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## Note

# Nucleophilic additions on α,β-unsaturated keto-nucleosides: preparation of 2-amino-2-deoxy- and 2-thio-hexopyranos-4-ulose nucleosides

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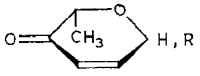
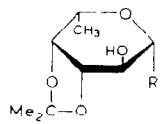
Nucleophilic additions on α,β-unsaturated keto-nucleosides are highly stereoselective[1,2] and are useful for preparing branched-chain or unsaturated nucleosides with predetermined stereochemistry.

The unsaturated keto-nucleosides derived from the L-*glycero*-hex-2′-enosyl structure **1** are intermediates in the synthesis of branched-chain 4′-keto-nucleosides[3] that inhibit the growth *in vitro* of the KB cell[4] and are active against L1210 leukemia in mice[5]. Moreover, the sugar moiety **1** is found in the collagen proline-hydroxylase inhibitor produced by *Streptomyces albogriseolus*[6]. Nucleophilic additions to **1** constitute a new approach to nucleosides of 2,3,6-trideoxy sugars which are components of some antibiotics[7].




**1** R = purine or pyrimidine

The reactions were performed on the 7-(2,3,6-trideoxy-β-L-*glycero*-hex-2-enopyranosyl-4-ulose)theophylline (**6**) prepared by the reaction[8,9] of 7-(2,3-anhydro-6-deoxy-β-L-*lyxo*-hexopyranosyl-4-ulose)theophylline (**5**) with sodium iodide and sodium acetate. Compound **5** was obtained from 7-(6-deoxy-3,4-*O*-isopropylidene-β-L-galactopyranosyl)theophylline[10] (**2**) as follows. Treatment of **2** with mesyl chloride followed by deacetalation[11] with trifluoroacetic acid–methanol gave 7-(6-deoxy-2-*O*-methanesulfonyl-β-L-galactopyranosyl)theophylline (**3**). The reaction of **3** with 2M methanolic sodium methoxide afforded 7-(2,3-anhydro-6-deoxy-β-L-talopyranosyl)theophylline (**4**); the structure of **4** was established by n.m.r. spectroscopy[12,13]. Cleavage of the epoxide ring in **4** was slow (aqueous acetic acid, 24 h), indicating the absence of participation of the neighboring acetate group and thus confirming the *talo* configuration. Treatment of **4** with the 3 Å molecular sieve/pyridinium dichromate reagent[15] afforded 7-(2,3-anhydro-6-deoxy-β-L-*lyxo*-hexo-

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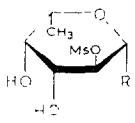


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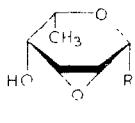


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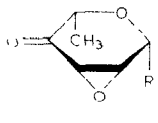


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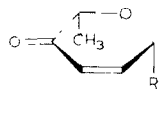


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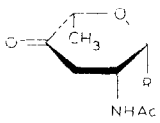


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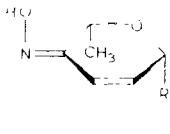


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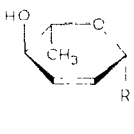


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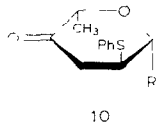


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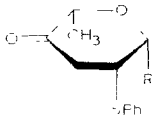


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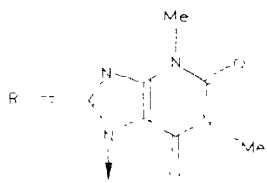


pyranosyl-4-ulose)theophylline (**5**), the first example of an epoxyketone in the nucleoside field.

Addition of ammonia to **6** was less stereospecific than the addition of amine to 7-(3-bromo-3,4,6-trideoxy-α-L-*glycero*-hex-3-enopyranosyl-2-ulose)theophylline[2]. Treatment of **6** with ammonia in acetonitrile and acetylation (pyridine–acetic anhydride) in the presence of 4-dimethylaminopyridine gave a 1 : 1 mixture of *erythro*- and *threo*-acetamidonucleosides, as indicated by the n.m.r. data (2 d at δ 7.6 and 7.5, $J$ 1.5 and 8 Hz). Only 7-(2-acetamido-2,3,6-trideoxy-β-L-*threo*-hexopyranosyl-4-ulose)theophylline (**7**) could be isolated from the mixture.

In contrast to ammonia, hydroxylamine reacted with **6** to give the oxime of 7-(2,3,4,6-tetradeoxy-β-L-*glycero*-hex-2-enopyranosyl-4-ulose)theophylline (**8**), a new type of unsaturated nucleoside. The structure of **8** was indicated by the n.m.r. data (see Experimental). Treatment of **6** with sodium borohydride reduced the carbonyl group and afforded 7-(2,3,6-trideoxy-β-L-*erythro*-hex-2-enopyranosyl)theophylline (**9**). The n.m.r. spectrum of acetylated **9** showed H-4,5 to be *trans*-diaxial and that axial addition of hydride to the carbonyl group of **6** had occurred.

The addition of thiophenol to **6** in the presence of a catalytic amount of tetrabutylammonium fluoride[10] afforded only the *trans* isomer, 7-(2,3,6-trideoxy-2-*S*-phenyl-2-thio-β-L-*erythro*-hexopyranosyl-4-ulose)theophylline (**10**), as evidenced by the value (8 Hz) of $J_{1,2}$.

In the absence of catalyst, **6** reacted with thiophenol to give 7-(2,3,6-trideoxy-2-*S*-phenyl-2-thio-β-L-*threo*-hexopyranosyl-4-ulose)theophylline (**11**). The *cis* relation-

ship of H-1,2 was established by the coupling constants $J_{1,2}$ 2, $J_{2,3e}$ 3, and $J_{2,3a}$ 4 Hz. These results suggest that the uncatalysed reaction gave the kinetic product (**11**) and that the catalysed reaction gave the thermodynamic product (**10**). This view was supported by the fact that the transformation **11**→**10** occurred in tetrahydrofuran containing tetrabutylammonium fluoride.

## EXPERIMENTAL

I.r. spectra were recorded with a Perkin–Elmer 137 spectrometer. A Varian T60 spectrometer was used for $^1$H-n.m.r. spectra (internal $Me_4Si$). Optical rotations were determined with a Roussel–Jouan, Quick polarimeter. Reactions were monitored by t.l.c. on Schleicher and Schüll silica gel (plastic sheets). Preparative t.l.c. (1.5-mm layers) was carried out on silica gel PF 254 (Merck). Nucleosides were detected by u.v. light or by charring with sulfuric acid. H.p.l.c. was performed on a Dupont Zorbax-Sil column (0.75 × 50 cm), using a Dupont 850 chromatograph equipped with a u.v.-absorbance detector and a Rheodyne 7000 sampling valve. Melting points were uncorrected. Elemental analyses were obtained from the Laboratoire de Microanalyse du CNRS.

Solutions were concentrated at 40° under reduced pressure. Dichloromethane was purified by storage for 1 week over 4 Å molecular sieve. Solutions in organic solvents were dried on 1 PS Whatman hydrophobic filter.

*7-(6-Deoxy-2-O-mesyl-β-L-galactopyranosyl)theophylline* (**3**). — To a solution of 7-(6-deoxy-3,4-*O*-isopropylidene-β-L-galactopyranosyl)theophylline (**2**; 10 g, 27 mmol) in dry pyridine (150 mL) was added mesyl chloride (4.68 mL, 60 mmol). After 90 min at room temperature, the solution was concentrated and toluene was distilled three times from the residue, a solution of which in dichloromethane was then washed three times with water, dried, and concentrated.

The syrupy residue was treated with trifluoroacetic–methanol (95:5, 5 mL) for 15 min and then concentrated *in vacuo*. The residue crystallised from ethanol, to give **3** (10.1 g, 90%), m.p. 194–195°, $[\alpha]_D^{20}$ −55° (*c* 0.1, methanol); $R_F$ 0.46 (ethyl acetate–methanol, 85:15); $\lambda_{max}^{MeOH}$ 276 nm (ε 11,000); $\nu_{max}^{KBr}$ 3390, 3279, 1694, and 1652 cm$^{-1}$. P.m.r. data ($CD_3COCD_3$): δ 8.1 (s, 1 H, H-8), 5.8 (d, 1 H, *J* 9 Hz, H-1′), 5.2 (t, 1 H, *J* 9 Hz, H-2′), 3.5 and 3.3 (2s, 6 H, 2 NMe), 3.1 (s, 3 H, $MeSO_2$), and 1.3 (d, 1 H, *J* 6.5 Hz, H-6′).

*Anal.* Calc. for $C_{14}H_{20}N_4O_8S$: C, 41.58; H, 4.95; N, 13.86. Found: C, 41.39; H, 4.95; N, 13.55.

*7-(2,3-Anhydro-6-deoxy-β-L-talopyranosyl)theophylline* (**4**). — A mixture of **3** (3 g, 9.9 mmol), methanolic 2M sodium methoxide (12 mL, 24 mmol), and ethanol (18 mL) was stirred for 1 h. The product was collected and washed with hot methanol (20 mL), to give **4** (1.5 g, 49.5%). The filtrate was neutralised with Amberlite IR-120 ($H^+$) resin and concentrated *in vacuo*, to give **3** (1.5 g). Compound **4** had m.p. 230°, $[\alpha]_D^{20}$ −37.5° (*c* 0.1, methanol); $R_F$ 0.48 (ethyl acetate–methanol, 85:15); $\lambda_{max}^{MeOH}$ 275 nm (ε 7900); $\nu_{max}^{KBr}$ 3600, 1694, and 1652 cm$^{-1}$. P.m.r. data ($CD_3COOD$):

$\delta$ 8.4 (s, 1 H, H-8), 6.6 (s, 1 H, H-1′), 4.25–3.65 (m, 4 H, H-2′,3′,4′,5′), 3.6 and 3.4 (2 s, 6 H, 2NMe), and 1.3 (d, 1 H, *J* 6 Hz, H-6′).

*Anal.* Calc. for $C_{13}H_{16}N_4O_5$: C, 50.64; H, 5.19; N, 18.18. Found: C, 50.49; H, 5.21; N, 18.15.

*7-(2,3-Anhydro-6-deoxy-β-*L*-lyxo-hexopyranosyl-4-ulose)theophylline* (**5**). — A mixture of pyridinium dichromate (12.26 g, 33 mmol), 3 Å molecular sieve, and **4** (5.4 g, 16.5 mmol) was stirred in dry dichloromethane (85 mL) for 4 h and then filtered through silica gel G (Merck). The silica gel was washed with ethyl acetate (1.5 L) and then the combined filtrate and washings were concentrated *in vacuo*. Crystallisation of the residue from ethanol gave **5** (3.8 g, 70%), m.p. 188–190°, $[\alpha]_D^{20}$ 135° (*c* 0.1, dichloromethane); $R_F$ 0.62 (ethyl acetate–methanol, 85:15); $\lambda_{max}^{MeOH}$ 279 nm ($\varepsilon$ 11,000). P.m.r. data ($CDCl_3$): $\delta$ 8.1 (s, 1 H, H-8), 6.8 (s, 1 H, H-1′), 4.3 (q, 1 H, *J* 6.5 Hz, H-5′), 4 (d, 1 H, *J* 4 Hz, H-3′), 3.6 (s, 4 H, H-2′ and NMe), 3.4 (s, 3 H, NMe), and 1.5 (d, 3 H, *J* 6.5 Hz, H-6′).

*Anal.* Calc. for $C_{13}H_{14}N_4O_5 \cdot 0.5\ H_2O$: C, 49.52; H, 4.76; N, 17.77. Found: C, 49.73; H, 4.78; N, 17.17.

*7-(2,3,6-Trideoxy-β-*L*-glycero-hex-2-enopyranosyl-4-ulose)theophylline* (**6**). — To a solution of sodium iodide (3 g, 20 mmol) and sodium acetate (0.21 g, 3 mmol) in acetic acid (6 mL) was added with stirring a solution of **5** (1.53 g, 5 mmol) in acetone (40 mL). After 15 min, the mixture was concentrated (0.1 mmHg). A solution of the residue in dichloromethane was washed with saturated, aqueous sodium thiosulfate, dried, and concentrated. The resulting oil was treated immediately with pyridine and acetic anhydride (25 mL of each) for 30 min at room temperature. The solvents were then evaporated, and toluene (3 × 20 mL) was distilled from the residue, to give **6** (1 g, 70%), m.p. 190°, $[\alpha]_D^{20}$ −2.5° (*c* 0.1, chloroform); $R_I$ 0.61 (ethyl acetate–methanol, 85:15); $\lambda_{max}^{CHCl_3}$ 278 nm ($\varepsilon$ 9000); $\nu_{max}^{KBr}$ 1692 and 1653 $cm^{-1}$. P.m.r. data ($CD_3COCD_3$): $\delta$ 8.1 (s, 1 H, H-8), 7.2 (dd, 1 H, *J* 10 and 2 Hz, H-2′), 6.9 (d, 1 H, *J* 2 Hz, H-1′), 6.4 (dd, 1 H, *J* 2 and 10 Hz, H-3′), 4.6 (m, 1 H, *J* 2 and 7 Hz, H-5′), 3.5 and 3.3 (2 s, 6 H, 2 NMe), and 1.3 (d, 3 H, *J* 7 Hz, H-6′).

*Anal.* Calc. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.82; N, 19.31. Found: C, 53.40; H, 5.02; N, 18.83.

Compound **6** (0.28 g, 1 mmol) was treated with a mixture of hydroxylamine hydrochloride (140 mg, 2 mmol) in ethanol (2.5 mL) and pyridine (2.5 mL) for 2 min at room temperature. The solvent was then removed and the residue was partioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate (5 × 10 mL), the combined solutions were concentrated, and the residue was crystallised from methanol or ethyl acetate to afford oxime **8** (0.188 g, 60%), m.p. 215–220°, $[\alpha]_D^{20}$ +110° (*c* 0.1, acetic acid); $R_F$ 0.64 (ethyl acetate–methanol, 85:15); $\nu_{max}^{KBr}$ 3350, 3150, and 1640 $cm^{-1}$. P.m.r. data ($CD_3COCD_3$): $\delta$ 7.3 (dd, 1 H, *J* 2, 10 Hz, H-2′), 7.1 (dd, 1 H, *J* 1.5, 2 Hz, H-1′), 6.7 (q, 1 H, H-3′), 4.8 (q, 1 H, *J* 6.5 Hz, H-5′), 3.5 and 3.3 (2 s, 6 H, 2 NMe), and 1.5 (d, 3 H, *J* 6.5 Hz, H-6′).

*Anal.* Calc. for $C_{13}H_{15}N_5O_4 \cdot 0.5\ H_2O$: C, 49.68; H, 5.09; N, 22.29. Found: C, 50.17; H, 4.92; N, 22.29.

*7-(2-Acetamido-2,3,6-trideoxy-β-*L*-*threo*-hexopyranosyl-4-ulose)theophylline* (**7**). — Compound **6** (580 mg, 2 mmol) was treated with a saturated solution of ammonia in acetonitrile (10 mL) for 4 h at 25°. The solvent was then removed, and to a solution of the glassy residue in dichloromethane (5 mL) were added pyridine (0.24 mL, 3 mmol), acetic anhydride (0.36 mL, 3 mmol), and a crystal of 4-dimethylaminopyridine. The solution was concentrated and the residue was subjected to chromatography on silica gel 60 with ethyl acetate–methanol (3:1). Crystallisation of the product from ethyl acetate gave **7** (249 mg, 40%), m.p. 153–154°, $[\alpha]_D^{20}$ −145° (*c* 0.1, water); $R_F$ 0.42 (ethyl acetate–methanol, 85:15); $\lambda_{max}^{H_2O}$ 275 nm (ε 7000); $\nu_{max}^{KBr}$ 3448, 3030, 1720, and 1660 $cm^{-1}$. P.m.r. data ($CD_3COOD$): δ 8.4 (s, 1 H, H-8), 6.9 (d, 1 H, *J* 1.5 Hz, H-1′), 5.3 (m, 1 H, H-2′), 4.8 (q, 1 H, *J* 7 Hz, H-5′), 3.7 and 3.5 (2 s, 6 H, 2 NMe), 1.9 (s, 3 H, NAc), and 1.5 (d, 3 H, H-6′).

*Anal.* Calc. for $C_{15}H_{19}N_5O_5 \cdot H_2O$: C, 49.04; H, 5.72; N, 19.07. Found: C, 48.43; H, 5.75; N, 18.44.

*7-(2,3,6-Trideoxy-β-*L*-*erythro*-hex-2-enopyranosyl)theophylline* (**9**). — When **6** (290 mg, 1 mmol) was treated with sodium borohydride (305 mg, 8 mmol) in methanol (10 mL), reaction was immediate, and the mixture was diluted with water and then extracted with ethyl acetate (3 × 10 mL). The combined extracts were concentrated and the residue was crystallised from ethanol, to give **9** (261 mg, 90%), m.p. 165–170°, $[\alpha]_D^{20}$ −35° (*c* 0.1, methanol); $R_F$ 0.53 (ethyl acetate–methanol, 85:15); $\lambda_{max}^{MeOH}$ 275 nm (ε 11,000); $\nu_{max}^{KBr}$ 3344, 1692, 1654, and 1634 $cm^{-1}$. P.m.r. data ($CDCl_3$): δ 7.9 (s, 1 H, H-8), 6.9 (d, 1 H, *J* 1 Hz, H-1′), 6.3 (dd, 1 H, *J* 1 and 10 Hz, H-2′), 5.9 (dd, 1 H, *J* 1 and 10 Hz, H-3′), 4.1 (m, 1 H, H-4′), 3.9 (m, 1 H, *J* 6.5 and 8 Hz, H-5′), 3.5 and 3.3 (2 s, 6 H, 2 NMe), and 1.7 (d, 3 H, *J* 6.5 Hz, H-6′).

*Anal.* Calc. for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.47; N, 19.17. Found: C, 53.44; H, 5.58; N, 18.83.

*7-(2,3,6-Trideoxy-2-*S*-phenyl-2-thio-β-*L*-*erythro*-hexopyranosyl-4-ulose)theophylline* (**10**). — A mixture of **6** (0.29 g, 1 mmol), benzenethiol (0.25 mL, 1.62 mmol), tetrabutylammonium fluoride (17 mg, 0.05 mmol), and tetrahydrofuran (12 mL) was stirred under nitrogen for 2 h and then concentrated *in vacuo* (0.1 mmHg). A solution of the residual oil in dichloromethane was washed with water (3 × 5 mL), dried, and concentrated. The residue was subjected to preparative t.l.c. ($R_F$ 0.33; di-isopropyl ether–ethyl acetate, 1:1) followed by crystallisation from ethanol, to give **10** (0.21 g, 52.2%), m.p. 164–165°, $[\alpha]_D^{20}$ −193° (*c* 0.1, chloroform); $\lambda_{max}^{MeOH}$ 275 nm (ε 7450). P.m.r. data ($CDCl_3$): δ 7.9 (s, 1 H, H-8), 7.2 (s, 1 H, Ph), 6.2 (d, 1 H, *J* 9 Hz, H-1′), 4.2–4.7 (m, 2 H, H-2′,5′), 3.5 (s, 3 H, NMe), 3.4 (s, 3 H, NMe), 3.3–2.4 (m, 2 H, H-3′*a*,3′*e*), 1.4 (d, 1 H, *J* 6.5 Hz, H-6′).

*Anal.* Calc. for $C_{19}H_{20}N_4O_4S$: C, 57.00; H, 5.00; N, 14.00; S, 8.00. Found: C, 56.72; H, 5.04; N, 13.72; S, 7.99.

*7-(2,3,6-Trideoxy-2-*S*-phenyl-2-thio-β-*L*-threo-hexopyranosyl-4-ulose)theophylline* (**11**). — A mixture of **6** (0.28 g, 1 mmol) and benzenethiol (0.31 mL, 2 mmol)

was stirred under nitrogen for 150 min and then kept at 5° for 2 days. After concentration under reduced pressure (0.1 mmHg), the residue was crystallised from methanol, and dried at 85° *in vacuo* for 5 days, to give **11** (130 mg, 32.5%), m.p. 133–134°, $[\alpha]_D^{20}$ −210° (*c* 0.1, chloroform); $R_f$ 0.85 (ethyl acetate–methanol, 11:1); $\lambda_{max}^{MeOH}$ 276 nm (ε 7740); $\nu_{max}^{KBr}$ 1730, 1680, and 1650 $cm^{-1}$. P.m.r. data ($CDCl_3$): δ 8.1 (s, 1 H, H-8), 7.1 (s, 5 H, Ph), 6.2 (d, 1 H, *J* 2 Hz, H-1′), 4.3–4.5 (m, 1 H, H-2′), 3.9 (q, 1 H, *J* 6 Hz, H-5′), 3.5 (s, 3 H, NMe), 3.3 (s, 3 H, OMe), 3.0 (q, 1 H, $J_{3'a,3'e}$ 15 Hz, H-3′*e*), 2.4 (q, 1 H, H-3′*a*), and 1.4 (d, 3 H, *J* 6.5 Hz, H-6′).

*Anal.* Calc. for $C_{19}H_{20}N_4O_4S$: C, 57.00; H, 5.00; N, 14.00; S, 8.00. Found: C, 56.66; H, 4.82; N, 14.27; S, 7.61.

A mixture of **11** (0.04 g, 0.1 mmol), tetrabutylammonium fluoride (17 mg, 0.155 mmol), and tetrahydrofuran (12 mL) was stirred for 2 h and then concentrated, to give **10** (15 mg), which was identical with the product described above.

ACKNOWLEDGMENT

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