ISSN 1070-4280, Russian Journal of Organic Chemistry, 2017, Vol. 53, No. 4, pp. 573–576. © Pleiades Publishing, Ltd., 2017. Original Russian Text © A.A. Harutyunyan, H.A. Panosyan, R.A. Tamazyan, A.G. Aivazyan, G.G. Danagulyan, 2017, published in Zhurnal Organicheskoi Khimii, 2017, Vol. 53, No. 4, pp. 567–570.

4-Alkylated 2-(2,3,5-Tri-*O*-acyl-β-D-ribofuranosyl)and 2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,4-triazine-3,5-diones

A. A. Harutyunyan^{*a, b*},* H. A. Panosyan^{*a*}, R. A. Tamazyan^{*a*}, A. G. Aivazyan^{*a*}, and G. G. Danagulyan^{*a, b*}

^a Mndzhoyan Institute of Fine Organic Chemistry, Scientific Technological Center of Organic and Pharmaceutical Chemistry, National Academy of Sciences of Armenia, pr. Azatutyan 26, Yerevan, 0014 Armenia

*e-mail: harutyunyan.arthur@yahoo.com

^b Russian–Armenian (Slavic) University, ul. Ovsela Emina 123, Yerevan, 0051 Armenia

Received October 21, 2016

Abstract—The alkylation of 2-(2,3,5-tri-*O*-acyl-β-D-ribofuranosyl)- and 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,4-triazine-3,5-diones with benzyl halides afforded the corresponding 4-benzyl derivatives whose structure was determined by spectral methods, including X-ray analysis. Some of the synthesized compounds were tested for antibacterial and antitumor activity.

DOI: 10.1134/S1070428017040121

6-Azauracil and its β-D-ribofuranosyl and tri-*O*acetyl-β-D-ribofuranosyl derivatives are active antitumor agents which also exhibit antiviral, immunosuppressive, and other biological activities [1–3]. Various 6-azauracil derivatives, nucleosides derived therefrom, and acyclic nucleoside analogs have been reported as promising antiviral, antibacterial, and antienzyme compounds [4, 5]. Although 6-azauracil belongs to the 1,2,4-triazine series, in terms of bioorganic and pharmaceutical chemistry it is regarded primarily as 6-aza analog of uracil acting as pyrimidine exchange antimetabolite. Therefore, synthesis of new 6-azauracil derivatives and study of their biological properties are important problems.

In continuation of our studies on the synthesis and biological activity of nitrogen heterocycles [6], in this work we performed glycosylation of 3,5-bis(trimethyl-siloxy)-1,2,4-triazine (1) with peracylated β -D-ribo-furanoses **2a** and **2b** and 1,2,3,4,6-penta-*O*-acetyl- β -D-glucopyranose (3) to obtain 2-(2,3,5-tri-*O*-acyl- β -D-ribofuranosyl)- and 2-(tetra-*O*-acetyl- β -D-glucopyranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-diones **4a**, **4b**, and **5** (Scheme 1) [7]. 2-(2,3,5-Tri-*O*-acetyl- β -D-ribofuranosyl)-1,2,4-triazine-3,5-dione (**4a**) was isolated as a thick oily material which was subjected to al-kylation without preliminary purification. The alkyla-

tion of nucleosides 4a, 4b, and 5 with alkyl halides in DMF in the presence of potassium carbonate afforded previously unknown 4-alkyl derivatives 6a-6d and 7a-7c (Scheme 1).

The structure of compound 6c was unambiguously determined by X-ray analysis (see table), which directly confirmed that the glycosylation of 3,5-bis(trimethylsiloxy)-1,2,4-triazine (1) with 1,2,3,5-tetra-Oacetyl- β -D-ribofuranose in the presence of SnCl₄ yields exclusively anomer 4a with β -configuration of the anomeric carbon atom. The benzene and triazine rings in molecule 6c in crystal are almost planar, and deviations of atoms from the mean-square planes do not exceed 0.0082(1) and 0.0138(2) Å, respectively. The ribofuranose ring adopts an envelope conformation with the C^{16} , C^{17} , C^{19} , and O^{20} atoms lying in one plane within 0.0199(1) Å and the C^{18} atom deviating from that plane by 0.5157(1) Å. The dihedral angles formed by the ribose envelope plane, on the one hand, and triazine and benzene rings, on the other, are 83.128(2)and 69.323(2)°, respectively.

The antibacterial activity of compounds **6a**, **6b** and **7a–7c** was assessed against gram-positive *Staphylococcus aureus* 209p and *S. aureus* 1 and gram-negative *Shigella flexneri* 6858 and *Escherichia coli* 0-55. Only glucopyranoside **7b** showed a weak antibacterial





2, **4**, R = Ac (**a**), Bz (**b**); **6**, R = Ac, R' = Bu (**a**); R = Bz, R' = 4-HO-3-MeOC(O)C₆H₃CH₂ (**b**); R = Ac, R' = PhCH₂ (**c**), 3-Br-4-MeOC₆H₃CH₂ (**d**); **7**, R' = 4-MeO-3-O₂NC₆H₃CH₂ (**a**), 3-Br-4-MeOC₆H₃CH₂ (**b**), 2-ClC₆H₄CH₂ (**c**).

activity against the four bacterial strains tested, whereas the other compounds turned out to be completely inactive. Nucleosides **6b**, **7a**, and **7b** showed no antitumor activity against early P388 ascite T-cell leukosis.

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Avatar 330 spectrometer from samples dispersed in mineral oil. The ¹H and ¹³C NMR spectra were measured on a Varian Mercury-300 VX instrument at 300.8 and 75.46 MHz, respectively, using tetramethylsilane as internal standard. The X-ray diffraction data for com-



Structure of the molecule of 4-benzyl-2-(tri-O-acetyl- β -D-ribofuranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (**6c**) according to the X-ray diffraction data.

pound **6c** were obtained at room temperature with an Enraf Nonius CAD-4 automated diffractometer (Mo K_{α} radiation, graphite monochromator, $\theta/2\theta$ scanning) [8, 9]. The progress of reactions was monitored by TLC on Silufol UV-254 plates using 2-methylpropan-1-ol as eluent; spots were detected by treatment with iodine vapor.

Compounds 6a–6d and 7a–7c. A mixture of 0.01 mol of 2-(2,3,5-tri-*O*-acetyl- β -D-ribofuranosyl)-, 2-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-, or 2-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione **4a**, **4b**, or **5**, 1.38 g (0.01 mol) of potassium carbonate, and 0.01 mol of the corresponding alkyl halide in 30 mL of anhydrous DMF was heated for 4 h at 70–80°C. The mixture was poured onto 50 g of ice and kept for 4 h in the cold, and the precipitate was filtered off, thoroughly washed with ice water, and recrystallized from ethanol.

4-Butyl-2-(2,3,5-tri-*O***-acetyl-**β**-D-ribofuranosyl)**-**2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (6a).** Yield 50%, mp 81–82°C, R_f 0.18. IR spectrum, v, cm⁻¹: 1757, 1720, 1674. ¹H NMR spectrum (CDCl₃), δ, ppm: 0.95 t (3H, CH₃CH₂, J = 7.3 Hz), 1.31–1.44 m (2H, CH₃CH₂), 1.57–1.68 m (2H, CH₂C₂H₅); 2.08 s, 2.11 s, and 2.12 s (3H each, COCH₃); 3.90 t (2H, NCH₂, J = 7.5 Hz), 4.16 d.d (1H, OCH₂, J = 11.5, 5.1 Hz), 4.35–4.37 d.d.d (1H, 4-H, J = 5.8, 5.2, 3.7 Hz), 4.39 d.d (1H, OCH₂), 5.43 d.d (1H, 3-H, J = 5.8, 5.6 Hz), 5.64 d.d (1H, 2-H, J = 5.6, 3.4 Hz), 6.31 d.d (1H, 1-H, J = 3.4 Hz), 7.46 s (1H, 6'-H). ¹³C NMR spectrum (CDCl₃), $\delta_{\rm C}$, ppm: 13.7 (CH₃); 20.1, 20.5, 20.5 (COCH₃); 20.8 (CH₂), 29.2 (CH₂), 40.9 (NCH₂), 63.3 (OCH₂), 70.7 (C³), 72.9 (C²), 79.5 (C⁴), 89.3 (C¹), 135.8 (NCH), 148.4 (NCO), 155.3 (NCO); 169.5, 169.6, 170.5 (COCH₃). Found, %: C 50.43; H 5.67; N 10.21. C₁₈H₂₅N₃O₉. Calculated, %: C 50.58; H 5.90; N 9.83.

Methyl 2-hydroxy-5-{[2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4triazin-4-yl]methyl}benzoate (6b). Yield 58%, mp 128–130°C, $R_{\rm f}$ 0.55. IR spectrum, v, cm⁻¹: 3190, 1733, 1673, 1601. NMR spectrum ¹H (CDCl₃), δ , ppm: 3.93 s (3H, OCH₃), 4.53 d.d (1H, OCH₂, J = 12.0, 4.5 Hz), 4.75 m (1H, 4-H), 4.83 d.d (1H, OCH₂, J = 12.0, 3.7 Hz), 4.99 s (2H, NCH₂), 5.97 d.d (1H, 3-H, J = 6.0, 5.5 Hz), 6.08 d.d (1H, 2-H, J = 5.5, 3.4 Hz), 6.60 d (1H, 1-H, J = 3.4 Hz), 6.92 d (1H, 3"-H, J =8.6 Hz); 7.34-7.46 m (6H), 7.53-7.62 m (4H), 7.92-7.99 m (5H), and 8.05-8.09 m (2H) (H_{arom}); 10.79 s (1H, OH). ¹³C NMR spectrum (CDCl₃), $\delta_{\rm C}$, ppm: 43.5 (NCH₂), 52.4 (OCH₃), 63.5 (OCH₂), 71.7 (OCH), 73.7 (OCH), 80.3 (OCH), 89.5 (OCH), 135.9 (N=CH), 148.5 (NC=O), 155.2 (NC=O); 165.2, 165.4, 166.1 (OCO). Found, %: C 63.61; H 3.93; N 6.04. C₃₈H₃₁N₃O₁₂. Calculated, %: C 63.24; H 4.33; N 5.82.

4-Benzyl-2-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (6c). Yield 62%, mp 138–139°C, R_f 0.58. IR spectrum, v, cm⁻¹: 1757, 1737, 1717, 1671. ¹H NMR spectrum $(CDCl_3)$, δ , ppm: 2.07 s, 2.10 s, and 2.10 s (3H each, OAc); 4.15 d.d (1H, 5-H), 4.33 d.d.d (1H, 4-H), 4.38 d.d (1H, 5-H), 5.07 s (2H, NCH₂), 5.43 d.d (1H, 3-H), 5.63 d.d (1H, 2-H), 6.32 d (1H, 1-H), 7.29-7.36 m (3H, Ph), 7.44-7.49 m (2H, Ph), 7.50 s (1H, 6'-H). ¹³C NMR spectrum (CDCl₃), δ_{C} , ppm: 20.5, 20.5, 20.7 (COCH₃); 44.2 (CH₂), 63.3 (C⁵), 70.7 (C³), 72.8 (C^2), 79.6 (C^4), 89.2 (C^1), 128.4 (C^p), 128.7 and 128.7 (C^o, C^m), 135.0 (Cⁱ), 135.9 (N=CH), 148.5 (NC=O), 155.2 (NC=O); 169.5, 169.6, 170.5 (COCH₃). Found, %: C 55.25; H 5.36; N 9.41. C₂₁H₂₃N₃O₉. Calculated, %: C 54.66; H 5.02; N 9.11.

4-(3-Bromo-4-methoxybenzyl)-2-(2,3,5-tri-*O*acetyl-β-D-ribofuranosyl)-2,3,4,5-tetrahydro-1,2,4triazine-3,5-dione (6d). Yield 62%, mp 111–113°C, R_f 0.36. IR spectrum, v, cm⁻¹: 1753, 1684, 1600. ¹H NMR spectrum (CDCl₃), δ, ppm: 2.07 s, 2.11 s, and 2.11 s (3H each, OAc); 3.88 s (OCH₃), 4.15 d.d (1H,

RUSSIAN JOURNAL OF ORGANIC CHEMISTRY Vol. 53 No. 4 2017

Crystallographic data for 4-benzyl-	2-(tri-O-acetyl-β-D-ribo-
furanosyl)-2,3,4,5-tetrahydro-1,2,4-t	triazine-3,5-dione (6c)

Formula	C ₂₁ H ₂₃ N ₃ O ₉
Molecular weight	461.42
Crystal system	Monoclinic
Space group	$P2_1$
a, Å b, Å c, Å	8.6424(17) 8.4641(17) 15.084(3)
β, deg	94.67(3)
<i>V</i> , Å ³	1099.7(4)
Ζ	2
$d_{\rm calc}, {\rm g/cm^3}$	1.393
$\mu(MoK_{\alpha}), mm^{-1}$	0.110
<i>F</i> (000)	484
Crystal size, mm	$0.12 \times 0.24 \times 0.40$
Temperature, K	293
Radiation wavelength, Å	0.71073
$\theta_{min}/\theta_{max}$, deg	1.4/30.0
hkl ranges	$0 \le h \le 12 \\ -11 \le k \le 11 \\ -21 \le l \le 21$
Total number of reflections	7207
Number of reflections with $I > 2.0\sigma(I)$	3854
Number of independent reflections	6376
Number of variables	357
R	0.0530
wR_2	0.1077
Goodness of fit S	1.04

5-H), 4.33 d.d. (1H, 4-H), 4.38 d.d (1H, 5-H), 4.98 s (2H, CH₂), 5.42 d.d (1H, 3-H), 5.63 d.d (1H, 2-H), 6.32 d (1H, 1-H), 6.84 d (1H, 3-H, J = 8.5 Hz), 7.43 d.d (1H, 4"-H, J = 8.5, 2.2 Hz), 7.50 s (1H, 6'-H), 7.70 d (1H, 6"-H, J = 2.2 Hz). ¹³C NMR spectrum (CDCl₃), $\delta_{\rm C}$, ppm: 20.6, 20.6, 20.8 (CH₃CO); 43.2 (CH₂), 56.4 (OCH₃), 63.3 (C⁵), 70.7 (C³), 72.9 (C²), 79.6 (C⁴), 89.2 (C¹), 111.8, 112.2, 128.5, 130.3, 134.7, 135.8 (N=CH), 135.8, 148.3 (NC=O), 155.1 (NC=O), 156.0, 169.5 (COCH₃), 169.6 (COCH₃), 170.4 (COCH₃). Found, %: C 46.21; H 3.87; Br 14.24; N 7.18. C₂₂H₂₄BrN₃O₁₀. Calculated, %: C 46.33; H 4.24; Br 14.01; N 7.37.

4-(4-Methoxy-3-nitrobenzyl)-2-(2,3,4,6-tetra-O-acetyl-B-D-glucopyranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (7a). Yield 62%, mp 148-150°C, $R_{\rm f}$ 0.33. IR spectrum, v, cm⁻¹: 1754, 1723, 1678, 1619. ¹H NMR spectrum (CDCl₃), δ , ppm: 1.91 s, 2.02 s, 2.05 s, and 2.07 s (3H each, OAc); 3.91 d.d.d (1H, 5-H, J = 10.1, 4.6, 2.3 Hz), 3.95 s (3H, OCH_3), 4.14 d.d (1H, 6-H, J = 12.5, 2.2 Hz), 4.26 d.d $(1H, 6-H, J = 12.5, 4.8 \text{ Hz}), 5.04 \text{ s} (2H, \text{NCH}_2),$ 5.17 d.d (1H, 4-H, J = 10.1, 9.5 Hz), 5.35 d.d (1H, 3-H, J = 9.5, 9.5 Hz, 5.64 d.d (1H, 2-H, J = 9.5, J)9.2 Hz), 5.88 d (1H, 1-H, J = 9.2 Hz), 7.04 d (1H, H_{arom} , J = 8.6 Hz), 7.51 s (1H, 6'-H), 7.68 d.d (1H, H_{arom} , J = 8.6, 2.3 Hz), 7.95 d (1H, H_{arom} , J = 2.3 Hz). ¹³C NMR spectrum (CDCl₃), δ_{C} , ppm: 20.5, 20.6, 20.6, 20.7 (CH₃CO), 43.0 (CH₂), 56.7 (OCH₃), 61.6 (C°), 67.7 (C⁴), 68.3 (C²), 73.6 (C³), 74.5 (C⁵), 83.1 (C¹), 113.7, 126.8, 127.3, 135.6, 135.6 (N=CH), 148.7 (NC=O), 154.9 (NC=O); 169.0, 169.4, 170.1, 170.6 (COCH₃). Found, %: C 49.55; H 4.93; N 9.63. C₂₅H₂₈N₄O₁₄. Calculated, %: C 49.35; H 4.64; N 9.21.

4-(3-Bromo-4-methoxybenzyl)-2-(2,3,4,6-tetra-O-acetyl-B-D-glucopyranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (7b). Yield 60%, mp 181-182°C, $R_{\rm f}$ 0.50. IR spectrum, v, cm⁻¹: 1754, 1723, 1678, 1619. ¹H NMR spectrum (CDCl₃), δ , ppm: 1.90 s, 2.02 s, 2.06 s, and 2.08 s (3H each, OAc); 3.88 s (3H, OCH₃), 3.91 d.d.d (1H, 5-H, J = 10.1, 4.8, 2.2 Hz), 4.14 d.d (1H, 6-H, J = 12.5, 2.2 Hz), 4.26 d.d $(1H, 6-H, J = 12.5, 4.8 \text{ Hz}), 4.98 \text{ s} (2H, \text{NCH}_2),$ 5.17 d.d (1H, 4-H, J = 10.1, 9.5 Hz), 5.35 d.d (1H, 3-H, J = 9.5, 9.3 Hz, 5.62 d.d (1H, 2-H, J = 9.3, J)9.3 Hz), 5.89 d (1H, 1-H, J = 9.2 Hz), 6.84 d (1H, H_{arom} , J = 8.5 Hz), 7.41 d.d (1H, H_{arom} , J = 8.5, 2.2 Hz), 7.49 s (1H, 6'-H), 7.66 d (1H, H_{arom}, J = 2.2 Hz). ¹³C NMR spectrum (CDCl₃), δ_{C} , ppm: 20.5, 20.6, 20.6, 20.8 (CH₃CO); 43.2 (CH₂), 56.4 (OCH₃), $61.7 (C^{6}), 67.8 (C^{4}), 68.4 (C^{2}), 73.7 (C^{3}), 74.5 (C^{5}),$ 83.0 (C¹), 111.8, 128.6, 130.2, 134.5, 135.7 (N=CH), 148.7 (NC=O), 154.9 (NC=O), 156.1; 169.0, 169.4, 170.2, 170.6 (COCH₃). Found, %: C 46.5; H 4.45; Br 12.24; N 6.90. C₂₅H₂₈BrN₃O₁₂. Calculated, %: C 46.75; H 4.39; Br 12.44; N 6.54.

4-(2-Chlorobenzyl)-2-(2,3,4,6-tetra-*O***-acetyl-β-D-glucopyranosyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (7c).** Yield 67%, mp 154–156°C, R_f 0.64. IR spectrum, v, cm⁻¹: 1754, 1747, 1678, 1593. ¹H NMR spectrum (DMSO-*d*₆), δ , ppm: 1.91 s, 1.97 s, 2.02 s, 2.03 s (3H each, Ac); 3.97–4.04 m (1H) and 4.18–4.24 m (2H) (5-H, 6-H); 5.01 t (1H, 4-H, *J* = 9.1 Hz), 5.08 s (2H, NCH₂), 5.40–5.51 m (2H, 2-H, 3-H), 6.10 d (1H, 1-H, *J* = 8.0 Hz); 7.03–7.08 m, 7.19–7.28 m, and 7.36–7.42 m (4H, C₆H₄); 7.62 s (1H, 6'-H). Found, %: C 50.45; H 4.45; CI 6.17; N 7.17. C₂₄H₂₆ClN₃O₁₁. Calculated, %: C 50.76; H 4.61; CI 6.24; N 7.40.

This study was performed in the framework of the Program for the Development of the Russian– Armenian University.

REFERENCES

- 1. Welch, A.D., Handschumacher, R.E., and Jaffe, J.J., J. Pharmacol. Exp. Ther., 1960, vol. 129, no. 3, p. 262.
- 2. Schaeffer, G.W. and Sorokin, T., *Plant Physiol.*, 1966, vol. 41, p. 971.
- Kabbaj, Y., Lazrek, H.B., Barascut, J.L., and Imbach, J.L., *Nucleosides, Nucleotides Nucleic Acids*, 2005, vol. 24, no. 3, p. 161.
- Malagon, F., Kireeva, M.L., Shafer, B.K., Lubkowska, L., Kashlev, M., and Strathern, J.N., *Genetics*, 2006, vol. 172, no. 4, p. 2201.
- 5. El-Brollosy, M.R., *Monatsh. Chem.*, 2008, vol. 139, p. 1483.
- Arutyunyan, A.A., Panosyan, G.A., Galstyan, M.V., Paronikyan, R.V., Stepanyan, G.M., Sukasyan, R.S., and Grigoryan, A.S., *Nekotorye uspekhi organicheskoi i* farmatsevticheskoi khimii. Sbornik trudov (Some Advances in Organic and Pharmaceutical Chemistry. A Collection of Papers), Erevan, 2015, no. 2, p. 299.
- Niedballa, U. and Vorbruggen, H., J. Org. Chem., 1974, vol. 39, no. 25, p. 3654.
- Palatinus, L. and Chapuis, G., J. Appl. Crystallogr., 2007, vol. 40, p. 786.
- Petricek, V., Dusek, M., and Palatinus, L., JANA Structure Determination Software Programs, Praha, Czech Republic, Institute of Physics, 2006.