through the resin (in the form of a column again) followed by 500 ml. of deionized water. The effluent was concentrated to dryness yielding a sirup-like residue, 31.7 g., which was dried by distillation of absolute ethanol. It was dissolved in hot methanol, seeded with a trace of D(+)-calcium pantothenate and set aside at room temperature overnight. The white solid that formed on standing was removed by filtration, 13.0 g. (49% yield), m.p. 226–230° dec., $[\alpha]D$ +21°. A bioassay with *L. arabinosus* indicated that this material was 67% D(+)-calcium pantothenate.

Anal. Calcd. for calcium pantothenate, $C_{18}H_{32}CaN_2O_{10}$: C, 45.36; H, 6.77; N, 5.88; Ca, 8.41. Found: C, 44.56; H, 6.85; N, 3.97; Ca, 9.57.

From the bioassay and the analytical data, it was obvious that the product was not D(+)-calcium pantothenate but was instead a mixed salt, calcium pantothenate-pantoate. Calcd. for $C_{15}H_{27}CaNO_9$: C, 44.43; H, 6.71; N, 3.46; Ca, 9.89. Found: C, 44.56; H, 6.85; N, 3.97; Ca, 9.57. The calcium pantothenate portion of the molecule represents about 64% of its total weight, in good agreement with the 67% activity determined in the bioassay.

A second crop of solids (4.1 g., 15.4%) was obtained after storage for an additional 24 hr. which proved to be D(+)-calcium pantothenate, m.p. 193–196°. Bioassay with *L. arabinosus* indicated a purity of 90%.

Acknowledgments.—The authors are grateful to Dr. J. L. Johnson and Mrs. G. S. Fonken for infrared analyses, to Mr. W. A. Struck and his associates for optical rotations and microanalyses and to Mr. L. Stubberfield and associates for bioassays.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Pyridine-1-oxides. III. Oxidative Coupling of 4-Nitro-3-picoline-1-oxide[1]

BY E. C. TAYLOR, A. J. CROVETTI[2] AND N. E. BOYER

RECEIVED NOVEMBER 7, 1956

4-Nitro-3-picoline-1-oxide (I) undergoes a facile oxidative coupling upon treatment in alkaline medium with oxygen, sodium nitrite or *n*-butyl nitrite to give 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl (II). Several reactions of II are discussed.

In the course of an investigation of the chemistry of pyridine-1-oxides, 4-nitro-3-picoline-1-oxide (I) was prepared and utilized as a key intermediate for the preparation of derivatives of nicotinic acid[3] and for a new synthesis of the alkaloid ricinine.[4] In the hope of extending further the usefulness of this versatile intermediate, an attempt was made to prepare 4-nitro-3-pyridyl aldehyde *via* the corresponding oxime by treatment of 4-nitro-3-picoline-1-oxide with *n*-butyl nitrite in the presence of a molar quantity of sodium ethoxide in ethanol. This method is similar to that reported by Lapworth[5] for the conversion of *o*-nitrotoluene to its oxime. Upon mixing the reactants at 0°, a rapid and pronounced color change from green-blue to red-brown took place with the simultaneous separation of a yellow, alkali-insoluble product (A). The same product was also obtained, although in lower yield, when a suspension of I in water containing an excess of sodium nitrite and a molar quantity of sodium hydroxide was shaken at room temperature or when oxygen was passed through a mixture of I in aqueous sodium hydroxide or in sodium ethoxide in ethanol.

The anticipated oxime structure for the product A was immediately suspect on the basis of its insolubility in alkali. Microanalytical values were almost identical with those calculated for I, but a molecular weight determination revealed that the product A was actually a "dimer" of I. An oxidative coupling had thus taken place to give 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl (II) (A) under conditions reminiscent of the oxidative coupling of *o*- and *p*-nitrotoluenes to the corresponding bibenzyls.[6–14] It is noteworthy that treatment of 4-nitropyridine-1-oxide with sodium nitrite and sodium hydroxide leads only to reduction to the corresponding azo compound,[15] and treatment of 4-nitro-2-picoline-1-oxide with sodium alkoxides results in normal nucleophilic displacement of the nitro group.[16]

It is curious that the formation of II from 4-nitro-3-picoline-1-oxide (I) has not been noted previously. Thus, Katritzky[17] treated I with sodium benzylate in benzyl alcohol and noted the formation of an intense green coloration (similar to that

(1) This work was supported in part by grants from the Smith, Kline and French Foundation and from the National Science Foundation.

(2) Parke, Davis and Co. Fellow, 1954–1955.

(3) E. C. Taylor and A. J. Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).

(4) E. C. Taylor and A. J. Crovetti, THIS JOURNAL, **78**, 214 (1956).

(5) A. Lapworth, *J. Chem. Soc.*, 1265 (1901).

(6) O. Fischer and E. Hepp, *Ber.*, **26**, 2231 (1893).

(7) A. Reissert, *ibid.*, **30**, 1030 (1897).

(8) A. G. Green, A. H. Davies and R. S. Horsfall, *J. Chem. Soc.*, **91**, 2076 (1907).

(9) A. K. Plisov, *Ukrainskii Khem. Zhur.*, **4**, Sci. Pt., 241 (1929); *C. A.*, **24**, 1108 (1930).

(10) R. C. Fuson and H. O. House, THIS JOURNAL, **75**, 1325 (1953).

(11) G. R. Yohe, D. R. Hill, J. E. Dunbar and F. M. Scheidt, *ibid.*, **75**, 2688 (1953).

(12) R. Oda and T. Tsuruta, *Repts. Chem. Research Inst.*, Kyoto Univ., **16**, 6 (1947); *C. A.*, **46**, 950 (1952).

(13) T. Tsuruta, R. Nagatomi and J. Furukawa, *ibid.*, **30**, 47 (1952); *C. A.*, **48**, 13376 (1954).

(14) T. Tsuruta, T. Fueno and J. Furukawa, THIS JOURNAL, **77**, 3265 (1955).

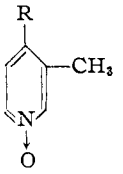
(15) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(16) I. Suzuki, *J. Pharm. Soc. Japan*, **68**, 126 (1948); *C. A.*, **47**, 8074 (1953).

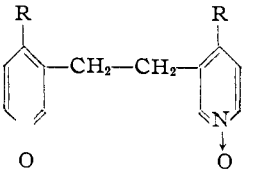
(17) A. R. Katritzky, *J. Chem. Soc.*, 2404 (1956).

observed here with sodium ethoxide), but no product was isolated from the reaction. Using similar conditions, Itai and Ogura[18] isolated 4-benzyloxy-3-picoline-1-oxide in 21.5% yield; it seems possible that the low yield of product may have been due to concomitant formation of the "dimer" II.

A careful examination of the reaction of I with sodium ethoxide in the presence of oxygen revealed that, in addition to the predominant formation of II, 4,4′-diethoxy-1,1′-dioxy-3,3′-dipicolyl (III, 0.72% yield), 4-ethoxy-3-picoline-1-oxide (IV, 2.9% yield) and a red solid (V, ~5% yield when pure) were formed. By addition of I and *n*-butyl nitrite to a solution of sodium ethoxide in ethanol, the yield of III could be raised to 19% without concomitant formation of II. Since II could not be converted to III with sodium ethoxide in ethanol, even under strenuous conditions, it would appear that III must arise by oxidative coupling of IV initially formed by the reaction of I with sodium ethoxide.



I, R = $-NO_2$
IV, R = $-OC_2H_5$

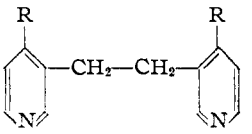


II, R = $-NO_2$
III, R = $-OC_2H_5$
VI, R = $-OH$
VII, R = $-Cl$
VIII, R = $-NHOH$

Formation of the red solid V also was noted in the other preparations of 4,4′-dinitro-1,1′-dioxy-3,3′-dipicolyl (II), and it could be formed directly from II by hydrogenation in dimethylformamide solution in the presence of palladium-on-carbon catalyst. It was a highly deliquescent material which proved difficult to purify; microanalysis of both V and its picrate indicated a probable empirical formula of $C_{12}H_{11}N_3O_3$, in which one nitrogen atom appears to have been lost from the "dimer" II, perhaps by cyclization across the 4,4′-positions. However, no definitive structure for this compound can be advanced at this time.

Hydrolysis of 4,4′-diethoxy-1,1′-dioxy-3,3′-dipicolyl (III) with two molar equivalents of aqueous potassium hydroxide yielded the dipotassium salt of 4,4′-dihydroxy-1,1′-dioxy-3,3′-dipicolyl (VI); hydrolysis with barium hydroxide yielded the corresponding barium salt, from which VI could be obtained by treatment with sulfuric acid. Attempts to prepare VI directly from II either with alkali or with alkaline hydrogen peroxide were unsuccessful. Somewhat surprisingly, III failed to react with liquid ammonia or with a mixture of sodium amide and liquid ammonia.

Although II failed to react with sodium alkoxides (a reaction typical of 4-nitropyridine-1-oxides),[15] it reacted readily with acetyl chloride to give 4,4′-dichloro-1,1′-dioxy-3,3′-dipicolyl (VII). The chlorine atoms in VII proved to be amazingly inert toward nucleophilic displacement. Thus, VII was recovered unchanged after refluxing in glacial acetic acid for 6 hr., after treatment with liquid ammonia at atmospheric pressure for 30 hr. or after refluxing in concentrated ammonium hydroxide. When VII was heated in a sealed steel bomb with liquid ammonia at 150° for 6 hr., 4,4′-dichloro-3,3′-dipicolyl (IX) was formed, and no displacement of chlorine was observed. This unusual deoxygenation reaction was confirmed by an independent preparation of IX involving catalytic reduction of VII in aqueous hydrochloric acid.



IX, R = $-Cl$
X, R = $-NH_2$

Catalytic reduction of II in aqueous hydrochloric acid led to the exclusive formation of 4,4′-dihydroxylamino-1,1′-dioxy-3,3′-dipicolyl (VIII). Further reduction to the corresponding diamine could not be achieved in this medium. When the reduction was carried out in glacial acetic acid as solvent, 4,4′-diamino-3,3′-dipicolyl (X) was formed, in which the N-oxide functions had also been reduced.

The possibility of utilizing these intermediates for the preparation of condensed heterocyclic systems containing large rings is under investigation.

Experimental[19]

4,4′-Dinitro-1,1′-dioxy-3,3′-dipicolyl (II). Method A.—One hundred and twenty grams (0.78 mole) of 4-nitro-3-picoline-1-oxide was dissolved in 3 l. of absolute ethanol by heating on a steam-bath and the resulting solution was chilled in an ice-bath. To it was added 86 g. (0.83 mole) of cold (0°) *n*-butyl nitrite, followed by the slow addition of a cold (0°) solution of 18 g. (0.78 mole) of sodium in 500 ml. of absolute ethanol. During the addition the reaction mixture was stirred continuously and maintained at 0° by means of a salt–ice-bath. The color of the mixture turned from red to green to blue-green; ten minutes after addition of the sodium ethoxide solution was complete, the color changed to dark brown. The reaction mixture was stirred at 0° for 6 hr. and then poured into 5 l. of ice-cold water. The precipitated yellow solid was collected by filtration, dissolved in concentrated hydrochloric acid and reprecipitated by the addition of water; yield 63 g. (53%), m.p. 240° dec. An analytical sample, m.p. 242° dec., was prepared by repetition of the above procedure.

Anal. Calcd. for $C_{12}H_{10}N_4O_6$: C, 47.1; H, 3.3; N, 18.3; mol. wt., 306.2. Found: C, 47.2; H, 3.2; N, 18.2; mol. wt., 317.0.

Method B.—To a solution of 1.3 g. of sodium hydroxide in 200 ml. of water was added 5.0 g. of 4-nitro-3-picoline-1-oxide. Oxygen was bubbled through the mixture at room temperature (35°) for a total of 3 hr.; a reaction commenced within the first ten minutes. The suspended solid was then filtered, washed with water and dried to yield 1.92 g. (39%) of the "dimer," m.p. 240° dec. The same material was formed in 24% yield when sodium nitrite was used as the oxidizing agent.

Method C.—A solution of 4.60 g. (0.20 mole) of sodium in 250 ml. of absolute ethanol was added slowly to a suspension of 30.8 g. (0.20 mole) of 4-nitro-3-picoline-1-oxide in 1.5 l. of absolute ethanol maintained at 0°. The solution acquired a blue-green color upon the addition of the first few drops of the base; the color soon changed to red. Oxygen was bubbled through the solution for 10 hr.; the temperature was maintained at 0° for the first 2 hr. and then allowed to warm up to 20°. Oxygen was again bubbled through the reaction mixture for 1 hr. after it had stood overnight at room temperature. Filtration then yielded 21 g. of a crude solid product and a dark green filtrate (see below). The solid was extracted with three 400-ml. portions of boiling chloroform, dissolved in concentrated hydrochloric acid and reprecipitated by the addition of ice-water to give 11.5 g.

(18) T. Itai and H. Ogura, *J. Pharm. Soc., Japan*, **75**, 292 (1955).

(19) All melting points are corrected. The microanalyses were performed by Dr. Joseph F. Alicino, Metuchen, N. J.

(38%) of 4,4'-dinitro-1,1'-dioxy-3,3'-dipicolyl, m.p. 240° dec.

4,4'-Diethoxy-1,1'-dioxy-3,3'-dipicolyl (III).—By evaporation of the chloroform extracts above and fractional crystallization of the residue from chloroform, there was obtained 0.22 g. (0.72%) of pale yellow prisms, m.p. 237°. Recrystallization from ethanol raised the m.p. to 245–246° dec.

Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.1; H, 6.6; N, 9.2. Found: C, 63.0; H, 6.6; N, 9.2.

By modification of the conditions of the "dimerization" reaction, the yield of this product could be significantly improved. Thus, to a solution of 15 g. (0.65 mole) of sodium in 200 ml. of absolute ethanol was added a solution of 50 g. (0.32 mole) of 4-nitro-3-picoline-1-oxide and 40 g. (0.39 mole) of *n*-butyl nitrite in 1.8 l. of absolute ethanol. The resulting blue-green solution was stirred at 0° for 2 hr. and then at room temperature for an additional 2 hr. Filtration of the solid product and fractional crystallization from ethanol yielded as the least soluble fraction 9.40 g. (19%) of 4,4'-diethoxy-1,1'-dioxy-3,3'-dipicolyl, m.p. 245–246° dec. No 4,4'-dinitro-1,1'-dioxy-3,3'-dipicolyl was formed in this reaction, and no 4-nitro-3-picoline-1-oxide could be recovered.

4-Ethoxy-3-picoline-1-oxide (IV).—The dark green ethanolic filtrate (method C above) was concentrated to a small volume under reduced pressure to give a brownish-yellow solid and a very dark filtrate. Treatment of the solid with absolute ethanol yielded a small amount (2 g.) of unreacted 4-nitro-3-picoline-1-oxide. The dark filtrate was evaporated to dryness and the residue extracted several times with small portions of ether. Evaporation of the ether extracts yielded 0.9 g. (2.9%) of colorless crystals, m.p. 135–136°. Recrystallization from absolute ethanol raised the melting point to 139–140°. The melting point of this compound has been reported previously as 134–135°.[16]

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.7; H, 7.2; N, 9.2. Found: C, 62.6; H, 7.2; N, 9.2.

Red Side Product (V).—The residue obtained in the above isolation of 4-ethoxy-3-picoline-1-oxide was a red, deliquescent solid. A similar solid was obtained by concentration of the filtrates from methods A and B. It was extracted with boiling chloroform and the red chloroform extracts evaporated to dryness under reduced pressure. Suspension of the residue in ethanol, filtration and recrystallization of the remaining solid from dry chloroform yielded a bright red solid, m.p. 242° dec., which was extremely hygroscopic.

Anal. Calcd. for $C_{12}H_{11}N_3O_3 \cdot 1.5H_2O$: C, 52.9; H, 5.2; N, 15.4. Found: C, 52.1; H, 5.1; N, 15.6.

Addition of picric acid to an aqueous solution of this material yielded a yellow picrate, m.p. 161° dec., which was recrystallized from water.

Anal. Calcd. for $C_{12}H_{11}N_3O_3 \cdot C_6H_3N_3O_7 \cdot {}^1/_2H_2O$: C, 44.7; H, 3.1; N, 17.4. Found: C, 44.7; H, 3.4; N, 16.9.

The same material was obtained from 4,4'-dinitro-1,1'-dioxy-3,3'-dipicolyl as follows: a mixture of 320 ml. of dimethylformamide, 9.19 g. of 4,4'-dinitro-1,1'-dioxy-3,3'-dipicolyl and 1.50 g. of 5% palladium-on-carbon catalyst was hydrogenated at 80° and 3 atmospheres pressure for 18 hr. The reaction mixture was then filtered to remove the catalyst and unreacted "dimer," and the red filtrate was concentrated to give 5.5 g. of a red, hygroscopic solid. Conversion of this material to its picrate (m.p. 161°) showed it to be identical with the red compound obtained above.

4,4'-Dihydroxy-1,1'-dioxy-3,3'-dipicolyl (VI).—A mixture of 9.13 g. (0.03 mole) of 4,4'-diethoxy-1,1'-dioxy-3,3'-dipicolyl, 3.37 g. (0.06 mole) of potassium hydroxide and 70 ml. of water was heated under reflux for 20 hr., cooled to room temperature and diluted with a 1:1 mixture of ethanol and acetone. The voluminous, yellow solid which separated was recrystallized from water; yield 6.74 g. (69%), m.p. 355° dec.

Anal. Calcd. for $C_{12}H_{10}N_2O_4K_2$: C, 44.4; H, 3.1; N, 8.6. Found: C, 44.4; H, 3.2; N, 8.6.

By dissolving the dipotassium salt in water and adding palladium chloride, the dipalladium salt of 4,4'-dihydroxy-1,1'-dioxy-3,3'-dipicolyl was obtained as red-brown crystals, m.p. 175–180°.

The barium salt was obtained conveniently by direct hydrolysis of 4,4'-diethoxy-1,1'-dioxy-3,3'-dipicolyl with an equivalent amount of aqueous barium hydroxide. The salt separated from the reaction solution in quantitative yield upon cooling.

Decomposition of the barium salt with sulfuric acid yielded 4,4'-dihydroxy-1,1'-dioxy-3,3'-dipicolyl as a pale yellow solid, m.p. 165–166°, which readily could be recrystallized from water. A satisfactory analytical sample could not be obtained from this material, however, because of its tenacious retention of small amounts of inorganic ions. It is best identified as its dipotassium salt as described above.

4,4'-Dichloro-1,1'-dioxy-3,3'-dipicolyl (VII).—To 90 ml. of cold (0°) acetyl chloride was added 9.19 g. of 4,4'-dinitro-1,1'-dioxy-3,3'-dipicolyl and the mixture heated under reflux on a steam-bath for 2 hr. The reaction mixture was then poured on 450 g. of crushed ice, the solution adjusted to *p*H 6 with sodium carbonate and extracted several times with chloroform. The combined extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The solid residue was triturated with cold water containing a little sodium carbonate and then recrystallized from ethanol to give 6.02 g. (70%) of white needles, m.p. 212–214° dec. Recrystallization from water raised the melting point to 219° dec.

Anal. Calcd. for $C_{12}H_{10}Cl_2N_2O_2$: C, 50.5; H, 3.5; N, 9.8. Found: C, 50.5; H, 3.8; N, 9.7.

This compound was converted to its dihydrochloride salt, m.p. 245° dec., by recrystallization from 10% aqueous hydrochloric acid.

Anal. Calcd. for $C_{12}H_{12}Cl_4N_2O_2$: C, 40.3; H, 3.4; N, 7.9. Found: C, 40.6; H, 3.6; N, 8.2.

4,4'-Dichloro-3,3'-dipicolyl (IX). Method A.—A mixture of 100 ml. of liquid, anhydrous ammonia and 2.73 g. of 4,4'-dichloro-1,1'-dioxy-3,3'-dipicolyl was sealed in a steel reaction vessel and heated with shaking at 150° for 6 hr. The bomb was then cooled, the excess ammonia bled off and the solid residue recrystallized from aqueous ethanol to give colorless crystals, m.p. 110–111°. The product was further purified by sublimation at 100° (0.02 mm.); m.p. 115–115.5°.

Anal. Calcd. for $C_{12}H_{10}N_2Cl_2$: C, 56.9; H, 4.0; N, 11.1. Found: C, 57.0; H, 4.0; N, 10.5.

Recrystallization of this material from a mixture of dilute hydrochloric acid and ethanol gave the dihydrochloride salt, m.p. 291° dec., which could be sublimed readily at 200° (0.05 mm.).

Anal. Calcd. for $C_{12}H_{12}N_2Cl_4$: C, 44.2; H, 3.7; N, 8.6. Found: C, 44.4; H, 3.7; N, 8.5.

Treatment of 4,4'-dichloro-3,3'-dipicolyl in aqueous ethanol with picric acid yielded a yellow crystalline picrate, m.p. 228° dec., which was purified readily by sublimation at 200° (0.005 mm.).

Anal. Calcd. for $C_{12}H_{10}N_2Cl_2 \cdot 2C_6H_3N_3O_7$: C, 40.5; H, 2.3; N, 15.8. Found: C, 40.5; H, 2.2; N, 15.7.

Method B.—A solution of 2.26 g. of 4,4'-dichloro-1,1'-dioxy-3,3'-dipicolyl in a mixture of 100 ml. of water and 10 ml. of concentrated hydrochloric acid containing 0.8 g. of 5% palladium-on-carbon catalyst was hydrogenated at 3 atmospheres pressure and at room temperature until hydrogen absorption ceased. The catalyst was removed by filtration and the acid filtrate was evaporated to dryness under reduced pressure. Recrystallization of the residue from a mixture of dilute hydrochloric acid and ethanol yielded the dihydrochloride of 4,4'-dichloro-3.3'-dipicolyl, m.p. 291° dec., identical in all respects with the sample prepared above. Likewise, a sample of the free base (m.p. 115°) was also identical with the authentic sample prepared above.

4,4'-Dihydroxylamino-1,1'-dioxy-3,3'-dipicolyl (VIII).—Hydrogenation of 8.42 g. of 4,4'-dinitro-1,1'-dioxy-3,3'-dipicolyl in 300 ml. of absolute ethanol containing 6 ml. of concentrated hydrochloric acid in the presence of 5% palladium-on-carbon catalyst at 50° under 3 atmospheres pressure was carried out until hydrogen absorption ceased. The reaction mixture was then concentrated to about half its volume, cooled and filtered, and the resulting solid was recrystallized from aqueous hydrochloric acid to give 8.51 g. (88%) of long, colorless prisms, m.p. 228° dec.

Anal. Calcd. for $C_{12}H_{16}N_4O_4Cl_2$: C, 41.0; H, 4.6; N, 16.0. Found: C, 41.0; H, 4.4; N, 15.9.

The dihydrochloride could be converted readily to the yellow free base, m.p. 295–300° dec., by dissolving in water

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]

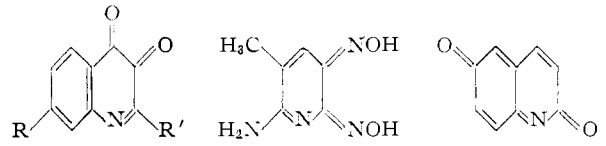
Azaquinones. I. Oxidation of Certain Hydroxy- and Aminopyridones[1]

BY J. H. BOYER AND S. KRUGER

RECEIVED JANUARY 26, 1957

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

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-

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(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).