Synthesis of Novel *N*-Acyclonucleosides: Benzotriazole, Benzothiazinone and Pyridooxazinone Acyclonucleosides

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Some novel benzotriazole, benzothiazinone and pyridooxazinone acyclonucleosides containing 4-hydroxybutyl, 4-hydroxybutoxy, 4-iodobutyl, 2-oxopropyl and 2,3-epoxypropoxy groups as a side chain was prepared.

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The antiviral activity of some acyclonucleocides has led in recent years to numerous examples of their preparations [1]. The synthesis and the antiviral activity of some ribonucleosides containing benzotriazole moiety such as benzotriazole nucleosides [2], 8-aza-1-deazapurine nucleosides [3], 1-(2,3-dihydroxypropyl)triazolo[4,5-*d*]pyrimidine [4], 8-aza-9-[2-(phosphonomethoxy)ethyl]guanine [5] are known. The synthesis and antiviral activity of some nucleosides and acyclonucleosides containing [6:6] fused heterocycles such as lumazine [6], pyrimido[4,5-*d*]pyrimidine [7], quinazoline [8] and thiano[3,2-*d*]pyrimidine [9] have been reported. Recently, 9-[(2-phosphonomethoxy)-ethoxy]adenine and its derivatives as acyclonucleosides containing a new side chain with potent and selective activity against human immunodeficiency virus-1 and 2-(HIV-1 and HIV-2) have been reported [10].

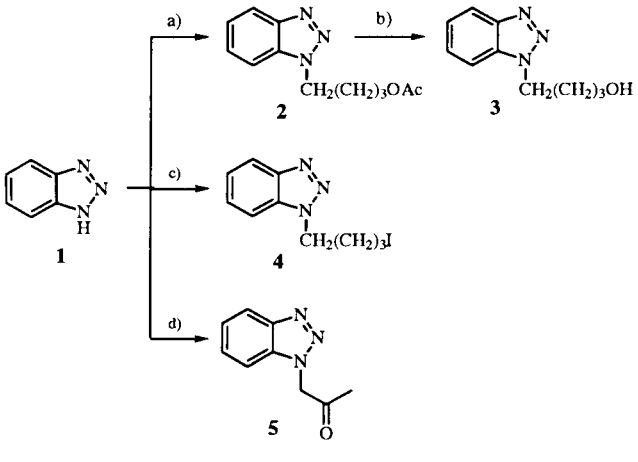
In previous papers [11], we also reported the synthesis of pyridazine acyclonucleosides containing 2-oxopropyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 4-hydroxybutyl groups as alkanol side chains.

Recently, our interest was focused on the development of new lead compounds for antiviral acyclonucleoside. Therefore, we attempted the synthesis of benzotriazole and [6:6] fused heterocyclic *N*-acyclonucleosides.

We now wish to report the synthesis of benzotriazole, benzothiazinone and pyridooxazinone acyclonucleosides containing some side chains such as 4-hydroxybutyl, 4-iodobutyl, 4-hydroxybutoxy, 2,3-epoxypropoxy and 2-oxopropyl groups.

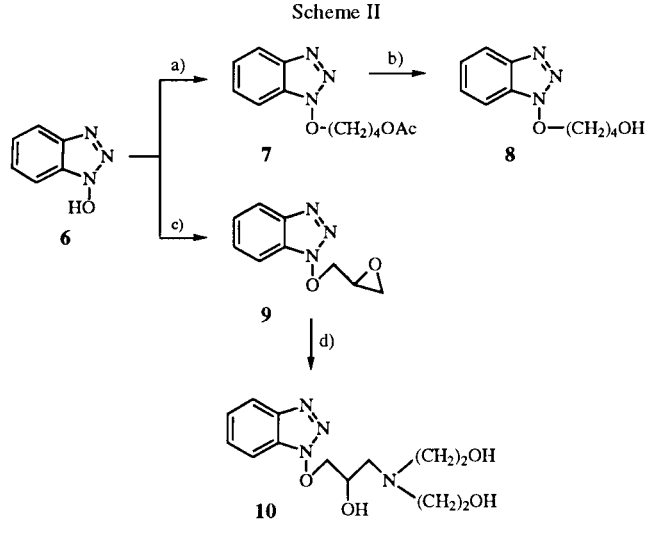
Reactions of compounds **1**, **11** and **15** with 4-iodobutyl acetate in the presence of potassium carbonate in tetrahydrofuran gave the corresponding esters **2**, **12** and **16** in good yield, respectively.

Scheme I



a) 4-Iodobutyl acetate, K_2CO_3, THF, b) i) MeONa, MeOH ii) Amberlite IRC-50 H^+, c) NaH, CH_3CN, 1,4-Diiodobutane, d) NaH, CH_3CN, 4-Bromoacetoacetic acid

Scheme II



a) 4-Iodobutyl acetate, K_2CO_3, THF, b) i) MeONa, MeOH ii) Amberlite IRC-50 H^+, c) NaOH, H_2O, Epichlorohydrin, d) Diethanolamine, MeOH

On the other hand, we attempted to synthesize new acyclonucleosides containing 4-hydroxybutoxy group. *O*-Alkylation of **6** with sodium hydride and 4-iodobutyl acetate in acetonitrile afforded **7** in 65% yield. Deacylation of esters **2**, **7**, **12** and **16** with methanolic sodium methoxide gave the corresponding acyclonucleosides **3**, **8**, **13** and **17** in good yield, respectively.

The infrared spectra of compounds **2**, **7**, **12** and **16** showed an absorption band of C=O bond for acyl group at 1750-1740 cm^{-1}. In addition, the infrared spectra of **12**

Table 1

^{1}H NMR Data of Compounds **2-5**, **7-10**, **12-14**, **16** and **17**

Compound No	Solvent [a]	δ (ppm) [b]
2	C	2.10 (m, 7H), 4.00 (t, 2H), 4.50-4.80 (t, 2H), 7.70 (m, 4H)
3	C	1.90 (m, 4H), 3.00 (bs, OH), 4.20 (m, 4H), 7.50 (m, 4H)
4	C	1.80 (m, 4H), 3.00 (t, 2H), 4.60 (t, 2H), 7.60 (m, 4H)
5	C	2.20 (s, 3H), 5.50 (s, 2H), 7.75 (m, 4H)
7	C	1.90 (m, 7H), 4.00 (t, 2H), 4.60 (t, 2H), 7.70 (m, 4H)
8	C	1.90 (m, 4H), 3.70 (t, 2H), 4.00 (bs, OH), 4.50 (t, 2H), 7.70 (m, 4H)
9	C	2.70 (m, 2H), 3.70 (m, 1H), 4.40 (m, 2H), 7.65 (m, 4H)
10	D	2.50 (m, 4H), 3.30 (m, 4H), 4.00 (bs, 2OH), 4.45 (m, 3H), 4.60 (d, 2H, J = 7.5), 5.10 (bs, OH), 7.75 (m, 4H)
12	C	1.80 (m, 4H), 2.00 (s, 3H), 3.50 (m, 4H), 4.80 (s, 2H), 7.20 (m, 4H)
13	C	1.65 (m, 4H), 3.40 (bs, OH), 3.60 (t, 2H), 4.00 (t, 2H), 4.80 (s, 2H), 7.20 (m, 4H)
14	C	2.20 (s, 3H), 3.50 (s, 2H), 4.80 (s, 2H), 7.10 (m, 4H)
16	C	1.70 (m, 4H), 2.00 (s, 3H), 4.00 (t, 4H), 4.80 (s, 2H), 7.55 (m, 3H)
17	C	1.70 (m, 4H), 3.20 (bs, OH), 3.90 (m, 4H), 5.60 (s, 2H), 7.00 (m, 3H)

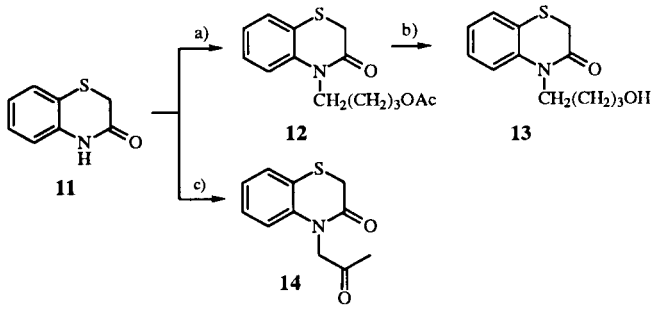
[a] C = Deuteriochloroform, D = DMSO-d_6. [b] The proton signals of the hydroxy group were detected by treatment of deuterium oxide; Coupling constants (J) in Hz; Abbreviations used: s = singlet, bs = broad singlet, d = doublet, t = triplet, m = multiplet.

and **16** also showed an absorption band for the amide carbonyl bond at 1680 and 1700 cm^{-1}, respectively. Also, proton signals of butyl and methyl groups were detected in the proton magnetic resonance spectra for compounds **2**, **7**, **12** and **16**. The infrared spectra of compounds **3**, **8**, **13** and **17** showed an absorption band of the OH group. In the proton magnetic resonance spectra of these compounds were observed proton signals for the hydroxy and butyl groups involving proton signals of the aromatic moiety. The molecular formulas of these compounds were also established by their elemental analyses.

Alkylation of benzotriazole (**1**) with 1,4-diiodobutane in the presence of sodium hydride in acetonitrile also furnished compound **4** in low yield. In this reaction, 1,4-dibenzotriazolylbutane as a by-product was also obtained [12]. The structure of **4** was established by elemental analysis, ir and pmr.

Reaction of **1** and **11** with 4-bromoacetoacetic acid in the presence of sodium hydride (or potassium carbonate for **11**) gave the corresponding *N*-2-oxopropyl derivatives **5** and **14**, respectively. This 2-oxopropylation under our reaction conditions progressed *via* two steps; substitution and then the decarboxylation [11d]. The infrared spectra of

Scheme III



a) 4-Iodobutyl acetate, K_2CO_3, THF, b) i) MeONa, MeOH ii) Amberlite IRC-50 H^+, c) NaH, THF, 4-Bromoacetoacetic acid

5 and **14** showed one or two absorption bands of carbonyl groups (for **5**, 1740 cm^{-1}; for **14**, 1740, 1680 cm^{-1}). The proton magnetic resonance spectra of **5** and **14** showed two signals as singlets for the 2-oxopropyl group at δ 2.20 for **5** and **14** which was assigned to three $H_{3'}$ and δ 5.50 for **5** or δ 4.80 for **14** which were assigned to two $H_{1'}$.

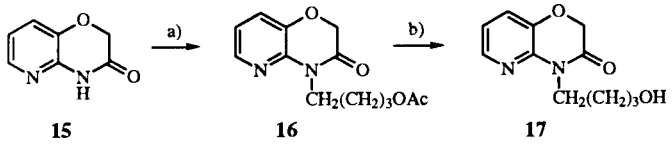
In addition, treatment of **6** with epichlorohydrin in aqueous sodium hydroxide solution gave oxirane **9** instead of chlorohydrin derivative. Compound **9** was allowed to react with diethanolamine in methanol to afforded compound **10** in 83% yield. The structures of **9** and **10** were established by elemental analysis, ir and pmr.

Table 2

Elemental Analysis of Compounds **2-5**, **7-10**, **12-14**, **16** and **17**

Compound No	Molecular Formula	Calcd/Found (%) C	H	N
2	$C_{12}H_{15}N_3O_2$	61.79	6.48	18.01
		61.82	6.52	18.06
3	$C_{10}H_{13}N_3O$	62.81	6.85	21.97
		62.92	6.95	22.12
4	$C_{10}H_{12}N_3I$	39.89	4.02	13.95
		40.02	4.01	13.93
5	$C_9H_9N_3O$	61.70	5.18	23.99
		61.58	5.22	23.70
7	$C_{12}H_{15}N_3O_3$	57.82	6.07	16.86
		57.68	6.23	16.74
8	$C_{10}H_{13}N_3O_2$	57.96	6.32	20.28
		57.78	6.62	20.35
9	$C_9H_9N_3O_2$	56.54	4.75	21.98
		56.37	4.92	21.78
10	$C_{13}H_{20}N_4O_4$	52.69	6.80	18.91
		52.49	6.75	19.02
12	$C_{14}H_{17}NSO_3$	60.19	6.13	5.01
		60.25	6.12	5.22
13	$C_{12}H_{15}NSO_2$	60.73	6.37	5.90
		60.72	6.13	5.77
14	$C_{11}H_{11}NSO_2$	59.71	5.01	6.33
		60.11	4.97	6.21
16	$C_{13}H_{16}N_2O_4$	59.08	6.10	10.60
		58.87	6.32	10.88
17	$C_{11}H_{14}N_2O_3$	59.45	6.35	12.61
		59.72	6.27	12.60

Scheme IV



15 16 17

a) 4-Iodobutyl acetate, K_2CO_3, THF, b) i) MeONa, MeOH ii) Amberlite IRC-50 H^+

Compounds **4**, **5** and **14** may be regarded as useful starting materials for the synthesis of other acylonucleosides. Therefore, additional chemical transformations of the novel compounds, along with an evaluation of their biological properties, are currently under investigation in our laboratory.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. The pmr 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). 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 column was packed as slurries with the elution solvent. 4-Iodobutyl acetate [11a], 1,4-diiodobutane [13] and 4-bromoacetoacetic acid [11d,14] were prepared following published methods.

1-(4-Acetoxybutyl)benzotriazole (**2**).

A mixture of benzotriazole (**1**, 0.65 g, 5.46 mmoles), potassium carbonate (0.76 g, 5.48 mmoles) and tetrahydrofuran (20 ml) was refluxed for 1 hour. 4-Iodobutyl acetate (1.32 g, 5.50 mmoles) was added to the reaction mixture. The mixture was refluxed for an additional 4 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (12 x 3 cm). The column was eluted with dichloromethane. Fractions containing the product were combined and then evaporated under reduced pressure to give compound **2** as a liquid in 81% (1.03 g) yield; ir (neat): 3060, 2950, 1750, 1250 cm^{-1}.

1-(4-Hydroxybutyl)benzotriazole (**3**).

A mixture of compund **2** (0.3 g, 1.28 mmoles), anhydrous sodium methoxide (0.4 g) and dry methanol (20 ml) was stirred for 2-3 hours at room temperature. After adding Amberlite IRC-50 (1.6 g, H^+ form), the mixture was stirred for an additional 4 hours at room temperature. The resin was filtered and washed with hot methanol (10 ml x 2). The combined filtrate was evaporated under reduced pressure to give compound **3** as a liquid in 86% (0.21 g) yield; ir (potassium bromide): 3500, 1620 cm^{-1}.

1-(4-Iodobutyl)benzotriazole (**4**).

A mixture of benzotriazole (**1**, 1 g, 8.39 mmoles), sodium hydride (0.36 g, 16 mmoles 60% in oil) and dry acetonitrile (20 ml) was stirred for 1 hour at room temperature. After adding 1,4-diiodobutane (1.1 ml, 8.3 mmoles), the reaction mixture was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (15 x 3 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure to give compound **4** in 66% (1.67 g) yield, mp 84-85°; ir (potassium bromide): 3050, 2950, 1600, 1570, 1330, 1200 cm^{-1}.

1-(2-Oxopropyl)benzotriazole (**5**).

A mixture of benzotriazole (**1**, 1 g, 8.39 mmoles), sodium hydride (0.36 g, 16 mmoles 60% in oil) and dry acetonitrile (20 ml) was stirred for 20 minutes at room temperature. After adding 4-bromoacetoacetic acid (1.4 g, 8.3 mmoles), the reaction mixture was refluxed for 25 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (15 x 3 cm). The column eluate was evaporated under reduced pressure to give compound **5** in 83% (1.22 g) yield, mp 118-119°; ir (potassium bromide): 3080, 2940, 1740, 1440 cm^{-1}.

1-(4-Acetoxybutoxy)benzotriazole (**7**).

A mixture of 1-hydroxybenzotriazole hydrate (**6**, 1 g, 7.4 mmoles), sodium hydride (0.35 g, 15 mmoles, 60% in oil) and dry acetonitrile (20 ml) was stirred for 30 minutes at room temperature. The mixture was stirred for an additional 30-31 hours at room temperature after 4-iodobutyl acetate (1.8 ml, 7.4 mmoles) was added to the reaction mixture. After adding water (50 ml), The product was extracted with chloroform (100 ml x 3). The chloroform solution was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (13 x 3 cm). The column was eluted with chloroform/methanol (95:5, v/v). Fractions containing the product were combined and evaporated to afford compound **7** as a liquid in 95% (1.82 g) yield; ir (potassium bromide): 3100, 2950, 1750, 1100 cm^{-1}.

1-(4-Hydroxybutoxy)benzotriazole (**8**).

A mixture of compound **7** (1 g, 0.44 mmoles), anhydrous sodium methoxide (0.45 g) and dry methanol (20 ml) was stirred for 3 hours at room temperature. After adding Amberlite IRC-50 (9 2 g, H^+ form), the mixture was stirred for an additional 12 hours at room temperature. The resin was filtered and washed with hot methanol (10 ml x 2). The combined filtrate was evaporated under reduced pressure to give compound **8** as a liquid in 87% (0.80 g) yield; ir (potassium bromide): 3400, 3080, 2950, 1100 cm^{-1}.

1-(2,3-Epoxypropoxy)benzotriazole (**9**).

A mixture of 1-hydroxybenzotriazole (**6**, 2 g, 14.8 mmoles), epichlorohydrin (2.5 ml, 32 mmoles) and aqueous sodium hydroxide solution (0.75 g, in 5 ml of water) was stirred for 2 hours at room temperature. The product was extracted with dichloromethane (25 ml x 2). The organic solution was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (12 x 3 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure to give compound **9** as a liquid in 73% (2.1 g) yield; ir (potassium bromide): 3080, 2950, 1600, 1450, 1100 cm^{-1}.

1-[3-[*N,N*-di(2-hydroxyethyl)amino]-2-hydroxypropoxy]benzotriazole (**10**).

A mixture of **9** (0.7 g, 3.6 mmoles), diethanolamine (0.6 g, 5.70 mmoles) and methanol (15 ml) was stirred for 51 hours 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 (12 x 3 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 compound **10** in 83% (0.92 g) yield, mp 66-67°; ir (potassium bromide): 3400, 3050, 2950, 1450, 1080 cm^{-1}.

4-(4-Acetoxybutyl)-2*H*-1,4-benzothiazin-3-one (**12**).

A mixture of compound **11** (1 g, 6.0 mmoles), potassium carbonate (0.83 g, 6.0 mmoles), 4-iodobutyl acetate (2 g, 8.2 mmoles) and tetrahydrofuran (20 ml) was refluxed for 49 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (12 x 3 cm). The column was eluted with dichloromethane. Fractions containing the product were combined and evaporated under reduced pressure to give compound **12** as a liquid in 72% (1.2 g) yield; ir (potassium bromide): 3080, 2950, 1740, 1680, 1240 cm^{-1}.

4-(4-Hydroxybutyl)-2*H*-1,4-benzothiazin-3-one (**13**).

A mixture of compound **12** (1.2 g, 4.3 mmoles), anhydrous sodium methoxide (1 g) and dry methanol (20 ml) was stirred for 5 hours at room temperature. After adding Amberlite IRC-50 (2 g, H^+ form), the mixture was stirred for an additional 18 hours at room temperature. The resin was filtered and washed with hot methanol (10 ml x 2). The combined filtrate was evaporated under reduced pressure to give compound **13** as a liquid in 80% (0.81 g) yield; ir (potassium bromide): 3400, 3080, 2950, 1660, 1460 cm^{-1}.

4-(2-Oxopropyl)-2*H*-1,4-benzothiazin-3-one (**14**).

A mixture of compound **11** (1 g, 6.5 mmoles), potassium carbonate (1.3 g, 10 mmoles), 4-bromoacetoacetic acid (1.46 g, 9 mmoles) and tetrahydrofuran (20 ml) was refluxed for 21 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (15 x 3 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure to give compound **14** in 83% (1.20 g) yield, mp 60-61°; ir (potassium bromide): 3050, 2940, 1740, 1680 cm^{-1}.

4-(4-Acetoxybutyl)-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3-one (**16**).

A mixture of **15** (1 g, 7.29 mmoles), potassium carbonate (1 g, 7.29 mmoles), 4-iodobutyl acetate (0.87 g, 7.29 mmoles) and tetrahydrofuran (20 ml) was refluxed for 16 hours. After filtering the salt, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (12 x 3 cm). The column was eluted with chloroform/methanol (99:1, v/v). Fractions containing the product were combined and evaporated under reduced pressure to give **16** as a liquid in 78% (1.5 g) yield; ir (potassium bromide): 3080, 2960, 1750, 1700, 1240 cm^{-1}.

4-(4-Hydroxybutyl)-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3-one (**17**).

A mixture of **16** (1.2 g, 4.54 mmoles), anhydrous sodium methoxide (1 g) and dry methanol (20 ml) was stirred for 1 hour at room temperature. After adding Amberlite IRC-50 (2 g, H^+ form), the mixture was stirred for an additional 22 hours at room temperature. The resin was filtered and washed with hot methanol (10 ml x 2). The combined filtrate was evaporated under reduced pressure to give compound **17** as a liquid in 80% (0.81 g) yield; ir (potassium bromide): 3500, 3080, 2950, 1700, 1100 cm^{-1}.

Acknowledgment.

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