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APPROACHES TO THE SYNTHESIS OF SUGAR THIOLACTONES

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ABSTRACT

Evidence is presented that aldonolactones undergo "alkyl–oxygen" fission when attacked by thionucleophiles. The reaction of 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone with potassium thioacetate gives 2,3-*O*-isopropylidene-4-thio-D-erythrono-1,4-lactone, the first example of a thiolactone of an aldonic acid. Deacetylation of 5-*S*-acetyl-2,3-*O*-isopropylidene-5-thio-D-ribono-1,4-lactone is accompanied by partial migration of sulphur from C-5 to C-4; a mechanism involving an intermediate 5,6-episulphide is suggested.

INTRODUCTION

The only carbohydrate thiolactone hitherto mentioned is 1-thio-D-glucopyranurono-6,1-lactone (**2**), obtained[1] as a crude, amorphous powder by ammonolysis of the dithiocarbonate **1**; no thioaldonolactone has been reported. γ-Butyrolactone undergoes attack by thionucleophiles at the "alkyl" position[2], and can therefore be readily converted[3] into 4-mercaptobutyric acid, which, when distilled, gives γ-thiobutyrolactone**. In principle, a similar transformation could occur with an aldonolactone, and this possibility has now been investigated.

RESULTS AND DISCUSSION

The reaction of D-glucono-1,5-lactone with thiourea in hydrobromic acid, followed by alkaline hydrolysis, gave a complex mixture which showed four bands (1660, 1700, 1740, and 1780 cm^{-1}) in the carbonyl region of the infrared spectrum. The characteristic absorption maxima for γ- and δ-thiolactones occur at ~1705 and 1665 cm^{-1}, respectively[5], and the reaction product clearly contained the γ- and the δ-forms of lactone and of thiolactone. To avoid the evident complication resulting from change of ring size during the reaction, and also to simplify the isolation

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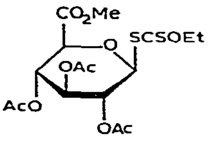
**Lactonisation of γ- and δ-mercapto acids occurs much less readily than that of the corresponding hydroxy acids, and, at equilibrium, aqueous solutions of the mercapto compounds contain much higher proportions of the free acids[4].

procedure, 2,3,4,6-tetra-*O*-methyl-D-glucono-1,5-lactone (prepared in high yield by oxidation of 2,3,4,6-tetra-*O*-methyl-D-glucose with dimethyl sulphoxide–acetic anhydride[6]) was treated with potassium thiobenzoate in *N*,*N*-dimethylformamide; the crude product, after alkaline hydrolysis, gave a very small yield of thiolactone, ν_{max} 1670 cm^{-1}.

Hanessian[7] succeeded in introducing the azido substituent at C-4 by reaction of 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone (3) with sodium azide, but he reported failure in attempts to effect such a displacement on lactones which engaged a secondary position. Our positive observations on the gluconolactones therefore encouraged us to examine the reactions of the lactone 3 with thionucleophiles. Treatment of 3 with potassium thioacetate in *N*,*N*-dimethylformamide, followed by acidification, extraction of the product, and distillation, gave crystalline 2,3-*O*-isopropylidene-4-thio-D-erythrono-1,4-lactone (4), ν_{max} 1705 cm^{-1}. Since no deliberate hydrolysis procedure was included, the isolation of the thiolactone, rather than 4-*S*-acetyl-2,3-*O*-isopropylidene-4-thio-D-erythronic acid (5), suggests that lactonisation, with displacement of acetic acid, occurred during the distillation process. By carrying out the reaction with benzyl sodium sulphide, instead of potassium thioacetate, it was possible to confirm the mode of attack on the lactone ring, 4-*S*-benzyl-2,3-*O*-isopropylidene-4-thio-D-erythronic acid (6) being obtained.



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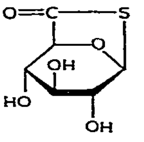

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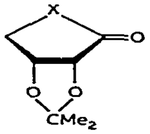
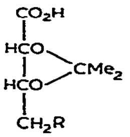
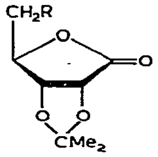


3 X = O
4 X = S



5 R = SAc
6 R = SCH2Ph



7 R = OTs
8 R = SAc
9 R = SH
10 R = H

Replacement of the ring oxygen in the lactone 3 by sulphur brings about a large upfield-shift of the H-4,4′ signals, with the result that the p.m.r. spectrum of the thiolactone 4 was much better resolved than that of 3, and a complete interpretation was possible (Table I).

An alternative approach to the synthesis of a sugar thiolactone would be to introduce sulphur into a sugar lactone at a position other than that engaged by the

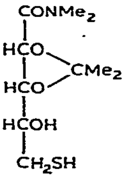
TABLE I

CHEMICAL SHIFTS (τ) AND *J* VALUES (Hz) FOR SOLUTIONS IN DEUTERIOCHLOROFORM

Compound	*H-2*	*H-3*	*H-4*	*H-4′*	*CMe₂*		$J_{2,3}$	$J_{3,4}$	$J_{3,4'}$	$J_{4,4'}$
3	5.35d	5.2m	5.65m		8.56s	8.64s	5.5			
4	5.52d	5.25m	6.39q	6.53q	8.54s	8.64s	5.0	4.0	1.5	12.5

lactone ring, and subsequently to set up conditions under which ring expansion (or contraction) could occur. The reaction of 2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribono-1,4-lactone (**7**) with potassium thioacetate (1.1 mol) in *N*,*N*-dimethylformamide gave an excellent yield of 5-*S*-acetyl-2,3-*O*-isopropylidene-5-thio-D-ribono-1,4-lactone (**8**), the required displacement of the primary sulphonyloxy group taking precedence over attack on the lactone ring. The constitution of the product was confirmed by treatment with dimethylamine, which opened the lactone ring and also effected deacetylation to give the amide **11**. Compound **11** was desulphurised with Raney nickel, and then subjected to alkaline hydrolysis and lactonisation, to give 5-deoxy-2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**10**); the p.m.r. spectrum of this product included a *C*-methyl doublet, thus precluding any possibility that rearrangement might have occurred during the introduction of the *S*-acetyl group in the original reaction.

Deacetylation of the *S*-acetyl compound **8** with sodium methoxide, followed by acidification and distillation, gave an oil which showed infrared absorption maxima at 1700, 1750, and 1785 cm^{-1}, indicating the presence of γ-thiolactone, δ-lactone, and γ-lactone, respectively; there was no absorption near 1665 cm^{-1} characteristic of the possible δ-thiolactone. The formation of a γ-thiolactone and of a δ-lactone could occur only by migration of the sulphur function from C-5 to C-4. It is known[8] that episulphides can be formed by intramolecular displacement of an acyloxy function by a neighbouring thiolate-anion, and such an attack at C-4 in the deacetylated compound **9** would result in the formation of the 4,5-epithio-acid **12**. Intramolecular attack by the carboxylate anion on the primary position of the episulphide ring would then generate 2,3-*O*-isopropylidene-4-thio-L-lyxono-1,5-lactone (**13**), and conventional rearrangement of this, *via* the free acid, would lead to 2,3-*O*-isopropylidene-4-thio-L-lyxono-1,4-lactone (**14**).



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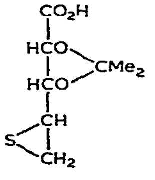

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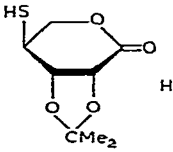

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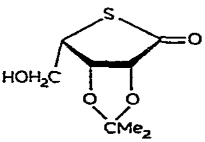

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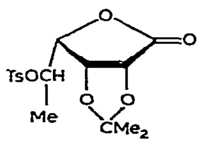

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In an attempt to discover whether such a rearrangement could occur when a secondary, rather than a primary, thiol group is involved, 2,3-*O*-isopropylidene-5-*O*-tosyl-L-rhamnono-1,4-lactone (**15**) was synthesised from L-rhamnono-1,4-lactone by formation of the 2,3-*O*-isopropylidene-1,4-lactone followed by tosylation. However, no recognisable product could be isolated after reaction of **15** with potassium thioacetate or potassium thiobenzoate, probably because selective displacement of the sulphonyloxy group, which had been readily achieved when it was primary (compound **7**), was not feasible with a less-reactive secondary group.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured, for chloroform solutions unless otherwise specified, with a Perkin–Elmer 141 polarimeter. Infrared spectra were recorded with a Perkin–Elmer 700 spectrophotometer. Recordings of p.m.r. spectra (solutions in deuteriochloroform) were made with a Varian T-60 instrument, supplemented when necessary by the use of a Varian HA-100 spectrometer. Ultraviolet spectra were measured, for solutions in ethanol, with a Unicam SP-800 instrument. The adsorbent for t.l.c. was Kieselgel GF_{254} (Merck) and, for column chromatography, silica gel MFC (Hopkin and Williams). Extracts were dried over magnesium sulphate. Light petroleum refers to the fraction with b.p. 40–60°.

Reaction of D*-glucono-1,5-lactone with thiourea.* — A solution of the lactone (5.0 g) and thiourea (2.1 g) in 48% hydrobromic acid (16 ml) was boiled under reflux for 12 h. It was then cooled, made strongly alkaline by the addition of 20% sodium hydroxide (20 ml), and boiled for a further 2 h under nitrogen. The cooled solution was then transferred to a column of Amberlite IR-120(H^+) resin, and the eluate was treated with small portions of silver oxide until bromide ion was no longer present. Evaporation of the filtered solution gave a mixture of lactones and thiolactones (2.0 g); $\nu_{\max}^{\text{film}}$ 1660, 1700, 1740, and 1780 cm^{-1}.

*2,3,4,6-Tetra-*O*-methyl-*D*-glucono-1,5-lactone.* — 2,3,4,6-Tetra-*O*-methyl-D-glucose[9] (4.0 g) was added to a mixture of dimethyl sulphoxide (45 ml) and acetic anhydride (30 ml). After storage at ambient temperature overnight, the solution was diluted with ice–water (200 ml) and stirred for 30 min; it was then saturated with salt and extracted with chloroform to give the lactone (3.2 g), b.p. 108–110°/0.1 mmHg, n_D^{22} 1.4552 (lit.[10] b.p. 106–107°/0.04 mmHg, n_D^{14} 1.4566), $\nu_{\max}^{\text{CCl}_4}$ 1760 cm^{-1}. P.m.r. data[11]: τ (CCl_4) 5.7–6.0 (m, 1 H); 6.50, 6.53, 6.56, and 6.64 (4 s, 4 OMe), superimposed on 6.3–6.7 (m, 17 H).

*Reaction of 2,3,4,6-tetra-*O*-methyl-*D*-glucono-1,5-lactone with potassium thiobenzoate.* — The lactone (0.5 g), the reagent (0.7 g), and *N,N*-dimethylformamide (5 ml) were heated together for 48 h at 120° under nitrogen. After concentration under reduced pressure and acidification with 10% sulphuric acid, the mixture was extracted with chloroform. The extract was washed with water, dried, and concentrated. The resulting oil was hydrolysed by being heated and stirred with 20% aqueous sodium hydroxide (2 ml) for 2 h at 100° under nitrogen, and the solution was then acidified and extracted with chloroform; evaporation of the washed and dried extract gave a brown syrup (0.12 g). T.l.c. (chloroform) revealed two components, which were separated by column chromatography (chloroform); the major constituent was unchanged lactone (identical infrared spectrum). The other compound, $\nu_{\max}^{\text{CCl}_4}$ 1670 cm^{-1}, isolated only in traces, was very probably the corresponding δ-thiolactone. Variations in conditions of time and temperature did not improve the yield.

*2,3-*O*-Isopropylidene-4-thio-*D*-erythrono-1,4-lactone* (4). — A solution of 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone (0.50 g) (prepared[12] from D-erythrono-

1,4-lactone[13]) and potassium thioacetate (0.38 g) in *N*,*N*-dimethylformamide (10 ml) was heated at 115° under nitrogen for 15 h. The mixture was then concentrated, acidified with 5% sulphuric acid (10 ml), and extracted with chloroform. The extract was washed with water, shaken with charcoal, filtered, dried, and evaporated to a syrup which was distilled at 80–82°/10^{-3} mmHg. The distillate (0.29 g) solidified, and crystallisation from ether–light petroleum gave the thiolactone **4** as needles, m.p. 53–54°, $[\alpha]_D^{20}$ −141° (*c* 1.3, carbon tetrachloride), λ_{max} 238 nm (ε 3700), $\nu_{max}^{CCl_4}$ 1705 cm^{-1} (Found: C, 48.0; H, 5.9; S, 18.3. $C_7H_{10}O_3S$ calc.: C, 48.3; H, 5.8; S, 18.4%). P.m.r. data: Table I.

The compound is very volatile and can be lost by prolonged storage under reduced pressure.

*4-S-Benzyl-2,3-O-isopropylidene-4-thio-*D*-erythronic acid* (**6**). — Benzyl sodium sulphide was prepared by treatment of toluene-α-thiol with 90% of the calculated amount of sodium methoxide in methanol, followed by evaporation to dryness; the residue was washed with dry ether and dried *in vacuo*. A solution of this salt (0.70 g) and 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone (0.62 g) in *N*,*N*-dimethylformamide (10 ml) was heated at 110° for 20 h under nitrogen (t.l.c. in ether then showed absence of the original lactone). Most of the solvent was then removed under reduced pressure, and the residue was acidified with 5% sulphuric acid and extracted with chloroform to give a brown oil. Purification by column chromatography (ether–acetic acid, 20:1) gave the *S*-benzyl compound **6** (0.25 g), m.p. 82–84° (from chloroform–light petroleum), $[\alpha]_D^{23}$ −52° (*c* 1.1, carbon tetrachloride), $\nu_{max}^{CCl_4}$ 1720 cm^{-1} (CO_2H) (Found: C, 59.4; H, 6.6; S, 11.1. $C_{14}H_{18}O_4S$ calc.: C, 59.55; H, 6.4; S, 11.35%). P.m.r. data: τ 1.5 br (1 H, CO_2H), 2.70 (s, 5 H, aromatic), 5.3–5.8 (m, 2 H, H-2 and H-3), 7.06 (d, 2 H, H-4), 8.40 and 8.62 (2 s, 6 H, CMe_2).

*5-S-Acetyl-2,3-O-isopropylidene-5-thio-*D*-ribono-1,4-lactone* (**8**). — A solution of 2,3-*O*-isopropylidene-5-*O*-*p*-tolylsulphonyl-D-ribono-1,4-lactone[14] (**7**, 0.55 g) and potassium thioacetate (0.20 g) in *N*,*N*-dimethylformamide (10 ml) was heated at 120° for 3 h under nitrogen; reaction was then complete (t.l.c., ether). The mixture was concentrated under reduced pressure and extracted with chloroform. The extract was washed with water, dried, and evaporated. Distillation of the residual oil afforded the thiolacetate **8** (0.32 g), b.p. 122–124/10^{-4} mmHg, m.p. 56–57° (from ether–light petroleum), $[\alpha]_D^{23}$ −71° (*c* 1.6, carbon tetrachloride), λ_{max} 228 nm (ε 4450) (SAc), $\nu_{max}^{CCl_4}$ 1685 (SAc) and 1790 (γ-lactone) cm^{-1} (Found: C, 48.8; H, 5.7; S, 13.15. $C_{10}H_{14}O_5S$ calc.: C, 48.8; H, 5.7; S, 13.0%). P.m.r. data: τ 5.3–5.7 (m, 3 H), 6.7–7.1 (m, 2 H), 7.65 (s, 3 H, SAc), 8.62 and 8.70 (2 s, 6 H, CMe_2).

*5-Deoxy-2,3-O-isopropylidene-*D*-ribono-1,4-lactone* (**10**). — A mixture of the thiolacetate **8** (0.40 g), dimethylamine (5 ml), and dry ether (10 ml) was kept at ambient temperature for 18 h, and then concentrated to give the crude amide **11** (0.41 g), $\nu_{max}^{CCl_4}$ 1650 cm^{-1} ($CONMe_2$) (absence of SAc and of lactone). This was treated with Raney nickel (~3 g) in boiling ethanol (30 ml) for 1 h; more nickel (~3 g) was then added, and the heating was continued for a further 2 h. Evaporation of the filtered solution gave an oil (0.20 g), which was then stirred and heated with

4% aqueous sodium hydroxide at 90° for 1 h. Acidification with hydrochloric acid and extraction with ether gave **10** (0.12 g), b.p. 66–68°/10^{-3} mmHg, $[\alpha]_D^{23}$ —61° (*c* 3.7), $\nu_{max}^{CHCl_3}$ 1790 cm^{-1} (Found: C, 55.65; H, 7.1. $C_8H_{12}O_4$ calc.: C, 55.8; H, 7.0%). P.m.r. data: τ 5.1–5.6 (m, 3 H), 8.50, 8.53, 8.58, and 8.64 (d + 2 s, 9 H, H-5 and CMe_2).

Deacetylation of thiolacetate **8**. — A solution of **8** (0.28 g) in 0.1M methanolic sodium methoxide (15 ml) was kept at ambient temperature under nitrogen overnight, and then neutralised with carbon dioxide and evaporated. The residue was extracted with ether to give an oil (0.21 g), b.p. 100–104°/10^{-4} mmHg, $[\alpha]_D^{23}$ —15° (*c* 1.4); ν_{max}^{film} 1700 (γ-thiolactone), 1750 (δ-lactone), 1785 (γ-lactone), and 2595 (SH) cm^{-1} (Found: C, 47.2; H, 5.8. $C_8H_{12}O_4S$ calc.: C, 47.1; H, 5.9%).

*2,3-*O*-Isopropylidene-5-*O*-*p*-tolylsulphonyl-*L*-rhamnono-1,4-lactone* (**15**). — A solution of L-rhamnono-1,4-lactone[15] (3.0 g) and sulphuric acid (0.2 ml) in dry acetone (200 ml) was kept for 18 h at ambient temperature, and then neutralised with barium hydroxide, filtered, and evaporated to give 2,3-*O*-isopropylidene-L-rhamnono-1,4-lactone (3.1 g), b.p. 110–112°/10^{-3} mmHg, $[\alpha]_D^{23}$ —28° (*c* 1.2, acetone), ν_{max}^{film} 1790 cm^{-1}. This product was dissolved in pyridine (10 ml), and a solution of toluene-*p*-sulphonyl chloride (3.5 g) in pyridine (10 ml) was added at 0°. The mixture was stored at 0° for 48 h, then slowly diluted with water, and extracted with chloroform to give **15** (3.9 g), m.p. 92–94° (from ether), $[\alpha]_D^{23}$ —4.5° (*c* 2.0), $\nu_{max}^{CHCl_3}$ 1790 (Found: C, 54.1; H, 5.7; S, 8.9. $C_{16}H_{20}O_7S$ calc.: C, 53.9; H, 5.7; S, 9.0%). P.m.r. data: τ 2.35 (q, 4 H, aromatic), 4.8–5.8 (m, 4 H), 7.55 (s, 3 H, aryl-Me), 8.45 (d, 3 H, H-6), 8.68 and 8.78 (2 s, 6 H, CMe_2).

T.l.c. (ether–light petroleum, 2:1) showed that the reaction of **15** (0.5 g) with potassium thioacetate (0.3 g) in *N,N*-dimethylformamide (10 ml) was incomplete after 18 h at 115°. Column chromatography (ether) recovered a small amount of **15**, but failed to give any other pure material. Variations in time and temperature, or the use of potassium thiobenzoate, were likewise unsuccessful.

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