

Synthesis of Novel Acyclonucleosides.
Reactions of 1-(2-Oxopropyl)pyridazin-6-ones
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Multi-substituted-1-(1-bromo-2-oxopropyl)pyridazin-6-ones **3**, **4**, multi-substituted-1-(1,1-dibromo-2-oxopropyl)pyridazin-6-ones **7**, **8**, and multi-substituted-1-(3-bromo-2-oxopropyl)pyridazin-6-ones **5**, **6** were synthesized from the corresponding 1-(2-oxopropyl)pyridazin-6-ones **1**, **2** by the selective bromination in acidic or neutral medium. And treatment of 1,1-dibromo-2-oxopropyl derivatives **7**, **8** with aqueous potassium carbonate gave the corresponding pyridazin-6-ones **9**, **10** by the dealkylation. Reaction of **1** with methanolic potassium cyanide afforded only the corresponding 4-methoxy derivative **11**, whereas reaction of **2** with methanolic potassium cyanide gave 4-methoxy derivative **12** and 2-cyano-2-hydroxypropyl derivative **13**. Reaction of **1** and **2** with hydroxylamine in methanol afforded the corresponding syn-2-hydroxyiminopropyl derivatives **14** and **15**.

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Recently, significant progress has been made in the development of antiviral chemotherapy due to the discovery of nucleoside analogues with potential activities [1]. Townsend, *et al.* also reported the synthesis and biological activity of the pyridazine nucleoside derivatives [2].

In connection with our research program for the synthesis of acyclonucleosides containing pyridazine base, we synthesized some 1-(2-oxopropyl)pyridazin-6-ones [3].

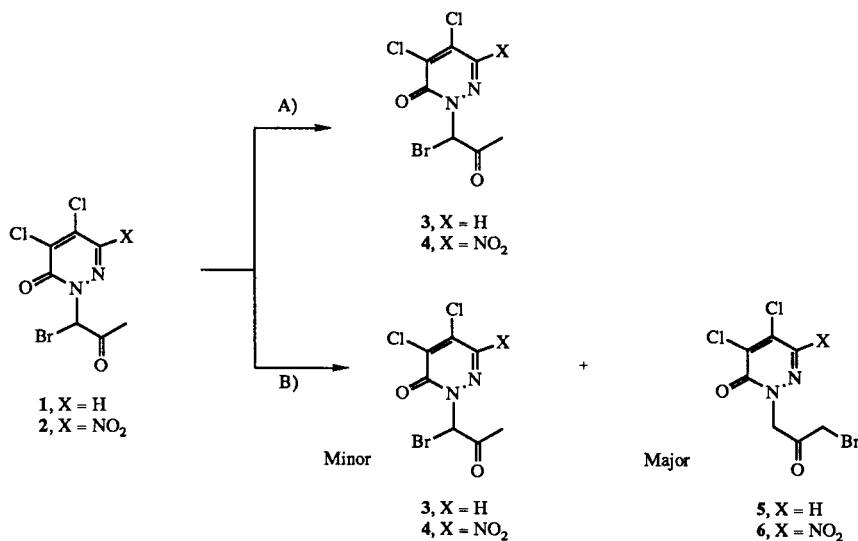
In this paper, we wish to report the bromination of the title compounds and also the reaction of the title compounds with hydroxylamine and methanolic potassium cyanide.

Selective bromination of acetoacetanilides in alkali or acidic medium was described as a review by Hussain, *et al.* [4]. In order to prepare C₁-bromo and C₃-bromo

derivatives of the title compound as intermediates for the synthesis of some acyclonucleosides, we attempted the bromination of 4,5-dichloro-1-(2-oxopropyl)pyridazin-6-one (**1**) and 4,5-dichloro-3-nitro-1-(2-oxopropyl)pyridazin-6-one (**2**) in neutral or acidic medium.

Bromination of **1** and **2** in chloroform-acetic acid-sodium acetate gave the corresponding C₁-bromo compound **3** and **4** in 60% and 62% yield, respectively (method A and B). Whereas treatment of **1** and **2** with bromine in chloroform afforded the corresponding C₃-bromo compound **5** and **6** as major and the corresponding C₁-bromo compound **3** and **4** as minor (method C and D). It was easy to distinguish between C₁-bromo compound and C₃-bromo compound by the comparison of proton magnetic resonance spectra of compound **3** and **4** with the spectra of **5** and **6**. The ¹H-nmr spectra of **3** and **4**

Scheme 1

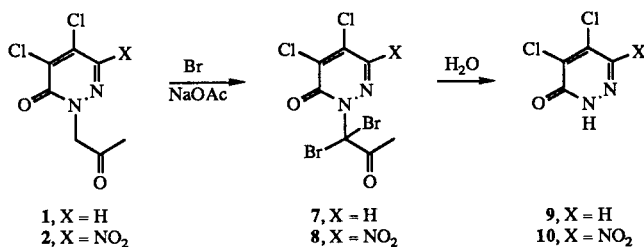


A) NaOAc, AcOH, CHCl₃, Br₂. B) CHCl₃, Br₂

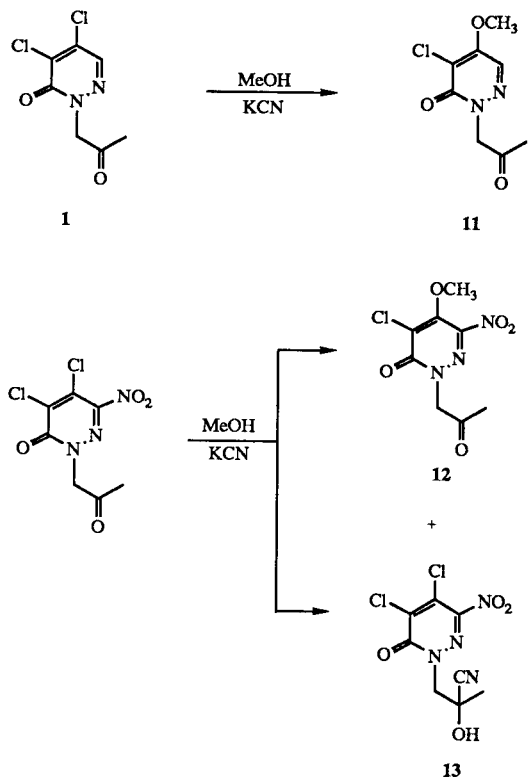
in deuterated chloroform showed two signals at 7.02 for **3** or 6.98 for **4** which were assigned to a H_1 of acetyl moiety and 2.40 for **3** or 2.52 for **4** which were assigned to three H_3 of acetyl moiety. However, the 1H -nmr spectra of **5** and **6** in deuterated chloroform showed two signals at 5.22 for **5** or 5.24 for **6** which were assigned to two H_1 of acetyl moiety and 4.50 for **5** or 4.00 for **6** which were assigned to two H_3 of acetyl moiety.

On the other hand, when an excess of bromine (2 moles) was used in acidic medium, compound **7** and **8** as 1,1-dibromo-2-oxopropyl derivatives were obtained in 88% and 89% yield, respectively. The 1H -nmr spectra of **7** and **8** in deuterated chloroform showed only one signal (at 2.58 for **7**, at 2.64 for **8**) for H_3 of the acetyl moiety.

Scheme 2



Treatment of compounds **7** and **8** with potassium carbonate in water-tetrahydrofuran furnished compounds **9** and **10** by the dealkylation on the N_1 position of the Scheme 3



pyridazine ring.

We also tried the synthesis of the corresponding cyanohydrin derivatives from compounds **1** and **2**. Reaction of **1** with methanolic potassium cyanide gave only compound **11** instead of the corresponding cyanohydrin, whereas treatment of **2** with methanolic potassium cyanide afforded **12** and **13** in 15% and 22% yield, respectively.

The proton nmr spectrum of **12** showed three signals at 2.22 (s, $3H_3$), 4.20 (s, OCH_3) and 4.98 (s, $2H_1$), whereas the proton nmr spectrum of **13** showed at 2.30 (s, $3H_3$), 4.38 (s,

Table 1

 1H NMR Spectral Data for Compound 3-8, 11-14 and 15

Compound No.	Solvent	H_1	H_3	Others
3	A	7.02 (s)	2.40 (s)	7.90 (s)
4	A	6.98 (s)	2.52 (s)	
5	B	5.22 (s)	4.50 (s)	8.22 (s)
6	A	5.24 (s)	4.00 (s)	
7	A	---	2.58 (s)	8.00 (s)
8	A	---	2.64 (s)	
11	B	5.00 (s)	2.18 (s)	8.24 (s) 4.10 (s, OCH_3)
12	A	4.98 (s)	2.22 (s)	4.20 (s, OCH_3)
13	A	5.00 (d) [a]	2.30 (s)	4.38 (s, OH) [b]
14	A	4.82 (s)	1.92 (s)	7.79 (s)
15	A	4.80 (s)	1.82 (s)	8.80-7.20 (bs, OH) [b] 10.50 (bs, OH) [b]

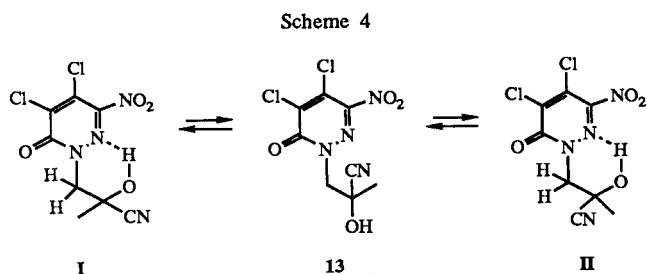
[a] J = 8 Hz. [b] D_2O exchangeable: s, singlet; bs, broad singlet; d, doublet; A, Deuteriochloroform; B, Deuteriodimethyl sulfoxide.

Table 2

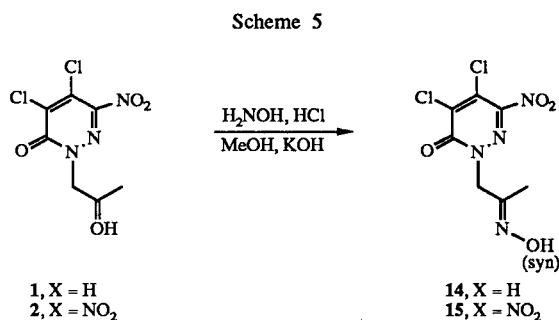
Elemental Analysis of 3-8, 11-14 and 15

Compound No.	Molecular Found	Calcd./Found (%)		
		C	H	N
3	$C_7H_5N_2O_2Cl_2Br$	28.03	1.68	9.34
		28.11	1.59	9.31
4	$C_7H_4N_3BrCl_2$	24.37	1.17	12.18
		24.30	1.20	12.05
5	$C_7H_5N_2O_2Cl_2Br$	28.03	1.68	9.34
		28.12	1.73	9.50
6	$C_7H_4N_3O_4BrCl_2$	24.37	1.17	12.18
		24.41	1.20	12.09
7	$C_7H_4N_2O_2Cl_2Br_2$	22.19	1.06	7.21
		22.54	0.93	7.30
8	$C_7H_3N_3O_4Cl_2Br_2$	19.84	0.71	9.91
		19.51	0.63	9.80
11	$C_8H_9N_2O_3Cl$	44.36	4.19	12.93
		43.97	3.87	12.94
12	$C_8H_8N_3O_5Cl$	36.73	3.08	16.06
		37.03	3.25	16.30
13	$C_8H_6N_4O_4Cl_2$	32.78	2.06	19.11
		33.03	2.10	19.40
14	$C_7H_7N_3O_2Cl_2$	35.62	2.99	17.80
		35.87	3.01	17.50
15	$C_7H_6N_4Cl_2$	29.91	2.15	19.93
		29.70	2.21	19.62

OH, deuterium oxide exchangeable) and 5.00 (d, 2H₁, J = 8 Hz), Two hydrogens of C₁-position for **13** appeared at 5.00 as a doublet. It may be due to the intramolecular hydrogen bond between the O-H hydrogen and nitrogen on the pyridazine ring such as structures **I** and **II**. Infrared spectrum of **13** also showed the peak of OH at about 3300 cm⁻¹ and CN at 2380 cm⁻¹. The position of methoxy group for compound **11** and **12** was proved by the further reactions of these compounds [5]. In previous paper [6], we also have reported the methoxylation of multi-substituted pyridazine nucleosides using methanolic potassium cyanide. Reaction of compound **1** and **2** with hydroxylamine hydrochloride in the presence of potassium hydroxide in



methanol gave the corresponding 2-hydroxyiminopropyl derivatives as a mixture of the syn and anti forms. Fractional crystallization of the mixture in carbon tetrachloride-methanol afforded only the syn form such as compounds **14** and **15**. These structures were assigned by comparison of the proton nmr spectra of the mixtures (syn + anti) with the spectra of the pure syn isomers. In ketoximes, the proton nmr signal of methyl group of the oxime carbon for syn form show more up field then it for anti form [7]. The proton nmr spectrum of **14** showed four signals at 1.92 (s, 3H₃), 4.82 (s, 2H₁), 7.79 (s, 1H) and 7.20-8.80 (bs, OH, deuterium oxide exchangeable). The proton nmr spectrum of **15** showed three signals at 1.82 (s, 3H₃), 4.80 (s, 2H₁) and 10.50 (bs, 1H, deuterium oxide exchangeable).



Further synthetic expolarations related to diazinone acyclonucleosides and biological activity of some new compounds are in progress, and will be that subject of further reports.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were obtained on a Bruker AW-80 MHz spectrometer with chemical shift values reported in δ units (parts per million) relative to an internal standard (tetramethylsilane). Infrared spectra were obtained on a Hitachi 270-50 spectrophotometer. Elemental analysis were performed with a LECO Micro Carbon Hydrogen Determinator (CHN-800). Open-bed column chromatography was carried out silica gel 60 (70-230 mesh, Merck) using gravity flow. The columns were packed as slurries with the elution solvent.

4,5-Dichloro-1-(1-bromo-2-oxopropyl)pyridazin-6-one (**3**).

Method A.

A mixture of **1** (2.2 g, 10 mmoles) [3], bromine (1.0 ml, 20 mmoles), sodium acetate (2.5 g, 25 mmoles) and acetic acid (0.6 ml, 10 mmole) in chloroform (30 ml) was stirred for 3 hours at room temperature. After the addition of an additional chloroform (30 ml), the reaction mixture was washed with distilled water (100 ml x 3), and dried over anhydrous magnesium sulfate. After adding 2 ml of acetone, the resulting solution was evaporated under reduced pressure. The residue was recrystallized from carbon tetrachloride to give **3** as pale yellow needles in 60% (1.8 g) yield, mp 97-98°; ir (potassium bromide): 3100, 1732, 1670, 1588, 740 cm⁻¹.

4,5-Dichloro-3-nitro-1-(1-bromo-2-oxopropyl)pyridazin-6-one (**4**).

Method B.

A mixture of **2** (2.7 g, 10 mmoles) [3], bromine (1.0 ml, 20 mmoles), sodium acetate (2.5 g, 25 mmoles) and acetic acid (0.6 ml, 10 mmoles) in chloroform (30 ml) was stirred for 3 hours at room temperature. After adding an additional chloroform (30 ml), the reaction mixture was washed with water (100 ml x 3), and dried over anhydrous magnesium sulfate. After adding 2 ml of acetone, the resulting solution was evaporated under reduced pressure. The residue was recrystallized from cyclohexane to give **4** as pale yellow needles in 62% (2.2 g) yield, mp 92-93°; ir (potassium bromide): 2984, 1736, 1698, 1558 cm⁻¹.

4,5-Dichloro-1-(1-bromo-2-oxopropyl)pyridazin-6-one (**3**) and 4,5-Dichloro-1-(3-bromo-2-oxopropyl)pyridazin-6-one (**5**).

Method C.

A mixture of **1** (2.15 g, 10 mmoles), bromine (1.80 g, 10 mmoles) and chloroform (20 ml) was refluxed for 30 minutes. After cooling in room temperature, the solvent was evaporated under reduced pressure. The resulting residue was applied to silica gel column (1.5 x 30 cm). The column was eluted with chloroform-cyclohexane (3:5 v/v). The fractions containing compound **3** (detection using tlc, R_f = 0.8 developing solvent, chloroform) was combined and evaporated under reduced pressure. The resulting solid was recrystallized from carbon tetrachloride to give **3** in 10% (0.3 g) yield. The spectral data, analytical data and melting point of this product was identical with data of compound **3** from method A. The fractions containing compound **5** (detection using tlc, R_f = 0.75, developing solvent, chloroform) were combined and evaporated under reduced pressure. The resulting solid was recrystallized from carbon tetrachloride to give **5** in 61% (1.8 g) yield, mp 170-171°; ir (potassium bromide): 3104, 2964, 1734, 1660, 1582 cm⁻¹.

4,5-Dichloro-3-nitro-1-(1-bromo-2-oxopropyl)pyridazin-6-one (**4**) and 4,5-Dichloro-3-nitro-1-(3-bromo-2-oxopropyl)pyridazin-6-one (**6**).

Method D.

A mixture of **2** (11.1 g, 41 mmol) and chloroform (100 ml) was heated to 45°. Bromine solution (bromine 2.8 ml and chloroform 10 ml) was then added during 10 minutes at the same temperature to above reaction mixture. After stirring for 1 hour, 1 ml of acetone was added to the reaction mixture. The solvent was evaporated under reduced pressure. The resulting residue was applied to a silica gel column (1.5 x 30 cm). The column was eluted with chloroform-cyclohexane (3:5 v/v). The fractions containing compound **4** (detection using tlc, $R_f = 0.5$, developing solvent, methylene chloride) were combined and evaporated under reduced pressure. The resulting solid was recrystallized from cyclohexane to give **4** in 39% (5.1 g) yield. The spectral and analytical data were identical with the data of compound **4** from the method B. The fractions containing compound **6** (detection using tlc, $R_f = 0.38$, developing solvent, methylene chloride) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from cyclohexane to give **6** in 53% (7.1 g) yield, mp 71-72°; ir (potassium bromide): 3004, 2960, 1742, 1690, 1584 cm^{-1} .

4,5-Dichloro-1-(1,1-dibromo-2-oxopropyl)pyridazin-6-one (**7**).

A mixture of **1** (4.4 g, 20 mmol), chloroform (50 ml), sodium acetate (6.0 g, 73 mmol), acetic acid (4.0 ml, 70 mmol) and bromine (3.8 ml, 78 mmol) was stirred for 17 hours at room temperature. Acetone (2 ml) was added to the reaction mixture. After the solvent was evaporated under reduced pressure, the resulting residue was applied to a silica gel column (3 x 20 cm). The column was eluted with chloroform. The fractions containing the product were combined and evaporated under reduced pressure. The resulting solid was recrystallized from carbon tetrachloride to give compound **7** as yellow crystals in 88% (7.3 g) yield, mp 113-114°; ir (potassium bromide): 3100, 2932, 1734, 1670, 1558 cm^{-1} .

4,5-Dichloro-3-nitro-1-(1,1-dibromo-2-oxopropyl)pyridazin-6-one (**8**).

A mixture of **2** (3.0 g, 15 mmol), sodium acetate (3.9 g, 48 mmol), acetic acid (2.0 ml, 33 mmol), chloroform (30 ml) and bromine (2 ml, 41 mmol) was stirred for 12 hours at room temperature. After adding additional chloroform (30 ml), the reaction mixture was washed with distilled water (100 ml x 3) and dried over anhydrous magnesium sulfate. Acetone (2 ml) was added to the resulting mixture. The solvent was evaporated under reduced pressure. The resulting residue was recrystallized from cyclohexane to give **8** as pale yellow crystals in 89% (4.5 g) yield, mp 90-91°; ir (potassium bromide): 1754, 1706, 1592, 1360 cm^{-1} .

Reactions of **7** and **8** with Potassium Carbonate.

A mixture of **7** (1 mmol) or **8**, (1 mmol), tetrahydrofuran (5 ml), potassium carbonate (0.27 g, 2 mmol) and distilled water (5 ml) was stirred for 2 hours at room temperature. After the solvent was evaporated under reduced pressure, 20 ml of water was added to the residue. The resulting mixture was filtered and dried in air to give **9** or **10** in 98% or 97% yield. These products **9** and **10** were spectroscopically, and analytically identical with authentic samples [8,9].

5-Chloro-4-methoxy-1-(2-oxopropyl)pyridazin-6-one (**11**).

A mixture of **1** (0.55 g, 2.5 mmol), potassium cyanide (0.36 g, 5.5 mmol) and methanol (15 ml) was stirred for 2 hours at 40°. The solvent was evaporated under reduced pressure. After the residue was dissolved in chloroform (50 ml), the solution was washed with water (150 ml x 3). To the solution, calcium chloride and Amberlite-IRC-50 (H^+ form, 1 g) were added. The mixture was stirred for an additional 24 hours and filtered. The solvent was evaporated under reduced pressure. The residue was recrystallized from carbon tetrachloride to give **11** as white needles in 53% (0.29 g) yield, mp 121-122°; ir (potassium bromide): 3004, 2960, 1726, 1663, 1610 cm^{-1} .

5-Chloro-4-methoxy-3-nitro-1-(2-oxopropyl)pyridazin-6-one (**12**) and 4,5-Dichloro-3-nitro-1-(2-cyano-2-hydroxypropyl)pyridazin-6-one (**13**).

A mixture of **2** (1.00 g, 2.8 mmol), potassium cyanide (0.25 g, 5 mmol) and methanol (10 ml) was stirred for 8 hours at room temperature under a nitrogen atmosphere. The solvent was evaporated under reduced pressure. This was subjected to preparative tlc (solvent chloroform). The fraction of $R_f = 0.55$ gave **12** as yellow crystals in 15% (0.15 g) yield, mp 73-74°. Recrystallization of a small sample from chloroform furnished an analytical sample, mp 74-75°; ir (potassium bromide): 1740, 1684, 1554, 792 cm^{-1} . The fraction of $R_f = 0.31$ gave **13** as yellow crystals in 22% (0.2 g) yield, mp 89-90°. Recrystallization of a small sample from methylene chloride furnished an analytical sample, mp 90-91°; ir (potassium bromide): 3300, 2380, 1698, 1584 cm^{-1} .

4,5-Dichloro-1-(syn-2-hydroxyiminopropyl)pyridazin-6-one (**14**).

A mixture of hydroxylamine hydrochloride (0.35 g, 5 mmol), potassium hydroxide (0.28 g, 5 mmol) and methanol (10 ml) was stirred for 10 minutes at room temperature. To above solution, compound **1** (1.20 g, 5 mmol) was added. The reaction mixture was stirred for 1 hour at 40°. After adding carbon tetrachloride (50 ml), the resulting crystals were filtered, and dried in air to give only **14** as white needles in 25% (0.30 g) yield. Recrystallization of a small sample from carbon tetrachloride furnished an analytical sample, mp 120-121°; ir (potassium bromide): 3232, 3048, 1650, 1578 cm^{-1} .

4,5-Dichloro-3-nitro-1-(syn-2-hydroxyiminopropyl)pyridazin-6-one (**15**).

A mixture of hydroxylamine hydrochloride (0.35 g, 5 mmol), potassium hydroxide (0.28 g, 5 mmol) and methanol (10 ml) was stirred for 10 minutes at room temperature. To above solution compound **2** (1.33 g, 5 mmol) was added. The reaction mixture was stirred for 30 minutes at room temperature. After the solvent was evaporated under reduced pressure, the residue was applied to silica gel column (1.5 x 30 cm). The column was eluted with methylene chloride. The fractions containing the compound of $R_f = 0.71$ (tlc solvent, methylene chloride/methanol = 9:1) were combined and evaporated under reduced pressure to give **15** as needles in 15% (0.5 g) yield. The analytical sample was recrystallized from carbon tetrachloride, mp 129-130°; ir (potassium bromide): 3262, 2980, 1690, 1580 cm^{-1} .

Acknowledgements.

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