*Carbohydrate Research*, 218 (1991) 223–227
Elsevier Science Publishers B.V., Amsterdam



# Note

## Synthesis and nuclear magnetic resonance spectra of the first 2,5-disubstituted 1,3,4-oxadiazoles from disaccharides

Miriam A. Martins Alho, Mirta L. Fascio, Norma B. D'Accorso, and Inge M. E. Thiel*
*Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales. Universidad de Buenos Aires, Pabellón 2, 1428 Buenos Aires (Argentina)*

(Received May 4th, 1990; accepted for publication, August 14th, 1990)

In the literature, the reactions of 5-alkyl- and 5-aryl-tetrazoles with aryl chlorides or acid anhydrides have been reported; they afforded the corresponding oxadiazoles in moderate yield[1–4]. We report herein an extension of the above-mentioned reaction with 5-[*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl)-(1→3)-(1,2,4,5-tetra-*O*-benzoyl-D-*gluco*-pentitol-1-yl]tetrazole[5] (**1**) which, on treatment with acetic anhydride or benzoyl chloride, yielded 2-methyl- (**2**) or 2-phenyl-5-[*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl)-(1→3)-(1,2,4,5-tetra-*O*-benzoyl-D-*gluco*-pentitol-1-yl]-1,3,4-oxadiazoles (**3**), respectively. Similar reactions, applied to 5-[*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→3)-(1,2,4,5-tetra-O-benzoyl-D-*gluco*-pentitol-1-yl]tetrazole[5] (**4**) gave 2-methyl- (**5**) or 2-phenyl-5-[*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→3)-1,2,4,5-tetra-*O*-benzoyl-D-*gluco*-pentitol-1-yl]-1,3,4-oxadiazole (**6**).

Some differences between the reaction to obtain the 2-phenyl and 2-methyl derivatives were observed. Compounds **3** and **6** were obtained under conditions milder than those used for compounds **2** and **5**, because a large excess of reagent and a long reflux time were necessary for the latter compounds.

The $^1$H-n.m.r. spectra of the oxadiazole derivatives were measured at 300 MHz and allowed first-order analysis (see Table I) to deduce the conformation of the compounds. In all, the cyclic part is in the $^4C_1$(D) conformation, and the acyclic part showed a deviation from the planar, extended, zig-zag conformation. This deviation may be attributed to one preponderant rotamer (as in compounds **5** and **6**) which has the antiperiplanar relationship that corresponds to a C-1′→C-2′ rotation[6] ($_1G^-$). An average between two rotamers was observed for compounds **2** ($J_{1',2'}$ 6.7 Hz) and **3** ($J_{1',2'}$ 6.4 Hz) which are (1″ → 3′)-α-D-linked. These values indicate the preponderance of the $_1G^-$ rotamer, but a $_3G^+$ must be postulated for compounds **2** and **3** ($J_{3',4'}$ 4.0 Hz). This conformation may be attributed to the bulky substituent at O-3′. Both possible rotamers, $_3G^-$ or $_3G^+$, show a 1,3-parallel interaction, one between BzO-2′ and -3′, and the

* To whom correspondence should be addressed.

0008-6215/91/$ 03.50 

TABLE I

$^1$H-N.m.r. chemical shift data ($\delta$) and vicinal proton–proton coupling constants (Hz)[a] of compounds **2**, **3**, **5**, and **6**

| *Compd.* | *H-1′* ($J_{1',2'}$) | *H-2′* ($J_{2',3'}$) | *H-3′* ($J_{3',4'}$) | *H-4′* ($J_{4',5'b}$) | *H-5′a* ($J_{4',5'a}$) | *H-5′b* ($J_{5'a,5'b}$) | *H-1″* ($J_{1'',2''}$) | *H-2″* ($J_{2'',3''}$) | *H-3″* ($J_{3'',4''}$) | *H-4″* ($J_{4'',5''}$) | *H-5″* ($J_{5'',6''b}$) | *H-6″a* ($J_{5'',6''a}$) | *H-6″b* ($J_{6''a,6''b}$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **2** | 6.69 | 6.21 | 4.91 | 5.89 | 4.85 | 4.87 | 5.71 | 5.48 | 6.18 | 5.65 | 4.63 | 4.23 | 4.10 |
| | (6.7) | (4.1) | (4.0) | (3.9) | (6.8) | (12.3) | (3.6) | (10.4) | (9.9) | (9.9) | (2.6) | (4.0) | (12.5) |
| **3** | [b] | 6.36 | 5.08 | 5.99 | 4.92 | 5.01 | 5.86 | 5.58 | 6.28 | 5.73 | 4.71 | 4.18 | 4.30 |
| | (6.4) | (4.3) | (4.0) | (4.4) | (6.6) | (12.2) | (3.6) | (10.2) | (9.9) | (9.9) | (2.5) | (4.0) | (12.5) |
| **5** | 7.06 | 6.33 | 5.15 | 5.56 | 4.69 | 4.41 | 5.18 | 5.77 | 5.88 | 5.72 | 4.02 | 4.38 | 4.18 |
| | (8.9) | (1.6) | (7.8) | (5.1) | (2.5) | (2.4) | (7.7) | (9.5) | (9.5) | (9.8) | (3.3) | (3.3) | (12.3) |
| **6** | [b] | 6.43 | 5.16 | 5.58 | 4.71 | 4.42 | 5.20 | 5.73 | 5.83 | 5.63 | 4.02 | 4.45 | 4.19 |
| | (9.6) | (1.6) | (7.8) | (5.0) | (2.6) | (12.4) | (7.7) | (9.6) | (9.5) | (9.8) | (2.8) | (3.2) | (12.4) |

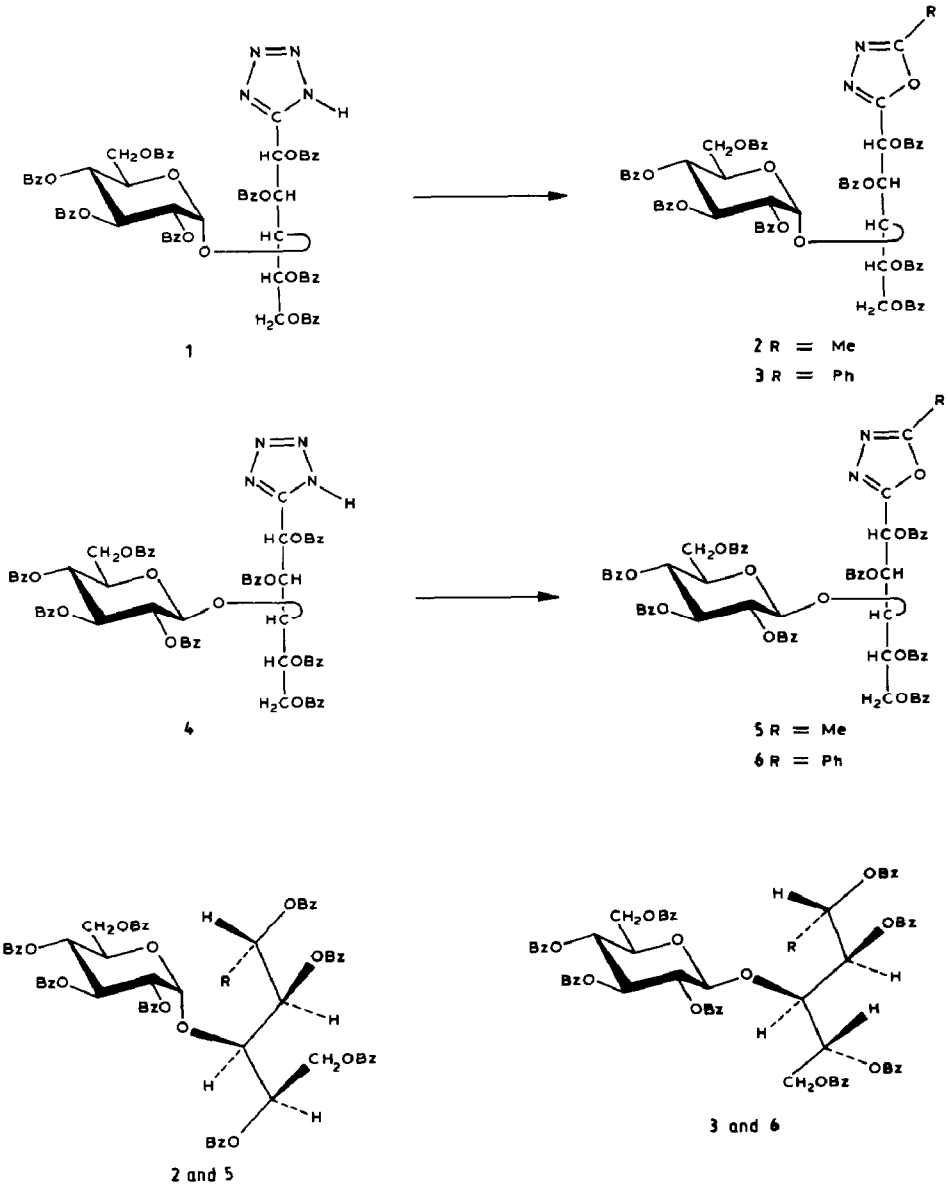
[a] In parentheses. [b] Possible superposition with the aromatic signals.

TABLE II

$^{13}$C-N.m.r. chemical shift data ($\delta$) of compounds **2**, **3**, **5** and, **6**

| *Compd.* | *C-Heter.* | *C-1′* | *C-2′* | *C-3′* | *C-4′* | *C-5′* | *C-1″* | *C-2″* | *C-3″* | *C-4″* | *C-5″* | *C-6″* | *C-$CH_3$* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **2** | 161.61 | 65.92 | 72.18 | 75.43 | 70.79 | 62.43 | 98.08 | 70.98 | 70.22 | 69.13 | 69.13 | 62.44 | 10.59 |
| **3** | 161.29 | 66.00 | 72.14 | 75.35 | 70.86[a] | 62.39[b] | 98.08 | 70.91[a] | 70.17 | 69.00 | 69.10 | 62.48[b] | |
| **5** | 162.41 | 64.85 | 69.07 | 74.89 | 69.42 | 62.33 | 100.85 | 72.26 | 71.97 | 69.81 | 72.79 | 62.15 | 10.76 |
| **6** | 162.05 | 65.23 | 68.86 | 75.04 | 69.62 | 62.34 | 100.97 | 72.86 | 72.72 | 69.90 | 72.04 | 61.84 | |

[a] C-4′ and C-2″ may be interchanged. [b] C-5′ and C-6″ may be interchanged.




2 and 3 R = 2-methyl-1,3,4-oxadiazol
5 and 6 R = 2-phenyl-1,3,4-oxadiazol

Scheme 1. Main conformation of compounds 2, 3, 5, and 6

other between BzO-3′ and -5′. The last interaction is probably less hindered and we report the rotation as ${}_3G^+$. The preferred conformation in solution is shown in Scheme 1.

The assignments of the $^{13}$C-n.m.r. signals of compounds **2** and **3** was made by comparison with 5-[*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl-(1→3)-1,2,4,5-te-

tra-*O*-benzoyl-D-*gluco*-pentitol-1-yl]tetrazole[5] (**1**) and those for compounds **5** and **6** by comparison with the signals of 5-[*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→3)-1,2,4,5-tetra-*O*-benzoyl-D-*gluco*-pentitol-1-yl]tetrazole[5] (**4**) (Table II). The most important difference between the signals of these compounds and their reference compounds were attributed to the different heterocyclic rings, and a good correlation was observed between the signals of **2** and **3** and between those of **5** and **6**, respectively, as they have the same conformation and configuration.

The comparison of the spectrum of **5** (having a 3-*O*-β-D-glucopyranosyl group) with that of **2** (having a 3-*O*-α-D-glucopyranosyl group) showed the expected change for the cyclic part due to the inversion of anomers (Δ C-1″ 2.77, Δ C-3″ 1.75, and Δ C-5″ 3.66 p.p.m.), as was reported earlier for other benzoylated derivatives[5,7–9]. The signals for the acyclic components showed differences due to the conformational changes (see Scheme 1). Similar differences were observed for compounds **3** and **6**.

## 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. $^1$H-N.m.r. spectra were recorded with a Bruker 300-MHz instrument, and $^{13}$C-n.m.r. for compounds **2** and **3** with a Bruker 75-MHz instrument, and for compounds **5** and **6** with a Varian XL-100 instrument at 25 MHz for solutions in $CDCl_3$ with $Me_4Si$ as the internal standard. T.l.c. was performed on plates coated with Silica Gel G (Merck, Darmstadt) with 9:1 benzene–ethyl acetate as eluent and $I_2$ vapor for detection.

*2-Methyl-5-[O-2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl)-(1→3)-1,2,4,5-tetra-*O*-benzoyl-*D*-gluco-pentitol-1-yl]-1,3,4-oxadiazole* (**2**). — Acetic anhydride (20 mL) was added to 5-[*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl)-(1→3)-1,2,4,5-tetra-*O*-benzoyl-D-*gluco*-pentitol-1-yl]tetrazol (2.5 g, 2 mmol). The mixture was heated at reflux during 10 h, cooled, and poured into cold water to give **2** as an amorphous solid. This was purified by flash chromatography on a dry column of Silica Gel G as adsorbent and various mixtures of benzene–ethyl acetate as eluent. Compound **2** was precipitated from ethyl alcohol–water (1.5 g, 60%) as an amorphous solid, m.p. 102–104°, $[\alpha]_D$ +85° (*c* 1, chloroform).

*Anal.* Calc. for $C_{70}H_{56}N_2O_{19}$: C, 68.40; H, 4.56; N, 2.28. Found: C, 68.18; H, 4.66; N, 2.31.

*2-Methyl-5-[O-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→3)-1,2,4,5-tetra-*O*-benzoyl-D-gluco-pentitol-1-yl]-1,3,4-oxadiazole* (**5**). — The same procedure, as described for compound **2**, was applied to 5-[*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→3)-tetra-*O*-benzoyl-D-*gluco*-pentitol-1-yl]tetrazol, to give **5** as an amorphous solid. This was dissolved in hot ethyl alcohol and precipitated with water (2.4 g, 96%), m.p. 104–106°, $[\alpha]_D$ +46° (*c* 1, chloroform).

*Anal.* Calc. for $C_{70}H_{56}N_2O_{19}\cdot C_6H_6$: C, 69.83; H, 4.74; N, 2.14. Found: C, 69.45; H, 4.78; N, 2.48.

*2-Phenyl-5-[O(-2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl)-(1→3)-1,2,4,5-te-*

*tra*-O-benzoyl-D-gluco-*pentitol-1-yl]-1,3,4-oxadiazole* (**3**). — 5-[*O*-(2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl)-(1→3)-tetra-*O*-benzoyl-D-*gluco*-pentitol-1-yl]tetrazole (6 g, 5 mmol) was dissolved in pyridine (16 mL) and benzoyl chloride (1.5 mL) was added. The mixture was heated at reflux for 1 h in a water bath. It was cooled to room temperature and poured into ice–water to give **3** as an amorphous solid. This was purified by a dry-column flash chromatography with Silica Gel G as adsorbent, and benzene and 19:1 benzene–ethyl acetate as eluents. Compound **3** was purified from ethyl alcohol–water and gave an amorphous compound (4.3 g, 67%), m.p. 98–100°, $[\alpha]_D$ +78° (*c* 1, chloroform).

*Anal.* Calc. for $C_{75}H_{58}N_2O_{19}$: C, 69.77; H, 4.50. N, 2.17. Found: C, 69.62; H, 4.74; N, 2.17.

*2-Phenyl-5-[*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→3)-1,2,4,5-tetra-*O*-benzoyl-*D-gluco-*pentitol-1-yl]-1,3,4-oxadiazole* (**6**). — The same procedure, as described for compound **3**, was applied to 5-[*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→3)-1,2,4,5-tetra-*O*-benzoyl-D-*gluco*-pentitol-1-yl]-tetrazole to give compound **6** as an amorphous solid (4.4 g, 68%), m.p. 113–114°, $[\alpha]_D$ +47.5° (*c* 1, chloroform).

*Anal.* Calc. for $C_{75}H_{58}N_2O_{19}$: C, 69.77; H, 4.50; N, 2.17. Found: C, 69.62; H, 4.71; N, 2.20.

ACKNOWLEDGMENTS

The authors thank the Consejo Nacional de Investigacions Cientificas y Técnicas and the Universidad de Buenos Aires for financial support. They acknowledge the Universidad de Buenos Aires for fellowships to M. A. Martins Alho and M. L. Fascio. They are grateful to Prof. Dr. T. N. Mitchell and Prof. Dr. W. P. Neumann, Universität Dortmund, West Germany, for the recording of the $^1$H-n.m.r. spectra of compounds **2**, **3**, **5**, and **6**, and the $^{13}$C-n.m.r. spectra of compounds **2** and **3**. They are indebted to UMYMFOR (CONICET–FCE y N UBA) for the recording of the $^{13}$C-n.m.r. spectra of compounds **5** and **6**, and for the microanalyses.

REFERENCES

1 J. Sauer, R. Huisgen, and H. J. Sturm, *Tetrahedron*, 11 (1960) 241–251; R. Huisgen, J. Sauer, H. J. Sturm, and J. Markgraf, *Chem. Ber.*, 93 (1960) 2106–2124; R. Huisgen, J. Sauer, and H. J. Sturm, *Angew. Chem.*, 70 (1958) 272–273.
2 H. El Khadem, M. Shaban, and M. Nassr, *Carbohydr. Res.*, 23 (1972) 103–109.
3 A. M. Seldes, E. G. Gros, I. M. E. Thiel, and J. O. Deferrari, *Carbohydr. Res.*, 49 (1976) 49–56.
4 A. M. C. Sanchez, N. B. D'Accorso, and I. M. E. Thiel, *An. Asoc. Quim. Argent.*, 77 (1989) 133–137.
5 L. C. Otegui, M. L. Fascio, M. A. Martins Alho, N. B. D'Accorso, and I. M. E. Thiel, *An. Asoc. Quim. Argent.*, 78 (1990) 65–74.
6 S. J. Angyal, R. Le Fur, and D. Gagnaire, *Carbohydr. Res.*, 23 (1972) 121–134; D. Horton and J. D. Wander, *J. Org. Chem.*, 39 (1964) 1859–1863.
7 N. B. D'Accorso, I. M. E. Thiel, and M. Schüller, *Carbohydr. Res.*, 124 (1983) 177–184.
8 N. B. D'Accorso, I. M. Vazquez, and I. M. E. Thiel, *Carbohydr. Res.*, 156 (1986) 207–213.
9 N. B. D'Accorso, B. N. Zuazo, and I. M. E. Thiel, *Carbohydr. Res.*, 172 (1988) 147–155.