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Synthesis of N-(2,4-dinitrophenyl) derivatives of D-ribosylamines; unexpected reaction and hydrolysis products

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ABSTRACT

Reaction of 2,3-*O*-isopropylidene-D-ribofuranosylamine with 2,4-dinitrofluorobenzene afforded the crystalline 2,3-*O*-isopropylidene-*N*-(2,4-dinitrophenyl)-β-D-ribofuranosylamine (**3**) and a 1:1 crystalline complex of 2,3-*O*-isopropylidene-*N*-(2,4-dinitrophenyl-α-D-ribofuranosylamine and 2,3-*O*-isopropylidene-β-D-ribofuranose; controlled acidic hydrolysis of **3** afforded *N*-(2,4-dinitrophenyl-α-D-ribopyranosylamine and not the expected β-D-furanosylamine derivative. The structures of the new compounds were confirmed by NMR spectroscopy and X-ray crystallography.

1. Introduction

Despite the fact that the interest in the synthesis of nucleoside analogues (fraudulent nucleosides) first arose in the 1950's as a result of the search for anti-cancer drugs, the later discovery of their potential for the treatment of AIDS [1,2] (e.g. AZT, DDI, D4T, 3-TC), led to a continuing interest in the synthesis of new members of this class of compounds. A comprehensive review [3] addressed the molecular mechanisms signaling cell death induced by nucleoside analogues. Current methods for combating Covid-19, initiated since the appearance of the virus in 2020 that led to the pandemic affecting all forms of world activity, is essentially through vaccination, although fraudulent nucleosides (e.g. Remdesivir [4] and the recently approved [5] Molnupiravir {Lagevrio}) suggest potential for application in this area. There is promise that modification of the heterocyclic base in nucleosides may provide lead compounds in developing antiviral chemotherapy.

2. Results and discussion

2.1. Synthesis

We previouly observed [6] that some simple glycosides which contained the 2,4-dinitrophenylamino group as a component of their aglycone showed moderate *anti*-HIV activity and reasoned that *N*-(2,4-dinitrophenyl)-β-D-ribofuranosylamine (**1**) and derivatives such as the 2,3-dideoxy- and 2,3-dideoxy-2,3-didehydro compounds, in view of the application of related compounds in chemotherapy [1,2], might be useful candidates for *anti*-HIV and *anti*-Covid-19 testing. To this end, we have investigated the synthesis of the parent compound by the seemingly simple route of reacting the easily prepared [7] salt of 2,3-*O*-isopropylidene-D-ribofuranosylamine (**2**) and *p*-toluenesulphonic acid with 2,4-dinitrofluorobenzene (Sanger's reagent) to afford acetal **3**, followed by acidic hydrolysis of the latter to yield **1**. These reactions, which were not straightforward, form the basis of this report.

Reaction of 2,3-*O*-isopropylidene-D-ribofuranosylammonium *p*-toluenesulphonate [7] with 2,4-dinitrofluorobenzene in aqueous ethanol under basic conditions and chromtography of the mixture of products gave, after removal of a trace amount of 2-ethoxy-2,4-dinitrobenzene, 2,3-*O*-isopropylidene-*N*-(2,4-dinitrophenyl)-β-D-ribofuranosylamine (**3**), whose structure was confirmed by elemental analysis, its NMR spectra, and through X-ray crystallography (Fig. 1) (crystal structure details of the newly prepared compounds are presented in section 2.2) and slower running material with mp 102–104 °C having an elemental analysis corresponding to $C_{22}H_{31}N_3O_{13}$. ^1H and ^{13}C NMR data clearly suggested two components were present and clarification was obtained by X-ray anslysis of the crystalline material which showed it to be a 1:1 complex of 2,3-*O*-isopropylidene-*N*-(2,4-dinitrophenyl)-α-D-ribofuranosylamine (**4**) and 2,3-*O*-isopropylidene-β-D-ribofuranose (**5**) (Fig. 2 and Fig. 3). This unexpected result arises from two reactions prior to complex formation: (a) isomerisation at the anomeric carbon in **3** from the β-to the α-configuration to give **4** and (b) hydrolysis of the 2,4-dinitrophenylamino group in **3** give 2,3-*O*-isopropylidene-β-D-ribofuranose (**5**). It is

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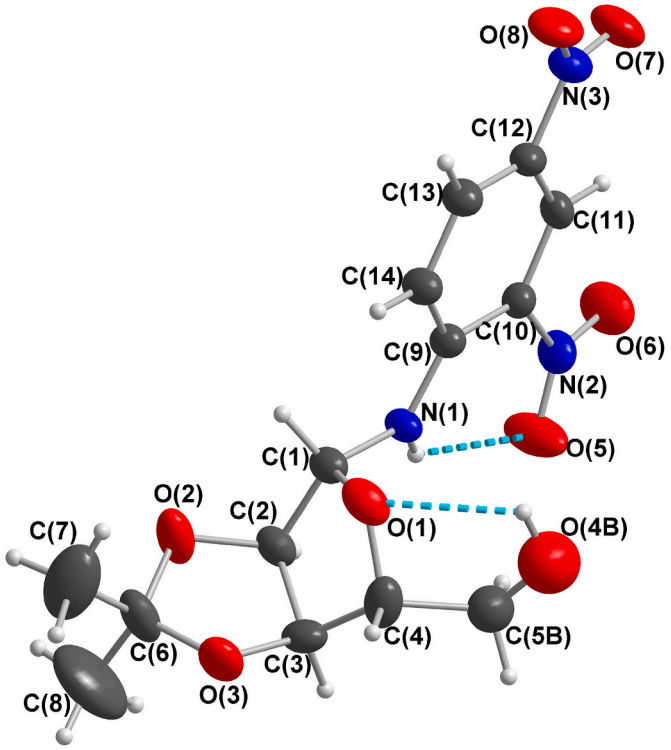


Fig. 1. Molecular structure of **3**. Minor disorder components of the $-CH_2OH$ group omitted for clarity; all atoms except C(5B) and O(4B) shown as 30% thermal ellipsoids; intramolecular H-bonds shown as light blue dashed lines.

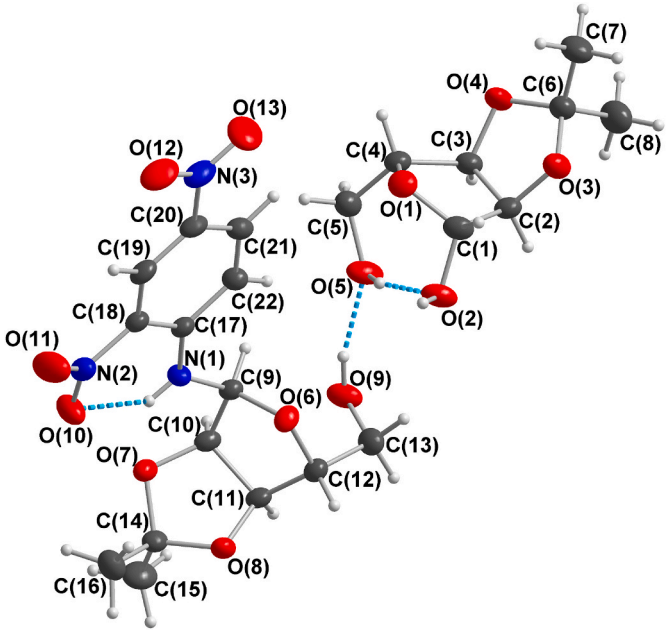
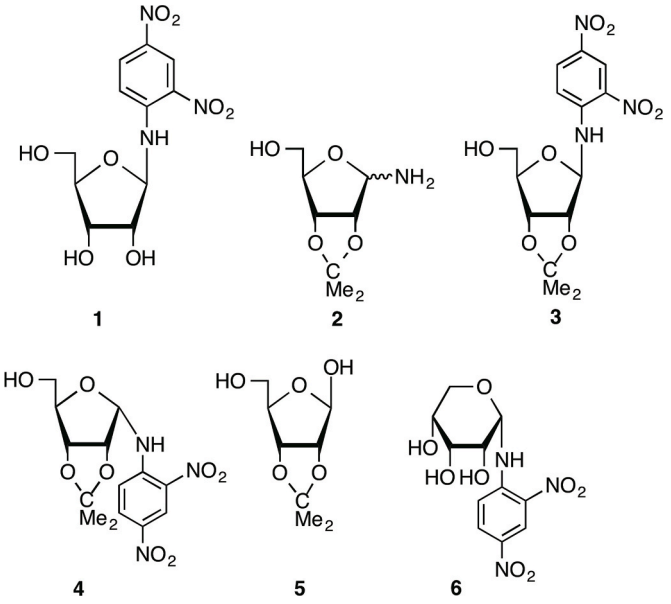


Fig. 2. Structure of the complex of **4** and **5** in the crystal. All atoms shown as 30% thermal ellipsoids; hydrogen bonds shown as light blue dashed lines.

relevant that the complexity of equilibrium produced on dissolution of 2,3-*O*-isopropylidene-D-ribofuranosylammomium *p*-toluenesulphonate in various solvents, and under different conditions of pH, has been reported [7].



In the expectation that simple removal of the *O*-isopropylidene group in the acetal **3** would give furanoside **1** (required for biological anti-viral testing), the compound was treated with aqueous trifluoroacetic acid, a reagent routinely used for this purpose in carbohydrate chemistry. Although NMR spectroscopy of the crystalline product confirmed loss of the protecting group at O-2 and O-3 and retention of the anomeric substituent, the data suggested the furanose ring was no longer present, Examination of the material by X-ray crystallography showed that ring expansion had occurred with inversion of configuration at the anomeric centre to yield a pyranose structure, and identified the compound as *N*-(2,4-dinitrophenyl-α-D-ribopyranosylamine (**6**) (Fig. 4).

It is relevant to compare our results with earlier and more recent studies on the reaction of D-ribose and its 2,3-*O*-isopropylidene derivative with amines. Imbach and co-workers [8] reported that whereas primary amines condense with the free sugar to give mainly D-ribopyranosylamines in which the α-anomer in the $^1C_4$ conformation preponderates, reaction of the 2,3-*O*-isopropylidene derivative gives furanoid compounds since the presence of the five-membered ring favours formation of a second, fused five-membered ring [9]. In our work, the formation in the reaction mixture of the α-isomer **4** and 2,3-*O*-isopropylidene-β-D-ribofuranose **5**, leading to formation of the complex **4.5**, is readily understood in view of mutarotation exhibited by glycosylamines and the presence of water causing hydrolysis. 2,4-Dinitroaniline, co-liberated with **5** on hydrolysis of **3** could afford α-isomer **4** on recombination with **5**, since reaction of aniline with **5** has been shown [8] to give α- and β-isomers of *N*-phenyl-D-ribofuranosylamine with the α-isomer in excess.

Formation of the pyranose derivative **6** under acidic conditions can be rationalised by loss of the 2,3-*O*-isopropylidene group, which would remove the stabilising factor of the second ring fusion on the furanose ring system in **3**. Ring opening and closure would give the most stable pyranose derivative, in accord with the observation [8] that aniline and D-ribose react to afford pyranose derivatives in ratios dependant on the conditions. The α- and β-forms of the *N*-phenyl-D-ribopyranosylamines have been identified by NMR spectroscopy [10].

There are other reports of the formation of *N*-aryl-α-D-ribopyranosylamines by reaction of D-ribose with arylamines, together with their crystal structures. Reaction of sulphanilamide [11] afforded *N*-(*p*-sulphamoylphenyl)-α-D-ribopyranosylamine with the pyranose ring in a $^1C_4$ conformation, stabilised by an intramolecular hydrogen bond, O(2)–H·····O-4 (carbohydrate ring numbering), similar to that observed in structure **6** (see section 2.2 and Fig. 4).

The crystal structure of supposed β-D-ribopyranosylamine has been

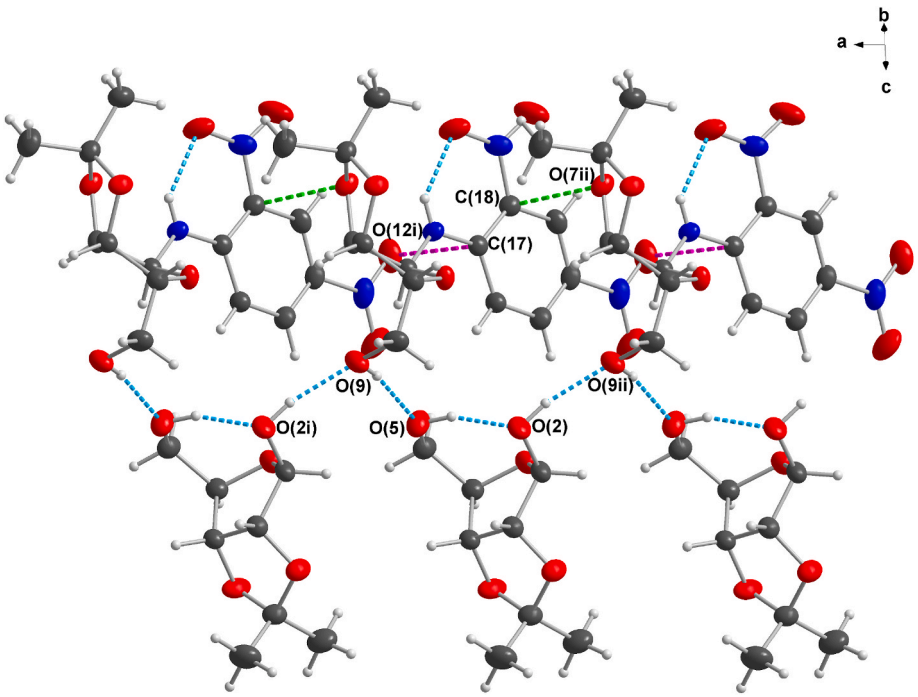


Fig. 3. Supramolecular linkages of the complex of **4** and **5** forming chains parallel to the crystal *a*-axis. Hydrogen bonds shown as light blue dashed lines; short (3.179(3) Å) O-πC interactions shown as green dashed lines; short (3.274(3) Å) πO-πC interactions shown as purple dashed lines. Symmetry codes: (i) x+1, y, z; (ii) x-1, y, z.

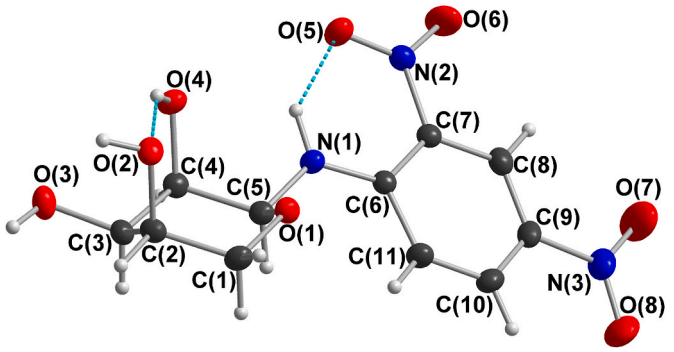


Fig. 4. Molecular structure of **6**. All atoms shown as 30% thermal ellipsoids; hydrogen bonds shown as light blue dashed lines

reported [12] but with the unfortunate serious error of the ORTEP diagram showing the enantiomeric L-ribose ring form, which means the α-L-isomer is represented, and that the authors have *incorrectly identified* their product. Their starting material was undoubtedly D-ribose which means that the correct representation in their Fig. 1 should be the mirror image of that shown and this would identify the product as α-D- ribopyranosylamine adopting a $^{1}C_{4}$ conformation (see Ref. [9], Fig. 3.8). Unusually, the compound possesses four intramolecular hydrogen bonds including bifurcated bonding from the hydrogen of the hydroxy group on C(2) to the oxygen atoms on C(3) and C(4), and bonding from the hydrogen of the hydroxy group on C(3) to the oxygen on C(2), and from the hydrogen on the hydroxy group on C(4) to the oxygen on C(3).

The crystal structure of *N-p*-nitrophenyl-α-D-ribopyranosylamine [13] is unusual in that in addition to crystallising with one molecule of water, an independent part of the unit cell is formed by three molecules of the sugar. This is in stark contrast to our observation regarding the related 2,4-dinitrophenyl compound (see section 2.2). Although the extra steric demands of the 2-nitro substituent in **6** might offer an explanation for this difference, the co-planar alignment of the aromatic rings in the *p*-nitro compound, together with the co-planarity of the nitro group with each aromatic ring suggests that extra steric bulk of the 2-nitro substituent in **6** may not be an overriding factor. Interestingly, the amino hydrogen in **6** is involved in an *intramolecular* hydrogen bond with an oxygen of the 2-nitro group whereas the hydrogen of the amino group in one (molecule B) of the three distinct molecules in the crystal of the *p*-nitrophenyl compound is involved in an *intermolecular* hydrogen bond with the ring oxygen of a second (molecule A) of the three distinct units. Thus, subtle changes in stereochemistry and also the presence of a molecule of water in the unit cell may be an important factors controlling the difference in the two crystal structures. In connection with our own observation on the supramolecular structure of complex **4.5** (see section 2.2 and Fig. 3), it is pertinent that the extended intermolecular hydrogen bonded network found in the *p*-nitrophenyl compound [13] efficiently stabilises its crystal lattice. The sugar moieties of the *p*-nitrophenyl compound all adopt a slightly distorted $^{1}C_{4}$ conformation.

2.2. Details of crystal structures

X-ray crystallographic measurements on compound **3** confirmed the β-furanose structure shown in Fig. 1. For improvement of the final resolution of the data file, the –CH_2OH group was considered as threefold disordered, and was refined with sets of isotropic partial occupancy (0.5, 0.3, 0.2) atoms, with similar restraints applied to the C–C and C–O bond lengths and to the thermal parameters of the methylene C atoms. In the crystals, the furanose ring adopts, essentially, a $^{4}T_{O}$ conformation.[2] A hydrogen bond occurs [length 2.08(7) Å] between the hydrogen attached to the nitrogen atom [N(1)] at the anomeric centre and an oxygen atom [O(5)] of the 2-nitro substituent of the aromatic ring, and a further intramolecular bond [length 2.28 Å] occurs between the hydrogen on the oxygen O(4B) of the hydroxymethyl group and the ring

[2] Note: the numbering of the atoms in this crystallographic section and in the Figures is different and distinct from the conventional numbering used in naming, and description of the conformation of carbohydrate compounds.

oxygen O(1).

Crystallographic measurements on the complex **4.5** revealed it to consist of molecules of **4** and **5** (Fig. 2) forming chains parallel to the crystal *a*-axis (see Fig. 3). The two chains are linked by hydrogen bonds between the hydrogen atom on the oxygen [O(9)] of the hydroxymethyl group in **4** and the oxygen O(5) of the hydroxymethyl group in **5** (length 1.85(3) Å). In addition, hydrogen bonding exists between the hydrogen atom on the oxygen O(2′) of the anomeric hydroxyl group in **5** and the oxygen atom O(9) in **4** (length 1.89(4) Å). Intramolecular hydrogen bonding occurs in **4** between a hydrogen on the nitrogen at the anomeric centre and an oxygen O(10) of the 2-nitro group (length 2.02(3) Å), and in **5** between the hydrogen atom on O(5) and O(2) (length 1.83(4) Å). Within the chain of molecules of **4**, there are short [3.179(3) Å] O-πC interactions shown (Fig. 3) as green dashed lines, and short [3.274(3) Å] πO-πC interactions, shown as purple dashed lines. The conformations of the furanose rings of **4** and **5** in the crystalline complex are most closely described as distorted ^{4}TO and *EO* conformations, respectively.

The crystal structure of compoud **6** (Fig. 4) confirms the α-pyranose structure with the pyranose ring adopting a $^{1}C_{4}$ conformation that places the hydroxy groups at C(2) and C(4) of the pyranose ring in axial positions and the electronegative nitrogen [N(1)] in an unfavourable (anomeric effect) equatorial position. This conformation is stabilised by an intramolecular hydrogen bond [length 2.13(3) Å] between the hydrogen on O(4) and oxygen O(2) and a hydrogen bond [length 1.92(3) Å] exists between N(1)–H(1) and O(5). The supramolecular structure of **6** (not shown) is formed from chains parallel to the crystal *b* axis with interchain hydrogen bonding between O(2)H and O(1), O(3)H and O(2), and O(1) and O(2)H, the second named atoms in each of these pairs referring to a symmetry related molecule.

Table 1
Crystal data.

Compound	3	4and5	6
Formula	$C_{14}H_{17}N_3O_8$	$C_{22}H_{31}N_3O_{13}$	$C_{11}H_{13}N_3O_8$
Formula weight	355.30	545.50	315.24
Crystal System	Monoclinic	Triclinic	Orthorhombic
Space Group	$P2_1$	$P1$	$P2_12_12_1$
a/Å	5.5910(10)	6.0628(9)	6.5916(3)
b/Å	12.766(3)	9.7053(11)	7.8838(8)
c/Å	11.379(2)	10.994(2)	25.0326(16)
α/°	90	99.535(12)	90
β/°	98.52(2)	94.612(14)	90
γ/°	90	91.071(11)	90
U/Å^3	803.2(3)	635.57(18)	1300.87(17)
Z	2	1	4
T/K	293(2)	293(2)	293(2)
F(000)	372	288	656
D_c/Mg m^{-3}	1.469	1.425	1.610
μ(Mo-Kα)/mm^{-1}	0.122	0.119	0.139
Crystal dimensions/ mm^3	0.50 × 0.40 × 0.10	0.45 × 0.35 × 0.05	0.20 × 0.15 × 0.03
Data Measured	3502	2810	1584
Unique Data	3423	2707	1416
R_{int}	0.0467	0.0134	0.0156
Data with I ≥ 2σ(I)	2480	2380	1296
wR_2 (all data)	0.1857	0.0944	0.0868
S (all data)	1.049	1.044	1.039
R_1 [I ≥ 2σ(I)]	0.0598	0.0322	0.0315
Parameters/ Restraints	242/11	360/7	216/4
Biggest diff. peak/ hole/eÅ^{-3}	+0.395/−0.252	0.188/−0.139	0.178/−0.191
CCDC number	2155664	2155665	2155663

3. Experimental

^{1}H and ^{13}C NMR spectra were run at 270 and 67.9 MHz, respectively, in $CDCl_3$ (internal Me_4Si) unless stated otherwise. *J* Values are given in Hz. Optical rotations were measured with a PerkinElmer 141 polarimeter and $[\alpha]_D$ units are recorded in 10^{-1} deg cm^2 g^{-1}. TLC and column chromatography were performed on silica gel (Machery-Nagel, SIL G-25UV254) and Silica Gel 60 (Merck, 70–230 mesh), respectively.

2,3-O-*Isopropylidene*-N-*(2,4-dinitrophenyl)*-β-D-*ribofuranosylamine* (**3**) To a solution of 2,3-*O*-isopropylidene-D-ribofuranosylammonium *p*-toluenesulphonate [7] (10 g, 27.7 mmol) in EtOH/H_2O (1:1 v/v, 140 mL) was added a solution of 2,4-dinitrofluorobenzene (7.3 g, 39.2 mmol) in EtOH (80 mL), and $NaHCO_3$ (10 g, 119 mmol) was added in portions with stirring. After storage for 12 h, the suspension was filtered, concentrated to a syrup (12.5 g) which was then subjected to chromatography using hexane/EtOAc (initially 7:3 v/v, then 6:4 v/v) as eluent. Concentration of fractions containing the initial component gave a solid (2.61 g, 7.35 mmol, 26.5%) which on recrystallisation from dichloromethane-hexane gave the title compound, mp 128–133 °C; $[\alpha]_D$ −177.6 (*c* 0.15, CH_2Cl_2); δ_H 1.389, 1.596 (2 s, 2 × 3 H, CMe_2), 2.047 (br t, 1 H, OH), 3.826 (t, 2 H, $J_{4,5} = J_{4,5'} = 3.14$, H-5,5′), 4.451 (br, 1 H, H-4), 4.754 (dd, 1 H, $J_{1,2}$ 1.98, $J_{2,3}$ 5.94, H-2), 4.942 (dd, 1 H, $J_{3,4}$ 1.32, H-3), 5.561 (dd, 1 H, $J_{1,NH}$ 7.91, H-1), 7.199 (d, 1 H, J_o 9.57, H-6″), 8.310 (dd, 1 H, J_m 2.64, H-5″), 9.132 (d, 1 H, H-3″), 9.142 (br d, 1 H, NH); δ_C 24.91, 26.76 (C*Me*$_2$), 63.58 (C-5), 82.25 (C-3), 86.20 (C-2), 86.70 (C-4), 91.07 (C-1), 113.62 (*C*Me$_2$), 115.40 (C-6′), 123.88 (C-3′), 130.24 (C-5′), 131.55.

(C-2′), 137.43 (C-4′), 146.58 (C-1′). Anal. Calcd for $C_{14}H_{17}N_3O_8$: C, 47.3; H, 4.8; N, 11.8. Found: C, 47.1; H, 4.7; N, 11.6.

A slower moving component was eluted from the chromatography column and identified (see below) as a 1:1 complex containing two ribofuranosyl residues, in **4** and **5**.

A 1:1 complex of 2,3-O-*isopropylidene*-N-*(2,4-dinitrophenyl)*-α-D-*ribofuranosylamine* (**4**) *and 2,3*-O-*isopropylidene*-β-D-*ribofuranose* (**5**) Concentration of fractions containing the slower running component gave a yellow syrup (2.64 g) which was crystallised from CH_2Cl_2/hexane to afford material mp 102–104 °C; $[\alpha]_D$ +21.1 (*c* 0.52, CH_2Cl_2); δ_H 1.325, 1.4651, 1.487, 1.695 (4 s, 4 × 3 H, 2 x CMe_2), 2.387 (br t, 1 H, OH), 3.680–3.980 (complex, 5 H, 2 x CH_2OH, OH), 4.250 (br dd, 1 H, H-4), 4.405 (br t, 1 H, CH_2OH), 4.577 (d, 1 H, $J_{3a,4a}$ 5.94, H-4a), 4.833 (d, 1 H, H-3a), 4.919 (dd,1 H, $J_{3,4}$ 1.98, $J_{2,3}$ 6.6, H-3), 4.969 (dd, 1 H, $J_{1,2}$ 4.62, 2-H), 5.083 (d, 1 H, $J_{1a,2a}$ 6.77, H-2a), 5.407 (d, 1 H, H-1a), 5.651 (dd, 1 H, $J_{1,NH}$ 6.77, H-1), 7.317 (d, 1 H, $J_{5',6'}$ 9.57, H-6), 8.302 (dd, 1 H, dd, $J_{3',5'}$ 2.64, H-5′), 9.133 (d, 1 H, 3′-H), 9.411 (d, 1 H, NH); δ_C 24.69, 24.80, 26.07, and 26.36 (2 x C*Me*$_2$), 63.59 and 63.81 (C-5, C-5a), 79.64, 81.69, 81.90, 82.37, 84.19, 86.86, 87.73 (C-1a), 102.95 (C-1), 112.63 and 114.82 (2 x *C*Me$_2$), 116.46 (C-6′), 123.75 (C-3′), 130.08 (C-5), 131.73 (C-2′), 137.55 (C-4′), 146.86 (C-1′). Anal. Calcd for $C_{22}H_{31}N_3O_{13}$: C, 48.4; H, 5.7; N, 7.7. Found: C, 48.5; H, 5.6; N, 7.6.

The structure of complex **4.5** was confirmed by X-ray crystallography (see following section and Figs. 2 and 3).

N-*(2,4-Dinitrophenyl*-α-D-*ribopyranosylamine* (**6**) Compound **3** (1.69 g, 4.76 mmol) was dissolved in a mixture of CF_3CO_2H/H_2O/EtOH (1:1:8 v/v/v, 130 mL) and after 15 min the solution was concentrated to a gum which was subjected to column chromatography (hexane/EtOAc 6:4 v/v, increasing to EtOAc) giving a yellow syrup (0.55 g, 37%) which solidified on storage. Recrystallisation from EtOH/hexane gave the title compound mp 201–208 °C (decomp.); $[\alpha]_D$ +220.9 (*c* 0.1, EtOH); δ_H (CD_3OD) 3.520–3.620.(1 H, complex, H-5a), 3.720–3.830 (complex, 2 H, H-4,5b), 3.892 (t, 1 H, $J_{1,2} = J_{2,3} = 3.3$, H-2), 4.016 (br t, 1 H, $J_{3,4}$ 2.5, H-3), 4.594 (br s, 1 H, NH), 5.230 (d, 1 H, H-1), 7.337 (d, 1 H, $J_{5',6'}$ 9.57, H-6′), 8.329 (dd, 1 H, $J_{3',5'}$ 2.64, H-5′), 9.048 (d, 1 H, H-3′); δ_C (CD_3OD, 125.8 MHz) 63.31 (C-5), 68.81, 69.95, 71.54, 81.46 (C-1), 117.14 (C-6′), 124.27 (C-3′), 130.84 (C-5′), 133.06 (C-2′), 138.52 (C-4′), and 148.85 (C-1). Anal. Calcd for $C_{11}H_{13}N_3O_8$: C, 41.9; H, 4.2; N, 13.3. Found: C, 41.8; H, 4.05; N, 13.1.

A summary of details for crystallographic measurements on compounds **3**, **4.5**, and **6** is given in the following section and measurements of molecular dimensions, torsion angles and hydrogen bond data are given under Supplementary data.

4. Crystallographic methods and measurements for compounds 3, 4.5, and 6

Data were collected on a Rigaku AFC7R diffractometer at room temperature using graphite-monochromated Mo-*K*a radiation. The structures were solved by direct methods (SHELXS) [14] and refined by full-matrix least-squares on F^2 (SHELXL-2018/3) [15]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms bonded to C were placed in idealised positions; the coordinates of N–H and O–H hydrogen atoms (located in difference maps) were refined with bond lengths restrained to 0.88(4) and 0.84(4) Å, respectively.

Crystal data and details of the data collections and structure refinements are summarised in Table 1. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 2155663–2155665. Copies of the data can be obtained, free of charge, from https://www.ccdc.cam.ac.uk/structures/

Experimental crystallographic details, including molecular dimensions, torsion angles and hydrogen bond data for compounds **3**, **4.5**, and **6** are recorded as Supplementary data (see Appendix A).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2022.108564.

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