Synthesis and Characterization of some Heterocyclic Derivatives from 1,2:3,4-Di-*O*-isopropylidene-α-D-galacto-1,6-hexadialdo-1,5-pyranose Oxime

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We report the synthesis of 5-[5'-(1',2':3',4'-di-*O*-isopropylidene-β-L-arabinopyranosyl)]tetrazole, from 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose oxime *via* 1,2:3,4-di-*O*-isopropylidene-α-D-galacturononitrile as intermediate by 1,3-dipolar cycloaddition. We also report the synthesis of 5-methyl- and 5-phenyl-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-β-L-arabinopyranosyl)]-1,3,4-oxadiazole from the tetrazole derivative.

The physical and spectroscopic characterizations of the heterocyclic derivatives as well as the intermediate nitrile and the principal byproduct are described and we discuss its possible formation pathway. We present the preferential conformation in solution using computational calculation and spectroscopic data.

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The synthesis of heterocyclic rings containing nitrogen atoms such as the tetrazole ring is of considerable interest in medicinal chemistry [1,2]. Some tetrazole derivatives have been prepared from carbohydrates and they have been used as glycosidases inhibitors [3-6]. On the other hand, the ring containing nitrogen and oxygen atoms, such as the oxadiazole derivatives, possess interesting antifungal and antibacterial activities [7,8].

In previous work [9], we reported the preparation of heterocyclic rings containing nitrogen and sulfur from

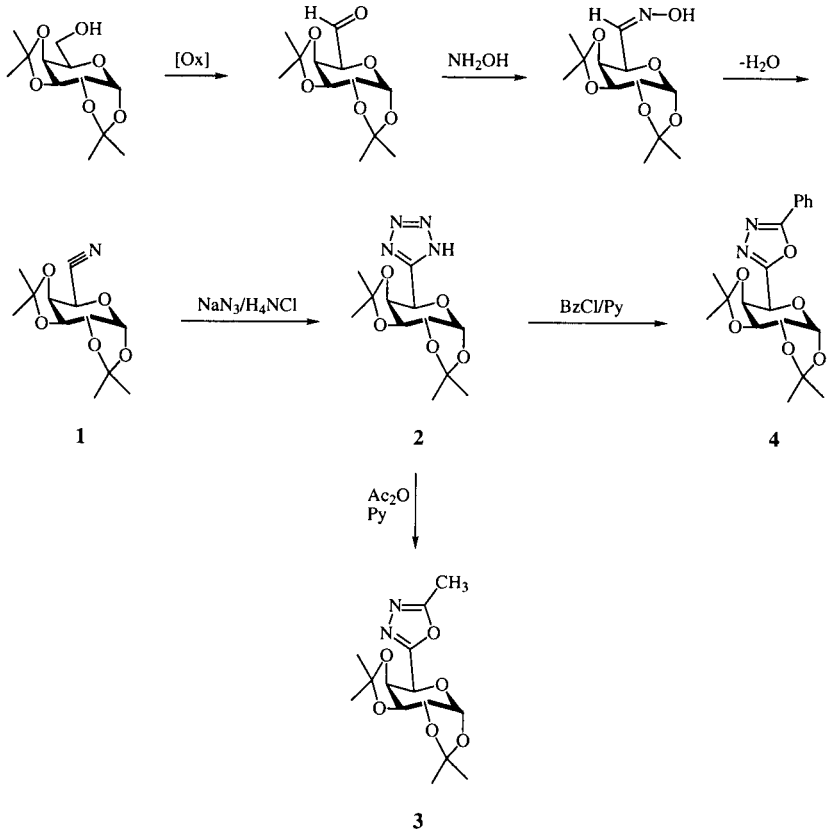

Figure 1

1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose thiosemicarbazone. In this paper we wish to report the synthesis of a tetrazole derivative from 1,2:3,4-di-*O*-isopropylidene-α-D-galacturononitrile by 1,3-dipolar cycloaddition [10], and the tetrazole conversion into 5-methyl- and 5-phenyl-1,3,4-oxadiazole derivatives by treatment with an acylating mixture, under a condition similar to that which we have described for other carbohydrate derivatives [11].

Reaction of 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose [12] with hydroxylamine hydrochloride in pyridine yielded 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose oxime [13]. When the oxime derivative was treated with an acylating mixture in basic media (see Experimental), we obtained 1,2:3,4-di-*O*-isopropylidene-α-D-galacturononitrile (**1**). The reaction of **1** with sodium azide and ammonium chloride in dimethylformamide gave the 5-[5'-(1',2':3',4'-di-*O*-isopropylidene-β-L-arabinopyranosyl)]-tetrazole (**2**) in good yield. Treatment of compound **2** with acetic anhydride afforded 5-methyl-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-β-L-arabinopyranosyl)]-1,3,4-oxadiazole (**3**). When we used benzoyl chloride in pyridine we obtained the 5-phenyl-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-β-L-arabinopyranosyl)]-1,3,4-oxadiazole (**4**).

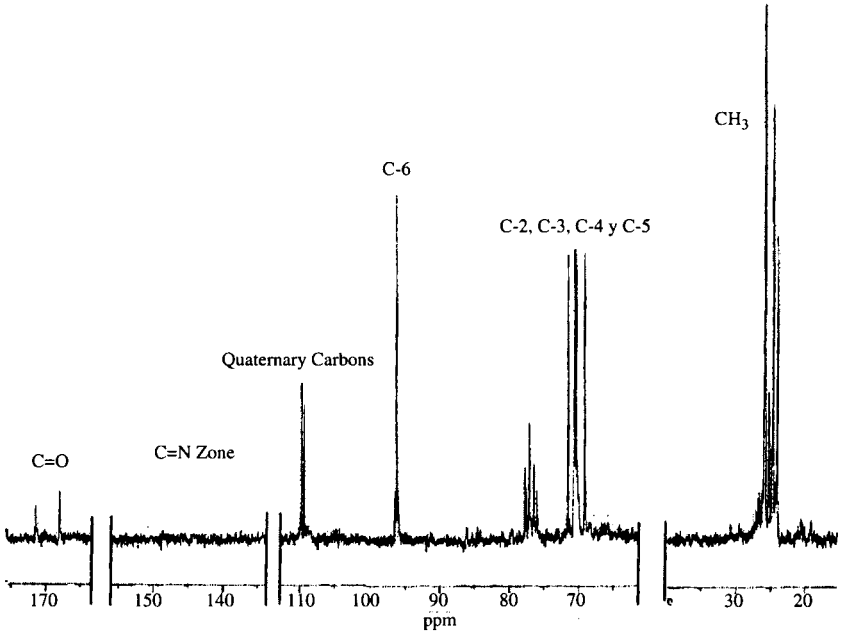

Figure 2

The synthesis of nitrile **1** was accomplished using two different acylating media: **a**, acetic anhydride/pyridine and **b**, benzoyl chloride/pyridine. The application of procedure **a** permits us to eliminate easily all excess reagents and the acid formed during the process by evaporation under diminished pressure, meanwhile in procedure **b** the excess reagents are destroyed by addition of water, with solid benzoic acid remaining providing impure compound **1**. Therefore procedure **a** is the procedure of choice. When procedure **a** was used with 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose oxime, we obtained product **5** in addition to nitrile **1** before all oxime was consumed. Since an *O*-acetylated oxime is considered as a nitrile precursor [14], we suspected that **5** was an acetylated oxime.

Examination of the ionization mass spectrum by positive fast atom bombardment we found a base peak at m/z 316 $(M+H)^+$, which corresponds to a relative molecular mass of 315 as is expected for the acylated oxime. However, when we analyzed the nmr spectra we found that, in the ^1H nmr spectrum, the signal corresponding to H-5 of pyranose ring is a doublet, instead of a double doublet as expected for the proposed structure. In the ^{13}C nmr spectrum there is not any signal which indicates the presence of a carbon-nitrogen double bond. On the other hand, we did not observe the classical mixture of *syn-anti* isomers, typical in this type of a nitrogen derivative, therefore we propose a different structure for compound **5**, where there is not an hydrogen atom on C-6 of the pyranose structure.

The 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose was used without further purification, so it could be supposed that the imide **5** was a direct consequence of an over oxidization, however, it could not arise from a carboxylic acid. Indeed, if it was formed, the resulting carboxylic acid should arise the corresponding salt with pyridine in excess or with the hydroxylamine, thus, compound **5** must be derived from compound **1**.

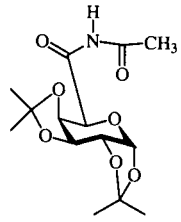

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Figure 3

Hydrolysis of nitriles to amides is a common process, but in all cases, water must be present. During the synthesis of the nitrile a large quantity of acetic acid is produced, and we might propose an addition of this reagent to the nitrile. This addition would be in contradiction with the normal dissociation of acetic acid, since the normal attack to a nitrile involves a protonation of nitrogen followed by an acylation of the carbon in a Ritter type reaction [15].

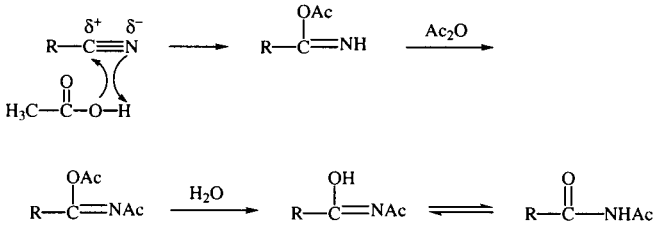


Figure 4

All these reactions are described in acid media or in presence of a Lewis acid, but in our case, the reaction was carried out with a large excess of pyridine. This fact considering the absence of water led us to propose an alternative way of degradation involving acetic anhydride itself.

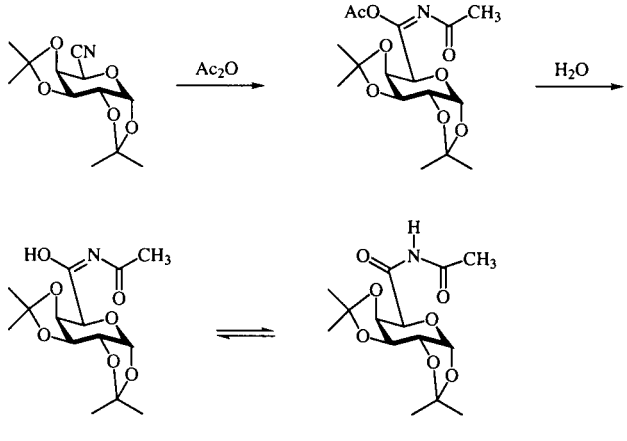


Figure 5

As it is shown in Figure 5, compound **5** would be a result of hydrolysis of an adduct during the isolation process. Independent of all speculations, formation of **5** indicates that while the oxime did not completely react, the nitrile is lost by hydrolysis to an adduct, a precursor of **5**, therefore an alternative synthesis must be used.

Procedure **b** which involves the treatment with benzoyl chloride, led us to obtain the compound **1** contaminated with benzoic acid generated by decomposition of the benzoyl chloride, but a further purification gave compound **1** in good yield.

The ^{1}H nmr spectra of compounds **1-5** was performed at 200 MHz and permitted a first order analysis, but we made some spectra simulations [16] in order to confirm these assignments. We found good correlation between the experimental and the simulated spectra. In Tables 1 and 2 we present the chemical shifts and coupling constants, respectively.

Table 1

^{1}H NMR Chemical Shifts (δ) and Multiplicities for Compounds **1** to **5**, Measured at 200 MHz in Deuteriochloroform

Compound	H-1	H-2	H-3	H-4	H-5
1	5.53	4.38	4.64	4.34	4.65
	d	m	m	m	m
5	5.09	4.40	4.70	4.64	4.35
	d	dd	dd	dd	d
	H-1'	H-2'	H-3'	H-4'	H-5'
2	5.71	4.56	4.79	4.60	5.25
	d	m	dd	m	d
3	5.68	4.43	4.73	4.56	5.19
	d	dd	dd	dd	d
4	5.72	4.47	4.77	4.60	5.31
	d	dd	dd	dd	d

Table 2

Measured Coupling Constants (Hz) for Compound **2** to **5**

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
1	4.9	2.8	7.6	2.2
5	4.8	2.2	7.8	2.0
Compound	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$
2	4.9	2.5	7.7	1.5
3	4.9	2.7	7.6	2.2
4	4.9	2.7	7.6	2.2

The main conformation in solution for the carbohydrate moiety is the same as that which we described for other related heterocycles [17]. The pyranose rings of compounds **1-5** are in a twisted boat conformation ($^OT_2$), and are influenced only slightly by changes in the substituent.

Assignment of the ^{13}C nmr data of compounds **1** to **5** was accomplished using 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose [18] as a model compound (Table 3).

Table 3

^{13}C NMR Chemical Shifts for Compounds **1**, **3** to **5**, Measured at 50 MHz in Deuteriochloroform.

Compound	C-1	C-2	C-3	C-4	C-5	C-6
1	95.9	70.6*	70.2*	59.9	69.7	115.0
5	96.3	70.7*	70.6*	69.6	71.6	171.5
Compound	C-1'	C-2'	C-3'	C-4'	C-5'	a
2 [a]	96.0	70.0	70.0	63.9	71.8	153.8
3	96.4	70.6*	70.4*	64.3	72.2	162.9
4	96.5	70.7*	70.3*	64.5	72.5	162.8

*Pairs of values which might be interchanged, **a:** C-2 for compound **2** and C-5 for compounds **3** and **4**. [a] Data for Compound **2** were recorded in hexadeuterated dimethyl sulfoxide.

In general we could see slight differences for C-1' to C-3' with the model compound. The greatest variations were observed for the carbon which support the change of functionalization. For C-5' we found few differences between **2**, **3** and **4** with its reference compound. When comparison was made using nitrile **1** as the model compound, these modifications are slightly increased, probably due to sp hybridization in the compound.

Variations at C-4' are very important overall, if we consider that this position should be relatively far from the changed site in the molecule. However, the conformation of these particular di-*O*-isopropylidene derivatives makes possible an interaction through space between the heterocycle and the substituent in a pseudoaxial position on C-4', so the relative position of the heterocyclic moiety must affect the displacement of this carbon.

When we compared the displacements for compounds **3** and **4**, we found good correlation between them. If the comparison was made between **3** or **4** with the corresponding 2-acetamido-5-[5'-(1',2':3',4'-di-*O*-isopropylidene-β-L-arabinopyranosyl)]-1,3,4-thiadiazole (**6**) [9], we observed a significant difference in C-4'. Performing a molecular minimization using MM+ force field [19] for compounds **3**, **4** and **6** we found that compounds **3** and **4** had a similar relative orientation of the plane of the heterocycle with the C-5' → O linkage of pyranose ring (about 5 degrees), meanwhile **6** had a torsion angle near 30 degrees (Figure 6).

Due to this orientation, the sulfur atom of the thiadiazole ring is nearest to the substituent on C-4' and as a consequence may have more interactions with the pyranose than the oxadiazole ring in compounds **3** and **4**. The tetrazole ring in compound **2** has approximately the same orientation that the oxadiazole ring has in compounds **3** and **4**. Despite they have the same conformation we did not make a direct comparison because the spectra were recorded in different solvents.

The mass spectra of compounds **1** to **5** possess typical fragmentation of the di-*O*-isopropylidene derivatives as described earlier [17] with loss of methyl groups, acetic acid, acetone, ketene and their combinations. The characteristic peaks for each heterocycle are shown in the Experimental.

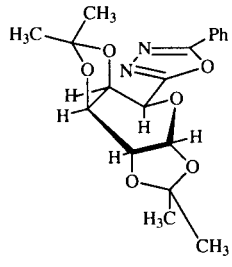
EXPERIMENTAL

General Methods.

The melting points were measured in a Thomas Hoover melting point apparatus and are uncorrected. The $[\alpha]_D$ were obtained using a 343 Perkin Elmer Polarimeter. All ^1H nmr spectra were recorded on a Bruker Spectrometer at 200 MHz in deuteriochloroform, using tetramethylsilane as the internal standard. The ^{13}C nmr were recorded at 50 MHz in the same apparatus. Mass spectra were obtained with a Shimadzu QP-5000 spectrometer by electron impact ionization. Mass spectra with fast atom bombardment ionization was performed with a ZAB-SEQ 4F using orthonitrobenzyl alcohol matrix.

1,2:3,4-Di-*O*-isopropylidene-α-D-galacturononitrile (**1**).

Title compound was prepared by procedure **a** from 9.6 g of crude 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose oxime [13]. The oxime was dissolved in 50 ml of



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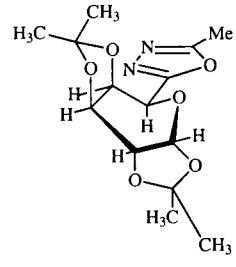

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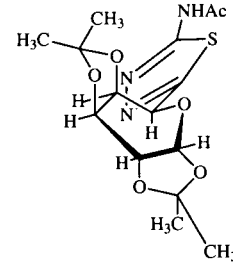

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Figure 6

pyridine and 50 ml of acetic anhydride. The mixture was heated in a water bath monitoring the reaction using tlc (silica gel G, benzene:ethyl acetate 3:2). Evaporation under reduced pressure gave a yellow syrup which was purified using flash chromatography (mixtures of benzene:ethyl acetate). From this syrup we isolated 3.5 g of **1** (yield 39%), and byproduct **5** in about 10% yield. In procedure **b,** 3.0 g of the crude oxime was dissolved in 5 ml of pyridine and to this 5 ml of benzoyl chloride was added in five portions of 1 ml each. The mixture was heated in a water bath monitoring the reaction using tlc (silica gel G, benzene:ethyl acetate 3:2), and then poured into ice water. A yellow syrup was obtained which was dissolved in dichloromethane, extracted with a saturated solution of sodium bicarbonate, then with 1*N* hydrochloric acid, dried with sodium sulfate and evaporated. The resulting syrup was purified by flash chromatography (silica gel G, mixtures of benzene:ethyl acetate), crystallized from ethanol resulting in 2.0 g of pure compound **1** (72% yield), mp 127-128°, $[\alpha]_D$ = -99.6° (chloroform); ^{1}H nmr: δ 1.55, 1.53, 1.39, 1.34 (s, CH_3- groups) ppm; ^{13}C nmr: δ 25.8, 25.7, 24.4, 24.4 (CH_3- groups), δ 110.7, 109.4 (quaternary carbons) ppm; ms: m/z 240 ($M^{+\bullet}$ -$CH_3^\bullet$ = A^+), 182 (A^+ -$(CH_3)_2CO$), 180 (A^+ -CH_3COOH), 154 (A^+ -$(CH_3)_2CO$-CO), 139 ($M^{+\bullet}$-2$(CH_3)_2CO$), 122 (A^+ -$(CH_3)_2CO$-CH_3COOH), 113 ($C_6H_9O_2^+$ = B^+), 100 ($C_5H_8O_2^{+\bullet}$ = $C^{+\bullet}$), 85 ($C^{+\bullet}$ -$CH_3^\bullet$), 43 (base peak, CH_3CO^+).

Anal. Calcd. for $C_{12}H_{17}NO_5$: C, 56.47; H, 6.67. Found: C, 56.38; H, 6.85.

Compound **5**, *N*-Acetyl-(1,2:3,4)-di-*O*-isopropylidene-α-D-galacturonamide.

This compound was a syrup; ^{1}H nmr: δ 2.49, 1.52, 1.42, 1.35, 1.34 (s, CH_3- groups), δ 8.8 (s, -NH-) ppm; ^{13}C nmr: δ 168.5 (acetate carbonyl group), δ 26.0, 26.0, 25.9, 24.8, 24.2 (CH_3- groups), δ 119.9, 108.9 (quaternary carbons) ppm; ms: fast atom bombardment m/z 316 $(M+H)^+$, electron impact m/z 300 ($M^{+\bullet}$-$CH_3^\bullet$ = A^+), 287 ($M^{+\bullet}$ -CO), 273 ($M^{+\bullet}$ -CH_2CO), 257 ($M^{+\bullet}$ -$(CH_3)_2CO$), 215 ($M^{+\bullet}$ -$C_4H_5O_2$), 113 ($C_6H_9O_2^+$ = B^+), 100 ($C_5H_8O_2^{+\bullet}$ = $C^{+\bullet}$), 85 ($C^{+\bullet}$ -$CH_3^\bullet$), 43 (base peak, CH_3CO^+).

This compound was only characterized by spectroscopic data because it was isolated as a syrup which suffers rapid decomposition upon standing.

5-[5'-(1',2':3',4'-Di-*O*-isopropylidene-β-L-arabinopyranosyl)]-tetrazole (**2**).

Compound **1** (1.8 g) was dissolved in 10 ml of dimethylformamide. Ammonium chloride (1.3 g) and 1.5 g of sodium azide were added. The mixture was heated at 100° in a water bath until all nitrile was consumed (checked by tlc). The reaction mixture was concentrated under diminished pressure and extracted with a dichloromethane:water system. The organic layer was separated, dried (anhydrous sodium sulfate), evaporated and purified by flash chromatography (silica gel G, mixtures of benzene:ethyl acetate). The pure product **2** slowly crystallized from ethyl acetate, 1.5 g, yield 71%, mp 241-243°, $[\alpha]_D$ = -92.4° (dimethyl sulfoxide); ^{1}H nmr: δ 1.50, 1.34, 1.34, 1.25 (s, CH_3- groups) ppm; ^{13}C nmr: δ 25.9, 25.8, 24.8, 24.2 (CH_3- groups), δ 109.1, 108.8 (quaternary carbons), ppm; ms: m/z 299 $(M+H)^+$, 283 ($M^{+\bullet}$ -$CH_3^\bullet$ = A^+), 240 ($M^{+\bullet}$ -$(CH_3)_2CO$), 225 (A^+ -$(CH_3)_2CO$), 182 ($M^{+\bullet}$ -2$(CH_3)_2CO$), 113 ($C_6H_9O_2^+$ = B^+), 100 ($C_5H_8O_2^{+\bullet}$ = $C^{+\bullet}$), 85 ($C^{+\bullet}$ -$CH_3^\bullet$), 69 (CHN_4^+ = Het^+), 43 (base peak, CH_3CO^+).

Anal. Calcd. for $C_{12}H_{18}N_4O_5 \cdot C_4H_8O_2$: C, 49.74; H, 6.74. Found: C, 49.45; H, 6.35.

5-Methyl-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-β-L-arabinopyranosyl)]-1,3,4-oxadiazole (**3**).

Product **2** (0.7 g) was dissolved in 50 ml of acetic anhydride and heated at reflux following the reaction by tlc (silica gel G, benzene:ethyl acetate 3:2) until disappearance of the tetrazole. The reaction was stopped by ethanol addition and the reaction medium was evaporated under diminished pressure using toluene to eliminate the residues of acetic acid. The solid was crystallized from a mixture of cyclohexane:ethyl acetate, 0.7 g of pure **3** was obtained (86%), mp 171-173°, $[\alpha]_D$ = -125.3° (chloroform); ^{1}H nmr: δ 2.54, 1.57, 1.47, 1.37, 1.33 (s, CH_3- groups) ppm; ^{13}C nmr: δ 26.0, 25.7, 24.7, 24.4, 10.9 (CH_3- groups), δ 110.4, 109.4 (quaternary carbons), ppm; ms: m/z 312 (base peak, $M^{+\bullet}$), 297 ($M^{+\bullet}$ -$CH_3^\bullet$ = A^+), 255 (A^+ -$(CH_3)_2CO$), 254 (A^+ -CH_2CO), 239 ($M^{+\bullet}$ -$(CH_3)_2CO$), 212 ($M^{+\bullet}$ -$C_5H_8O_2$), 197 (A^+ -$C_5H_8O_2$), 179 (A^+ -$(CH_3)_2CO$-CH_3COOH), 153 (A^+ -$(CH_3)_2CO$-CH_3COOH-CH_3CN), 113 ($C_6H_9O_2^+$ = B^+), 100 ($C_5H_8O_2^{+\bullet}$ = $C^{+\bullet}$), 85 ($C^{+\bullet}$ -$CH_3^\bullet$), 83 ($C_3H_3N_2O^+$ = Het^+), 43 (CH_3CO^+).

Anal. Calcd. for $C_{14}H_{20}N_2O_6$: C, 53.85; H, 6.41. Found: C, 54.10; H, 6.68.

5-Phenyl-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-β-L-arabinopyranosyl)]-1,3,4-oxadiazole (**4**).

Product **2** (1.4 g) was dissolved in 15 ml of pyridine and 2.5 ml of benzoyl chloride was added. The mixture was heated in a water bath, following the reaction by tlc (silica gel G, benzene:ethyl acetate 3:2) until disappearance of the tetrazole. The reaction was stopped by addition of water and then evaporated under diminished pressure. The syrup obtained was dissolved in dichloromethane, washed with sodium bicarbonate solution, diluted hydrochloric acid and water. The organic layer was separated, dried (anhydrous sodium sulfate) and evaporated until a syrup was obtained. The syrup was purified by flash chromatography (silica gel G, mixtures of benzene:ethyl acetate). Pure **4** (0.7 g) was obtained as a colorless solid with great tendency to sublime (yield 41%), mp 166-168°, $[\alpha]_D$ = -111.7° (chloroform); ^{1}H nmr: δ 1.60, 1.52, 1.38, 1.32, (s, CH_3- groups), δ 8.10-7.27 (m, aromatic protons) ppm; ^{13}C nmr: δ 26.0, 25.8, 24.7, 24.6 (CH_3- groups), δ 110.4, 109.4 (quaternary carbons), δ 133.2-123.8 (aromatic carbons), ppm; ms: m/z 374 ($M^{+\bullet}$), 359 ($M^{+\bullet}$ -$CH_3^\bullet$ = A^+), 317 (A^+ -CH_2CO), 301 (A^+ -$(CH_3)_2CO$), 274 ($M^{+\bullet}$ -$C_5H_8O_2$), 259 (A^+ -$C_5H_8O_2$), 241 (A^+ -$(CH_3)_2CO$-CH_3COOH), 213 ($M^{+\bullet}$ -$(CH_3)_2CO$-PhCN), 145 ($C_8H_5N_2O^+$ = Het^+), 113 ($C_6H_9O_2^+$ = B^+), 105 ($PhCO^+$), 100 ($C_5H_8O_2^{+\bullet}$ = $C^{+\bullet}$), 85 ($C^{+\bullet}$-$CH_3^\bullet$), 77 ($C_6H_5^+$), 43 (base peak, CH_3CO^+).

Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C, 60.96; H, 5.88. Found: C, 61.06; H, 5.68.

Acknowledgments.

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