Synthesis of 4-(2-Chloroethyl)-2,3-dihydro[1,4]oxazino[2,3-*b*]quinoline and 4-(2-Chloroethyl)-2,3-dihydropyrido[2,3-*b*][1,4]oxazine

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The title compounds were synthesized from 3-[bis(2-hydroxyethyl)amino]quinolin-2(1*H*)-one **11a** and 3-[bis(2-hydroxyethyl)amino]pyridin-2(1*H*)-one **18** respectively. The preparation involved a tandem chlorination/cyclization reaction.

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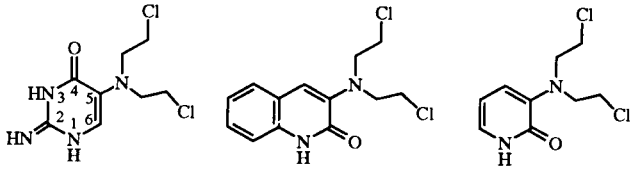
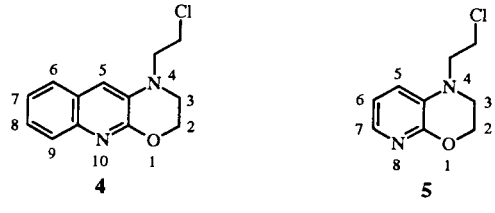
During the course of an investigation of sequence specificity of the uracil mustard **1** against 'PyGC' sequences in the DNA [1-3], we proposed compounds **2** and **3** (Figure 1) as analogues of **1**. The quinolinone mustrad **2** and the pyridinone mustard **3** were designed in order to evaluate the significance of the 3,4-amide functionality (Figure 1) in the uracil mustard.



1 **2** **3**

Figure 1

Subsequent efforts aimed at synthesizing the above compounds however led to some unexpected results such as the formation of intriguing ring systems *viz*; 4-(2-chloroethyl)-2,3-dihydro[1,4]oxazino[2,3-*b*]quinoline **4** and 4-(2-chloroethyl)-2,3-dihydropyrido[2,3-*b*][1,4]oxazine **5** (Figure 2). To the best of our knowledge, no reports for the preparation of these substituted heterocycles exist in the literature. This report describes the endeavors that were undertaken to prepare **2** and **3** and the unanticipated formation of **4** and **5**.



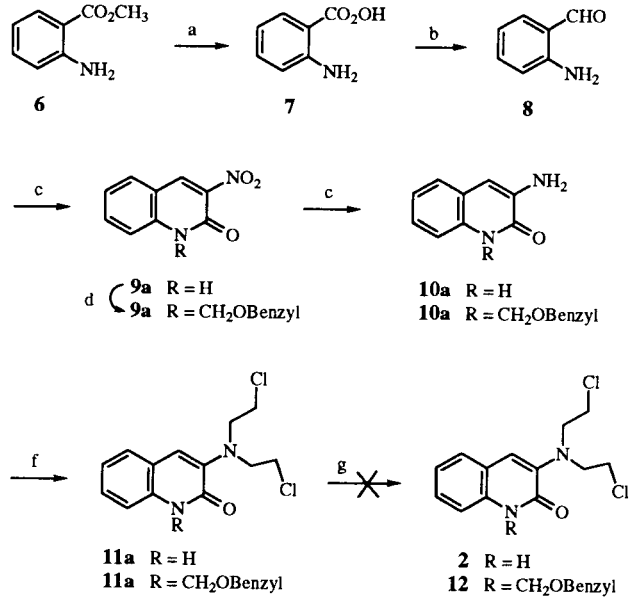
4 **5**

Figure 2

Results and Discussion.

The synthesis of oxazinoquinoline **4** is depicted in Scheme 1. The aldehyde **8** [4] was prepared by reduction of methyl anthranilate **6** with lithium aluminum hydride [5] followed by oxidation of the corresponding alcohol **7** with manganese dioxide [6]. Condensation [7] of **8** with ethyl nitroacetate in the presence of piperidine, in refluxing xylene gave 3-nitroquinolinone **9a** in 42% yield. Hydrogenation of **9a** in the presence of 10% Pd/C afforded **10a** in 95% yield. Alkylation of **10a** with a large excess of ethylene oxide in 75% acetic acid gave the diol **11a** in 40% yield. The product was isolated from the reaction mixture by adsorbing it on an acid ion exchange resin, followed by elution with 10% ammonium hydroxide solution as described in the experimental section.

Scheme 1



Lithium Aluminum Hydride; b) Manganese dioxide; c) Ethyl nitroacetate, piperidine, xylene, reflux; d) Benzyloxymethyl chloride, potassium carbonate; e) H_2, 10% Pd/C, atm pressure; f) Ethylene oxide, acetic acid; g) Thionyl chloride.

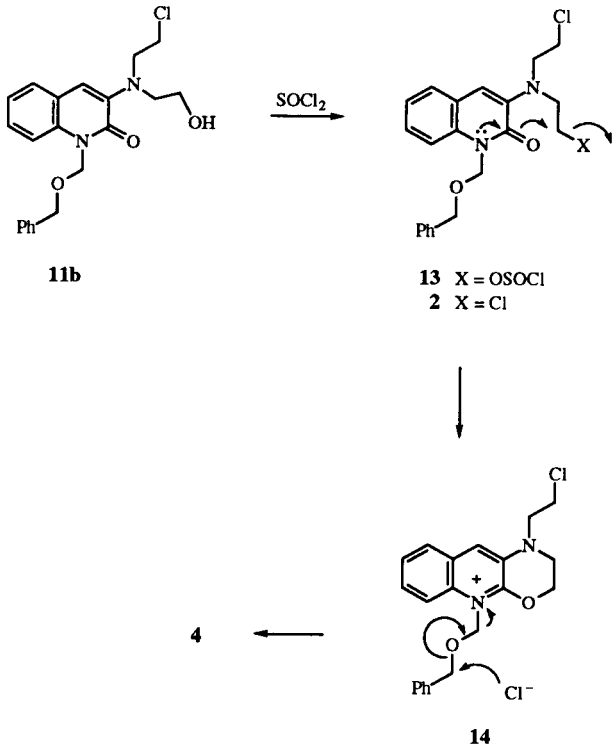
Treatment of **11a** with thionyl chloride using the conditions of Lyttle and Petering [8] afforded a solid product in 75% yield. The ir spectrum of the compound did not show the amide absorption as expected for the desired mustard **2**. The ^{1}H nmr spectrum of the compound showed a pat-

tern consistent with the formation of a substituted benzfused-2,3-dihydro[1,4]oxazine ring [9]. The downfield shift of methylene protons in the region of 4.5 ppm confirmed its position adjacent to oxygen. Based on the above spectral characteristics the compound was assigned the structure **4**. This was further confirmed by its molecular ion peak at 248 in its mass spectrum.

As a consequence of this cyclization the use of the blocking groups on the quinolinone nitrogen seemed to be necessary. The benzyloxymethyl group [10] was considered to be potentially useful due to its stability to the conditions that were used in the synthesis. The diol **11b** was prepared by alkylating **9a** with benzyloxymethyl chloride followed by reduction with zinc/ammonium chloride [12] and hydroxyethylation of the resulting amine as shown in Scheme 1. However, as a note of interest, treatment of *N*-benzyloxymethyl-quinolinone diol **11b** (Scheme 1) with thionyl chloride also yielded **4** instead of the mustard **12**.

The plausible mechanism for the formation of **4** from **11b** was hypothesized as illustrated in Scheme 2. Reaction

Scheme 2

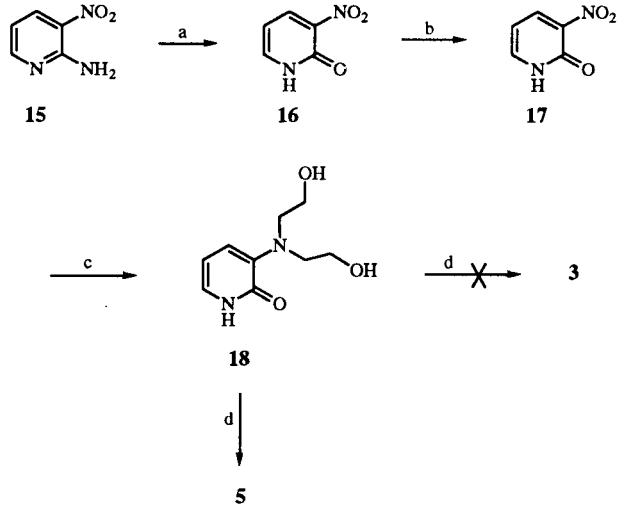


11b **13** X = OSOCl; **2** X = Cl; **14**

of **11b** with thionyl chloride results in the formation of a key intermediate the chlorosulfite ester **13** in the conversion of alcohols to chloride. Consequently, the nucleophilic attack by carbonyl oxygen (which serves as an ambient nucleophile) on the ester (or the mustard **12**) results in the cyclization to intermediate **14**. The chloride ion can then attack the benzyloxymethyl group at the benzylic position and eliminate benzyl chloride and formaldehyde.

A similar cyclization reaction was observed in an attempted synthesis of the mustard **3** as shown in Scheme 3. Diazotization [13] of 3-nitro-2-aminopyridine **15**, followed by hydrogenation of the corresponding nitropyridinone **16** in the presence of 10% Pd/C gave aminopyridinone **17** [4]. Hydroxyethylation of the amine **17** with ethylene oxide as described above afforded the diol **18** in 84% yield. Optimum yields were obtained when the reaction was carried

Scheme 3



15 **16** **17** **18**

a) Sodium nitrite, sulphuric acid, room temp; b) H_2, 10% Pd/C, atm pressure; c) Ethlyene oxide, acetic acid; d) Thionyl chloride

out in 6% aqueous acetic acid. Treatment of **18** with thionyl chloride also resulted in the cyclized product **5** in 80% yield. The compound was characterized by ^{1}H nmr, ir, and mass spectrometery. The spectral data was similar to that of **4** with respect to the chemical shifts of the methylene protons and the disappearance of the carbonyl absorption. In addition, the mass spectrum of the compound gave a molecular ion peak at 199. Although our efforts to synthesize the desired congeners **2** and **3** were unsuccessful, attempts to prepare these compounds resulted in the formation of intriguing 4-substituted oxazinoquinoline and pyridooxazine rings *via* tandem chlorination/cyclization reaction.

EXPERIMENTAL

Melting points (uncorrected) were determined in an unsealed capillary tube with a Thomas-Hoover Unimelt apparatus. The ir spectra were determined with a Mattson Polaris FT-ir interferometer. The ^{1}H nmr spectra were determined with a Varian EM390 spectrometer. The chemical ionization mass spectra were determined using UG-SE mass spectrometer. Elemental analyses were performed by Atlantic Microlabs Inc., Atlanta, Georgia.

4-(2-Chloroethyl)-2,3-dihydro[1,4]oxazino[2,3-*b*]quinoline **4**.

Freshly distilled thionyl chloride (0.789 g, 6.6 mmoles) was

added to a stirred solution of the diol **11a** (0.532 g, 2.1 mmoles) in dichloromethane (25 ml) at 0° (ice bath) under a positive pressure of argon. The reaction mixture was allowed to warm to room temperature, then stirred for *ca.* 10 hours. The precipitate obtained was filtered and washed with dry ether. The hydrochloride salt thus obtained was further purified by recrystallization from anhydrous ethanol/ether to give **4** (0.400 g, 75%), mp 200-203°; ir (potassium bromide): 3014, 2962, 1609, 1479, 1452 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6, TMS): δ 3.5 (t, J = 6 Hz, 2 H), 3.8 (s, 4 H), 4.5 (t, J = 6 Hz, 2 H), 7.0 (s, 1 H), 7.2-7.9 (m, 4 H); ms: m/z 248 (55.8), 199 (100), 128 (17.3).

Anal. Calcd. for $C_{13}H_{13}N_2OCl$·HCl: C, 54.74; H, 4.94; N, 9.82; Cl, 24.87. Found: C, 54.67; H, 5.00; N, 9.78; Cl, 24.93.

4-(2-Chloroethyl)-2,3-dihydropyrido[2,3-*b*][1,4]oxazine **5**.

A solution of **18** (0.310 g, 1.5 mmoles) in anhydrous dichloromethane (25 ml) was treated with freshly distilled thionyl chloride (0.558 g, 4.69 mmoles) at 0° (ice bath) under argon. The reaction mixture was allowed to warm to room temperature and stirred for 12 hours. The volatiles were evaporated *in vacuo* and the dark residue that was obtained was dissolved in water (10 ml), basified with ice cold 10% sodium bicarbonate solution (5 ml) and extracted with ether (2 x 20 ml). The organic layer was washed with water (2 x 10 ml), brine (10 ml), dried (sodium sulfate) and concentrated *in vacuo*. The residue was chromatographed (silica gel, ethyl acetate) to give **5** as a gum. The gum was dissolved in dry ether (5 ml) and was treated with ethanolic hydrogen chloride (prepared by bubbling hydrogen chloride gas through absolute ethanol, 5 ml). The precipitate formed was filtered and crystallized from anhydrous ethanol-ether (1:1, 10 ml) to give the hydrochloride salt of **5** (0.251 g, 80%), mp 165-168°; ir (potassium bromide): 3057, 2957, 2867, 1585, 1477, 1452 cm^{-1}; ^1H nmr (deuteriochloroform-TMS): δ 3.4 (t, J = 6 Hz, 2 H), 3.7 (s, 4 H), 4.4 (t, J = 6 Hz, 2 H), 6.8 (m, 2 H), 7.5 (m, 1 H); ms: m/z 199 (100), 149 (40).

Anal. Calcd. for $C_9H_{11}N_2OCl$·HCl: C, 45.97; H, 5.14; N, 11.91; Cl, 30.15. Found: C, 46.02; H, 5.18; N, 11.84; Cl, 30.08.

2-Aminobenzaldehyde **8**.

A solution of **7** [5] (5.0 g, 40 mmoles) in anhydrous dichloromethane (100 ml) was added to a suspension of manganese dioxide (14.0 g, 161 mmoles) in dry dichloromethane (100 ml) at room temperature under a positive pressure argon. The mixture was allowed to stir at room temperature for 15 hours and filtered through celite. The solid was washed with dichloromethane (3 x 40 ml) and the combined filtrate and washings were concentrated *in vacuo* and chromatographed (silica gel, dichloromethane) to give **8** (4.4 g, 86%), mp 37-38° (lit [4] 38°); ir (nujol): 3464, 3328, 2851, 2759, 1674, 1460 cm^{-1}; ^1H nmr (deuteriochloroform-TMS): δ 5.8 (broad s, 2 H), 6.5 (m, 2 H), 6.9-7.3 (m, 2 H), 9.6 (s, 1 H).

3-Nitroquinolin-2(1*H*)-one **9a**.

A solution of **8** (15.2 g, 125 mmoles) in dry xylene (50 ml) was treated with ethyl nitroacetate (16.68 g, 125 mmoles) and piperidine (12.8 g, 150 mmoles) at room temperature under a positive pressure of argon. The reaction mixture was refluxed for 1 hour and the solid and precipitated was filtered, washed with ether and recrystallized from glacial acetic acid to give **9a** (10.0 g, 42%) mp 264-267° (lit [14] 259-260°); ir (potassium bromide): 3332, 3147, 3064, 2889, 1666, 1334 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6-TMS): δ 7.1-7.4 (m, 2 H), 7.5-7.9 (m, 2 H), 8.7 (s, 1 H), 11.5 (broad s, 1 H).

1-Benzyloxymethyl-3-nitroquinolin-2-one **9b**.

A mixture of **9a** (1.5 g, 7.8 mmoles) and potassium carbonate (2.18 g, 15.7 mmoles) in dry dimethoxyethane (20 ml) was refluxed for 30 minutes under a positive pressure of argon. Benzyloxymethyl chloride (1.8 g, 11.8 mmoles) was then added to it in a dropwise manner and the mixture was further refluxed for 3 hours. The suspension was filtered and the potassium salts were washed with dichloromethane (2 x 10 ml) and the combined filtrate and washings were concentrated *in vacuo*. The residue was chromatographed (silica gel, ethyl acetate-hexanes, 1:1) to give **9b** (2.0 g, 88%), mp 116-118°; ir (nujol): 2923, 2854, 1681, 1523, 1454, 1050 cm^{-1}; ^1H nmr (deuteriochloroform-TMS): δ 5.2 (s, 2 H), 6.4 (s, 2 H), 7.2 (m, 6 H), 7.7 (m, 3 H), 8.5 (s, 1 H).

Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.79; H, 4.54; N, 9.02. Found: C, 65.84; H, 4.55; N, 9.02.

3-Aminoquinolin-2(1*H*)-one **10a**.

A solution of **9a** (1.0 g, 5.25 mmoles) in methanol (150 ml) was treated with 10% Pd/C (0.239 g) and stirred under an atmosphere of hydrogen at room temperature for 2 hours. The mixture was filtered through celite and the solid residue was washed with methanol (50 ml). The combined filtrate and washings were evaporated *in vacuo* and the residue was chromatographed (silica gel, dichloromethane-ethyl acetate, 9.5:0.5) to give **9a** (0.804 g, 95%), mp 211° (lit [15] 211-213°); ir (potassium bromide): 3437, 3329, 1665, 1573, 1461 cm^{-1}; ^1H nmr (methanol-d_4-TMS): δ 4.5 (s, 2 H), 6.5 (s, 1 H), 6.6-6.9 (m, 4 H), 11.5 (broad s, 1 H).

1-Benzyloxymethyl-3-aminoquinolin-2-one **10b**.

Zinc (4.73 g, 72 mg-atoms) was added portion wise to a mixture of **10a** (1.5 g, 4.8 mmoles) and ammonium chloride (3.94 g, 73 mmoles) in methanol (50 ml) over a period of 10 minutes at 10° (ice cooled water). The mixture was allowed to warm up to room temperature, then stirred for 2 hours. The reaction mixture was filtered through celite and zinc and zinc oxide residue was washed with dichloromethane (3 x 30 ml). The combined filtrate and washings were evaporated *in vacuo* and the residue was chromatographed (silica gel, ethyl acetate-hexanes, 7:3) to give **10b** (0.819 g, 63%), mp 128-131°; ir (nujol): 3477, 3354, 2928, 2854, 1652, 1625, 1460 cm^{-1}; ^1H nmr (deuteriochloroform-TMS): δ 4.8 (s, 2 H), 5.2 (s, 2 H), 6.3 (s, 2 H), 7.1 (s, 1 H), 7.5-7.6 (m, 9 H).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75, N, 9.99. Found: C, 72.75; H, 5.75; N, 9.93.

3-[Bis(2-hydroxyethyl)amino]quinolin-2(1*H*)-one **11a**.

A solution of **10a** (1.6 g, 10.0 mmoles) in glacial acetic acid (40 ml) was added dropwise to a stirred solution of ethylene oxide (8.8 g, 10.6 ml, 20 mmoles) in acetic acid (75%) at 7° (cold water bath). The reaction mixture was allowed to warm to room temperature, then stirred for 24 hours. The reaction mixture was then treated with water (50 ml) and Dowex 50(H) resin (10 g), stirred at room temperature for another 15 minutes and filtered. The resin was washed with water (3 x 10 ml) and the filtrate and the washings were discarded. The resin was then stirred with 10% ammonium hydroxide (50 ml) and water (20 ml) for 1.5 hours, and the ammoniacal mixture was filtered. The resin was washed with an additional 10% ammonium hydroxide (50 ml) followed by water (20 ml) and the combined filtrate and washings were evaporated *in vacuo* to give a solid which was chromatographed (silica gel, chloroform-methanol, 4:1) to give **11a** (1.0 g, 40%), mp 171-172°;

ir (potassium bromide): 3388, 3311, 2885, 1644, 1567, 1426, cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6-TMS): δ 3.5-3.9 (m, 8 H), 4.8 (broad s, 2 H), 7.8-7.1 (m, 5 H), 11.9 (broad s, 1 H).

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.49; N, 11.28. Found: C, 62.73; H, 6.55; N, 11.23.

1-Benzyloxymethyl-3-[bis(2-hydroxyethyl)amino]quinolin-2-one **11b**.

The diol **11b** was obtained (by the method described for **11a**) from **10b** as a gum (58%); ir (neat): 3376, 2929, 2871, 1639, 1595, 1455 cm^{-1}; ^1H nmr (deuteriochloroform-TMS): δ 3.3 (t, 4 H), 3.5 (t, 4 H), 4.3 (s, 2 H), 4.5 (s, 2 H), 5.2 (s, 2 H), 6.4 (s, 2 H), 7.0-7.2 (m, 10 H). The product was used without further purification for the next reaction.

3-Nitropyridin-2(1*H*)-one **16**.

The title compound was prepared by the procedure of Bintz [13]. A solution of sodium nitrite (4.9 g, 71.01 mmoles) in water (20 ml) was cooled to 5° and added dropwise to a solution of **15** (5.09 g, 35.94 mmoles) in concentrated sulfuric acid (10 ml) at 0° (ice bath). After the addition was complete, the solution was allowed to warm to room temperature, then stirred for 5 hours. The precipitate was filtered and the filtrate was extracted with ethyl acetate (2 x 100 ml). The organic layer was dried (sodium sulfate) and the solvent evaporated *in vacuo*. The combined residues were recrystallized from ethanol to give **16** (3.14 g, 68%), mp 222-224° (lit [13] 224°); ir (potassium bromide): 3111, 2967, 1656, 1550 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6-TMS): δ 6.35 (t, J = 6 Hz, 1 H), 7.9 (doublet of doublet, J = 6 Hz, J = 1.5 Hz, 1 H), 8.4 (doublet of doublet, J = 6 Hz, J = 1.5 Hz, 1H), 12.7 (broad s, 1 H).

3-Aminopyridin-2(1*H*)-one **17**.

The amine **17** was obtained (by the method described for **10a**) to give a solid (89%), mp 133-135° (lit [13] 132-133°); ir (potassium bromide): 3425, 3300, 3130, 2185, 1656, 1470 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6-TMS): δ 5.0 (broad s, 2 H), 6.1 (t, J = 7.5 Hz, 1 H), 6.5 (doublet of doublet, J = 7.5 Hz, J = 1.5 Hz, 1 H), 6.7 (doublet of doublet, J = 7.5 Hz, J = 1.5 Hz, 1 H), 11.5 (broad s, 1 H).

3-[Bis(2-Hydroxyethyl)amino]pyridin-2(1*H*)-one **18**.

The aminopyridinone **17** was alkylated with ethylene oxide as described for **11a** except that the reaction was carried out in 6% aqueous acetic acid and the reaction mixture was stirred for 48 hours at room temperature. The ammoniacal filtrate and washings were evaporated *in vacuo* and the gummy mass obtained was extracted with hot ethyl acetate (50 ml). The undissolved substances were filtered and washed with hot ethyl acetate (3 x 25 ml) and the combined filtrate and washings were dried (sodium sulfate) and evaporated *in vacuo* to give 84% of the diol **18** as a gum, ir (nujol): 3367, 3362, 2920, 2855, 1639, 1632, 1555 cm^{-1}; ^1H nmr (methanol-d_4-TMS): δ 3.4 (t, J = 6 Hz, 4 H), 3.6 (t, J = 6 Hz, 4 H), 5.0 (broad s, 2 H), 6.4 (t, J = 6 Hz, 1 H), 7.0 (d, J = 6 Hz, 2 H), 11.5 (broad s, 1 H). The compound was used without further purification in the next reaction.

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