Reactions of 1-Glucosyl-5-nitro-1,2,4-triazole With Nucleophiles

María José Camarasa and Federico G. De Las Heras*

Instituto de Química Médica, Juan de la Cierva 3,
Madrid-6, Spain

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1-Glucosyl-5-nitro-1,2,4-triazole reacted with nucleophiles, such as water, aziridine, chloride ion and 4-dimethylaminopyridine to give the corresponding 5-substituted 1-glucosyl-1,2,4-triazole derivatives.

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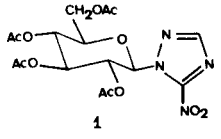
Nucleophilic substitution of diazoles, pyrazole [1] and imidazole [2] is a well known reaction. However, there are few reports on similar nucleophilic displacements on 1,2,3- [3] and 1,2,4-triazoles [4]. In the course of research on the synthesis of nitro-1,2,4-triazole derivatives as antiprotozoan agents we prepared 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-nitro-1,2,4-triazole (**1**), having cytostatic activity, and its 3-nitro-1,2,4-triazole isomer **2** [5]. In this paper we describe the high reactivity of compound **1** toward nucleophiles, which could explain, through an alkylating type mechanism of action, the observed significant cytostatic activity of **1** against HeLa cells [5].

We first observed that, on standing at room temperature in an open flask, compound **1** was quantitatively transformed to 1-glucosyl-1,2,4-triazolin-5-one (**6**). This transformation also took place in an aqueous solution of **1** in an organic solvent, such as acetonitrile. This implied the hydrolytic substitution of the 5-nitro group of **1** by atmospheric humidity. Under the same conditions 1-glucosyl-3-nitro-1,2,4-triazole **2** was completely stable [6]. According to this we thought that compound **1** could also react with other nucleophiles.



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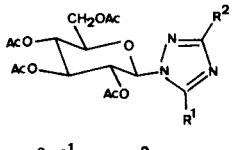


2, $R^1 = H$; $R^2 = NO_2$

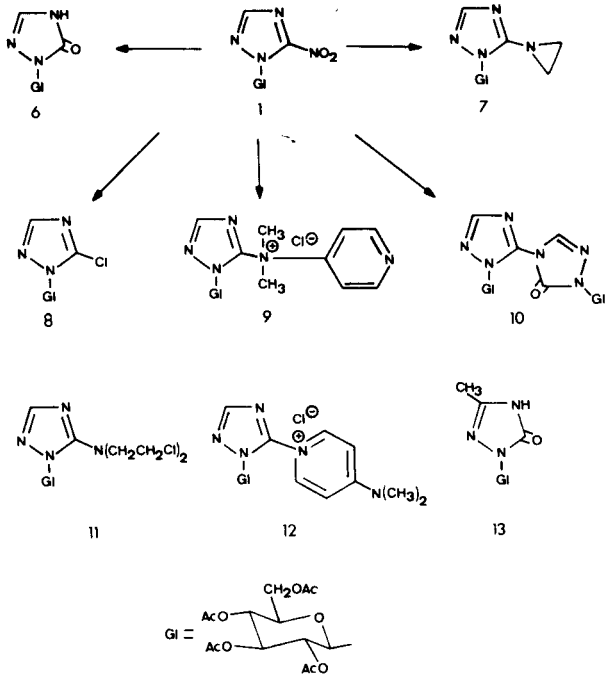
3, $R^1 = R^2 = H$

4, $R^1 = NH_2$; $R^2 = H$

5, $R^1 = H$; $R^2 = NH_2$

Reaction of 5-nitro-1,2,4-triazole (**1**) with aziridine in dry acetone in the absence of moisture afforded the 5-(aziridin-1-yl)-1,2,4-triazole derivative **7**, which in spite of having an alkylating aziridino group, did not show cytostatic activity against HeLa cells [7]. Similarly, compound **1** reacted with bis(2-chloroethyl)amine, freshly liberated from its hydrochloride to yield, not the expected 5-bis(2-chloroethyl)amino-1,2,4-triazole derivative (**11**), but the 1-glucosyl-5-chloro-1,2,4-triazole (**8**). This compound was formed by nucleophilic substitution of the 5-nitro group of **1** by a Cl^- ion from the bis(2-chloroethyl)amine [6c,8]. When the reaction between compound **1** and bis(2-chloroethyl)amine was carried out in the presence of 4-dimethylaminopyridine, as an acceptor of the hydrogen chloride liberated, the quaternary ammonium chloride derivative **9** was obtained in 48% yield. The formation of **9** instead of the alternative pyridinium glucoside **12** was confirmed by comparison of the nmr spectra of **9** with those of 4-dimethylaminopyridine, 1-methyl-4-dimethylaminopyridinium iodide [9] and 2-pyridyl trimethyl ammonium iodide [9].

In the above reactions, small amounts of **10** were also obtained by reaction of triazolinone **6**, already present as a minor component in the starting material **1**, or formed during the reaction, with 5-nitro-1,2,4-triazole (**1**). The yield of **10** was increased up to 50% when an acetonitrile solution of **1** was refluxed in the presence of 18-crown-6. The structure of **10** was suggested by the above demonstrated reactivity of the 5-position of **1** toward nucleophiles and the reactivity of **6** as a nucleophile. It has been reported that 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-methyl-1,2,4-triazolin-5-one (**13**), is glucosylated at N-4 by reaction with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide [10]. Similarly, 1,3-dimethyl-1,2,4-triazolin-5-one reacted with methyl iodide or diazomethane to give



6 **1** **7**

8 **9** **10**

11 **12** **13**

Gl =

Table 1

^{13}C-NMR Chemical Shifts of 1-Glucosyl-5-substituted-1,2,4-triazole Derivatives in DMSO-d_6 Solution [a]

Compound	C-1′	C-2′	C-4′	C-3′ - C-5′	C-6′	C-3	C-5	Others
3	83.45	70.19	67.92	72.71 [b] 73.57 [b]	61.95	152.08	145.20	
4	80.91	68.77	67.74	73.02	61.78	149.31	156.10	
5	82.83	69.54	67.79	72.95	61.83	164.29	144.29	
6	78.74	68.72	67.72	72.58 [b] 73.02 [b]	61.69	135.35	154.14	
7	80.36	69.11	67.74	72.91	61.71	149.44	161.83	29.35 $(CH_2)_2N$
8	81.53	69.24	67.41	72.24 [b] 73.15 [b]	61.38	152.10	142.51	
9	81.70	69.05	67.05	72.26 [b] 73.42 [b]	61.16	151.09	156.91	40.51 [$^+N(CH_3)_3$]
								108.23 (pyridine C-3, C-5)
								140.34 (pyridine C-2, C-6)
								149.63 (pyridine C-4)
10 [c]	81.55	69.48	67.57	72.50	61.55	151.65	150.20	
	79.93	68.57	67.57	72.50 [b] 73.48 [b]	61.55	136.66	143.27	
13	78.56	68.66	67.73	72.37 [b] 73.04 [b]	61.77	144.31	154.30	11.93 (3-CH_3)

[a] ^{13}C Chemical shifts of the glucosyl residue were assigned from the decoupled and off-resonance spectra and by comparison with previously reported data [17,18]. [b] Peaks not unequivocally assigned to C-3′ or C-5′. [c] Peaks not assigned to a particular moiety of **10**.

1,3,4-trimethyl-1,2,4-triazolin-5-one as the only or major product, respectively [11]. According to this, the nitro group of **1** should be displaced by the N-4 atom of triazolin-5-one **6** to give **10**. Analytical and mass, ^{1}H and ^{13}C nmr spectroscopic data of **10** were in agreement with the assigned structure.

The position of the triazole substituent in the above compounds was determined on the basis of the differences in chemical shifts of the triazole proton in DMSO-d_6 and deuteriochloroform, since the chemical shift of the proton adjacent to the substituted (H-5) in 1,2,4-triazoles is more sensitive to solvent changes than is H-3 [12]. Thus, the $\Delta\delta$ = δ DMSO-d_6-δ deuteriochloroform values for aziridine derivative **7** and 5-chloro-1,2,4-triazole **8** were 0.07 and 0.28 ppm, respectively. These small values were very similar to those of known 1-substituted-5-amino-1,2,4-triazoles [5,13] and 1-substituted-5-chloro-1,2,4-triazoles [14] and indicated that both substituents were at 5 position. However, the intermediate $\Delta\delta$ values of compounds **6** and **9** precluded an unequivocal assignment by this criterion. Thus, their structures were determined by ^{13}C nmr (Table 1).

The structures of aziridino derivative **7** and ammonium salt **9**, as 5-substituted-1,2,4-triazoles were demonstrated by comparing their C-3 and C-5 ^{13}C chemical shifts with those of 1-glucosyl-1,2,4-triazole **3** [15], 1-glucosyl-5-amino-1,2,4-triazole **4** [5], and 1-glucosyl-3-amino-1,2,4-triazole **5** [5]. The C-3 and C-5 chemical shifts of **7** and **9** were similar to those of 5-amino derivative **4** and clearly different from those of 3-amino-1,2,4-triazole (**5**). The structure of **8** as a 5-chloro-1,2,4-triazole was determined in a similar way by comparing the C-3 and C-5 chemical shifts of **8** and **3** and taking into account the ^{13}C shifts induced by halogen atoms in azoles [16]. The structure of triazolin-5-one **6** was determined by comparing the ^{1}H and ^{13}C nmr spectra of **6** and 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3-methyl-1,2,4-triazolin-5-one (**13**), the structure of which has been demonstrated by chemical means [10]. The sugar bands in the ^{1}H nmr spectra of both compounds were almost identical. The similarity in the chemical shifts of the anomeric protons δ DMSO = 5.66 for **6** and δ DMSO = 5.63 for **13** indicated the similarity of both bases and their glycosidation positions. The ^{13}C nmr spectra of **6** and **13** were also very similar, and the only difference was the chemical shift of C-3, which appeared at lower field for **13** than for **6** due to the shifting effect of the 3-methyl group.

EXPERIMENTAL

Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. Proton and ^{13}C nuclear magnetic resonance spectra were recorded with a Varian EM-390 and a Bruker WP 80 SY spectrometer, respecively, using TMS as the internal standard. The uv absorption spectra were taken with a Perkin-Elmer 402 spectrophotometer. The ir spectra were recorded with a Perkin-Elmer 257 spectrophotometer and mass spectra with a Hitachi-Perkin-Elmer RMV-GMG instrument. Analytical tlc was performed on aluminium sheets coated with a 0.2 mm layer of silica gel 60 F_{254} (Merck) and preparative layer chromatography was prepared on 20 × 20 cm glass plates coated with a 2 mm layer of silica gel PF_{254} (Merck).

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,4-triazolin-5-one (**6**).

A solution of **1** (1 g, 2.2 mmoles) in acetonitrile (5 ml) and water (1 ml) was allowed to stand 15 days. On evaporation of the solvents compound **6** was obtained quantitatively, mp 250° (from ethanol-ethyl ether); ir (potassium bromide): 1710 cm^{-1} (triazolinone C=O); pmr (DMSO): δ 5.66 (d, 1H, H-1′, $J_{1',2'}$ = 9 Hz), 7.86 (s, 1H, H-3); (deuteriochloroform): δ 5.68 (d, 1H, H-1′), 7.47 (s, 1H, H-3).

Anal. Calcd. for $C_{16}H_{20}N_3O_{10}$: C, 46.37; H, 4.86; N, 10.14. Found: C, 46.47; H, 5.04; N, 10.12.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-(aziridin-1-yl)-1,2,4-triazole (**7**).

A solution of **1** (0.5 g, 1.1 mmoles), dry acetone (10 ml) and aziridine (0.1 ml, 1.9 mmoles) was stirred at room temperature overnight in the absence of humidity. After chromatographic purification 0.31 g (63%) of **7** was obtained; mp 194-195° (from ethanol); pmr (DMSO): δ 2.39 (s, 4H, aziridine CH_2), 6.15 (d, 1H, H-1', $J_{1',2'}$ = 9 Hz), 7.65 (s, 1H, H-3); (deuteriochloroform): δ 5.83 (d, 1H, H-1'), 7.58 (s, 1H, H-3).

Anal. Calcd. for $C_{18}H_{24}N_4O_9$: C, 49.09; H, 5.45; N, 12.72. Found: C, 49.04; H, 5.31; N, 12.60.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-chloro-1,2,4-triazole (**8**).

A mixture of **1** (0.5 g, 1.1 mmoles), acetontrile (10 ml) and bis(2-chloroethyl)amine (2 g, 14 mmoles), freshly liberated from its hydrochloride, was refluxed overnight. On evaporation of the solvent and chromatographic purification 0.25 g (52%) of **8** was obtained, mp 161-163° (from ethyl acetate-hexane); ms: m/e 434 and 436 (M^+ +1, 1 and 0.3%), 374, 376 (1, 0.3%), 360, 362 (3, 1%), 331 (sugar ion, 47%), 102, 104 (5-chloro-1,2,4-triazole ions, 30, 10%); pmr (DMSO): δ 6.30 (d, 1H, H-1', $J_{1',2'}$ = 9 Hz), 8.20 (s, 1H, H-3); (deuteriochloroform): δ 5.76 (d, 1H, H-1'), 7.92 (s, 1H, H-3).

Anal. Calcd. for $C_{16}H_{20}ClN_3O_9$: C, 44.29; H, 4.61; Cl, 8.18; N, 9.68. Found: C, 43.91; H, 4.55; Cl, 8.40; N, 9.68.

[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,4-triazol-5-yl]dimethyl-(pyridin-4-yl) Ammonium Chloride (**9**).

A mixture of **1** (0.5 g, 1.1 mmoles), DMF (10 ml), bis(2-chloroethyl)amine (0.5 g, 3.6 mmoles) freshly liberated from its hydrochloride, and 4-dimethylaminopyridine (0.3 g, 2.4 mmoles) was stirred at room temperature for 7 hours. After filtration, evaporation of the filtrate and chromatographic purification, 0.3 g (48%) of **9** were obtained, mp 190-191° (ethanol-ethyl ether); ir (potassium bromide): 2300-3300 cm^{-1} (ammonium salt); pmr (DMSO + deuterium oxide): δ 3.40 (s, 6H, N-CH_3), 6.15 (d, 1H, H-1', $J_{1',2'}$ = 9 Hz), 7.26, 8.33 (2d, 4H, pyridine, J = 7 Hz), 8.33 (s, 1H, H-3); (deuteriochloroform): δ 7.92 (s, 1H, H-3).

Anal. Calcd. for $C_{23}H_{30}ClN_5O_9$: C, 49.68; H, 5.40; Cl, 6.39; N, 12.60. Found: C, 49.30; H, 5.62; Cl, 6.51; N, 12.34.

1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,4-triazol-5-yl]-1,2,4-triazolin-5-one (**10**).

A mixture of compound **1** (0.5 g, 1.1 mmoles), dry acetonitrile (5 ml) and 18-crown-6 (0.1 g, 0.37 mmoles) was refluxed for 4 hours. After evaporation and chromatographic purification, compound **10** (0.23 g, 50%) was obtained as a white foam; ms: m/e 812 (M^+, 0.1%), 752 (M^+ −60, 0.5%), 692 (M^+ −120, 1.5%), 650 (M^+ −60 −42, 1.5%), 632 (M^+ −180, 3%), 331 (sugar ion, 60%); pmr (DMSO): δ 5.90 and 6.16 (2d, 2H, H-1', H-1', $J_{1',2'}$ = 9 Hz), 8.30 and 8.46 (2s, 2H, H-3, H-3); (deuteriochloroform): δ 7.67 and 7.74 (2s, 2H, H-3, H-3).

Anal. Calcd. for $C_{32}H_{40}N_6O_{19}$: C, 47.29; H, 4.92; N, 10.36. Found: C, 47.33; H, 5.40; N, 10.08.

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