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Some Nucleophilic Substitutions in 2,4- and 2,4,8-Trichloro- pyrido [3,2-d] pyrimidines

Said M. Boyomi*, Abdel-Kader M. Ismaiel, Hassan M. Eisa and Mohamed M. El-Kerdawy

**Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia and Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura, Egypt.*

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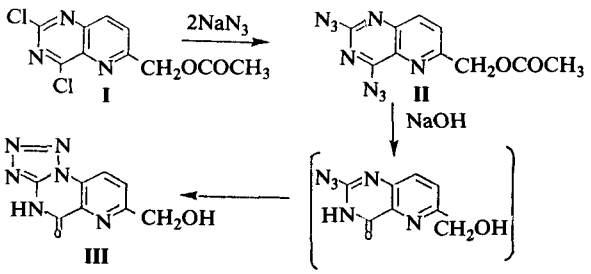
Abstract □ Reaction of 6-(acetoxymethyl)-2,4-dichloropyrido[3,2-d]pyrimidine (**I**) with some nucleophiles was investigated. When I reacted with sodium azide afforded 2,4-diazido derivative (**II**). Treatment of II with sodium hydroxide underwent cyclization of the 2-azido group to tetrazolo, replacement of 4-azido group by hydroxide ion, and hydrolysis of 6-acetoxy moiety to hydroxy methyl derivative (**III**). While, reaction of I with hydrazine hydrate resulted in the formation of 2,4-dihydrozino-6-hydroxymethyl derivative (**IV**).

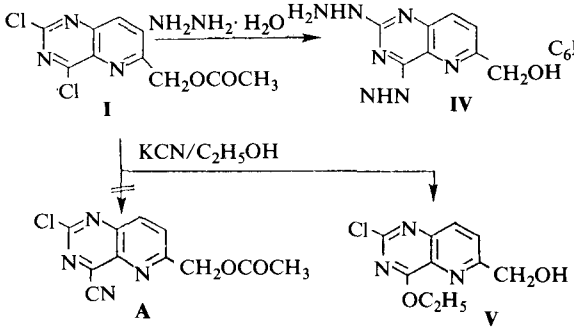
Keywords □ Reactivity, Nucleophilic Replacement, Cyclization.

Recently, various pyrido[3,2-d]pyrimidines have been claimed to be the main precursor in the synthesis of human thymidylate synthetase inhibitors[1,2] and 8-deazafolic acid analogues.[3,4] The chemistry of pyridopyrimidines has been described by Hitchings *et al.*[5] In continuation of our earlier investigation[6] of the action of hydrazine hydrate on 2,4-dimethoxypyrido [3,2-d]pyrimidines, we report here the reactivity of some 2,4-dichloro- and 2,4,8-trichloro-pyrido [3,2-d]pyrimidines towards some nucleophilic substitution reactions. It has been reported that 4-chloro group in 2,4-dichloropy-rido [3,2-d]pyrimidines underwent nucleophilic displacement much more readily than 2-chloro.[7] Moreover, reaction of 2,4,8-trichloropyrido[3,2-d] pyrimidine with ammonia gave the corresponding 4-amino-2,8-dichloropyrido[3,2-d]pyrimidine-6-carboxamide. Further studies on the same trichloro intermediate revealed that the reactivity of this compound towards nucleophilic substitution reaction was in order of 4,2,8.[8] In the present work, the previously prepared 6-acetoxymethyl)-2,4-dichloro-pyrido [3,2-d]pyrimidine[4] (**I**) was subjected to reaction with a variety of nucleophile. Thus, reaction of **I** with two equivalents of sodium azide in absolute ethanol afforded the corresponding diazido derivative (**II**) in the same manner where 2,4-diazidopyrimidine was formed from 2,4-dichloropyrimidine and sodium azide.[9] The ir spectrum exhibited sharp and clear bands at 2160 cm^{-1} and 1760 cm^{-1} due to N_3 group and CO group, respectively. The mass spectrum supported the structural assignment with the molecular ion peak at m/z 285 (M^+). A peak at (M-42) corresponding to loss N_3 assured the stability of the azide moiety. Treatment of **II** with 1N sodium hydroxide provided selective replacement of the azide group at 4-position by hydroxide ion as well as hydrolysis of the acetoxy moiety at 6-position to produce 2-azido -6-(hydroxymethyl)-4-oxopyrido[3,2-d]pyrimidine, which undergoes ring closure with the formation of tetrazole ring derivative (**III**). The ir spectrum exhibited a sharp and clear band at 3500 cm^{-1} due to absorption of OH group but no absorption due to N_3 group. The nmr spectrum confirmed the presence of NH group at 11.6 ppm.



Reaction of **I** with hydrazine hydrate in absolute ethanol gave 2,4-dihydrazino-6-(hydroxymethyl)pyrido[3,2-d]pyrimidine (**IV**). This means that such reaction allowed nucleophilic displacement of

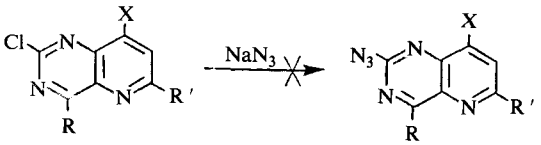
both chloro groups at 2- and 4- positions equally with hydrazino group together with hydrolysis of the acetoxy moiety at 6-position. Unequivocal evidence of the presence of **IV** was provided by its reaction with *o*-nitrobenzaldehyde to give the respective hydrazone. The ir spectrum exhibited two sharp bands at 1580 and 1540 cm^{-1} (-N = CH-).



When **I** was heated under reflux in alcoholic potassium cyanide for 24 h, 2-chloro-4-ethoxy-6-(hydroxymethyl)pyrido[3,2-d]pyrimidine (**V**) rather than (**A**) was obtained as indicated by IR, NMR and mass spectroscopy as well as elemental analysis. No carbonyl absorption due to CO, but instead a sharp and clear band at 3470 cm^{-1} (OH) was observed. The ^1H NMR spectrum displayed signals due to ethoxy and hydroxymethyl groups in addition to aromatic protons. The presence of chlorine atom was verified by the presence of peaks at *m/z* 239 and 241 in the ratio of 3:1 for M^+, due to the isotope abundance of chlorine.

Attempt to prepare 4-benzyloxy-6-carbomethoxy-2,8-dichloropyrido[3,2-d]pyrimidine (**B**) from the previously reported 2,4,8-trichloro-6-methoxycarbonylpyrido[3,2-d]pyrimidine[8] (**VI**) by reaction with one equivalent of sodium benzylate in dimethylsulphoxide resulted only in the recovery of a small amount (35% yield) of 4-benzyloxy-6-carbobenzyloxy-2,8-dichloropyrido[3,2-d]pyrimidine (**VII**). However, by using two equivalents of sodium benzylate in dimethylsulphoxide, **VIII** can be obtained in good yield (84%). This revealed that nucleophilic displacement of 4-chloro group by benzylate ion was accompanied by transesterification. On the other hand reaction of **VI** with excess sodium benzylate in benzyl alcohol afforded, 2,4-dibenzyloxy-6-carbobenzyloxy-8-chloropyridon[3,2-d]pyrimidine (**VIII**). The observed selectively enabled the preparation of 2-benzyloxy-4-hydrazino-6-acid hydrazide (**IX**) by reaction of **VIII** with hydrazine hydrate in boiling ethanol. The spectrum of **IX** exhibited absorption bands at 3400, 3360 and 3220 cm^{-1} (NH & NH_2), 1665 cm^{-1} (CO) and at 1185, 1130 and 1095 cm^{-1} (C-O-C). Further confirmation for **IX** has been done by its reaction with *o*-nitrobenzaldehyde to give the respective hydrazone.

Attempted nucleophilic displacement of the 2-chloro group for either **VIII** or the previously prepared 6-acetoxymethyl-4-amino-2-chloropyrido[3,2-d]pyrimidine[4] (**X**) by reaction with sodium azide in boiling ethanol for several hours was ended by failure and the starting materials was recognised unchanged. This revealed that the presence of electron donating NH_2 or $OCH_2C_6H_5$ group in 4-position of pyrido[3,2-d]pyrimidine ring system inhibits nucleophilic substitution of 2-chloro group by azide ion.



X = Cl R = $OCH_2C_6H_5$ R' = $COOCH_2C_6H_5$ (**VII**)
X = H R = NH_2 R' = CH_2OCOCH_3 (**X**)

EXPERIMENTAL

Melting points were recorded on an electrothermal melting point apparatus (Fisher-Johns) and are uncorrected. Ir spectra in KBr disc were recorded on a Pye Unicam SP 1000 infrared spectrophotometer. ^1H-nmr spectra were recorded on an IBM FT-200 NMR spectrometer in DMSO-d_6. Mass spectra were taken on a Varian 1125 spectrometer. Satisfactory elemental analysis for C, H and N was obtained for all compounds.

6-(Acetoxymethyl)-2,4-diazidopyrido[3,2-d]pyrimidine (II)

Sodium azide (2.86g, 0.044mol) was added to a solution of **I** (5.42g, 0.02mol) in dry ethanol (100ml). The reaction mixture was stirred at am-

bient temperature for 3h. Cold water (200m*l*) was added and the separated solid product was filtered off, washed with cold water, dried and recrystallized from dry ether to give **II** as white crystals, m.p. 130 °C, 82% yield.

8-(Hydroxymethyl)-6-oxotetrazolo[1,5-a]pyrido [3,2-d]pyrimidine (III)

A suspension of **II** (2.85g, 0.01mol) in 1N sodium hydroxide (50m*l*) was refluxed for 10h. The solution was cooled, filtered and neutralized with 2N acetic acid (pH 6). The precipitated solid was filtered, washed with cold water and recrystallized from water to give **III** as white crystals, m.p. 142 °C, 81% yield.

6-(Hydroxymethyl)-2,4-dihydrazinopyrido[3,2-d]-pyrimidin (IV)

Hydrazine hydrate (5g, 0.1mol) was added to a solution of **I** (2.71g, 0.01mol) in ethanol (50m*l*). The reaction mixture was heated to boil and then allowed to set aside for 3h with occasional shaking. The separated solid product was filtered off, dried and recrystallised from water to give **IV** as orange crysatals, m.p. 290 °C, 92% yield.

2,4-Bis(o-Nitrophenylmethylenehydrazino)-6-(Hydroxymethyl)pyrido[3,2-d]pyrimidine

A mixture of IV (2.21 g, 0.01 mol) and *o*-nitrobenzaldehyde (3.22 g, 0.022 mol) In glacial acetic acid (10 m*L*) was heated under reflux for 1 h. After cooling, the separated solid was filtered off, dried and crystallized from glacial acetic acid to give orange crystals, m.p. 290 °C, 85% yield.

4-Ethoxy-6-(hydroxymethyl)-2-chloropyrido[3,2-d]pyrimidine (V)

Potassium cyanide (0.65 g, 0.01 mol) was added to a solution of **I** (2.71 g, 0.01 mol) in ethanol (50 m*l*). The reaction mixture was heated under reflux for 24 h. After cooling, water (100 m*l*) was added and the separated solid product was filtered off, washed with water, dried and recrystallised from water to give **V** as dark violet crystals, m.p. 148 °C 74% yield, NMR (DMSO-d_6) δ: 1.5(*t*, 3H, OCH_2CH_3), 4.6(q, 2H, OCH_2CH_3), 4.8(s, 2H, CH_2OH), 5.7(s, 1H, CH_2OH), 8.0(d, 1H, C^7H), 8.3(d, 1, C^8H).

4-Benzyloxy-6-carbobenzyloxy-2,8-dichloropyrido [3,2-d]pyrimidine (VII)

Compound **VI**(2.91 g, 0.01 mol) was suspended in dimethylsulphoxide (20 m*l*). Benzyl alcohol (7 m*l*) in which sodium (0.46 g, 0.02 m*l*) was previously dissolved, was added dropwise over 2 h. After another 2 h, the yellow solution was poured into water (100 m*l*) andthe obtained solid filtered and recrystallized from alcohol to give **VII** as white crystals, mp 173 °C, 84% yield.

2,4-Dibenzyloxy-6-carbobenzyloxy-8-chloropyrido [3,2-d]pyrimidine (VIII)

Compound **VI** (2.91 g, 0.01 mol) was added to benzyl alcohol (250 m*l*) in which sodium (4.14g, 0.18 mol) was previously dissolved. The reaction mixture was stirred at room temperature for 3 days. The separated solid after dilution with ether (600 m*l*) was filtered, dried and crystallized from ethanol to give **VIII** as white crystals, m.p. 163 °C, 87% yield.

2-Benzyloxy-8-chloro-4-hydrazinopyrido[3,2,-d]-pyrimidine-6-carbohydrazide (IX)

Hydrazine hydrate (5 g, 0.1 mol) was added to a suspension of **VIII** (5.11 g, 0.01 mol) in ethanol (50 m*l*). The reaction mixture was heated to boil and then allowed to set aside for 3 h with occasional shaking. The separated solid product was filtered off, dried and crystallized from DMF/H_2O to give **IX** as yellowish brown crystals, m.p. 225 °C, 91% yield.

8-Chloro-2-(o-nitrophenylmethylene)-4-(o-nitrophenylmethylenehydrazinolenehydrazino)-2-benzyloxypyrido[3,2-d]pyrimidine-6-carbohydrazide

A mixture of **IX** (3.59 g, 0.01 mol) and *o*-nitrobenzaldehyde (3.22 g, 0.022 mol) in glacial acetic acid (10 m*l*) was heated under reflux for 1 h. After cooling, the separated solid was filtered off, dried and recrystallized from glacial acetic acid to give as yellow crystals, mp 290 °C, 93% yield.

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