β-Ribo- and α-Arabinonucleosides Containing the 1,2-Benzisoxazole and 1,2-Benzisothiazole Rings

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The reaction of the silylated base of 1,2-benzisoxazol-3(2*H*)-one (**1**) and its 7-methyl derivative **5** and 5-methyl-1,2-benzisothiazol-3(2*H*)-one (**9**), respectively, with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose followed by basic deprotection gave the corresponding β-D-ribonucleosides, and the silylated base of **1**, when treated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α-D-arabinofuranose in the presence of stannic chloride, afforded the corresponding α-arabinonucleoside. Structural proofs of these nucleosides are provided from elemental analyses and ^1H and ^{13}C nmr spectra.

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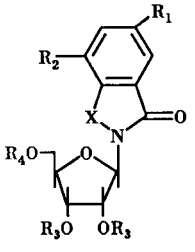
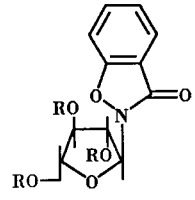
Biological activities of natural nucleosides maybe altered by modifying their heterocyclic moiety. From our interest in this field, we have synthesized nucleosides of isoxazoles [1], cyclohepta[*b*]pyrroles [2,3], and cycloheptimidazoles [3], though most of them did not exhibit significant biological activity. In the light of the pharmacological activity exhibited by some benzisoxazol-3(2*H*)-ones [4-6] and biocidal activity of benzisothiazol-3(2*H*)-ones [7,8], we extended the study to the synthesis of β-ribonucleosides containing a 1,2-benzisoxazole and 1,2-benzisothiazole ring, respectively, and one α-arabinonucleoside containing a 1,2-benzisoxazole ring, though a study undertaken at a pharmaceutical laboratory has shown that they have no significant biological activity.

Benzisoxazol-3(2*H*)-one (**1**) [9] was ribosylated by the conventional procedure, namely, by the reaction of its silylated base with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of stannic chloride giving 2-(2′, 3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2-benzisoxazol-3-one (**2**) in good yield, which was deprotected with methanolic ammonia. As the oily nucleoside **3** defied chromatographical purifications, it had to be characterized after conversion to the corresponding isopropylidene derivative **4**. However, 7-methyl-2-(β-D-ribofuranosyl)-1,2-benzisoxazol-3-one (**7**) obtained by the deprotection of compound **6**, itself being prepared from 7-methylbenzisoxazol-3(2*H*)-one (**5**) [9], was crystalline, being characterized as such by elemental analyses and spectral data and by further conversion to the corresponding isopropylidene derivative **8** with acetone and sulfuric acid. Similarly, 5-methylbenzisothiazol-3(2*H*)-one (**9**) [10] gave the corresponding crystalline ribonucleoside **11** after basic deprotection of compound **10**.

Scheme



2, X = O, $R_1 = R_2 = H$, $R_3 = R_4 = Bz$
3, X = O, $R_1 = R_2 = R_3 = R_4 = H$
4, X = O, $R_1 = R_2 = R_4 = H$, $R_3 = >CMe_2$
6, X = O, $R_1 = H$, $R_2 = Me$, $R_3 = R_4 = Bz$
7, X = O, $R_1 = R_3 = R_4 = H$, $R_2 = Me$
8, X = O, $R_1 = R_4 = H$, $R_2 = Me$, $R_3 = >CMe_2$
10, X = S, $R_1 = Me$, $R_2 = H$, $R_3 = R_4 = Bz$
11, X = S, $R_1 = Me$, $R_2 = R_3 = R_4 = H$
12, X = S, $R_1 = Me$, $R_2 = R_4 = H$, $R_3 = >CMe_2$



13, R = Bz
14, R = H

Treatment of the silylated base of **1** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α-D-arabinofuranose [11] gave a good yield of the protected α-arabinonucleoside **13**. Despite a discouraging report that the 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-arabinofuranose/stannic chloride system is not a good selection as the glycosidation reagents [12], our earlier [3], present, and unpublished works [13] suggest that the glycosidation may be achieved even with this system. To minimize the formation of undesirable materials including the β-anomer, it was found preferable to maintain the reaction temperature below 100°. Removal of the protecting group by base led to the corresponding α-arabinonucleoside **14**.

The assigned structure of the ribonucleosides followed from elemental analyses (Table 1), the presence of carbonyl absorptions in their ir spectra, and the ^1H nmr spectra (Table 2) of the deprotected products **7** and **11** which display the anomeric proton as a doublet [$J_{1'}$, $H_{2'}$ = 5 Hz] at δ 5.8-6.0 ppm and the confirmation of the β configuration was provided from the ^1H (Table 2) and ^{13}C nmr spectra (Table 3) of the isopropylidene derivatives **4**, **8**, and **12**. The isopropylidene Me signals in the ^{13}C nmr spectra are observed at δ 25.3-25.4 and 27.2-27.4 ppm which fall in the range reported for the β-anomer by Ohrui *et al.* [14], and the Δδ value between the chemical shifts of the two Me groups in the ^1H nmr spectra is >0.15 ppm and the anomeric proton appears as a doublet [$J_{1'}$, $H_{2'}$ = 3.0-3.4 Hz] at δ 5.83-6.10 ppm. The α-configuration of **14** (Table 1) was inferred on the basis of the *trans* rule and also by comparison of its ^1H nmr spectrum (Table 2) with those of the

Table 1

Elemental Analyses of Compounds **2**,**4**,**6**,**7**,**8**,**10**,**11**, and **12**

Compound	Mp °C	Molecular Formula	Elemental Analyses Calcd. C	H	N	Found C	H	N
2	53-56	$C_{33}H_{25}NO_9$	68.39	4.35	2.42	68.15	4.47	2.60
4	Oil	$C_{15}H_{17}NO_6$	58.63	5.57	4.56	58.85	5.55	4.60
6	60-62	$C_{34}H_{27}NO_9 \cdot 0.2H_2O$	68.38	4.62	2.35	67.96	4.65	2.22
7	190-192	$C_{13}H_{15}NO_6$	55.51	5.38	4.98	55.31	5.39	4.89
8	98-99	$C_{16}H_{19}NO_6$	59.80	5.96	4.36	59.82	6.01	4.27
10	156-157	$C_{34}H_{27}NO_8S$	66.99	4.46	2.30	66.98	4.38	2.14
11	149-150	$C_{13}H_{15}NO_5S$	52.52	5.08	4.71	52.47	5.02	4.56
12	Oil	$C_{16}H_{19}NO_5S$	56.96	5.68	4.15	56.65	5.46	3.98
13	53-56	$C_{33}H_{25}NO_9$	68.38	4.35	2.42	68.08	4.30	2.30
14	136-137	$C_{12}H_{13}NO_6$	53.93	4.90	5.24	53.67	4.87	5.43

Table 2

^{1}H NMR Spectra of Compounds **2**,**4**,**6**,**7**,**8**,**10**,**11**, **12**, **13**, and **14**

Compound	Chemical Shifts (δ_H in ppm)
2 [a,c]	4.52 (1H, dd, $J_{4',5'}$ = 3.7, $J_{5'a,5'b}$ = 12.2 Hz, $H_{5'}$), 4.67-4.78 (1H, m, $H_{4'}$), 4.83 (1H, dd, $J_{4',5'}$ = 3.7, $J_{5'a,5'b}$ = 12.2 Hz, $H_{5'}$), 6.03 (1H, dd, $J_{2',3'}$ = 4.9, $J_{3',4'}$ = 4.9 Hz, $H_{3'}$), 6.29 (1H, dd, $J_{1',2'}$ = 4.9 Hz, $J_{2',3'}$ = 4.9 Hz, $H_{2'}$), 6.53 (1H, d, $J_{1',2'}$ = 4.9 Hz, H_1), 6.84 (1H, d, $J_{6,7}$ = 8.5 Hz, H_7), 7.20-7.89 (12H, m, aromatic) 7.91-8.21 (6H, m, aromatic)
4 [b,d]	1.35 (3H, s, Me), 1.55 (3H, s, Me), 3.10-3.35 (1H, m, $O_{5'}$ H), 3.60-3.80 (2H, m, $H_{5'}$), 4.10-4.40 (1H, m, $H_{4'}$), 4.85 (1H, dd, $J_{3',4'}$ = 3.0, $J_{2',3'}$ = 6.0 Hz, $H_{3'}$), 5.25 (1H, dd, $J_{1',2'}$ = 3.0, $J_{2',3'}$ = 6.0 Hz, $H_{2'}$), 6.05 (1H, d, $J_{1',2'}$ = 3.0 Hz, $H_{1'}$), 7.05-7.90 (4H, m, aromatic)
6 [a,d]	2.20 (3H, s, Me), 4.50-4.90 (3H, m, $H_{4'}$, $H_{5'}$), 5.90-6.15 (1H, m, $H_{3'}$), 6.30 (1H, dd, $J_{1',3'}$ = 5.5, $J_{2',3'}$ = 5.5 Hz, $H_{2'}$), 6.55 (1H, d, $J_{1',2'}$ = 5.5 Hz, $H_{1'}$), 7.10-7.80 (12H, m, aromatic), and 7.80-8.30 (6H, m, aromatic)
7 [b,c]	2.36 (3H, s, Me), 3.40-3.70 (2H, m, $H_{5'}$), 3.80-3.90 (1H, m, $H_{4'}$), 4.03-4.15 (1H, m, $H_{3'}$), 4.40-4.50 (1H, m, $H_{2'}$), 4.80 (1H, t, $J_{5',05'H}$ = 5.5 Hz, $O_{5'}$ H), 5.21 (1H, d, $J_{3',03'H}$ = 6.11 Hz, $O_{3'}$ H), 5.54 (1H, d, $J_{2',02'H}$ = 6.1 Hz, $O_{2'}$ H), 5.76 (1H, d, $J_{1'2'}$ = 4.9 Hz, $H_{1'}$), 7.27 (1H, dd, $J_{4,5}$ = 7.63, $J_{5,6}$ = 7.63 Hz, H_5), 7.58-7.64 (2H, m, H_4, H_6)
8 [a,d]	1.40 (3H, s, Me), 1.60 (3H, s, Me), 2.40 (3H, s, Me), 2.60-2.83 (1H, m, $O_{5'}$ H), 3.45-3.90 (2H, m, $H_{5'}$), 4.25-4.50 (1H, m, $H_{4'}$), 4.95 (1H, dd, $J_{2',3'}$ = 6.0, $J_{3',4'}$ = 3.0 Hz, $H_{3'}$), 5.35 (1H, dd, $J_{1',2'}$ = 3.0, $J_{2',3'}$ = 6.0 Hz, $H_{2'}$), 6.10 (1H, d, $J_{1',2'}$ = 3.0 Hz, $H_{1'}$), 7.70-7.80 (3H, m, aromatic)
10 [a,c]	2.42 (3H, s, Me), 4.63 (1H, dd, $J_{4',5'}$ = 3.66, $J_{5'a,5'b}$ = 11.9 Hz, $H_{5'}$), 4.69-4.77 (1H, m, $H_{4'}$), 4.87 (1H, dd, $J_{4',5'}$ = 2.75, $J_{5'a,5'b}$ = 11.9 Hz, $H_{5'}$), 5.87-6.00 (2H, m, $H_{2'}$, $H_{3'}$), 6.78 (H, d, $J_{1',2'}$ = 5.19 Hz, $H_{1'}$), 7.25-7.86 (12H, m, aromatic), 7.86-8.24 (6H, m, aromatic)
11 [b,c]	2.42 (3H, s, Me), 3.49-3.58 (2H, m, $H_{5'}$), 3.80-3.89 (1H, m, $H_{4'}$), 3.93-4.05 (1H, m, $H_{3'}$), 4.10-4.19 (1H, m, $H_{2'}$), 4.95 (1H, t, $J_{5',05'H}$ = 5.35 Hz, $O_{5'}$ H), 5.22 (1H, d, $J_{3',03'H}$ = 4.88 Hz, $O_{3'}$ H), 5.48 (1H, d, $J_{2',02'H}$ = 6.10 Hz, $O_{2'}$ H), 5.98 (1H, d, $J_{1',2'}$ = 5.80 Hz, $H_{1'}$), 7.55 (1H, d, $J_{6,7}$ = 8.24 Hz, H_6), 7.71 (1H, s, H_4), and 7.88 (1H, d, $J_{6,7}$ = 8.24 Hz, H_7)
12 [a,c]	1.37 (3H, s, Me), 1.60 (3H, s, Me), 2.45 (3H, s, Me), 3.04 (1H, br s, $O_{5'}$ H), 3.80 (1H, dd, $J_{4',5'}$ = 3.51, $J_{5'a,5'b}$ = 12.4 Hz, $H_{5'}$), 3.93 (1H, dd, $J_{4',5'}$ = 2.45, $J_{5'a,5'b}$ = 12.4 Hz, $H_{5'}$), 4.27-4.35 (1H, m, $H_{4'}$), 5.00 (1H, dd, $J_{3',4'}$ = 3.36, $J_{2',3'}$ = 6.11 Hz, $H_{3'}$), 5.22 (1H, dd, $J_{1',2'}$ = 3.36, $J_{2',3'}$ = 6.11 Hz, $H_{2'}$), 5.83 (1H, d, $J_{1',2'}$ = 3.36 Hz, $H_{1'}$), 7.40-7.52 (2H, m, H6, H_7), and 7.82 (1H, s, H_4)
13 [a,d]	4.55-5.00 (3H, m, $H_{4'}$, $H_{5'}$), 5.83 (1H, dd, $J_{2',3'}$ = 3.5, $J_{3',4'}$ = 4.5 Hz, $H_{3'}$), 6.28 (1H, dd, $J_{1',2'}$ = 3.5, $J_{2',3'}$ = 3.5 Hz, $H_{2'}$), 6.45 (1H, d, $J_{1',2'}$ = 3.5 Hz, $H_{1'}$), 7.00-7.70 (13H, m, aromatic), and 7.70-8.25 (6H, m, aromatic)
14 [b,c]	3.31-3.47 (1H, m, $H_{5'}$), 3.53-3.66 (1H, m, $H_{5'}$), 3.80-4.00 (2H, n, $H_{3'}$, $H_{4'}$), 4.55 (1H, m, dd, $J_{1',2'}$ = 6.72 $J_{2',3'}$ = 6.72 [after deuteration], $H_{2'}$), 4.82 (1H, t, $J_{5',05'H}$ = 5.49 Hz, $O_{5'}$ H), 5.55 (1H, d, $J_{3',03'H}$ = 5.50 Hz, $O_{3'}$ H), 5.67 (1H, d, $J_{1',2'}$ = 6.10 Hz, $H_{1'}$), 5.85 (1H, d, $J_{2',02'H}$ = 6.10 Hz, $O_{2'}$ H), 7.39 (1H, dd, $J_{4,5}$ = 7.37, $J_{5,6}$ = 7.33 Hz, H_5), 7.58 (1H, d, $J_{6,7}$ = 7.94 Hz, H_7), 7.82 (1H, dd, $J_{5,6}$ = 7.33, $J_{6,7}$ = 7.94 Hz, H_6), and 7.84 (1H, d, $J_{4,5}$ = 7.37 Hz, H_4).

[a] In deuteriochloroform. [b] In hexadeuteriodimethyl sulfoxide. [c] At 250 MHz. [d] At 60 MHz.

Table 3

^{13}C NMR Spectra of the Isopropylidene Derivatives **4**, **8**, and **12**

Compound	Chemical Shifts (δ_C in ppm) [a]
4	25.33 and 27.18 (Me), 62.91 ($C_{5'}$), 80.81, 81,77, and 86.31 ($C_{2'}$, $C_{3'}$, $C_{4'}$), 91.23 ($C_{1'}$), 109.90 (C_7), 113.84 (isopropylidene-C), 115.97 (C_{3a}), 123.70 and 124.56 (C_5, C_6), 134.37 (C_4), 160.76, and 163.62 (C_3, C_{7a})
8	13.98 (Me) , 25.38 and 27.24 (Me), 63.04 ($C_{5'}$), 80.91 and 81.86 ($C_{2'}$, $C_{3'}$), 86.37 ($C_{4'}$), 91.57 ($C_{1'}$), 113.78 (isopropylidene C), 115.51 (C_{3a}), 120.47, 121.76, 123.76, 134.99 (C_4, C_5, C_6, C_7), 159.74 and 164.13 (C_3, C_{7a})
12	20.99 (Me), 25.28 and 27.42 (Me), 62.85 ($C_{5'}$), 80.52, 83.40, 85.93 ($C_{2'}$, $C_{3'}$, $C_{4'}$), 91.33 ($C_{1'}$), 114.05 (isopropylidene C), 119.91 (C_{3a}), 124.57, 126.37, 133.89, 135.75, 137.65 (C_4, C_5, C_6, C_{7a}), 165.40 (C_3)

[a] In deuteriochloroform.

α-and β-arabinonucleosides prepared in our laboratory [13] with respect to the anomeric proton signal.

EXPERIMENTAL

Melting points were determined in capillary tubes. All solutions were dried over sodium sulfate and all evaporations were carried out *in vacuo* with a rotary evaporator. The ^1H nmr spectra were obtained on Hitachi R-24B (at 60 MHz) and Hitachi R-250H (at 250 MHz) spectrometers with tetramethylsilane as an internal standard and the assignments were confirmed by deuterium exchange and decoupling experiments, where necessary, and ^{13}C nmr spectra on a Hitachi R-250H spectrometer with tetramethylsilane as an internal standard. Kieselgel 60 was used for column chromatography. Preparative liquid chromatography was carried out over Woelm with *n*-hexane-ethyl acetate (3:1) unless otherwise stated. Optical rotations were taken with an ATAGO POLAX-D polarimeter.

2-(2',3',5'-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2-benzisoxazol-3-one (**2**).

A mixture of 0.526 g (3.89 mmoles) of 1,2-benzisoxazol-3(2*H*)-one (**1**), 15 ml of hexamethyldisilazane, and 0.8 ml of chlorotrimethylsilane was heated for 30 minutes at 110° and then evaporated leaving a syrupy silylated base. The silylated base and 1.96 g (3.89 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose were dissolved in 20 ml of 1,2-dichloroethane, and 1.5 ml of stannic chloride was added to this solution. The mixture was heated under reflux for 40 minutes, 15 ml of water and 4 g of sodium hydrogencarbonate were added, and the mixture stirred at room temperature for 30 minutes and filtered through celite. The dried filtrate was evaporated and preparative liquid chromatography of the residue gave the protected ribonucleoside (**4**) as a powder, yield 1.67 g (74%); ir (potassium bromide): 1730 cm^{-1} (C=O).

2-(2',3'-*O*-Isopropylidene-β-D-ribofuranosyl)-1,2-benzisoxazol-3-one (**4**).

A solution of 0.722 g (1.25 mmoles) of **2** in 150 ml of methanolic ammonia was stirred at room temperature for 3 days and evaporated. The residue was dissolved in water and the solution extracted with chloroform. Evaporation of the aqueous solution and column chromatography of the residue gave an oily 2-(β-D-ribofuranosyl)-1,2-benzisoxazol-3-one (**3**), yield 0.300 g (98%). A mixture of 0.300 g of **3**, 30 ml of acetone, and 0.5 ml of sulfuric acid was stirred at room temperature for 36 hours, neutralized with pyridine, and evaporated. The residue was dissolved in chloroform and the solution filtered through celite. The filtrate was washed with water, dried, and evaporated. Preparative liquid chromatography of the residue gave the isopropylidene derivative **4** as an oil, yield 0.180 g (47%); ir (neat): 3450 (OH) and 1695 cm^{-1} (C=O).

2-(2',3',5'-Tri-*O*-benzoyl-β-D-ribofuranosyl)-7-methyl-1,2-benzisoxazol-3-one (**6**).

This hygroscopic powder compound was prepared in 63% yield as described for **2**, from 7-methylbenzisoxazol-3(2*H*)-one (**5**); ir (potassium bromide): 1730 cm^{-1} (C=O).

7-Methyl-2-(β-D-ribofuranosyl)-1,2-benzisoxazol-3-one (**7**) [15].

This compound, prepared in 61% yield as described for 3 by basic hydrolysis of 6, was recrystallized from ethanol as needles; ir (potassium bromide): 3325 (OH) and 1670 cm^{-1} (C=O).

2-(2',3'-*O*-Isopropylidene-β-D-ribofuranosyl)-7-methyl-1,2-benzisoxazol-3-one (**8**).

This compound, prepared in 57% yield as described for **4** from **7**, was recrystallized from methylene chloride-hexane as needles; ir (potassium bromide): 3200-3600 (OH) and 1680 cm^{-1} (C=O).

5-Methyl-2-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2-benzisothiazol-3-one (**10**).

This compound, prepared in 69% yield as described for **2**, from 5-methylbenzisothiazol-3(2*H*)-one (**9**), was recrystallized from ethanol as needles; ir (potassium bromide): 1675 and 1730 cm^{-1} (C=O).

5-Methyl-2-(β-D-ribofuranosyl)-1,2-benzisothiazol-3-one (**11**).

This compound, prepared in 89% yield as described for **3** from **10**, was recrystallized from ethanol as needles; ir (potassium bromide): 3380 (OH) and 1650 cm^{-1} (C=O); rotation $[\alpha]^{21}$ −33.6° (c 1.34 in ethanol).

2-(2',3'-*O*-Isopropylidene-β-D-ribofuranosyl)-1,2-benzisothiazol-3-one (**12**).

A mixture of 0.480 g (1.61 mmoles) of compound **11**, 40 ml of acetone, 1.0 ml of ethyl orthoformate, and 0.070 g of *p*-toluenesulfonic acid was stirred at room temperature for 6 days, neutralized with sodium hydrogencarbonate, and filtered through celite. The solvent was evaporated and preparative liquid chromatography of the residue with *n*-hexane-ethyl acetate (1:1) gave the isopropylidene derivative **12** as an oil, yield 0.194 g (36%); ir (neat): 3390 (OH) and 1650 cm^{-1} (C=O).

2-(2',3',5'-Tri-*O*-benzoyl-α-D-arabinofuranosyl)-1,2-benzisoxazol-3-one (**13**).

A mixture of 0.526 g (3.89 mmoles) of the benzisoxazolone **1**, 5 ml of hexamethyldisilazane, and 0.8 ml of chlorotrimethylsilane was heated for 30 minutes at 110° and evaporated leaving a syrupy silylated base. This silylated base and 1.96 g (3.89 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α-D-arabinofuranose [11] were dissolved in 20 ml of 1,2-dichloroethane and 1.5 ml of stannic chloride was added to this solution. The mixture was heated under reflux for 40 minutes and treated as described for **2**. Preparative liquid chromatography of the product afforded the protected arabinonucleoside **13** as powders, yield 1.67 g (74%); ir (potassium bromide): 1725 cm^{-1} (C=O).

2-(α-D-Arabinofuranosyl)-1,2-benzisoxazol-3-one (**14**).

A solution of 1.00 g (1.73 mmoles) of compound **13** in 100 ml of methanolic ammonia was stirred at room temperature for 3 days and treated as described for **3**. Trituration of an oily product with *n*-butanol gave a solid. Recrystallization from *n*-butanol gave the nucleoside **14** as needles, yield 0.300 g (65%); ir (potassium bromide): 3345 (OH) and 1670 cm^{-1} (C=O); rotation $[\alpha]^{25}$ +123° (c 1.06 in ethanol).

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