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Note

A simple synthesis of epimeric 2-azidoinososе derivatives

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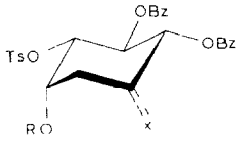
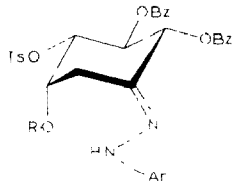
Aminoinositols are key intermediates in the total synthesis of aminocyclitol antibiotics. There are several procedures[1] leading to inososes, the precursors of aminoinositols, and Ferrier[2] recently described a new stereospecific method for producing 2L-(2,4,5/3)-2,3-dibenzoyloxy-5-hydroxy-4-toluene-*p*-sulphonyloxycyclohexanone (**1**) from the corresponding 6-deoxy-hex-5-enopyranoside.

Although a new crystalline oxime (**2**) was obtained from **1** using the method of Bachmann *et al.*[3], it was unsuitable for conversion into the corresponding amino compound because of difficulties caused by the protecting groups. Likewise, attempts to reduce an analogous oxime synthesised from maltose by the Ferrier method were unsuccessful[4]. Thus, an alternative means of introducing an amino function into **1** was sought.



1 R = H, X = O
2 R = H, X = N—OH
3 R = Ac, X = O



4 R = Ac, Ar = *p*-NC$_6$H$_4$-phenyl
5 R = H, Ar = *p*-NO$_2$-phenyl

On treatment with acetic anhydride–pyridine, **1** underwent β-elimination to give the conjugate enone[2]. However, reaction of **1** with acetic acid–trifluoroacetic anhydride gave the 5-acetate **3**, the $J_{4,5}$ value (2.8 Hz) of which (Table II) showed unambiguously that the acetoxy substituent was axial.

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TABLE I

^{1}H-CHEMICAL SHIFTS (δ)

Compound (solvent)	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6e*	*Ar-Me*	*MeCO*	*Aryl*	*NH*
3										
($CDCl_3$)	5.73d	6.07t	5.27dd	5.70m	←2.88d (2 H)→		2.21s (3 H)	2.10s (3 H)	6.94d (2 H) 7.2–8.0 (12 H)	
(C_6D_6)	5.81d	6.52t	5.30dd	5.72q	1.99dd	2 53dd	2.64s (3 H)	2.34s (3 H)	6.42d (2 H) 7.60d (2 H) 7.8–8.15 (4 H) 6.7–7.1 (6 H)	
4[a]										
($CDCl_3$)		←5.0–6.1 (4 H)→			←2.73d (2 H)→		2.25s (3 H)	2.10s (3 H)	6.7–7.1 (4 H) 7 2–8.1 (14 H)	8.4s (1 H)
5										
($CDCl_3$)	5.68d	6.00t	4.86dd	4.74m	2.32dd	3.25dd	2.13s (3 H)		6.60d (2 H) 6.83d (2 H) 7 2–8.0 (14 H)	8.45s (1 H)
7										
(CD_3CN)	4.76dd	5.62dd	4.98dd	4.36dd	2.55ddd	3.06dd	2.37s (3 H)		7.1–8.2 (13 H)	9.03s (1 H)
8										
(CD_3CN)	4.30dd	5.46dd	4.88dd	4.40m	2.30m	3.36dd	2.36s (3 H)		7.0–8.2 (13 H)	9.03s (1 H)

[a]Recorded with a Varian EM-360A (60 MHz) instrument.

TABLE II

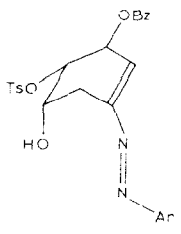
COUPLING CONSTANTS (Hz) OF RING PROTONS

Compound (solvent)	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6e}$	$^2J_{6a,6e}$
3						
($CDCl_3$)	10.0	10.0	2.8			
(C_6D_6)	10.0	10.0	3.0	3.2	3.6	16.0
5						
($CDCl_3$)	10.0	10.0	~2	5.5	~2	16.0
7[a]						
(CD_3CN)	4.2	9.5	2.7	3.0	4.2	15.4
8						
(CD_3CN)	10.0	9.5	2.7	~3	4.1	15.4

[a] $^4J_{2,6e}$ 1.0 Hz

With *p*-nitrophenylhydrazine in boiling ethanol–acetic acid, **3** was converted into the crystalline hydrazone **4**. However, **4** was too unstable for the subsequent reactions, and attention was therefore turned to the hydrazone **5** prepared crystalline and in good yield from **1** and *p*-nitrophenylhydrazine as described for **4**. The structure of **5** was supported by the n.m.r. data (Tables I and II).

Because of the benzoyloxy substituent adjacent to the *p*-nitrophenylhydrazone moiety, **5** seemed to be suitable for conversion into the corresponding *p*-nitrophenylazocyclohexene derivative **6** by published[5–8] methods. However, attempts to isolate **6** were unsuccessful, probably because of secondary reactions, under the basic conditions, involving the benzoyloxy and tosyloxy substituents.



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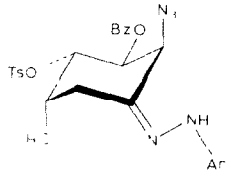

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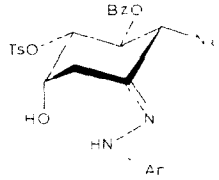

8

Ar = *p*-NO_2-phenyl

Treatment of **5** with sodium azide in aqueous 1,2-dimethoxyethane at 60–65° for 20 h gave two products (**7** and **8**), in similar proportions, which were isolated crystalline after chromatography. The i.r. spectra of **7** and **8** were almost identical and contained a band characteristic of the azido group at 2110 cm^{-1}. The ^{1}H-n.m.r. data (Tables I and II) indicated that BzO-2 in **5** had been replaced by an axial azido group in **7** and by an equatorial azido group in **8**. Thus, the $J_{2,3}$ values for **7** and **8** were 4.2 and 10.0 Hz, respectively. Also **7**, but not **8**, showed long-

range coupling ($^4J_{2,6e}$ 1.0 Hz) consistent with H-2 and H-6*e* being equatorial.

Evidence for the *E* configuration of the *p*-nitrophenylhydrazone group shown in formula **8** was also provided by the ^{1}H-n.m.r. data. The difference in chemical shifts (1.06 p.p.m.) for H-6*a* and H-6*e*, which is remarkably higher than that (~0.5 p.p.m.) of methylene protons in similarly substituted cyclohexanones, can be attributed to the interaction between the methylene protons and the N-H group of the arylhydrazone moiety. In the corresponding *Z* isomer, there would be steric hindrance between the hydrazone group and the equatorial azido group. Similarly, the chemical-shift difference (0.93 p.p.m.; Table I) for the signals of the methylene protons in **5** suggests the *E* configuration.

The configuration of the *p*-nitrophenylhydrazone group in **7** could not be elucidated unambiguously. The small difference (0.51 p.p.m.) in chemical shifts of the signals of the methylene protons could be consistent with the *Z* isomer, which is sterically allowed by the axial azido group at C-2. However, an equilibrium mixture of *E* and *Z* isomers cannot be excluded.

The mechanism of the reaction of **5** with sodium azide can be formulated[7] as a nucleophilic 1,4-elimination–addition process. Release of the proton from the imino-nitrogen of the arylhydrazone group of **5** and subsequent elimination of BzO-2 gives the azoalkene intermediate **6**, which undergoes addition of azide anion at C-2. Fast protonation of the resulting hydrazone anions yields the epimers **7** and **8**.

Thus, use of **7** and **8** as potential starting-materials for the synthesis of aminodeoxy or diaminodideoxy derivatives of inositols is being studied.

EXPERIMENTAL

General. — T.l.c. was performed on Silica Gel F_{254} (Merck). Optical rotations were measured with a Zeiss POLAMAT A polarimeter. I.r. spectra were recorded with a Zeiss Infracord 75 spectrometer. ^{1}H-N.m.r. spectra (internal Me_4Si) were recorded with a JEOL FX-100 (100 MHz) instrument. Microanalyses were performed in the Microanalytical Laboratory of the Institute.

2L-(2,4,5/3)-2,3-Dibenzoyloxy-5-hydroxy-4-toluene-p-*sulphonyloxycyclohexanone* p-*nitrophenylhydrazone*[9] (**5**). — To a solution of **1**[2] (2.1 g, 4 mmol) in hot, dry ethanol (60 mL) containing acetic acid (2 mL) was added *p*-nitrophenylhydrazine (0.68 g, 4.44 mmol), and the mixture was boiled under reflux for 2 h and then cooled. The yellow crystals (2.53 g, 96%) were collected, and recrystallised from methanol to give **5** (2.09 g, 79%), m.p. 107–108°, $[\alpha]_D$ −147° (*c* 1, chloroform).

Anal. Calc. for $C_{33}H_{29}N_3O_{10}S$: N, 6.37; S, 4.86. Found: N, 6.10; S, 4.68.

2L-(2,4,5/3)-5-Acetoxy-2,3-dibenzoyloxy-4-toluene-p-*sulphonyloxycyclohexanone* (**3**). — A mixture of **1** (0.52 g, 1 mmol), trifluoroacetic anhydride (2.1 mL), and acetic acid (0.4 mL) at 0° was stored for 20 h at room temperature and then poured into ice–water. The crude product (0.52 g, 93%) was collected, and recrys-

tallised from ethanol to give **3** (0.42 g, 75%), m.p. 146–147°, $[\alpha]_D$ +19° (*c* 1, chloroform), R_f 0.40 (carbon tetrachloride–ethyl acetate, 6:4).

Anal. Calc. for $C_{29}H_{26}O_{10}S$: C, 61.48; H, 4.63; S, 5.66. Found: C, 61.82; H, 4.81; S, 5.65.

2l-(2,4,5/3)-5-Acetoxy-2,3-dibenzoyloxy-4-toluene-p-*sulphonyloxycyclohexanone* p-*nitrophenylhydrazone* (**4**). — A solution of **3** (0.34 g, 0.6 mmol) and *p*-nitrophenylhydrazine (0.13 g, 0.66 mmol) in ethanol (13 mL) containing acetic acid (0.2 mL) was boiled under reflux for 1.5 h and then cooled overnight. The yellow crystals (0.20 g, 48%) were collected, and recrystallised from ethanol to give **4** (0.13 g, 31%), m.p. 118–119°, $[\alpha]_D$ +21° (*c* 0.5, chloroform), R_f 0.35 (carbon tetrachloride–ethyl acetate–1,4-dioxane, 6:3:1).

Anal. Calc. for $C_{35}H_{31}N_3O_{11}S$: N, 5.99; S, 4.57. Found: N, 5.94; S, 4.59.

2D-(2,3/4,5)-2-Azido-3-benzoyloxy-5-hydroxy-4-toluene-p-*sulphonyloxycyclohexanone* p-*nitrophenylhydrazone* (**7**) *and 2L-(2,4,5/3)-2-azido-3-benzoyloxy-5-hydroxy-4-toluene*-p-*sulphonyloxycyclohexanone* p-*nitrophenylhydrazone* (**8**). — To a solution of **5** (2.0 g, 3 mmol) in 1,2-dimethoxyethane (32 mL) was added a solution of sodium azide (2.4 g, 37 mmol) in water (16 mL), and the mixture was stirred for 20 h at 60–65°. T.l.c. (carbon tetrachloride–ethyl acetate–1,4-dioxane, 6:3:1) then revealed two products and no starting material. The mixture was poured into ice–water (240 mL), and the resulting yellow precipitate was subjected to column chromatography on silica gel (carbon tetrachloride–ethyl acetate–1,4-dioxane, 6:3:1), to yield **7** (0.72 g, 41%). Recrystallisation from methanol afforded yellow needles (0.62 g, 35%), m.p. 103–104°, $[\alpha]_D$ −335.5° (*c* 0.5, chloroform), ν_{max}^{KBr} 2110 cm^{-1} (N_3).

Anal. Calc. for $C_{26}H_{24}N_6O_8S$: N, 14.48; S, 5.52.Found: N, 14.08; S, 5.49.

Eluted second was **8**. The yellow crystals (0.70 g, 40%) were recrystallised from methanol, to give material (0.38 g, 22%) having m.p. 93–94°, $[\alpha]_D$ −215° (*c* 0.5, chloroform), ν_{max}^{KBr} 2110 cm^{-1} (N_3).

Anal. Calc. for $C_{26}H_{24}N_6O_8S$: N, 14.48; S, 5.52. Found: N, 14.27; S, 5.85.

2L-(2,4,5/3)-2,3-Dibenzoyloxy-5-hydroxy-4-toluene-p-*sulphonyloxycyclohexanone oxime* (**2**). — To a solution of **1** (0.52 g, 1 mmol) in dry pyridine (2 mL) was added a solution of hydroxylamine hydrochloride (0.08 g, 1.1 mmol) in ethanol (2 mL), and the mixture was boiled under reflux for 2.5 h and then concentrated to dryness. The residue was treated with water to give a solid (0.52 g, 96%), recrystallisation of which from ethanol afforded colorless crystals of **2** (0.36 g, 67%), m.p. 131–132°, $[\alpha]_D$ −53.5° (*c* 1, chloroform).

Anal. Calc. for $C_{27}H_{25}NO_9S$: N, 2.60; S, 5.94. Found: N, 2.48; S, 5.86.

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