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Note

Preparation of some 1,2-*cis*-*p*-nitrophenyl 1-thio-D-aldopyranosides*

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The Koenigs–Knorr reaction[1] has been the reaction most widely used in the synthesis of glycosides. However, the glycosides obtained from this reaction are, usually, almost exclusively of the 1,2-*trans* configuration, in accordance with the *trans* rule[2]. For the synthesis of 1,2-*cis*-glycosides, especially prepared glycosylating agents must be used[3]. The success of these types of glycosylating agents is still rather limited, and the stereoselective synthesis of 1,2-*cis*-1-thioglycosides has not yet been reported.

1-Thioaldosides having the 1,2-*cis* configuration can be obtained, together with 1,2-*trans*-1-thioaldosides and dithioacetals, from the reaction of an aldose with a thiol in the presence of a strong acid catalyst[4–6]. Mixtures of 1,2-*cis*- and 1,2-*trans*-1-thioaldosides can also be obtained from Helferich reactions, involving the reaction of a thiol with a fully acetylated sugar. Either of these reactions can be utilized for the synthesis of 1,2-*cis*-1-thioaldosides provided that suitable methods of purification are available.

Recently, we observed[7] that anomeric pairs of aryl aldosides and aryl 1-thioaldosides could be effectively separated on a column of a cation-exchange resin, using only water as the eluant. We have now successfully used this method to obtain 1,2-*cis*-1-thioaldosides from reaction mixtures in which both a 1,2-*trans*- and a 1,2-*cis*-1-thioglycoside were present, thus demonstrating the utility of our previously reported separation scheme for preparative purposes. Although the overall yields of the 1,2-*cis*-1-thioaldosides were not very high, the efficient separation of the mixtures described has enabled us to isolate the 1,2-*cis*-1-thioaldosides with ease.

Despite its rather low yields, the direct condensation method is attractive because of its simplicity. The direct condensation gave somewhat more of the 1,2-*cis* than of the 1,2-*trans* derivatives. On the other hand, the Helferich reactions conducted as described here gave a preponderance of the 1,2-*trans* derivatives.

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EXPERIMENTAL

Materials. — Monosaccharides were obtained from Sigma Chemical Co. (St. Louis, Mo.). *p*-Nitrobenzenethiol (Aldrich Chemical Co., Milwaukee, Wis.) was recrystallized from ethanol before use. Penta-*O*-acetyl-β-D-galactopyranose (Koch–Light Lab., Colnbrook, Buckinghamshire, England) and penta-*O*-acetyl-β-D-glucopyranose (Pfanstiehl Lab., Waukegan, Illinois) were used without purification. Dowex 50-W X-4 (200–400 mesh) was obtained from Bio-Rad (Richmond, Calif.), and converted into the sodium form in the usual way.

General Methods. — Melting points (uncorrected) were determined with a Fisher–Johns apparatus. Proton magnetic resonance (p.m.r.) spectra were recorded with a JEOL NMH-100 spectrometer. Optical rotation measurements were made with a Cary 60 spectropolarimeter. Neutral sugars were analyzed by a modified phenol–sulfuric acid method[8]. Formaldehyde was determined by the chromotropic acid method[9].

Reaction of D-*galactose with* p-*nitrobenzenethiol.* — To a solution of D-galactose (2.52 g, 14 mmoles) in concentrated hydrochloric acid (30 ml) was added *p*-nitrobenzenethiol (1.09 g, 7 mmoles), the vessel was flushed with nitrogen, and the mixture was stirred overnight at room temperature, and then carefully made neutral with 10M sodium hydroxide, avoiding an excessive rise in temperature. The suspension was warmed to 45°, and filtered, and the filtrate (60 ml) was applied directly to a column (5 × 76 cm) of Dowex 50-W X-4 (Na^+) (200–400 mesh, maintained at 45°), which was then eluted with water at a rate of 6–8 ml.min^{-1}. The effluent fractions were analyzed by the phenol–sulfuric acid method[8]. A typical elution profile is shown in Fig. 1.

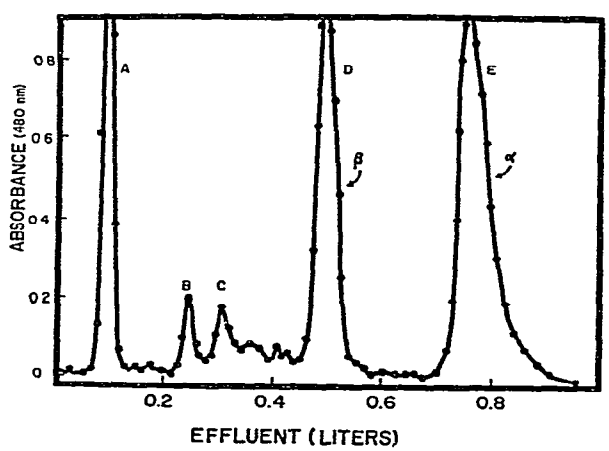

Fig. 1. Fractionation, on Dowex-50 X-4 (Na^+) ion-exchange resin, of the reaction products from the direct condensation of D-galactose with *p*-nitrobenzenethiol. (Peaks: A, unreacted D-galactose; B and C, unidentified products; D, *p*-nitrophenyl 1-thio-β-D-galactopyranoside; E, *p*-nitrophenyl 1-thio-α-D-galactopyranoside. The column effluent was analyzed by the phenol–sulfuric acid method[8].)

The unreacted D-galactose appeared at the void volume (peak A). The fractions of peak D, upon evaporation, gave 151 mg (yield 7.1%) of crystalline *p*-nitrophenyl 1-thio-β-D-galactopyranoside, m.p. 170–171°, $[\alpha]_D^{25}$ −123.3° (water), indistinguishable from the product obtained by the reaction of *p*-nitrobenzenethiol and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide in the presence of sodium hydroxide[7,10]. P.m.r. spectroscopy (Me_2SO-d_6) showed the anomeric proton signal, δ 4.98, doublet, $J_{1,2}$ 9.0 Hz. Evaporation of the fractions constituting peak E gave crystalline *p*-nitrophenyl 1-thio-α-D-galactopyranoside, 154 mg (yield 7.3%), m.p. 180–181°, $[\alpha]_D^{25}$ +295° (water). P.m.r. spectroscopy (Me_2SO-d_6) showed the anomeric proton signal (doublet) at δ 5.96, $J_{1,2}$ 5.0 Hz.

When the crystals isolated from peaks D and E were treated[9] with sodium periodate (100-fold excess) for 5 min at room temperature, no formaldehyde was produced. Under the same conditions, methyl α-D-galactofuranoside and the diethyl dithioacetal of D-mannose[5] produced the expected amount of formaldehyde.

Other p-*nitrophenyl 1-thio-α-D-aldopyranosides.* — Essentially the same reaction conditions were used for the condensation of *p*-nitrobenzenethiol with D-glucose and with D-mannose. The neutralized reaction mixtures were separated on a column (5 × 53 cm) of Dowex 50-W X-4 (Na^+) (200–400 mesh) maintained at 52°. The results were essentially the same as those shown in Fig. 1. The yields and physical constants of the 1-thio-α-D-aldopyranosides prepared are recorded in Tables I and II.

Preparation of p-*nitrophenyl 1-thio-α,β-D-aldopyranosides by the Helferich reaction.* — A mixture of penta-*O*-acetyl-β-D-glucopyranose (2.5 g, 6.4 mmoles), *p*-nitrobenzenethiol (2.86 g, 18.4 mmoles), and freshly fused zinc chloride (100 mg) was heated for 75 min at 145 ±5° under a constant, gentle stream of nitrogen, with efficient stirring. The dark melt was cooled to 50–60°, and diluted with benzene (100 ml), and the solution was washed with four 100-ml portions of M sodium hydroxide and evaporated to a solid mass which was freed of residual water by repeated addition and evaporation of absolute ethanol. The mixture of crystalline

TABLE I

YIELDS OF 1,2-*cis*- AND 1,2-*trans*-*p*-NITROPHENYL 1-THIO-D-ALDOPYRANOSIDES

Reaction conditions		*Yields of glycosides* (%)	
Sugar	*Sugar:thiol (molar ratios)*	*1,2*-trans	*1,2*-cis
Direct condensation			
D-Galactose	2:1	7.1	7.3
D-Glucose	2:1	<1.0	3.6
D-Mannose	2:1	2.2	5.0
Helferich reaction			
D-Galactose	1:3	54.2	5.4
D-Glucose	1:3	58.1	3.1
D-Mannose	1:3	26.7	7.9

TABLE II

PHYSICAL CONSTANTS OF *p*-NITROPHENYL 1-THIO-α- AND β-D-ALDOPYRANOSIDES

p-Nitrophenyl 1-thiopyranosides	*M.p.(degrees)*	$[\alpha]_D$ *(degrees)*[a]	*P.m.r. data (anomeric proton)*[b]	
			Chemical shift (p.p.m.)	*Coupling constant (Hz)*
α-D-Galacto-	180–181	+295.0 (*c* 0.1)	5.96	5
β-D-Galacto-	170–171 (lit.[11] 165–170)	−123.3 (*c* 0.3)	4.98	9
α-D-Gluco-	149–150	+216.5 (*c* 0.2)	5.90	5
β-D-Gluco-	162–163	−111.0 (*c* 0.4)	4.99	9
α-D-Manno-	182–183 (lit.[11] 186–188)	+258.0 (*c* 0.2)	5.73	~1
β-D-Manno-	172–174	−180.0 (*c* 0.2)	5.31	~1

[a]In water. [b]Signals from aryl protons: δ 7.7–7.8 (d, *J* 8 Hz) and 8.2–8.3 (d, *J* 8 Hz).

products was deacetylated with 15mM sodium methoxide in methanol (100 ml), and the solution was acidified and evaporated to a syrup; this was dissolved in water, and the solution applied to a Dowex column as already described. The yields of α- and β-D-glucopyranosides thus isolated are given in Table I.

Similar reactions were performed with penta-*O*-acetyl-β-D-galactopyranose and penta-*O*-acetyl-β-D-mannopyranose, and these also gave mixtures of α- and β-glycopyranosides. The physical constants of the 1-thio-α,β-D-aldopyranosides were identical to those of the products obtained from the direct condensation reaction (see Table II).

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