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STRUCTURE AND ANOMERIC CONFIGURATION OF THE *C*-NUCLEOSIDE ANALOGS OBTAINED BY DEHYDRATION OF 7-DEOXY-L-*manno*-2-HEPTULOSE PHENYLOSAZONE*

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ABSTRACT

Dehydration of 7-deoxy-L-*manno*-2-heptulose phenylosazone with methanolic sulfuric acid afforded two 3,6-anhydro-osazone derivatives (**2** and **3**). Refluxing the anhydro-osazones with copper sulfate gave two *C*-nucleoside analogs, namely, 4-(5-deoxy-α-L-arabinofuranosyl)-2-phenyl-*v*-triazole (**4**) and 4-(5-deoxy-β-L-arabinofuranosyl)-2-phenyl-*v*-triazole (**5**). The structure and anomeric configurations of **2**, **4**, and **5** were determined by n.m.r. spectroscopy. The preponderant conformation of **4** and **5**, and the mass spectra of **2**, **4**, and **5** are discussed.

INTRODUCTION

Monosaccharide phenylosazones are readily dehydrated[2–5] with methanolic sulfuric acid, with subsequent cyclization at the polyhydroxyalkyl chain, giving 3,6-anhydro-osazones. This reaction constitutes a simple route for introduction of a wide variety of configurations of the glycosyl moiety, required for the synthesis of *C*-nucleoside analogs, especially those of rare configuration which cannot be readily obtained by other synthetic methods. The main problem militating against the extensive use of this reaction in the field of *C*-nucleosides has been that of determination of the anomeric configuration of the products. The dehydration of 2-hexulose phenylosazones is a stereoselective process giving preponderantly the isomer having a *trans* relationship between the bis(hydrazone) residue and the 4-hydroxyl group (OH-2 of the aldosyl group formed). A mechanism for explanation of the stereoselective course of this process, suggested by El Khadem[6], has recently been supported by n.m.r. spectroscopy[7] and studies on the dehydration of 3-epimeric 2-hexulose phenylosazones of the D series[8,9] and L series[1]. The latter studies indicated that inversion takes place at C-3 of the starting 2-hexulose phenylosazone, regardless of the configurations of the rest of the carbon atoms of the polyhydroxyalkyl chain. The inversion process is controlled by the selective formation of the preponderant isomer having the *trans* arrangement of the bis(hydrazone) residue and the OH-2 group in

*Studies on Anhydro-osazones, Part VII. For Part VI, see ref. 1.

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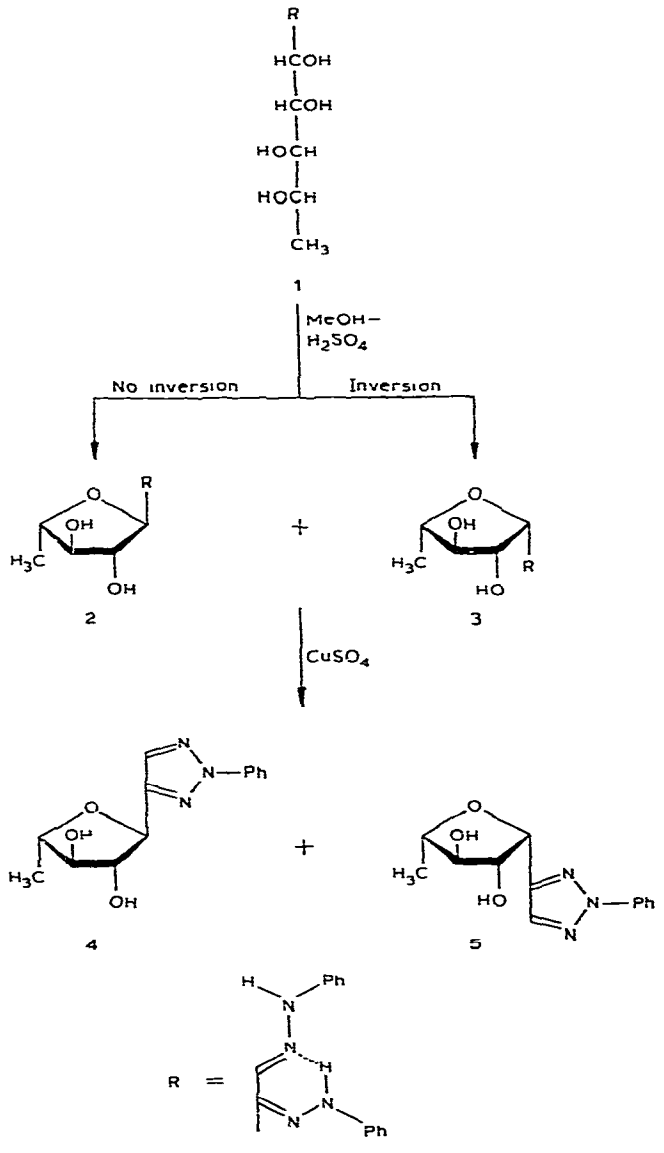
the furanosyl group formed. The inversion (that is, the anomeric configuration) can be assigned by circular dichroism (c.d.)[10], or, more conveniently, by n.m.r. spectroscopy[7]. In some cases[11], the c.d. results contradict those from n.m.r. spectroscopy; this was attributed to the mutarotation exhibited by the chelated ring-structure of osazones[12]. Although the n.m.r. spectra of 3,6-anhydro-osazones show overlapping of the sugar-proton signals, the n.m.r. spectra of their *C*-nucleoside triazole analogs show downfield resolution for the anomeric proton, far from the other glycosyl protons, which facilitates the anomeric assignment. A novel method was found[13]



Scheme 1

for the anomeric assignment of the *C*-nucleoside triazole anomers from the chemical shift of H-5 of the triazole-base moieties.

The dehydration of 2-heptulose phenylosazones[11,14,15] with methanolic sulfuric acid did not show the stereoselectivity found for the 2-hexulose analogs. Indeed, the dehydration process differs from one higher-sugar phenylosazone to another, according to the configuration of the polyhydroxyalkyl chain. The *trans* criterion[10] for determining the anomeric configuration of the preponderant isomer of a 3,6-anhydro-2-hexulose phenylosazone is not applicable to the higher monosaccharide analogs. In the present work, the dehydration of 7-deoxy-L-*manno*-2-heptulose phenylosazone (**1**) by refluxing with methanolic sulfuric acid (with monitoring of the reaction by t.l.c.) afforded 3,6-anhydro-7-deoxy-L-*gluco*-2-heptulose phenylosazone (**2**) and 3,6-anhydro-7-deoxy-L-*manno*-2-heptulose phenylosazone (**3**) (see Scheme 1). The two isomers (**2** and **3**) showed very close R_F values in t.l.c., which made their chromatographic separation difficult; however, isomer **2** could be separated by fractional recrystallization[16]. It was assigned the L-*manno* configuration, formed from **1** without inversion of the configuration of C-3; this was based on c.d. studies[10] and on the subsequently derived *trans* correlation, which has recently proved valid only for the 2-hexulose analogs. The n.m.r. spectrum of compound **2** (see Fig. 1) showed the anomeric proton at δ 4.49 ($J_{1',2'}$ 6.62 Hz); this large value for the coupling constant is not in accord[17] with the suggested L-*manno* configuration (the α-L configuration **3**

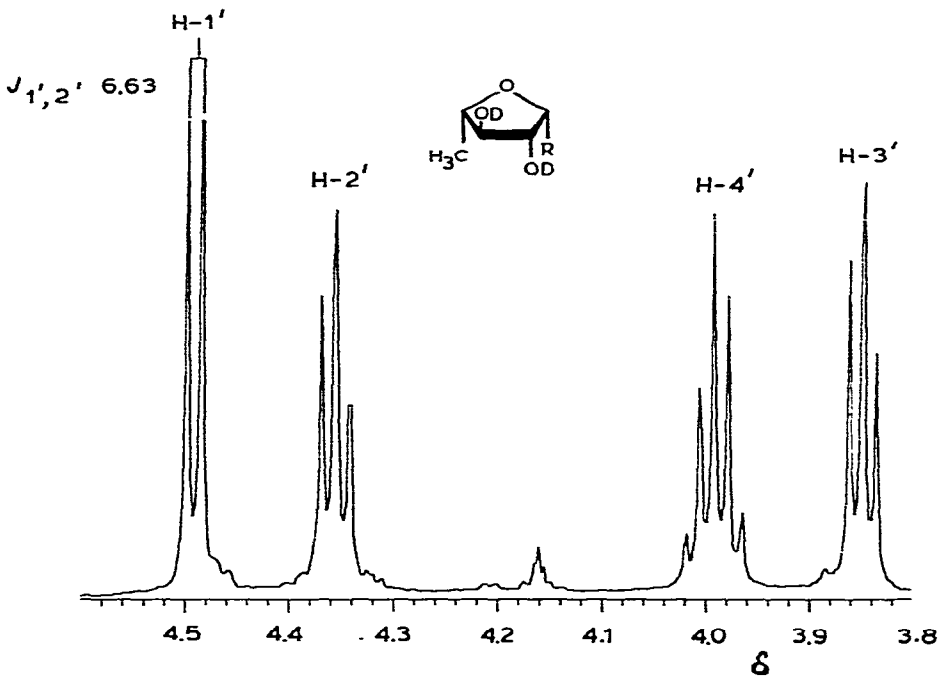


Fig. 1. N.m.r. spectrum, at 470 MHz, of 3,6-anhydro-7-deoxy-L-*gluco*-2-heptulose phenylosazone (**2**) + CD_3CO_2D (high resolution of the sugar moiety); R = bis(hydrazone) residue.

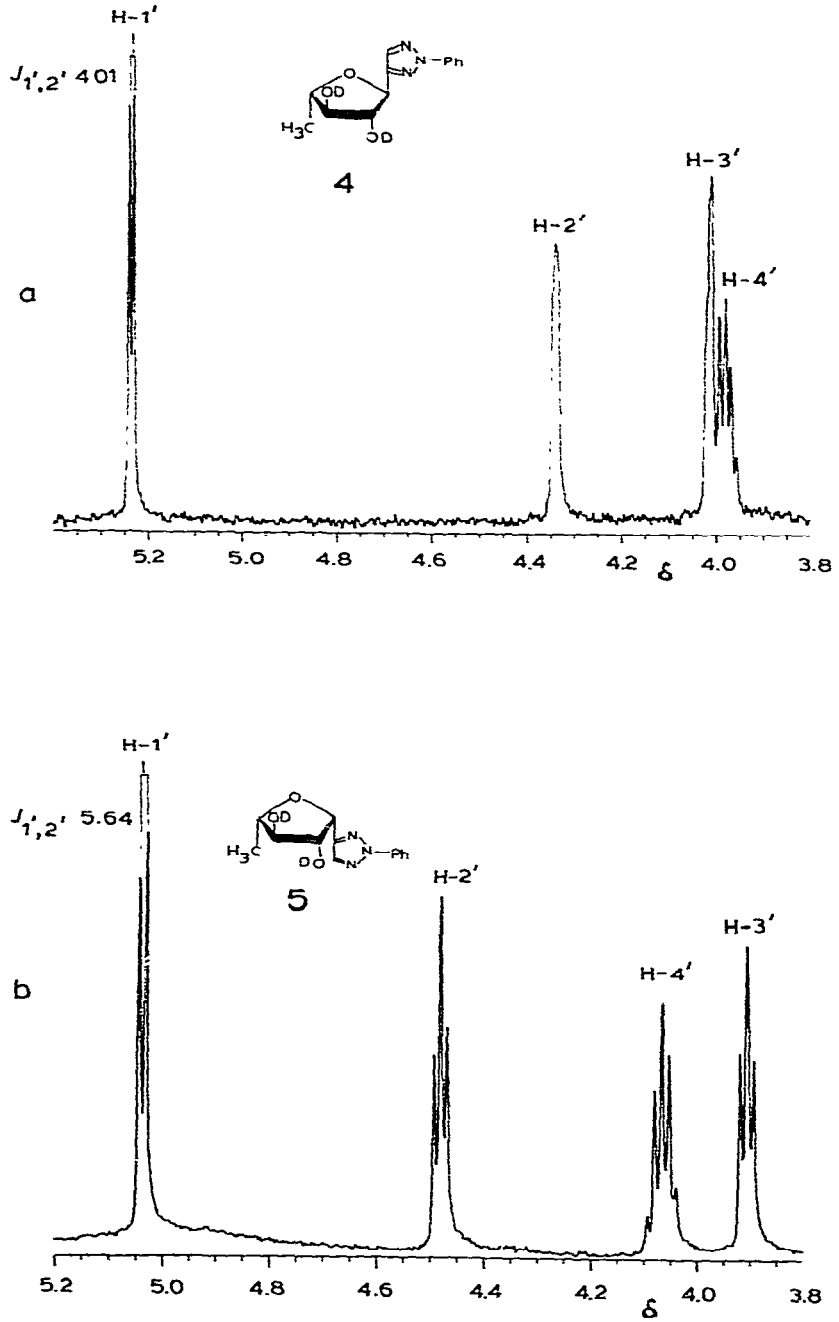


Fig. 2. N.m.r. spectra, at 470 MHz, of (a) 4-(5-deoxy-α-L-arabinofuranosyl)-2-phenyl-*v*-triazole (4), and (b) 4-(5-deoxy-β-L-arabinofuranosyl)-2-phenyl-*v*-triazole (5), + CD_3CO_2D (high resolution of the sugar moiety).

having the *trans* arrangement of H-1′ and H-2′. However, the L-*gluco* configuration (the β-L configuration **2**) was confirmed by n.m.r. spectroscopy from the chemical shift of the methyl group and H-4′. The signal of the methyl group was a shielded doublet at δ 1.291, and that of H-4′, a deshielded multiplet at δ 3.963–4.017, shifted to lower field than that of H-3′ (the same spectral pattern was observed for the sugar moiety of the *C*-nucleoside triazole derivative **5**), in agreement with the β-L configuration **2**, obtained from **1** by inversion in the configuration of C-3. This provides an additional example of contradiction of the c.d. measurements by the n.m.r.-spectral results for 3,6-anhydro-osazones. It may, therefore, be concluded that, unlike the n.m.r.-spectral results for 3,6-anhydro-osazones, the c.d. measurements are less indicative of the anomeric configuration, especially for higher monosaccharide analogs.

After refluxing a methanolic suspension of the 3,6-anhydro-osazone mixture with copper sulfate, chromatography of the resulting triazole *C*-nucleoside analogs (**4** and **5**) on an ion-exchange resin[18,19], with gradient elution with aqueous methanol, resulted in clean separation of the isomers, isomer **4** being eluted first. The n.m.r. spectrum of compound **4** (see Fig. 2a) showed the anomeric proton as a doublet at δ 5.233 ($J_{1',2'}$ 4.01 Hz). The small value of the coupling constant is in close agreement[17] with the *trans* arrangement between H-1′ and H-2′, *i.e.*, the α-L configuration.

The n.m.r. spectrum of compound **5** (see Fig. 2b) showed the anomeric proton as a doublet at δ 5.015 ($J_{1',2'}$ 5.64 Hz). This relatively large value of the coupling constant might suggest the β-L configuration, but it still left uncertain[17] the anomeric configuration of compound **5**, as it agrees with either a *cis* or a *trans* arrangement for H-1′ and H-2′ of the furanosyl group. On the other hand, the anomeric configuration of compounds **4** and **5** cannot be determined from the chemical shift[15] of the anomeric proton, as with other nucleosides (where the signal of the anomeric proton of the *cis* anomer usually appears at lower field than that of the *trans* anomer). Compounds **4** and **5** showed opposite correlation, which is a general feature for all triazole *C*-nucleoside analogs.

However, the anomeric configuration of compounds **4** and **5** could be ascertained from the relative chemical-shifts of the methyl group and H-4′. The methyl protons appeared as a doublet upfield of, and widely separated from, the rest of the peaks for both compounds **4** and **5**. The methyl doublet of compound **4** was located at lower field (δ 1.443) than that of compound **5** (1.328), indicating the α-L configuration for **4** and the β-L configuration for **5**. This can be explained by the anomeric effect[20,21], which is also operative for the furanoside ring, and which influences, in a regular manner, the electron-density environment around the methyl group. The anomeric effect of the axially oriented, base moiety for compound **5** exerts less polarization on the CH_3–C-4 bond. On the other hand, the signal for H-4′ of compound **5** was a deshielded multiplet (δ 4.039–4.093) and that of compound **4** was at δ 3.957–3.993, supporting the β-L configuration for compound **5** and the α-L configuration for compound **4**. Identical observations have been made for 6-deoxypyranosides[22,23].

The anomeric configuration of compounds **4** and **5** could also be confirmed from the chemical shift of the H-5 signal of the triazole-base moiety; it appeared as a signal more deshielded for compound **4** (δ 7.883) than that for compound **5** (δ 7.781), in agreement[13] with the α-L configuration of **4** and the β-L configuration for **5**.

Additional support for the anomeric configuration of **4** and **5** was obtained from their optical properties. Compound **4** showed the larger (negative) specific rotation ($[\alpha]_D^{20}$ in methanol: **4**, −138.4°; **5**, −28.7°) in agreement with the α-L configuration according to Hudson's isorotation rules[24].

The 3,6-anhydro-7-deoxy-L-*manno*-2-heptulose phenylosazone (**3**) was assigned the α-L configuration by correlation with its *C*-nucleoside triazole analog (**4**).

In connection with the conformation of the aldofuranosyl moiety of the *C*-nucleoside triazole analogs **4** and **5**, it is generally recognized[25] that, in order to relieve nonbonded interactions between *cis*-1,2 substituents, furanoid rings tend to pucker in such a manner as to have the carbon atom *meta* to the ring-oxygen atom (either C-2 or C-3) farthest out of the mean plane of the ring (*i.e.*, ${}^2E$, E_2, ${}^3E$, or E_3).

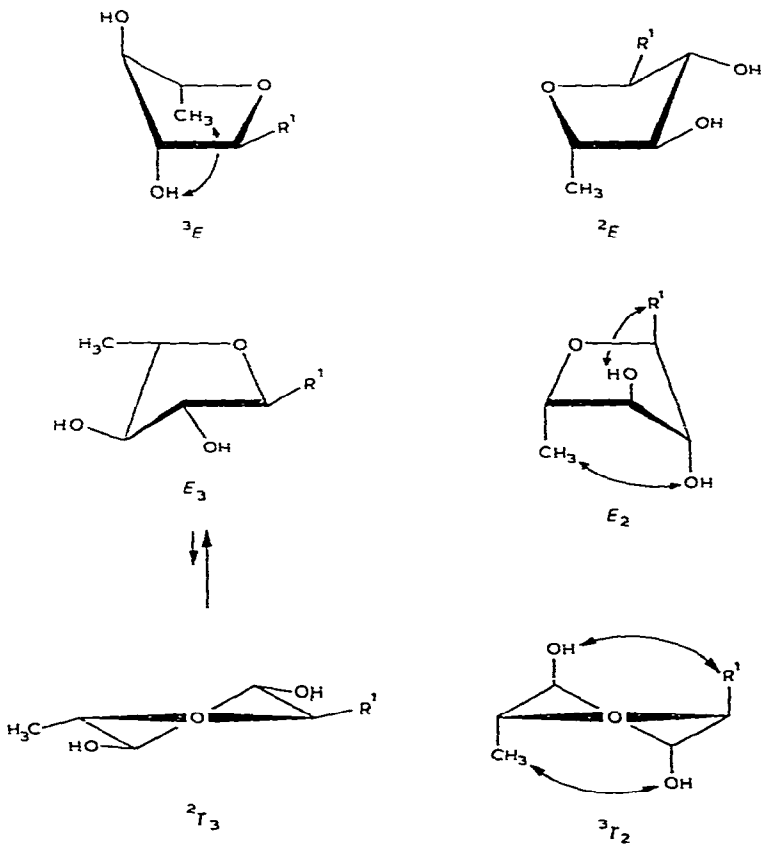


Fig. 3. The pseudorotational, itinerary conformers of 4-(5-deoxy-α-L-arabinofuranosyl)-2-phenyl-*v*-triazole (**4**).

These envelope conformers exist in equilibrium with the twist (T) conformers. Accordingly, the pseudorotational itinerary equilibrium for compounds **4** and **5**, may be represented as follows.

$$^2E \rightleftharpoons {}^2T_3 \rightleftharpoons E_3 \rightleftharpoons E_2 \rightleftharpoons {}^3T_2 \rightleftharpoons E_3$$

On the basis of conformational analysis, the conformers E_2, $^3T_2$, and ^3E for compound **4** (see Fig. 3) are disfavored, because of the axial orientation of substituents and the presence of two 1,3-*syn*-axial interactions in the E_2 and $^3T_2$ conformers, and one 1,3-*syn* interaction in the ^3E conformer. Conformers E_3 and $^2T_3$ are relatively more stable than ^2E, due to the presence of the maximum number of groups in the stable, quasi-equatorial and equatorial orientations and the absence of 1,3-*syn*-axial interactions. Analogously, compound **5** will be present as the most stable conformers E_3 and $^2T_3$. The axially attached, base moiety on the anomeric carbon atom of compound **5**, not being involved in strong, 1,3-*syn*-axial interactions, stabilizes conformers E_3 and $^2T_3$, owing to the anomeric effect[20,21]. The n.m.r. spectra of compounds **4** and **5** reflect the time-average of the equilibrating, puckered structures.

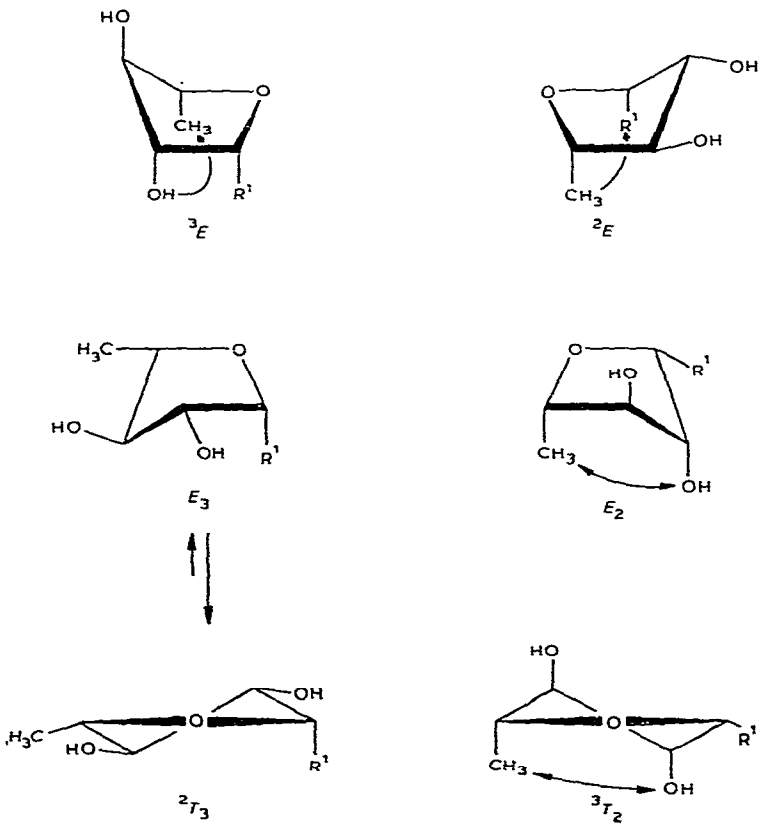


Fig. 4. The pseudorotational, itinerary conformers of 4-(5-deoxy-β-L-arabinofuranosyl)-2-phenyl-*v*-triazole (**5**).

Knowledge of the vicinal-proton coupling-constant permits determination of the stereochemistry of the furanoid ring by determination of the values of the torsion angle ($\phi_{H,H}$). Owing to the fact that the coupling constant cannot assume random values, independent of each other, but must obey interrelationships governed by the law of pseudorotation, knowledge of the $J_{1',2'}$ value can alone pinpoint[27] the equilibrium composition. However, the $J_{1',2'}$ value (4.01 Hz) for compound **4** corresponds to a calculated[28] torsion angle ($\phi_{H\text{-}1',H\text{-}2'}$) of 132°. This value, on comparison with

TABLE I

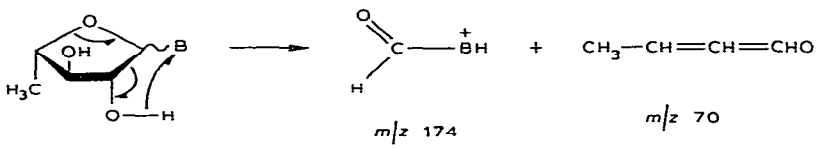
RELATIVE INTENSITIES (%) OF MAIN IONS IN THE MASS SPECTRA OF COMPOUNDS **4** AND **5**

m/z	*Fragment*	*Percent*	
		4	**5**
262	M + 1	2	1
261	M	9	5
188	$BHCH_2CHO$	23	30
187	BCH_2CHO	6	7
186		7	6
175	B + 31	24	18
174	BHCHO	100	81
173	BCHO	10	8
172	BCO	5	4
171		8	8
159	$BHCH_2$	1	1
158	BCH_2	6	5
146	BH_2	2	1
145	BH	1	1
144	B	1	1
118	B − CN	3	4
117	B − HCN	4	4
104		5	8
103	PhCN	5	6
93	$PhNH_2$	6	10
92	PhNH	22	36
91	PhN	58	94
88		12	21
83		1	6
78	PhH	5	10
77	Ph	53	100
73		15	42
70	$CH_3CHCHCHO$	24	66
69		14	45
65		16	38
64		19	44
57		11	40
55		8	33
51		16	42
43	CH_3CO	17	47
42	CH_2CO	17	49

the values obtained from Dreiding models of the favored coformers of **4**, indicated the equilibrium $E_3 \rightleftarrows {}^2T_3$. Similarly, the $J_{1',2'}$ value (5.64 Hz) for compound **5** indicated a torsion angle ($\phi_{H\text{-}1',H\text{-}2'}$) of 33.4° and the equilibrium $E_3 \leftrightarrows {}^2T_3$ (see Fig. 4).

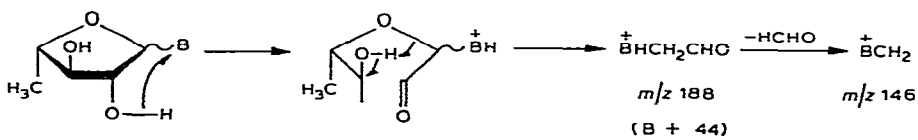
The mass spectrum of the 3,6-anhydro-osazone **2** showed the molecular-ion peaks at *m/z* 355 and 354, corresponding to M + 1 and M, respectively. The base peak was at *m/z* 93, corresponding to $PhNH_2$. The peaks at *m/z* 118 and 119 result from initial cleavage of the two hydrazone residues. The series of peaks at *m/z* 108, 107, 106, and 105 correspond to $PhNHNH_2$, PhNHNH, PhNHN, and PhN=N. The peaks common to the 5-(hydroxymethyl) analogs were at *m/z* 104 (PhCNH) and 103 (PhNC), and (intense) 94 (PhN^+H_3), 93 ($PhNH_2$), 91 (PhN), and 77 (Ph).

The mass spectra of compounds **4** and **5** showed the molecular ion peaks (M + 1) and M at *m/z* 262 and 261, respectively. The two anomers showed an identical, abundant ion, with some change in the intensity (see Table I). The characteristic, major fragment-ion for *C*-nucleoside triazoles[9,11], B + 30 (174), was shown as a base peak for **4**, and an abundant peak for **5**. The base peak for compound **5** was at *m/z* 77, corresponding to the Ph group. The carbon–carbon linkage between the furanosyl



B = 2-Phenyl-v-triazole-4-yl group

Scheme 2



B = 2-Phenyl-v-triazole-4-yl group

Scheme 3

group and the heterocyclic base is confirmed[29] by the abundance of the peak B + 30 (174), and the lessened intensity of the ions B + 1 (145) and B + 2 (147). The abundance of the peak at *m/z* 174 indicates a type of fragmentation similar to that of the 5-(hydroxymethyl) analogs[11], by cleavage of the O–C-4′ and C-1′–C-2′ bonds (see Scheme 2). The B + 44 ion, also occurring for the 5-(hydroxymethyl) analogs[15], indicates cleavage of the O–C-1′ and C-2′–C-3′ bonds (see Scheme 3) for compounds **4** and **5**, but with less abundance; this type of fragmentation is more abundant for the furanosyltriazole *C*-nucleosides than for the pyranosyl analogs[15].

EXPERIMENTAL

General. — Melting points are uncorrected. Evaporations were performed under diminished pressure below 60°. Thin-layer chromatography (t.l.c.) was conducted on silica gel (Kiesel gel G, Merck) with 3:1 benzene–ethanol (solvent *A*) and 1:2:1 chloroform–benzene–ethanol (solvent *B*). I.r. absorption spectra were recorded with a Unicam SP 1025 instrument, and the u.v. absorption spectra, with a Unicam SP 1750 spectrometer. N.m.r. spectra were recorded with a Nicolet 470-MHz instrument, using internal tetramethylsilane as the reference. Mass spectra were recorded with a Dupont M21–492 B Finnigan 6100 Data System Gas-Chromatograph/e.i.–c.i. spectrometer. Combustion analyses were performed in the Department of Chemistry, Purdue University.

3,6-Anhydro-7-deoxy-L-gluco-*2-heptulose phenylosazone* (**2**). — 7-Deoxy-L-*manno*-2-heptulose phenylosazone (**1**; 19 g) was boiled for 4 h under reflux with methanolic sulfuric acid[9] (500 mL); t.l.c. (solvent *A*) then showed the absence of the starting osazone, and formation of two close spots, R_F 0.54, 0.52 (solvent *A*) and 0.65, 0.61 (solvent *B*). The solution was diluted with hot water (300 mL), and the methanol was evaporated under diminished pressure. The precipitate obtained was filtered off, washed with water, and dried; yield 18 g. The mixture was purified by chromatography on a column (3 × 60 cm) of silica gel, with solvent *A* as the eluant (to remove the brown impurities). The eluate was evaporated to dryness, and the solid residue was recrystallized from dilute methanol, to give chromatographically (t.l.c.) pure, yellow needles, m.p. 215–217° (lit.[16] m.p. 212–215°), $[\alpha]_D^{20}$ −108.2° (*c* 1.03, acetone): n.m.r. data (470 MHz, acetone-d_6 + CD_3CO_2D): δ 1.291 (d, 3 H, CH_3, $J_{H\text{-}4',CH_3}$ 6.36 Hz), 3.834–3.860 (t, 1 H, H-3′, $J_{2',3'}$ 6.14, $J_{3',4'}$ 6.0 Hz), 3.964–4.017 (m, 1 H, H-4′, $J_{3',4'}$ 6.1 Hz), 4.341–4.367 (t, 1 H, H-2′, $J_{2',3'}$ 6.13 Hz), 4.490 (d, 1 H, H-1′, $J_{1',2'}$ 6.62 Hz), 6.867–7.376 (m, 10 H, aromatic protons), 7.817 (s, 1 H, CH=N), 9.784 (s, 1 H, nonchelated NH, disappears slowly), and 12.357 (s, 1 H, chelated NH, disappears slowly); mass-spectral data (selected ions): *m/z* 355 (1, M + 1), 354 (6, M), 362 (2, M − PhNH), 188 (13), 175 (4), 174 (9), 158 (9), 146 (3, M − $PhNHNH_2$), 145 (5, M − $PhNH^+_3$), 119 (13, CH=NNHPh), 118 (5, $C{\equiv}N^+NHPh$), 108 (9, $PhNHNH_2$), 107 (4, PhNHNH), 106 (5, PhNHN), 104 (8, PhCNH), 103 (2, PhNC), 94 (17, PhN^+H_3), 93 (100, $PhNH_2$), 92 (85, PhNH), 91 (23, PhN), 78 (9, PhH), 77 (76, Ph), 73 (13), 66 (16), 65 (67, cyclopentadiene ion), 57 (10), 54 (5), 43 (9), and 42 (10).

Anal. Calc. for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81. Found: C, 64.10; H, 6.53; N, 15.88.

Conversion of the anhydro-osazone mixture into 2-phenyltriazole C-nucleoside analogs. — A suspension of the crude 3,6-anhydro-osazone mixture (15 g) in methanol (250 mL) was boiled under reflux, with stirring, a solution of copper sulfate (15 g) in water (200 mL) was added, and the mixture was boiled for 6 h, cooled, filtered, the filtrate evaporated to dryness, the residue extracted with hot methanol, and the suspension filtered. The filtrate was freed of copper sulfate by bubbling H_2S gas

through it, filtering the suspension, and then stirring the filtrate with barium carbonate, and filtering. The filtrate was stirred with Amberlite IR-MB cation-anion-exchange resin, and the resin was filtered off, and washed thoroughly with methanol. The filtrate and washings were combined, and evaporated to a syrup which was dissolved in methanol; the solution was applied to a column (4 × 75 cm) of Dowex-1 X-8 (OH^-) ion-exchange resin, and this was eluted with water, and 30, 60, and 90% aqueous methanol.

4-(5-Deoxy-α-L-arabinofuranosyl)-2-phenyl-v-triazole (**4**). — Evaporation of the 60%-methanol fractions, and recrystallization of the solid residue from water, gave colorless needles, yield 1.7 g; m.p. 118–120°, $[\alpha]_D^{20}$ −138.4° (*c* 1.5, methanol); R_F 0.72 (solvent *A*), 0.77 (solvent *B*); ν_{max}^{KBr} 4320 (OH), 1595 (C=N), and 1500 and 760 cm^{-1} (Ph); λ_{max}^{MeOH} 267 nm (log ε 4.3); n.m.r. data (470 MHz, $CDCl_3$): δ 1.443 (d, 3 H, CH_3, $J_{CH_3,H\text{-}4'}$ 6.33 Hz), 2.706 (bs, 1 H, OH), 3.961–3.987 (m, 1 H, H-4′), 4.010 (bs, 1 H, H-3′), 4.310 (bs, 1 H, H-2′), 5.220 (d, 1 H, H-1′, $J_{1',2'}$ 4.01 Hz), 7.337–7.369 (t, 1 H, *para* proton of the phenyl group), 7.454–7.484 (t, 2 H, *meta* protons of the phenyl group), 7.882 (s, H-5), and 8.016 (d, 2 H, *ortho* protons of the phenyl group). After addition of CD_3CO_2D, the two OH protons disappeared. For mass-spectral data, see Table I.

Anal. Calc. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.70; H, 5.52; N, 16.20.

4-(5-Deoxy-β-L-arabinofuranosyl)-2-phenyl-v-triazole (**5**). — The 90%-methanol fractions were combined, evaporated to dryness, and the solid residue recrystallized from benzene–hexane, giving colorless needles, yield 2.8 g; m.p. 88°, $[\alpha]_D^{20}$ −28.7° (*c* 3.0, methanol); R_F 0.73 (solvent *A*), 0.78 (solvent *B*); ν_{max}^{KBr} 3300 (OH), 1600 (C=N), and 1500 and 760 cm^{-1} (Ph); λ_{max}^{MeOH} 268 nm (log ε 4.3); n.m.r. data (470 MHz, $CDCl_3$): δ 1.314 (d, 3 H, CH_3, $J_{CH_3,H\text{-}4'}$ 6.28 Hz), 3.872–3.895 (t, 1 H, H-3′, $J_{3',4'}$ 5.9 Hz), 4.039–4.093 (m, 1 H, H-4′, $J_{H\text{-}4',CH_3}$ 6.31 Hz), 4.283 (bs, 1 H, OH), 4.424 (bs, 1 H, OH), 4.449–4.72 (t, 1 H, H-1′, $J_{1',2'}$ 5.64 Hz), 7.273–7.304 (t, 1 H, *para* proton of the phenyl group), 7.377–7.410 (t, 2 H, *meta* protons of the phenyl group), 7.767 (s, 1 H, H-5), and 7.923 (d, 2 H, *ortho* protons of the phenyl group). After addition of CD_3CO_2D, the two OH protons disappeared. For mass-spectral data, see Table I.

Anal. Calc. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.78; H, 6.03; N, 15.85.

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