

Mirta L. Fascio and Norma B. D'Accorso*

Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales,
 Universidad de Buenos Aires, Ciudad Universitaria, Pabellón II, 3º Piso, (1428) Buenos Aires, Argentina

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The syntheses of 2-methyl-5-[1',2',3',4',5'-penta-*O*-benzoyl-D-manno-pentitol-1'-yl]-1,3,4-oxadiazole and 5-methyl-3-[1',2',3',4',5'-penta-*O*-benzoyl-D-manno-pentitol-1'-yl]-1,2,4-oxadiazole, as well as their intermediate products, are described. Their ^1H and ^{13}C nmr and ms spectra are presented and their preferential conformation in solution are proposed.

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Several references of the biological activity for some oxadiazoles are given in literature. Interesting antifungal activity is described by Giri *et al.* [1] for some lipophylic 1,3,4-oxadiazole derivatives; on the other hand antibacterial activity was detected on Gram⁺ and Gram⁻ bacteria with other 1,3,4-oxadiazoles [2].

We were interested in obtaining 1,2,4- and 1,3,4-oxadiazoles from different carbohydrate precursors.

In this field, Sanchez *et al.* [3] described the synthesis

of 2-methyl-5-[1',2',3',4',5'-penta-*O*-benzoyl-D-galacto-pentitol-1'-yl]-1,3,4-oxadiazole by treatment of the 5-[1',2',3',4',5'-penta-*O*-benzoyl-D-galacto-pentitol-1'-yl]-tetrazole with acetic anhydride. Reple *et al.* [4] reported the synthesis of some 3-*O*- β -D-ribofuranosyl-1,2,4-oxadiazoles from 2,3,5-tri-*O*-benzoyl- β -D-ribofuranosylamid-oxime.

We report herein, the syntheses of 2-methyl-5-[1',2',3',4',5'-penta-*O*-benzoyl-D-manno-pentitol-1'-yl]-1,3,4-oxadiazole and 5-methyl-3-[1',2',3',4',5'-penta-*O*-benzoyl-D-manno-pentitol-1'-yl]-1,2,4-oxadiazole from the same precursor 2,3,4,5,6-penta-*O*-benzoyl-D-mannonoitrile (1) using two different synthetic routes.

2-Methyl-5-[1',2',3',4',5'-penta-*O*-benzoyl-D-manno-pentitol-1'-yl]-1,3,4-oxadiazole (3) was obtained from 2,3,4,5,6-penta-*O*-benzoyl-D-mannonoitrile (1) [5] using the 5-[1',2',3',4',5'-penta-*O*-benzoyl-D-manno-pentitol-1'-yl]tetrazole (2) [6] as the intermediate, according to the technique of Sanchez *et al.* [3].

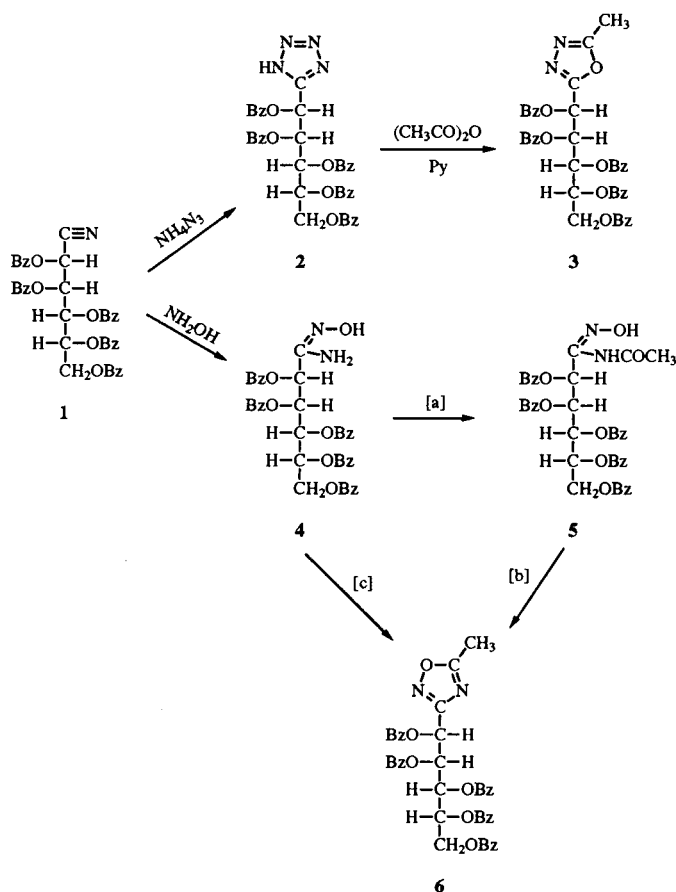
5-Methyl-3-[1',2',3',4',5'-penta-*O*-benzoyl-D-manno-pentitol-1'-yl]-1,2,4-oxadiazole (6) was prepared from compound 1, using the 2,3,4,5,6-penta-*O*-benzoyl-D-mannonoamidoxime (4), as the intermediate product. Another compound was also isolated and was characterized as *N*-acetyl-2,3,4,5,6-penta-*O*-benzoyl-D-mannonoamidoxime (5). The different synthetic routes are shown in Figure 1.

The ^1H nmr spectra of compounds 3, 4, 5 and 6 were performed in deuteriochloroform and allowed a first order analysis. In the spectra of compounds 3 and 6 a superposition of the signals of H-2' and H-3' is observed. Computer simulation was used to confirm their chemical shifts and the coupling constant between them.

The chemical shifts and the coupling constants are listed in Tables 1 and 2.

Their conformational analyses were carried out taking into account the coupling constants and the Newman projection formulae.

From these data we can deduce that: a) Compounds 3 and 6 have an anti-periplanar relationship between H-1' and H-2' ($J = 7.2$ Hz and $J = 6.9$ Hz, respectively), and their preferential conformations in solution are planar, zig-zag and extended. The same conformation is postu-



[a] $(\text{CH}_3\text{CO})_2\text{O}$, N_2 , benzene, 8 hours. [b] $(\text{CH}_3\text{CO})_2\text{O}$, N_2 , benzene, 4 hours. [c] $(\text{CH}_3\text{CO})_2\text{O}$, N_2 , benzene, 12 hours.

Figure 1 [7].

Table 1
¹H NMR Chemical Shifts (δ) Multiplicities of Compounds 3, 4, 5 and 6

Compound	H-1'	H-2'	H-3'	H-4'	H-5'a	H-5'b	CH ₃
3	6.49 d	6.33 dd	6.35 dd	5.84 ddd	4.85 dd	4.50 dd	2.30
6	6.43 d	6.36 dd	6.35 dd	5.84 ddd	4.83 dd	4.50 dd	2.35
	H-2	H-3	H-4	H-5	H-6a	H-6b	CH ₃
4	5.92 d	6.21 dd	6.28 dd	5.79 ddd	4.81 dd	4.51 dd	
5	5.92 d	6.25 dd	6.31 dd	5.83 ddd	4.87 dd	4.52 dd	1.98

Measured at 300 MHz for a solution in deuteriochloroform with TMS as the internal standard. For compound 4 we observed two broad singlets at δ 5.61 and 5.56 that corresponded to the hydroxyl and amide proton respectively. For compound 5 we observed only one broad singlet at δ 5.19 corresponding at hydroxyl proton.

Table 2
 Vicinal Proton-Proton Coupling Constants (Hz)
 of Compounds 3, 4, 5 and 6

Compound	J _{1',2'}	J _{2',3'}	J _{3',4'}	J _{4',5'a}	J _{4',5'b}	J _{5'a,5'b}
3	7.2	2.1	6.9	5.3	3.3	12.4
6	6.9	2.0	7.2	5.4	3.5	12.3
	J _{2,3}	J _{3,4}	J _{4,5}	J _{5,6a}	J _{5,6b}	J _{6a,6b}
4	4.6	3.4	6.8	5.2	3.6	11.7
5	6.5	2.3	6.9	5.5	3.3	12.3

lated for compound 5, even so J_{2,3} = 6.5 Hz shows a slight deviation from the antiperiplanar relationship. b) Compound 4 has J_{2,3} = 4.6 Hz; due to this a periplanar relationship between H-2 and H-3 is supposed. Compound 4 does not show a 1,3 interaction in the extended, planar, zig-zag conformation, however the coupling constant permits us to postulate a rotation of the C-2 → C-3 linkage. Accepting this rotation, a ₂G⁻ as well as ₂G⁺ rotation could be proposed [8], but both introduce 1-3 interactions, the first between a benzoyl and an amidoxime group which are electronically different; the second, between two benzoyl groups. We suppose that this is the less favorable situation and therefore we propose a ₂G⁻ rota-

tion. A similar situation was observed by Vazquez *et al.* [9] for the 2,3,4,5,6-penta-*O*-benzoyl-D-mannonitrile (1).

The preferred conformation in solution is shown in Scheme 1.

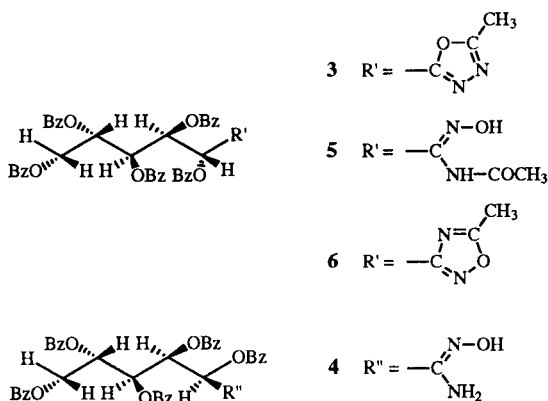
The assignment of the ¹³C nmr signals in compounds 3 and 6, was made by comparison with 5-[1',2',3',4',5'-penta-*O*-benzoyl-D-manno-pentitol-1'-yl]tetrazole (2) while compounds 4 and 5 have been assigned using 2,3,4,5,6-penta-*O*-benzoyl-D-mannonitrile (1) [10] as the reference compound (Table 3).

Table 3
¹³C NMR Chemical Shifts (δ) of Compounds 3, 4, 5 and 6

Compound	C-Het.	C-1'	C-2'	C-3'	C-4'	C-5'	CH ₃
3	161.7	65.5	69.6	69.6	68.8	62.5	10.7
6	177.0	66.4	69.7	69.6	68.8	62.4	12.0
	C-1	C-2	C-3	C-4	C-5	C-6	CH ₃
4	168.6	72.3	69.9	69.9	69.5	62.5	
5	168.6	69.0	69.9	70.0	69.9	62.5	19.5

Recorded at 25.50 MHz for a solution in deuteriochloroform. The aromatic signals appeared at δ 128.1-133.7 and the carbonyl signals at δ 164.4-166.4, and in compound 5 the amide carbonyl signal appears at δ 152.5.

Scheme 1



In the literature [3] the ¹³C nmr signals of the heterocyclic carbon in some 1,3,4-oxadiazole derivatives appear at 158.1 and 156.7 ppm. Compound 6 shows a signal at 177.0 ppm for the heterocyclic carbon, which can be attributed to the different distribution of heteroatoms in the heterocyclic ring.

The comparative analysis of the spectra of compounds 3 and 6 with 2 shows important differences for the heterocyclic carbon, and lesser differences for the carbons more distant from the oxadiazole group.

The same comparative analysis between the spectra of compounds 4 and 5 with 1, shows the most important difference in the signal of the C-1 [nitrile (1), amidoxime (4)]

or *N*-acetylamidoxime carbon (5)], and smaller differences in the rest of the molecule.

Compound **5** shows a peak at 152.5 ppm, different from the other ester carbonyl groups (154.4-165.7 ppm) which could be attributed to the *N*-acetyl group.

The mechanism of formation of 1,3,4-oxadiazoles from *N*-acetylated tetrazoles is given in literature [11]. It may be considered that the acetylated tetrazole is a probable intermediate also in our case. A similar situation is given for the formation of compound **6**, where a first step acetylation of the amino group is observed, giving compound **5** and after it the nucleophilic attack and dehydration with formation of the 1,2,4-oxadiazole ring.

EXPERIMENTAL

General Methods.

Melting points were measured on a Unimelt apparatus and are uncorrected. Optical rotations were determined at 20° with a Perkin-Elmer 141 Polarimeter. The ¹H nmr spectra were recorded with a Bruker EM360A instrument at 300 MHz and the ¹³C nmr spectra were recorded at 25.20 MHz for solutions in deuteriochloroform with TMS as the internal standard. Mass spectra were performed by chemical ionization. Analysis (tlc) was performed on plates coated with Silica Gel G (Merck, Darmstadt) with a) benzene-ethyl acetate (95:5), and b) cyclohexane-2-propanol (7:3) as eluents and iodine vapor for detection.

2-Methyl-5-[1',2',3',4',5'-penta-*O*-benzoyl-D-manno-pentitol-1'-yl]-1,3,4-oxadiazole (**3**).

5-[1',2',3',4',5'-Penta-*O*-benzoyl-D-manno-pentitol-1'-yl]tetrazole (**2**) [6] (1.38 g, 1.86 mmoles) was dissolved in 4 ml of acetic anhydride and kept at 110° until **2** disappeared (controlled by tlc, solvents a) and b), 4 hours). The mixture was poured into ice water and gave a solid which was recrystallized from ethanol. Compound **3** (0.77 g, 55%) was obtained as needles, mp 180-181°; [α]_D + 42.9 (c 1, dichloromethane); ms: 754 (M⁺), 632 (M⁺ - C₆H₅CO₂H), 537 (M⁺ - C₁₁H₉N₂O₃), 510 (M⁺ - 2 C₆H₅CO₂H), 122 (C₆H₅CO₂H⁺), 105 (C₆H₅CO⁺, base peak). The ¹H and ¹³C nmr signals are listed in Tables 1, 2 and 3.

Anal. Calcd. for C₄₃H₃₄N₂O₁₁: C, 68.43; H, 4.51; N, 3.71. Found: C, 68.32; H, 4.62; N, 3.52.

2,3,4,5,6-Penta-*O*-benzoyl-D-mannonoamidoxime (**4**).

A methanol (30 ml) solution of 2,3,4,5,6-penta-*O*-benzoyl-D-mannononitrile (**1**) (3 g, 4.3 mmoles) and hydroxylamine (prepared from 0.4 g of hydroxylamine hydrochloride) was heated at 65° until the starting material disappeared by tlc, then the solvent was evaporated and the reaction mixture separated by flash chromatography on Silica Gel G, using benzene and benzene-ethyl acetate (95:5). Compound **4** (1.95 g, 62%) was obtained as amorphous solid, mp 98-100°; [α]_D + 87.4 (c 1; dichloromethane); ms: 730 (M⁺), 671 (M⁺ - CH₃N₂O), 537 (M⁺ - C₉H₉N₂O₃), 122 (C₆H₅CO₂H⁺, base peak), 105 (C₆H₅CO⁺). The ¹H and ¹³C nmr signals are listed in Tables 1, 2 and 3.

Anal. Calcd. for C₄₁H₃₄N₂O₁₁: C, 67.40; H, 4.66; N, 3.84. Found: C, 68.00; H, 4.82; N, 4.04.

N-Acetyl-2,3,4,5,6-penta-*O*-benzoyl-D-mannonoamidoxime (**5**).

The acetic anhydride solution (70 ml) of 2,3,4,5,6-penta-*O*-benzoyl-D-mannonoamidoxime (**4**) (0.85 g, 1.16 mmoles) was refluxed in the dark under nitrogen during 8 hours, the solvent was evaporated and the oily residue was evaporated several times with dichloromethane and purified by flash chromatography on Silica Gel G, using benzene and benzene-ethyl acetate (9:1). Compound **5** (1.33 g, 86%) was obtained as an amorphous solid, mp 100-102°; [α]_D + 86.1 (c 1, dichloromethane); ms: 671 (M⁺ - C₃H₅N₂O₂), 619 (M⁺ - H₂O - C₆H₅CO₂CH₂), 537 (M⁺ - C₁₁H₁₁N₂O₄), 485 (M⁺ - H₂O - C₆H₅CO₂CH₂CHOCOC₆H₅), 311 [537 - (C₆H₅CO)₂O], 122 (C₆H₅CO₂H⁺), 105 (C₆H₅CO⁺, base peak). The ¹H and ¹³C nmr signals are listed in Tables 1, 2 and 3.

Anal. Calcd. for C₄₃H₃₆N₂O₁₂: C, 66.84; H, 4.66; N, 3.63. Found: C, 66.92; H, 5.02; N, 3.94.

5-Methyl-3-[1',2',3',4',5'-penta-*O*-benzoyl-D-manno-pentitol-1'-yl]-1,2,4-oxadiazole (**6**).

2,3,4,5,6-Penta-*O*-benzoyl-D-mannonoamidoxime (**4**) (3 g, 4.2 mmoles) in acetic anhydride (70 ml) was refluxed in the dark under nitrogen during 12 hours, then it was poured on ice-water. It gave a white solid which was separated by flash chromatography on Silica Gel G with benzene and benzene-ethyl acetate (95:5). Compound **6** (1.33 g, 42%) was obtained as needles, mp 153-155°; [α]_D + 50.2 (c 1, dichloromethane); ms: 754 (M⁺), 632 (M⁺ - C₆H₅CO₂H), 537 (M⁺ - C₁₁H₉N₂O₃), 510 (M⁺ - 2 C₆H₅CO₂H), 122 (C₆H₅CO₂H⁺), 105 (C₆H₅CO⁺, base peak). The ¹H and ¹³C nmr signals are listed in Tables 1, 2 and 3.

Anal. Calcd. for C₄₃H₃₄N₂O₁₁: C, 68.43; H, 4.51; N, 3.71. Found: C, 68.72; H, 4.72; N, 3.60.

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