Also, substitution for (AH_3^{-1}) in eq. 17 from eq. 2 yields

$$(AH_4)_0 = \frac{(AH_2^{-2})}{K_2(OH)} + (AH_2^{-2}) + (P) \quad (20)$$

Hence

$$(AH_2^{-2}) = \frac{(AH_4)_0 - (P)}{\frac{1}{K_2(OH)} + 1} \quad (21)$$

Substituting the values for (AH_3^{-1}) and (AH_2^{-2}) from eq. 19 and 21 into eq. 18 results in

$$\frac{dP}{dt} = k_1\left[\frac{(AH_4)_0 - (P)}{1 + K_2(OH)}\right] + k_2\left[\frac{(AH_4)_0 - (P)}{\frac{1}{K_2(OH)} + 1}\right] \quad (22)$$

which is transformed readily into

$$\frac{dP}{(AH_4)_0 - (P)} = \left[\frac{k_1 + k_2K_2(OH)}{1 + K_2(OH)}\right] dt \quad (23)$$

Integrating, solving for the integration constant, and resubstituting gives

$$\ln\left[\frac{(AH_4)_0}{(AH_4)_0 - (P)}\right] = k_{obs} \times t \quad (24)$$

where

$$k_{obs} = \frac{k_1 + k_2K_2(OH)}{1 + K_2(OH)} \quad (25)$$

As a first approximation

$$K_2 = K_{a2}/K_w = 10^4 \text{ (lit.}^{15}\text{ value of } pK_{a\,2} = 10)$$

If $(OH) = 10^{-6}$, then $1 >> K_2(OH)$, and thus eq. 25 reduces to

$$k_{obs} = k_1 + k_2K_2(OH) \quad (26)$$

A linear relationship of this nature is found to occur in the range of pH greater than 7 yet less than 8.5 having a slope equal to k_2K_2 and intercept k_1. Table I gives the values of k_2, K_2 and pK_{a2} obtained therefrom.

In the high pH range the only species in appreciable concentration are (AH_2^{-2}) and (AH^{-3}); *i.e.*

$$(AH_4)_0 = (AH_2^{-2}) + (AH^{-3}) + (P) \text{ (mass balance)} \quad (27)$$

$$(AH_2^{-2}) \xrightarrow{k_2} (P)$$

$$(AH^{-3} \xrightarrow{k_3} (P)$$

A derivation procedure similar to that given above produces

$$k_{obs} = \frac{k_2 + k_2K_2(OH)}{1 + K_3(OH)} \quad (28)$$

and if $k_{obs} >> k_2$

$$k_{obs} = k_3 - (k_{obs}/K_3(OH)) \quad (29)$$

The implied linear relationship can be viewed on Fig. 4 and this provides an estimate of k_3, K_3 and pK_{a3}.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, TULANE UNIVERSITY, NEW ORLEANS, LA.]

Conversion of 3-Amino-1,2-quinones to 6-Hydroxypicolinic and Isocarbostyril-3-carboxylic Acids[1]

BY J. H. BOYER[2] AND L. R. MORGAN, JR.[3]

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Both organic peroxyacids and paraperiodic acid transform 3-amino-1,2-quinones (VI) to corresponding 6-hydroxypicolini- and isocarbostyril-3-carboxylic acids (VII). Although peroxybenzoic acid transforms 3-aminobenzoquinone-1,2 (VIa) to 6-hydroxypicolinic acid (VIIa), the substitution of peroxyacetic for peroxybenzoic acid followed by hydriodic acid leads to the unexpected formation of pyridine and 2-hydroxypyridine. The latter is produced in similar reactions between this aminoquinone and peroxytrifluoroacetic or paraperiodic acid or more concentrated solutions of peroxyacetic acid.

In an enzymatic degradation of tryptophan, 3-hydroxyanthranilic acid (I) is converted by an unknown sequence to α-amino-β-carboxymuconic acid semialdehyde (II).[4] With decarboxylation and/or intramolecular cyclization the amino aldehyde gives quinolinic (III, R = R′ = CO_2H), nicotinic (R = H, R′ = CO_2H) and picolinic acids (III, R = CO_2H, R′ = H).[5] Both 3,4-dihydroxyanthranilic acid (V, X = CO_2H, Y = Z = H)[6] and a fused ring peroxide (IV)[7] have been considered

$$(OCH(R)C(AH)(R')O)_m \rightleftharpoons$$
$$A - O, NR''$$

$$m\ RCHC(AH)R' \rightleftharpoons m\ RCHC(=A)R'$$
$$\quad O—O \qquad\qquad\quad OOH$$

as intermediates in the unknown sequence from I to II.

Chemical conversions of benzene derivatives to pyridine derivatives by cleavage of the carbocyclic ring and recyclization have not been developed.[8]

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(3) (a) This investigation was carried out during the tenure of a Predoctoral Fellowship from the National Heart Institute, U. S. Public Health Service, 1959–1960; (b) Chemistry Department, Imperial College, University of London, London, Eng.

(4) O. Wiss and G. Bettendorf, *Hoppe-Seyler's Z. physiol. Chem.*, **306**, 145 (1957); A. Mujake, A. N. Bokman and B. S. Schweigert, *J. Biol. Chem.*, **211**, 391 (1954).

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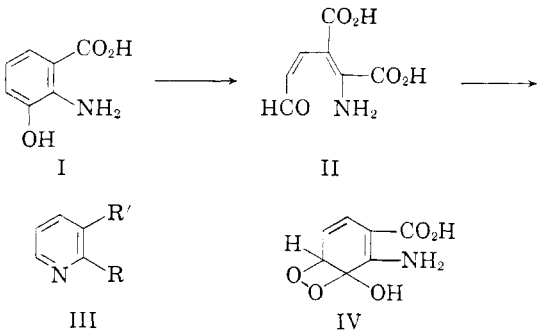
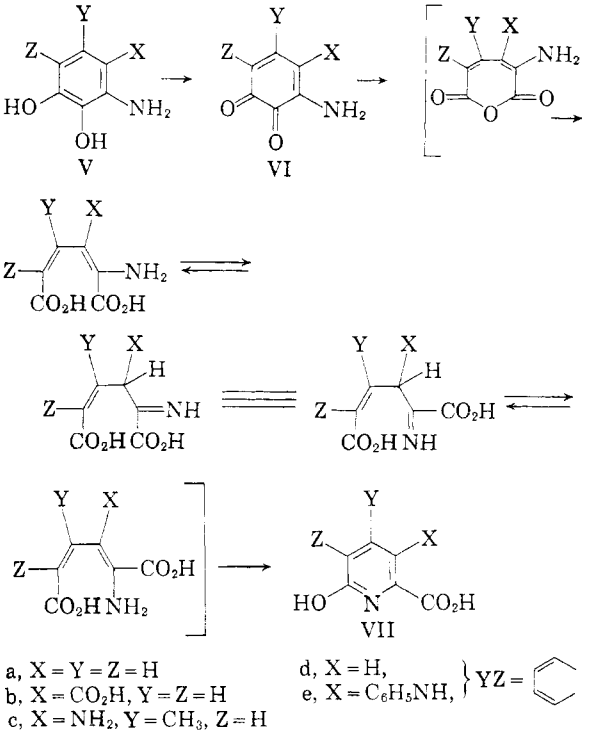
(6) K. Makino, F. Itoh and K. Nishi, *Nature*, **167**, 115 (1951).

(7) B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956). Peroxides from enols and oxygen have been assumed to be four-membered rings (W. von E. Doering and R. M. Haines, *ibid.*, **76**, 482 (1954)) and tautomeric hydroperoxides (A. A. Patchett and B. Witkop, *J. Org. Chem.*, **22**, 1477 (1957)). In a similar way peroxides from eneamines and oxygen have been assigned structures as hydroperoxides (C. L. Stevens and R. J. Gasser, *J. Am. Chem. Soc.*, **79**, 6059 (1957)) and tautomeric cyclic four-membered rings (C. D. Lunsford, R. E. Lutz and E. E. Bowden, *J. Org. Chem.*, **20**, 1513 (1955)). Dimeric and/or polymeric olefin peroxides may be in equilibrium with monomeric enol and eneamine peroxides and, in certain examples, may conceivably supply the predominating species; *cf.* the peroxide $(OCH_2CHClO)_2$ from vinyl chloride and oxygen (M. Lederer, *Angew. Chem.*, **71**, 162 (1959)).

(8) Ozonolysis of a substituted aminomethylcatechol ether followed by cyclization accounts for the construction of ring III as a pyridone in the synthesis of strychnine (R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daenker and K. Scheinker, *J. Am. Chem. Soc.*, **76**, 4749 (1954)). Pyridine is reported to be one of the products from benzene and active nitrogen (P. M. Aronovich, N. K. Bel'skii



I II III IV



V VI VII

a, X = Y = Z = H
b, X = CO_2H, Y = Z = H
c, X = NH_2, Y = CH_3, Z = H
d, X = H, } YZ =
e, X = C_6H_5NH, }

At this time we wish to describe a new method for the chemical conversion of 3-aminocatechols and 3-amino-1,2-dihydroxynaphthalenes, respectively, to 6-hydroxypicolinic and isocarbostyril-3-carboxylic acids.[9]

Unstable deeply colored (violet or blue-black) aminoquinones are obtained in solution on oxidation of 3-aminocatechol and four ring-substituted derivatives (V).[10] In an extension of the application of the Baeyer–Villiger reaction to *o*-quinones[11] each aminoquinone is oxidized with an organic peroxyacid to a corresponding derivative of 6-hydroxypicolinic or isocarbostyril-3-carboxylic acid, with the probable formation of an intermediate aminomuconic acid anhydride. The presence of strong ultraviolet light leads to intractable tars, possibly the result of isomerization of initially formed *cis-cis*-muconic acids to *trans-trans* modifications[12] followed by intermolecular condensation. Tautomerism of *cis-cis* acids gives the *cis-trans* modifications required for condensation to pyridines.[13] Paraperiodic acid may be substituted for peroxyorganic acids for the conversion of aminoquinones (VI) to 6-hydroxypicolinic or isocarbostyril-3-carboxylic acids (VII) in comparable yields.

Whereas peroxybenzoic acid transforms 3-amino-1,2-benzoquinone (VIa) to 6-hydroxypicolinic acid (VIIa), decarboxylation at an undetermined point and ring closure accounts for the formation of 2-hydroxypyridine from VIa and peroxyacetic, peroxytrifluoroacetic or paraperiodic acids. Treatment of VIa with more dilute peroxyacetic acid followed by hydriodic acid leads to the formation of pyridine along with 2-hydroxypyridine. Apparently a reductive cleavage of an intermediate peroxide occurs in competition with the Baeyer–Villiger transformation.[14] Decarboxylation at an undetermined stage and ring closure of 5-aminopentadien-2,4-al-1, or a derivative, are believed to be required in the reaction sequence leading to pyridine. Additional investigations are planned to clarify this transformation since similar treatment of other aminoquinones (VIb-e) brings about the formation of the expected derivatives of hydroxypicolinic or isocarbostyril carboxylic acids (VIIb-e) with no trace of a corresponding non-hydroxylated pyridine derivative.

Experimental[15]

6-Hydroxyquinolinic Acid.—After a mixture of 0.41 g. (0.0024 mole) of 3,4-dihydroxyanthranilic acid, 3.6 g. of silver oxide, 10 g. of anhydrous sodium sulfate and 600 ml. of anhydrous ethyl acetate was shaken at room temperature for 15 minutes, insoluble inorganic material was removed and the solution, concentrated to about 50 ml., was treated with 4.0 g. of 20% peroxyacetic acid in glacial acetic acid added dropwise at 0° as the color changed from violet to orange. After storage for 2 days at 10° evaporation in an air stream left an oil residue which was dissolved in a minimum amount of hot 10% sodium hydroxide. The alkaline solution was neutralized at room temperature with the addition of 0.1 *N* hydrochloric acid. On standing at 5° for 2 days, 6-hydroxyquinolinic acid separated as colorless needles, 0.17 g. (41.2%), m.p. 253–254° after recrystallization from boiling water.

A 16.1% yield was obtained when peroxytrifluoroacetic acid was substituted for peroxyacetic acid.

To a solution of 3-amino-4-carboxy-1,2-benzoquinone (from 0.41 g., 0.0024 mole, of 3,4-dihydroxyanthranilic acid with 3.6 g. of silver oxide in 50 ml. of absolute ethanol and 350 ml. of ethyl acetate) 2.95 g. (0.014 mole) of paraperiodic acid in 15 ml. of ethyl acetate was added. The heterogeneous mixture was stirred for 2 hours at 10° and allowed to stand undisturbed at 10° in the dark for 24 hours. Extraction of an oil residue from the dark brown filtered solution with 100 ml. of hot benzene afforded upon cooling

and B. M. Mikhailov, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 696 (1956); *C. A.*, **51**, 1893 (1957)) and from benzene and certain azides (A. Bertho, T. Curtius and K. Schmidt, *Ber.*, **60**, 1717 (1927)).

(9) J. H. Boyer and L. R. Morgan, Jr., *J. Am. Chem. Soc.*, **82**, 4748 (1960).

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(11) P. Karrer, R. Schwyzer and A. Neuwirth, *Helv. Chim. Acta*, **31**, 1210 (1948).

(12) In boiling water exposed to an ultraviolet lamp, *cis-cis*-muconic acid is quantitatively changed to the *trans-trans* isomer (J. A. Elvidge, R. P. Linstead, B. H. Orkin, P. Sims, H. Baer and D. P. Patison, *J. Chem. Soc.*, 2228 (1950)).

(13) It has been demonstrated that tautomerism of primary vinylamines allows the imine form to be predominant in most examples.[7]

(14) Solvolytic opening of the quinone ring probably leads to tar formation; however, solvolysis experiments with VIa in both acids and bases did not result in the formation of detectable quantities of a pyridine compound. Compare the facile alkaline hydrolysis of biacetyl in 0.05 *N* sodium hydroxide at 25° to acetic acid and acetaldehyde (G. Machell, *J. Chem. Soc.*, 683 (1960)).

(15) Semi-micro analyses by Alfred Bernhardt, Max Planck Institut Microanalytisches Laboratorium, Mulheim (Ruhr), Germany. Melting points are uncorrected.

slender colorless needles of 6-hydroxyquinolinic acid, 41 mg. (11.1%), m.p. and mixture m.p. 252–254° after recrystallization from water.

6-Hydroxypicolinic Acid.—To the concentrated (about 50 ml.) filtrate, from the oxidation of 1.2 g. (0.0074 mole) of 3-aminocatechol hydrochloride, m.p. 196–202° dec., with 5.0 g. of silver oxide and 15 g. of anhydrous sodium sulfate in 300 ml. of anhydrous chloroform, a solution of 1.4 g. (0.0093 mole) of peroxybenzoic acid in 30 ml. of anhydrous chloroform was added slowly. During 24 hours at room temperature, the deep blue color changed to pale yellow. The solution was treated with 50 ml. of aqueous sodium bicarbonate, washed with 100 ml. of water and dried over anhydrous sodium sulfate. A yellow residue remained after removal of the solvent *in vacuo* and was recrystallized from acetic acid as amorphous colorless powder, 0.12 g. (12.3%), m.p. 273.5–276° dec.[16] On pyrolysis at 285°, carbon dioxide, isolated in the usual way as barium carbonate, and 2-hydroxypyridine, m.p. and mixture m.p. 106–107°, were formed.

Peroxyacetic, Peroxytrifluoroacetic or Paraperiodic Acid and 3-Aminobenzoquinone-1,2.—From 2.0 g. (0.012 mole) of 3-aminocatechol hydrochloride in 80 ml. of anhydrous ethyl acetate containing 10 g. of anhydrous silver oxide and 15 g. of anhydrous sodium sulfate, shaken at room temperature for 25 minutes, a deep violet solution of 3-aminobenzoquinone was obtained and separated from insoluble material. The filtrate, concentrated to about 25 ml., was treated dropwise with 5.0 g. of 25% peroxyacetic acid in glacial acetic acid at 10–15° with stirring. After 24 hours at 10°, a 10% solution of potassium iodide was added until a negative peroxide test was indicated by starch–iodide paper. The organic layer was extracted with two 15-ml. portions of 0.1 *N* sodium carbonate solution and the extracts applied dropwise to a chromatographic column of 25 g. of Dowex 2-X resin. The column was washed with two 10-ml. portions of water and the washings combined with previous eluate. This combined solution gave a negative test for a phenolic hydroxyl group with 10% ferric chloride. On acidification of this alkaline solution to a *p*H 3 with 0.1 *N* hydrochloric acid and evaporation to dryness, a residue was obtained and extracted with ethanol. Evaporation of ethanol left 150 mg. (12%) of **pyridine hydrochloride** m.p. 143–144° dec.[17] Pyridine picrate, m.p. and mixture m.p. 163–164°,[18] was obtained by treating the hydrochloride with 10% sodium carbonate followed by ethanolic picric acid. Lower yields of pyridine hydrochloride were obtained when weaker solutions of peroxyacetic acid were used or when the temperature was maintained lower than 0°.

The column then was washed with two 10-ml. portions of 0.05 *N* hydrochloric acid and two 10-ml. portions of water. Evaporation of the combined washings left a residue, 161 mg. (14.1%), m.p. and mixture m.p. 107.5°,[19] of **2-hydroxypyridine.** Lower yields of 2-hydroxypyridine were obtained when the temperature was maintained below 0°. No product could be isolated when the reaction temperature was 24°. The best yield of pyridine (18%) without a detectable amount of pyridine hydrochloride was obtained in a similar reaction at 10° with 30% peroxyacetic acid in glacial acetic acid.

A trifluoroperoxyacetic acid solution prepared in 25 ml. of ethylene chloride from 4.2 ml. (0.03 mole) of trifluoroacetic anhydride and 0.85 g. (0.025 mole) of 90% hydrogen peroxide was added slowly at 0° to an ethylene chloride solution of 3-amino-1,2-benzoquinone prepared by oxidation of 1.0 g. (0.006 mole) of 3-aminocatechol hydrochloride in 80 ml. of ethylene chloride with 5 g. of silver oxide and 15 g. of anhydrous sodium sulfate at room temperature for 2 days in the dark. The amber solution was treated with 10% potassium iodide until a negative test for peroxide was obtained. Two 15-ml. extracts of the residue, after removal of the solvent *in vacuo*, were obtained with hot 0.1 *N* aqueous sodium carbonate and applied dropwise to a chromatographic column of 50 g. of Dowex 2-X resin. The column was washed with two 10-ml. portions of water. Pyridine hydrochloride was not detected in the residue obtained on evaporation to dryness of the combined washings and original eluate after acidification with hydrochloric acid. The column was next washed with three 10-ml. portions of 0.1 *N* hydrochloric acid and two 10-ml. portions of water. Evaporation of the combined washings left 52 mg. (9.5%) of **2-hydroxypyridine**, m.p. and mixture m.p. 106–107°.

A similar reaction in refluxing ethylene chloride gave a resin from which neither pyridine, 2-hydroxypyridine nor 6-hydroxypicolinic acid could be detected. At 0° unreacted starting material was recovered (10–20%) and pyridine compounds were not detected.

To a solution of 3-amino-1,2-benzoquinone (from 1.0 g. (0.006 mole) of 3-aminocatechol hydrochloride and 10 g. of silver oxide in 300 ml. of ethyl acetate and 50 ml. of absolute ethanol), 2.9 g. (0.014 mole) of paraperiodic acid in 15 ml. of ethyl acetate was added and stirred for 1 hour at room temperature and stored at room temperature in the dark for 24 hours. Removal of the filtered solvent *in vacuo* left a residue which was extracted with 25 ml. of 10% sodium carbonate. The sodium carbonate solution was passed over 25 g. of Dowex 2-X resin, and the column washed with 15 ml. of distilled water, two 15-ml. portions of 0.5 *N* hydrochloric acid and two 10-ml. portions of water. The combined washings, evaporated to dryness, gave 132 mg. (11.5%) of **2-hydroxypyridine**, m.p. and mixture m.p. 107–108°. Pyridine hydrochloride was not detected.

3-Amino-4-methyl-6-hydroxypicolinic Acid.—An ethyl acetate solution of 3,4-diamino-5-methylbenzoquinone-1,2 (from 3,4-dihydroxy-5,6-diaminotoluene hydrobromide and silver oxide) on treatment with peroxyacetic acid gave a compound assigned the structure of 3-amino-4-methyl-6-hydroxypicolinic acid as yellow plates, m.p. 285–288° dec., from benzene in 11.3% yield.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 49.70; H, 4.76; N, 16.56; O, 28.38; Found: C, 50.23; H, 4.82; N, 16.59; O, 28.49.

Isocarbostyril-3-carboxylic Acid.—In 60 ml. of anhydrous pyridine 2.0 g. (0.0095 mole) of 3-amino-1,2-dihydroxynaphthalene hydrochloride was oxidized with 4.4 g. of silver oxide in the presence of 10 g. of anhydrous sodium sulfate over a period of 15 minutes at room temperature; the color changed from pale orange to deep violet. Distillation *in vacuo* of the filtrate separated from inorganic material left 1.91 g. of a dark residue which was treated with 9.6 g. (0.0058 mole) of 25% peroxyacetic acid in glacial acetic acid, added slowly with stirring at 10° as the color changed back to pale orange. After storage at 10° for 2 days excess peroxide was removed by the addition of 10% potassium iodide and the mixture was made alkaline with 10% potassium hydroxide. A colorless precipitate dissolved on heating to a red solution from which deposited flocculent micro-crystals of isocarbostyril-3-carboxylic acidon acidification of the cooled solution. Recrystallization from acetone gave colorless needles, 1.1 g. (65.2%), m.p. 318–319.5°.[20] Isocarbostyril, m.p. 208°,[21] was obtained on heating the acid for 15 minutes at 250–300°.

Yields of 54.5% and 47.1% were obtained when peroxytrifluoroacetic and paraperiodic acids were substituted for peroxyacetic acid.

4-Anilinoisocarbostyril-3-carboxylic Acid.—An ethyl acetate solution of 3-amino-4-anilino-1,2-naphthoquinone (from 3-amino-4-anilino-1,2-dihydroxynaphthalene hydrochloride and silver oxide) on treatment with peroxyacetic acid according to the above procedure gave a compound assigned the structure of 4-anilinoisocarbostyril-3-carboxylic acid; orange plates, m.p. 250–256.1° dec., from *p*-xylene in 31.2% yield.

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99; O, 17.12. Found: C, 68.35; H, 4.08; N, 9.81; O, 17.21.

A 19.1% yield was obtained when peroxytrifluoroacetic acid was substituted for peroxyacetic acid.

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