2,4,6-Trichloropyrimidine. Reaction with Ethanolamine and Diethanolamine

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2,4,6-Trichloropyrimidine, **1**, reacts with neutral nucleophiles, such as ethanolamine and diethanolamine, to produce both mono- and disubstituted derivatives resulting from replacement of either one (**2** and **3**) or two (**4**) chlorine atoms. The third chlorine could not be replaced by these nucleophiles. Failure of this final step was attributed to intramolecular hydrogen bonding of the nucleophiles.

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Pyrimidines receive an extraordinary amount of attention by synthetic and medicinal chemists because of the unique role played by this heteroaromatic ring in biological systems. The extent of this interest is reflected in the substantive reviews by Brown [1]. The electron deficient nature of the pyrimidine ring facilitates the synthesis of a large number of pyrimidine derivatives through nucleophilic aromatic substitution of suitable leaving groups. The halogens have been especially useful in this regard [2].

2,4,6-Trichloropyrimidine (**1**) has been a convenient starting point for reactions with nucleophiles for a long time. Winkelmann provided one of the earliest examples of sequential nucleophilic displacement of the chloro groups in **1** using methylamine [3]. A mixture of **2a** and **3a** was obtained at 100°, **4a** at 133°, and the completely substituted **5a** at 180°. Other amines, such as ammonia [4], dimethylamine [5], benzylamine [6], pyrrolidine [7], and aniline [8], have been employed as nucleophiles to replace one or more of the chloro substituents of **1**.

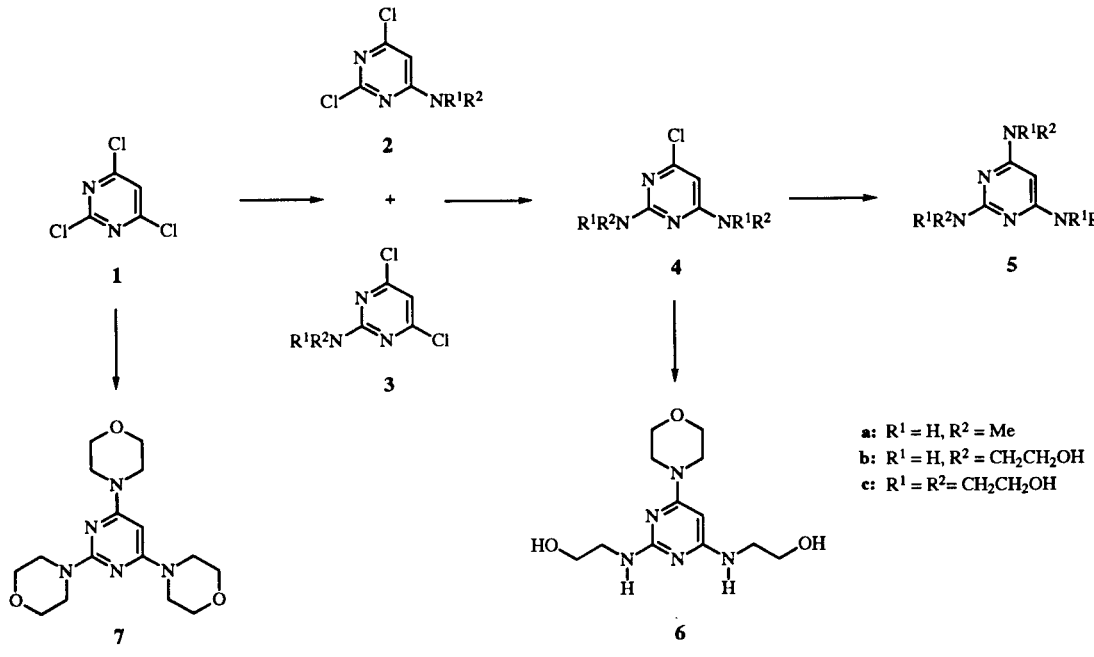
As part of a larger program directed toward the synthesis of complex pyrimidine derivatives, nucleophilic reactions of **1** were investigated. We were interested in substituents that had functional groups which could be elaborated into more complex substituents. Only one amine nucleophile, aminoacetaldehyde diethyl acetal, which possesses a functional group other than the nitrogen serving as the nucleophile has been employed in this type of reaction [9]. Upon liberating the free aldehyde, however, ring cyclization occurs spontaneously. This paper describes our intitial efforts involving ethanolamine and diethanolamine as nucleophiles.

Because of the differences in nucleophilicity between the amine and hydroxy functionalities we decided not to protect the hydroxy group. Thus, a solution of **1** in tetrahydrofuran was added dropwise to two equivalents of ethanolamine in tetrahydrofuran at room temperature. Upon workup the resulting solid was examined by ^{1}H nmr spectroscopy and determined to be a mixture of two products, in a ratio of approximately 1:2. Column chromatography effected a separation of the two substances into 4,6-dichloro-2-(2-hydroxyethyl)aminopyrimidine (19%), **2b**, and 2,4-dichloro-6-(2-hydroxyethyl)aminopyrimidine (49%), **3b**. The ^{1}H nmr spectra, mass spectra, and elemental analysis confirmed the structures as monosubstituted derivatives. The assignment of the two isomers is based on the ratios observed in other systems [3-6] and the downfield shift of the C-5 proton in the ^{1}H nmr spectrum of **2b** compared to **3b**. The neighboring electron-withdrawing groups, *i.e.* two chlorine atoms in **2b**, deshield the C-5 proton more than the neighboring chlorine and amine groups in **3b**.

Relying on the reported sequential nature of substitution reactions described in the literature, we treated **1** with an excess of ethanolamine in tetrahydrofuran at reflux. Compound **4b** was obtained in about 80% yield after workup. The assignment of structure **4b** is based on elemental analysis, mass spectrum, and ^{1}H nmr spectra.

The final step in our strategy involved replacing the third chlorine by ethanolamine. We were not able to accomplish this conversion. Compound **1** was treated with ethanolamine under a variety of conditions. Heating a tetrahydrofuran solution in a sealed vessel at ~160° for up to four days and using the same conditions, with the addition of triethylamine, failed to achieve the desired reaction.

Treatment of **1** with excess diethanolamine at room temperature gave a mixture of **2c** and **3c** in a 1:2 ratio, indicated by ^{1}H nmr. Separation of the isomers by flash chromatography was accomplished, although with significant loss of material due to the overlap of the two compounds on elution. Additional quantities of the two isomers can be obtained by a second chromatography. This ratio is consistent with earlier literature results and our results with ethanolamine. The structures were confirmed by ^{1}H nmr, mass spectra, and elemental analysis. However, the C-5 proton in **3c** was observed further downfield than the C-5 proton in **2c**. This was not expected since the two neighboring chlorine atoms in **2b** have previously been shown to exert a stronger influence on the C-5 proton. To confirm our assignment, hplc was



used to identify the ratios of the two isomers and to ascertain the polarities of the two molecules. The more polar isomer **3c** was found to be the predominant component in the mixture. It is postulated that the two hydroxyethyl branches in the 4-position of **3c** exert a significant deshielding effect, compared to the one hydroxyethyl branch of **3b**.

The disubstituted product could also be obtained from either **1** or a mixture of **2c** and **3c** and excess diethanolamine at *ca.* 70°. The structure of **4c** was confirmed by ^{1}H nmr, mass spectra, and elemental analysis.

Failure to achieve replacement of the final chlorine in **4c** was similar to the results obtained for the ethanolamine reactions. A variety of conditions were employed, including heating a solution containing excess diethanolamine, the use of triethylamine as base, and high temperatures in a sealed vessel.

The failure of the third chlorine to be replaced with either ethanolamine or diethanolamine was unexpected. These results suggested that the hydroxyethyl moieties of either the reagent or the disubstituted compounds must play a role in preventing further reaction. It has been demonstrated that intramolecular hydrogen bonding in 2-aminoethanol is substantial [10]. The hydrogen bonding between the hydroxylic proton and the nitrogen is the more stable form and can easily diminish the nucleophilicity of the amino group. This diminished capacity to behave as a nucleophile, coupled with a now very much less labile chlorine atom, provides a barrier to reaction that cannot be overcome with a neutral nucleophile.

Support for this explanation is provided by the successful reaction between **4b** and morpholine. Compound **6** was obtained in 84% yield and the structure was confirmed by ^{1}H nmr, mass spectra, and elemental analysis. In this case, there is no free hydroxyl group which eliminates any possibility of hydrogen bonding while retaining a structure similar to diethanolamine. As further indication of the ease with which morpholine behaves as a nucleophile, treatment of **1** with excess morpholine under reflux provides a nearly quantitative yield of **7**.

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes using a Thomas Hoover instrument. The ^{1}H nmr spectra were recorded in the solvents indicated with TMS as the internal standard on either a Bruker NR80 spectrometer at 80 MHz or a QE-300 NMR spectrometer at 300 MHz. All values are reported in ppm relative to TMS. Relative integrals of peak areas are in agreement with assigned structures. Mass spectra were measured on a Hewlett Packard 5995A GC/MS instrument, using a direct insertion probe. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Column chromatographic purifications were done with silica gel (Mallinckrodt, 60-200 mesh for gravity chromatography and Fisher Scientific, 230-425 mesh for flash chromatography).

4,6-Dichloro-2-(2-hydroxyethyl)aminopyrimidine (**2b**) and 2,4-Dichloro-6-(2-hydroxyethyl)aminopyrimidine (**3b**).

A solution of 2,4,6-trichloropyrimidine, **1**, (0.01 mole) in tetrahydrofuran (10 ml) was added dropwise to a stirred solution of ethanolamine (0.02 mole) in tetrahydrofuran (20 ml) at room temperature. The turbid mixture was allowed to stir at room temperature overnight. The solvent was removed by evaporation under vacuum to give a white solid. The ^{1}H nmr of the solid

indicated the presence of two products. The solid was separated by flash chromatography. Compound **2b** was eluted with 20% ethyl acetate in hexane while **3b** was eluted with ethyl acetate.

Crystallization of **2b** occurred upon slow evaporation of the solvent to give white matted needles, mp 125-127° (19%); ^{1}H nmr (deuteroacetone): 2.85 (m, 4H), 3.60 (m, 1H), 6.70 (s, 1H); ms: m/z 209 (6), 207 (11), 180 (9), 179 (11), 178 (73), 177 (19), 176 (100).

Anal. Calcd. for $C_6H_7Cl_2N_3O$: C, 34.64; H, 3.39; N, 20.20. Found: C, 34.90; H, 3.37; N, 19.96.

Crystallization of **3b** occurred upon slow evaporation of the solvent to give small white crystals, mp 129-131° (49%); ^{1}H nmr (deuteroacetone): 3.60 (m, 4H), 3.70 (m, 1H), 6.60 (s, 1H); ms: m/z 209 (7), 207 (11), 180 (11), 179 (26), 178 (65), 177 (37), 176 (100), 165 (12), 163 (19).

Anal. Calcd. for $C_6H_7Cl_2N_3O$: C, 34.64; H, 3.39; N, 20.20. Found: C, 34.62; H, 3.33; N, 20.03.

4-Chloro-2,6-bis(2-hydroxyethyl)aminopyrimidine (**4b**).

A solution of 2,4,6-trichloropyrimidine, **1**, (0.01 mole) in tetrahydrofuran (10 ml) was added dropwise to a stirred solution of ethanolamine (0.04 mole) in tetrahydrofuran (20 ml) at room temperature. The turbid mixture was allowed to stir at room temperature overnight. The solvent was removed by evaporation under vacuum and the residual yellow oil began to crystallize. The solid mass was washed with water (30 ml), filtered, and dried to give 2.13 g of a white powder (92%). The product was purified either by flash chromatography using ethyl acetate or by recrystallization from ethyl acetate to give white crystals, mp 148-149°; ^{1}H nmr (dimethyl sulfoxide-d_6): 3.30 (m, 4H), 3.50 (m, 4H), 4.78 (bt, 2H), 5.80 (s, 1H), 6.80 (br, 1H), 7.25 (br, 1H); ms: m/z 234 (9), 232 (23), 203 (39), 202 (52), 201 (100).

Anal. Calcd. for $C_8H_{13}ClN_4O_2$: C, 41.29; H, 5.63; N, 24.08. Found: C, 41.21; H, 5.43; N, 23.82.

4,6-Dichloro-2-(bis-2-hydroxyethyl)aminopyrimidine (**2c**) and 2,4-Dichloro-6-(bis-2-hydroxyethyl)aminopyrimidine (**3c**).

To a stirred solution of 2,4,6-trichloropyrimidine, **1**, (0.01 mole) in tetrahydrofuran (10 ml) at room temperature was added slowly a solution of diethanolamine (0.025 mole) in tetrahydrofuran (10 ml) and absolute ethanol (5 ml). The reaction was exothermic and an ice bath was used to maintain ambient temperature. After an additional hour of stirring at room temperature, the solvents were removed by evaporation under vacuum. To the residue was added water (6 ml) to remove excess diethanolamine and the remaining white solid was collected and washed with water. The crude yield was 90% after drying. Chromatography of the solid gave **2c** (30%) with ethyl acetate-hexane (3:7) and **3c** (60%) with ethyl acetate.

Compound **2c** crystallized as a white powder from water, mp 145-147°; ^{1}H nmr (methanol-d_4): 3.75 (br, 8H), 6.65 (s, 1H); ms: m/z 251 (16), 222 (57), 220 (100), 190 (44), 178 (43), 176 (72), 45 (29).

Anal. Calcd. for $C_8H_{11}Cl_2N_3O_2$: C, 38.11; H, 4.40; N, 16.67. Found: C, 38.28; H, 4.43; N, 16.35.

Compound **3c** crystallized as a white powder from water, mp 107-110°; ^{1}H nmr (methanol-d_4): 3.75 (br, 8H), 6.75 (s, 1H); ms: m/z 251 (16), 222 (55), 220 (94), 194 (54), 190 (73), 178 (52), 176 (68), 45 (100).

Anal. Calcd. for $C_8H_{11}Cl_2N_3O_2$: C, 38.11; H, 4.40; N, 16.67. Found: C, 38.24; H, 4.43; N, 16.45.

4-Chloro-2,6-di(bis-2-hydroxyethyl)aminopyrimidine (**4c**).

To a solution of **2c** and **3c** (0.008 mole) in tetrahydrofuran (10 ml) and absolute ethanol (5 ml) was added diethanolamine (0.02 mole) in absolute ethanol (10 ml). The mixture was heated to reflux for 72 hours. The solvents were removed by evaporation under vacuum to give a dark yellow oil. Acetone (30 ml) was added and the mixture shaken vigorously. The upper acetone layer was separated, evaporated under vacuum to give a bright yellow oil. Trituration of the chilled oil with cold ethyl acetate produced a tan solid. Crystallization from acetone gave a tan powder, **4c**, (40%), mp 94-96°; ^{1}H nmr (methanol-d_4): 3.75 (br, 16H), 8.00 (s, 1H); ms: m/z 320 (18), 291 (37), 289 (100), 259 (45), 245 (41), 45 (14).

Anal. Calcd. for $C_{12}H_{21}ClN_4O_4$: C, 44.93; H, 6.60; N, 17.47. Found: C, 44.68; H, 6.72; N, 17.08.

2,6-Bis(2-hydroxyethyl)amino-4-morpholinopyrimidine (**6**).

A solution of 4-chloro-2,6-bis(2-hydroxyethyl)aminopyrimidine, **4b**, (0.160 g, 5.6 mmoles) in morpholine (8 ml) was heated to reflux for two hours. The solvent was removed by evaporation under vacuum and acetone (3 ml) added to the residue. The precipitate of morpholine hydrochloride was removed by filtration. After removal of the solvent from the filtrate, the residue was purified by flash chromatography using chloroform as the eluant. The product was collected as brown-yellow gum which, upon trituration with acetone, gave a white solid (0.163 g, 84%). Recrystallization from acetone gave a white solid, mp 132-134°; ^{1}H nmr (deuteriochloroform): 2.82 (m, 2H), 3.35 (m, 2H), 3.47 (m, 4H), 3.70 (m, 8H), 4.45 (br, 2H), 4.93 (s, 1H), 5.52 (br, 1H), 5.65 (br, 1H); ms: m/z 286 (42), 285 (68), 284 (50), 283 (18), 256 (40), 255 (80), 254 (100), 239 (23), 240 (45), 241 (54), 242 (34).

Anal. Calcd. for $C_{12}H_{21}N_5O_3$: C, 50.88; H, 7.42; N, 24.73. Found: C, 50.96; H, 7.73; N, 24.88.

2,4,6-Trimorpholinopyrimidine (**7**).

An exothermic reaction occurred when 2,4,6-trichloropyrimidine, **1**, (0.63 g, 0.0034 mole) and morpholine (10 ml) were combined. The mixture was heated to reflux for 6 hours. Upon cooling, the contents of the flask solidified. The resulting yellow mass was washed with water (3 x 10 ml) to yield a white solid which, upon drying, provided 1.11 g (98%) of **7**. Recrystallization from ethanol gave white crystals, mp 267-268°; ^{1}H nmr (deuteriochloroform): 3.45 (t, 12H), 3.66 (m, 12H), 5.50 (s, 1H); ms: m/z 335 (100), 305 (40), 278 (45), 260 (29).

Anal. Calcd. for $C_{16}H_{25}N_5O_3$: C, 57.29; H, 7.51; N, 20.88. Found: C, 57.29; H, 7.39; N, 20.75.

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