

Trihalogenated Aminopyridinols

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Received September 17, 1974

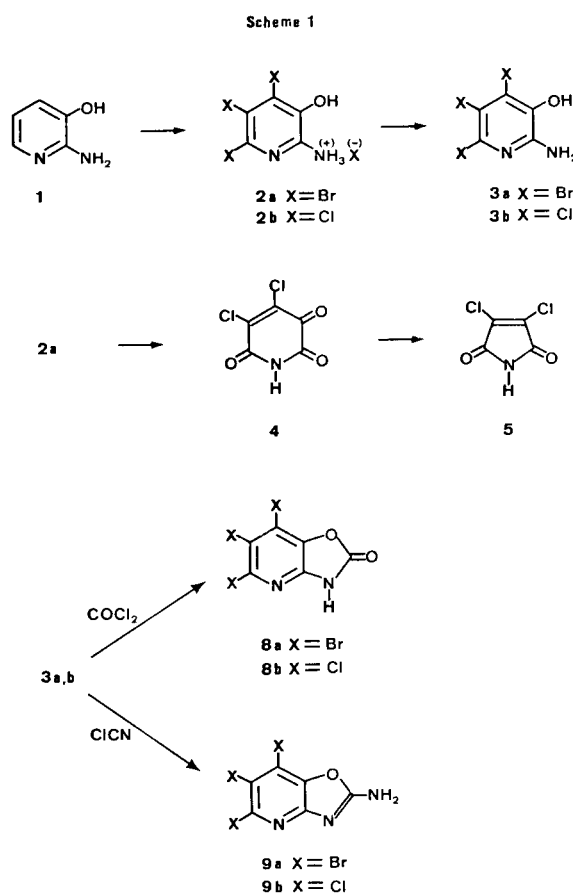
The chlorination of 2,6-diaminopyridine with chlorine in concentrated mineral acids at elevated temperatures proceeds with complete hydrolysis of amino- to hydroxy groups and results in the formation of 2,6-dihydroxy-3,4,5-trichloropyridine (1). If such chlorinations, however, are carried out in dilute sulfuric acid at 25°, the amino functions of 2-amino-6-methylpyridine and of 2-aminopyridine are not hydrolyzed and 2-amino-3,5-dichloro-6-methylpyridine (2) and 2-amino-5-chloropyridine (3) are obtained.

Several authors have studied the hydrolysis of 2,6-diaminopyridine in acid solution of different concentrations and the reaction products obtained were again dihydroxy- and aminohydroxypyridines (4).

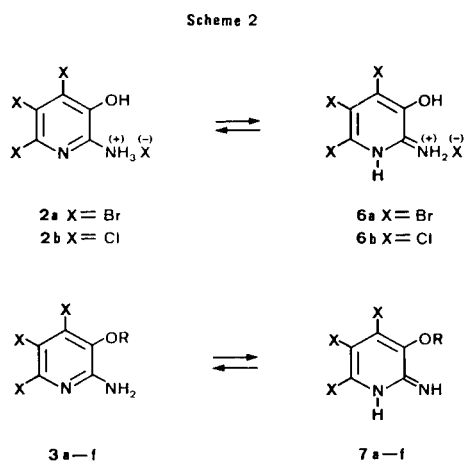
We now report the chlorination and the bromination of 2-amino-3-hydroxypyridine (1) and show that if the chlorination was carried out at a low enough temperature and with short reaction times no exchange of amino-versus the hydroxy function will occur.

The chlorination of 2-amino-3-hydroxypyridine (1) in concentrated hydrochloric acid at 30-33° yielded 2-amino-3-hydroxy-4,5,6-trichloropyridine hydrochloride (2b) (Scheme 1). Elevated temperatures and extended reaction times tended to favor greatly the formation of partially hydrolyzed products. If the reaction, for example, were carried out at 80° and a reaction period of 3 hours one obtained 27.8% of 4 which was derived from the hydrochloride 2b by hydrolysis of the chlorinated 2,6-positions and an additional 35.2% of 2b was isolated. The structure of 4 found unexpected support when 4 was reacted with a mixture of thionylchloride and dimethylformamide. Instead of the expected 3,4,5-trichloro-2-aza-1,4-quinone, however, the compound 5 was formed with extrusion of carbon monoxide. The structure of 5 was confirmed by preparing an authentic sample according to a known procedure (5).

The corresponding hydrobromide (2a) was obtained exclusively on adding bromine to a solution of 1 in concentrated hydrobromic acid at 100° without hydrolysis simultaneously occurring in the 2,6-positions of the pyridine ring. Free bases 3a,b were obtained by treatment of 2a,b with dilute aqueous sodium hydroxide solution.



The hydrogen halides (2a,b) were rather insoluble in all solvents and they started to decompose on extended heating in solution. Small samples of 2a could be recrystallized from acetonitrile while no solvent was found for 2b. The experimental procedures described, however, gave the hydrogen halides 2a,b in fairly pure states which meet analytical specifications. The free bases (3a,b) could be recrystallized from an alcohol-water mixture. Correct molecular weights of 3a,b were ascertained from the mass spectral data. Acetyl and pivalyl derivatives (3c-f) were prepared from the parent compounds for comparison of their spectra with the unsubstituted compounds (see below).



Compounds 3, 7	X	R
a	Br	H
b	Cl	H
c	Br	CH ₃
d	Cl	CH ₃
e	Br	(CH ₃) ₂ C-CO
f	Cl	(CH ₃) ₂ C-CO

Characteristic ir absorption bands of **2** and **3** and their derivatives are listed in Table I. Several bands for the NH-stretching vibrations were observed in the solid state because of various associations. In nonpolar solvents, such as methylene chloride, only two bands appeared instead which were characteristic for the unassociated primary amine group of the structures represented by **3a-f**.

Both the hydrogen bromide and the hydrogen chloride salts (**2a,b**) had broad bands centered at 2688 cm^{-1} and 2600 cm^{-1} , respectively, which are due to the protonated amino or imino functions of **2a,b** and **6a,b**.

The absorptions of the C=N and the C=C groups in the 1600 cm^{-1} region show that the compounds described exist in two tautomeric forms (Scheme II) depending partially on the polarity of the solvent. The data in Table I indicate that in the solid state (potassium bromide disc) and in a solution of hexamethyl phosphorus triamide (HMPT) all the compounds exist predominantly in the imino form. Its exocyclic C=N function absorbs near 1640 cm^{-1} while in a solution of methylene chloride the amino structure is the prevalent one as shown by the absorption of the unaltered pyridine ring near 1606 cm^{-1} . Two compounds **2b** and **3b** show both bands in HMPT-solution which demonstrates that for each of those compounds two tautomeric forms are present in solution **2b** \leftrightarrow **6b** and **3b** \leftrightarrow **7b**, respectively.

The polarity of the solvent can greatly change the equilibrium between the two tautomeric forms which has been studied in some more detail with the *O*-acetylated derivative

Table I
Characteristic Infrared Absorptions of the Tautomeric Forms of Halogenated Aminoxy Pyridines

Compound	NH-stretching cm^{-1}		R-CO-stretching cm^{-1}		C=N stretching cm^{-1}	
	Dichloromethane	Potassium bromide	Dichloromethane	Potassium bromide	Potassium bromide	HMPT
2a	-	3305, 3225	-	-	1650	1645
2b	-	3198, 3113	-	-	1657	1645/1613
3a	3484, 3390	3098, 2959	-	-	1620	1650
3b	3484, 3390	3413, 3279	-	-	1634	1650/1613
3c	3472, 3373	3155	1775	1768	1642	1640
3d	3484, 3390	3442, 3373	1778	1760	1640	1650
3e	3509, 3396	3279, 3155	1770	1755	1613	1631
3f	3484, 3390	3442, 3322	1768	1757	1613	1626
		3190				
		3425, 3311				
		3448, 3279				
		3125				
		3448, 3279				
		3145				

3d and **7d**. In the solid state (potassium bromide disc) and in HMPT-solution it exists in the imino form (**7d**) and absorbs at 1640 cm^{-1} and 1650 cm^{-1} . In a solution of methylene chloride, however, the amino structure (**3d**) prevails as shown by the absorption band of the pyridine ring at 1606 cm^{-1} . In a solution consisting of 5% HMPT and 95% methylene chloride both bands can be observed (1625 cm^{-1} and 1605 cm^{-1}) and, therefore, both tautomeric forms (**3d** \leftrightarrow **7d**) are realized in the same solvent. Related cases of automerism have been reported for the amino pyridines (**6**) and for the amino pyrimidines (**7**).

The hydroxyl and the amino groups of the trihalogenated pyridines still react, although sluggishly with phosphene (**8**) to yield **8a,b** and with cyanogen chloride ring closure to **9a,b** was readily achieved.

EXPERIMENTAL

Ultraviolet spectra were recorded on a Beckman DK-2A spectrophotometer and the ir spectra on a Perkin-Elmer-221 instrument. Melting points are not corrected.

2-Amino-3-hydroxy-4,5,6-tribromopyridine Hydrobromide (**2a**).

A solution of 220 g. (2 moles) of **1** in 1200 ml. of 48% hydrobromic acid was heated to 100° and, with stirring, 1100 g. (6.88 moles) (= 350 ml.) of bromine was added through a dropping funnel which extends below the surface of the solution, over the period of 1 hour, at such a rate that the temperature of the reaction mixture remains at $100\text{--}103^\circ$. After the addition had been completed stirring was continued for another 6 hours. The crystals which precipitated were filtered from the cold solution over a glass sintered funnel protected from air. The yellow precipitate was immediately dispersed in 1 liter of acetone, filtered and washed on the filter with acetone. After drying for 24 hours at $40^\circ/12$ torr, 640 g. (74.8%) of crude **2a** was obtained as yellow crystals, m.p. slow dec. above 240° ; ir (potassium bromide): 3135, 2703, 1626, 1563, 1534, 1297, 1156, 719.

Anal. Calcd. for $\text{C}_5\text{H}_4\text{Br}_3\text{N}_2\text{O}$: C, 14.04; H, 0.95; Br, 74.73; N, 6.56. Found: C, 14.15; H, 1.08; Br, 74.74; N, 6.50.

2-Amino-3-hydroxy-4,5,6-tribromopyridine (**3a**).

In 3.5 l. of 1 *N* sodium hydroxide solution was dissolved 640 g. (1.5 moles) of **2a** and the solution was acidified by adding a solution of hydrobromic acid/water (1:1). After the precipitate was filtered off, washed with water and dried for 24 hours at $40^\circ/12$ torr, 495 g. (95.6%) of yellow brown material was obtained. Two hundred g. of the crude material was dissolved in 2500 ml. of boiling ethanol and 2300 ml. of water was added. Crystals (155 g.) were filtered from the ice cold solution, m.p. $170\text{--}180^\circ$ slow dec. without any starting melting point; ir (potassium bromide): 3425, 3258, 3145, 1634, 1562, 1538, 1453, 1364, 1182, 856, 718; uv (methanol): λ max (ϵ) 249.5 (9200), 316.5 (6600); m/e: 344.

Anal. Calcd. for $\text{C}_5\text{H}_3\text{Br}_3\text{N}_2\text{O}$: C, 17.32; H, 0.87; Br, 69.13; N, 8.08. Found: C, 17.40; H, 1.01; Br, 68.82; N, 8.20.

2-Amino-3-hydroxy-4,5,6-trichloropyridine Hydrochloride (**2b**).

Into a solution of 2-amino-3-hydroxypyridine (220.0 g., 2 moles) in 1200 ml. of concentrated hydrochloric acid, 1060 g. (15 moles) of chlorine was introduced with vigorous stirring over a period of 5 hours. Initially the reaction was exothermic and was

kept below 42° by external cooling. The product began to separate after about 1.5 hours. The temperature slowly decreased in the course of the reaction to 36° and towards the end of the reaction extensive foaming occurred. The mixture was brought to 5° , filtered over a glass sintered funnel, washed 4 times each with 200 ml. of acetone and 334 g. (66.8%) of **2b** was collected. The crude material melted at $195\text{--}200^\circ$ dec., and met analytical specifications. Small samples can be recrystallized from a large excess of acetonitrile, m.p. 210° dec., ir cm^{-1} (potassium bromide): 3226, 3135, 3030, 2631, 1667, 1590, 1553, 1397, 1316, 1183.

Anal. Calcd. for $\text{C}_5\text{H}_4\text{Cl}_4\text{N}_2\text{O}$: C, 24.02; H, 1.61; Cl, 56.72; N, 11.21. Found: C, 23.95; H, 1.69; Cl, 56.66; N, 11.20.

2-Amino-3-hydroxy-4,5,6-trichloropyridine (**3b**).

2-Amino-3-hydroxy-4,5,6-trichloropyridine hydrochloride (316 g., 1.26 moles) was dissolved in 2 l. of 1.5 *N* of sodium hydroxide solution and the clear solution acidified (pH, 2) at 0° with a mixture of concentrated hydrochloric acid-water (1:1). The light yellow precipitate was filtered, washed with water and dried at $60^\circ/12$ torr for 24 hours: 259 g. (96.4%) of **3** (X = Cl) was obtained. For recrystallization 180 g. of the product was dissolved in 500 ml. of boiling ethanol and 700 ml. of hot water was added. Crystals (126 g.) were filtered from the cold solution, m.p. $130\text{--}140^\circ$ dec., ir cm^{-1} (potassium bromide): 3460, 3413, 3290, 3185, 1640, 1585, 1471, 1389, 1191, 1176, 893, 781; uv (methanol): λ max (ϵ) 245.5 (8000), 314.5 (7400); m/e: 212.

Anal. Calcd. for $\text{C}_5\text{H}_3\text{Cl}_3\text{N}_2\text{O}$: C, 28.13; H, 1.41; Cl, 49.82; N, 13.12. Found: C, 28.30; H, 1.51; Cl, 49.58; N, 13.22.

O-acyl derivatives of **3a,b** were prepared following the general procedure for the preparation of **3c**.

2-Amino-3-acetoxy-4,5,6-tribromopyridine (**3c**).

To a solution of 20.0 g. (0.06 mole) of **3a** in 100 ml. of tetrahydrofuran was added 15 ml. of triethylamine followed by 5 g. (0.064 mole) of acetyl chloride. The mixture was heated to reflux for 3 minutes and then poured into ice water. The crystals were filtered and washed with water to yield 18.6 g. (80.2%) of **3c**. Recrystallization from ethylcellosolve gave white crystals, m.p. 253° dec.

Anal. Calcd. for $\text{C}_7\text{H}_5\text{Br}_3\text{N}_2\text{O}_2$: C, 21.62; H, 1.30; Br, 61.66; N, 7.20. Found: C, 21.71; H, 1.25; Br, 61.38; N, 7.32.

2-Amino-3-acetoxy-4,5,6-trichloropyridine (**3d**).

This compound was obtained in 84.4% yield, m.p. 175° (white crystals from ethanol).

Anal. Calcd. for $\text{C}_7\text{H}_5\text{Cl}_3\text{N}_2\text{O}_2$: C, 32.90; H, 1.98; Cl, 41.63; N, 10.96. Found: C, 33.21; H, 2.02; Cl, 41.72; N, 11.11.

2-Amino-3-trimethylacetoxy-4,5,6-tribromopyridine (**3e**).

This compound was obtained in 88% yield, m.p. $165\text{--}166^\circ$ (white crystals from cyclohexane).

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{Br}_3\text{N}_2\text{O}_2$: C, 27.88; H, 2.58; Br, 55.63; N, 6.50. Found: C, 27.92; H, 2.54; Br, 55.49; N, 6.61.

2-Amino-3-trimethylacetoxy-4,5,6-trichloropyridine (**3f**).

This compound was obtained in 88.5% yield, m.p. $168\text{--}169^\circ$ (from benzene-pentane mixture 1:1).

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{Cl}_3\text{N}_2\text{O}_2$: C, 40.36; H, 3.73; Cl, 35.74; N, 9.41. Found: C, 40.46; H, 3.81; Cl, 35.64; N, 9.44.

2,3,6-Triketo-4,5-dichloro-1,2,3,6-tetrahydropyridine (**4**).

Into a stirred solution of 55 g. (0.5 mole) of **1** in 400 ml. of concentrated hydrochloric acid was passed 300 g. (4.2 moles) of chlorine at $80\text{--}86^\circ$ over a 3 hour period while a slow current of

hydrogen chloride passing through the solution was maintained during the reaction period. After the chlorine addition has been completed, stirring was continued for an additional 2 hours. The suspension was cooled to 10°, the crystals were filtered off, washed with 50 ml. of concentrated hydrochloric acid followed by washing with acetone four times with 50 ml. each. The combined acetone extracts were evaporated to dryness, the yellow crystalline residue stirred with 100 ml. of water and 27 g. (27.8%) of **4** was filtered from the suspension. Recrystallization from water yielded light colored crystals, m.p. 235-236° dec., ir (potassium bromide): 3205, 3077, 1709, 1590, 1360, 1294, 1053, 8920, 870, 806, 803.

Anal. Calcd. for C₅H₁Cl₂NO₃: C, 30.96; H, 0.52; Cl, 36.55; N, 7.22. Found: C, 31.10; H, 0.51; Cl, 36.61; N, 7.38; uv (dichloromethane): λ max (ε) 264.5 (10,600), 313 (3050). The acetone insoluble product (44 g., 35.2%) was identified as **2b** by comparison of the ir spectra with the one of the previously prepared sample of **2b**.

Dichloromaleic Acid Imide (**5**).

A solution of 3.88 g. (0.02 mole) of **4** in 18 ml. of thionyl chloride was heated to reflux for a period of 30 minutes. After addition of 6 ml. of dimethylformamide, reflux was continued for another 30 minutes. Excess thionyl chloride was removed *in vacuo*, the residue treated with ice water and evaporated to dryness. Water (15 ml.) was added to the remaining oil, yellow crystals 2.4 g. (72%) of **5** were filtered off, m.p. 175-177° (after sublimation) and identified by comparison of the ir spectra with the one of an authentic sample of **5**(**5**).

5,6,7-Tribromooxazolo[4,5-*b*]pyridin-2(3*H*)one (**8a**).

To a solution of 17.3 g. (0.05 mole) of **3a** and 15.2 ml. of triethylamine in 150 ml. of dimethoxyethane was added 5 ml. of phosgene. The reaction mixture was worked up as described for **8b** and yielded 11.0 g. (59.2%) of **8a**, which was recrystallized from ethanol, m.p. 250°; ir (potassium bromide): 3195, 1852, 1823, 1597, 1449, 1255, 935.

Anal. Calcd. for C₆H₁Br₃N₂O₂: C, 19.34; H, 0.27; Br, 64.39; N, 7.51. Found: C, 19.51; H, 0.40; Br, 64.09; N, 7.60.

4,5,6-Trichlorooxazolo[4,5-*b*]pyridin-2(3*H*)one (**8b**).

Into a solution of 170 g. (0.8 mole) of **3b** in 1.8 l. of dimethoxyethane was introduced 84 g. (0.85 mole) of phosgene at 65-70° within a period of 45 minutes, followed after 5 minutes by a solution of 80.8 g. (0.8 mole) of triethylamine in 200 ml. of dimethoxyethane which was added over the same period of time. After the exothermic reaction had subsided, the suspension was stirred for 15 minutes at 70° and an additional 15 minutes at reflux temperature. Triethylamine hydrochloride was filtered from the cold solution and washed twice with 150 ml. of acetone. The filtrate was

concentrated to half its volume and the remaining solution added with stirring to 500 ml. of water and 500 g. of ice and stirred for 15 minutes. Crystals of **8b** were filtered from the solution, washed with 500 ml. of water and dried *in vacuo*, 156 g. (81.2%). Recrystallization from ethanol yielded crystals, m.p. 241-243° dec., ir (potassium bromide): 3195, 1845, 1818, 1757, 1623, 1600, 1460, 1274, 956, 806, 699.

Anal. Calcd. for C₆H₁Cl₃N₂O₂: C, 30.10; H, 0.42; Cl, 44.43; N, 11.70. Found: C, 30.09; H, 0.50; Cl, 43.95; N, 12.01.

5,6,7-Trichloro-2-aminooxazolo[4,5-*b*]pyridine (**9b**).

To a solution of 21.3 g. (0.1 mole) of **3b** in 1 *N* aqueous sodium hydroxide solution was added 100 ml. of water and 8 g. (0.13 mole) of gaseous cyanogen chloride was passed into the solution with stirring. After an additional 30 minutes, the solid was collected and washed with water to yield 22.8 g. (95.8%) of **9b**. Recrystallization from 1,2-dimethoxyethane gave white crystals, m.p. 260-265° dec., ir (potassium bromide): 3460, 1720, 1630, 1550, 1420, 1290, 958.

Anal. Calcd. for C₆H₂Cl₃N₃O: C, 30.22; H, 0.85; Cl, 44.60; N, 17.62. Found: C, 30.31; H, 1.0; Cl, 44.38; N, 17.50.

5,6,7-Tribromo-2-aminooxazolo[4,5-*b*]pyridine (**9a**).

The compound was prepared by the same procedure as **9b** in 93% yield. Recrystallization from 1,2-dimethoxyethane, m.p. 300° dec.; ir (potassium bromide): 3450, 1690, 1625, 1528, 1400, 1256, 930.

Anal. Calcd. for C₆H₂Br₃N₃O: C, 19.39; H, 0.54; Br, 64.48; N, 11.31. Found: C, 19.54; H, 0.61; Br, 64.21; N, 11.38.

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