Note

Synthesis of 3-aryl(alkyl)-4-(D-*arabino*-tetrahydroxybutyl)imidazoline-2-thiones*

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The synthesis of 1-aryl(alkyl)-4-(D-*arabino*-tetrahydroxybutyl)imidazoline-2-thiones (**1**, R = aryl or alkyl) by the reaction of 1-aryl(alkyl)amino-1-deoxy-D-fructoses with ammonium thiocyanate, and also by isomerization of 1-aryl(alkyl)-4,5-(1,2-D-glucofurano)imidazolidine-2-thiones (**2**, R = aryl or alkyl) by heating with acetic acid has been previously reported[1-4]. The 1-aryl(alkyl)-4,5-(1,2-D-glucofurano)-imidazolidine-2-thiones are obtained by condensation of 2-amino-2-deoxy-D-glucose with aryl(alkyl) isothiocyanates. In earlier publications, the structure 1-aryl(alkyl)-4,5-(1,2-D-glucopyrano)imidazolidine-2-thione (**3**, R = aryl or alkyl) was proposed[2,3,5-8] for these condensation products. Later, a furanoid structure for the sugar moiety of these compounds (**2**, R = aryl) was established by n.m.r. spectroscopy, periodate degradation[9], and by oxidative estimation of a terminal glycol group with periodate and lead tetra-acetate[10]. The structure 1-aryl-5-hydroxy-4-(D-*arabino*-tetrahydroxybutyl)imidazolidine-2-thione (**4**, R = aryl) has been also proposed[11] for the first isolable products of reaction of aryl isothiocyanates with 2-amino-2-deoxy-D-glucose, which were originally formulated[8] as 2-arylthioureido-2-deoxy-D-glucose. The conversion of **4**, with loss of a molecule of water, into either **2** or an imidazoline-2-thione **1** has been explained[11] on the basis of the pseudo-basic properties of **4**. The spiro structure **5** has been proposed[11] for the reaction product of 1-amino-1-deoxy-D-fructose with phenyl isothiocyanate. Although this compound was not isolated, the structure was formulated by consideration of its electrophoretic behaviour.

We now report the synthesis of 3-aryl(alkyl)-4-(D-*arabino*-tetrahydroxybutyl)-imidazoline-2-thiones (**6**, **7**, and **8**) by treatment of 1-amino-1-deoxy-D-fructose with the appropriate isothiocyanates. Compound **8** has been also obtained by treatment of 2-deoxy-2-methylamino-D-glucose hydrochloride with potassium thiocyanate. Treatment of **6** and **8** with benzyl chloride and sodium hydrogen carbonate in aqueous ethanol gave the benzylthioimidazoles **9** and **10**. The u.v. spectra of these compounds are in accordance with the structures proposed. The imidazoline-2-thiones have[12] a characteristic absorption at *ca.* 260 nm, and the *S*-alkylthioimidazoles absorb[12] at a

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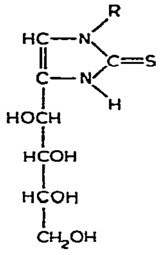
*Part 9 in the series "Thiolglucimidazoles". For Part 8, see Ref. 4.



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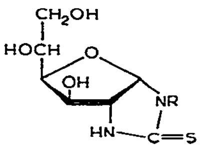

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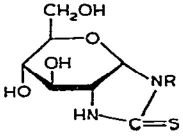

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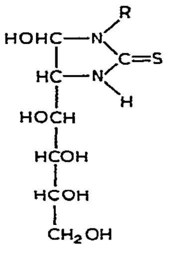

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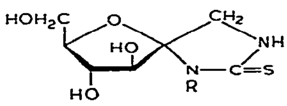

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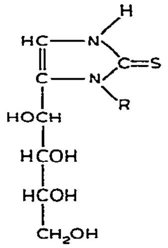
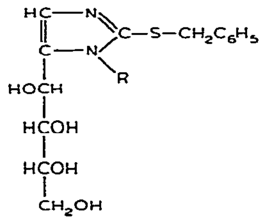
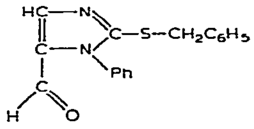


6 R = Ph
7 R = p-BrC$_6$H$_4$
8 R = Me



9 R = Ph
10 R = Me



11

slightly lower wavelength. Compounds **6** and **8** have characteristic absorption maxima at 265 nm and 258 nm, respectively, and the benzylthio derivatives **9** and **10** at 261 and 256 nm, respectively. The tetrahydroxybutyl chain of the benzylthioimidazoles **9** and **10** was cleaved by periodate to give the imidazolecarboxaldehyde **11**.

EXPERIMENTAL

General. — Optical rotations at 5461 Å were determined with a Bendix–NPL Automatic Polarimeter 143C. U.v. spectra were obtained on Beckman DU and Unicam SP-800 spectrophotometers. Paper chromatography was carried out on Whatman No. 1 paper by the horizontal and descending techniques, with 1-butanol–acetic acid–water (1:1:5), 1-butanol–pyridine–water (1:1:1), or 1-butanol saturated with water as eluting solvents. Chromatograms were developed with silver nitrate–sodium hydroxide[13], sodium metaperiodate–potassium permanganate[14], and a diazotisation reagent[15]. T.l.c. was performed on silica gel (G, Merck), with benzene–methanol (9:1), ether–toluene (1:1), or ether–light petroleum (1:1) as the solvents and 50% sulphuric acid as the spray reagent.

Periodate oxidation. — The tetrahydroxybutyl chain of **9** and **10** was estimated by the periodate consumption by the Fleury–Lange method[16], and by titration with 10mM sodium hydroxide of the formic acid produced during the periodate oxidation[17].

3-Phenyl-4-(D-arabino*-tetrahydroxybutyl*)*imidazoline-2-thione* (**6**). — (*a*) A mixture of 1-amino-1-deoxy-D-fructose acetate[18] (1 g, 4.1 mmoles) and phenyl isothiocyanate (0.5 ml, 4.2 mmoles) in ethanol (2.5 ml) was refluxed for 2 h. The product obtained after cooling was crystallized from 90% ethanol. Yield, 52%; m.p. 204–205°; $[\alpha]_{5461}^{29}$ −13.3° (*c* 1.26, pyridine); λ_{max} 265 nm (ε 8150).

Anal. Calc. for $C_{13}H_{16}N_2O_4S$: C, 52.68; H, 5.44; N, 9.45; S, 10.82. Found: C, 52.95; H, 5.85; N, 9.26; S, 10.86.

(*b*) To a solution of 1-amino-1-deoxy-D-fructose acetate (1.2 g, 4.1 mmoles) in water (3.6 ml), containing sodium hydrogen carbonate (0.36 g, 4.1 mmoles), phenyl isothiocyanate (0.7 g, 5.2 mmoles) was added, and the mixture made homogeneous with acetone. The mixture was kept at 50–60° for 10 h and at room temperature for 4 days. The solution was evaporated, and the residue was dissolved in 20% acetic acid (10 ml), heated at 100° for 0.5 h, and then concentrated. The product obtained was crystallized from 90% aqueous ethanol. Yield, 12%; m.p. 201–202°.

*3-*p*-Bromophenyl-4-(*D-*arabino*-tetrahydroxybutyl)imidazoline-2-thione* (**7**). — Treatment of 1-amino-1-deoxy-D-fructose acetate with *p*-bromophenyl isothiocyanate by the procedure used for **6**, part (*b*), gave **7**. Yield, 15%; m.p. 187–188°; $[\alpha]_{5461}^{26}$ −18.3° (*c* 1.02, pyridine).

Anal. Calc. for $C_{13}H_{15}BrN_2O_4S$: C, 41.61; H, 4.03. Found: C, 41.87; H, 3.98.

*3-Methyl-4-(*D-*arabino*-tetrahydroxybutyl)imidazoline-2-thione* (**8**). — (*a*) To a solution of 1-amino-1-deoxy-D-fructose acetate (0.5 g, 2 mmoles) in water (1.8 ml), sodium hydrogen carbonate (0.17 g, 2 mmoles) and methyl isothiocyanate (0.15 g, 2 mmoles) were added, and the mixture was made homogeneous with acetone. The solution was kept at 50–60° for 10 h and at room temperature for 5 days and then evaporated, and the residue was extracted with ethanol. The compound was isolated by chromatography on a column of Whatman "Standard Grade" cellulose powder, using 1-butanol saturated with water as eluting solvent. The fractions (15 ml) were monitored by descending paper chromatography with the same solvent. The fractions containing the compound having R_F 0.19 were combined and evaporated. The residue was crystallized from ethanol. Yield, 25%; m.p. 164–165°; $[\alpha]_{5461}^{22}$ +37.6° (*c* 1.3, pyridine); λ_{max} 258 nm (ε 15,200).

Anal. Calc. for $C_8H_{14}N_2O_4S$: C, 41.01; H, 6.02; N, 11.96; S, 13.68. Found: C, 40.90; H, 6.02; N, 12.01; S, 12.75.

(*b*) A mixture of 1-amino-1-deoxy-D-fructose acetate (1 g, 4.1 mmoles) and methyl isothiocyanate (0.3 g, 4.1 mmoles) in ethanol (2 ml) were heated at 90–100° for 2 h. Some unreacted amino-sugar acetate separated on cooling and was filtered off. Compound **8** was isolated from the filtrate by chromatography on a cellulose column by the procedure described in (*a*). Yield, 42%; m.p. and mixed m.p. with **8** (*a*) 161–163°.

(*c*) A solution of 2-deoxy-2-methylamino-D-glucose hydrochloride[19] (0.3 g, 1.5 mmoles) in M hydrochloric acid (12 ml) was heated with potassium thiocyanate (0.17 g, 1.8 mmoles) at 50° for 0.5 h. The solution was evaporated and the residue was extracted with ethanol. After removal of insoluble material, the solvent was evaporated and the residue crystallized from water. Yield, 23%; m.p. 160–162°, and mixed m.p. with **8** (*a*) 162–163°.

*2-Benzylthio-3-phenyl-4-(*D-*arabino*-tetrahydroxybutyl)imidazole* (**9**). — To a suspension of **6** (1.7 g, 5.7 mmoles) in 90% aqueous ethanol (17 ml) benzyl chloride (0.7 ml, 5.7 mmoles) and sodium hydrogen carbonate (0.48 g, 5.7 mmoles) were added. The mixture was boiled under reflux for 1 h, and then cooled. The product obtained was crystallized from ethanol–water (4:1). Yield, 98%; m.p. 226–227°; $[\alpha]_{5461}^{26}$ $-6.7°$ (c 0.068, pyridine); λ_{max} 261 nm (ε 12,300).

Anal. Calc. for $C_{20}H_{22}N_2O_4S$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.15; H, 5.83; N, 7.02.

Compound **9** consumed 3.04 mol. of periodate.

2-Benzylthio-3-methyl-4-(D-arabino*-tetrahydroxybutyl)imidazole* (**10**). — This compound was obtained by the same procedure used for **9**. Yield, 67%; m.p. 182–183°; $[\alpha]_{5461}^{26}$ $+0.5°$ (c 1.95, pyridine); λ_{max} 256 nm (ε 10,600).

Anal. Calc. for $C_{15}H_{20}N_2O_4S$: C, 55.54; H, 6.21; N, 8.64. Found: C, 55.76; H, 6.28; N, 8.53.

On oxidation with sodium metaperiodate, compound **10** gave 2.01 mol. of formic acid.

2-Benzylthio-3-phenyl-4-imidazolecarboxaldehyde (**11**). — To a solution of **9** (1 g, 2.6 mmoles) in ethanol–water (1:1) (300 ml) was added sodium metaperiodate (1.7 g, 7.9 mmoles) in water (12 ml), and the reaction mixture was kept at 40–50° for 1 h. The solution was extracted with chloroform (4 × 50 ml), and the combined extracts were washed with water and then dried (Na_2SO_4). The solvent was evaporated and the residue crystallized from ethanol. Yield, 83%; m.p. 126–128°; λ_{max} 301 nm (ε 30,000); ν_{max} (chloroform) 1674 cm^{-1} (C=O).

Anal. Calc. for $C_{17}H_{19}N_2OS$: C, 69.35; H, 4.79; N, 9.52. Found: C, 69.03; H, 4.96; N, 9.35.

2-Benzylthio-3-phenyl-4-imidazolecarboxaldehyde 2,5-dichlorophenylhydrazone. — To a solution of **11** (0.1 g, 0.35 mmole) in 80% aqueous ethanol (3 ml) was added 2,5-dichlorophenylhydrazine (60 mg, 0.35 mmole) in 80% aqueous ethanol (1 ml), and the reaction mixture was kept at room temperature for 24 h. The product obtained was crystallized from ethanol. Yield, 88%; m.p. 182–183°.

Anal. Calc. for $C_{23}H_{19}Cl_2N_4S$: C, 60.79; H, 4.22; N, 12.33. Found: C, 60.44; H, 4.12; N, 12.13.

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