Synthesis and Characterization of Some Nitrogen Heterocycles From D-Galactose Derivatives

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The tetrazoles 5-(6'-acetamido-6'-deoxy-1',2':3',4'-di-*O*-isopropylidene-D-*glycero*-α-D-galactohexopyranos-6'-yl)tetrazole (**1**) and 5-(6'-acetamido-6'-deoxy-1',2':3',4'-di-*O*-isopropylidene-L-*glycero*-α-D-galactohexopyranos-6'-yl)-tetrazole (**2**) were synthesized by the 1,3-dipolar cycloaddition reaction of the epimeric α-acetamidonitriles **5** and **6**, respectively, with sodium azide. Reaction of tetrazole **1** with acetic anhydride in the presence of pyridine afforded the *N*-acetyl-1,3,4-oxadiazole derivative **3** and the *N*-acetylacetamido-1,3,4-oxadiazole derivative **7**. The *N*-acetylacetamido-1,3,4-oxadiazole derivative (**8**) was isolated when the tetrazole **2** was allowed to react under the same conditions. The physical and spectroscopic data of the five new compounds **1**, **2**, **3**, **7** and **8** are presented.

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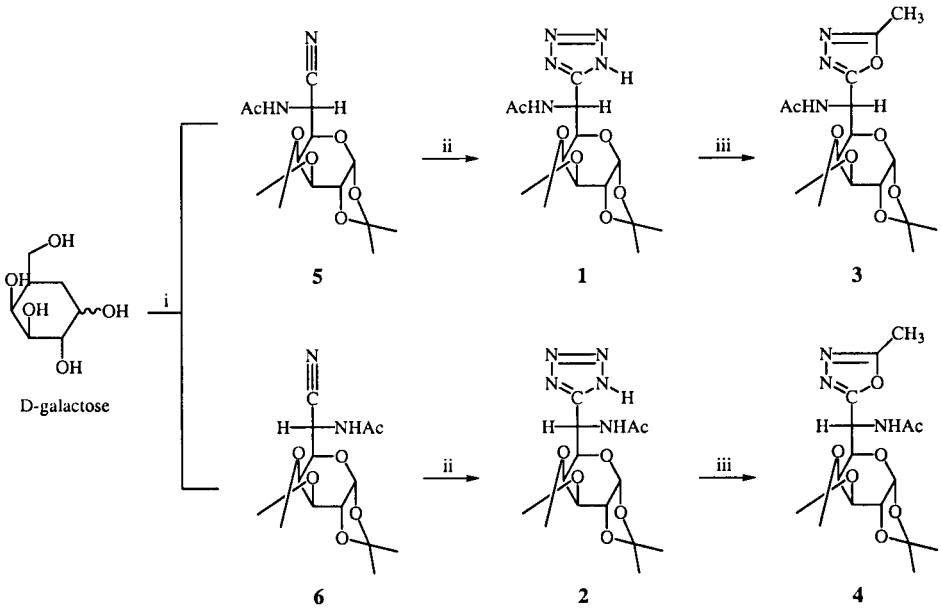
Tetrazole derivatives have received increasing interest amongst medicinal chemists, since the tetrazole group is similar to the carboxylic function in terms of size and acidity but is apparently more stable metabolically [1,2]. Its bioisosteric replacement in a number of drugs bearing a carboxy group has been reported [1]. The discovery by researchers at Dupont of a non-peptide angiotensin receptor antagonist containing a 5-aryltetrazole moiety (Dup 753) is only one of many examples arising from the impressive amount of work on these derivatives as can be judged by the number of publications that have appeared in the past few years [2]. The broad-spectrum antiviral activity of ribavirin, a ribonucleoside of triazole, has stimulated interest in the synthesis of ribonucleosides of tetrazole, which is an isosteric ring equivalent of triazole [3]. Several tetrazole derivatives, glycosi-

Scheme 1



i: ref [10]. ii: NaN_3, NH_4Cl, *N,N*-dimethylformamide, 80°, 120 hours. iii: Ac_2O, Py, 120°, 20 hours.

dases inhibitors, have been prepared from carbohydrates [4-7]. On the other hand, interesting antifungal and antibacterial activities are described for some 1,3,4-oxadiazole derivatives [8,9].

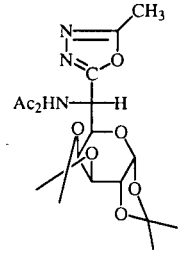
In the context of our interest in the synthesis of heterocycles using carbohydrates as starting materials and considering the potential biological activities of tetrazole and oxadiazole derivatives, we wished to synthesize the tetrazoles **1** and **2** and the oxadiazoles **3** and **4**.

The most popular procedure for building tetrazole ring is the classical heating of a suitable nitrile with sodium azide in a variety of solvents in the presence of ammonium salts [2]. To prepare the tetrazoles **1** and **2** by this procedure, suitable starting materials are the epimeric α-acetamidonitriles, the D-*glycero* **5** and the L-*glycero* **6**, respectively (Scheme 1). We described previously [10] the synthesis of **5** and **6**, from D-galactose. The synthesis of 2-methyl-1,3,4-oxadiazoles from tetrazoles by heating a suitable tetrazole derivative with acetic anhydride, are described in the literature [11,12,13]. We wished to synthesize the unknown oxadiazole derivatives **4** and **5** by this methodology (Scheme 1).

The α-acetamidonitriles **5** and **6** were obtained from D-galactose [10] in four steps: preparation of 1,2:3,4-di-*O*-isopropylidene derivative, oxidation to the aldehyde, cyanoamination to give two epimeric aminonitriles, which were separated by column chromatography, and subsequent *N*-acetylation.

The α-acetamidonitriles **5** and **6** were converted in tetrazoles D-*glycero* **1** and L-*glycero* **2**, respectively, by treatment with sodium azide and ammonium chloride in dimethylformamide at 80° [14].

Neither decreasing the temperature, nor decreasing of reaction time improved the yield of **3**. Treatment of tetrazole **2** as described above for **1** also gave two main products, as observed by tlc. The *N*-acetylacetamido oxadiazole **8** was isolated after column chromatography in 42% yield. The other compound could not be purified by the usual chromatographic methods. The product which was not isolated and oxadiazole **3** have the same tlc profile. Since the C-6 epimeric tetrazoles **1** and **2** and the C-6 epimeric oxadiazoles **7** and **8** show similar behavior in tlc, we supposed that the product observed in the tlc can be the desired L-*glycero*oxadiazole **4**. Attempts to improve the formation of **4** by decreasing either the temperature or the reaction time were not successful.



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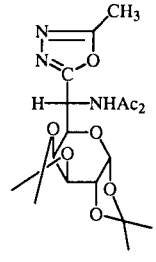

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The structures of **1**, **2**, **3**, **7** and **8** are supported by their spectroscopic data (ir, ms, ^{1}H-nmr and ^{13}C-nmr).

The ^{1}H-nmr data of these compounds are listed in Tables 1, 2 and 3. From the coupling constants of the ^{1}H-nmr (Table 2) we propose a twisted boat ($^oT_2$) as the preferential conformation for these compounds in solution. This conformation is similar to other 1,2:3,4-di-*O*-isopropylidene derivatives described in literature [15] and it is due to the two fused 1,3-dioxolane rings.

Table 1

^{1}H-NMR Data of Compounds **1**, **2**, **3**, **7** and **8**: Chemical Shifts (δ) and Multiplicities of the H-1', H-2', H-3', H-4', H-5', H-6' and N-*H* Atoms

Compound	H-1'	H-2'	H-3'	H-4'	H-5'	H-6'	*H*-N
1	5.53 d	4.35 dd	4.67 dd	4.70 dd	4.51 dd	5.61 dd	7.77 d
2	5.60 d	4.37 dd	4.61 dd	4.22 dd	4.56 dd	5.56 dd	6.89 d
3	5.56 d	4.33 dd	4.61 dd	4.50 dd	4.30 dd	5.62 dd	7.08 d
7	5.52 d	4.35 dd	4.66 dd	4.09 dd	5.21 dd	5.09 d	--
8	5.47 d	4.34 dd	4.72 dd	4.95 dd	4.79 dd	5.45 d	--

Measured at 400 MHz in deuteriochloroform solution with tetramethylsilane as the internal standard.

Treatment of tetrazole **1** with acetic anhydride and pyridine at 120° [11] led to two main products, as observed by tlc. Both substances were isolated after acidification, extraction with dichloromethane and column chromatography. The main product, obtained in 41% yield, was identified as the desired D-*glycero*-1,3,4-oxadiazole (**3**). The major side product, obtained in 30% yield, was identified as the D-*glycero*-*N*-acetylacetamidooxadiazole (**7**).

Table 2

^{1}H-NMR Data of Compounds **1**, **2**, **3**, **7** and **8**: Vicinal Hydrogen-Hydrogen Coupling Constants (Hz)

Compound	$J_{1'-2'}$	$J_{2'-3'}$	$J_{3'-4'}$	$J_{4'-5'}$	$J_{5'-6'}$	$J_{6'-NH}$
1	4.9	2.0	7.9	1.0	5.8	7.6
2	4.9	2.5	7.9	1.7	8.3	6.2
3	4.9	2.3	7.9	1.5	5.4	8.5
7	4.8	2.6	8.0	1.5	8.8	--
8	5.3	2.6	7.9	1.7	9.5	--

Table 3

^{1}H-NMR Data of Compounds **1**, **2**, **3**, **7** and **8**: Chemical Shifts (δ) and Integration of the Methyl Groups

Compound	CH_3 of isopropylidene group	CH_3-C=O	CH_3-C-2
1	1.52 (3H), 1.49 (3H), 1.37 (3H), 1.32 (3H)	2.05 (3H)	-
2	1.56 (3H), 1.34 (3H), 1.33 (3H), 1.23 (3H)	2.09 (3H)	-
3	1.53 (3H), 1.44 (3H), 1.34 (3H), 1.33 (3H)	2.04 (3H)	2.51 (3H)
7	1.67 (3H), 1.48 (3H), 1.36 (3H), 1.33 (3H)	2.49 (6H)	2.54 (3H)
8	1.50 (3H), 1.45 (3H), 1.35 (3H), 1.30 (3H)	2.45 (6H)	2.50 (3H)

For ^{13}C-nmr assignments of the carbohydrate moiety of compounds **1**, **2**, **3**, **7** and **8** we used 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose as the model [16]. Chemical shifts values for the carbohydrate moiety and for the other carbon atoms of these compounds are presented in Tables 4 and 5, respectively.

Table 4

^{13}C-NMR Data of Compounds **1**, **2**, **3**, **7** and **8**: Chemical Shifts (δ) of the Carbohydrate Moiety

Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
1	96.6	71.0	70.5	65.9	71.4	46.7
2	96.4	70.4	70.5	66.8	70.7	45.3
3	96.6	70.9	70.4	65.8	71.5	47.3
7	96.3	70.5	70.0	66.5	70.6	53.5
8	96.2	71.0	70.6	65.1	71.0	52.0

Recorded at 100.6 MHz in deuteriochloroform solution.

The ir spectrum of the D-*glycero*-1,3,4-oxadiazole (**3**) is characterized by a CO band at 1670 cm^{-1} and by the NH bands (3300 cm^{-1} and 1550 cm^{-1}). The ^{13}C-nmr spectrum indicates the presence of the two carbons of oxadiazole ring (signals at δ 164.4 and δ 164.0). The spectrum also shows the signal of the C of the methyl group attached to C-2 of oxadiazole ring (δ 10.9). In the ^{1}H-nmr spectrum, a singlet at δ 2.51, corresponding to 3 H of methyl group attached to C-2 of oxadiazole ring, and other at δ 2.04, corresponding to the hydrogen atoms of acetamido group, are observed. A doublet is also observed at δ 7.08 (J = 8.5 Hz), corresponding to an amide hydrogen, and a double doublet at δ 5.62 (J = 8.5 and 5.4 Hz) relative to H-6'. The ms of **3** shows the molecular ion 383 (0.87%) and the base peak at m/z 43.

The structure of the L-*glycero*-acylamide-1,3,4-oxadiazole (**8**) was confirmed by its spectroscopic data. The ir spectrum shows the CO band (1700 cm^{-1}), but shows no NH absorption. The characteristic signals of the 2-methyl-substituted oxadiazole are observed in the ^{13}C-nmr spectrum of **8** (δ 163.2, 163.1, 10.9). The ^{1}H-nmr spectrum of **8** shows a singlet at δ 2.50 (3 H of the methyl group bound to the oxadiazole ring), another singlet at δ 2.45, corresponding to 6 H of acetylacetamido group, and a doublet at δ 5.45 (J = 9.9 Hz), corresponding to H-6'. In the mass spectrum of **8** the molecular peak is found at m/z 425 (0.22%) and the base peak is found at m/z 43 (CH_3CO^+).

Table 5

^{13}C-NMR Data of Compounds **1**, **2**, **3**, **7** and **8**: Chemical Shifts (δ) of Heterocyclic Rings, Isopropylidene and Acetamido Groups

Compound	*C*=O	C-5 or C-2, C-5	Cq[a]	*C*H_3[b]	*C*H_3[c]	*C*H_3[d]
1	171.9	154.3	109.8 and 109.3	25.9, 25.6, 24.8, 24.0	23.0	--
2	172.2	153.8	109.7 and 109.4	25.9, 25.7, 24.8, 24.1	22.9	--
3	169.8	164.4 and 164.0	109.7 and 109.0	26.0, 25.7, 24.8, 24.1	23.1	10.9
7	173.7	164.8 and 163.7	109.7 and 109.6	25.9, 25.8, 25.7, 25.2	24.2	10.9
8	173.4	163.2 and 163.1	109.5	26.0, 25.6, 25.0	24.2	10.9

[a] Quaternary carbon of isopropylidene group. [b] *C*H_3 of isopropylidene group. [c] *C*H_3 of acetamido or acetylacetamido group. [d] *C*H_3-C-2 of oxadiazole ring.

In the ^{13}C-nmr spectra of **1** and **2**, the characteristic signal of the tetrazole C-atom is observed at δ 154.3 (**1**) and δ 153.8 (**2**), replacing the CN signals of **5** and **6** (δ 116.4).

The mass spectra by electron impact of the compounds **1** and **2** show the molecular ion (m/z 369) with small relative abundance (2.08 and 2.75%, respectively) and the base peak at m/z 43, corresponding to fragment CH_3CO^+, as it is described in literature for 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose and derivatives [15,17].

The oxadiazole **7** was obtained as an oil. Purification by columm chromatography and crystallization failed, but **7** was unambiguously identified on the basis of its ir, ^1H and ^{13}C-nmr spectra, as for **8**.

EXPERIMENTAL

All melting points were determined on a Kofler Sybron apparatus and are uncorrected. Optical rotations were determined at 25° with a Bellingham & Stanley P20 Polarimeter. The nmr spectra were measured in deuteriochloroform with tetramethylsilane as the internal standard with a Bruker Avance DRX-400 instrument. Chemical shifts are given in δ scale. The infrared spectra (ir) were recorded with a Perkin Elmer 283 B or a Schimadzu ir 408 spectrometer. The electron impact mass spectra (ms) were obtained on a Schimadzu QP-5000 spectrometer and the high resolution mass spectra (hrms) were acquired with a ZAB-SEQ4F instrument. Thin layer chromatography (tlc) was performed with silica gel 60 G (Merck) as the adsorbant, ethyl acetate/methanol 1:1 (synthesis of tetrazoles) or ethyl acetate (synthesis of oxadiazoles) as eluents and iodine vapor and ethanolic solution of sulfuric acid (15% v/v) and heating for detection. Column chromatography was performed with silica gel 60, 70-230 mesh (Merck). The term "standard workup" means that the organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure.

General Procedure for the Synthesis of Tetrazoles **1** and **2**.

A mixture of acetamidonitrile, **5** or **6**, (0.20 g, 0.61 mmole), sodium azide (0.24 g, 3.69 mmoles), ammonium chloride (0.20 g, 3.74 mmoles) and dry dimethylformamide (7.5 ml) was stirred under heating (80°) until disappearance of the starting material (controlled by tlc, 120 hours). Distillation under reduced pressure gave a residue. Addition of aqueous hydrogen chloride solution (3 mol/l), followed by extraction with dichloromethane and standard workup gave the corresponding tetrazole **1** or **2**, as a syrup, which crystallized as a white solid from dichloromethane-petroleum ether.

5-(6'-Acetamido-6'-deoxy-1',2':3',4'-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*hexopyranos-6'-yl)tetrazole (**1**).

This compound (0.16 g, 0.44 mmole, 73%) was obtained as white solid, mp, 127-129°; $[\alpha]_D$ -87.5° (c 1; chloroform); ir ν (potassium bromide, cm^{-1}): 3400 (NH), 1700 (C=O), 1550 (NH); ms: m/z 369 (2.08%, $M^{+\cdot}$), 43 (100%, CH_3CO^+); hrms required for $C_{14}H_{20}N_5O_6$ ($M^{+\cdot}$ - $CH_3\cdot$): m/z 354.1415. Found: m/z 354.1414. The ^1H and ^{13}C-nmr signals are listed in Tables 1, 2, 3, 4 and 5.

Anal. Calcd. for $C_{15}H_{23}N_5O_6 \cdot 1.5H_2O$: C, 45.45; H, 6.57; N, 17.68. Found: C, 45.19; H, 6.41; N, 17.24.

5-(6'-Acetamido-6'-deoxy-1',2':3',4'-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*hexopyranos-6'-yl)tetrazole (**2**).

This compound (0.22 g, 0.6 mmole, 98%) was obtained as white solid, mp, 119-123°; $[\alpha]_D$ -50.9° (c 1; chloroform); ir ν (potassium bromide, cm^{-1}): 3400 (NH), 1660 (C=O), 1550 (NH); ms: m/z 369 (2.75%, $M^{+\cdot}$), 43 (100%, CH_3CO^+); hrms required for $C_{14}H_{20}N_5O_6$ ($M^{+\cdot}$ - $CH_3\cdot$): m/z 354.1415. Found: m/z 354.1414. The ^1H and ^{13}C-nmr signals are listed in Tables 1, 2, 3, 4 and 5.

General Procedure for the Synthesis of Oxadiazoles.

A mixture of tetrazole, **1** or **2**, (100 mg, 0.27 mmole), acetic anhydride (6.6 ml) and pyridine (3.3 ml) was stirred under heating (110°) until disappearance of starting material (controlled by tlc, 20 hours). Addition of aqueous hydrogen chloride solution (3 mol/l), followed by extraction with dichloromethane and standard workup gave a residue.

2-Methyl-5-(6'-*N*-acetylacetamido-6'-deoxy-1',2':3',4'-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*hexopyranos-6'-yl)-1,3,4-oxadiazole (**7**) and 2-Methyl-5-(6'-acetamido-6'-deoxy-1',2':3',4'-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*hexopyranos-6'-yl)-1,3,4-oxadiazole (**3**).

The residue obtained from **1** was submitted to column chromatography. Elution with hexane/ethyl acetate 6:4 (v/v) afforded **7**, as an oil (34.6 mg, 0.08 mmole, 30%); $[\alpha]_D$ -139.50° (c 1.9; chloroform); ir ν (potassium bromide, cm^{-1}): 1700 (C=O). The ^1H and ^{13}C-nmr signals are listed in Tables 1, 2, 3, 4 and 5. Successively, elution with ethyl acetate gave **3** as a syrup, which crystallized as a white solid from ethyl ether-petroleum ether (43 mg, 0.11 mmole, 41%); mp, 185-88°; $[\alpha]_D$ -82.88° (c 1; chloroform); ir ν (potassium bromide, cm^{-1}): 3300 (NH), 1670 (C=O), 1550 (NH); ms: m/z 383 (0.87%, $M^{+\cdot}$), 43 (100%, CH_3CO^+); hrms required for $C_{17}H_{25}N_3O_7$ ($M^{+\cdot}$ - $CH_3\cdot$): m/z 368.1459. Found: m/z 368.1471. The ^1H and ^{13}C-nmr signals are listed in Tables 1, 2, 3, 4 and 5.

Anal. Calcd. for $C_{17}H_{25}N_3O_7$ (compound **3**): C, 53.26; H, 6.52; N, 10.97. Found: C, 53.69; H, 6.64; N, 10.88.

Anal. Calcd. for $C_{19}H_{27}N_3O_8 \cdot 0.5C_4H_8O_2$ (compound **7**): C, 53.73; H, 6.61; N, 8.95. Found: C, 54.04; H, 6.78; N, 8.98.

2-Methyl-5-(6'-*N*-acetylacetamido-6'-deoxy-1',2':3',4'-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*hexopyranos-6'-yl)-1,3,4-oxadiazole (**8**).

The residue obtained from **2** was submitted to column chromatography. Elution with hexane/ethyl acetate 6:4 (v/v) afforded **8**, as syrup, which crystallized as white solid from ethyl ether-petroleum ether (48 mg, 0.11 mmole, 42%), mp, 205-207°; $[\alpha]_D$ +23.44 (c 0.6; chloroform); ir ν (potassium bromide, cm^{-1}) 1700 (C=O); ms: m/z 425 (0.22%, $M^{+\cdot}$), 43 (100%, CH_3CO^+); hrms required for $C_{19}H_{27}N_3O_8$ ($M^{+\cdot}$ - $CH_3\cdot$): m/z 410.1564. Found: m/z 410.1638. The ^1H and ^{13}C-nmr signals are listed in Tables 1, 2, 3, 4 and 5.

Anal. Calcd. for $C_{19}H_{27}N_3O_8 \cdot H_2O$: C, 51.46; H, 6.59; N, 9.48. Found: C, 51.93; H, 6.46; N, 9.21.

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