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Note

Reaction of 1-deoxy-1-methylamino-D-*lyxo*-hexulose with phenyl isothiocyanate*

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The reaction of 1-aryl(alkyl)amino-1-deoxy-D-*arabino*-hexuloses with aryl(alkyl)isothiocyanates yields[1–3] 1-aryl(alkyl)-3-aryl(alkyl)-1,3-dihydro-4-(D-*arabino*-tetritol-1-yl)-2*H*-imidazole-2-thiones (**1**). The spiro structure **2** was proposed[4] for the product of reaction of 1-amino-1-deoxy-D-*arabino*-hexulose with phenyl isothiocyanate, although this compound was not isolated.

We now report the reaction of 1-deoxy-1-methylamino-D-*lyxo*-hexulose with phenyl isothiocyanate, which yields a mixture of **3**, **5**, and **7**, which were isolated by chromatography. Compound **3** was isolated as a syrup and characterised by mass spectrometry, by u.v. and i.r. data, and by conversion into the tetra-acetate **4**; **3** had λ_{max} 261 nm, characteristic of 1,3-dihydro-2*H*-imidazole-2-thiones[5,6]. The other products have spiro structures and are formulated as (2*R*,3*R*,4*S*,5*S*)-3,4-dihydroxy-2-hydroxymethyl-8-methyl-6-phenyl-7-thioxo-1-oxa-6,8-diazaspiro[4.4]nonane (**5**) and (2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-2-hydroxymethyl-8-methyl-6-phenyl-7-thioxo-1-oxa-6,8-diazaspiro[4.4]nonane (**7**). The structures of these compounds are supported by elemental analyses and spectral data. Both **5** and **7** have λ_{max} 245 nm, characteristic of imidazolidine-2-thiones[6,7].

The ^{1}H-n.m.r. spectrum of **5** confirmed the presence of three hydroxyl groups (2 d for CHOH and t for CH_2OH). The mass spectra of **5** and **7** contained peaks at *m/z* 310 ($M^{+\cdot}$) and 279 (M − CH_2OH). The ion B + 30 (B = heterocycle), characteristic of polyhydroxyalkylheterocycles[3,8], was not present, but significant peaks at

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*Thiolglucimidazoles, Part XVI. For Part XV, see ref. 3.

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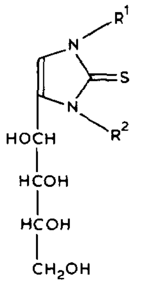

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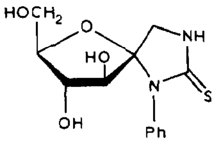

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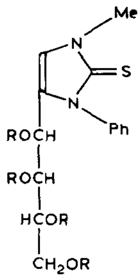

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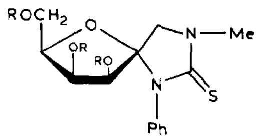
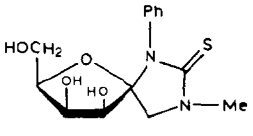
4 R = Ac



5 R = H
6 R = Ac



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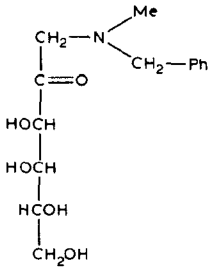
m/z 207 and 206 were assigned to ions having the probable structures **9** and **10**, thereby proving the presence of an imidazolidine ring joined to an oxygen atom. The atomic composition of these ions is confirmed by the high-resolution mass spectrum of the triacetate **6**. The structure and stereochemistry of **5** have been demonstrated by X-ray diffraction[9].



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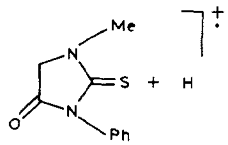

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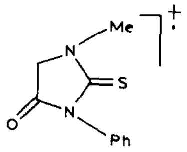

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Conventional treatment of **3** and **5** with acetic anhydride–pyridine gave the tetra- (**4**) and tri-acetate (**6**), respectively; see Tables I and II for the ^{1}H-n.m.r. data. The $J_{H,H}$ values were determined in the presence of Eu(fod)$_3$; J values generally are not greatly influenced by the addition of a shift reagent[10,11]. The

TABLE I

CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (Hz) FOR **4** IN $CDCl_3$

Chain						*Heterocycle*		
H-1'	*H-2'*	*H-3'*	*H-4'*	*H-4''*	*OAc*	*H-5*	*Me*	*Ph*
5.58d $J_{1',2'}$ 7.8	5.46dd[b] $J_{2',3'}$ 3.0[a]	5.28m[b]	4.13dd $J_{3',4'}$ 4.8 $J_{4',4''}$ 12.0	3.88dd $J_{3',4''}$ 6 3	2.08s (3 H) 2.00s (3 H) 1.91s (6 H)	6.98s	3.66s	7.65–7.25m

[a]Obtained by extrapolation to zero concentration of Eu(fod)$_3$. [b]Obtained in the presence of Eu(fod)$_3$.

TABLE II

CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (Hz) FOR **6** IN $CDCl_3$

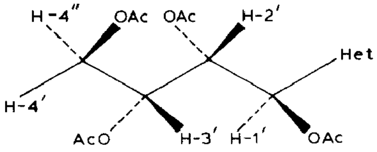
Carbohydrate moiety						*Imidazolidine*			
H-2	*H-3*	*H-4*	$^{H}_{H}C\text{-}C_2$	$^{H}_{H}C\text{-}C_2$	*OAc*	*H-9*	*H-9'*	*N-Me*	*Ph*
4.13m[a] J_{2,CH_2} 6.5[b]	5.29dd[a] $J_{2,3}$ 3.2[b]	5.26d[a] $J_{3,4}$ 4.0[b]	4.30dd J_{2,CH_2} 12.0[b]	4.30dd[a]	2.10s (3 H) 2.08s (3 H) 2.02s (3 H)	4.13d[a]	3.72d $J_{9,9'}$ 11.9	3.28s	7.6–7.2m (5 H)

[a]Obtained by extrapolation to zero concentration of Eu(fod)$_3$ [b]Obtained in the presence of Eu(fod)$_3$.

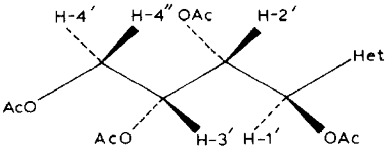
values of the chemical shifts were estimated by extrapolation of the approximately linearly dependent, paramagnetically altered, field positions to zero concentration of added lanthanide.

The mass spectrum of the triacetate **6** contained peaks at m/z 436.1326 (M^+), 207.0660 ($C_{10}H_{11}N_2OS$), and 206.0518 ($C_{10}H_{10}N_2OS$) as in those of **5** and **7**. The loss of the acetoxymethyl group gives the ion m/z 363.0995.

The $^3J_{H,H}$ values for **4** (Table I) established that, in solution in chloroform, the molecules exist essentially in $_3G^-$ (**11**) and P (**12**) conformations[12]. The intermediate values (4.8 and 6.3 Hz) of $J_{3',4'}$ and $J_{3',4''}$ accord with the chain-end flexibility encountered in other examples of acyclic sugar derivatives[3,12,13].



11 ($_3G^-$)



12 (P)

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were measured at 5461 Å, using a 10-cm cell. I.r. spectra were recorded for KBr discs. ^{1}H-N.m.r. spectra (35.5°) were recorded at 90 MHz. The coupling constants were measured directly from spectra recorded at 300-MHz sweep-width. Assignments were confirmed by double resonance experiments, and H/D exchange. Overlapping signals were gradually shifted and separated from one another by incremental additions of $Eu(fod)_3$. E.i.-mass spectra were obtained at 70 eV, with an ion-source temperature of 200°. For **3**, **4**, and **6**, the exact mass measurements were determined with a resolution of 10,000 (10% valley definition). T.l.c. was performed on silica gel HF_{254} (Merck) with chloroform–methanol (7:1). Detection was effected with u.v. light, iodine vapour, or by charring with sulphuric acid. Column chromatography was conducted on silica gel 60 (Merck, 70–230 mesh).

*1-*N*-Benzylmethylamino-1-deoxy-*D-lyxo*-hexulose*[14] (**8**). — A mixture of D-galactose (18 g, 100 mmol), *N*-benzylmethylamine (15.4 mL, 120 mmol), and ethanol (50 mL) was heated under reflux for 1 h. Ammonium chloride (1 g, 19.8 mmol) was added and boiling under reflux was continued for 3 h. The mixture was filtered and cooled to give **8** (11.33 g, 40%). Recrystallisation from ethanol gave material having m.p. 146–148°, $[\alpha]_D^{22}$ +27° (*c* 1, pyridine).

Anal. Calc. for $C_{14}H_{21}NO_5$: C, 59.34; H, 7.47; N, 4.94. Found: C, 59.07; H, 7.60; N, 4.96.

*Reaction of 1-deoxy-1-methylamino-*D-lyxo*-hexulose with phenyl isothiocyanate.* — A solution of **8** (2.5 g, 8.8 mmol) in aqueous 96% ethanol (100 mL) and acetic acid (16 mL) was hydrogenated at 3 atm. and room temperature in the presence of 10% Pd/C (0.5 g) for 7 h, then filtered, and concentrated to dryness. Ethanol was repeteadly evaporated from the residue to remove acetic acid. The syrupy residue, 1-deoxy-1-methylamino-D-*lyxo*-hexulose acetate (1.1 g, 4.3 mmol), phenyl isothiocyanate (0.57 g, 4.0 mmol), and ethanol (50 mL) were heated at 70° for 25 h. T.l.c. revealed **3**, **5**, and **7**. Compound **3** (R_F 0.25) was isolated by column chromatography, and **5** (R_F 0.50) and **7** (R_F 0.44) were isolated by preparative t.l.c. (3 developments, extraction with ether, and crystallisation from methanol).

1,3-Dihydro-1-methyl-3-phenyl-4-(D-*lyxo*-tetritol-1-yl)-2*H*-imidazole-2-thione (**3**; 0.145 g, 11%) was a hygroscopic syrup, $[\alpha]_{546}^{19}$ +6° (*c* 1, methanol); λ_{max}^{MeOH} 261 nm (ε_{mM} 8.7); ν_{max} 3380 (OH), 3080 (CH aromatic), 2940, 2900 (C-H), 1620 (C=C), 1605, 1560 and 1505 cm^{-1} (phenyl ring). Mass spectrum: *m/z* 310.0986 (25%, calc. for $M^{+\cdot}$ 310.0986), 292.0877 (30), 276. 1112 (6), 232.0674 (12), 219.0573 (100, $C_{11}H_{11}N_2OS$), 218.0514 (41), 217.0443 (31), 203.0651 (27), 190.0536 (7), 189.0493 (14).

(2*R*,3*R*,4*S*,5*S*)-3,4-Dihydroxy-2-hydroxymethyl-8-methyl-6-phenyl-7-thioxo-1-oxa-6,8-diazaspiro[4.4]nonane (**5**; 0.1 g, 7%) had m.p. 162–164°, $[\alpha]_{546}^{22}$ +20° (*c* 1, methanol); λ_{max}^{MeOH} 245 nm (ε_{mM} 18.0); ν_{max} 3460, 3340 and 3200 (OH), 2965 and 2910 (C-H), 1600, 1520 and 1500 cm^{-1} (phenyl ring). ^{1}H-N.m.r. data (Me_2SO-d_6):

δ 7.20–7.60 (m, 5 H, Ph), 5.65 (d, 1 H, OH, $J_{H,OH}$ 6.5 Hz), 5.01 (d, 1 H, OH, $J_{H,OH}$ 4.1 Hz), 4.55 (t, 1 H, $J_{H,OH}$ 5.3 Hz, CH_2OH), and 3.14 (s, 3 H, N-Me). Mass spectrum: *m/z* 310 (49%, M^{+}), 309 (1), 292 (87), 276 (5), 275 (2), 271 (2), 207 (80), 206 (28), 77 (100).

Anal. Calc. for $C_{14}H_{18}N_2O_4S$: C, 54.17; H, 5.84; N, 9.02. Found: C, 53.83; H, 5.87; N, 9.20.

(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-2-hydroxymethyl-8-methyl-6-phenyl-7-thioxo-1-oxa-6,8-diazaspiro[4.4]nonane (**7**; 0.015 g, 1%) had m.p. 155–157°, $[\alpha]^{22}_{546}$ −37° (*c* 0.75, methanol); λ^{MeOH}_{max} 245 nm (ε_{mM} 14.0); ν_{max} 3550, 3310 and 3180 (OH), 2955, 2935, and 2860 (C-H), 1600, 1520 and 1505 cm^{-1} (phenyl ring). Mass spectrum: *m/z* 310 (100%, M^{+}), 309 (3), 292 (33), 291 (4), 276 (4), 271 (1), 207 (95), 206 (71).

Anal. Found: C, 54.14; H, 5.97; N, 9.01.

*1,3-Dihydro-1-methyl-3-phenyl-4-(1,2,3,4-tetra-*O*-acetyl-*D-lyxo-*tetritol-1-yl)-2*H-*imidazole-2-thione* (**4**). — Conventional treatment of **3** (0.35 g, 1.13 mmol) with pyridine (1.5 mL) and acetic anhydride (1.5 mL), with column chromatography (ether–hexane, 9:1) of the product, gave **4** (0.124 g, 22%) as an amorphous and hygroscopic powder, $[\alpha]^{22}_{546}$ +17° (*c* 1, chloroform); λ^{MeOH}_{max} 267 (ε_{mM} 10.4); ν_{max} 1750 (C=O) and 1240 cm^{-1} (C-O-C). The ^{1}H-n.m.r. data are given in Table I. Mass spectrum: *m/z* 478.1423 (6%; calc. for M^{+} 478.1409), 360.1151 (1), 316.0902 (3), 274.0774 (1), 258.0850 (3), 257.0739 (3), 245.0770 (3), 242.0878 (16), 219.0598 (32), 43.0190 (100).

*(2*R*,3*R*,4*S*,5*S*)-3,4-Diacetoxy-2-acetoxymethyl-8-methyl-6-phenyl-7-thioxo-1-oxa-6,8-diazaspiro*[*4.4*]*nonane* (**6**). — Conventional treatment of **5** (0.1 g, 0.32 mmol) with pyridine (0.5 mL) and acetic anhydride (0.5 mL), with recrystallisation of the product (0.095 g, 73%) from ethanol, gave **6**, m.p. 142–143°, $[\alpha]^{22}_{546}$ +31° (*c* 1, chloroform); λ^{MeOH}_{max} 249 nm (ε_{mM} 16.6); ν_{max} 1760 and 1740 (C=O) and 1240 cm^{-1} (C-O-C). The ^{1}H-n.m.r. data are given in Table II. Mass spectrum: *m/z* 436.1326 (14%, M^{+}, $C_{20}H_{24}N_2O_7S$), 435.1267 (1), 363.0995 (1), 261.0707 (2), 219.0593 (2), 207.0660 (38, $C_{10}H_{11}N_2OS$), 206.0518 (8, $C_{10}H_{10}N_2OS$), 43.0188 (100).

Anal. Calc. for $C_{20}H_{24}N_2O_7S$: C, 55.03; H, 5.54; N, 6.41; S, 7.34. Found: C, 55.06; H, 5.63; N, 6.19; S, 7.70.

ACKNOWLEDGMENTS

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