Synthesis and Debenzoylation Products of Two Perbenzoylated 2-Substituted 5-*D*-Galactosyl-1,3,4-oxadiazoles

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The synthesis of 2-(*p*-chlorophenyl)-5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1-yl]-1,3,4-oxadiazole is described. Its debenzoylation gave an equilibrium mixture of the 1,3,4-oxadiazole derivative without protection of the hydroxyl group and the *N*-benzoyl-*D*-galactono-1,4-lactonehydrazone. A similar equilibrium was observed by debenzoylation of 2-phenyl-5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1-yl]-1,3,4-oxadiazole. The ^1H, ^{13}C nmr and ms spectra of these compounds are presented.

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In the literature, the reactions of 5-alkyl- and 5-aryltetrazoles with aryl chlorides or anhydrides, afforded the corresponding 1,3,4-oxadiazoles in moderate yield [1-4] and El Khadem [5] obtained them by oxidation of the carbohydrate hydrazone.

Giri, Singh, and Yadav [6] described the antifungical activity for some lipophylic 1,3,4-oxadiazole derivatives, while Ramalingan *et al.* [7] found antiinflammatory, central depressant and hypotensive activity on the nervous system in animals with 2,5-disubstituted oxadiazoles. On the other hand antibacterial activity was detected on Gram positive and Gram negative bacteria with other 2-(*p*-chlorophenyl)-1,3,4-oxadiazole-5-acylureas [8].

We report here the synthesis of 2-(*p*-chlorophenyl)-5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1-yl]-1,3,4-oxadiazole (**1**) by the reaction of 5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1-yl]tetrazole [9] with *p*-chlorobenzoyl chloride.

To propose the preferred conformation for compound **1** in solution, the ^1H nmr spectrum of **1** was observed in deuteriochloroform. It permitted a first order analysis, but we observed a superposition of the signals of H-2' and H-3'. Computer simulation was used to confirm their chemical shifts and coupling constants.

The values of the coupling constants of 2-(*p*-chlorophenyl)-5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1-yl]-1,3,4-oxadiazole (**1**) for antiperiplanar protons ($J_{2,3}$ = 8.0. Hz) and gauche protons ($J_{1,2}$ = 2.3 Hz, $J_{3,4}$ = 3.1 Hz) are consistent with a planar, zig-zag arrangement of the carbon skeleton. The coupling constants and chemical shifts are presented in the Experimental.

The assignment of the ^{13}C nmr signals in compound **1** was made by comparison with the corresponding signals of 2-phenyl-5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1-yl]-1,3,4-oxadiazole [3]. We observed a very good

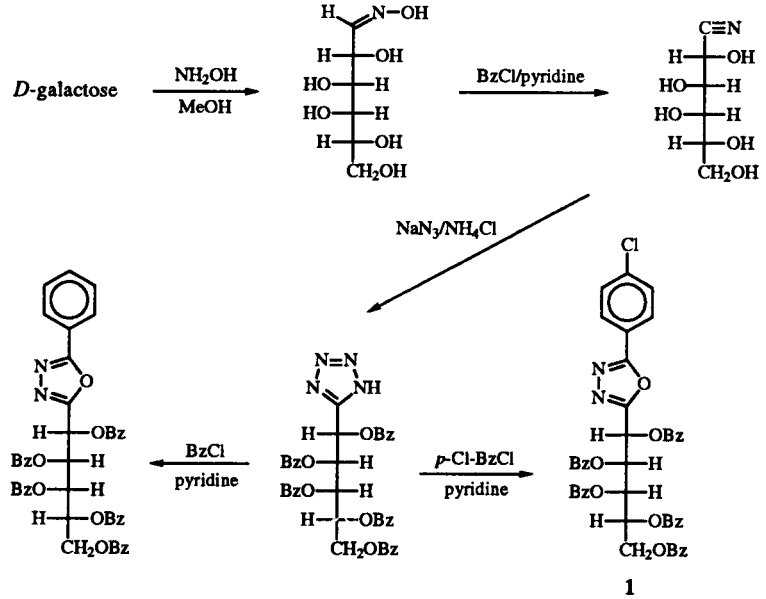

Figure 1.

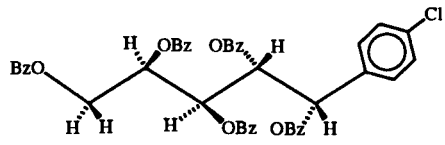

Figure 2.

correlation because both compounds present the same preferential conformation in solution. The different signals and their assignment are shown in the Experimental.

In the mass spectra, the characteristic isotopic cluster for chlorine was observed. The principal fragments are presented in Table I.

The debenzoylation of compound **1** with triethylamine/methanol/water gave an equilibrium mixture of two different structures. One of them was the debenzoylated oxadiazole **2a**. The other showed the rearrangement into the 1,4-lactone **2b**, and are shown in Figure 3.

Similar results were obtained by debenzoylation of 2-phenyl-5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1-yl]-1,3,4-oxadiazole **3a** and **3b**. El Khadem *et al.* [5] reported the equilibrium of two compounds when they deacetylated 2-phenyl-5-[1',2',3',4',5'-penta-*O*-acetyl-*D*-galactopentitol-1-yl]-1,3,4-oxadiazole with methanolic ammonia at room temperature. They described the unprotected oxadiazole and a benzoyliminohydrazonolactone, which were characterized by their ir spectra and physical constants.

Table I

Major Fragments Resulting from Electron Impact Ionization of (*p*-Chlorophenyl)-5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1'-yl]-1,3,4-oxadiazole (**1**)

m/z	AR%	Assignment
731	0.23	$(M+2)^{+\bullet}$ - PhCOO•
730	0.35	$(M+2)^{+\bullet}$ - PhCOOH
729	0.70	$M^{+\bullet}$ - PhCOO•
728	1.05	$M^{+\bullet}$ - PhCOOH
626	1.07	$(M+2)^{+\bullet}$ - $(PhCO)_2O$
624	3.20	$M^{+\bullet}$ - $(PhCO)_2O$
565	1.30	$M^{+\bullet}$ - $ClC_6H_4\bullet$ - CO - N_2 - PhCOOH
504	0.27	$(M+2)^{+\bullet}$ - $(PhCO)_2O$ - PhCOOH
502	0.80	$M^{+\bullet}$ - $(PhCO)_2O$ - PhCOOH
475	0.45	$M^{+\bullet}$ - $(PhCO)_2O$ - N_2 - PhCOO•
474	3.60	$M^{+\bullet}$ - $(PhCO)_2O$ - N_2 - PhCOOH
471	10.00	$M^{+\bullet}$ - $(PhCO)_2O$ - $C_7H_4NOCl\bullet$
420	0.23	$(M+2)^{+\bullet}$ - $(PhCO)_2O$ - H_2CO - N_2 - CH_2=CHOCOPh
418	0.70	$M^{+\bullet}$ - $(PhCO)_2O$ - H_2CO - N_2 - CH_2=CHOCOPh
382	0.34	$(M+2)^{+\bullet}$ - $(PhCO)_2O$ - 2PhCOOH
380	1.00	$M^{+\bullet}$ - $(PhCO)_2O$ - 2PhCOOH
379	1.82	$M^{+\bullet}$ - $(PhCO)_2O$ - 2PhCOOH - H•
369	0.27	$(M+2)^{+\bullet}$ - $(PhCO)_2O$ - PhCOOH - $PhCOOCH_2\bullet$
367	0.82	$M^{+\bullet}$ - $(PhCO)_2O$ - PhCOOH - $PhCOOCH_2\bullet$
353	0.13	$(M+2)^{+\bullet}$ - $(PhCO)_2O$ - PhCOOH - $PhCOOCH_2\bullet$
351	0.40	$M^{+\bullet}$ - $(PhCO)_2O$ - N_2 - 2PhCOOH - H•
311	1.10	$M^{+\bullet}$ - $(PhCO)_2O$ - $C_{16}H_{10}N_2O_3Cl\bullet$
269	2.00	$M^{+\bullet}$ - $C_{18}H_{22}N_2O_5Cl\bullet$
122	3.00	$PhCOOH^{+\bullet}$
105	100.00	$PhCO^{+\bullet}$
77	11.00	$C_6H_5^+$
51	3.00	$C_4H_3^+$

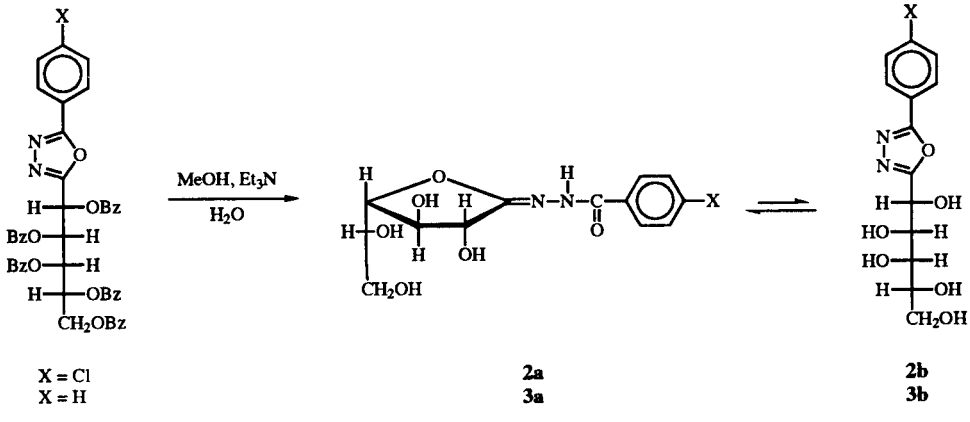

Figure 3.

The ^1H , ^{13}C nmr and mass spectra of these mixtures in equilibrium are shown in the Experimental.

Even so the debenzoylation of compounds **1** and of 2-phenyl-5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1-yl]-1,3,4-oxadiazole give a mixture of two structures, the cyclic oxadiazole derivative and the open chain structure, however either of them could have biologic activity [10].

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 ^{13}C nmr spectra were recorded at 25.20 MHz with tetramethyl-

silane as the internal standard. Mass spectra were performed by electron impact ionization at 70 eV and 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-isobutane (7:3) as eluents and iodine vapor for detection.

Synthesis of 2-(*p*-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole.

5-Phenyltetrazole (0.74 g) was dissolved in 50 ml of anhydrous pyridine, 2.3 ml of freshly distilled *p*-chlorobenzoyl chloride was added, and the solution heated 1.5 hours at 100°. The mixture was cooled, poured into ice water and the solid filtered and recrystallized from ethanol. The 2-(*p*-chlorophenyl)-5-phenyl-1,3,4-oxadiazole (0.93 g, 72%) was obtained as an amorphous solid, mp 162-163°; ^{13}C nmr: heterocyclic carbons 163.7 and 164.6, aromatic carbons 122.7-137.5; ms: 258 [33.3, $(M + 2)^{+\bullet}$], 256 [base peak, $M^{+\bullet}$], 202 [4.4, $(M + 2)^{+\bullet} - N_2 - CO$], 200 [1.4, $M^{+\bullet} - N_2 - CO$], 165 [80, $(M^{\bullet} + 2)^{+\bullet} - N_2 - CO - Cl^{37\bullet}$ or $M^{+\bullet} - N_2 - CO - Cl^{35\bullet}$], 141 [24.4, $Cl^{37}C_6H_4CO^+$], 77 [60, $C_6H_5^+$].

Anal. Calcd. for $C_{14}H_9N_2OCl$: C, 65.50; H, 3.51; N, 10.92; Cl, 13.84. Found: C, 65.66; H, 3.79; N, 11.17; Cl, 14.08.

Synthesis of 2-(*p*-Chlorophenyl)-5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1'-yl]-1,3,4-oxadiazole (**1**).

5-(1',2',3',4',5'-Penta-*O*-benzoyl-*D*-galactopentitol-1'-yl)tetrazole [9] (2.43 g) was dissolved in 40 ml of anhydrous pyridine, 1.10 ml of freshly distilled *p*-chlorobenzoyl chloride was added, and the mixture heated 2 hours at 100°. It was cooled, poured into ice water, filtered and recrystallized from acetone, and then from ethanol. Compound **1** (2.54 g, 70%) was obtained as an amorphous solid of mp 198-199°, $[\alpha]_D$ +6.9 (c 1, pyridine); ^1H nmr: H-1' 6.67 (d, $J_{1',2'} = 2.7$), H-2' 6.28 (dd, $J_{2,3'} = 8.0$), H-3' 6.28 (m, $J_{3',4'} = 3.1$), H-4' 6.04 (ddd, $J_{4',5'a} = 5.0$), H-5'b 4.55 (dd, $J_{4',5'b} = 7.3$), H-5'a 4.66 (dd, $J_{5'a,5'b} = 11.6$), aromatic protons 7.2-7.9; ^{13}C nmr: C-1' 65.2, C-2' 69.7, C-3' 69.1, C-4' 68.9, C-5' 62.8; heterocyclic carbons 161.6; aromatic carbons 128.2-133.5; carbonyl carbons 162.6-165.7; ms: see Table I.

Anal. Calcd. for: $C_{48}H_{35}N_2O_{11}Cl$: C, 67.72; H, 4.16; N, 3.33; Cl, 4.22. Found: C, 67.55; H, 4.13; N, 3.64; Cl, 4.43.

Synthesis of 2-Phenyl-5-[1',2',3',4',5'-penta-*O*-benzoyl *D*-galactopentitol-1-yl]-1,3,4-oxadiazole.

5-(1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1'-yl)tetrazole (2.0 g) was treated with benzoyl chloride (2.5 ml) by the same technique as given for compound **1**; 1.53 g of 2-phenyl-5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1-yl]-1,3,4-oxadiazole (yield 55%) was obtained mp 194-196° (lit [3] mp 195-196°).

Debenzoylation of 2-(*p*-Chlorophenyl)-5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1'-yl)-1,3,4-oxadiazole (**1**).

Compound **1** (0.53 g) was shaken with 50 ml of ethanol/water/triethylamine (5:2.1:1 v/v) at 45-50° until the starting material disappeared (9 days). The solvent was evaporated and water added and the methyl benzoate extracted with ethyl ether. The water layer was freeze dried and gave a white solid (0.16 g, 86%) which was recrystallized from ethanol, mp 237-239°, $[\alpha]_D$ +78° (c, 1, pyridine). The debenzoylated product in solution was a mixture of two components **2a** and **2b**; ^1H nmr (dimethyl-d_6 sulfoxide): compound **2a**: H-2 5.78 (d, $J_{2,3} = 4.5$), H-3 4.94 (t, $J_{3,4} = 6.6$), H-4 6.07, H-6a 4.42, H-6b 4.10 (m), compound **2b**: H-1' 5.15 (d), H-2' 3.80, H-3' 3.65, H-4' 3.75, H-5'a and H-5'b 3.50, aromatic protons 7.4-7.9 and a signal at 10.27 corresponding to the NH proton; ^{13}C nmr (dimethyl-d_6 sulfoxide): compound **2a**: C-1 87.9, C-2 74.3, C-3 74.8, C-4 83.8, C-5 69.2, C-6 63.3; compound **2b**: C-1' 66.5, C-2' 72.3, C-3' 70.8, C-4' 70.6, C-5' 64.1, aromatic carbons 126.5-133.0, C=O 158.1, heterocyclic carbon 162.5; ms: 332 [0.2, $(M + 2)^{+\bullet}$], 330 [0.6, $M^{+\bullet}$], 271 [0.3, $(M + 2)^{+\bullet} - C_2H_5O_2^{\bullet}$], 269 [0.8, $[M^{+\bullet} - C_2H_5O_2^{\bullet}]$], 241 [0.5, $(M + 2)^{+\bullet} - C_3H_7O_3^{\bullet}$], 239 [1.7, $(M^{+\bullet} - C_3H_7O_3^{\bullet}$], 225 [0.8, $(M + 2)^{+\bullet} - N_2 - H_2O - C_2H_5O_2^{\bullet}$], 223 [2.6, $M^{+\bullet} - N_2 - H_2O - C_2H_5O_2^{\bullet}$], 212 [5.0, $C_9H_7N_2O_2Cl^{37+\bullet}$], 210 [18.0, $C_9H_7N_2O_2Cl^{35+\bullet}$], 181 [1.6, $C_8H_4N_2OCl^{37+\bullet}$], 179 [1.3, $C_8H_4N_2OCl^{35+\bullet}$], 172 [3.8, $C_7H_4NOCl^{37+\bullet}$], 170 [12.7, $C_7H_4NOCl^{35+\bullet}$], 155 [10.8, $(M + 2)^{+\bullet} - C_7H_4NOCl^{37} - H_2O$ or $M^{+\bullet} - C_7H_4NOCl^{35} - H_2O$], 141 [34.3, $Cl^{37}C_6H_4CO^+$], 139 [base peak, $Cl^{35}C_6H_4CO^+$], 121 [0.9, $C_4H_9O_4^+$], 113 [12.9, $C_6H_4Cl^{37+}$], 111 [38.4, $C_6H_4Cl^{35+}$], 91 [1.9, $C_3H_7O_3^+$], 87 [1.8, $C_4H_2Cl^{37+}$], 85 [7.5, $C_4H_2Cl^{35+}$], 73 [7.8, $C_3H_7O_3^+ - H_2O$], 61 [16.7, $C_2H_5O_2^+$].

Anal. Calcd. for $C_{13}H_{15}N_2O_6Cl$: C, 47.20; H, 4.54; N, 8.47; Cl, 10.74. Found: C, 46.98; H, 4.73; N, 8.23; Cl, 11.02.

Debenzoylation of 5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1'-yl)-1,3,4-oxadiazole.

5-[1',2',3',4',5'-penta-*O*-benzoyl-*D*-galactopentitol-1'-yl)-1,3,4-oxadiazole (0.8 g) were treated with 80 ml of methanol/water/triethylamine (5:2.1:1 v/v) at 45-50° by the same technique as given for compound **1**. A white solid was obtained (0.25 g, 78%) which was recrystallized from ethanol, mp 227-229°, $[\alpha]_D$ +75° (c, 1, pyridine). The debenzoylated product in solution was a mixture of two components **3a** and **3b**; ^1H nmr (dimethyl-d_6 sulfoxide): compound **3a**: H-2 5.75 (d, $J_{2,3} = 5.7$), H-3 4.43 (dd, $J_{3,4} = 6.1$), H-4 6.01 (dd, $J_{4,5} = 2.2$), H-6a 4.07, H-6b 4.14 ($J_{6a,6b} = 11.2$); compound **3b**: H-1' 5.2 (d, $J_{1',2'} = 2$), H-2' H-3' H-4' H-5'a and H-5'b appeared between 3.5-3.9 as complicated signals, aromatic protons 7.4-7.9 and a signal at 10.14 corresponding to the NH proton; ^{13}C nmr (dimethyl-d_6 sulfoxide): compound **3a**: C-1 82.7, C-2 74.4, C-3 74.4, C-4 83.8, C-5 69.8, C-6 62.2; compound **3b**: C-1' 66.3, C-2' 72.3, C-3' 69.8, C-4' 69.2, C-5' 63.3, aromatic carbons 126.8-132.1, C=O 157.6, heterocyclic carbon 161.2; ms: 296 [1.0, $M^{+\bullet}$], 265 [0.7, $M^{+\bullet} - CH_2OH^{\bullet}$], 247 [0.5, $M^{+\bullet} - H_2O - CH_2OH^{\bullet}$], 235 [2.8, $M^{+\bullet} - C_2H_5O_2^{\bullet}$], 205 [4.5, $M^{+\bullet} - C_3H_7O_3^{\bullet}$], 189 [8.1, $M^{+\bullet} - H_2 - C_6H_5CO^{\bullet}$], 187 [0.5, $M^{+\bullet} - H_2O - C_3H_7O_3^{\bullet}$], 176 [60.9, $C_9H_8N_2O_2^{+\bullet}$], 121 [28.1, $C_4H_9O_4^+$], 105 [base peak, $C_6H_5CO^+$], 91 [3.8, $C_3H_7O_3^+$], 77 [89.4, $C_6H_5^+$], 73 [7.8, $C_3H_7O_3^+ - H_2O$], 61 [16.7, $C_2H_5O_2^+$], 51 [25.4, $C_4H_3^+$].

Anal. Calcd. for $C_{13}H_{15}N_2O_6Cl$: C, 52.70; H, 5.44; N, 9.45. Found: C, 52.55; H, 5.70; N, 9.69.

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