Synthesis of Novel Pyridazine Acyclonucleosides

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Some pyridazine acyclonucleosides containing hydroxymethyl and 4-hydroxybutyl groups as an alkanol side chain were prepared. Nucleophilic displacement of N_1-alkyl-4,5-dichloropyridazin-6-ones is discussed.

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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. Thus, major efforts have been directed by the nucleoside researchers toward the synthesis of *N*-acyclonucleosides with various side chains and aglycones. In addition, the skeletal modification of the heterocyclic portion of acyclonucleosides have provided numerous azine nucleosides possessing a wide variety of biological actions [1].

As a part of a study on novel diazine *N*-acyclonucleosides, we synthesized some pyridazine and pyrimidine *N*-acyclonucleosides containing 2-oxopropyl, 2-hydroxypropyl and 2,3-dihydroxypropyl groups [2].

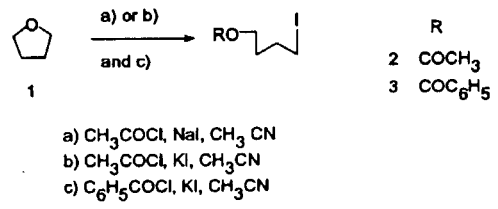
In the present paper, we report the synthesis of some pyridazine acyclonucleosides containing some alkanol side chains such as hydroxymethyl and 4-hydroxybutyl groups.

Our approach to the synthesis of pyridazine acyclonucleosides containing the 4-hydroxybutyl group involved the cleavage of cyclic ethers. Therefore, we chose to use tetrahydrofuran (THF) as the starting material for the synthesis of alkanol side chain.

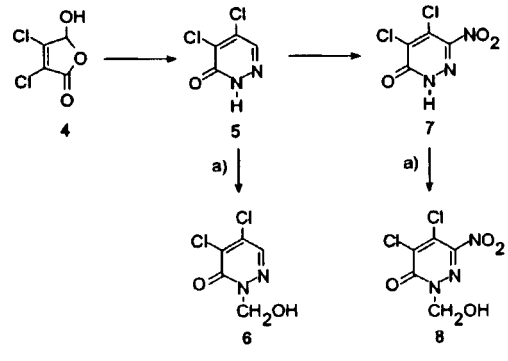
According to Oku's method [3], cleavage of tetrahydrofuran (**1**) with acetyl chloride and sodium iodide in acetonitrile for 21 hours at room temperature gave 4-iodobutyl acetate (**2**) as a liquid in 95% yield (Method A). Whereas, reaction of **1** with acetyl chloride and potassium iodide in the same solvent for 3 hours at room temperature afforded **2** in 95% yield (Method B). Cleavage of **1** with benzoyl chloride and potassium iodide in acetonitrile for 3 hours at room temperature also gave 4-iodobutyl benzoate (**3**) in 96% yield. The structure of **3** follows from elemental analysis, ir and pmr. To be convenient to handle, we selected compound **3** as the starting material for the alkylation reactions. Our modified method is more convenient then Oku's method for the cleavage of cyclic ether.

Reaction of **5** [4] with a formalin solution (35%) gave **6** in 59% yield. Also, condensation of **7** [5] with a formalin solution (35%) afforded **8** in 76% yield. We detected the absorption peak of the hydroxy group in the infrared spectra of **6** and **8**. The proton magnetic resonance spectra of **6** and **8** showed two methylene protons as a doublet at δ 5.40 and 5.60, respectively.

Scheme I



Scheme II



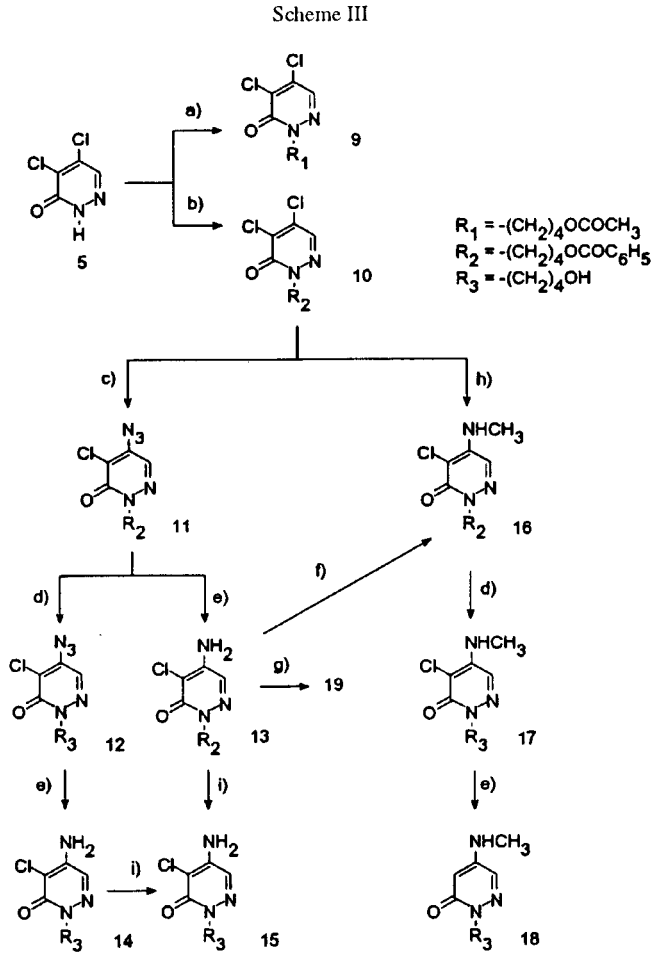
Alkylation of **5** with **2** or **3** in dimethyl sulfoxide in the presence of sodium hydride gave **9** or **10** in 83% or 82% yield, respectively. The infrared spectra of **9** and **10** showed the absorption peak of two carbonyl groups. In the proton magnetic resonance spectra of **9** and **10**, we also observed proton signals of four methylene groups involving the signals of methyl protons for **9** and phenyl protons for **10**.

Reaction of **10** with sodium azide in dimethyl sulfoxide gave **11** in 56% yield. The infrared spectrum of **11** showed the absorption peak of the azido group at 2116 cm^{-1}. The proton magnetic resonance spectrum of **11** showed proton

signals of four methylene groups involving the signals of the phenyl protons and one proton at C-3 on the pyridazine ring. Debenzoylation of **11** with methanolic sodium methoxide afforded **12** in good yield. The infrared spectrum of **12** revealed the absorption peaks of the azido group at 2114 cm^{-1} and the hydroxy group at 3400 cm^{-1}, and the proton magnetic resonance spectrum of **12** also showed the proton signals for four CH_2 groups, the OH and =C-H at C-3 on the pyridazine ring. Reduction of **11** with Pd/C-H_2 gave **13** in excellent yield. The infrared spectrum of **13** showed the absorption peaks of two carbonyl groups and an amino group. We also detected the signals of the protons for the amino, four methylene and phenyl groups involving the signal of one proton at C-3 on the pyridazine ring in the proton magnetic resonance spectrum of **13**. Treatment of **12** with Pd/C-H_2 gave **14** in excellent yield (Method C). Also, compound **14** was prepared from **13** by the debenzoylation in excellent yield (Method D). These two compounds were identical. In the proton magnetic resonance spectrum of **14**, we detected proton signals for four CH_2, the OH and NH_2 groups. Dechlorination of **13** and **14** with Pd/C-H_2 in the presence of aqueous sodium hydroxide (30%) furnished **15** in 73% (Method F) and 86% (Method E) yield, respectively. The proton magnetic resonance spectrum of **15**, 4-substituted derivatives, revealed characteristic signals [5.66 (d, J = 2.8, 1 H_5), 7.43 (d, J = 2.8, 1 H_3)] for the aromatic protons at C-3 and at C-5 on the pyridazine ring involving proton signals for four CH_2, the NH_2, and OH groups. The resonance signals for **15** in the δ 5.0-8.0 region also compared well to those reported [6] for other 4-substituted pyridazin-6-ones. Therefore, we established firmly the site of the azido for **11** and **12** and the amino group for **13** and **14** from the structure of **15**.

Reaction of **10** with methylamine hydrochloride in methanol in the presence of triethylamine gave **16** in good yield (Method G). Reaction of **13** with methyl iodide in methanol in the presence of potassium carbonate also afforded **16** in low yield (Method H). Therefore, we established the position of the methylamino group of **16** by the synthesis of **16** from **13**. The infrared spectrum of **16** showed the absorption peaks for the NH and two carbonyl groups. We detected the proton signals for NH, four CH_2, CH_3 and phenyl groups involving one proton at C-3 on the pyridazine ring in the proton magnetic resonance spectrum of **16**. Debenzoylation of **16** with methanolic sodium methoxide furnished **17** in good yield. The structure of **17** was established by elemental analysis, ir and pmr. And dechlorination of **17** with Pd/C-H_2 afforded **18** in excellent yield. The infrared spectrum of **18** showed the absorption peaks for OH at 3400 cm^{-1}, NH at 3300 cm^{-1} and carbonyl groups at 1638 cm^{-1}. The resonance signals of the aromatic protons on the pyridazine ring in δ 5.0-8.0 region for **18** also revealed the characteristic pattern of 4-substituted pyridazin-6-ones.

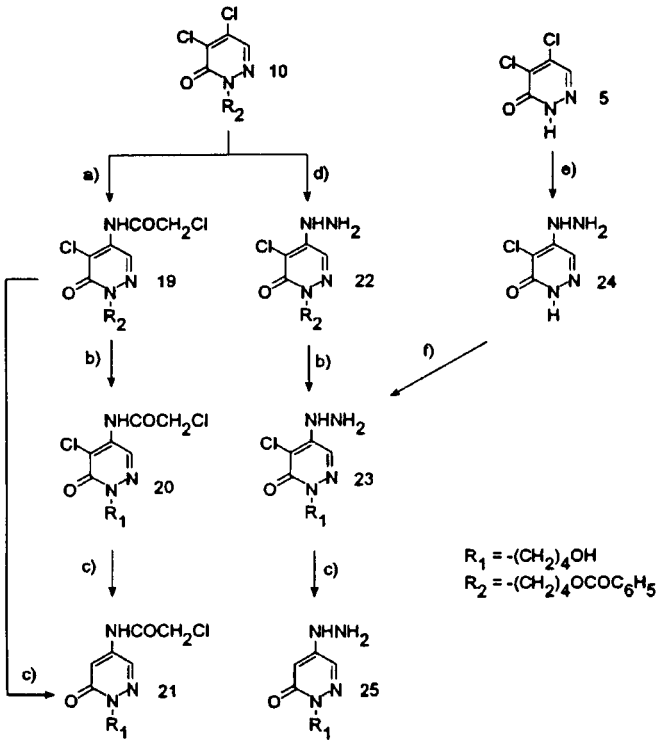
Scheme III



Reaction of **10** with 2-chloroacetamide in methanol in the presence of triethylamine afforded **19** in good yield (Method I). Compound **19** was also synthesized from **13** (Method J). Therefore, we distinguished easily the site of the 2-chloroacetamido group for **19**. The infrared spectrum of **19** showed the absorption peak for NH at 3350 cm^{-1} involving the absorption peaks of the carbonyl groups. The proton magnetic resonance spectrum of **19** also showed the proton signals for five CH_2, =C-H at C-3 on the pyridazine ring and phenyl groups. But we did not detect the signal for the proton for NH. This observation is due to the intramolecular hydrogen bond between NH at the 4-position and chlorine at the 5-position. Debenzoylation of **19** with methanolic sodium methoxide gave **20** in good yield. The structure of **20** was confirmed by elemental analysis, ir and pmr.

On the other hand, dechlorination of **19** and **20** with Pd/C-H_2 in the presence of aqueous sodium hydroxide (30%) yielded **21** (Methods K and L). The resonance signals of the protons on the pyridazine ring for **21** also showed the characteristic pattern of 4-substituted pyridazin-6-ones.

Scheme IV

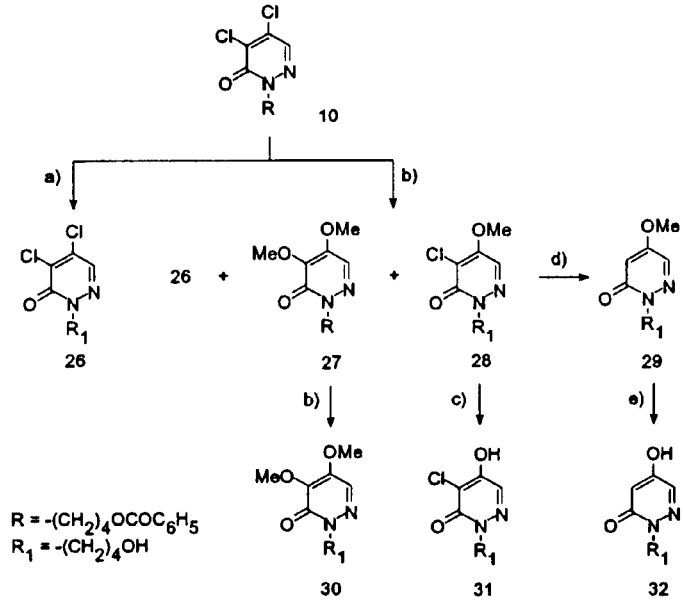


a) $ClCH_2CONH_2$, $(Et)_3N$, MeOH
b) i; NaOMe, MeOH ii) Amberlite IRC-50H$^+$
c) Pd/C, H_2, MeOH, NaOH (30%, aq)
d) $NH_2NH_2{\cdot}H_2O$, K_2CO_3, DMSO
e) NH_2NH_2, MeOH, reflux
f) 3, MeOH, NaH

Reaction of **10** with hydrazine hydrate in dimethyl sulfoxide in the presence of potassium carbonate furnished **22** in 66% yield. Debenzoylation of **22** with methanolic sodium methoxide afforded **23** in 78% yield (Method M). We also attempted the synthesis of **23** from **24** in order to determine the site of the hydrazino group in compound **23**. Reaction of **24** which was prepared from **5** by Osner's method [7] with **3** in the presence of sodium hydride also gave compound **23** in 36% yield (Method N). Treatment of **23** with Pd/C-H_2 in the presence of aqueous sodium hydroxide (30%) furnished **25** in low yield. The structures of **22** and **23** were established by elemental analysis, ir and pmr. In the proton magnetic resonance spectrum of **25**, we also detected the characteristic proton resonance signals on the pyridazine ring for 4-substituted pyridazin-6-ones involving the signals of the protons for NH, NH_2 and OH groups.

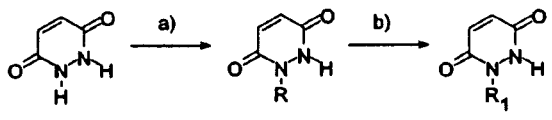
Reaction of **10** with 2,6-dihydroxypyridine in *N,N*-dimethylformamide also afforded **26** instead of a substitution product in 46% yield (Method O). The infrared spectrum of **26** showed the absorption peaks of the hydroxy group at 3450 cm^{-1} and the carbonyl groups at 1670 cm^{-1}. Treatment of **10** with methanolic sodium methoxide for 24 hours at room temperature gave **26**, **27** and **28** as white crystals in 18% (0.47 g, for **26**), 42% (1.64 g, for **27**) and 23% (0.63 g, for **28**) yields, respectively (Method P). Reaction of **10** with methanolic sodium methoxide for 4 hours under reflux conditions afforded **28** as the main product in good yield (Method Q). Product **26** was identical with the product which was prepared by the Method O. The infrared spectrum of **27** showed absorption peaks for two carbonyl groups at 1715 and 1660 cm^{-1}, whereas the infrared spectrum of **28** showed the absorption peak of only one carbonyl group at 1660 cm^{-1} involving the peak of the hydroxy group at 3450 cm^{-1}. The signals of the two methoxy protons in the proton magnetic resonance spectrum of **27** were also detected. The proton magnetic resonance spectrum of **28** showed the signal of only one methoxy proton. The position of the methoxy group in **28** was proved by the structure of **29**. Debenzoylation of **27** with methanolic sodium methoxide at room temperature afforded **30** in excellent yield. The structure of **30** was established by elemental analysis,

Scheme V



a) 2,6-Dihydroxypyridine, DMF, reflux
b) i; NaOMe, MeOH, at r.t. ii; Amberlite IRC-50H$^+$
c) NaOH (7%, aq), MeOH, reflux
d) Pd/C, H_2, MeOH, NaOH (30%, aq)
e) i; NaOH (20%, aq), reflux, ii; HCl

Scheme VI



33 34 35

R = -$(CH_2)_4OCOC_6H_5$
R_1 = -$(CH_2)_4OH$

a) 3, NaH, DMSO
b) I; NaOMe, MeOH II; Amberlite IRC-50H$^+$

ir and pmr. Dechlorination of **28** with Pd/C-H_2 gave **29** in 74% yield. On the other hand, treatment of **28** and **29** with aqueous sodium hydroxide gave compounds **31** and **32** in 68% and 86% yield, respectively. In the infrared spectra of **31** and **32**, we detected the absorption peaks of the hydroxy and carbonyl groups. The proton magnetic resonance spectrum of **31** also showed one aromatic proton signal, whereas we observed the characteristic resonance pattern of two aromatic protons on the pyridazine ring **29** and **32**.

Alkylation of **33** [8] with **3** in the presence of sodium hydride gave **34** in excellent yield. Debenzolyation of **34** with methanolic sodium methoxide afforded **35** in excellent yield. The structures of **34** and **35** were confirmed by elemental analysis, ir and pmr.

Further work including biological activity and other reactions are under way in our laboratory.

Table 1
^{1}H-NMR Spectral Data for Certain Pyridazine Acyclonucleosides

Compound No.	Solvent [a]	δ (ppm) [b]
2	C	1.80 (s, CH_3), 1.40-1.60 (m, $2CH_2$), 2.40-2.60 (m, $2CH_2$)
3	C	2.12-2.80 (m, $2CH_2$), 4.10-4.40 (m, $2CH_2$), 7.56-8.14 (m, bz H's)
6	D + C	5.40 (d, J = 7.5, CH_2), 6.60 (t, OH), 7.80 (s, $1H_3$)
8	C	5.60 (d, J = 7.5, CH_2), 6.80 (t, OH)
9	D	1.50-2.10 (m, $2CH_2$ + CH_3), 3.80-4.36 (m, $2CH_2$), 8.04 (s, $1H_3$)
10	D	1.70-2.40 (m, $2CH_2$), 4.00-4.20 (m, $2CH_2$), 7.30-8.00 (m, bz H's)
11	D	1.62-2.12 (m, $2CH_2$), 3.80-4.23 (m, $2CH_2$), 7.30-8.14 (m, bz H's + $1H_3$)
12	C	1.64-2.20 (m, $2CH_2$), 3.84-4.22 (m, $2CH_2$), 4.70 (bs, OH), 7.87 (s, $1H_3$)
13	D	1.71 (m, CH_2), 1.80 (m, CH_2), 4.03 (t, CH_2), 4.28 (t, CH_2), 6.73 (bs, NH_2), 7.50-7.97 (m, bz H's + $1H_3$)
14	D	1.39 (m, CH_2), 1.65 (m, CH_2), 3.36 (t, CH_2) 3.94 (t, CH_2), 4.37 (t, OH), 6.60 (bs, NH_2), 7.56 (s, $1H_3$)
15	C	1.57 (m, $2CH_2$), 3.43 (t, CH_2), 3.94 (m, CH_2), 4.33 (t, OH), 5.66 (d, J = 2.8, $1H_5$), 6.16 (bs, NH_2), 7.43 (d, J = 2.8, $1H_3$)
16	D	1.69 (m, CH_2), 1.80 (m, CH_2), 2.88 (d, J = 7.5, CH_3), 4.06 (t, CH_2), 4.27 (t, CH_2), 6.60 (m, NH), 7.48-7.95 (m, $1H_3$ + bz H's)
17	D	1.40 (m, CH_2), 1.69 (m, CH_2), 2.90 (d, J = 7.5, CH_3), 3.39 (t, CH_2), 4.00 (t, CH_2), 4.38 (t, OH), 6.60 (d, J = 7.5, NH), 7.83 (s, $1H_3$)
18	D	1.38 (m, CH_2), 1.63 (m, CH_2), 2.63 (d, J = 7.5, CH_3), 3.37 (t, CH_2), 3.88 (t, CH_2), 4.45 (t, OH), 5.37 (d, J = 2.9, $1H_5$), 7.20 (d, J = 7.5, NH), 7.51 (d, J = 2.9, $1H_3$)
19	D	1.73 (m, CH_2), 1.83 (m, CH_2), 4.05 (s, CH_2), 4.15 (t, CH_2), 4.28 (t, CH_2), 7.48-7.95 (m, bz H's), 8.23 (s, $1H_3$), NH (no detection)
20	D	1.40 (m, CH_2), 1.73 (m, CH_2), 3.40 (t, CH_2), 4.07-4.12 (m, $2CH_2$), 4.41 (t, OH), 8.25 (s, $1H_3$), NH (no detection)
21	C	1.66-1.71 (m, $2CH_2$), 3.63-4.20 (m, $3CH_2$ + OH), 6.16 (d, J = 2.8, $1H_5$), 7.52 (d, J = 2.8, $1H_3$), NH (no detection)
22	D	1.80-1.92 (m, CH_2) + 1.93-2.08 (m, CH_2), 4.18-4.30 (m, CH_2), 4.32-4.41 (m, CH_2), 4.96 (bs, NH), 6.22 (d, J = 7.5, NH_2), 7.43-8.07 (m, bz H's + $1H_3$)
23	D	1.55-1.69 (m, CH_2), 1.84-1.97 (m, CH_2), 3.65-3.74 (t, CH_2), 4.18-4.27 (t, CH_2), 4.78 (bs, NH), 5.10 (bs, OH), 6.25 (d, J = 7.5, NH_2), 7.54 (d, J = 7.5, $1H_3$)
25	D	1.50 (m, $2CH_2$), 3.38 (m, CH_2), 4.00 (m, CH_2), 4.23 (bs, NH), 4.51 (t, OH), 6.60, (d, J = 4.5, $1H_5$), 7.40 (bs, NH_2), 7.54 (d, J = 4.5, $1H_3$)
26	D	2.62-2.74 (m, $2CH_2$), 2.76-3.00 (m, $2CH_2$), 3.40 (bs, OH), 7.90 (s, $1H_3$)
27	D	1.66-1.79 (m, CH_2), 1.80-1.92 (m, CH_2), 3.84 (s, OCH_3), 4.12-4.23 (t, CH_2), 4.24-4.35 (m, CH_2), 4.12 (s, OCH_3), 7.45-7.98 (m, bz H's), 8.24 (s, $1H_3$)
28	D + C	1.56-1.69 (m, CH_2), 1.83-1.89 (m, CH_2), 3.64-3.76 (t, CH_2), 4.12-4.21 (t, CH_2), 4.26 (bs, OCH_3 + OH), 7.80 (s, $1H_3$)
29	C	1.57-1.69 (m, $2CH_2$), 3.67-3.77 (m, CH_2), 3.81 (s, OCH_3), 4.13-4.28 (m, CH_2 + OH), 6.13 (d, J = 2.9, $1H_5$), 7.56 (d, J = 2.9, $1H_3$)
30	D	1.68 (m, $2CH_2$), 3.67 (t, CH_2), 4.08 (s, $2OCH_3$), 4.24 (t, CH_2), 4.62 (bs, OH), 7.86 (s, $1H_3$)
31	D	1.42-1.45 (m, CH_2), 1.60-1.66 (m, CH_2), 3.20-3.40 (m, OH + CH_2), 4.00-4.12 (m, CH_2), 7.78 (s, $1H_3$)
32	C	1.31-1.32 (m, $2CH_2$), 3.58-3.60 (m, CH_2), 4.07-4.18 (m, CH_2 + OH), 6.58 (d, J = 2.8, $1H_5$), 7.83 (d, J = 2.8, $1H_3$)
34	D	1.60-2.00 (m, $2CH_2$), 4.00-4.42 (m, $2CH_2$), 6.81 (d, J = 10.2, $1H_4$), 7.05 (d, J = 10.2, $1H_5$), 7.60-8.10 (m, bz H's), NH (no detection)
35	C	1.34-1.63 (m, CH_2), 1.64-2.12 (m, CH_2), 3.40-3.43 (t, CH_2), 4.03-4.07 (t, CH_2), 4.50 (bs, OH), 6.85 (d, J = 10.2, $1H_4$), 7.14 (d, J = 10.2, $1H_5$), 8.51 (bs, NH)

[a] C = Deuteriochloroform, D = DMSO-d_6. [b] Coupling constant (J) in Hertz. All NH, NH_2 or OH signals were exchangeable with deuterium oxide, abbreviations used: s = singlet, bs = broad singlet, d = doublet, t = triplet, m = multiplet, bz = benzoyl.

Table 2

Elemental Analysis of Certain Pyridazine Acyclonucleosides

Compound No.	Molecular Formula	Calcd./Found(%) C	H	N
2	$C_6H_{11}O_2I$	29.77	4.58	
		29.58	4.54	
3	$C_{11}H_{13}O_2I$	43.44	4.31	
		42.99	4.28	
6	$C_5H_4N_2O_2Cl_2$	30.80	2.07	14.37
		30.78	2.10	14.36
8	$C_5H_3N_3O_4Cl_2$	25.02	1.26	17.51
		25.10	1.27	17.50
9	$C_{10}H_{12}N_2O_3Cl_2$	43.03	4.33	10.04
		42.94	4.21	9.80
10	$C_{15}H_{14}N_2O_3Cl_2$	52.81	4.14	8.21
		52.73	4.25	8.22
11	$C_{15}H_{14}N_5O_3Cl$	51.81	4.06	20.14
		51.72	3.89	19.70
12	$C_8H_{10}N_5O_2Cl$	39.44	4.14	28.74
		39.79	4.32	29.02
13	$C_{15}H_{16}O_3N_3Cl$	55.99	5.01	13.06
		55.88	5.41	12.69
14	$C_8H_{12}O_2N_3Cl$	44.15	5.56	19.31
		43.82	5.91	19.04
15	$C_8H_{13}N_3O_2$	52.45	7.15	22.94
		52.67	7.34	23.11
16	$C_{16}H_{18}O_3N_3Cl$	57.23	5.40	12.51
		57.38	5.69	12.46
17	$C_9H_{14}N_3O_2Cl$	46.66	6.09	18.14
		46.29	6.35	18.54
18	$C_9H_{15}O_2N_3$	54.81	7.67	21.30
		54.95	7.88	21.54
19	$C_{17}H_{17}O_4N_3Cl_2$	51.27	4.30	10.55
		51.34	4.89	10.77
20	$C_{10}H_{13}O_3N_3Cl_2$	40.84	4.46	14.29
		40.97	4.68	14.66
21	$C_{10}H_{14}O_3N_3Cl$	46.25	5.43	16.18
		46.46	5.78	16.54
22	$C_{15}H_{17}N_4O_3Cl$	53.50	5.09	16.64
		53.68	5.12	16.96
23	$C_8H_{13}N_4O_2Cl$	41.30	5.63	24.08
		41.45	5.89	24.33
25	$C_8H_{14}N_4O_2$	48.47	7.12	28.26
		48.63	7.54	28.45
26	$C_8H_{10}N_2O_2Cl_2$	40.53	4.25	11.82
		40.12	4.21	11.43
27	$C_{17}H_{20}N_2O_5$	61.44	6.07	8.43
		61.42	5.98	8.29
28	$C_9H_{13}N_2O_3Cl$	46.46	5.63	12.04
		46.32	5.59	12.01
29	$C_9H_{14}N_2O_3$	54.53	7.12	14.13
		54.86	7.47	14.36
30	$C_{10}H_{16}N_2O_4$	52.62	7.07	12.27
		52.73	7.16	12.45
31	$C_8H_{11}N_2O_3Cl$	43.95	5.07	12.81
		43.82	5.11	12.67
32	$C_8H_{12}N_2O_3$	52.17	6.57	15.21
		52.35	6.62	15.32
34	$C_{15}H_{16}N_2O_4$	62.49	5.59	9.72
		62.26	5.52	9.70
35	$C_8H_{12}N_2O_3$	52.17	6.57	15.21
		51.97	6.55	15.14

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 analyses were performed with a LECO Micro Carbon Hydrogen Determinator (CHN-800). Open-bed column chromatography was carried out on silica gel 60 (70-230 mesh, Merck) using gravity flow. The columns were packed as slurries with the elution solvent.

4-Iodobutyl Acetate (**2**).

Method A [3].

A mixture of tetrahydrofuran (**1**, 8 ml, 0.078 mole), acetyl chloride (6 ml, 0.078 mole), sodium iodide (11.8 g, 0.079 mole) and acetonitrile (35 ml) was stirred for 3 hours at room temperature. The reaction mixture was poured into aqueous sodium bisulfite solution (50%, 50 ml) with stirring. The resulting organic layer was separated using a separatory funnel. After the organic layer was washed with water (100 ml x 3), the mixture was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give **2** as a yellow liquid in 95% (18 g) yield; ir (neat): 2950, 2900, 1740, 1242, 1035 cm^{-1}.

Method B.

A mixture of tetrahydrofuran (**1**, 8 ml, 0.078 mole), acetyl chloride (6 ml, 0.078 mole), potassium iodide (13.15 g, 0.079 mole) and acetonitrile (35 ml) was stirred for 3 hours at room temperature. The reaction mixture was poured into aqueous sodium bisulfite solution (50%, 50 ml) with stirring. The resulting organic layer was separated using a separatory funnel. After the organic layer was washed with water (100 ml x 3), the mixture was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give **2** as a yellow liquid in 95% (18 g) yield. This product was identical with **2** which was prepared by Method A.

4-Iodobutyl Benzoate (**3**).

A mixture of tetrahydrofuran (**1**, 6.3 ml, 0.078 mole), benzoyl chloride (9.1 ml, 0.078 mole), potassium iodide (13 g, 0.079 mole) and acetonitrile (35 ml) was stirred for 3 hours at room temperature. An aqueous solution of sodium bisulfate (50%, 50 ml) was added to the reaction mixture. And the mixture was then stirred for 1 hour at room temperature, washed with water (100 ml x 4) and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give **3** as a yellow liquid in 96% (22.77 g) yield; ir (potassium bromide): 3072, 2952, 1734, 1278, 1116, 714 cm^{-1}.

4,5-Dichloro-1-hydroxymethylpyridazin-6-one (**6**).

A mixture of **5** [4] (7.1 g, 4.3 mmoles) and a formalin solution (35%, 34 ml, 4.3 mmoles) was refluxed for 1 hour. After cooling to the room temperature, the precipitate was filtered, and washed with cold water (100 ml x 2). The crude product was recrystallized from methanol to give **6** as white needles in 59% (5 g) yield, mp 111-113° (lit [9] 114-115°); ir (potassium bromide): 3400, 3100, 2960, 2875, 1670, 1580 cm^{-1}.

4,5-Dichloro-1-hydroxymethyl-3-nitropyridazin-6-one (**8**).

A mixture of **7** [5] (5 g, 23.8 mmoles), formalin solution (35%, 10 ml) and water (20 ml) was refluxed 1 hour. After cooling to the room temperature, the precipitate was filtered, and then washed with cold water (50 ml x 2). The crude product was recrystallized from diethyl ether/*n*-hexane (5:5, v/v) to give **8** as yellow crystals in 76% (4.35 g) yield, mp 85-86°; ir (potassium bromide): 3400, 3100, 1670, 1600, 1540, 1350 cm^{-1}.

1-(4-Acetoxybutyl)-4,5-dichloropyridazin-6-one (**9**).

A mixture of **5** (5 g, 3 mmoles), sodium hydride (1.32 g, 3.3 mmoles, 60% in oil) and dimethyl sulfoxide (30 ml) was stirred for 10 minutes at room temperature. To the solution, compound **2** (9.12 g, 3 mmoles) was added. The reaction mixture was stirred for 2 hours at room temperature. After adding chloroform (50 ml), the reaction mixture was washed with excess water. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (1.5 x 13 cm). The column was eluted with chloroform. Fractions containing the product were combined, and the solvent was then evaporated under reduced pressure. The resulting crude product was recrystallized from ethyl acetate to give **9** as white crystals in 83% (6.95 g) yield, mp 83-84°; ir (potassium bromide): 3160, 3100, 2960, 2900, 1758, 1684, 1600, 1236, 1046 cm^{-1}.

1-(4-Benzoyloxybutyl)-4,5-dichloropyridazin-6-one (**10**).

A mixture of **5** (2 g, 12.12 mmoles), sodium hydride (0.5 g, 12.5 mmoles, 60% in oil) and dimethyl sulfoxide (25 ml) was stirred for 10 minutes at room temperature. Compound **3** (3.68 g, 12.31 mmoles) was added to the reaction mixture, and the reaction mixture was then stirred for 3 hours at room temperature. After adding chloroform (30 ml), the mixture was washed with excess water. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (1.5 x 8 cm). The column was eluted with chloroform/*n*-hexane (9:1, v/v). Fractions containing the product were combined, and the solvent was then evaporated under reduced pressure. The resulting crude product was recrystallized from diethyl ether to give **10** as white crystals in 82% (3.4 g) yield, mp 79-80°; ir (potassium bromide): 3080, 2960, 2880, 1716, 1664, 1280, 718 cm^{-1}.

4-Azido-1-(4-benzoyloxybutyl)-5-chloropyridazin-6-one (**11**).

A mixture of **10** (3 g, 9.6 mmoles), sodium azide (3.25 g, 0.01 mole) and dimethyl sulfoxide (20 ml) was refluxed for 6 hours with stirring. After cooling to room temperature, methylene chloride (50 ml) was added to the reaction mixture. The resulting mixture was washed with excess water. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (1.5 x 10 cm). The column was eluted with diethyl ether/*n*-hexane (10:4, v/v). Fractions containing product were combined, and the solvent was evaporated under reduced pressure. The crude product was recrystallized from diethyl ether/*n*-hexane (1:1, v/v) to give **11** as yellow crystals in 56% (1.87 g) yield, mp 54-55°; ir (potassium bromide): 3010, 2988, 2116, 1720, 1660, 1260, 1120, 710 cm^{-1}.

4-Azido-5-chloro-1-(4-hydroxybutyl)pyridazin-6-one (**12**).

A mixture of **11** (0.9 g, 0.26 mmole), sodium methoxide (0.16 g, 0.28 mmole) and methanol (20 ml) was stirred for 13 hours at room temperature. After adding Amberlite IRC-50 resin (H^+ form, 1 g), the mixture was stirred for an additional 15 hours at room temperature. The mixture was filtered and the resin was washed with boiling methanol (50 ml). The combined filtrates were evaporated under reduced pressure. The resulting residue applied to the top of an open-bed silica gel column (1.5 x 12 cm). The column was eluted with chloroform/methanol (9:1, v/v). Fractions containing the product were combined and evaporated under reduced pressure to give **12** as a liquid in 80% (0.5 g) yield; ir (potassium bromide): 3400, 2970, 2114, 1640, 1258, 1110, 710 cm^{-1}.

4-Amino-5-chloro-1-(4-benzoyloxybutyl)pyridazin-6-one (**13**).

A mixture of **11** (1 g, 2.9 mmoles), palladium on charcoal (0.3 g, 10%) and methanol (25 ml) was stirred for 10 minutes at room temperature. The reaction mixture was stirred for 26 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the solvent was evaporated under reduced pressure. The resulting crude product was applied to the top of an open-bed silica gel column (1.5 x 7 cm). The column was eluted with diethyl ether. Fractions containing the product were combined and then evaporated under reduced pressure to give **13** as white crystals in 93% (0.87 g) yield, mp 133-134°; ir (potassium bromide): 3300, 3200, 2960, 1738, 1644, 1618, 1430, 1284, 1122, 720 cm^{-1}.

4-Amino-5-chloro-1-(4-hydroxybutyl)pyridazin-6-one (**14**).

Method C.

A mixture of **12** (1 g, 4.1 mmoles), palladium on charcoal (0.7 g, 10%) and methanol (150 ml) was stirred for 26 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 6 cm). The column was eluted with diethyl ether/methanol (8:2, v/v). Fractions containing the product were combined and then evaporated under reduced pressure to give **14** as white crystals in 86% (0.77 g) yield. This product was identical with **14** which was prepared by the Method D.

Method D.

A mixture of **13** (0.5 g, 1.6 mmoles), sodium methoxide (0.3 g, 5.3 mmoles, 95%) and methanol (30 ml) was stirred for 24 hours at room temperature. After adding Amberlite IRC-50 (H^+ form, 0.4 g), the reaction mixture was stirred for an additional 12 hours at room temperature. The resin was filtered and then washed with hot methanol (10 ml x 2). The solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (1.5 x 7 cm). The column was eluted with diethyl ether/methanol (10:1, v/v). Fractions containing the product were combined, and the solvent was then evaporated under reduced pressure to give the crude product. The crude product was recrystallized from diethyl ether to afford **14** as white crystals in 95% (0.33 g) yield, mp 170-171°; ir (potassium bromide): 3380, 3340, 3200, 3080, 2960, 1622, 1606, 1438, 1360, 1300, 1062, 802 cm^{-1}.

4-Amino-1-(hydroxybutyl)pyridazin-6-one (**15**).

Method E.

A mixture of **14** (0.6 g, 2.76 mmoles), palladium on charcoal (0.3 g, 10%), aqueous sodium hydroxide (5 ml, 30%) and methanol (30 ml) was stirred for 4 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 6 cm). The column was eluted with diethyl ether. Fractions containing the product were combined, and the solvent was then evaporated under reduced pressure to furnish **15** as dense yellow liquid in 86% (0.43 g) yield. This product was identical with **15** which was prepared by the Method F.

Method F.

A mixture of **13** (0.7 g, 2.2 mmoles), palladium on charcoal (0.3 g, 10%), aqueous sodium hydroxide (5 ml, 10%) and methanol (30 ml) was stirred for 18 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 5 cm) . The column was eluted with ethyl acetate/diethyl ether (2: 1, v/v) . Fractions containing the product (detection by tlc, developing solvent = ethyl acetate, Rf = 0.25) were combined, and the solvent was then evaporated under reduced pressure to give **15** as a dense yellow liquid in 73% (0.46 g) yield; ir (potassium bromide): 3450, 3400, 3250, 3080, 2960, 2910, 1650, 1593, 1460, 1372, 1280, 1070, 1044, 1012 cm^{-1}.

1-(4-Benzoyloxybutyl)-5-chloro-4-methylaminopyridazin-6-one (**16**).

Method G.

A mixture of **10** (2 g, 5.9 mmoles), methylamine hydrochloride (1 g, 14.8 mmoles), methanol (30 ml) and triethylamine (3.3 ml, 0.015 mole) was refluxed for 8 hours. The solvent was evaporated under reduced pressure. Chloroform (20 ml) and water (40 ml) were added to the residue and the mixture was then stirred for 10 minutes at room temperature. After separating the organic layer using a separatory funnel, the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (1.5 x 7 cm). The column was eluted with diethyl ether. Fractions containing the product were combined and the solvent was then evaporated under reduced pressure. The crude product was recrystallized from diethyl ether/*n*-hexane (1:1, v/v) to afford **16** as white crystals in 91% (1.66 g) yield, mp 106-107°; ir (potassium bromide): 3364, 3064, 1725, 1640, 1608, 1527, 1425, 1275, 1128, 843, 711 cm^{-1}.

Method H.

A mixture of **13** (0.2 g, 0.6 mmole), potassium carbonate (0.3 g), methyl iodide (1 ml, 16 mmoles) and methanol (20 ml) was refluxed for 18 hours. After cooling to the ambient temperature, the precipitates were filtered off. The solvent was evaporated under reduced pressure. The product was separated using a preparative tlc plate (solvent; chloroform/methanol = 30:1, v/v; Rf = 0.2) in 54% (0.11 g) yield. This product was identical with **16** which was prepared by the Method G.

5-Chloro-1-(4-hydroxybutyl)-4-methylaminopyridazin-6-one (**17**).

A mixture of **16** (0.8 g, 2.6 mmoles), sodium methoxide (0.3 g, 5.3 mmoles, 95%) and methanol (20 ml) was stirred for 21 hours at room temperature. After adding Amberlite IRC-50 (H^+ form 0.5 g), the mixture was stirred for an additional 13 hours at room temperature. The resin was filtered and then washed with methanol (10 ml x 2). After evaporating the solvent, the resulting residue was applied to the top of an open-bed silica gel column (1.5 x 6 cm). The column was eluted with methanol. Fractions containing the product were combined and the solvent was then evaporated under reduced pressure to give the crude product. The crude product was crystallized from diethyl ether to afford **17** as white crystals in 89% (0.47 g) yield, mp 148-149°; ir (potassium bromide): 3370, 3280, 3110, 2970, 2900, 1628, 1540, 1362, 1318, 1228, 1064, 1004, 890, 792 cm^{-1}.

1-(4-Hydroxybutyl)-4-methylaminopyridazin-6-one (**18**).

A mixture of **17** (0.45 g, 2.2 mmoles), palladium on charcoal (0.2 g, 10%) and methanol (25 ml) was stirred for 24 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (1.5 x 7 cm). The column was eluted with diethyl ether. Fractions containing the product were combined and the solvent was then evaporated under reduced pressure. The resulting crude product was recrystallized from diethyl ether to give **18** as white crystals in 95% (0.36 g) yield, mp 142-143°; ir (potassium bromide): 3400, 3300, 2946, 2850, 1638, 1594, 1346, 1040, 980, 820 cm^{-1}.

1-(4-Benzoyloxybutyl)-5-chloro-4-(2-chloroacetamido)pyridazin-6-one (**19**).

Method I.

A mixture of **10** (2 g, 5.9 mmoles), 2-chloroacetamide (0.66 g, 7.1 mmoles), triethylamine (3 ml) and methanol (30 ml) was refluxed for 11 hours. After the solvent was evaporated under reduced pressure, chloroform (20 ml) and water (50 ml) were added to the residue. The resulting organic layer was separated and then dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (1.5 x 10 cm). The column was eluted with diethyl ether/chloroform (2:8, v/v). Fractions containing the product were combined. The solvent was evaporated under reduced pressure. The resulting crude product was recrystallized from *n*-hexane/diethyl ether (1:1, v/v) to give **19** as white crystals in 87% (2.0 g) yield, mp 99-100°; ir (potassium bromide): 3350, 3070, 2962, 1712, 1630, 1600, 1444, 1276, 1016, 704 cm^{-1}.

Method J.

A mixture of **13** (0.3 g, 0.93 mmole), potassium carbonate (0.3 g), 2-chloroacetyl chloride (0.2 ml, 2.5 mmoles) and methanol (20 ml) was refluxed for 24 hours. After cooling to the ambient temperature, the precipitate was filtered off. The solvent was evaporated under reduced pressure. The product was separated using a preparative tlc plate (solvent, ethyl acetate/*n*-hexane = 9:1, v/v, Rf = 0.25) in 46% (0.17 g) yield. This product was identical with **19** which was prepared by the Method I.

5-Chloro-4-(2-chloroacetamido)-1-(4-hydroxybutyl)pyridazin-6-one (**20**).

A mixture of **19** (0.58 g, 1.5 mmoles), sodium methoxide (0.5 g, 8.8 mmoles, 95%) and methanol (25 ml) was stirred for 12 hours at room temperature. After adding Amberlite IRC-50 (H^+ form, 0.35 g), the mixture was stirred for an additional 11 hours at room temperature. The resin was filtered and then washed with hot methanol (10 ml x 2). The solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (1.5 x 5 cm). The column was eluted with methanol. Fractions containing the product were combined. The solvent was evaporated under reduced pressure. The resulting crude product was recrystallized from diethyl ether to give **20** as white crystals in 85% (3.65 g) yield, mp 86-87°; ir (potassium bromide): 3450, 3140, 3110, 3060, 2964, 2890, 1740, 1660, 1474, 1422, 1338, 1224, 1120, 1070, 894 cm^{-1}.

4-(2-Chloroacetamido)-1-(4-hydroxybutyl)pyridazin-6-one (**21**).

Method K.

A mixture of **20** (0.4 g, 1.36 mmoles), palladium on charcoal (0.3 g, 10%), aqueous sodium hydroxide (5 ml, 30%) and methanol (30 ml) was stirred for 8 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by the filtration using Celite 545, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 7 cm). The column was eluted with diethyl ether. Fractions containing the product were combined, and the solvent was evaporated under reduced pressure to give the crude product. Recrystallization of the crude **21** from diethyl ether afforded **21** as white crystals in 88% (0.31 g) yield, mp 76-77°; ir (potassium bromide): 3400, 3100, 2960, 2882, 1664, 1646, 1460, 1414, 1342, 1240, 1164, 1062, 1022, 854 cm^{-1}.

Method L.

A mixture of **19** (0.46 g, 1.27 mmoles), palladium on charcoal (0.3 g, 10%), aqueous sodium hydroxide (5 ml, 30%) and methanol (30 ml) was stirred for 28 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by the filtration using Celite 545, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 10 cm). The column was eluted with chloroform/methanol (9:1, v/v). Fractions containing the product were combined and then evaporated under reduced pressure to give **21** in 83% (0.346 g) yield. This product was identical with **21** which was prepared by the Method K.

1-(4-Benzoyloxybutyl)-5-chloro-4-hydrazinopyridazin-6-one (**22**).

A mixture of **10** (2.86 g, 9.1 mmoles), hydrazine hydrate (0.51 g, 0.01 mole), potassium carbonate (1.38 g, 10 mmoles) and dimethyl sulfoxide (30 ml) was refluxed for 1 hour. After cooling to room temperature, water (50 ml) was added to the reaction mixture. The product was extracted with chloroform (50 ml x 4). The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (1.5 x 10 cm). The column was eluted with diethyl ether. Fractions containing the product were combined, and the solvent was then evaporated under reduced pressure to give the crude product. The crude product was recrystallized from diethyl ether/*n*-hexane (1:2, v/v) to give **22** as yellow crystals in 66% (2.02 g) yield, mp 74-76°; ir (potassium bromide): 3470, 3340, 3060, 2956, 1720, 1650, 1610, 1280, 1120, 710 cm^{-1}.

5-Chloro-4-hydazino-1-(4-hydroxybutyl)pyridazin-6-one (**23**).

Method M.

A mixture of **22** (1.3 g, 3.9 mmoles), sodium methoxide (0.21 g, 3.9 mmoles) and methanol (20 ml) was stirred for 16 hours at room temperature. Amberlite IRC-50 (H^+ form, 1.2 g) was added, and the mixture was stirred for an additional 24 hours at room temperature. The resin was filtered and then washed with boiling acetone (100 ml). The combined filtrates were evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (1.5 x 10 cm). The column was eluted with diethyl ether/methanol (9:1, v/v). Fractions containing the product were combined and the solvent was then evaporated under reduced pressure to give **23** as a liquid in 78% (0.71 g) yield; ir (potassium bromide): 3325, 3050, 2945, 2860, 1640, 1600, 1530, 1370, 1297, 1060, 838 cm^{-1}.

Method N.

A mixture of **24** [7] (1.62 g, 0.01 mole), sodium hydride (0.5 g, 0.035 mole, 60% in oil), **3** (3.1 g, 0.011 mole) and methanol (50 ml) was stirred for 8 hours at room temperature. The precipitate was filtered off and washed with acetone (25 ml x 2). The combined filtrate was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column. The column was eluted with diethyl ether/chloroform (1:1, v/v). Fractions containing the main product [detection by tlc, solvent = diethyl ether /chloroform (1:1, v/v), Rf = 0.15] were combined, and evaporated under reduced pressure to afford **23** as a liquid in 58% (1.35 g) yield. This product was identical with **23** which was prepared by the Method M.

4-Hydrazino-1-(4-hydroxybutyl)pyridazin-6-one (**25**).

A mixture of **23** (0.3 g, 1.46 mmoles), palladium on charcoal (0.5 g, 10%) and ethanol (100 ml) was stirred for 28 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 8 cm). The column was eluted with chloroform/methanol (9:1, v/v). Fractions containing the product were combined and then evaporated under reduced pressure to give the crude product. Recrystallization of the crude product from diethyl ether gave **25** as white crystals in 36% (0.11 g) yield, mp 157-158°; ir (potassium bromide): 3412, 3080, 2938, 1626, 1599, 1548, 1488, 1389, 1371, 1350, 1320, 1125, 1065, 1053, 930, 873, 831 cm^{-1}.

4,5-Dichloro-1-(4-hydroxybutyl)pyridazin-6-one (**26**).

Method O.

A mixture of **10** (1 g, 3 mmoles), 2,6-dihydroxypyridine (0.45 g, 3.1 mmoles) and *N,N*-dimethylformamide (20 ml) was refluxed for 4 hours. After cooling to room temperature, chloroform (50 ml) was added to the reaction mixture with stirring. The mixture was washed with water (100 ml x 3). The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (1.5 x 10 cm), and the column was then eluted with diethyl ether. Fractions containing the product were combined, and the solvent was evaporated under reduced pressure. The resulting crude

product was recrystallized from diethyl ether to give **26** as white crystals in 46% (0.33 g) yield, mp 92-93°; ir (potassium bromide): 3450, 3014, 2946, 1670, 1392, 1100, 668 cm^{-1}.

4,5-Dichloro-1-(4-hydroxybutyl)pyridazin-6-one (**26**), 1-(4-Hydroxybutyl)-4,5-dimethoxypyridazin-6-one (**27**) and 5-Chloro-1-(4-hydroxybutyl)-4-methoxypyridazin-6-one (**28**).

Method P.

A mixture of **10** (4 g, 11.73 mmoles), sodium methoxide (1.465 g, 28 mmoles, 95%) and methanol (35 ml) was stirred for 24 hours at room temperature. After adding Amberlite IRC-50 (H^+ form, 3 g), the reaction mixture was stirred for an additional 23 hours at room temperature. The resin was filtered, and then washed with boiling methanol (100 ml). The combined filtrates were evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (1.5 x 10 cm). The column was eluted with diethyl ether. Fractions containing **26** (detection using tlc, solvent = diethyl ether, Rf = 0.53) were combined and then evaporated under reduced pressure to furnish the crude **26**. Recrystallization of the crude **26** from diethyl ether yielded pure **26** as white crystals in 18% yield. This compound was identical with compound **26** which was prepared by the Method O. Fractions containing **27** (detection using tlc, solvent = diethyl ether, Rf = 0.68) were combined and then evaporated under reduced pressure to give **27** in 42% (1.64 g) yield, mp 95-96°; ir (potassium bromide): 3085, 3020, 2960, 2858, 1715, 1660, 1605, 1280, 1120, 720 cm^{-1}. Fractions containing **28** (detection using tlc, solvent = diethyl ether, Rf = 0.18) were combined and then evaporated under reduced pressure to furnish **28** in 23% (0.63 g) yield, mp 74-76°; ir (potassium bromide): 3450, 3100, 2950, 2870, 1660, 1220, 1160, 956 cm^{-1}.

5-Chloro-1-(4-hydroxybutyl)-4-methoxypyridazin-6-one (**28**).

Method Q.

A mixture of **10** (3 g, 8.8 mmoles), sodium methoxide (1.5 g, 26.4 mmoles, 95%) and methanol (40 ml) was refluxed for 4 hours. After cooling the mixture to the ambient temperature, Amberlite IRC-50 (H^+ form, 2 g) was added. The mixture was then stirred for an additional 12 hours at room temperature. Acetone (20 ml) was added. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 8 cm). The column was eluted with diethyl ether. Fractions containing the product were combined, and the solvent was then evaporated under reduced pressure to give the product which was identical with **28** (by the Method P) in 85% (1.74 g) yield.

1-(4-Hydroxybutyl)-4-methoxypyridazin-6-one (**29**).

After a mixture of **28** (1.5 g, 6.45 mmoles), palladium on charcoal (0.7 g, 10%) and methanol (30 ml) was cooled to 0°, aqueous sodium hydroxide (10 ml, 30%) was added slowly. The mixture was stirred for 24 hours under a hydrogen atmosphere (using a toy balloon) at room temperature. After removal of the catalyst by filtration using Celite 545, the solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 7 cm). The column was eluted with diethyl ether. Fractions containing the product were combined, and the solvent was evaporated under reduced pressure to afford the crude product. Recrystallization of the crude product from diethyl ether/*n*-hexane (1:1, v/v) yielded **29** as white crystals in 74% yield (0.95 g), mp 85-86°; ir (potassium bromide): 3350, 3060, 2950, 2878, 1656, 1204, 1050, 1020, 882, 724 cm^{-1}.

1-(4-Hydroxybutyl)-4,5-dimethoxypyridazin-6-one (**30**).

A mixture of **27** (1.07 g, 3.22 mmoles), sodium methoxide (0.5 g, 8.79 mmoles, 95%) and methanol (20 ml) was stirred for 23 hours at room temperature. After adding Amberlite IRC-50 (H^+ form, 1.3 g), the mixture was stirred for an additional 6 hours at room temperature. The resin was filtered and washed with acetone (20 ml). The combined filtrate was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (1.5 x 5 cm). The coulmn was eluted with ethyl acetate/chloroform (1:1, v/v). Fractions containing the product were combined and then evaporated under reduced pressure to give the crude product. The crude product was recrystallized from diethyl ether to afford **30** as white crystals in 93% (0.68 g), mp 63-64°; ir (potassium bromide): 3450, 3020, 2980, 1674, 1600, 1338, 1222, 940, 662 cm^{-1}.

5-Chloro-1-(4-hydroxybutyl)-4-hydroxypyridazin-6-one (**31**).

A mixture of **28** (1.2 g, 5.2 mmoles), aqueous sodium hydroxide (7%, 5 ml) and methanol (20 ml) was refluxed for 6 hours. The reaction mixture was cooled to the room temperature. After adding diluted hydrochloric acid (5%, 5 ml), the mixture was stirred for 20 minutes at room temperature. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (1.5 x 10 cm). The column was eluted with methylene chloride/*n*-hexane (7:3, v/v). Fractions containing the product were combined and the solvent was then evaporated under reduced pressure. The resulting crude product was recrystallized from ethanol/diethyl ether (1:1, v/v) to give **31** in 68% (0.77 g) yield, mp 132-133°; ir (potassium bromide): 3340, 2958, 1650, 1611, 1457, 1418, 1054, 872, 660 cm^{-1}.

4-Hydroxy-1-(4-hydroxybutyl)pyridazin-6-one (**32**).

A mixture of **29** (0.5 g, 2.5 mmoles) and aqueous sodium hydroxide (20 ml, 20%) was refluxed for 3 hours. After cooling to the room temperature, diluted hydrochloric acid (4 ml, 10%) was slowly added with stirring. The solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 6 cm). The column was eluted with chloroform/methanol (8:2, v/v). Fractions containing the product were combined, and the solvent was then evaporated under reduced pressure to give the crude product. Recrystallization of the crude product from methanol/ethyl acetate (1:3, v/v) yielded **32** as white crystals in 86% (0.4 g) yield, mp 140-141°; ir (potassium bromide): 3460, 3010, 2950, 1620, 1520, 1416, 1340, 1254, 1058, 1030, 850 cm^{-1}.

1-(4-Benzoyloxybutyl)pyridazine-3,6-dione (**34**).

A mixture of **33** (2 g, 1.79 mmoles) [8], sodium hydride (0.8 g, 1.97 mmoles) and dimethyl sulfoxide (25 ml) was stirred for 10 minutes at room temperature. After adding compound **3** (5.43 g, 1.79 mmoles) to the mixture, the reaction mixture was stirred for 16 hours at room temperature. Methylene chloride (50 ml) was added with stirring, and the mixture was then washed with water (100 ml x 3). The organic layer was dried over anhydrous magnesium sulfate. The solvent was allowed to evaporate under reduced pressure. The crude product was recrystallized from acetone to give **34** in 91% (4.34 g) yield, mp 139-140°; ir (potassium bromide): 3150, 3070, 2962, 2880, 1724, 1680, 1604, 1184, 998 cm^{-1}.

1-(4-Hydroxybutyl)pyridazine-3,6-dione (**35**).

A mixture of **34** (0.92 g, 0.322 mmole), sodium methoxide (0.185 g, 0.354 mmole, 95%) and methanol (20 ml) was stirred for 13 hours at room temperature. After adding Amberlite IRC-50 (H^+ form, 1.2 g), the mixture was stirred for an additional 6 hours. The resin was filtered and then washed with boiling methanol (50 ml). The combined filtrates were evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (1.5 x 10 cm). The column was eluted with methylene chloride/*n*-hexane (8:2, v/v). Fractions containing the product were combined and allowed to evaporate under reduced pressure. The crude product was recrystallized from methanol to afford **35** as white crystals in 94% (0.55 g) yield, mp 140-141°; ir (potassium bromide) 3240, 3030, 2980, 2900, 1708, 1622, 1480, 1302, 1080, 1002, 845 cm^{-1}.

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