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Note

New cyclic isourea derivatives of D-glucofuranosylamine

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1,2-Cyclic isourea ethers [2-amino-4,5-dihydro(glyco)oxazoles] † have been found to be simple precursors of anhydronucleosides [1] but only a few compounds of this class have been synthesised [1,2]. Recently, natural products containing similar structures have been isolated [3], which has increased the interest in such derivatives.

Our studies of the transformations of cyclic carbamates [4] and thiocarbamates of aldosylamines led to the synthesis of 2-(*p*-chlorobenzylthio)-4,5-dihydro-(1,2-dideoxy-α-D-glucofuranoso)[1,2-*d*]oxazole (**2**) by treatment of the corresponding oxazolidine-2-thione [5] (**1**) with *p*-chlorobenzyl chloride (1.1 mol).

Since the *p*-chlorobenzylthio moiety of **2** is suitable for displacement with nucleophiles, **2** was allowed to stand in a large excess of morpholine at ambient temperature. After 3 days, white crystals of the pure 2-morpholino-isourea compound (**3**) were obtained in 75% yield. The reaction was accelerated in boiling acetonitrile with a smaller excess of morpholine (3 mol), when the transformation was complete after 24 h and **3** was isolated in 57% yield.

However, when **2** was treated in boiling morpholine at 130°C, an unexpected new compound (**4**) separated from the dark mixture in good yield.

Evidence for the structures of **2–4** was obtained from ^{1}H and ^{13}C NMR studies (Tables 1 and 2). All the ^{1}H spectra allowed first-order analyses of the signals. The assignments of the ^{13}C signals for **3** and **4** were supported by inverse detected 2D

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† Literature names for this type of compound use '2-amino(glyco)oxazoline' terminology, but names for partially hydrogenated heterocycles ending in 'oline' were abandoned by IUPAC in 1983 [*Pure Appl. Chem.*, 55 (1983) 409–416].

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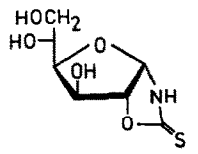

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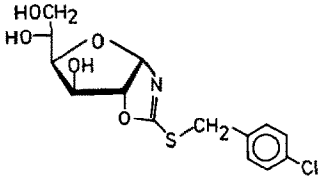

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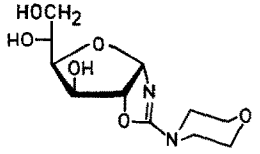

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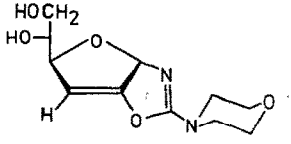

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Table 1
^{1}H NMR chemical shifts (δ ppm) and coupling constants (Hz, in parentheses) of **2–4**

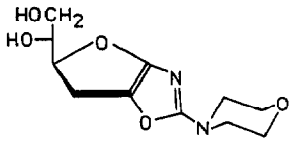
Compound	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6a}$)	($J_{5,6b}$)	H-6a	H-6b ($J_{6a,6b}$)	Others
2 [a]	6.01d	4.82d	4.15d	3.23dd	3.78ddd		3.78dd	3.61dd	7.44–7.38m (H-Ar)
	(5.4)	(0)	(2.4)	(8.5)	(6.1)	(2.8)			4.24d, 4.30d (CH_2S)
3 [b]	5.88d	4.93d	4.41d	3.61dd	3.93ddd		3.78dd	3.63dd	3.73 (CH_2O)
	(5.1)	(0)	(2.6)	(8.8)	(2.8)	(5.8)	(11.9)		3.44m (CH_2N)
4 [b]	6.73s		4.87d	3.85	3.71		3.78	3.62	3.81tm (CH_2O)
			(4.1)	(7.2)	(3.0)	(6.6)	(11.7)		3.49tm (CH_2N)

[a] Recorded at 250 MHz in $(CD_3)_2SO$, internal standard Me_4Si. [b] Recorded at 500 MHz in D_2O, calibrated to $Me_3Si(CH_2)_3SO_3Na$.

Table 2
^{13}C NMR chemical shifts (δ ppm) of **2–4**

Compound	C-1	C-2	C-3	C-4	C-5	C-6	N=C(O)X	Others
2 [a]	98.9	88.2	72.7	78.5	68.2	63.7	167.7	132.7, 132.1, 130.7, 128.4 (C-Ar), 34.4 (CH_2S)
3 [b]	100.1	89.6	75.5	79.6	70.7	66.0	166.8	68.2 (CH_2O), 47.5 (CH_2N)
4 [b]	123.5	147.7	67.3	74.9	73.6	65.0	164.1	68.2 (CH_2O), 47.8 (CH_2N)

[a] Recorded at 62.5 MHz in $(CD_3)_2SO$, internal standard Me_4Si. [b] Recorded at 125 MHz in D_2O, calibrated to $Me_3Si(CH_2)_3SO_3Na$.



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H/C-correlation measurements. NMR data for **2** and **3** are in good agreement with the expected structures.

As for the structure of **4**, both ^{1}H and ^{13}C NMR spectra indicate a double bond between C-2 and C-3 in the furanoid ring. H-1 and C-1 signals exhibit high chemical shifts, while H-3 and C-3 signals are strongly shielded because of the effect of the vinyl ether moiety. The unsaturated structure is corroborated also by the additional band at 1590 cm^{-1} in the IR spectrum of **4**.

The formation of the aromatic oxazole compound **5**, the tautomer of **4**, was excluded by the presence of only three different CH_2-groups in the ^{1}H and ^{13}C NMR spectra of the product. Tautomerisation of **4** into **5** could not be observed either in acidic or in basic solutions of **4** during some days *.

The formation of the double bond in the furanoid ring of **4** results from an unexpected elimination of water following the nucleophilic displacement of the *p*-chlorobenzylthio group. The same transformation was observed when pure **3** was boiled in morpholine, which provided evidence for the secondary transformation **3** → **4**. Structural conditions and the influence of the reagents on the elimination are being investigated.

1. Experimental

General methods.—TLC was performed on Silica Gel F_{254} (Merck) with 7:3 EtOAc–EtOH. Detection was effected by UV light at 254 nm or by heating and charring with H_2SO_4. Optical rotations were measured with a Zeiss Polamat A polarimeter at 25°C. IR spectra were recorded with a Nicolet 205 FT spectrometer. NMR measurements were performed with Bruker AC-250 and Varian ARX-500 spectrometers. Microanalyses were performed in the Microanalytical Laboratory of the Institute.

2-(p-Chlorobenzylthio)-4,5-dihydro-(1,2-dideoxy-α-D-glucofuranoso)[1,2-d]-oxazole (**2**).—To a suspension of **1** [5] (4.87 g, 22 mmol) in 9:1 MeCN–water (100 mL) were added *p*-chlorobenzyl chloride (3.90 g, 24.2 mmol) and $NaHCO_3$ (3.70 g, 44 mmol). The mixture was refluxed with stirring for 5 h, then concentrated. The inorganic salts were dissolved by treatment with cold water (200 mL) and, after

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filtration, the residue was also washed three times with $CHCl_3$ to give crude **2** (7.1 g, 93%). Crystallisation from MeCN gave pure **2** (5.86 g, 77%); mp 139°C; $[\alpha]_D$ +37° (*c* 1, MeOH). Anal. Calcd for $C_{14}H_{16}ClNO_5S$: C, 48.62; H, 4.66; Cl, 10.25; N, 4.05. Found: C, 48.50; H, 4.78; Cl, 10.26; N, 3.85.

2-Morpholino-4,5-dihydro-(1,2-dideoxy-α-D-glucofuranoso)[1,2-d]oxazole (**3**).—(*a*) A solution of **2** (1.0 g, 2.9 mmol) in morpholine (2.5 mL, 29 mmol) was allowed to stand at room temperature. TLC revealed no starting material in the mixture after 3 days; meanwhile, white crystals of the product separated. After filtration and washing with CH_2Cl_2, the filtrate was evaporated to give an additional crop of crude **3**. The collected products were recrystallised from EtOH to afford pure **3** (0.59 g, 75%); mp 166–167°C; $[\alpha]_D$ −21° (*c* 1, Me_2SO); ν_{max}^{KBr} 1631 cm^{-1} (C=N). Anal. Calcd for $C_{11}H_{18}N_2O_6$: C, 48.17; H, 6.62; N, 10.21. Found: C, 47.83; H, 6.74; N, 9.90.

(*b*) To a solution of **2** (1.0 g, 2.9 mmol) in MeCN (20 mL) was added morpholine (0.76 g, 8.7 mmol), and the mixture was refluxed. After 24 h, TLC indicated the reaction to be complete. On cooling, crude **3** separated, which was recrystallised from EtOH to give pure **3** (0.45 g, 57%); mp 164–166°C; identical with the authentic specimen from (*a*).

2-Morpholino-4,5-dihydro-(1,2,3-trideoxy-α-D-gluco-2-enofuranoso)[1,2-d]-oxazole (**4**).—Compound **2** (1.0 g, 2.9 mmol) was refluxed in morpholine (2.5 mL, 29 mmol) solution for 5 h, when TLC revealed no starting material in the mixture. After cooling, the mixture was treated with EtOH (30 mL) to precipitate white crystals (0.47 g). The filtrate was evaporated, and the residue was treated with $CHCl_3$ and then filtered off to give an additional crop of the product (0.44 g). After recrystallisation from EtOH, a crystalline hydrate of **4** was obtained (0.39 g, 50%); mp 156–158°C; $[\alpha]_D$ −1.7° (*c* 1, Me_2SO); ν_{max}^{KBr} 1630 (C=N) and 1590 cm^{-1} (C=C). Anal. Calcd for $C_{11}H_{16}N_2O_5 \cdot H_2O$: C, 48.17; H, 6.62; N, 10.21. Found: C, 47.98; H, 6.74; N, 10.20.

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