Facile Acidic Hydrolysis and Displacement Reactions of 2-Chloro- and 2,9-Dichloro-1,10-phenanthroline

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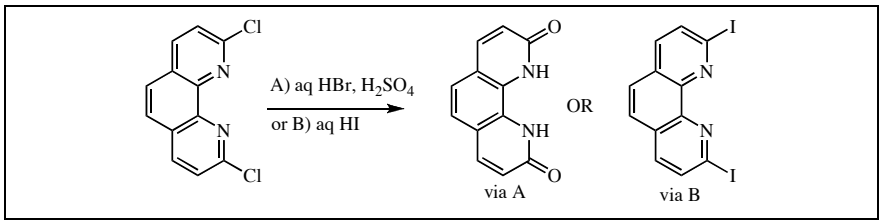

Treatment of 2-chloro- or 2,9-dichloro-1,10-phenanthroline with aqueous HBr or aqueous H_2SO_4 at 120°C yielded 1,10-phenanthroline-2(1*H*)-one or 1,10-dihydro-1,10-phenanthroline-2,9-dione, respectively. The hydrolysis of 2,9-dichloro-1,10-phenanthroline with 37% aqueous HCl led to the half hydrolyzed amide and the bis-amide. Under comparable reactions conditions, using aqueous HBr, H_2SO_4 or HCl, 2-chloropyridine was found to be hydrolytically stable. On the other hand, 2-chloro- or 2,9-dichloro-1,10-phenanthroline on heating with 57% aqueous HI afforded the HI salts of 2-iodo- or 2,9-diiodo-1,10-phenanthroline, which could be isolated. These salts on treatment with aqueous ammonium hydroxide led to good yields of 2-iodo- and 2, 9-diiodo-1,10-phenanthroline, respectively. Treatment of 2-chloropyridine with 57% aqueous HI under similar reaction conditions led to 2-iodopyridine in a 10% conversion.

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INTRODUCTION

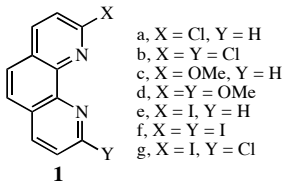
Our interest in the synthesis of analogues with 1,10-phenanthroline chromophores is based on their potential applications as inhibitors of telomerase, an enzyme found in tumor cells which control the continued growth of malignant tumors [1]. For example a platinium-phenanthroline complex has been reported as an inhibitor of telomerase [2]. Recently we have reported a convenient and multigram synthetic pathway to 2-chloro- (**1a**) and 2,9-dichloro-1,10-phenanthroline (**1b**) [3]. We have investigated displacement reactions of chloride from **1a** using nitrogen, oxygen and sulfur nucleophiles. The preparation of the thioamide **2a** by treatment of **1a** with Na_2S nonahydrate or NaSH hydrate has been reported and other displacement reactions of **2a** have been studied [4]. In this paper we report the facile hydrolysis of **1a** and **1b** with aqueous solutions of HCl, HBr and H_2SO_4 and displacement reactions with aqueous HI. Comparative hydrolytic and displacement data for the model 2-chloropyridine will be presented and discussed.

Pertinent to the results described in this paper, it might be noted that in a 1930 patent [5] Rath reported that 2-chloropyridine on treatment with concd HCl at 150°C for 5 h (bomb tube) led to 2-hydroxypyridine (2-pyridone). Subsequently it was found that 2-chloro-pyridine was stable to hydrolysis on treatment with refluxing 6 *N* HCl for 24 h [6].

RESULTS AND DISCUSSION

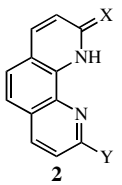
Treatment of **1a** with 36% (w/w) HCl at 120-130°C (oil bath temperature) for 5 h led to recovered **1a** (64%) and the hydrolyzed product **2b** (36%) [7, 8]. Upon heating **1b** with 37% aqueous HCl, **2c** (54%) and **3** (46%) were formed.

As a comparative model we have also found that 2-chloropyridine on heating in 48% aqueous HBr, 37% aqueous HCl or 50% aqueous sulfuric acid did not undergo hydrolysis [6].



1

a, X = Cl, Y = H
b, X = Y = Cl
c, X = OMe, Y = H
d, X =Y = OMe
e, X = I, Y = H
f, X = Y = I
g, X = I, Y = Cl



2

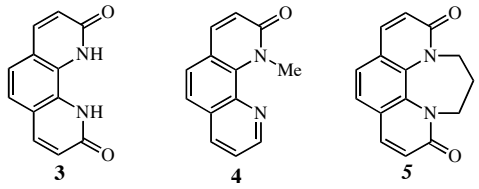
a, X = S, Y = H
b, X = O, Y = H
c, X = O, Y = Cl

The mono amide **2b** [7,8] or bis-amide **3,** respectively, were isolated in good yields by heating **1a** or **1b** in 64% aqueous H_2SO_4 or 57% aqueous HBr at 120-130°C for 4-5 h.

The dealkylation of 2-methoxy- (**1c**) [9] and 2,9-dimethoxy-1,10-phenanthroline (**1d**) [9] on heating with 48% aqueous HBr also afforded **2b** or **3**, respectively. A prior report dealing with the demethylation of **1c** with 57% aqueous HI (reflux, 6 h) in our hands led to dark products which were difficult to purify [10]. The

preparation of 2-pyridone has been reported by heating 2-*n*-butoxypyridine hydrochloride at 220°C [11].

The structures for the products as **2b** and **3**, rather than tautomeric structures, are strongly supported by ^{1}H and ^{13}C nmr data.



3 **4** ***5***

Mono amide **4** [3,12] which cannot tautomerize, exhibits the H-3 and H-4 resonances ($CDCl_3$) at 6.90 ppm (d, J = 9.5 Hz) and δ 7.78 ppm (J = 9.3 Hz) while the H-3 and H-4 absorptions for **2b** occur at 6.84 (J = 9.5 Hz) and δ 7.88 (d, J = 9.5 Hz) ppm, respectively. The NH peak occurs as a broad singlet at 10.70 ppm. The ^{13}C resonances for C=O ($CDCl_3$) appear at 162.0 ppm for **2b** and 164.2 ppm for **4**.

The formulation of **3**, rather than the alternative tautomeric structures, is also based on ^{1}H and ^{13}C nmr analysis. Bis amide **5** [13], which cannot tautomerize, exhibited the H-3 and H-4 absorptions in the NMR at 6.72 (d, J = 9.4 Hz) and 7.97 (d, J = 9.5 Hz) ppm, respectively, while the H-3 and H-4 absorptions in **3** occur at 6.65 (d, J = 9.5 Hz,) and 8.00 (d, J = 9.5 Hz) ppm, respectively. The H-5 singlets in **3** and **5** occur at 7.47 and 7.55 ppm, respectively. The C=O ^{13}C resonances for **3** and **5** occur at 161.8 and 161.7 ppm (both in DMSO-d_6), respectively. The NH absorption occurs at 11.10 ppm (br s) for **3**. These nmr comparative agreements indicate that the predominant isomer in solution is **3**.

The structures of **2b** and **3** parallel those found for the 2-pyridone/2-hydroxypyridine tautomeric equilibrium which has been studied extensively, and in polar solvents and the 2-pyridone is dominant due to its associative ability[14,15].

The displacements of chloride by iodide in **1a** or **1b** to afford **1e** or **1f,** respectively, have been accomplished using aqueous HI in the presence of NaI [16,17]. We have found that treatment of **1a** or **1b** with 57% aqueous HI at 100°C, in the absence of any NaI, readily afforded the corresponding isolable HI salts, which on treatment with aqueous NH_4OH led to good yields of **1e** or **1f**, respectively. These displacements of chloride from **1a** and **1b** can be formally classified as acid catalyzed aromatic Finkelstein reactions.

Treatment of 2-chloropyridine with aqueous 57% HI under comparable conditions led to the HI salt of 2-iodopyridine (12%) which was converted into 2-iodopyridine on treatment with aqueous KOH and identified by ^{1}H nmr comparison to an authentic sample.

Neutralization of the filtrate, after removal of the HI salt, led to recovered starting material. In general the acid-mediated chloro to iodo exchange in 2-chloro- and 2-bromopyridine require the presence of NaI. Treatment of 2,6-dichloropyridine with aqueous HI and NaI (reflux, 12 h) led to 2,6-diiodopyridine (42%) [18]. The hydrochloride salt of 2-chloropyridine on treatment with NaI in acetonitrile (reflux, 24 h) led to 2-iodopyridine (75%) [19]. On refluxing 2-bromopyridine with aqueous HI for 6 h, a low yield of 2-iodopyridine (35%) was obtained [20].

The facile acidic hydrolytic reactions of **1a** and **1b** (relative to 2-chloropyridine) are probably due to the protonated 1,10-phenanthroline moiety which activates the electrophilicity at the carbon bearing the chlorine for nucleophilic water attack to afford **2b** and **2c**. Further hydrolysis of **2c** yields **3**.

In the case of HI, the nucleophilic soft iodide anion (unsolvated in water) is probably displacing the chloride anion *via* a S_NAr mechanism initially from the protonated phenanthroline nucleus of **1a** or **1b**. The intermediate **1g** (formed initially from **1b**) then undergoes a similar second displacement of chloride anion to yield **1f**. The displacement rate is considerably more rapid in **1a** than the model 2-chloropyridine.

The chemoselectivity of reactions at N or O in **2b** and **3** with electrophilic reactants such as alkyl halides and metal cationic species are currently under investigation.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover or a Fisher-Johns apparatus and are uncorrected. The nmr spectra were recorded on a Bruker AX-500 pulsed FT or a Varian Inova 500 spectrometer. The ^{1}H nmr shifts are reported in δ (ppm) relative to internal TMS as a standard. The ^{13}C nmr data are reported in δ values relative to the solvent ($CDCl_3$, 77.0 ppm and DMSO-d_6, 39.5 ppm).

1,10-Phenanthrolin-2(1*H*)-one (2b). Procedure 1. A solution of **1a** (256 mg, 1.2 mmoles) and 64% (w/w) H_2SO_4 (2 mL, 1 mL of water and 1 mL of concd H_2SO_4 (18.8 mmoles of acid) was heated in an oil bath held at 120-125°C for 5 h. Water (3 mL) was added to the cooled solution and solid $NaHCO_3$ was slowly added. The resultant solid was collected by filtration, dried, taken up in CH_2Cl_2 and filtered to remove a trace of insoluble. Concentration of the filtrate led to **2b** as a white solid (210 mg, 90%), mp 160-162°C, (lit. [8], mp 159-160°C), which readily crystallized from benzene. ^{1}H nmr ($CDCl_3$): δ 10.70 (br s, 0.8H), 8.92 (dd, J =1.6, 4.2 Hz, 1H), 8.20 (dd, J = 1.6, 8.2 Hz, 1H), 7.88 (d, J = 9.5 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.56 (dd, J = 4.2, 8.2 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 9.4 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 162.0, 149.3, 140.2, 136.5, 136.0 135.2, 128.2 125.2, 123.5, 123.1, 120.9, 117.3.

Procedure 2. A mixture of **1a** (253 mg, 1.17 mmoles) and 48% (w/w) aqueous HBr (3 mL, 2.16 g, 26.7 mmoles of acid) was heated in an oil bath held at 125-130°C for 4.25 h. Water (5 mL) was added to the cooled mixture which was then neutralized with $NaHCO_3$. The product **2b** (131 mg) was

collected by filtration. The filtrate on extraction with CH_2Cl_2 and concentration afforded additional **2a** (40 mg), total 171 mg (75%).

Procedure 3. A yellow solution of **1c** (0.20 g, 0.95 mmol) and 48% (w/w) aqueous HBr (2 mL, 2.98 g, 36.8 mmoles) was heated at 90°C for 18 h. The resultant yellow solid was collected by filtration and washed with water to afford **2b** (0.10 g, 57%).

2-Chloro-1,10-phenanthroline (1a) and **1,10-Phenanthrolin-2(1*H*)-one (2b)**. A mixture of **1a** (1.0 g, 4.6 mmoles) and 36% (w/w) HCl (2.5 mL, 30 mmoles) was heated in an oil bath held at 120-125°C for 5 h. Water (10 mL) was added to the cooled solution followed by solid Na_2CO_3. The resultant oil was extracted with $CHCl_3$ (2 x 10 mL), the extract dried over Na_2SO_4 and concentrated to afford a white solid (850 mg) which on ^{1}H nmr analysis indicated the presence of **1a** (64%) and **2b** (36%). No attempt was made to purify this mixture.

1,10-Dihydro-1,10-phenanthroline-2,9-dione (3). Procedure 1. A mixture of **1b** (202 mg, 0.80 mmol) and 64% (w/w) aqueous H_2SO_4 (1 mL concd acid + 1 mL water, 18.8 mmoles acid) was heated in an oil bath at 120-123°C for 5 h. The mixture was cooled, allowed to stand overnight, the white solid was collected by filtration, washed with water and dried to afford **3** (140 mg, 82%); mp > 320°C; ^{1}H nmr (DMSO-d_6): δ 11.70 (brs), 8.00 (d, J = 9.5 Hz, 2H), 7.47 (s, 2H), 6.65 (d, J = 9.5 Hz, 2H); ^{13}C nmr (DMSO-d_6): δ 161.8, 140.9, 126.2, 122.5, 121.3, 119.6. *Anal.* Calcd. For $C_{12}H_8N_2O_2{\cdot}3H_2O$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.00; H, 5.14; N, 10.56.

Procedure 2. A mixture of **1b** (236 mg, 0.95 mmoles) and 48%(w/w) aqueous HBr (2 mL, 2.98 g, 17.6 mmoles) was heated for 6 h at 120-125°C in an oil bath. The solid was collected by filtration to yield a quantitative yield of **3.**

Procedure 3. A yellow solution of **1d** (0.22 g, 0.91 mmol) and 48 % (w/w) hydrobromic acid (2 mL, 2.98 g, 36.8 mmoles) was heated at 90° C for 18 h. The solid was collected by filtration and washed with ethyl alcohol to afford **3** as a pale brown solid (0.10 g, 53 %), m.p.>320 °C.

9-Chloro-1,10-dihydro-1,10-phenanthroline-2,9-dione (2c) and 1,10-dihydro-1,10-phenanthroline-2,9-dione (3). A mixture of **1b** (244 mg, 1 mmole) and 36% (w/w) aqueous HCl (2 mL, 23 mmoles) was heated at 120-125°C for 7 h. The resultant solid was collected by filtration, washed with water and dried to afford **2c** (54%) and **3** (46%), as ascertained from the ^{1}H nmr spectrum.

2-Methoxy-1,10-phenanthroline (1c). Compound **1a** (1.0 g, 4.6 mmoles) was added to a solution of $NaOCH_3$ (treatment of 50 mL of MeOH with 2 g Na metal) and the yellow solution was refluxed for 19 h. The mixture was filtered to remove salts and the filtrate concentrated. Water (40 mL) was added and the product **1c** (1.0 g, quantitative) was collected by filtration; mp 81-83°C (lit. [9] mp 49°C). ^{1}H nmr ($CDCl_3$): δ 9.18 (dd, J = 1.5, 4.0 Hz, 1H), 8.24 (dd, J = 2.0, 8.0 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 9.0 Hz, 1H), 7.59 (dd, J = 4.5, 8.0 HZ, 1H), 7.13 (d, J = 8.5 Hz, 1H), 4.38 (s, 3H); ^{13}C nmr (DMSO-d_6) δ 162.3, 149.5, 144.5, 143.7, 139.4, 135.9, 128.7, 126.1, 124.5, 123.8, 122.8, 113.2, 53.4.

2,9-Dimethoxy-1,10-phenanthroline (1d). To a solution of $NaOCH_3$, prepared by reacting Na metal (0.26 g, 11 mmoles) with MeOH, **1b** (0.2 g, 0.80 mmole) was added in one portion and the mixture was refluxed for 19 hours. The yellow solution was taken to dryness under vacuum and then $CHCl_3$ (8 mL) was added. The insoluble material solid was removed by filtration, washed with a little $CHCl_3$ and the filtrate was concentrated on a rotary evaporator to give a pale yellow product **1d** (0.17 g, 88%). A portion of the crude product was crystallized from pentane (in freezer) to afford **1d** as white needles, mp 83-85ºC; (lit. [9], mp 110-111°C). ^{1}H nmr ($CDCl_3$): δ 8.09 (d, J = 8.7 Hz, 2H), 7.62 (s, 2H), 7.09 (d, J = 8.7 Hz, 2H), 4.29 (6H): ^{1}H nmr (DMSO-d_6) δ 8.33 (d, J = 8.7 Hz, 2H), 7.78 (s, 2 H), 7.17 (d, J = 8.6 Hz, 2H), 4.15 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 161.7, 142.4, 139.3, 124.9, 123.3, 113.0, 52.8.

2-Iodo-1,10-phenanthroline (1e). The 57% aqueous HI (w/w, stablilized with H_3PO_2) (3 mL, 22.7 mmoles) was added to **1a** (142 mg, 0.66 mmole) at rt. The yellow suspension was placed in an oil bath held at 100-103°C for 5 h during which period a yellow solid separated. The mixture was cooled, the solid was collected by filtration, washed with cold water and methanol to afford the HI salt (175 mg, 63%); ^{1}H nmr (DMSO-d_6): δ 9.28 (dd, J = 1.5, 5.0 Hz, 1H), 9.17 (d, J = 8.0 Hz, 1H), 8.36 (m, 2H), 8.28 (m, 3H), 4.16 (br s). The salt (155 mg) was suspended in water (2 mL) and while cooling in an ice bath concd ammonium hydroxide was added. The resultant white solid was collected and dried (85 mg, 80% conversion from salt). The crude solid was crystallized from aqueous ethanol to afford **1e** as pale yellow needles, mp 196-197°C, (lit. [17], mp 190°C (dec)). ^{1}H nmr ($CDCl_3$): δ 9.23 (dd, J = 2.0, 4.5 Hz, 1H), 8.25 (dd, J = 2.0, 8.5 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 4.0 Hz, 1H), 7.82 (d, J = 5.0 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.66 (dd, J = 4.5, 8.0 Hz, 1H).

2,9-Diiodo-1,10-phenanthroline (1f). The 57% aqueous HI (w/w, stablilized with H_3PO_2) (3 mL, 22.7 mmoles) was added to **1b** (160 mg, 0.64 mmole) at rt. The yellow suspension was placed in an oil bath and then held at 100-105°C for 5 h during which period a red solid separated. The mixture was cooled and the red salt was collected by filtration and washed with methanol and dried to afford a yellow salt (300 mg, 84%); ^{1}H nmr (DMSO-d_6): δ 8.22 (d, J = 8.4 Hz, 2H), 8.18 (d, J = 8.4 Hz, 2H), 8.06 (s, 2H), 3.6(br s). This salt was suspended in water (3 mL) and treated with concentrated NH_4OH which led to a grey solid which was collected by filtration and air dried to afford the crude product (248 mg, 90%, 96% purity). A portion was crystallized from ethanol to afford beautiful slightly yellow needles of mp 263-265°C (dec); (lit. [17], mp 251°C (dec)). ^{1}H nmr ($CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H), 7.88 (s, 2H), identical to lit. [17].

2-Iodopyridine. The 2-chloropyridine (1.18 g, 10.35 mmoles) was added to 57% (w/w) aqueous HI (stabilized with H_2PO_2) (6 mL, 45.2 mmoles) and the mixture was heated in oil bath at 120-125°C for 6 h. Water (5 mL) was added to the cooled mixture and the HI salt of 2-iodopyridine was collected (390 mg, 12%). Treatment of this salt with aqueous KOH, extraction with CH_2Cl_2 and concentration gave 2-iodopyridine, which was identified by ^{1}H nmr comparison with that of an authentic sample. The filtrate was neutralized with solid $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated. The ^{1}H nmr analysis indicated only starting material (about 1 g). A longer heating time of 22 h led to about 22% of the HI salt.

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[13] Yamada, M.; Nakamura, Y.; Kuroda, S.; Shimao, I. *Bull. Chem. Soc. Jpn.* **1960**, 63, 2710. **5,** ^{1}H nmr (DMSO-d_6) δ 7.97 (d, J = 9.5 Hz, 2H), 7.55 (s, 2H), 6.72 (d, J = 9.4 Hz, 2H), 4.18 (t, J = 5.9 Hz, 4H), 2.22 (quintet, J = 6.5 Hz, 2H). ^{13}C nmr (DMSO-d_6) δ 161.7, 139.2, 131.7, 122.6, 122.4, 122.3, 44.8, 25.3.

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