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2-PHENYL-1,2,3-OSOTRIAZOLE C-NUCLEOSIDE ANALOGS SYNTHESIS AND DETERMINATION OF ANOMERIC CONFIGURATION

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Summary: A series of anomeric 2-phenyl-1,2,3-osotriazole C-nucleoside analogs has been prepared. The anomeric configuration was determined by a novel method from the chemical shift of the C-5 proton of the osotriazole base moieties.

C-Nucleoside analogs are useful tools for biochemical investigations and for antimitotic or antiviral research[1]. The carbon-carbon linkage between the glycosyl and base moieties, makes these compounds more stable towards acid and enzymatic cleavage, than N-nucleosides. A satisfactory method for synthesis is by dehydration of the hydroxyalkyl chain of C-(hydroxyalklated) nitrogen heterocyclic derivatives by use of a strong acid[2-5]. This method has not been extensively used because of the uncertainty of their anomeric configuration[6].

In the present work 2-phenyl-1,2,3-osotriazole C-nucleoside analogs having the D-lyxo-, D-arabino-, and D-ribo-furanosyl configuration were prepared from their precursors 3,6-anhydro-heptulose phenylosazones by cyclization of the bis-(phenylhydrazone) residues with copper sulphate. Dehydration of D-galacto-heptulose phenyloszone with methanolic sulphuric acid solution[8,9], then refluxing the product with copper sulphate, (Scheme 1), gave the anomeric mixture 4-(β-D-lyxofuranosyl)-2-phenyl-1,2,3-osotriazole 1, and 4-(α-D-lyxofuranosyl)-2-phenyl-1,2,3-osotriazole 2, in 52% overall yield, they were separated by fractional crystallization. Compound 1; m.p. 125°, $[\alpha]_D^{22}$ + 4.3° (C 2.4, methanol), high resolution mass spectrum showed m/e 277.105 (cal. for $C_{13}H_{15}N_3O_4$; 277.106). UV (methanol) λ_{max} 265 nm (log ε 4.4). Compound 2; m.p. 204°, $[\alpha]_D^{22}$ + 51° (C 0.4, methanol), high resolution mass spectrum showed m/e 277.106 (calc. 277.106). UV (methanol) λ_{max} 266 nm (log ε 4.3). Acetylation of 1 and 2 with acetic anhydride and pyridine afforded 3 and 4 in 70% and 75% yield, respectively. Compound 3 was obtained as a syrup, high resolution mass spectrum showed m/e 403.139 (calc. for $C_{19}H_{21}N_3O_7$; 403.139). IR($CHCl_3$) 1735 cm^{-1}(OAc). Compound 4; m.p. 114-115°, high resolution mass spectrum showed m/e 403.139 (calc. 403.139). IR (KRr) 1740 cm^{-1} (OAc).

D-gluco-Heptulose phenylosazone afforded the anomeric mixture, 4-(β-D-arabinofuranosyl)-2-phenyl-1,2,3-osotriazole 5 and 4-(α-D-arabinofuranosyl)-2-phenyl-1,2,3-osotriazole 6, in 46% overall yield. Compound 5; m.p. 130°, $[\alpha]_D^{22}$ -56,5° (C 1.1, methanol), high resolution mass spectrum showed m/e 277·107 (calc. for $C_{13}H_{15}N_3O_4$; 277·106). Compound 7; m.p. 144°, $[\alpha]_D^{22}$ + 66.2° (C 0.13, methanol), high resolution mass spectrum showed m/e 277·107 (calc. 277·106).

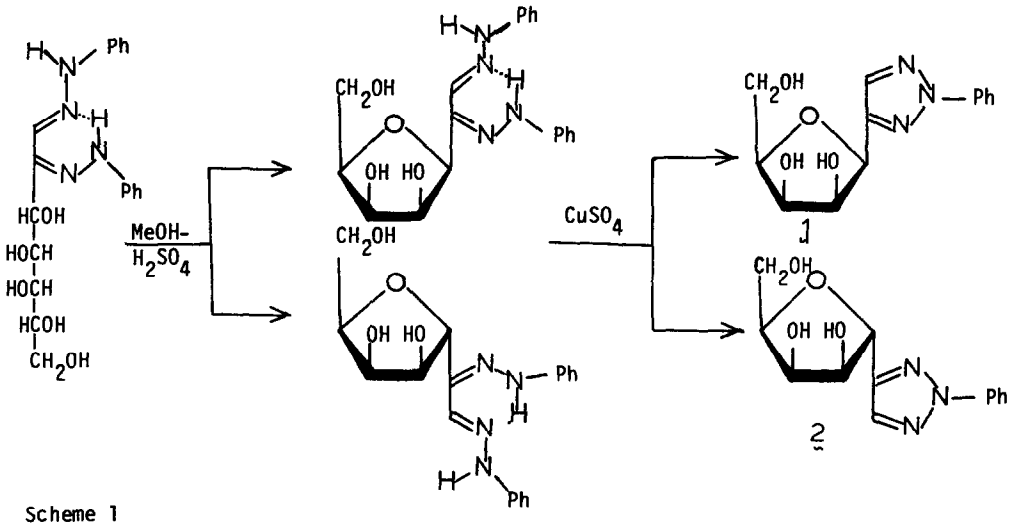
The anomeric configuration was determined by a novel method from the n.m.r. spectra of these compounds. The chemical shift of the C-5 proton of the osotriazole ring in β-nucleosides showed a down field shift, compared to the corresponding α-nucleosides (Table 1). This deshielding effect can be explained by the proximity of the C-5 proton to the furanosyl ring oxygen in the β-anomer. The assignment of the anomeric configuration by this method is more advantageous than that from the chemical shift of the anomeric proton[10,11] since the C-5 proton can be easily distinguished as a sharp, well resolved, peak at the aromatic region. Additionally the anomeric proton of these nucleosides was exceptional; the trans 1',2' proton resonance was found down field in place of the expected cis 1',2' proton[12,13]. This is in accord with the values of the coupling constant $J_{1',2'}$ of the anomeric proton (Table 1). Low coupling constants (less than 3.5 Hz)[14] can be assigned to the trans 1',2' anomeric protons.

Table 1

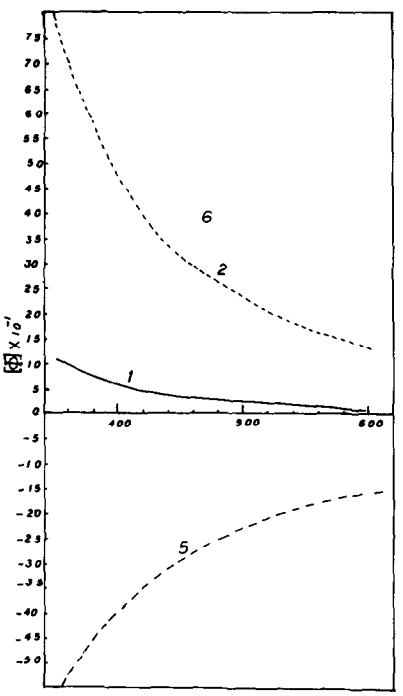
Compd.	Chemical Shift		Coupling Constant
	H-1'	H-5	
1	4.64	8.04	9.5
2	4.73	7.94	1.1
3	5.02	7.83	8.4
4	4.92	7.76	1.0
5	4.28	8.04	9.2
6	4.94	7.93	0
7a	4.60	8.04	-
7b	5.20	8.04	0

n.m.r. spectra at 80 MHz, in dimethyl sulphoxide-d_6 with CD_3COOD added, for compounds 1,2,5,6 and 7a; compounds 3,4 and 7b chloroform-d. Internal reference tetramethylsilane.

The n.m.r. spectra were supported by the optical properties of these C-nucleosides. They obeyed Hudson isorotation rule[15] at the sodium D-line and were consistent with the o.r.d. results in the long wavelength region (Figure 1).



Scheme 1



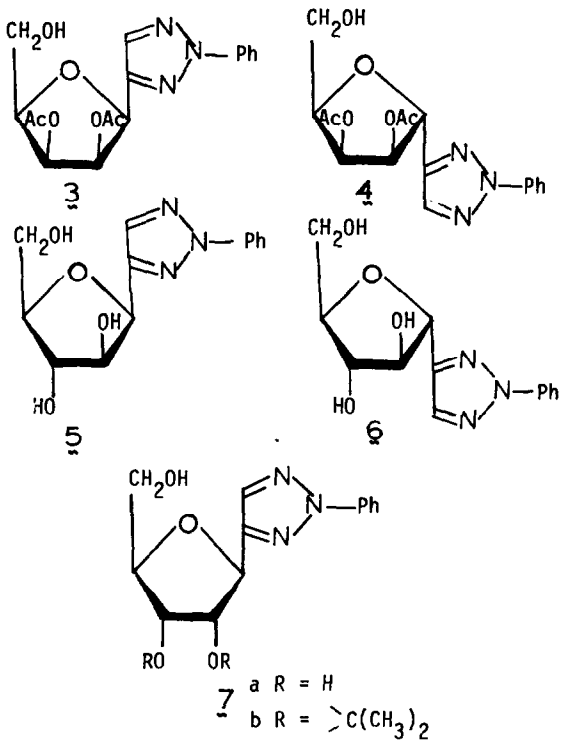


Figure 1. ORD curves in methanol of:

(———) 4-(β-D-lyxofuranosyl) 2-phenyl-1,2,3-osotriazole (1),

(- - - - -) 4-(α-D-lyxofuranosyl) 2-phenyl-1,2,3-osotriazole (2),

(-·-·-) 4-(β-D-arabinofuranosyl) 2-phenyl-1,2,3-osotriazole (5),

(.....) 4-(α-D-arabinofuranosyl) 2-phenyl-1,2,3-osotriazole (6).

4-(β-D-Ribofuranosyl)-2-phenyl-1,2,3-osotriazole 7, was obtained by similar treatments of D-altro-heptulose phenylosazone and was assigned the β-D-configuration from the chemical shift of the C-5 proton. Its isopropylidene derivative 7b had a low coupling constant for the anomeric proton (Table 1), the difference, Δδ, between the chemical shifts of the two methyl signals (0.20 ppm) confirms the β-D-configuration[16-18], (Δδ for β-nucleosides is $\geq$ 0.18, and for α anomers is $\leq$ 0.10).

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