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Note

New imino sugar derivatives from a 6-azido-6-deoxy sugar formazan

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Reaction of azido sugars with triphenylphosphine affords sugar phosphinimines [1,2], that are good precursors [3–5] for various nitrogen derivatives of sugars. In order to obtain ω-amino sugar formazan derivatives, the reduction of 6-azido-6-deoxy-D-galactose *N,N'*-diphenylformazan [6] (**1**) was carried out with triphenylphosphine. The reaction took place in dioxane or 1,2-dimethoxyethane containing methanol, moreover best in 2-methoxyethanol, and afforded a red formazan compound (**4**) as main product. Acetylation of this latter with pyridine–acetic anhydride gave an *N*-acetyl-tri-*O*-acetyl-derivative (**5**).

On the basis of their visible, IR, ^{1}H and ^{13}C NMR spectra these compounds proved to be 2,6-dideoxy-2,6-imino-D-talose *N,N'*-diphenylformazan (**4**) and its tetraacetyl derivative (**5**) instead of the expected 6-deoxy-6-phosphinimino- (**2**) or 6-amino-6-deoxy- (**3**) compounds and their acetates. The presence of the formazan chelate was supported by maxima at 458 nm for **4** and 464 nm for **5**, respectively, in the visible spectra.

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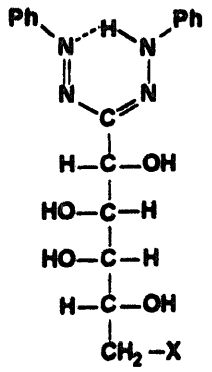
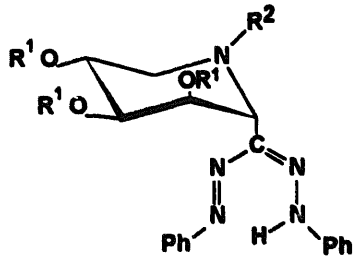


1 X=N_3

2 X=$NPPh_3$

3 X=NH_2



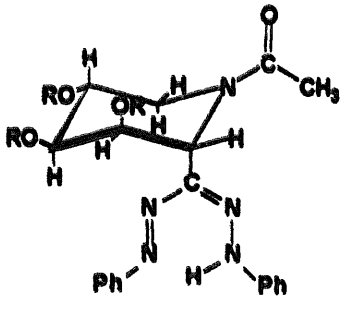
4 R^1=H, R^2=H

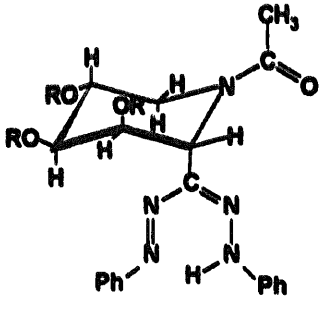
5 R^1=Ac, R^2=Ac

6 R^1=H, R^2=Ac

While the ^{1}H NMR spectrum of **5** at 100 MHz, and at room temperature, showed broad peaks, at 400 MHz two well distinguishable groups of signals separated for all sugar protons in the ratio of 3:2 were seen (Table 1). In accordance, in the ^{13}C NMR spectrum of **5** all signals were doubled due to the presence of two isomers. The exact assignment of all protons and carbons was performed by 2D proton–proton homocorrelated and carbon–proton heterocorrelated spectra.

In the ^{13}C NMR spectrum of **5**, the pair of peaks for C-2 (δ 59.326 and 54.084 ppm) and C-6 (δ 39.386 and 44.593 ppm), respectively, appeared at higher field than the other sugar carbons (67.02–70.40 ppm), indicating that both atoms are adjacent to nitrogen (Table 2).





5a R=Ac

6a R=H

5b R=Ac

6b R=H

In the ^{1}H NMR spectrum, the proton–proton coupling constants were very similar for both isomers. The value of $^3J_{2,3}$ (2.3 Hz) was in accordance with *gauche* arrangement,

Table 1
^{1}H NMR chemical shifts and first order coupling constants [a] for compounds **5a** and **5b**

Protons	Chemical shifts (δ in ppm)		Coupling constants [a] (J in Hz)		
	5a	**5b**		**5a**	**5b**
H-2	5.448(dd)	6.337 (dd)	$^3J_{2,3}$	2.3	2.3
H-3	5.980(dd)	5.969 (dd)	$^4J_{2,6e}$	1.6	1.6
H-4	5.863(dd)	5.744 (dd)	$^3J_{3,4}$	3.5	3.4
H-5	5.220(ddd)	5.168 (ddd)	$^3J_{4,5}$	10.1	10.3
H-6e	4.866 (m)	4.104(m)	$^3J_{5,6e}$	5.7	5.4
H-6a	2.737(dd)	3.374 (dd)	$^3J_{5,6a}$	11.1	11.0
CH_3(OAc)	2.192; 2.058; 2.021 (s each)	2.142; 2.063; 2.055 (s each)	$^2J_{6a,6e}$	13.1	13.4
CH_3(NAc)	2.314 (s)	2.263 (s)			
Ar–H-2′	7.61 (m)				
Ar–H-3′	7.44 (m)				
Ar–H-4′	7.29 (m)				
N–H	13.32 (s)	13.26 (s)			

[a] At 400 MHz in $CDCl_3$ solution at room temperature.

while $^3J_{4,5}$ (10.1 Hz for **5a** and 10.3 Hz for **5b**) and $^3J_{5,6a}$ (11.1 Hz for **5a** and 11.0 Hz for **5b**) indicated *trans* diaxial arrangement of these protons (Table 1). Long-range coupling ($^4J_{2,6e}$ 1.6 Hz) between H-2 and H-6e proved the equatorial position of these hydrogens in both **5a** and **5b** (*W* coupling), and an unusual axial arrangement of the bulky formazyl group.

On the basis of these data, we could establish that the equilibrium is rather caused by restricted rotation around the N–CO bond [7,8] than by conformational equilibrium between two six-membered rings or by occurrence of C-2 epimers. Nitrogen inversion [9] in compound **5** could also be precluded by these NMR data, as well as by differential nuclear Overhauser enhancement experiments.

Irradiation at 5.45 ppm (H-2 of **5a**) caused a significant enhancement at N–$COCH_3$ of **5a** (2.31 ppm). At the same time, saturation was partly transferred to 6.34 ppm (H-2 of **5b**), providing further evidence for the rotational equilibrium. As a consequence, a smaller enhancement at the N–$COCH_3$ signal of **5b** (at 2.26 ppm) was also observed. Additionally, irradiation at 2.31 ppm (N–$COCH_3$ of **5a**) caused a large enhancement at 5.45 ppm (H-2 of **5a**), and a smaller one at 6.34 ppm (H-2 of **5b**). Finally, irradiation at 2.26 ppm (N–$COCH_3$ of **5b**) resulted in a large enhancement at 5.45 ppm (H-2 of **5a**), at 6.34 ppm (H-2 of **5b**), and at 4.10 ppm (H-6e of **5b**), confirming the presence of amide isomerism.Table 2

In the ^{13}C NMR spectrum of **4**, a similar pattern was found for the sugar carbons as in the spectrum of **5**, i.e. C-6 and C-2 appeared again at higher field (46.557 and 55.997 ppm, respectively) than the others (69.51–71.83 ppm), in accordance with the vicinal position of the nitrogen atom in the ring.

On deacetylation by the Zemplén method [10], **5** gave the *N*-acetyl-imino sugar derivative **6**. The same compound was formed from **4** by acetylation with acetic anhydride in methanol. In both the ^{1}H and ^{13}C NMR spectra of **6**, all lines were doubled again in a ratio of ~ 7:3, indicating restricted rotation around the CO–N bond. Carbons

Table 2
^{13}C NMR chemical shifts [a] (δ in ppm) for compounds **4** [b], **5a**, **5b**, **6a** and **6b**

Compound	Chemical shifts				
	4	**5a**	**5b**	**6a**	**6b**
C-1	146.733	139.063	139.426	140.499	140.656
C-2	55.997	59.326	54.084	60.907	56.332
C-3	71.833 [c]	69.636	69.212	73.237 [c]	73.237 [c]
C-4	67.765 [c]	70.403	69.747	70.497 [c]	70.203 [c]
C-5	69.511 [c]	67.022	68.198	67.613 [c]	67.613 [c]
C-6	46.557	39.386	44.593	42.706	48.061
CH_3(OAc)		20.792	20.792		
		20.851	20.924		
		20.948	20.966		
CH_3(NAc)		21.650	21.804	21.897	22.098
Ar-C-1′	147.982	147.123	147.325	147.137	147.137
Ar-C-2′	118.826	118.855	118.822	118.583	118.676
Ar-C-3′	128.836	129.596	129.451	127.600	127.600
Ar-C-4′	126.554	128.061	127.691	129.424	129.301
CO(OAc)		169.700	169.843		
		170.055	170.086		
		170.111	170.146		
CO(NAc)		170.694	170.534	172.732	172.510

[a] At 100 MHz in $CDCl_3$ solution at room temp. (except **4**).
[b] At 100 MHz in $CDCl_3$–$(CD_3)_2SO$ (4:1) solution at 50 °C.
[c] Assignments may be interchanged.

adjacent to ring nitrogen were well identified also in this case, on the basis of their upfield shift: C-6 appeared at 42.706 and 48.061 ppm; C-2 at 60.907 and 56.332 ppm, respectively.

For the interpretation of the reaction mechanism, we suppose that triphenylphosphine reacts first with the 6-azido group providing a nucleophilic phosphinimine or amine function at C-6. The position of the latter is favourable for an intramolecular attack at C-2. Earlier, acetoxy-2 groups of sugar formazan acetates were found [6,11] to be good leaving group due to the activating effect of the adjacent formazyl group. In the present case, OH-2 is probably activated by triphenylphosphine in a way analogous to the Mitsunobu-type TPP-DEAD reaction [12], while the role of diethyl-azodicarboxylate (DEAD) is performed by the phenylazo group of the formazan moiety.

Consequently, the nucleophilic attack of the basic nitrogen substituent of C-6 at C-2 results in the formation of the piperidinose ring with inversion of the configuration at C-2.

Reaction of azido sugar formazans with triphenylphosphine provides then a new alternative for the synthesis of imino sugar derivatives and nojirimycin analogues.

1. Experimental

General methods.—TLC was performed on aluminium plates precoated with Silica Gel 60 F_{254} (E. Merck) developed with solvent mixtures *A*, 3:1 $CHCl_3$–MeOH; *B*, 4:1

EtOAc–EtOH; *C*, 7:3 CH_2Cl_2–EtOAc; *D*, 9:1 $CHCl_3$–MeOH. The spots were detected visually and the plates were also checked by exposure to UV light. Column chromatography was made on silica gel (E. Merck, 0.020–0.043 mesh) with argon overpressure. IR spectra were recorded with a Nicolet 205 FT spectrometer using KBr pellets; UV spectra with a HP 8452 A spectrometer, in (19:1 EtOH–H_2O) solution. Nuclear magnetic resonance spectra were determined on Varian XL-100 and Varian XLAA-400 spectrometers in $CDCl_3$ solutions using internal Me_4Si, unless otherwise stated. Assignment was confirmed by proton–proton homocorrelated and carbon–proton heterocorrelated spectra.

2,6-Dideoxy-2,6-imino-D-*talose* N,N′-*diphenylformazan* (**4**).—To a stirred suspension of 6-azido-6-deoxy-D-galactose *N,N′*-diphenylformazan [6] (**1**, 2.0 g, 5 mmol) in 2-methoxyethanol (30 mL) was added triphenylphosphine (2.1 g, 8 mmol). The mixture was stirred for 6 h and left to stand at room temperature for 24 h, when TLC (solvents *A* and *B*) indicated the reaction to be complete. Cyclohexane (800 mL) and EtOH (20 mL) were added to the mixture which was kept overnight at 0 °C. Dark red crystals separated (0.93 g, 52%), mp 164–167 °C. Trituration (2:1 EtOAc–ether) gave a pure product (0.80 g, 45%), mp 172–174 °C. Recrystallization of **4** (0.2 g) by dissolving in hot CH_3CN (25 mL), concentrating the solution below 30 °C to one third of its volume and precipitating with ether (25 mL) and cyclohexane (25 mL) resulted in 0.12 g red crystals, mp 173–175 °C; R_f 0.36 (solvent *A*); λ_{max} 458 nm; ν_{max} 3550–3200 (OH and NH), 1595 cm^{-1} (C=C). Anal. Calcd for $C_{18}H_{21}N_5O_3$: C, 60.83; H, 5.95; N, 19.71. Found: C, 60.26; H, 5.86; N, 19.49.

2,3,4-Tri-O-*acetyl-2,6-(*N-*acetylimino)-2,6-dideoxy*-D-*talose* N,N′-*diphenylformazan* (**5**).—Crude 2,6-dideoxy-2,6-imino-D-talose *N,N′*-diphenylformazan (**4**, 0.30 g, 0.844 mmol) was acetylated for 2 days at 0 °C with a mixture of pyridine (3 mL) and Ac_2O (2 mL), and then poured into ice–water. The red solid (0.40 g, 90%) was purified by column chromatography with a mixture of CH_2Cl_2–EtOAc (7:3) and crystallized from CCl_4 by precipitation with petroleum ether, 0.28 g (64%), mp 156–159 °C; R_f 0.45 (solvent *C*); λ_{max} 464 nm; ν_{max} 1740 (ester CO), 1661 and 1546 (NAc), 1600 (C=C), 1223 and 1230 cm^{-1} (ester COC). Anal. Calcd for $C_{26}H_{29}N_5O_7$: C, 59.65; H, 5.58; N, 13.38. Found: C, 59.92; H, 5.65; N, 13.22. On the basis of its NMR spectra the product is a 3:2 mixture of **5a** and **5b** in $CDCl_3$ solution at room temperature.

*2,6-(*N-*Acetylimino)-2,6-dideoxy*-D-*talose* N,N′-*diphenylformazan* (**6**).—(*a*) To a solution of **5** (0.2 g, 0.38 mmol) in dry MeOH (6 mL) and $CHCl_3$ (2 mL) was added dropwise methanolic M NaOMe (0.08 mL, 0.21 equiv.). After 5 h, TLC (solvent *A*) showed complete reaction. The solution was neutralized with AcOH and evaporated. Column chromatography of the residue (9:1 $CHCl_3$–MeOH) afforded pure **6**, which was crystallized from CH_2Cl_2 by precipitation with CCl_4, resulting in red crystals, 96 mg (63%), mp 108–111 °C; R_f 0.49 (solvent *D*); λ_{max} 464 nm; ν_{max} 3600–3100 (OH), 1627 and 1540 (NAc), 1600 cm^{-1} (C=C). ^1H NMR (400 MHz, $CDCl_3$): isomeric equilibrium of **6a** and **6b** in the ratio of 7:3; δ 2.27 (3 H, s, N–$COCH_3$), 2.66 (1 H, t, H-6a), 2.93 (1 H, m, OH); 3.99 (1 H, m), 4.31 (1 H, m), 4.54–4.68 (2 H, m), 4.95–5.10 (2 H, m): H-3, H-4, H-5, H-6e and OH; 5.34 (1 H, s, H-2), 7.07 (2 H, m, Ar–H-4′), 7.21–7.44 (8 H, m, Ar–H-2′ and Ar–H-3′), 12.86 (1 H, s, N–H) ppm for **6a**, and δ 2.18 (3 H, s, N–$COCH_3$), 2.82 (1 H, m, OH), 3.42 (1 H, t, H-6a); 3.93 (1 H, m), 4.12 (1

H, m), 4.54–4.68 (2 H, m), 4.75 (1 H, m), 4.85 (1 H, m): H-3, H-4, H-5, H-6e and OH; 6.24 (1 H, s, H-2), 7.02 (2 H, m, Ar–H-4'), 7.21–7.44 (8 H, m, Ar–H-2' and Ar–H-3'), 12.90 (1 H, s, N–H) ppm for **6b**.

(*b*) To a stirred suspension of crude **4** (0.36 g, 1.0 mmol) in MeOH (5 mL) was added Ac_2O (0.3 mL) at 0 °C, and the mixture was left at room temperature for 20 h. It was poured into ice–water and triturated several times while the red oil solidified. Column chromatography and crystallization, as described in method (*a*), resulted in red crystals of **6**, 0.27 g (67%), mp 107–110 °C, identical with the product from (*a*).

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