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Note

Synthesis of uracil nucleosides of D-xyluronic acid derivatives*

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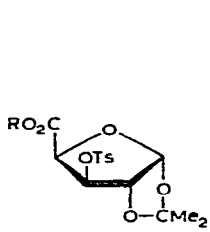
The isolation of nucleoside antibiotics[1] containing aminodeoxy and unsaturated derivatives of uronic acids has stimulated interest in this class of compound. The nucleoside fragments of these antibiotics, as well as of various analogues, have been synthesised, and many of these products display significant physiological activity[2].

We now report on the synthesis of 1-(methyl 2-*O*-acetyl-3-*O*-toluene-*p*-sulphonyl-β-D-xylofuranosyluronate)uracil (**4**).

Selective, acid hydrolysis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose[3] followed by oxidation of the resulting 1,2-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose successively with potassium periodate and permanganate yielded 1,2-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-xylofuranuronic acid (**1**). Aqueous acetic acid was used as solvent for the second oxidation step in order to prevent elimination of the tosyl group[4], and the use of sulphurous acid[5] for dissolution of manganese peroxide simplified the isolation and markedly improved the yield of **1**. Treatment of **1** with ethereal diazomethane gave the ester **2**. The n.m.r. data (Table I) of **2** are characteristic of the structure (*cf.* ref. 6).

Compound **2** was unexpectedly resistant to acetolysis; an acetic acid–acetic anhydride–sulphuric acid mixture containing 20% of sulphuric acid was necessary to effect the conversion of **2** into syrupy methyl 1,2-di-*O*-acetyl-3-*O*-toluene-*p*-sulphonyl-D-xylofuranuronate (**3**), which was shown by n.m.r. spectroscopy to be a



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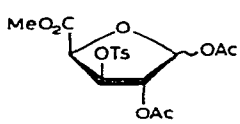
2 R = Me



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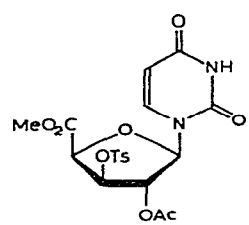

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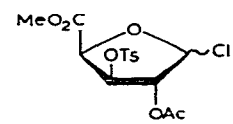

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*Modified Nucleosides: Part II. Part I: A. A. Akhrem, N. I. Garbuz, G. V. Zaitseva, I. A. Mikhailopulo, and T. E. Prokofyev, *Tetrahedron*, in press.

TABLE I

P.M.R. SPECTRAL DATA[a]

Compound (solvent)	*Sugar*				*Uracil*		*Others*	*Sugar*			*Uracil*
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{5,6}$
2 (Me_2SO-d_6)	6.22d	4.90d	5.03 or 5.09ud				1.30s, 1.44s } CMe_2 2.50s MePh 3.46s COOMe 7.64d, 7.90d } Ph	3.6	<0.3	3.2	
4 ($CDCl_3$)	6.03d	5.28ut	5.40q	5.09d	5.89d	8.04d	2.16s AcO 2.50s MePh 3.92s COOMe 7.44d, 7.82d } Ph 9.64s NH	1.6	1.8	4.4	8.0
7 ($CDCl_3$)	5.14ud	4.90ut	5.26uq	4.70ud			1.86s AcO 2.38s MePh 3.28s OMe 3.66s COOMe 7.24d, 7.66d } Ph	4.5	5.5	6.5	
8 ($CDCl_3$)	6.20ud	6.06ut	6.44d		5.82d	7.24d	2.16s AcO 3.90s COOMe	2.5	3.5		8.0

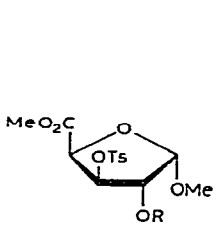
[a]Chemical shifts, δ p.p.m.; coupling constants, Hz. Key:s, singlet; d, doublet; t, triplet; q, quadruplet; u, unsymmetrical.

mixture of anomers. The stability of the isopropylidene group in **2** parallels that of the aryl glycosides of D-glucuronic acid[7].

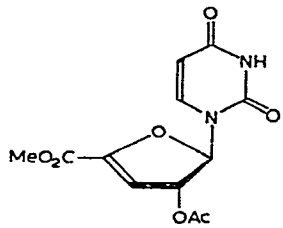
Condensation of **3** with bis(trimethylsilyl)uracil in the presence of stannic chloride, by the modified[8] silyl method[9] of nucleoside synthesis, gave the substituted nucleoside **4** (32%).

Condensation of the glycosyl chloride **5** with bis(trimethylsilyl)uracil by the Wittenburg procedure[10] also gave **4** (26.7%). The β-configuration of **4** was established by the p.m.r. data (Table I); the α-anomer was not detected in the reaction products.

A two-step transformation of **1** into methyl (methyl 2-*O*-acetyl-3-*O*-toluene-*p*-sulphonyl-α-D-xylofuranosid)uronate (**7**) was achieved in high yield by treatment of **1** with 3% methanolic hydrogen chloride to give **6**, followed by acetylation in pyridine. The values of $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ for **7** establish the α-configuration[11,12]. Treatment of **7** with stannic chloride or hydrogen bromide–acetic acid followed by reaction of the products with bis(trimethylsilyl)uracil gave **4** in poor yield (7%).



6 R = H
7 R = Ac



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Treatment of **4** with sodium azide in hexamethylphosphoric triamide at room temperature or with sodium hydrogen carbonate in boiling benzene gave the methyl ester of 1-(2-*O*-acetyl-3-deoxy-β-D-*glycero*-pent-3-enofuranosyluronic acid)uracil (**8**) in high yield. The facile elimination reaction (*cf.* ref. 4) is consistent with H-4 being activated by the methoxycarbonyl group and by the strong basicity of the azide ion. The product of the competing reaction involving nucleophilic substitution was not detected.

EXPERIMENTAL

I.r. spectra were obtained using a Model UR-20 spectrometer (Carl Zeiss). P.m.r. spectra were recorded on a JNM PS-100 instrument (Jeol); Me_4Si was used as an internal standard. Optical rotations were determined with a model JASCO J-20 spectropolarimeter.

1,2-O-Isopropylidene-3-O-toluene-p-sulphonyl-α-D-xylofuranuronic acid (**1**). — Hydrolysis of the 5,6-*O*-isopropylidene group in 1,2:5,6-di-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-α-D-glucofuranose (10 g, 24 mmol) followed by periodate oxidation of the product were performed conventionally. To a solution of the syrupy

product in 200 ml of 50% acetic acid at 10–15°, potassium permanganate (7.6 g, 52 mmol) was added in small portions with stirring. The mixture was stirred for 6 h at room temperature and then cooled to 5°, 10 g of potassium sulphide were added, and the solution was adjusted to pH 2 with hydrochloric acid. The product was collected, washed with water, and recrystallised from aqueous methanol to give **1** (4.2 g, 48%), m.p. 156–158° (dec.), $[\alpha]_D$ −42° (*c* 1.25, chloroform), $\nu_{max}^{CHCl_3}$ 1785 and 1750 cm^{-1} (C=O).

Anal. Calc. for $C_{15}H_{18}O_8S$: C, 50.28; H, 5.03; S, 8.93. Found: C, 50.31; H, 5.01; S, 8.98.

*Methyl 1,2-O-isopropylidene-3-O-toluene-*p*-sulphonyl-α-*D*-xylofuranuronate* (**2**). — A solution of **1** (10 g, 28 mmol) in methanol (100 ml) was treated with excess of ethereal diazomethane, the solvents were evaporated, and the residue was recrystallised from aqueous methanol to give **2** (10 g, 97%) as needles, m.p. 90°, $[\alpha]_D$ −39° (*c* 1.23, chloroform); $\nu_{max}^{CHCl_3}$ 1770 and 1750 cm^{-1} (C=O).

Anal. Calc. for $C_{16}H_{20}O_8S$: C, 51.62; H, 5.35; S, 8.60. Found: C, 51.58; H, 5.38; S, 8.56.

*1-(Methyl 2-O-acetyl-3-O-toluene-*p*-sulphonyl-β-*D*-xylofuranosyluronate)uracil* (**4**). — Methyl 1,2-di-*O*-acetyl-3-*O*-toluene-*p*-sulphonyl-D-xylofuranuronate (**3**) was obtained as a colourless syrup (96%) by acetolysis of **2** (21 mmol) with glacial acetic acid (105 ml), acetic anhydride (12 ml), and sulphuric acid (29 g) at room temperature for 24 h.

(*a*) To a solution of **3** (1.4 g, 3 mmol) in dichloroethane (20 ml) was added bis(trimethylsilyl)uracil (0.84 g, 3.5 mmol) and stannic chloride (0.35 ml; 3 mmol). The reaction mixture was kept at room temperature for 48 h, then treated with saturated aqueous sodium hydrogen carbonate (25 ml), and extracted with chloroform (3 × 100 ml). The combined extracts were washed with water, dried (Na_2SO_4), and concentrated. The resulting syrup (1.41 g) was eluted from silica gel (100 g) with benzene to give **3** (0.42 g). Elution with ether then gave **4** (0.51 g, 32%). A single recrystallisation from methanol gave **4**, m.p. 159–160°, $[\alpha]_D$ +67° (*c* 0.72, chloroform); $\nu_{max}^{CHCl_3}$ 1695 (NHCO), 1770 (C=O), 1720 (C=O), and 3400 cm^{-1} (NH).

Anal. Calc. for $C_{19}H_{20}N_2O_{10}S$: C, 48.74; H, 4.27; N, 5.98; S, 6.83. Found: C, 48.82; H, 4.33; N, 5.74; S, 6.63.

(*b*) A solution of **3** (10 g, 29 mmol) in ether (100 ml) saturated with hydrogen chloride was kept at 3° for 4 days and then concentrated to dryness. Toluene, followed four times with benzene, was distilled from the syrupy residue, which was then condensed with bis(trimethylsilyl)uracil (7 g, 27 mmol) according to Wittenburg's procedure[10], giving **4** (3 g, 26.7%) after one crystallisation from benzene.

(*c*) The reaction of bis(trimethylsilyl)uracil and the methyl glycoside **7** in the presence of $SnCl_4$, followed by work-up and chromatographic separation as in (*a*), yielded **4** (7%), with almost all of the starting sugar recovered.

*1-(Methyl 2-O-acetyl-3-deoxy-β-*D*-glycero-pent-3-enofuranosyluronate)uracil* (**8**). — (*a*) To a solution of **4** (0.8 g, 1.7 mmol) in hexamethylphosphoric triamide (4 ml), sodium azide (0.8 g) was added. The reaction mixture was kept overnight at

room temperature, then diluted with pentane (200 ml), filtered, and cooled for 24 h. The syrupy product, isolated by decantation, was eluted from silica gel (50 ml) with ether to give hexamethylphosphoric triamide. Elution with methanol then yielded **8** (0.25 g, 58%), which was obtained as an amorphous powder on trituration with ether, $[\alpha]_D$ −165° (*c* 0.81, methanol); ν_{max}^{KBr} 1695 (CONH), 1745 and 1733 (C=O), and 3450 cm^{-1} (NH).

Anal. Calc. for $C_{12}H_{12}N_2O_7$: C, 48.65; H, 4.05; N, 9.46. Found: C, 48.98; H, 4.41; N, 9.14.

(*b*) Compound **4** (1.85 g, 3.9 mmol) was stirred in boiling benzene with sodium hydrogen carbonate (12 g) for 18 h. The mixture was then filtered and concentrated, and the filtrate was concentrated to dryness to give **8** (1 g, 75%) as an amorphous powder.

Methyl (*methyl 3*-O-*toluene*-p-*sulphonyl*-α-D-*xylofuranosid*)*uronate* (**6**). — To a stirred, ice-cold solution of **1** (0.92 g, 2.6 mmol) in methanol (50 ml), acetyl chloride (2.5 ml) was added dropwise. The mixture was stirred for 6 h at 50°, then cooled, neutralized with barium carbonate, filtered, and concentrated to dryness. The residue was extracted with chloroform and the extract was concentrated to yield **6** (0.97 g, 97.8%), m.p. 146–148° (from methanol), $[\alpha]_D$ −11° (*c* 1.06, methanol); ν_{max}^{KBr} 1765 and 1740 (C=O), and 3450 cm^{-1} (OH).

Anal. Calc. for $C_{14}H_{18}O_8S$: C, 48.55; H, 5.20; S, 9.24. Found: C, 48.54; H, 5.27; S, 9.27.

Methyl (*methyl 2*-O-*acetyl*-*3*-O-*toluene*-p-*sulphonyl*-α-D-*xylofuranosid*)*uronate* (**7**). — A solution of **6** (0.87 g, 2.5 mmol) in 5 ml of anhydrous pyridine was treated with 5 ml of acetic anhydride. After 24 h, the reaction mixture was poured into ice–water, and the product was collected, and recrystallized from methanol to give **7** (0.9 g, 89%), m.p. 89–90°, $[\alpha]_D$ +19° (*c* 0.73, chloroform); ν_{max}^{KBr} 1770 and 1735 cm^{-1} (C=O).

Anal. Calc. for $C_{16}H_{20}O_9S$: C, 49.48; H, 5.15; S, 8.24. Found: C, 49.61; H, 5.22; S, 8.22.

REFERENCES

1 R. J. Suchadolnik, *Nucleoside Antibiotics*, Wiley–Interscience, New York, 1970.
2 T. Kondo, W. Nacai, and T. Joto, *Tetrahedron Lett.*, (1972) 1881; K. A. Watanabe, H. P. Kotik, and J. J. Fox, *J. Org. Chem.*, 35 (1970) 231; N. P. Domodoran, J. H. Jones, and J. G. Moffatt, *J. Amer. Chem. Soc.*, 93 (1971) 3812; H. Ohrui, H. Kuzuchara, and S. Emoto, *Tetrahedron Lett.*, (1971) 4267; M. Kawana, R. J. Rousseau, and R. K. Robins, *J. Org. Chem.*, 37 (1972) 288.
3 L. Vargha, *Ber.*, 69 (1936) 2098.
4 J. Žemlicka, J. V. Freisler, R. Gasser, and J. P. Horwitz, *J. Org. Chem.*, 38 (1973) 990.
5 M. Fieser and L. F. Fieser, *Reagents for Organic Synthesis*, Moscow, Mir, 1970.
6 B. Coxon, *Carbohyd. Res.*, 8 (1968) 125.
7 L. K. Semke, N. S. Thompson, and D. G. Williams, *J. Org. Chem.*, 29 (1964) 1041.
8 U. Niedballa and H. Vorbrüggen, *Angew. Chem.*, 82 (1970) 449.
9 T. Nishimura, B. Shimizu, and I. Iwai, *Chem. Pharm. Bull.*, 12 (1964) 807.
10 E. Wittenburg, *Chem. Ber.*, 101 (1968) 1095.
11 G. Casini and L. Goodman, *J. Amer. Chem. Soc.*, 86 (1964) 1427.
12 J. D. Stevens and H. G. Fletcher, Jr., *J. Org. Chem.*, 33 (1968) 1799.