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Note

A novel synthesis of 2-azido-2-deoxyinososе oximes

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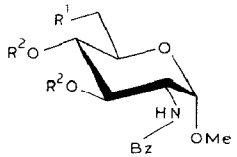
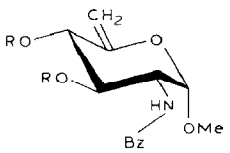
Due to the activating effect of the arylhydrazone moiety[1–5], a 2-benzoyloxy substituent of inosose *p*-nitrophenylhydrazones can be replaced easily by azide anion.

Since azidoinososes are precursors of aminodeoxycyclitols, we sought to extend the method to the preparation of aminoazidoinosose derivatives, which are potential intermediates for the synthesis of diaminodideoxycyclitol building-units of analogues of aminoglycoside antibiotics.

Conventional substitution of the 6-tosyloxy group with iodide in methyl 2-benzamido-3,4-di-*O*-benzoyl-2-deoxy-6-*O*-tosyl-α-D-glucopyranoside (**1**), prepared from methyl 2-benzamido-2-deoxy-α-D-glucopyranoside[6] (**2**), afforded the iodide **3**. Treatment of **3** with silver(I) fluoride in pyridine gave methyl 2-benzamido-3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-*xylo*-hex-5-enopyranoside (**4**).





1 R^1 = TsO, R^2 = Bz
2 R^1 = HO, R^2 = H
3 R^1 = I, R^2 = Bz

4 R = Bz
5 R = Ac

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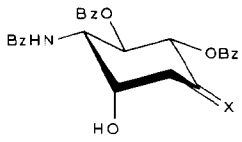
Ferrier transformation[7] of **4** into 2L-(2,4,5/3)-4-benzamido-2,3-dibenzoyloxy-5-hydroxycyclohexanone (**6**) was performed by the method described[8] for the synthesis of the corresponding diacetate (**5**). Variation of the catalyst Hg(II)salt, *e.g.*, chloride, acetate, trifluoroacetate, and sulfate, did not influence markedly the yield of **6**.

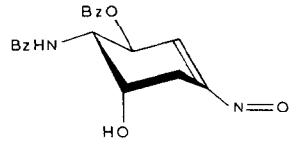


6 X = O

7 X = N—NH—$C_6H_4NO_2$(*p*)

8 X = N—OH

13 X = N—OCH_3



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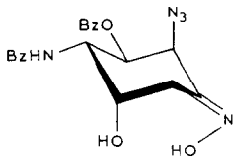

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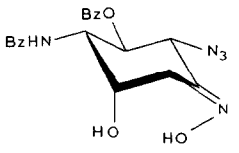

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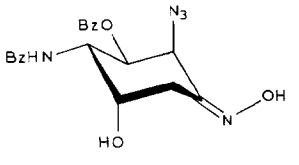

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The structure of **6** was supported by the signals of the keto group (C-1) at 198.0 and C-6 at 44.7 p.p.m. in the ^{13}C-n.m.r. spectrum (Table I). The additional ^{13}C and ^{1}H chemical shifts (Table II) were also consistent with structure **6**. The $^{3}J_{H,H}$ values support the equatorial position of substituents at C-2,3,4 and the axial position of HO-5.

Treatment of **6** with *p*-nitrophenylhydrazine gave the crystalline *p*-nitrophenylhydrazone (**7**), the structure of which was corroborated by the ^{1}H- and ^{13}C-n.m.r. data (Tables I and II). The upfield shifts of 13.6 and 3.1 p.p.m. for the resonances of C-6 and C-2 caused by the hydrazone bond accorded with the *E* configuration of the *p*-nitrophenylhydrazone group[9]. The same conclusion is indicated[1,10] by the upfield and downfield shifts of the signals of H-6*a* and H-6*e*, respectively.

In contrast to the foregoing reactions, however, the reaction of **7** with sodium azide in 1,2-dimethoxyethane resulted in introduction of the azido group at C-2, as proved by the i.r. spectrum of the crude product, but there were further rearrangements that resulted in a multicomponent mixture.

Since the hydroximino group shows[11,12] an activating effect similar to that of the arylhydrazone group on the adjacent leaving group, attention was turned to oxime **8**, prepared from **6** by the method of Bachman *et al.*[13]. The n.m.r. data of **8** (Tables I and II) corresponded to the structure expected, and the *E* configuration followed[14,15] from the upfield shift of 15.7 p.p.m. for the resonance of C-6 and from the characteristic increase of the $\Delta\delta$ value (1.13 p.p.m.) for H-6*a* and H-6*e*.

TABLE I

CHARACTERISTIC ^{13}C CHEMICAL SHIFTS (δ)

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
4[a]	99.1	52.9	69.7[c]	71.3[c]	150.6	97.4
6[a]	198.0	77.4	71.7	53.8	67.4	44.7
7[b]	151.2	74.3	72.3	53.2	67.2	31.1
8[b]	149.1	72.9	72.4	53.3	67.0	29.0
9[b]	152.1	64.4	72.1	51.5	67.6	28.7
10[b]	148.8	63.1	72.7	54.2	67.1	29.4
11[b]	149.2	54.3	70.8	50.9	67.2	34.4
13[a]	148.4	71.6	71.3	53.2	66.5	28.8

[a]In $CDCl_3$. [b]In $(CD_3)_2SO$. [c]Tentative assignments.

Treatment of **8** with sodium azide in aqueous 1,2-dimethoxyethane did not effect benzoyloxy → azide replacement, probably because of the poor activating effect of the hydroximino group. However, replacement was observed when sodium azide was substituted by tetrabutylammonium azide[16] and, as basic catalysts, tertiary amines were added to the solution of **8** in ethoxyethanol (Table III). The transformation without the addition of base can be attributed to contami-

TABLE II

CHARACTERISTIC ^1H CHEMICAL SHIFTS (δ) AND VICINAL COUPLINGS (Hz)

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6b*
1[a]	4.91d	4.67td	5.76t	5.48t	4.15 ———		4.30
3[a]	5.02d	4.75ddd	5.81dd	5.44dd	4.05ddd	3.88	
4[a]	5.08d	4.98td	5.83t	6.07d	—	4.80dt	
6[a]	—	5.91d	6.10d	5.16td	4.42q	2.83dd[c]	3.00dd[d]
7[b]	—	6.08d	5.90t	4.94td	4.27m	2.65dd[c]	3.48dd[d]
8[b]	—	6.07d	5.92t	4.96td	4.22m	2.45dd[c]	3.58dd[d]
9[b]	—	4.74d	5.64dd	4.85m	4.23q	2.26dd[c]	3.52dd[d]
10[b]	—	4.34d	5.61t	4.64td	4.23q	2.18dd[c]	3.67dd[d]
11[b]	—	5.80d	5.54dd	4.88td	4.22q	2.65	
13[a]	—	6.0 ———	5.97	4.83td	4.29q	2.27dd[c]	3.63dd[d]

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{4,NH}$
1[a]	3.3	9.6	10.0	10.0			9.6
3[a]	3.5	10.5	9.5	9.5	8.5	3.5	9.5
4[a]	3.0	10.0	10.0	—	—	—	8.8
6[a]	—	10.2	10.5	2.0	3.5	3.0	9.4
7[b]	—	9.5	9.5	2.0			9.0
8[b]	—	9	9	2.0	2.5	3.0	9
9[b]	—	4.0	10.8	2.6	3.0	3.2	10
10[b]	—	9.6	10.4	2.5	3.6	3.2	10
11[b]	—	4.0	11.0	2.6	2.9	2.9	10
13[a]	—		10.0	2.0	3.0	3.0	9.0

[a]In $CDCl_3$. [b]In $(CD_3)_2SO$. [c]*Ha*. [d]*He*.

TABLE III

CONDITIONS AND RESULTS OF THE REACTION OF **8** WITH TETRABUTYLAMMONIUM AZIDE[a]

Base (0.5 mol)	*Azide (mol)*	*Time (h)*	*Yield (%)*	**9**	**10**	**11**
—	1.1	4	39	75	25	—
Triethylamine	3.0	4	83	75	25	—
Triethylamine[b]	3.0	4	63	67	24	9
Triethylenediamine (DABCO)	3.0	7	68	64	36	—
1,8-Bis(dimethylamino)naphthalene (proton sponge)	3.0	11	78	56	44	—
Pyridine	3.0	14	71	50	50	—
		25	59	65	35	—
sym-Collidine	3.0	10	60	49	39	12

[a]In 2-ethoxyethanol at 60°. [b]In 1,2-dimethoxyethane.

nation of tetrabutylammonium azide by tributylamine. Chromatography of the products afforded epimers (**9** and **10**) of 2-azido-4-benzamido-3-benzoyloxy-5-hydroxycyclohexanone-(*E*)-oxime.

The large $J_{2,3}$ value (9.6 Hz, Table II) indicated an equatorial azido group in **10**, and the value (4 Hz) for **9** showed an axial azide substituent. The same conclusion can be drawn from the chemical shifts for the H-2 resonances, δ 4.74 for H-2*e* in **9** and δ 4.34 for H-2*a* in **10**, or from the γ-effect of -2.6 p.p.m. at C-4 (Table I) caused by the axial azido group in **9**. The *E* configuration of the oxime in **9** and **10** is supported by the characteristic shielding of C-6 (28.7 and 29.4 p.p.m., respectively) and by the increased $\Delta\delta$ values (1.26 and 1.49 p.p.m., respectively) of the resonances for H-6,6'.

With *sym*-collidine in methoxyethanol or with triethylamine in 1,2-dimethoxyethane (Table III), in addition to **9** and **10**, **8** gave a third product with an azide substituent (**11**, ν_{max} 2100 cm^{-1}) after chromatography. The value (4 Hz) of $J_{2,3}$ (Table II) and the shielding at C-4 (50.9 p.p.m.) (Table I) for **11** are consistent with an axial azido group, and the *Z* configuration of the oxime was proved by the upfield shift of the C-2 signal (54.3 p.p.m.) caused by the steric proximity of the OH group at N.

It is probable that formation of the fourth possible isomer, *i.e.*, the *Z* isomer of the equatorial azido compound is not allowed because of steric hindrance (*peri*-effect) between the hydroxyl of the hydroximino group and the equatorial azide substituent.

The stereoselectivity of the reactions of **8**, including the formation of the *Z* isomer **11**, is markedly influenced by the catalyst base (Table III). The 3:1 ratio (^{13}C-n.m.r. data) of **9** and **10** obtained with triethylamine decreased to 1:1 when pyridine was used.

The experimental data can be interpreted by a nucleophilic 1,4-elimination–addition process on **8** *via* a nitroso-cyclohexene type intermediate (**12**), formed by

deprotonation of the oxime and subsequent elimination of BzO-2, which then adds azide anion at C-2. In accord with this mechanism, no azide introduction occurred with the *O*-methyloxime **13**, prepared from **6** with *O*-methylhydroxylamine hydrochloride in pyridine.

Evidence for thermodynamic control in the formation of the azide epimers was provided by the reaction with pyridine catalyst. The 1:1 ratio of **9** and **10** after 14 h changed to 1.8:1 after 25 h. When **10** was kept in the presence of triethylamine under the conditions of the azide replacement, t.l.c. revealed not only the appearance of the axial isomers **9** and **11** but also that the spot of **9** became stronger after 20 h. A similar equilibrium mixture was obtained by epimerization of **9** with *sym*-collidine which indicates that epimerization, as for the BzO → N_3 replacement, follows a nucleophilic 1,4-elimination–addition mechanism *via* the nitrosocyclohexene intermediate **12**.

EXPERIMENTAL

General. — T.l.c. was performed on Silica Gel F_{254} (Merck), unless otherwise stated, with *A*, carbon tetrachloride–ethyl acetate (7:3); or *B*, carbon tetrachloride–ethyl acetate–ethanol (6:3:1). Optical rotations were measured with a Zeiss POLAMAT A polarimeter and i.r. spectra with a Zeiss Infracord 75 spectrometer. The ^{1}H- (250 and 100 MHz) and ^{13}C-n.m.r. (62.5 and 25 MHz) spectra (internal Me_4Si) were measured with a Bruker AC-250, JEOL FX-100, or Varian XL-100-15 F.t. spectrometer.

*Methyl 2-benzamido-3,4-di-*O*-benzoyl-2-deoxy-6-*O*-tosyl-α-*D*-glucopyranoside* (**1**). — To a stirred and cooled solution of methyl 2-benzamido-2-deoxy-α-D-glucopyranoside[6] (13.4 g, 45 mmol) in dry pyridine (270 mL) was added a solution of toluene-*p*-sulphonyl chloride (12.9 g, 67.5 mmol) in pyridine (32 mL) during 0.5 h at −10°, and the mixture was stored at −18° for 2 days. Ice–water (50 mL) was then added during 1 h at room temperature, the mixture was concentrated, and a solution of the syrupy residue in chloroform was washed with 2M hydrochloric acid, water, saturated aq. sodium hydrogencarbonate, and water, dried (Na_2SO_4), and concentrated. The syrupy residue was treated with benzoyl chloride (13.0 mL, 112 mmol) in dry pyridine (150 mL) at room temperature for 24 h. The mixture was poured into ice–water and the precipitate was recrystallised from ethanol–chloroform (10:1), to give **1** (21.4 g, 72%), m.p. 191–193°, $[\alpha]_D$ +77° (*c* 1, chloroform).

Anal. Calc. for $C_{35}H_{33}NO_{10}S$: C, 63.72; H, 5.04; N, 2.12; S, 4.86. Found: C, 63.53; H, 5.21; N, 2.25; S, 4.95.

*Methyl 2-benzamido-3,4-di-*O*-benzoyl-2,6-dideoxy-6-iodo-α-*D*-glucopyranoside* (**3**). — To a solution of **1** (19.7 g, 3 cmol) in *N,N*-dimethylformamide (220 mL) was added potassium iodide (24.9 g, 15 cmol), and the mixture was stirred at 70° for 5 h, then poured into ice–water. The precipitate was recrystallised from ethanol to afford **2** (18.5 g, 85%), m.p. 175–178°, $[\alpha]_D$ +45° (*c* 1, ethanol).

Anal. Calc. for $C_{28}H_{26}INO_7$: C, 54.65; H, 4.26; N, 2.28; I, 20.62. Found: C, 54.39; H, 4.35; N, 2.13; I, 19.32.

*Methyl 2-benzamido-3,4-di-O-benzoyl-2,6-dideoxy-α-*D*-xylo-hex-5-enopyranoside* (**4**). — To a solution of **3** (9.2 g, 15 mmol) in dry pyridine (140 mL) was added powdered silver(I) fluoride (8.8 g, 60 mmol) gradually, and the mixture was stirred in the dark for 24 h, then poured into ether (300 mL). The ether layer was decanted and the residue was extracted several times with ether. The combined ethereal solutions were washed with aq. sodium thiosulfate and water, dried (Na_2SO_4), and concentrated. Toluene was evaporated from the residue to remove pyridine. Treatment of the resulting syrup with hot cyclohexane gave **3** (5.5 g, 75%), m.p. 74–77°, $[\alpha]_D$ +103° (*c* 1, chloroform).

Anal. Calc. for $C_{28}H_{25}NO_7$: C, 68.98; H, 5.17; N, 2.87. Found: C, 68.14; H, 5.59; N, 2.82.

2L-(2,4,5/3)-4-Benzamido-2,3-dibenzoyloxy-5-hydroxycyclohexanone (**6**). — A mixture of **4** (4.9 g, 10 mmol) and mercury(II) chloride (2.7 g) in 2:1 acetone–water (250 mL) was boiled under reflux for 4.5 h, when t.l.c. (solvent *A*) revealed no **4**. The acetone was evaporated, the aqueous solution was extracted with chloroform, and the extract was washed, dried (Na_2SO_4), and concentrated. Crystallisation of the residue (3.8 g) from chloroform–light petroleum (1:1) gave **6** (1.7 g, 36%), m.p. 194–196°, $[\alpha]_D$ −3.8° (*c* 1, chloroform).

Anal. Calc. for $C_{27}H_{23}NO_7$: C, 68.49; H, 4.90; N, 2.96. Found: C, 68.45; H, 5.05; N, 3.02.

2L-(2,4,5/3)-4-Benzamido-2,3-dibenzoyloxy-5-hydroxycyclohexanone p-*nitrophenylhydrazone* (**7**). — A solution of crude **6** (2.5 g, 5.7 mmol) and *p*-nitrophenylhydrazine (0.88 g, 5.7 mmol) in ethanol containing acetic acid (3.8 mL) was boiled under reflux for 3 h, then poured into ice–water. The precipitate (2.36 g, 68%) was recrystallised from acetonitrile to give yellow crystals of **5** (1.0 g, 29%), m.p. 190–193°, $[\alpha]_D$ +61° (*c* 1, *N,N*-dimethylformamide).

Anal. Calc. for $C_{33}H_{28}N_4O_8$: C, 65.12; H, 4.63; N, 9.21. Found: C, 63.75; H, 4.67; N, 8.60.

2L-(2,4,5/3)-4-Benzamido-2,3-dibenzoyloxy-5-hydroxycyclohexanone (E)-*oxime* (**8**). — To a solution of **6** (2.37 g, 5 mmol) in dry pyridine (24 mL) was added a solution of hydroxylamine hydrochloride (0.38 g, 5.5 mmol) in ethanol (38 mL), and the mixture was boiled under reflux for 5 h, when t.l.c. [Aluminumoxid 60 F_{254} (Merck), solvent *B*] revealed no **6**. The solution was concentrated to dryness, the residue was treated with water, and the resulting solid (2.10 g, 86%) was recrystallised from ethanol to afford **6** (1.66 g, 66%), m.p. 201–203°, $[\alpha]_D$ −60° (*c* 1, ethanol).

Anal. Calc. for $C_{27}H_{24}N_2O_7$: C, 66.39; H, 4.95; N, 5.74. Found: C, 66.37; H, 4.96; N, 5.75.

2L-(2,4,5/3)-4-Benzamido-2,3-dibenzoyloxy-5-hydroxycyclohexanone O-*methyloxime* (**13**). — To a solution of **6** (470 mg, 1 mmol) in dry pyridine (5 mL) was added a solution of *O*-methylhydroxylamine hydrochloride (92 mg, 1.1 mmol) in ethanol (9 mL). The mixture was boiled under reflux for 5 h, then concentrated to one-third volume, and poured into ice–water. The precipitate was recrystallized

from ethanol to give **13** (310 mg, 62%), m.p. 218–219°, $[\alpha]_D$ −29° (*c* 1, chloroform).

Anal. Calc. for $C_{28}H_{26}N_2O_7$: C, 66.92; H, 5.22; N, 5.57. Found: C, 66.55; H, 5.47; N, 5.49.

Reaction of **8** *with tetrabutylammonium azide.* — A solution of **8**, tetrabutylammonium azide, and tertiary base in 2-ethoxyethanol was kept at 60° until t.l.c. (Aluminumoxid 60 F_{254}, solvent *B*) revealed no **8**. The mixture was poured into ice–water, and the precipitate was collected, dried, and subjected to dry column chromatography[17] [Silica Gel 60 (230–240 mesh), dichloromethane–toluene–ethyl acetate, 5:2:3] to give the following products.

2D-(2,3/4,5)-2-Azido-4-benzamido-3-benzoyloxy-5-hydroxycyclohexanone (*E*)-oxime (**9**), R_F 0.30, m.p. 160–162°.

Anal. Calc. for $C_{20}H_{19}N_5O_5$: C, 58.67; H, 4.68; N, 17.11. Found: C, 58.78; H, 4.82; N, 15.55.

2L-(2,4,5/3)-2-Azido-4-benzamido-3-benzoyloxy-5-hydroxycyclohexanone (*E*)-oxime (**10**), R_F 0.19, m.p. 157–158°.

Anal. Calc. for $C_{20}H_{19}N_5O_5$: C, 58.67; H, 4.68; N, 17.11. Found: C, 60.21; H, 4.91; N, 15.24.

2D-(2,3/4,5)-2-Azido-4-benzamido-3-benzoyloxy-5-hydroxycyclohexanone (*Z*)-oxime (**11**), R_F 0.11, m.p. 147–151°.

Anal. Calc. for $C_{20}H_{19}N_5O_5$: C, 58.67; H, 4.68; N, 17.11. Found: C, 56.57; H, 5.03; N, 15.13.

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