574. *Dithiols. Part X. A Thio-analogue of BAL-Intrav.*

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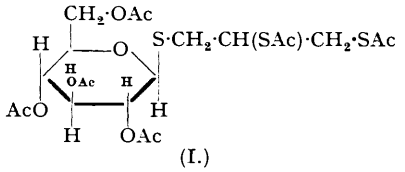
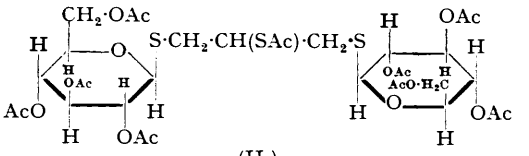
Derivatives of (2 : 3-dimercaptopropyl)thioglucoside ("thio-BAL-Intrav") have been synthesised (i) by reaction of acetobromoglucose with propane-1 : 2 : 3-trithiol, prepared by an improved method, (ii) by reaction of penta-acetyl glucose with the trithiol, and (iii) by reaction of acetobromoglucose with the 1 : 2-benzylidene derivative of the trithiol. Method (ii) has not previously been used for the synthesis of thioglucosides.

In Part I (Fraser, Owen, and Shaw, *Biochem. J.*, 1947, **41**, 328), the *O*-glucoside (BAL-Intrav) of 2 : 3-dimercaptopropanol (BAL) was described. The preparation of the corresponding thioglucoside appeared to be of interest, and an investigation has therefore been made of several possible routes to this compound. There are two general methods for the synthesis of thioglucosides: (i) the reaction of acetobromoglucose with the sodium or the silver salts of thiols, which gives β-pyranosides, and (ii) the action of mercuric chloride on mercaptals of glucose, which gives α-furanosides (Schneider and Sepp, *Ber.*, 1916, **49**, 2054; Green and Pacsu, *J. Amer. Chem. Soc.*, 1937, **59**, 1025, 2569; Pacsu and Wilson, *ibid.*, 1939, **61**, 1450, 1930; Wolfrom, Waisbrot, Weisblat, and Thompson, *ibid.*, 1944, **66**, 2063).

For the preparation of the required thioglucoside, it was necessary to obtain propane-1 : 2 : 3-trithiol. This compound, which had earlier been prepared by the action of metallic hydrogen sulphides on trichloro- or tribromo-propane (Carius, *Annalen*, 1862, **124**, 236; Rheinboldt and Tetsch, *Ber.*, 1937, **70**, 675; Simpson, *Canadian J. Res.*, 1947, **25**, *B*, 20), was more conveniently made by the cleaner reaction of 1 : 2 : 3-tribromopropane with potassium



(I.)



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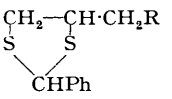
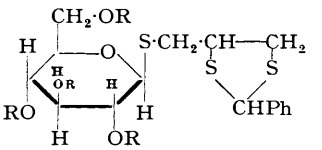
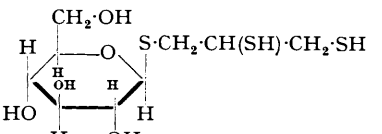


(III; R = Br.)
(IV; R = SAc.)
(V; R = SH.)



(VI; R = Ac.) (VII; R = H.)



(VIII.)

thiolacetate, and alkaline hydrolysis of the triacetate. Attempts to prepare the glucose mercaptal from this trithiol gave a liquid mixture from which no homogeneous material could be obtained, but the monosodium derivative of the trithiol reacted readily with acetobromoglucose in methanol and gave, after complete acetylation, 2 : 3 : 4 : 6-tetra-acetyl β-(2 : 3-bisacetylthiopropyl)glucoside (I), which was separated from a small amount of 1 : 3-bis-(2 : 3 : 4 : 6-tetra-acetyl β-thioglucosidyl)-2-acetylthiopropane (II) by chromatography. Although the yield was good, (I) was probably a mixture of stereoisomers, since only a portion of it was obtained crystalline; the presence of the asymmetric centre at $C_{(2)}$ in the propyl group can evidently account for this.

Phenols are known to form glucosides by reaction with penta-acetyl glucose in the presence of catalysts such as toluene-*p*-sulphonic acid (Helferich and Schmitz-Hillebrecht, *Ber.*, 1933, **66**, 378; Hudson *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 690; Coleman *et al.*, *Ind. Eng. Chem.*, 1944, **36**, 1040), and the more reactive β-penta-acetyl fructose readily reacts with ethanethiol in the presence of zinc chloride to give the β-fructoside (Wolfrom and Thompson, *J. Amer. Chem. Soc.*, 1934, **56**, 880), the loss of one molecule of acetic acid occurring in each case. It seemed possible therefore that under more vigorous conditions β-penta-acetyl glucose would react with thiols. When β-penta-acetyl glucose was heated *in vacuo* with a large excess of propane-1 : 2 : 3-trithiol in the presence of toluene-*p*-sulphonic acid complete condensation took place. The excess of trithiol was removed by distillation, the last traces by co-distillation with trimethylene glycol diacetate, and the product, presumably 2 : 3 : 4 : 6-tetra-acetyl (2 : 3-dimercaptopropyl)thioglucoside, was acetylated to give the crude hexa-acetyl derivative (I), which was purified to some extent by short-path distillation in small quantity, and by chromatography, but failed to crystallise. Deacetylation with cold methanolic barium methoxide (Fraser, Owen, and Shaw, *loc. cit.*) gave a crude barium salt of the dithiol.

A third route to the thioglucoside involved the use of 2 : 3-benzylidenedithiopropyl bromide (III) (Part IX, preceding paper), which reacted readily with potassium thiolacetate in ethanol, to give 2 : 3-benzylidenedithiopropyl thiolacetate (IV); deacetylation of the latter by heating it with methanolic hydrogen chloride gave 2 : 3-benzylidenedithiopropanethiol (V). The sodium salt of (V) condensed readily with acetobromoglucose in methanol at room temperature, and reacetylation of the product gave crystalline 2 : 3 : 4 : 6-tetra-acetyl β-(2 : 3-benzylidenedithiopropyl)thioglucoside (VI) in good yield. Catalytic deacetylation with a trace of sodium in methanol then gave the thioglucoside (VII) as a glass.

Reduction of (2 : 3-benzylidenedithiopropyl)thioglucoside (VII) with sodium and liquid ammonia in the presence of ethanol (cf. Stocken, *J.*, 1947, 592) proceeded in the desired direction, giving toluene and a viscous ethanol-soluble syrup; there was no ether-soluble thiol in the products, indicating that the thioglucoside linkage had not been broken. Although the syrup must have been essentially the free thioglucoside (VIII), in view of its hygroscopic nature and susceptibility towards oxidation it was then acetylated to give (I), the formation of which confirmed that (VIII) had actually been obtained.

Experimental.

Propane-1 : 2 : 3-*trithiol.*—1 : 2 : 3-Tribromopropane (92 g.) (*Org. Synth.*, Coll. Vol. I, p. 521) was added to thiolacetic acid (83 g.) and potassium hydroxide (61 g.) in ethanol (600 c.c.), and the solution was stirred and heated under reflux for 8 hours. Addition of ether (200 c.c.) to the cooled solution precipitated more potassium bromide, which was filtered off and washed with ether. The aqueous filtrate was extracted with ether, using first the ethereal washings, and the extract was dried (Na_2SO_4) and evaporated to a red oil. Distillation gave *trisacetylthiopropane* (67 g., 77%) as an orange liquid, b. p. 140°/0·5 mm., n_D^{22} 1·5563 (Found: C, 40·4; H, 5·2; S, 36·4. $C_9H_{14}O_3S_3$ requires C, 40·6; H, 5·3; S, 36·1%). Light absorption: max. 2320 A., $\varepsilon = 11{,}400$.

Hydrolysis. (i) A solution of the triacetate (10 g.) in 2% methanolic hydrogen chloride (60 c.c.) was heated under reflux for 3 hours. The solvent was removed by distillation, and the residue was poured into aqueous sodium hydrogen carbonate and extracted with ether. Drying and evaporation of the ethereal solution left a yellow mobile liquid (1 g.) (Found: thiol-S, 8·0%). The bulk of the hydrolysis product was insoluble in water and ether, and further extraction with chloroform gave a viscous orange liquid (4 g.) (Found: thiol-S, 7·5%). These liquids were not further examined.

(ii) To a solution of the triacetate (8·4 g.) in methanol (70 c.c.) under nitrogen, cooled in an ice–salt bath, sodium hydroxide (7·7 g.) was added; the solution was then set aside at room temperature for 24 hours, whereupon it set to a gel. Hydrochloric acid (20 c.c.; *d* 1·19) was added, with external cooling, and the solution was poured into water (200 c.c.) and extracted with ether (200 c.c.). The dried (Na_2SO_4) extract was evaporated and the residual oil distilled. Propane-1 : 2 : 3-trithiol (3·9 g., 88%) was thus obtained as a mobile yellow liquid, b. p. 80°/2 mm., n_D^{22} 1·6105 (Found: thiol-S, 68·2. Calc. for $C_3H_8S_3$: thiol-S, 68·5%). Simpson (*Canadian J. Res.*, 1947, **25**, *B*, 20) records b. p. 60°/0·4 mm.

2 : 3 : 4 : 6-*Tetra-acetyl* β-(2 : 3-*Bisacetylthiopropyl*)*thioglucoside.*—To a solution of propane-1 : 2 : 3-trithiol (2·1 g.) in dry methanol (30 c.c.), under nitrogen, sodium (0·32 g.) was added, followed by acetobromoglucose (5·8 g.), and the solution was left at room temperature for 3 days. After removal of the methanol under reduced pressure, the residual glass was heated on the steam-bath for 4 hours with acetic anhydride (30 g.) and anhydrous sodium acetate (5 g.). The acetic acid and anhydride were removed at the water-pump, the residue was extracted with chloroform, and the extract was washed with water and dried (Na_2SO_4). Removal of the chloroform left an orange-red glass (7·8 g.).

A portion (0·5 g.) in benzene (10 c.c.) was transferred to a column of acid-washed magnesium silicate (30 g.) and developed with benzene, and then eluted with 500 : 1 benzene–ethanol. A middle fraction (50 mg.) readily crystallised, and was used to seed the main bulk of the crude product, which was triturated with ethanol. A sticky solid (1 g.) was thus obtained. Recrystallisation from hot acetone–light petroleum (b. p. 40—60°) gave 0·4 g., m. p. 168—171°. Further recrystallisation from methanol gave pure 1 : 3-*bis*-(2 : 3 : 4 : 6-*tetra-acetyl* β-*thioglucosidyl*)-2-*acetylthiopropane*, m. p. 174°, $[\alpha]_D^{16}$ −31·8° (*c*, 1·7 in chloroform) (Found: C, 47·3; H, 5·7; S, 11·5. $C_{33}H_{46}O_{19}S_3$ requires C, 47·0; H, 5·5; S, 11·4%).

A portion (1·0 g.) of the residual glass was re-chromatographed. From the first two fractions, a crude solid (230 mg.), m. p. 100—105°, was obtained. Recrystallisation from ethanol gave a purer material (170 mg.), m. p. 110—112°. Further recrystallisation afforded pure *hexa-acetyl* β-(2 : 3-*dimercaptopropyl*)*thioglucoside*, m. p. 114—115°, $[\alpha]_D^{18}$ −23·7° (*c*, 1·9 in chloroform) (Found: C, 45·7; H, 5·5; S, 17·4. $C_{21}H_{30}O_{11}S_3$ requires C, 45·5; H, 5·5; S, 17·4%). Light absorption: max. 2330 A., $\varepsilon = 8600$.

Condensation of Propane-1 : 2 : 3-*triol with* β-*Penta-acetyl Glucose.*—β-Penta-acetyl glucose (16 g.), propane-1 : 2 : 3-trithiol (20 g., 4 mols.) and toluene-*p*-sulphonic acid (0·2 g.) were heated on a steam-bath for 3 hours at 30 mm., with a slow stream of nitrogen passing through the liquid mixture. Excess of the trithiol was distilled off at 0·1 mm., the last traces being removed by co-distillation with two 10-g. portions of methylene glycol diacetate, b. p. 65°/0·0001 mm. To the orange viscous residue was added acetic anhydride (60 g.) and anhydrous sodium acetate (12 g.), and the solution was heated on the steam-bath for 4 hours. Excess of acetic anhydride was removed on the water-pump, the residue was extracted with chloroform, and the extract washed with aqueous sodium hydrogen carbonate and then with water. Drying (Na_2SO_4) and evaporation of the chloroform solution gave an orange-red glass (18·9 g.). Short-path distillation of a portion at 200° (bath)/0·0001 mm. gave crude 2 : 3 : 4 : 6-tetra-acetyl (2 : 3-bisacetylthiopropyl)thioglucoside as a straw-coloured glass (Found: S, 18·4. $C_{21}H_{30}O_{11}S_3$ requires S, 17·4%). Light absorption: max. 2330 A., $\varepsilon = 8900$. Chromatography on magnesium silicate, using 100 : 1 benzene–ether as the eluting solvent, removed the colour, but no crystalline material was obtained.

Deacetylation. The crude hexa-acetyl thioglucoside (1 g.) was dissolved in dry methanol (15 c.c.) under nitrogen, and the solution was cooled in a carbon dioxide–ethanol bath. N-Methanolic barium methoxide (5 c.c.) was added dropwise to the solution, with stirring. Ethanol (10 c.c.) was then added, and the precipitated solid was filtered off and washed with ethanol, then with ether, under a rapid stream of nitrogen. Drying in a vacuum desiccator ($CaCl_2$, then P_2O_5) gave the crude *barium* salt of 2 : 3-dimercaptopropylthioglucoside (0·65 g., 95%) (Found: S, 18·2; Ba, 30·4; thiol-S, 13·0. $C_9H_{16}O_5S_3Ba$ requires S, 22·0; Ba, 31·4; thiol-S, 14·6%).

2 : 3-*Benzylidenedithiopropanethiol.*—2 : 3-Benzylidenedithiopropyl bromide (10 g.), potassium thiolacetate (4·5 g.), and thiolacetic acid (0·5 c.c.) in ethanol (30 c.c.) were heated under reflux for 1½ hours. The solution was cooled and diluted with ether, and the salts were removed by filtration. The filtrate was concentrated, and the residue was dissolved in ether and washed with water, dried (Na_2SO_4) and concentrated, and the residual oil was distilled. 2 : 3-*Benzylidenedithiopropyl thiolacetate* (9 g., 90%) was thus obtained as an orange liquid, b. p. 140° (bath)/0·0001 mm., n_D^{15} 1·6290 (Found: S, 36·0. $C_{12}H_{14}OS_3$ requires S, 36·0%). Light absorption: max. 2280 A., $\varepsilon = 8900$.

The acetate (8·5 g.) in 2% methanolic hydrogen chloride (40 c.c.) was heated under reflux for 3 hours. On cooling, 2 : 3-*benzylidenedithiopropanethiol* (6 g., 84%), m. p. 50°, crystallised. Recrystallisation from ethanol–ether gave 5 g., m. p. 52° (Found : S, 42·7. $C_{10}H_{12}S_3$ requires S, 42·1%).

β-(2 : 3-Benzylidenedithiopropyl)thioglucoside.—To a solution of the 2 : 3-benzylidenedithiopropanethiol (1·2 g.) in dry methanol (10 c.c.), sodium (0·12 g.) and acetobromoglucose (2·2 g.) were added. After 3 days, the methanol was removed by distillation and the residue was heated on the steam-bath for 4 hours with acetic anhydride (15 g.) and anhydrous sodium acetate (2 g.). The acetic acid and anhydride were removed under reduced pressure, and the residue was extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution and then with water, dried, and concentrated. Digestion of the residue (3 g.) with methanol gave a crystalline solid (2·4 g., 81%), m. p. 115—118°. Recrystallisation from methanol gave pure 2 : 3 : 4 : 6-*tetra-acetyl β-(2 : 3 benzylidenedithiopropyl)thioglucoside*, m. p. 121—122°, $[\alpha]_D^{18}$ −22·0° (*c*, 1·9 in chloroform) (Found : S, 17·3. $C_{24}H_{30}O_9S_3$ requires S, 17·2%).

Deacetylation of the tetra-acetate, by treatment overnight in methanol with a trace of sodium, and chromatography of the product on a column of magnesium trisilicate, using aqueous ethanol (75%) as eluent, gave *β-(2 : 3-benzylidenedithiopropyl)thioglucoside* as a pale yellow glass, $[\alpha]_D^{20}$ −32·6° (*c*, 1·4 in 30% aqueous ethanol) (Found : C, 48·3; H, 6·0; S, 23·8. $C_{16}H_{22}O_5S_3$ requires C, 49·2; H, 5·7; S, 24·6%). After long storage and trituration with dry acetone, a small quantity of hygroscopic solid separated, m. p. 55—60° (Found : S, 24·8%).

2 : 3 : 4 : 6 : 2′ : 3′-*Hexa-acetyl β-(2 : 3-Dimercaptopropyl)thioglucoside.*—The above thioglucoside (3·5 g.) and ethanol (5 c.c.) were dissolved in liquid ammonia (100 c.c.), and sodium was added with stirring, *ca.* 0·2 g. at a time as the initial blue colour disappeared. When 5 g. had been added a stable blue colour was obtained; solid ammonium chloride (10 g.) was then added and the ammonia was allowed to evaporate. The residue was extracted with dry ether (2 × 100 c.c.), evaporation of which gave toluene (0·3 g., b. p. 110°). Further extraction of the residue with cold ethanol (100 c.c.), then hot ethanol (50 c.c.), gave a clear, colourless syrup (2·1 g.), to which acetic anhydride (25 c.c.) and anhydrous potassium acetate (2 g.) were added; the solution was heated on the steam-bath for 6 hours. Excess of acetic anhydride was decomposed by stirring with water for 4 hours, and the acid was neutralised with aqueous sodium hydrogen carbonate. Extraction with chloroform gave the hexa-acetyl compound as a pale-orange viscous syrup (2·8 g., 57%) (Found : C, 46·1; H, 5·6; S, 16·9%). Light absorption : max. 2330 A., ε = 7900 (cf. ε = 8600 for pure material). Chromatography on magnesium trisilicate with 10 : 1 benzene–ether as eluent produced no apparent separation of stereoisomers.

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