A new approach to the synthesis of nucleosides of 1,2,4-triazole †

El Sayed H. El Ashry,*[a] Laila F. Awad[a] and Martin Winkler[b]

[a] *Department of Chemistry, Faculty of Science, Alexandria University, Alexandria, Egypt. Fax: +20-3-4271360*
[b] *Fakultät Chemie, Universität Konstanz, D-78457 Konstanz, Germany*

Received (in Cambridge, UK) 25th May 1999, Accepted 3rd December 1999

Reaction of benzamidrazone hydroiodide **1** with D-glucose **2**, D-galactose **3** and D-arabinose **8** followed by acetylation afforded 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-, 1-(2,3,5,6-tetra-*O*-acetyl-α-D-galactofuranosyl)- and 1-(1,2,3,4,5-penta-*O*-acetyl-D-*manno*-pentitol-1-yl)-5-methyl-3-phenyl-1*H*-1,2,4-triazole **6**, **7** and **13**, respectively. Structural analyses of these products were carried out by ^{1}H, ^{13}C, and 2D NMR spectra (DQFCOSY, HMQC and HMBC experiments), as well as by MS, FABMS and X-ray crystallography.

Introduction

Much attention has been focused on the synthesis of 1,2,4-triazole derivatives because of their role in a broad spectrum of biological activities such as antiinflammatory, antimycotic, antifungal, antitumor and anticancer agents.[1–4] Moreover, antiradical and antioxidant properties were found for some members of this ring system.[5] Consequently, the synthesis of N- and C-nucleosides as well as their acyclic analogues possessing a 1,2,4-triazole moiety has attracted many workers[6–16] in the field in their attempts to enhance the biological activity of these compounds, particularly after the recognized biological properties of ribavirin.[17] Therefore synthetic approaches towards 1,2,4-triazole nucleosides are our targets.

Results and discussion

The versatility of amidrazones in heterocyclic synthesis has long been recognised.[18,19] However they have remained less familiar than their well known analogues such as aminoguanidine[20] or amidines,[21] especially in their reactions with carbohydrates for the construction of nucleosides. Accordingly, the reaction of benzamidrazone hydroiodide[22] **1** (benzimidohydrazide) with some aldoses has been studied. Thus, equimolar condensation of **1** with concentrated solutions of D-glucose **2**, D-galactose **3** and D-arabinose **8** in water was achieved, within 5-15 min, to give the respective highly soluble hydroiodide salts **4**, **5** and **9**; they form yellow precipitates with aq. silver nitrate. Their attempted crystallisations were unsuccessful because of their high solubilities, and no attempt was made to prepare the free base, but their direct conventional acetylation was carried out with acetic anhydride in pyridine whereby crystalline products were obtained in moderate yields. They could be characterised as the 5-methyl-3-phenyl-1*H*-1,2,4-triazole derivatives **6**, **7** and **13** rather than the respective *N*-acetyl derivatives, but the structure of the sugar part was found to be dependent on its configuration. The presence of the 5-methyl-3-phenyl-1,2,4-triazole ring in each product was established from the study of their ^{1}H and ^{13}C NMR spectra which showed a characteristic singlet for the methyl protons in the range δ 2.53–2.62 and its carbon signal in the range δ_C 11.86–12.15. Characteristic signals for both C-3 and C-5 of the triazole ring were assigned at δ_C 161.11–162.03 and 154.52–155.08, respectively. Their mass spectra showed ion peaks at *m*/*z* 160 corresponding to the protonated 5-methyl-3-phenyl-1*H*-1,2,4-triazole fragment (BH^+). The cyclisation may be readily realised from the conversion of amidrazones and, in particular, their acyl derivatives to the 1,2,4-triazole derivatives[18,23] which in the present cases arise *via* prior acylation of the N-substituted amidrazones.

The formation of products from the condensation of monosaccharides with amino compounds is generally discussed in the terms of acyclic and cyclic forms which are often present in solution as equilibrium mixtures that are strongly influenced by the pH of the solution.[24–28] The respective derivatives from aminoguanidine as well as their 1,2,4-triazole nucleosides analogues exist exclusively in the β-pyranosyl form as deduced from their ^{1}H and ^{13}C NMR and X-ray studies.[10,27,29] Accordingly, we expected the prepared nucleosides to possess the 1-(2,3,4,6-tetra-*O*-acetyl-β-D-aldopyranosyl)-1*H*-1,2,4-triazole structure. However, we have found that the structure of the prepared nucleosides was dependent on the nature of the sugar.

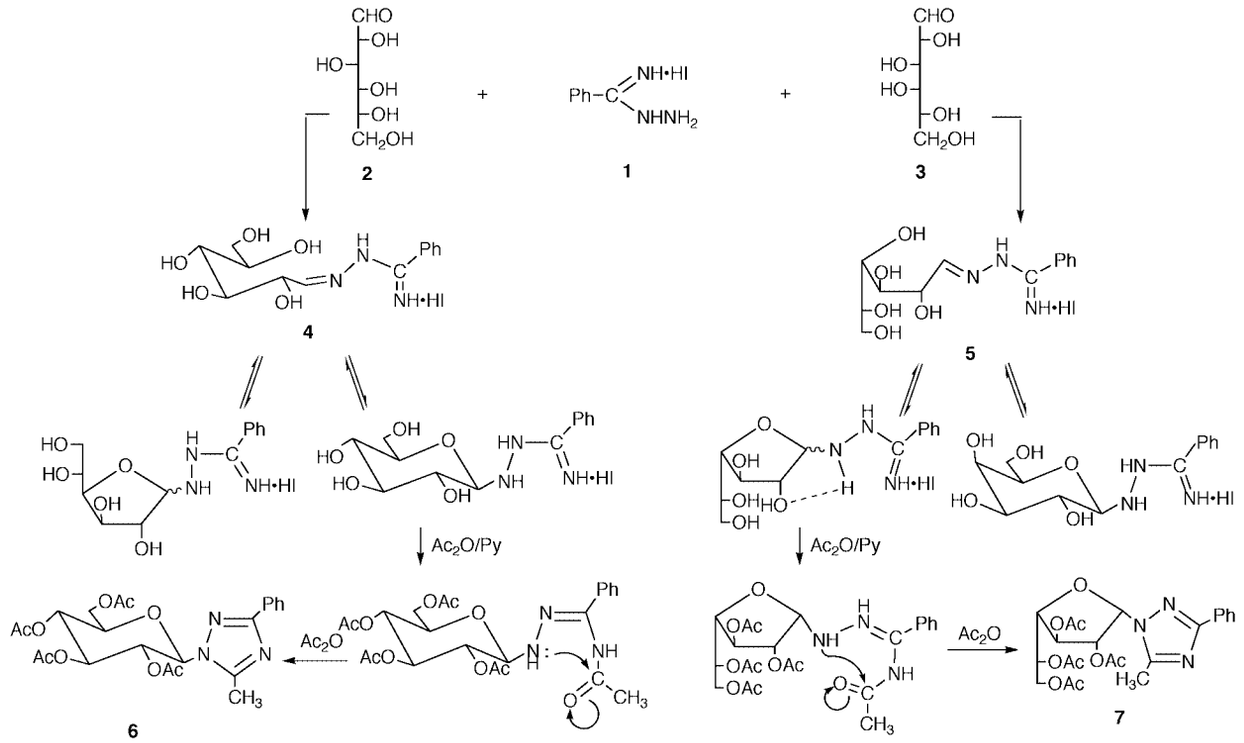
The cyclic natures of products **6** and **7** were readily realised from their mass spectra as well as their FABMS, which showed a molecular ion peak for **7** at *m*/*z* 489 and its protonated ion peak at *m*/*z* 490 for **6** and **7**. This was in agreement with their molecular formula ($C_{23}H_{27}N_3O_9$) as deduced from their elemental analysis. Furthermore, a fragmentation involving the fission of the triazole ring gave a fragment at *m*/*z* 331 corresponding to a cyclic sugar acetate.

Their ^{1}H NMR spectra were in accord with the cyclic structures, since there are only four signals corresponding to the four acetoxy groups in the downfield region at δ 1.82–2.11. The ^{1}H and ^{13}C NMR data (Experimental section) of **6** were consistent with the pyranose ring structure, namely 5-methyl-3-phenyl-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,4-triazole **6**. The assignment of the multiplet in the upfield region at δ 3.95–3.98 to H-5 (H-2, H-3 and H-4 resonated in a more downfield region) indicated that H-5 is linked to a carbon bearing the oxygen of the pyranose ring. Its ^{13}C NMR spectra showed a downfield shift of C-5 (δ_C 74.77) compared with those of C-2 (δ_C 69.79) and C-4 (δ_C 67.77) which further confirmed such a pyranosyl ring structure. Furthermore, the anomeric signals for H-1 at δ 5.56 and for C-1 at δ_C 83.94 are in accord with the existence of **6** in a cyclic structure rather than the corresponding acyclic one, which requires a signal at much

† Atomic coordinates and isotropic displacement parameters for compound **13** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/a9/a904200h/

DOI: 10.1039/a904200h

This journal is © The Royal Society of Chemistry 2000



Scheme 1

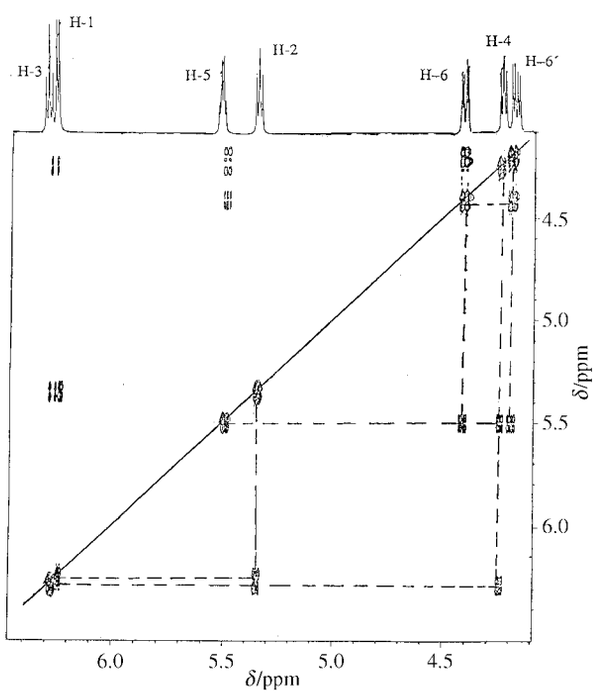


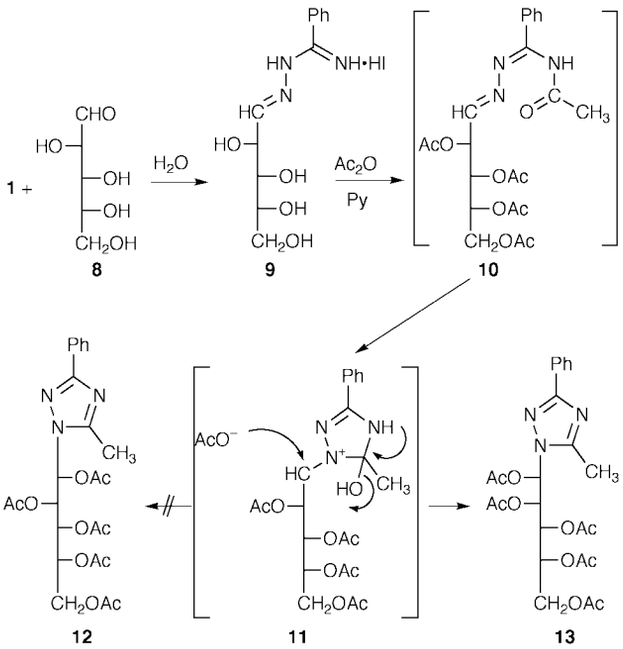
Fig. 1 ^{1}H–^{1}H DQFCOSY of compound **7**.

lower field. Its anomeric purity was apparent from its spectra, and its β-configuration could be readily deduced from the large coupling constant ($J_{1,2}$ 9.24 Hz) for the doublet of H-1 and from the chemical shift of C-1.

On the other hand, the product from D-galactose **3** was assigned the α-D-galactofuranoside structure **7**. The ^{1}H–^{1}H DQFCOSY and ^{1}H–^{13}C HMQC spectral data help in the assignment of both the proton and carbon signals. The galactofuranoside nature of **7** was established by the characteristic downfield shift of both C-4 (δ_C 78.20) and C-2 (δ_C 76.28), whereas C-3 and C-5 resonated at lower frequency (δ_C 72.27, 70.07). The ^{1}H–^{1}H DQFCOSY correlation (Fig. 1) of H-4 with both H-3 and H-5 led to its assignment as the doublet of doublets that resonated at the lower frequency region at δ 4.25, whereas H-3 and H-5 were shifted to the downfield region at δ 6.29 and 5.50, respectively, which was in accord with the furanoside ring system of **7**. The high value of $J_{1,2}$ (6.34 Hz) indicated a *cis* configuration of H-1 and H-2, since the *trans* configuration would require a smaller $J_{1,2}$-value.[30–34] The doublet of H-1 was correlated with the anomeric C-1 at δ_C 83.22 in its HMQC spectrum, which agreed with an α-configuration upon comparison with those of the acetyl derivatives of α- and β-D-galactofuranosyl nucleosides and related derivatives.[31–34]

The product **13**, obtained from D-arabinose **8**, showed in its mass spectrum a molecular-ion peak at *m/z* 519 agreeing with the molecular formula $C_{24}H_{29}N_3O_{10}$ obtained from its elemental analysis. No fragment ion for a cyclic sugar acetate was observed, but an acetoxy and acetoxyalkyl C-1–C-2 fission led to an ion at *m/z* 188 due to the formation of the ion 1-hydroxymethylium-5-methyl-3-phenyl-1*H*-1,2,4-triazole. Its ^{1}H NMR spectrum showed five signals in the range δ 2.07–2.16 for five acetoxy groups, indicating the acyclic nature of the sugar moiety. The ^{1}H and ^{13}C NMR spectra of **13** revealed the presence of only one isomer since only five groups of signals for both the protons and the carbons were found. Correlation of the ^{13}C chemical shifts with those of the attached protons was deduced from its ^{1}H–^{13}C HMQC spectrum. The assignment of C-1 at δ_C 74.99, C-4 at δ_C 67.88 and C-5 at δ_C 61.60, which are in lower frequency regions than expected for carbons in the furanose or pyranose ring structures, led us to rule out the ring structures whereas the unexpected seco (acyclo) nucleoside 5-methyl-1-(1,2,3,4,5-penta-*O*-acetyl-D-alditol-1-yl)-3-phenyl-1*H*-1,2,4-triazole was assigned as the product. The generation of a new asymmetric centre would, thus, be visible whereby the products possessing the D-*gluco*- **12** or D-*manno*- **13** configurations could be formed.

The observed large coupling-constant value for $J_{1,2}$ (9.28 Hz) for the product indicated an antiparallel disposition of H-1 and H-2 as in the conformer **13a** or **12b**. The latter one is a result of rotation about the C-1–C-2 bond in the D-*gluco* zig-zag conformation **12a** which has H-1 and H-2 in a *gauche* disposition but has a 1,3-interaction of the two acetoxy groups.



Scheme 2

This is a situation which is usually unfavorable in the conformational studies of acyclic free and partially or fully acetylated sugars which have in solution the polyhydroxyalkyl chain present in the favored extended planar zig-zag conformation; otherwise a bend or a sickle conformation[35] would be adopted, which would occur also in the crystalline state, and which may be tolerated even in the presence of a 1,3-parallel interaction.[36]

Considering the Newman projection of C-1–C-2 of the intermediate **11** (see Scheme 3), two possible nucleophilic attacks of the acetate anion could take place on C-1. The attack *via* route **i** would give the D-*gluco*-isomer **12** but it is sterically less favourable due to the presence of two bulky substituents on both sides. Moreover, the Newman projection of the product suffers from the presence of the four bulky groups in a *gauche* arrangement with each other. Rotation around the C-1–C-2 bond would remedy this situation to generate a conformer having the two acetoxy groups as well as C-3 and the triazole in *gauche* arrangements. On the other hand, the attack *via* route **ii** would take place from the less sterically hindered side to give the D-*manno* structure **13** with a favorable *gauche* arrangement of substituents.

However, confirmation of the assignment of the absolute configuration at C-1 in an unambiguous manner is required. Accordingly, this has been achieved from a single-crystal X-ray diffraction experiment. Single crystals of **13** were grown by slow evaporation of a chloroform solution. The crystallographic data for **13** are given in Table 1.‡ The structure was solved by direct methods using SHELX-97.[37] All atoms were located by Fourier and difference-Fourier synthesis. Anisotropic refinement was used for all non-hydrogen-atoms; hydrogen atoms were refined isotropically. The final refinement on F^2 converged to the R indices are given in Table 1. Selected bond lengths and angles, and torsional angles, as key conformational parameters, are given in Table 2. The final coordinates of C-, O- and N-atoms are listed in Table S1 as supplementary material.

The crystallographic perspective drawing (Fig. 2) shows that the structure of the product in the solid state is in full accord with the acyclic structure **13** present in the extended planar zig-zag conformation, free from any 1,3-interactions and having both H-1 and H-2, as well as H-3 and H-4, in an antiparallel

‡ CCDC reference number 207/385.

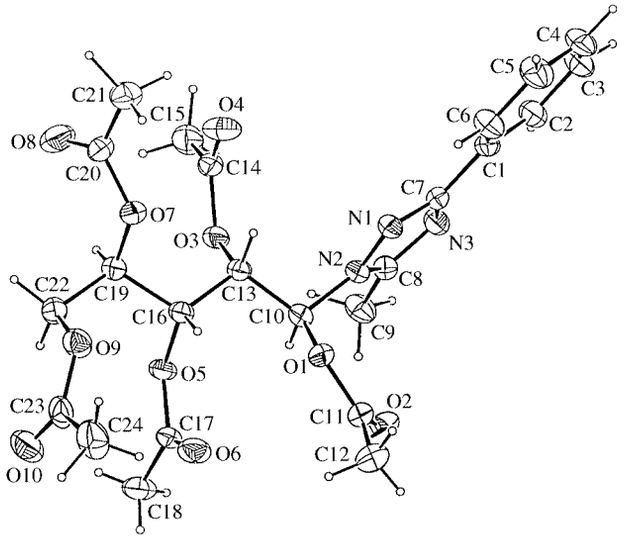


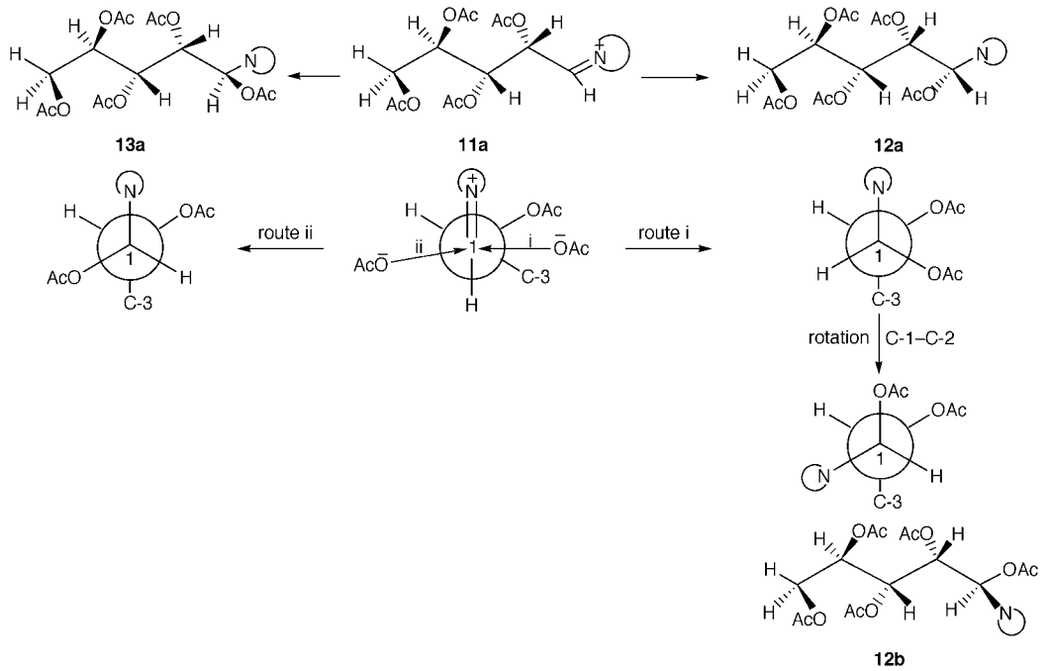
Fig. 2 ORTEP representation of 5-methyl-1-(1,2,3,4,5-penta-*O*-acetyl-D-*manno*-pentitol-1-yl)-3-phenyl-1*H*-1,2,4-triazole **13**, with crystallographic numbering scheme.

Table 1 Crystallographic data and structure refinement for **13**

Crystal data	
Chemical formula	$C_{24}H_{29}N_3O_{10}$
Formula weight	519.50
Crystal size	0.4 × 0.3 × 0.3 mm
Crystal system	Monoclinic
Unit-cell dimensions	
(a, b, c/Å)	10.519(3), 9.8910(10), 13.385(5)
(α, β, γ/deg)	90, 112.120(10), 90
Space group	$P2_1$
Unit-cell volume (Å^3)	1290.1(6)
Z (formulae/cell)	2
Absorption coefficient (μ/mm^{-1})	0.105
Data collection	
Wavelength (Å)	0.710 69
Temperature (K)	183(2)
Independent reflections	5055 [R(int) = 0.0149]
Observed reflections [$I > 2\sigma(I)$]	4555
Refinement	
Final R-indices [$I > 2\sigma(I)$]	$R_1 = 0.0348$, w$R_2 = 0.0773$
R-indices (all data)	$R_1 = 0.0419$, w$R_2 = 0.0813$

disposition whereas both pairs H-2, H-3 and H-4, H-5 are in a *gauche* disposition, which findings are in agreement with the observed coupling constants. The average value of $J_{4,5'}$ (4.75 Hz), which is small for an antiperiplanar disposition of these protons, required a rotation along the C-4–C-5 bond, so that H-5′ will be an extension of the planar zig-zag conformation (Fig. 2) . The triazole ring in **13** is not coplanar with the sugar moiety but is coplanar with the phenyl group. Therefore, from the spectroscopic data as well as from the X-ray crystallographic study, compound **13** exists in the D-*manno* structure, namely 5-methyl-1-(1,2,3,4,5-penta-*O*-acetyl-D-*manno*-pentitol-1-yl)-3-phenyl-1*H*-1,2,4-triazole **13**.

In order to account for the formation of products of different structures from different sugars, the equilibria of sugars in their aqueous solutions can be considered. The pyranoid ring compounds with equatorial hydroxy groups may fit tightly into water and be stabilised by hydrogen bonding more than those with the axial OH groups[38–43] as in D-glucose **2**. Considering this hypothesis, the reaction of benzamidrazone **1** with **2** afforded the stable β-D-glucopyranosyl derivative **4** which may be present in equilibrium with the other forms in solution and that upon acetylation afforded the cyclic nucleoside **6** as the isolated product (Scheme 1).



Scheme 3

Table 2 Selected bond lengths (Å), angles (deg) and torsion angles (deg) for **13**

N(1)–N(2)	1.369(2)	C(7)–N(1)–N(2)–C(8)	−0.72(18)
N(2)–C(8)	1.348(2)	C(7)–N(1)–N(2)–C(10)	178.33(15)
N(2)–C(10)	1.455(2)	N(2)–N(1)–C(7)–N(3)	0.7(2)
N(3)–C(8)	1.323(2)	N(2)–N(1)–C(7)–C(1)	179.65(15)
N(3)–C(7)	1.367(2)	C(8)–N(3)–C(7)–N(1)	−0.3(2)
C(10)–C(13)	1.521(2)	C(8)–N(3)–C(7)–C(1)	−179.35(16)
C(11)–C(12)	1.479(3)	C(6)–C(1)–C(7)–N(1)	3.4(3)
C(13)–C(16)	1.522(2)	C(2)–C(1)–C(7)–N(1)	−174.96(17)
C(14)–C(15)	1.482(3)	C(6)–C(1)–C(7)–N(3)	−177.68(18)
C(16)–C(19)	1.529(20)	C(2)–C(1)–C(7)–N(3)	4.0(3)
C(17)–C(18)	1.485(3)	C(7)–N(3)–C(8)–N(2)	−0.1(2)
C(19)–C(22)	1.512(3)	C(7)–N(3)–C(8)–C(9)	179.13(19)
C(23)–C(24)	1.477(3)		
		N(1)–N(2)–C(8)–N(3)	0.6(2)
C(7)–N(1)–N(2)	102.00(14)	C(10)–N(2)–C(8)–N(3)	−178.39(16)
C(8)–N(2)–N(1)	110.46(14)	N(1)–N(2)–C(8)–C(9)	−178.74(18)
C(8)–N(2)–C(10)	128.78(15)	C(10)–N(2)–C(8)–C(9)	2.3(3)
N(1)–N(2)–C(10)	120.76(14)	C(11)–O(1)–C(10)–N(2)	−79.22(18)
C(8)–N(3)–C(7)	103.67(15)	C(11)–O(1)–C(10)–C(13)	160.11(14)
N(1)–C(7)–N(3)	114.60(15)	C(8)–N(2)–C(10)–O(1)	126.15(18)
N(3)–C(7)–C(1)	122.50(16)	N(1)–N(2)–C(10)–O(1)	−52.8(2)
N(3)–C(8)–N(2)	109.27(15)	C(8)–N(2)–C(10)–C(13)	−115.31(19)
N(3)–C(8)–C(9)	126.80(17)	N(1)–N(2)–C(10)–C(13)	65.8(2)
N(2)–C(8)–C(9)	123.93(17)	C(14)–O(3)–C(13)–C(10)	−125.45(15)
O(1)–C(10)–N(2)	110.70(14)	C(14)–O(3)–C(13)–C(16)	112.69(16)
O(1)–C(10)–C(13)	107.14(14)	O(1)–C(10)–C(13)–O(3)	−173.10(13)
N(2)–C(10)–C(13)	110.68(14)	N(2)–C(10)–C(13)–O(3)	66.12(17)
O(1)–C(10)–H(101)	111.3(11)	O(1)–C(10)–C(13)–C(16)	−53.14(18)
N(2)–C(10)–H(101)	106.0(11)	N(2)–C(10)–C(13)–C(16)	−173.92(14)
C(13)–C(10)–H(101)	111.0(11)	C(17)–O(5)–C(16)–C(13)	120.78(16)
O(3)–C(13)–C(10)	104.48(14)	C(17)–O(5)–C(16)–C(19)	−117.22(16)
O(3)–C(13)–C(16)	110.27(14)	O(3)–C(13)–C(16)–O(5)	63.90(17)
C(10)–C(13)–C(16)	113.12(14)	C(10)–C(13)–C(16)–O(5)	−52.69(19)
O(3)–C(13)–H(131)	110.4(10)	O(3)–C(13)–C(16)–C(19)	−54.19(19)
C(10)–C(13)–H(131)	110.6(10)	C(10)–C(13)–C(16)–C(19)	−170.78(14)
C(16)–C(13)–H(131)	107.9(10)	C(20)–O(7)–C(19)–C(22)	−91.35(18)
O(5)–C(16)–C(13)	109.36(14)	C(20)–O(7)–C(19)–C(16)	146.11(15)
O(5)–C(16)–C(19)	106.35(13)	O(5)–C(16)–C(19)–O(7)	177.79(13)
C(13)–C(16)–C(19)	112.73(14)	C(13)–C(16)–C(19)–O(7)	−62.37(18)
O(5)–C(16)–H(161)	109.0(11)	O(5)–C(16)–C(19)–C(22)	57.31(19)
C(13)–C(16)–H(161)	108.8(10)	C(13)–C(16)–C(19)–C(22)	177.15(16)
C(19)–C(16)–H(161)	110.5(10)	O(7)–C(19)–C(22)–O(9)	−62.00(19)
O(7)–C(19)–C(22)	110.12(15)	C(16)–C(19)–C(22)–O(9)	55.8(2)
O(7)–C(19)–C(16)	105.40(13)		
C(22)–C(19)–C(16)	113.30(15)		
O(7)–C(19)–H(191)	111.4(13)		
C(22)–C(19)–H(191)	103.7(12)		
C(16)–C(19)–H(191)	113.1(12)		

On the other hand, D-galactose tends to exist in both pyranose and furanose forms in water, where the proportion of the galactofuranose structure is increased because it permits the attachment of all the large groups in alternate *trans* positions on the ring.[43] Its proportion was increased in DMSO solution[43] whereas in pyridine it lies between the value in aqueous solution and that in DMSO.[43,44] Since the acetylation of sugars was carried out in pyridine as solvent and catalyst, the esterification reaction proceeds faster than ring–chain interconversion and consequently the main product is the respective furanosyl derivative. Sugars with a relatively stable furanose ring give more complex mixture of acetates whereby galactose gives appreciable proportions of the furanose acetate. Therefore, the formation of the galactofuranosyl derivative 5-methyl-3-phenyl-1-(2,3,5,6-tetra-*O*-acetyl-α-D-galactofuranosyl)-1*H*-1,2,4-triazole **7** would be acceptable. The formation of the α-anomer may be attributed to formation of a hydrogen bond between the C-2 OH and the C-1 NH in a *cis* configuration. The formation of the galactofuranosyl nucleoside **7** as well as the acyclic D-*manno*-alditol nucleoside **13** were contrary to the outcome of the reaction of aminoguanidine with D-galactose and L-arabinose.[10]

Experimental

Mps were determined on a Mel-temp apparatus and are uncorrected. IR spectra were recorded with a Unicam SP 1025 spectrometer. Mass spectra were recorded using electron ionisation (EI) on a Finnigan MAT 312 spectrometer and fast-atom-bombardment (FAB) on a Kratos MS 50 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AC 250 MHz or a Bruker Avance DRX 600 MHz spectrometer. The chemical shifts are expressed on the δ-scale using Me_4Si as a standard, and coupling-constant values are given in Hz. The assignments of ^{1}H NMR spectra were based on chemical-shift correlation (DQFCOSY) spectra. The assignment of ^{13}C NMR spectra was based on carbon–proton shift-correlation spectra (HMQC) and (HMBC). The X-ray structure determination was performed at 183 K. The relevant options of the SHELX-97 program[37] were used for calculation of geometrical parameters. TLC was performed on Merck Silica Gel 60F254 with detection by charring in sulfuric acid and by UV light. Microanalyses were performed in the Microanalysis Unit at Faculty of Science, Alexandria University.

Reaction of benzamidrazone hydroiodide[22] 1 with aldoses

A solution of an aldose **2**, **3** or **8** (2.6 mmol) in water (5.0 ml) was treated with **1** (2.6 mmol). The reaction mixture was heated on a water-bath for 5–15 min, whereby a dark solution was obtained. The resulting solution was evaporated under reduced pressure to give a syrupy residue which was used without purification in the next step.

Acetylation of benzamidrazone derivatives

General method. The syrupy residue from above was dissolved in pyridine (5.0 ml), then the mixture was cooled to 0 °C and acetic anhydride (5.0 ml) was added. The reaction mixture was left at room temperature for 48 h, and then poured into ice-cold water.

5-Methyl-3-phenyl-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,4-triazole 6. The above solution (from **2**) was extracted with chloroform, and the extract was washed well with water, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure. The resulting syrup was crystallised from absolute ethanol to give **6** as *white crystals* (0.58 g, 46%); mp 213–215 °C; ν_{max} (KBr)/cm^{-1} 1747 (OAc); δ_H ($CDCl_3$) 1.85, 2.05, 2.07, 2.08 (4 s, 12 H, 4 × Ac), 2.60 (s, 3H, Me), 3.95–3.98 (m, 1H, H-5), 4.19 (dd, 1H, $J_{5,6'}$, 2.82, $J_{6,6'}$, 12.55 Hz, H′-6), 4.30 (dd, 1H, $J_{5,6}$ 4.96 Hz, H-6), 5.29 (t, 1H, $J_{4,5}$, 9.80 Hz, H-4), 5.41 (t, 1H, $J_{3,4}$ 9.51 Hz, H-3), 5.56 (d, 1H, $J_{1,2}$ 9.24, H-1), 5.83 (t, 1H, $J_{2,3}$ 9.40 Hz, H-2), 7.39–7.41 (m, 3H, Ph), 8.06 (d, 2H, Ph); δ_C ($CDCl_3$) 12.15 (Me), 20.33, 20.55, 20.66 (Ac), 61.71 (C-6), 67.77 (C-4), 69.79 (C-2), 73.11 (C-3), 74.77 (C-5), 83.94 (C-1), 126.40, 128.53, 129.45, 130.31 (Ph), 154.58 (C-5′), 161.11 (C-3′), 168.66, 169.26, 170.26, 170.50 (C=O); FABMS ($CHCl_3$–MNBA) *m*/*z* (%) 490 (29, $MH^{\bullet+}$), 331 (9, $M^{\bullet+}$ − B), 160 (35, BH^+) (Found: C, 55.97; H, 5.41; N, 8.26. $C_{23}H_{27}N_3O_9$ requires C, 56.43; H, 5.56; N, 8.58%).

5-Methyl-3-phenyl-1-(2,3,5,6-tetra-*O*-acetyl-α-D-galactofuranosyl)-1*H*-1,2,4-triazole 7. The solid product that precipitated after the acetylation (of **3**) was filtered off, washed well with water, dried and crystallised from ethanol to give **7** as *white crystals* (0.63 g, 50%); mp 178–180 °C; ν_{max} (KBr)/cm^{-1} 1762 (OAc); δ_H ($CDCl_3$) 1.82, 2.00, 2.04, 2.11 (4 s, 12H, 4 × Ac), 2.53 (s, 3H, Me), 4.21 (dd, 1H, $J_{5,6'}$ 5.60, $J_{6,6'}$ 12.11 Hz, H′-6), 4.25 (dd, 1H, $J_{4,5}$ 5.89 Hz, H-4), 4.42 (dd, 1H, $J_{5,6}$ 4.30 Hz, H-6), 5.36 (t, 1H, $J_{2,3}$ 7.42 Hz, H-2), 5.49–5.50 (m, 1H, H-5), 6.24 (d, 1H, $J_{1,2}$ 6.34, H-1), 6.29 (t, 1H, $J_{3,4}$ 7.69 Hz, H-3), 7.40–7.44 (m, 3H, Ph), 8.11 (d, 2H, Ph); δ_C ($CDCl_3$) 11.99 (Me), 20.09, 20.72 (Ac), 62.08, (C-6), 70.07 (C-5), 72.27 (C-3), 76.28 (C-2), 78.20 (C-4), 83.22 (C-1), 126.67, 128.66, 129.40, 130.70 (Ph), 154.52 (C-5′), 161.48 (C-3′), 169.88, 170.36 (C=O); FABMS ($CHCl_3$–MNBA) *m*/*z* (%) 490 (44, $MH^{\bullet+}$), 331 (5, $M^{\bullet+}$ − B); MS *m*/*z* (%) 489 (14, $M^{\bullet+}$), 446 (3, $M^{\bullet+}$ − Ac), 430 (4, $M^{\bullet+}$ − AcO), 387 (7, 430 − Ac), 331 (14, $M^{\bullet+}$ − B), 169 (100), 160 (28, BH^+) 127 (28), 109 (28) (Found: C, 56.43; H, 5.66; N, 8.59%).

5-Methyl-1-(1,2,3,4,5-penta-*O*-acetyl-D-*manno*-pentitol-1-yl)-3-phenyl-1*H*-1,2,4-triazole 13. The solution obtained from the acetylation of **8** was extracted with chloroform, and the extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness, and the syrup obtained was crystallised from absolute ethanol to give **13** as *white crystals* (0.54 g, 40%); mp 187–188 °C; ν_{max} (KBr)/cm^{-1} 1756 (OAc); δ_H ($CDCl_3$) 2.07, 2.11, 2.14, 2.15, 2.16 (5 s, 15H, 5 × Ac), 2.62 (s, 3H, Me), 4.13 (dd, 1H, $J_{4,5'}$ 4.75, $J_{5,5'}$ 12.62 Hz, H′-5), 4.27 (dd, 1H, $J_{4,5}$ 2.77 Hz, H-5), 5.06–5.08 (m, 1H, H-4), 5.67 (dd, 1H, $J_{3,4}$ 9.22 Hz, H-3), 6.15 (dd, 1H, $J_{2,3}$ 2.14 Hz, H-2), 6.50 (d, 1H, $J_{1,2}$ 9.28, H-1), 7.36–7.42 (m, 3H, Ph), 8.03 (d, 2H, Ph); δ_C ($CDCl_3$) 11.86 (Me), 19.95, 20.52, 20.56, 20.65, 20.91 (Ac), 61.60, (C-5), 67.56 (C-3), 67.88 (C-4), 68.86 (C-2), 74.99 (C-1), 126.58, 128.52, 129.47, 130.43 (Ph), 155.08 (C-5′), 162.03 (C-3′), 167.93, 169.27, 169.53, 169.96, 170.52 (C=O); MS *m*/*z* (%) 519 (64, $M^{\bullet+}$), 476 (3, $M^{\bullet+}$ − Ac), 460 (17, $M^{\bullet+}$ − AcO), 417 (10, 460 − Ac), 400 (16, 460 − AcOH), 358 (20, 400 − C_2H_2O), 259 (20), 201 (12), 188 (22, BC^+HOH), 159 (100, B^+), 139 (15) (Found: C, 55.41; H, 5.65; N, 8.34. $C_{24}H_{29}N_3O_{10}$ requires C, 55.48; H, 5.62; N, 8.08%).

Acknowledgements

We thank Professor Dr R. R. Schmidt for making available some of the spectral measurements at Konstanz University. Thanks are also due to Dr Armin Geyer for measuring the NMR spectra and to Mr Klaus Hägele for measuring the mass spectra. The support from the Alexander von Humboldt foundation is highly appreciated.

References

1 M. C. Hosur, M. B. Talawar, R. S. Bennur, S. C. Bennur and P. A. Patil, *Indian J. Pharm. Sci.*, 1993, **55**, 86.

2 M. Tokizawa, S. Takeda, Y. Kaneko, H. Eto, K. Ishida, K. Maebashi, M. Matsumoto, T. Asaska, S. Susumu and H. Matsuda, *Eur. Pat. Appl. EP* 1997, 780 380 (*Chem. Abstr.*, 1997, **127**, 121738w); S. Oida, T. Tanaka, W. Tajima, T. Kounosu, A. Somaki, T. Miyaoka and H. Yasuda, *Jpn. Kokai Tokkyo Koho JP*, 1998, 10 158167 (*Chem. Abstr.*, 1998, **129**, 117825w).

3 Y. Yang, W. Lu and Y. Shi, *Huaxue Tongbao*, 1996, **10**, 6 (*Chem. Abstr.*, 1997, **126**, 31291v); A. S. Bell, M. J. Fray, A. P. Marchington, K. Richardson, P. T. Stephenson and P. J. Whittle, *PCT Int. Appl. WO* 1997, 97 01552 (*Chem. Abstr.*, 1997, **126**, 186093f).
4 J. B. Camden, *PCT Int. Appl. WO* 1996, 96 40119 (*Chem. Abstr.*, 1997, **126**, 126894h).
5 V. V. Dunaev, I. F. Belenichev, S. I. Kevalenko, I. V. Bashkin, N. A. Avramenko, I. A. Mazur, E. G. Knysh and V. S. Tishkin, *Ukr. Biokhim. Zh.*, 1996, **68**, 100 (*Chem. Abstr.*, 1997, **126**, 84546p).
6 G. Wagner, G. Valz, B. Dietzsch and G. Fischer, *Pharmazie*, 1974, **29**, 90.
7 J. C. Rius and F. Gomes de las Heras Maestro, *Span. ES*, 1982, 502989 (*Chem. Abstr.*, 1983, **98**, 179832w).
8 H. M. Chem, J. Zhang, J. M. Mao and M. S. Cai, *Gaodeng Huexiao Huaxue Xuebao*, 1994, **15**, 705 (*Chem. Abstr.*, 1994, **121**, 231255v); *Chem. Res. Chin.Univ.*, 1996, **12**, 258 (*Chem. Abstr.*, 1996, **125**, 329263d).
9 N. A. Al Masoudi, F. B. Issa and U. A. Al Timari, *Bull. Soc. Chim. Belg.*, 1997, **106**, 215.
10 Z. Györgydeák, W. Holzer and J. Thiem, *Carbohydr. Res.*, 1997, **302**, 229.
11 H. Kristen, I. Meerwald and A. Börner, *Pharmazie*, 1986, **41**, 551.
12 E. S. H. El Ashry and Y. El Kilany, *Adv. Heterocycl. Chem.*, 1996, **67**, 391; 1997, **68**, 1; 1998, **69**, 129.
13 T. H. Dinh, J. Igolen, E. Bisagni, J. P. Marquet and A. Civier, *J. Chem. Soc., Perkin Trans. 1*, 1979, 761.
14 M. S. Poonian and E. F. Nowoswiat, *J. Org. Chem.*, 1977, **42**, 1109.
15 T. Vanek, J. Frakas and J. Gut, *Collect. Czech. Chem. Commun.*, 1979, **44**, 1334.
16 L. F. Awad and E. S. H. El Ashry, *Carbohydr. Res.*, 1998, **312**, 9.
17 J. T. Witkowski, R. K. Robins, R. W. Sidwell and L. N. Simon, *J. Med. Chem.*, 1972, **15**, 1150.
18 D. G. Neilson, R. Roger, J. W. M. Heatle and L. R. Newlands, *Chem. Rev.*, 1970, **70**, 151.
19 N. V. Sidgwick, *The Organic Chemistry of Nitrogen compounds*, Clarendon Press, Oxford, 3rd edn., 1966, p. 529.
20 E. Lieber and G. B. L. Smith, *Chem. Rev.*, 1939, **25**, 213; F. Kurzer and L. E. A. Godfrey, *Chem. Ind.* (*London*), 1962, 1584; E. Lieber and G. B. L. Smith, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 459.
21 R. L. Shriner and F. W. Neumann, *Chem. Rev.*, 1944, **35**, 351; R. Roger and D. G. Neilson, *Chem. Rev.*, 1961, **61**, 179, 193.
22 K. M. Doyle and F. Kurzer, *Synthesis*, 1974, 583.
23 M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, 1954, 3319; D. Jerchel and R. Kuhn, *Justus Liebigs Ann. Chem.*, 1950, **568**, 191; M. Regitz and B. Eistert, *Chem. Ber.*, 1963, **96**, 1321; H. Stetter, R. Engl and H. Rauhut, *Chem. Ber.*, 1959, **92**, 1184.
24 L. Mester, *Dérivés Hydraziniques des Glucides*, Hermann, Paris, 1967.
25 H. Simon and K. Kraus, *Fortschr. Chem. Forsch.*, 1970, **14**, 430.
26 J. M. Williams, *Carbohydr. Res.*, 1983, **117**, 89.
27 L. Szilágyi, Z. Györgydeák and H. Duddeck, *Carbohydr. Res.*, 1986, **158**, 67.
28 H. J. Tweeddal and J. W. Redmond, *J. Carbohydr. Chem.*, 1998, **17**, 27.
29 J. Hirsch, E. Petrakova, M. S. Feather and C. L. Barnes, *Carbohydr. Res.*, 1995, **267**, 17.
30 D. R. Bundle and R. U. Lemieux, *Methods Carbohydr. Chem.*, 1976, **7**, 79.
31 L. V. Backinowsky, S. A. Nepogod'Ev, A. S. Shashkov and N. K. Kochetkov, *Carbohydr. Res.*, 1984, **138**, 41.
32 O. Varela, C. Marino and R. M. de Lederkremer, *Carbohydr. Res.*, 1986, **155**, 247; C. Marino, M. J. Cancio, O. Varela and R. M. de Lederkremer, *Carbohydr. Res.*, 1995, **276**, 209; G. Gallo-Rodriguez, O. Varela and R. M. de Lederkremer, *Carbohydr. Res.*, 1998, **305**, 163.
33 W. C. Kett, M. Batley and J. W. Redmond, *Carbohydr. Res.*, 1997, **299**, 129.
34 A. K. Choudhury and N. Roy, *Carbohydr. Res.*, 1998, **308**, 207.
35 D. Horton and J. D. Wander, *J. Org. Chem.*, 1974, **39**, 1859; D. Horton and O. Varela, *Carbohydr. Res.*, 1998, **308**, 85.
36 P. Köll, M. Bischoff, C. Bretzke and J. Kopf, *Carbohydr. Res.*, 1994, **262**, 1; J. Kopf, M. Morf, B. Hagen, M. Bischoff and P. Köll, *Carbohydr. Res.*, 1994, **262**, 9; P. Köll and J. Kopf, *Aust. J. Chem.*, 1996, **49**, 391; P. Köll, R. Bruns and J. Kopf, *Carbohydr. Res.*, 1998, **305**, 147.
37 G. M. Sheldrick, SHELX-97, *Crystal Structure Refinement*, University of Göttingen, Germany, 1997.
38 M. A. Kabayama and D. Patterson, *Can. J. Chem.*, 1958, **36**, 563.
39 A. Suggett, *J. Solution Chem.*, 1976, **5**, 33.
40 J. M. Harvey and M. C. R. Symons, *J. Solution Chem.*, 1978, **7**, 571.
41 S. Bociek and F. Franks, *J. Chem. Soc., Faraday Trans. 1*, 1979, **75**, 262.
42 R. J. Abraham, E. J. Chambers and W. A. Thomas, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1061.
43 S. J. Angyal, *Carbohydr. Res.*, 1994, **263**, 1.
44 S. J. Angyal, *Adv. Carbohydr. Chem. Biochem.*, 1984, **42**, 15; 1991, **49**, 19.

Paper a904200h