Studies on the Reactions of 2,6-Pyridinediols and Related Compounds (1a)

B. C. Pathak, S. P. Dutta, and T. J. Bardos (1b)

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo

The syntheses and interconversions of a number of new 2,6-pyridinediol derivatives and related compounds are described. These include a "pyridyne" reaction, brominations with hydrobromic acid - nitrite mixture, and N-benzylations with benzyl alcohol.

Earlier work of this research group showed that 3-diazocitrazinic acid, a 2,6-pyridinediol derivative structurally derived from orotic acid by replacement of the N_1-nitrogen of the pyrimidine ring with a $>CN_2$ group, is an effective antimetabolite of orotic acid in bacterial systems (2). A similar structural alteration of uracil would lead to 3-diazo-2,6-pyridinediol (4a) which, by analogy, could be expected to act as an antimetabolite of uracil. In the course of several unsuccessful attempts to prepare this compound and its logical synthetic precursor, the corresponding 3-amino derivative 4, some interesting reactions of 2,6-disubstituted pyridines were observed, and a number of new pyridine derivatives were synthesized. These are reported in the present paper.

Reaction of 2,6-pyridinediol (1) with benzenediazonium chloride gave a mixture of the mono- and diphenylazo derivatives (2 and 3) which could be separated by chromatography on a silica gel column. However, hydrogenation of 2 in the presence of platinum oxide or palladium on carbon catalyst, in strong acid media (in an effort to stabilize the amine 4 by salt formation) gave a product which could not be purified nor converted in situ by diazotization to the desired 4a. Similarly, hydrogenation of the known 3-nitroso-2,6-pyridinediol

(5) (3) with palladium-on-carbon catalyst, in trifluoroacetic acid, and subsequent diazotization in situ with amyl nitrite (2), resulted in the formation of a black polymeric product.

Attempts to prepare the aminopyridine 4 from 2,6-dibenzyloxy-3-bromopyridine (7) (4), by treatment with liquid ammonia for a period of 12 hours, led only to the recovery of unchanged starting material. 3-Aminopyridines, as well as 3,5-diaminopyridines, were prepared by Zwart and Wibaut (5) by heating the corresponding bromopyridine with aqueous ammonia in the presence of cupric sulfate. When compound 7 was treated in a similar manner, only 10% of the halogen could be displaced (as shown by determination of the inorganic bromide formed), and the amino compound could not be isolated from the reaction mixture. However, treatment of 7 with liquid ammonia and sodamide resulted in 48% bromine displacement, and from the reaction mixture, by extraction and chromatography, a pure amino compound could be isolated in 38% yield. This, however, was proved to be the 4-amino derivative, (8), on the basis of its n.m.r. spectrum as well as by its conversion to the known N-acetyl glutazine (10) (6) (See Scheme I). Attempted replacement of the amino group of 8 with bromine by diazotization in

SCHEME I
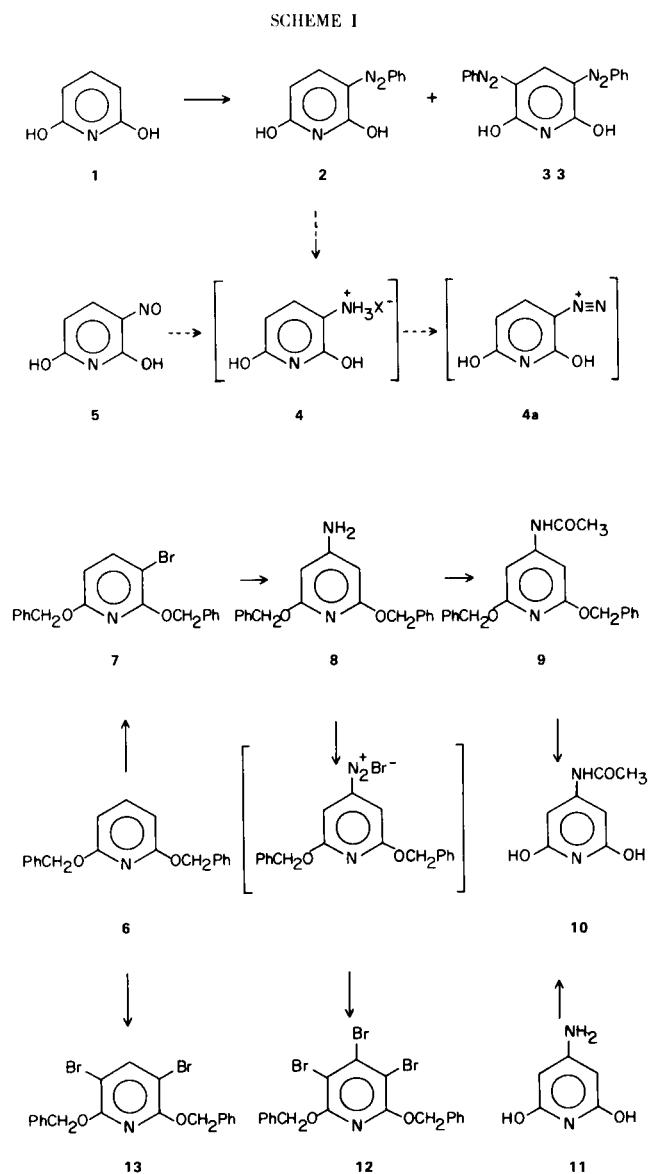
hydrobromic acid gave directly, in over 60% yield, the 3,4,5-tribromo derivative **12**; this might not have been obtained from 3-amino-2,6-pyridinediol *via* the corresponding diazonium compound, since only the 3 and 5 positions of the pyridine ring are sufficiently activated by the benzyloxy-groups to undergo bromination under such mild conditions (see below). Even so, the high yield of **12** obtained in this reaction, involving facile replacement of the amino group and bromination of all open positions of **8** (without cleavage of the benzyl-ether linkages) by the hydrobromic acid-nitrite mixture, appeared to be somewhat surprising. For this reason, the reaction of 2,6-dibenzyl-oxypyridine (**6**) with the same reagent (sodium nitrite in 48% aqueous hydrobromic acid) was investigated under identical conditions. The product, obtained in over 60%

yield, was identified as 3,5-dibromo-2,6-dibenzyloxy-pyridine (**13**). The same product also resulted from bromination of **6**, with bromine in glacial acetic acid (Scheme I).

The formation of 4-amino-2,6-dibenzyloxypyridine (**8**) in the reaction of 3-bromo-2,6-dibenzyloxypyridine (**7**) with sodamide in liquid ammonia presents a new example of reactions involving a "pyridyne" intermediate (7a-7e). The course of addition of ammonia to give the 4-amino derivative, corresponds to previous observations concerning the *meta* directing influence of alkoxy substituents in the addition reactions of pyridyne or benzyne (8).

In another approach toward the preparation of **4**, the known 2,6-dibromo-3-aminopyridine, **14**, was acetylated to give **15** which was then treated with a mixture of sodium benzyloxide and benzyl alcohol at 180°. Three products were isolated from the reaction mixture in pure state, by chromatography on alumina (See Scheme II). These were identified by spectra and analyses as (a) 2-benzyloxy-3-benzylamino-6-bromopyridine (**17**), (b) 2-benzyloxy-3-amino-6-bromopyridine (**18**) and (c) 2,6-dibenzyloxy-3-aminopyridine (**19**), in a molar ratio of 10.3:42.8:20.0. Thus, while one, or both halogens were in this reaction replaced with a benzyloxy-group, the N-acetyl group was completely lost by solvolysis and, in the case of **17**, replaced by a benzyl group. The structure of **17** was further confirmed by hydrogenolysis in the presence of palladium on carbon to give the hydrobromide of 3-amino-2-pyridone (2-hydroxy-3-aminopyridine) (**20**), identical with the product obtained by the hydrogenation of 2-benzyloxy-3-aminopyridine (**23**) in the presence of hydrobromic acid. Compound **23** was one of the two products isolated from the reaction of the known 2-chloro-3-aminopyridine (2) (**22**) with sodium benzyloxide in benzyl alcohol; the other product of the latter reaction was identified by spectra and analysis as 2-benzyloxy-3-benzylaminopyridine (**24**). An attempt to prepare the hydrochloride of **24** resulted in cleavage of the benzyl-ether linkage, to give the hydrochloride of 2-hydroxy-3-benzylaminopyridine (**27**) (See Scheme II).

Compound **18**, the major product from the reaction of **15**, was benzoylated to give **21** which then was hydrogenolyzed in alcohol solution (palladium on carbon). The product of this reaction was identified as 2-hydroxy-3-benzamidopyridine (**26**) identical with the product obtained from **23** by benzoylation to **25** and subsequent hydrogenolysis (See Scheme II).

Hydrogenation of compound **19**, the third product isolated from the reaction of **15**, did not however, lead to the isolation of the desired amine **4** or its hydrochloride salt. The product obtained after consumption of the theoretical amount of hydrogen, could not be purified as it underwent rapid oxidation and/or self-condensation

(Scheme II).

SCHEME II
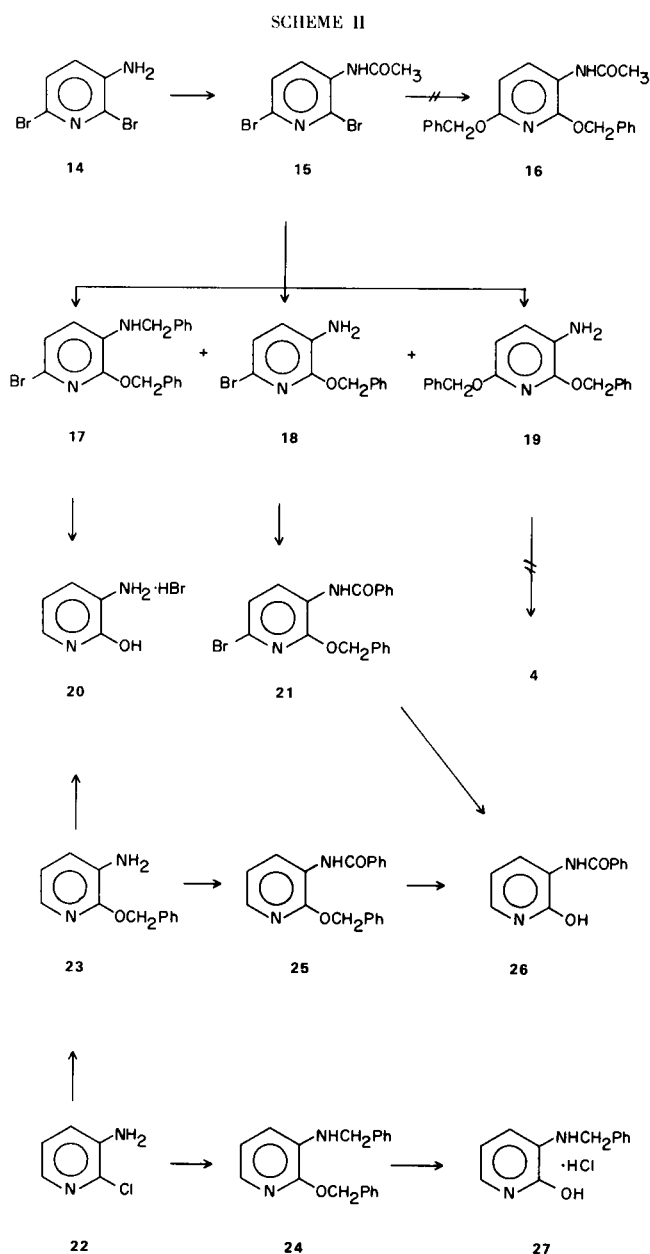
The observed N-benzylations of the two aminopyri-dines, **14** (resulting from the solvolysis of its N-acetyl derivative **15**) and **22**, with sodium benzyloxide and benzyl alcohol, are similar to the benzylation of aromatic amines with benzyl alcohol and potassium hydroxide, a reaction described by Sprinzak (10). The mechanism of this reaction was proposed to involve intermediate oxidation of the benzyl alcohol to benzaldehyde followed by Schiff base formation and reduction. Another similar reaction

described in the literature is the N-alkylation of 2-amino-pyridine with cyclohexanol, or isopropyl alcohol, in the presence of sulfuric acid (11). However, subsequent experiments showed that **14** could be N-benzylated by heating with benzyl alcohol at 180°, in the absence of either base or acid. In this case, neither of the two bromo-substituents underwent replacement, and the only product obtained (in 54% yield) was 2,6-dibromo-3-benzyl-aminopyridine (**28**).
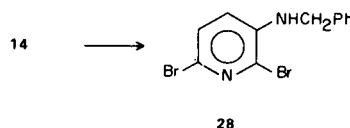
It cannot be excluded, however, that a small amount of bromine displacement did occur, and the liberated hydro-gen bromide could have catalyzed the benzylation of the amino group.

The fact that the desired 3-amino-2,6-pyridinediol (**4**) could not be isolated from any of the reaction mixtures obtained in the attempted reductions of either **2, 5** or **19**, is apparently due to the reactivity of its o-aminocarbonyl functions, leading to self-condensation. The observed in situ polymerization of the 3-diazo derivative **4a** probably involves the reaction of the diazonium group with the highly reactive 5-position of the 2,6-pyridinediol.

EXPERIMENTAL

3-Phenylazo-2,6-pyridinediol (**2**) and 3,5-Bis(phenylazo)-2,6-pyridinediol (**3**).

To a solution of 2,6-pyridinediol (**1**, 0.01 mole) in 10% aqueous sodium hydroxide (20 ml.), a solution of diazotized aniline (0.01 mole) in dilute hydrochloric acid (12 ml., 1.4 N) was slowly added. After stirring at room temperature for 18 hours, the mixture was acidified with acetic acid, the precipitate was collected by filtration, washed with water and dried. The crude product on TLC in a mixture of chloroform-ethanol (19:1) showed two major spots (one yellow and the other red); this material was then chromatographed over silica gel (200 g.). Elution of the column with chloroform-ethanol (99:1) resulted in the isolation of 520 mg. (yield 24.2%) of a yellow compound, 3-phenylazo-2,6-pyridine-diol (**2**), m.p. 218-220°, crystallized from aqueous methanol; infrared cm^{-1} (potassium bromide) 3180 (NH), 1700, 1675 (α-pyridone), 1590, 1525. N.M.R. (trifluoroacetic acid) δ 7.15

(5H, s; phenyl), 7.50 and 6.05 (1H each, d; J = 10 cps; pyridine).

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.40; H, 4.19; N, 19.53. Found: C, 61.46; H, 4.29; N, 19.35.

Continued elution of the column with chloroform-methanol (49:1) led to the isolation of 1.7 g. (53%) of a red compound, 3,5-bis(phenylazo)-2,6-pyridinediol (3), m.p. 200-202°, crystallized from chloroform-methanol; infrared cm^{-1} (potassium bromide) 3200, 3100 (NH), 1700, 1660 (α-pyridone), 1590, 1570 and 1515. N.M.R. (trifluoroacetic acid) δ 8.45 (1H, s; pyridine) 7.52-7.30 (10H, m; phenyl).

Anal. Calcd. for $C_{17}H_{13}N_5O_2$: C, 63.95; H, 4.08; N, 21.94. Found: C, 63.33; H, 4.43; N, 21.49.

2,6-Dibenzyloxy-4-aminopyridine (8).

A mixture of 2,6-dibenzyloxy-3-bromopyridine (7, 0.01 mole), prepared by the bromination of 2,6-dibenzyloxypyridine (6), sodamide (0.015 mole) and liquid ammonia (150 ml.) was stirred for 8 hours at room temperature. After allowing the excess liquid ammonia to evaporate at room temperature, the residue was triturated with water and the dark, insoluble material was extracted with benzene (200 ml.). The benzene solution was washed with water (4 x 50 ml.), dried over sodium sulfate and evaporated to dryness. The crude material was chromatographed over neutral alumina (50 g.). Elution with chloroform led to the isolation of 2,6-dibenzyloxy-4-aminopyridine (8, 1.29 g., 38%), m.p. 74-75°, crystallized from benzene-petroleum ether; infrared cm^{-1} (potassium bromide) 3400 and 1640 (NH₂), 1570, 1445, 750, and 735. N.M.R. δ 7.32 (10H, s; phenyl), 5.65 (2H, s; pyridine), 5.3 (4H, s; -OCH₂Ph).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.51; H, 5.88; N, 9.15. Found: C, 74.35; H, 6.07; N, 8.94.

2,6-Dibenzyloxy-4-acetamidopyridine (9).

A mixture of 8 (100 mg.) and acetic anhydride (5 ml.) was heated on a steam bath for 8 hours and evaporated to dryness under reduced pressure. The crude product was worked up in the usual manner to yield 2,6-dibenzyloxy-4-acetamidopyridine (9, 85 mg., 75.9%), m.p. 88-89°, crystallized from cyclohexane; infrared cm^{-1} (potassium bromide) 3300 (NH), 1680 (C=O), 1590, 1445, 1058, 750 and 730.

Anal. Calcd. for $C_{21}H_{20}N_2O_3$: C, 72.41; H, 5.75; N, 8.05. Found: C, 72.07; H, 6.09; N, 8.03.

2,6-Dihydroxy-4-acetamidopyridine (10).

A solution of 9 (0.005 mole) in glacial acetic acid (50 ml.) was hydrogenated for 8 hours under atmospheric pressure in presence of palladium-charcoal (10%; 250 mg.). During this period the theoretical amount of hydrogen was consumed, after which the catalyst was filtered off and the residue was crystallized from hot water (charcoal), m.p. 296-297° (608 mg., 72.4%). The melting point was undepressed on admixture with a sample of N-acetyl glutazine (10), prepared via glutazine (11) according to literature procedures (6). The identity of these two compounds was further confirmed by comparison of their infrared spectra.

2,6-Dibenzyloxy-3,4,5-tribromopyridine (12).

A solution of 8 (0.001 mole) in aqueous hydrobromic acid (48%, 15 ml.) was cooled to 0° and treated with aqueous sodium nitrite solution (50%, 4 ml.) under constant stirring. After the addition of sodium nitrite solution was over, the reaction mixture was stirred for two hours and then extracted with chloroform (100 ml.), the chloroform extract was washed with water (4 x 50 ml.) until the washings were free of acid, with aqueous sodium

thiosulphate solution (2 x 50 ml.), again with water (3 x 50 ml.), and dried over sodium sulfate. On evaporation of the solvent, a residue was left which was chromatographed over silica gel (50 g.). Elution of the column with petroleum ether-chloroform (1:1) resulted in the isolation of 2,6-dibenzyloxy-3,4,5-tribromopyridine (12)(3.30 g., 60.8%), m.p. 108-109°, crystallized from chloroform-methanol; infrared cm^{-1} (potassium bromide) 1550, 1445, 735. N.M.R. δ 7.6 (10 H, s; phenyl), 5.55 (4H, s; -OCH₂Ph).

Anal. Calcd. for $C_{19}H_{14}Br_3NO_2$: C, 43.18; H, 2.65; N, 2.65; Br, 45.45. Found: C, 43.37; H, 2.68; N, 2.71; Br, 45.75.

2,6-Dibenzyloxy-3,5-dibromopyridine (13).

Method a.

To a solution of 6 (0.008 mole) in glacial acetic acid (25 ml.) was slowly added a solution of bromine (0.024 mole) in acetic acid (10 ml.). The mixture was stirred for 1 hour at room temperature and then diluted with water. The precipitate was filtered, washed with water (3 x 25 ml.), dried and crystallized from methanol to yield 13, (3.2 g., 88.9%), m.p. 74°; infrared cm^{-1} (potassium bromide 1560, 1455, 740. N.M.R. δ 7.53 (10H, s; phenyl), 8.05 (1H, s: pyridine), 5.56 (4H, s; -OCH₂Ph).

Anal. Calcd. for $C_{19}H_{15}Br_2NO_2$: C, 50.78; H, 3.34; N, 3.12; Br, 35.63. Found: C, 50.96; H, 3.51; N, 3.00; Br, 35.85.

Method b.

To a solution of 6 (0.001 mole) in aqueous hydrobromic acid (48%, 15 ml.) at 0° was added an aqueous sodium nitrite solution (50%, 4 ml.) with constant stirring. After the addition was over, the reaction mixture was stirred for an additional 2 hours at 0°. The reaction mixture was then filtered, the precipitate was washed with water (5 x 30 ml.), dried and crystallized from methanol, m.p. and mixed m.p. with 13, 73-74° (yield 270 mg, 60%). The identity of this compound with 13 was further confirmed by a comparison of their infrared spectra.

2,6-Dibromo-3-acetamidopyridine (15).

A solution of 2,6-dibromo-3-aminopyridine(9)(14, 0.020 mole) in acetic anhydride (20 ml.) was heated on a steam bath for 3 hours after which the excess acetic anhydride was decomposed by heating with water. The reaction mixture was diluted with water, the precipitate was filtered off, washed with water (4 x 10 ml.), dried and crystallized from 95% ethanol, m.p. 148-150° (4.5 g., 76.3%); infrared cm^{-1} (potassium bromide) 3350 (NH), 1700 (C=O).

Anal. Calcd. for $C_7H_6Br_2N_2O$: C, 28.57; H, 2.04; N, 9.52; Br, 54.42. Found: C, 28.60; H, 1.92; N, 9.34; Br, 54.56.

Reaction of 2,6-Dibromo-3-acetamidopyridine (15) with Sodium Benzyloxide and Benzyl Alcohol.

A mixture of sodium benzyloxide (0.044 mole), (15, 0.02 mole) and benzyl alcohol (20 ml.) was heated at 180° for 4 hours. After the reaction, the excess benzyl alcohol was removed under reduced pressure and the residue was extracted with ether (4 x 50 ml.). On evaporation of the solvent an oily residue was obtained which was chromatographed over neutral alumina. Elution of the column, first with petroleum ether, then with mixtures of petroleum ether with increasing concentration of methylene chloride and finally with pure methylene chloride afforded three products:

Product a. 2-Benzyloxy-3-benzylamino-6-bromopyridine (17).

Compound 17 melted at 78-80° when crystallized from cyclohexane (0.76 g. 10.3%), infrared cm^{-1} (potassium bromide) 3480 (NH), 1580, 1450, 1420, 745 and 735. N.M.R. (carbon tetrachloride) δ 7.35 and 7.20 (5H each, s; phenyl), 6.35 and

6.80 (1H each, d; J = 8 cps; pyridine), 5.35 (2H, s; -OCH₂Ph), 4.45 (1H, m; -NH), 4.15 (2H, broad singlet; -N-CH₂Ph).

Anal. Calcd. for C₁₉H₁₇BrN₂O: C, 61.79; H, 4.61; N, 7.59; Br, 21.68. Found: C, 61.88; H, 4.55; N, 7.44; Br, 21.91.

Product b. 2-Benzyloxy-3-amino-6-bromopyridine (18).

Compound **18** melted at 53-54° when crystallized from *n*-heptane (2.38 g., 42.8%); infrared cm⁻¹ (potassium bromide) 3500(NH₂), 1600, 1460 and 735. N.M.R. δ 7.45 (5H, s; phenyl), 6.54 (1H, d; J = 8 cps; 4-H of pyridine), 6.77 (1H, d; J = 7 cps; 5-H of pyridine), 5.35 (2H, s; -OCH₂Ph), 3.75 (2H, s; -NH₂).

Anal. Calcd. for C₁₂H₁₁BrN₂O: C, 51.61; H, 3.94; N, 10.04; Br, 28.67. Found: C, 51.80; H, 4.07; N, 9.91; Br, 28.81.

A solution of **18** (0.004 mole) in pyridine (5 ml.) was stirred at room temperature with benzoyl chloride (0.01 mole) for 16 hours. The reaction mixture was then diluted with water, the precipitate was collected by filtration, washed with water, dried and crystallized from ethanol to yield 2-benzyloxy-3-benzamido-6-bromopyridine (21), m.p. 116° (0.92 g., 60%); infrared cm⁻¹ (potassium bromide) 3310 (NH), 1640 (C=O), 1580, 1460, 750 and 730.

Anal. Calcd. for C₁₉H₁₅BrN₂O₂: C, 59.53; H, 3.92; N, 7.31; Br, 20.89. Found: C, 59.58; H, 4.10; N, 7.37; Br, 21.42.

Product c. 2,6-Dibenzyloxy-3-aminopyridine (19).

This compound was isolated as the hydrochloride (yield 1.4 g., 20%), crystallized from ethanol-ethyl acetate, m.p. 174-175°; infrared cm⁻¹ (potassium bromide) 2900 (NH₃⁺ assoc.), 1625, 1460 and 760. N.M.R. δ 7.35 (10H, s; phenyl) 6.75 and 6.15 (1H each d, J 8 cps; pyridine), 5.2 and 5.3 (2H each, s; -OCH₂Ph).

Anal. Calcd. for C₁₉H₁₉ClN₂O₂: C, 66.57; H, 5.55; N, 8.18; Cl, 10.36. Found: C, 66.45; H, 5.43; H, 8.32; Cl, 10.57.

Reaction of 2-Chloro-3-aminopyridine (22) with Sodium Benzyl-oxide and Benzyl Alcohol.

A mixture of 2-chloro-3-aminopyridine (22, 0.033 mole), sodium benzyloxide (0.036 mole) and benzyl alcohol (13 ml.) was stirred at 180° in a nitrogen atmosphere for 3 hours. The excess solvent was then removed under reduced pressure and the residue was extracted with ether (3 x 40 ml.). The ethereal extract on evaporation yielded a gummy residue. TLC in the solvent system chloroform-methanol (49:1) showed two major spots. This material was chromatographed over neutral alumina (100 g.). Elution of the column with chloroform resulted in the isolation of two products:

Product a. 2-Benzyloxy-3-benzylaminopyridine (24).

This compound melted at 95-97°, crystallized from chloroform-petroleum ether, (1.4 g., yield 14.6%); infrared cm⁻¹ (potassium bromide) 3350 (NH), 1580, 1445, 1420, 740 and 730. N.M.R. δ 7.35 (10H, s; phenyl), 6.80 and 6.20 (1H and 2H, respectively, m; pyridine), 5.25 (2H, s; -OCH₂Ph), 4.35 (2H, m; -NCH₂Ph).

Anal. Calcd. for C₁₉H₁₈N₂O: C, 78.62; H, 6.21; N, 9.66. Found: C, 78.10; H, 6.24; N, 9.34.

On treatment with alcoholic hydrochloric acid, **24** yields a crystalline compound which from analytical data appears to be 2-hydroxy-3-benzylaminopyridine hydrochloride (27), m.p. 178-180°, crystallized from ethyl acetate; infrared cm⁻¹ (potassium bromide) 2900 (assoc. NH⁺), 1660 (α-pyridone), 1550, 1440, 750. N.M.R. (deuteriomethanol) δ 7.42 (7H, m; five phenyl and two pyridine protons at positions 4 and 6), 6.45 (1H, t; J = 7 cps; pyridine 5-H), 4.58 (2H, s; -NHCH₂Ph).

Anal. Calcd. for C₁₂H₁₃ClN₂O: C, 60.89; H, 5.50; N, 11.84; Cl, 15.01. Found: C, 60.53; H, 5.78; N, 11.69; Cl, 15.10.

Product b. 2-Benzyloxy-3-aminopyridine (23).

This product melted at 114-116°, crystallized from chloroform-petroleum ether (1.3 g., 19.7%); infrared cm⁻¹ (potassium bromide) 3500 (NH₂), 1580, 1440, 745. N.M.R. δ 7.4 (5H, s; phenyl), a number of peaks in the region 6.1-6.9 (3H; pyridine) 5.25 (2H, s; -OCH₂Ph), 4.15 (2H, m; NH₂).

Anal. Calcd. for C₁₂H₁₂N₂O: C, 72.0; H, 6.00; N, 14.00. Found: C, 72.10; H, 6.14; N, 13.88.

This compound was benzoylated with benzoyl chloride in pyridine as in the case of **18** mentioned above. The product, 2-benzyloxy-3-benzamidopyridine (25), was crystallized from aqueous ethanol, (yield 71%), m.p. 115°; infrared cm⁻¹ (potassium bromide) 3400 (NH), 1650 (C=O), 1525, 1460, 760, 730.

Anal. Calcd. for C₁₉H₁₆N₂O₂: C, 75.00; H, 5.26; N, 9.21. Found: C, 74.92; H, 5.22; N, 9.27.

3-Amino-2-pyridone Hydrobromide (20).

Method a. From 17.

Compound **17** was hydrogenolyzed in ethanolic solution in presence of palladium-charcoal. After working up the reaction mixture in the usual manner, **20** was crystallized as the hydrobromide from ethanol-ethyl acetate (yield 78%), m.p. 225-230° (dec.); infrared cm⁻¹ (potassium bromide) 2800 (assoc. NH₃⁺), 1650 (α-pyridone).

Anal. Calcd. for C₅H₇BrN₂O: C, 31.41; H, 3.66; N, 14.66; Br, 41.88. Found: C, 31.56; H, 3.80; N, 14.47; Br, 42.07.

Method b. From 23.

Hydrogenolysis of **23**, in the same manner as above but with the addition of aqueous hydrogen bromide to the hydrogenation mixture resulted in the formation of **20** in 76% yield. The identity of the product with that obtained from **17** (above) was established by mixed melting point and infrared spectra comparisons.

The free base and the corresponding hydrochloride are described in the literature (12).

2-Hydroxy-3-benzamidopyridine (26).

Hydrogenolysis of both **21** and **25** in the usual manner afforded **26**, m.p. and mixed m.p. 190-192°, crystallized from ethanol (yield 78%); infrared cm⁻¹ (potassium bromide) 3590 (OH), 1640 (C=O), 1520 and 760. N.M.R. δ 7.75 (5H, m; phenyl), 7.2 and 6.45 (1H and 2H, respectively, m; pyridine).

Anal. Calcd. for C₁₂H₁₀N₂O₂: C, 67.29; H, 4.67; H, 13.08. Found: C, 67.14; H, 4.76; N, 13.12.

Hydrogenolysis of 19.

Hydrogenolysis of **19** was carried out in the same manner as above. Attempts to crystallize the product resulted in the formation of a dark green material which could not be further characterized.

2,6-Dibromo-3-benzylaminopyridine (28).

A solution of **14** (0.005 mole) in benzyl alcohol (10 ml.) was heated at 180° for 14 hours. After removal of solvent, the crude product was chromatographed over silica gel (150 g.). Elution of the column with benzene-petroleum ether (1:1) resulted in the isolation of **28**, m.p. 74-75°, crystallized from petroleum ether (0.92 g., 54% yield); infrared cm⁻¹ (potassium bromide) 3500 (NH), 1580, 1420, 735. N.M.R. (carbon tetrachloride) δ 7.35 (5H, s; phenyl), 7.15 and 6.60 (1H each, d; pyridine), 4.95 (1H, m; NH), 4.4 (2H, m; -N-CH₂Ph).

Anal. Calcd. for $C_{12}H_{10}Br_2N_2$: C, 42.11; H, 2.92; N, 8.19; Br, 46.78. Found: C, 42.39; H, 2.92; N, 8.08; Br, 46.65.

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