REDUCTIVE CLEAVAGE WITH METAL IN LIQUID AMMONIA

I. THE SELECTIVE CLEAVAGE OF THE BENZYLTHIO C—S BOND VERSUS THE BENZYLIDENEDIOXY C—O BOND IN METHYL *S*-BENZYL-4,6-*O*-BENZYLIDENE-2-THIO-α-D-ALTROPYRANOSIDES; THE INFLUENCE OF THE COSOLVENT 1,2-DIMETHOXYETHANE ON THE COURSE OF THE REACTION

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ABSTRACT

The improved solubility of methyl *S*-benzyl-4,6-*O*-benzylidene-2-thio-α-D-altropyranoside (I) in liquid ammonia diluted with 1,2-dimethoxyethane has permitted the selective cleavage by metallic sodium or lithium of the C—S bond to give methyl 4,6-*O*-benzylidene-2-thio-α-D-altropyranoside in 70–75% yield. On the other hand, the slight solubility of I in liquid ammonia alone results only in the completely hydrogenolyzed material, methyl 2-thio-α-D-altropyranoside, along with unchanged I.

Generally, in liquid ammonia alone, reductive cleavage is rapid (15–20 min) and the benzylidene and benzyl groups are converted largely into toluene accompanied by a small amount of bibenzyl. In liquid ammonia – 1,2-dimethoxyethane mixtures the reaction is much slower ($\gg$1.5 h); under these conditions the benzylidene and benzyl groups are converted to a larger extent into bibenzyl, the rest becoming toluene.

The two strong infrared absorption bands (in Nujol) in the region of 766 to 778 cm^{-1} and 706 to 718 cm^{-1} have been assigned to the phenyl moiety of the benzylidene group, and the one strong band in the region of 702 cm^{-1} to the phenyl moiety of the *S*-benzyl group.

INTRODUCTION

Birch (1, 2) has pointed out that a carbonyl group can be converted into a non-reducible species by acetal or ketal formation, but only if the resulting alkoxy group involved is neither benzylic nor allylic. Groups such as benzyl, benzyloxycarbonyl, and *p*-toluenesulfonyl, which are used to protect amino, hydroxy, or mercapto functions, are readily removed by the reducing action of sodium and liquid ammonia. Several articles have appeared (3–6) which illustrate the use of this technique in the synthesis of carbohydrate derivatives.

A report from this laboratory (3) has described the preparation of some monomercaptomonosaccharides by reductive cleavage of *S*-benzyl-4,6-*O*-benzylidene-2- (or -3-) thioglycopyranosides with sodium and liquid ammonia. At that time some attempts were made, by use of a limited proportion of sodium, to effect a selective cleavage of the *S*-benzyl group with retention of the protecting 4,6-*O*-benzylidene moiety (III, Reaction Scheme 1). However, the only isolable compounds were the unchanged methyl *S*-benzyl-4,6-*O*-benzylidene-2- (or -3-) thioglycoside (I) and the glycoside minus both protecting groups (II, Reaction Scheme 1).

To our knowledge few accounts exist wherein attempts at such selective metal–ammonia hydrogenolysis have been reported. In this connection it is noteworthy that a large excess of Raney nickel removes both the benzylidene and the methylthio groups from methyl 4,6-*O*-benzylidene-*S*-methyl-3-thio-α-D-altropyranoside (7) whereas, with only a fourfold excess of the metal, reductive desulfurization takes place unaccompanied by extensive removal of the benzylidene group (8).

Pinder and Smith (9) found no selective cleavage in the sodium – liquid ammonia reduction of 2-methyl-2-phenyl-1,3-oxathiolane or of 2-methyl-2-phenyl-1,3-dioxolane.

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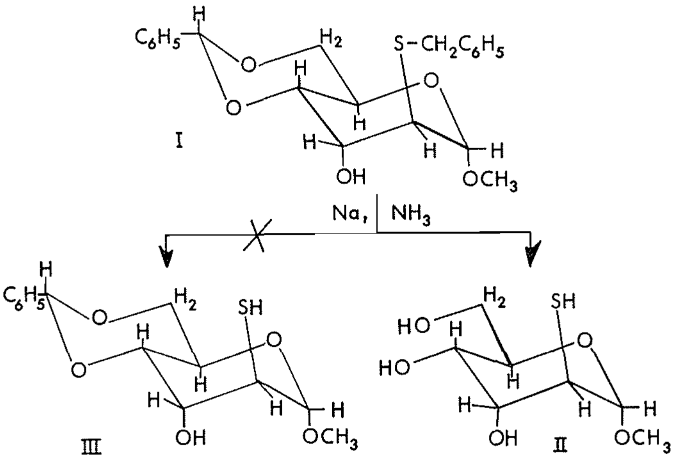


Reaction Scheme 1.

It has been shown, however, that dialkyl thioethers are readily cleaved by sodium in liquid ammonia whereas the analogous oxygen ethers are practically unaffected (10). Thus one would expect, in a competitive reaction, that a benzylthio group should be hydrogenolyzed in preference to a benzyloxy group. This paper describes the results of attempts at selective cleavage of the benzylthio linkage with sodium and liquid ammonia in the presence of the benzylidene dioxy moiety, examples from the field of carbohydrate chemistry being used as substrates.

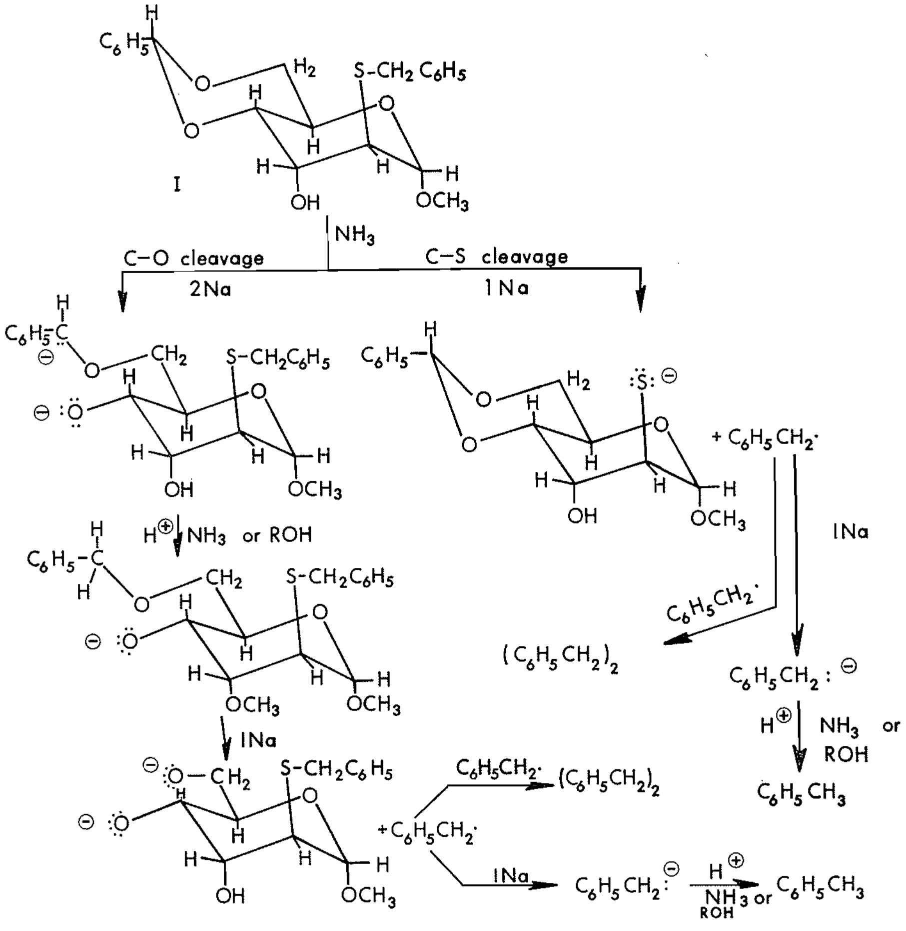
RESULTS AND DISCUSSION

Amount of Sodium Required for Cleavage of the C—S and C—O Bonds

Experiments were designed to measure the proportion of sodium required to cleave the C—S and C—O bonds in a molecule such as methyl *S*-benzyl-4,6-*O*-benzylidene-2-thio-α-D-altropyranoside (I). This information was deemed to be necessary in approaching the problem of selective bond cleavage.

The theoretically required amounts of metal are illustrated in Reaction Scheme 2. It is seen that C—S cleavage requires 2 g-atoms of sodium if toluene alone is produced but just 1 g-atom of sodium if bibenzyl is formed exclusively. Whether bibenzyl is made by free-radical coupling as shown in Reaction Scheme 2 or by an anionic process as suggested by Birch (1) is not yet clear, but by either process 1 g-atom of sodium is required for C—S cleavage of 1 mole of compound I to produce the half mole of bibenzyl. For C—O cleavage, 2 g-atoms of sodium are expected to cleave one leg of the acetal (either at C_4—O or C_6—O) to form the *O*-benzyl group, after proton abstraction from the solvent or any alcoholic group present. This is followed by consumption of either 1 or 2 g-atoms of sodium to produce bibenzyl or toluene respectively. Thus, 3 or 4 g-atoms of sodium are required per mole of I depending upon the fate of the benzylidene group (as bibenzyl or toluene).

These predictions were substantiated by the results of experiments which measured the proportion of sodium metal required for the reductive cleavage of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (IV), methyl *S*-benzyl-4,6-O-ethylidene-3-thio-α-D-altropyranoside (V*a*), and methyl *S*-benzyl-4,6-*O*-ethylidene-2-*O*-methyl-3-thio-α-D-altropyranoside (V*b*) (Table I, experiments 1–5). The ethylidene group in compounds V*a* and



REACTION SCHEME 2.

V*b* is unaffected by the metal, and hence permitted estimation of the sodium consumption in the cleavage of the benzyl group from sulfur. In liquid ammonia, the 4,6-*O*-benzylidene group required 4 equivalents of sodium[2] for cleavage, yielding essentially toluene along with a minor amount (3%) of bibenzyl (expt. 1). But in the mixed solvent NH_3–1,2-dimethoxyethane somewhat less than 4 equivalents of sodium were consumed and a larger amount of bibenzyl was formed (16%, expt. 2). Accordingly, as expected, methyl *S*-benzyl-4,6-*O*-benzylidene-2-thio-α-D-altropyranoside (I) in liquid ammonia required 6 equivalents of sodium for complete reduction to methyl 2-thio-α-D-altropyranoside (II) (Table I, expt. 6).

Selective Cleavage of the C—S Rather Than the C—O Bond

When 2 equivalents of sodium was added to 1 equivalent of methyl *S*-benzyl-4,6-*O*-benzylidene-2-thio-α-D-altropyranoside (I) in liquid ammonia, only methyl 2-thio-α-D-altropyranoside (II), bibenzyl, and much unchanged I were obtained. This lack of selective reduction was due to the sparing solubility of I in liquid ammonia.[3] When 1,2-dimethoxy-

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[2] *The hydroxyl groups in IV and Va consumed no metal under our conditions.*

[3] *A separate test showed that the bulk of a 100 mg quantity of I failed to dissolve in 500 ml of liquid ammonia*

TABLE I

Metal consumption and products obtained in the reductive cleavage of C—O and C—S bonds by sodium in liquid ammonia

				Products (%)*				
Expt. No.	Compound (1 mole)	Solvent	Amount of Na consumed (g-atoms)	Reduced substrate	Starting compound	Bibenzyl	Toluene	Unknown
1	IV	NH_3	4	VI (79)	0	3	69	
2	IV	NH_3–DME (3:2)	~4	VI (?)	0	16	?	
3	V*a*	NH_3	~2	VII*a* (95)	0	~10	$\geqslant$58	
4	V*b*	NH_3	~2	VII*b* (98)	0	8	?	
5	V*a*	NH_3–DME (1:1)	~1	VII*a* (66)	33	32	?	
6	I	NH_3	~6	II (87–94)	0	9	$\geqslant$56	
7	I	NH_3–DME (6:5)	1.5	III (71)	21	48	?	~7

*The question mark indicates that the percentage yield was not measured but that the compound was found to be present in the product.

NOTE: I, methyl *S*-benzyl-4,6-*O*-benzylidene-2-thio-α-D-altropyranoside; II, methyl 2-thio-α-D-altropyranoside; III, methyl 4,6-*O*-benzylidene-2-thio-α-D-altropyranoside; IV, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside; V*a*, methyl *S*-benzyl-4,6-*O*-ethylidene-3-thio-α-D-altropyranoside; V*b*, methyl *S*-benzyl-4,6-*O*-ethylidene-2-*O*-methyl-3-thio-α-D-altropyranoside; VI, methyl α-D-glucopyranoside; VII*a*, methyl 4,6-*O*-ethylidene-3-thio-α-D-altropyranoside; VII*b*, methyl 4,6-*O*-ethylidene-2-*O*-methyl-3-thio-α-D-altropyranoside; DME, 1,2-dimethoxyethane.

ethane was added as a cosolvent, to improve the solubility of I in liquid ammonia (4, 11, 13), selective reductive cleavage of the C—S bond did occur (Table I, expt. 7). Optimum results were obtained when the ratio of 1,2-dimethoxyethane to NH_3 was 4 or 5 to 6 (by volume).

Several interesting features became evident when 1,2-dimethoxyethane was used as cosolvent. (*i*) For the quantities of reagents taken (see Table II), the time required for consumption of sodium increased from 15 to 20 min when only ammonia was used, to $1\frac{1}{2}$–$3\frac{1}{2}$ h in the mixed solvent. A larger ratio of 1,2-dimethoxyethane to NH_3 increased the time to several hours. (*ii*) The proportion of bibenzyl increased markedly (>50% of theory) over that (~9%) obtained in just liquid ammonia. The yield of toluene dropped sharply as a consequence. (*iii*) The proportion of sodium metal required for C—S cleavage decreased also. This is in keeping with the requirement of 1 g-atom of metal when bibenzyl is the product of C—S cleavage, and 2 g-atoms when only toluene is obtained (see Reaction Scheme 2). The influence of solvent composition and amount of metal on the proportion of products obtained is shown in Table II. It is noteworthy that the use of lithium instead of sodium, under otherwise identical conditions, gave a larger yield (76%) of the selectively cleaved product III. Table III shows the effects, on the reduction of V*a*, of solvent composition and proportion of metal to substrate, with particular attention to bibenzyl (and therefore toluene) production.

Assignment of Absorption Bands for the Benzylthio and Benzylidene Dioxy Groups

The selective removal of the benzyl group from I has permitted the assignment of infrared absorption bands caused by the two monosubstituted phenyl groups. Strong absorption for monosubstituted phenyl in compound I in Nujol is found at 770 cm^{-1}, 710 cm^{-1}, and 702 cm^{-1}. For methyl 4,6-*O*-benzylidene-2-thio-α-D-altropyranoside (III), absorption (in Nujol) occurred at 766 cm^{-1} and 706 cm^{-1} caused by the benzylidene moiety. The completely reduced substance, methyl 2-thio-α-D-altropyranoside (II), showed none of these three absorption bands. Accordingly, for these altrosides, the 4,6-*O*-benzylidene group absorbs in the region of 766–770 cm^{-1} and 706–710 cm^{-1} ($\Delta cm^{-1} = \sim 60$) whereas the 2-benzylthio group absorbs at 702 cm^{-1}. In agreement with this, methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-altropyranoside (14) shows absorption bands at 778 cm^{-1} and 718 cm^{-1} ($\Delta cm^{-1} = 60$), methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-altropyranoside (14) exhibits strong absorption at both 766 cm^{-1} and 706 cm^{-1} ($\Delta cm^{-1} = 60$), and methyl 4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside absorbs at 778 cm^{-1} and 718 cm^{-1} ($\Delta cm^{-1} = 60$) (Fig. 1).

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were taken with a Perkin–Elmer model 421 instrument. Nuclear magnetic resonance spectra were obtained with a Varian Associates A-60 instrument. Gas–liquid chromatography was accomplished with a Burrell K-2 Kromo-Tog by using a 2.5 m column packed with 25% silicone rubber on Gas Chrom P (60–80 mesh) and a helium flow rate of 100 ml/min.

Syntheses of Compounds

Methyl 4,6-O-Ethylidene-2-O-(p-toluenesulfonyl)-α-D-glucopyranoside

The published procedure (12, 15) was employed, but with the following modifications which improved the isolation and more than tripled the yield. (*a*) The methyl 4,6-*O*-ethylidene-α-D-glucopyranoside (12) was treated with a 15% rather than 48% excess of *p*-toluenesulfonyl chloride. (*b*) The chloroform extract of the reaction mixture was first washed with ice-cold 6 *N* HCl to remove pyridine, and then washed with bicarbonate solution and water. (*c*) The oil left upon removal of the chloroform from the decolorized solution was dissolved in ether. When this was left in a refrigerator overnight a solid was obtained. A hot absolute ethanol solution of this solid, when cooled, gave 11.7% of pure methyl 4,6-*O*-ethylidene-2,3-di-*O*-(*p*-toluenesulfonyl)-α-D-glucopyranoside, m.p. 156° (lit. m.p. 156–157° (12), 154–155° (16)). (*d*) The brownish solid left after removal of solvent from the above alcoholic filtrate, when dissolved in chloroform and diluted with petroleum

TABLE II

Influence of solvent composition and amount of metal on the proportion of products in the ammonia–1,2-dimethoxyethane–sodium reduction of I

Solvent composition (ml)		I		Sodium consumed		Time (h)	Yield of III (%)	Yield of bibenzyl (%)	Recovered I (%)	Yield of II (%)
NH_3	1,2-Dimethoxyethane	g	Mole	g	Mole					
600	0	19.4	0.05	6.7	0.29	$\frac{1}{4}$	—	—	—	94
150	0	3.88	0.01	1.34	0.058	$\frac{1}{4}$	—	99	—	87
400	250	9.7	0.025	1.15	0.05	$2\frac{1}{2}$	48	35	21.7	19
400	250	9.7	0.025	1.725	0.075	$3\frac{1}{2}$	36	35	23.7	41
350	200	7.76	0.02	0.69	0.03	$1\frac{1}{2}$	56.6	45	27	13
300	250		0.02		0.03	$2\frac{1}{2}$	70.5	48	21	0.409 of impure viscous oil
300	250		0.02		0.03*	$1\frac{1}{2}$	75.7	60	16.1	0.429 of impure viscous oil
300	450		0.025		0.05	7	28	—	—	—
200	300		0.025		0.05	5	30.6	—	—	—

*Lithium.

NOTE: I, methyl *S*-benzyl-4,6-*O*-benzylidene-2-thio-α-D-altropyranoside; II, methyl 2-thio-α-D-altropyranoside; III, methyl 4,6-*O*-benzylidene-2-thio-α-D-altropyranoside.

TABLE III

Influence of solvent composition and amount of metal on the proportion of products in the ammonia–1,2-dimethoxyethane–sodium reduction of V*a* to VII*a* (amount of V*a* used in all cases = 3.26 g (0.01 mole))

Solvent composition (ml)		Sodium consumed		Time required for Na consumption (min)	Yield of VII*a* (%)*	Recovered V*a* (%)*	Yield of bibenzyl (mg)	Theoretical amount of Na required for reduction		
NH$_3$	1,2-Dimethoxyethane	mg	Mole					For the amount of bibenzyl produced‡ (mg)	For the amount of toluene produced§ (mg)	Total (mg)
200	0	230	0.01	5	51	49	Negligible		~230	~230
150	0	440	0.019	15	100	Nil	80	20	420	440
150	100	230	0.01	45	72.4	27.6	400	102	131	233
150	100	310	0.135	150	84.3	13.9	300	76	236	312
250	250	230	0.01	40	67.3	32.7	300	76	158	234
250	300	230	0.01	45	67.5	32.5	350	88	133	221
250	200	310	0.019	150	86.1	13.9	400	102	205	307
150	125	92	0.0133†	120	85.5	14.5	394	30	59	89

*Yield is based on the total amount of V*a* used.

†Lithium.

‡Calculated on the basis that 1 g-atom equivalent of sodium is required by 1 mole of V*a* if only bibenzyl is produced.

§Calculated on the assumption that the metal not used to produce bibenzyl was used to form toluene, thus requiring 2 equivalents of sodium for 1 mole of V*a*. The toluene was not actually isolated or estimated quantitatively.

NOTE: V*a*, methyl *S*-benzyl-4,6-*O*-ethylidene-3-thio-α-D-altropyranoside; VII*a*, methyl 4,6-*O*-ethylidene-3-thio-α-D-altropyranoside.

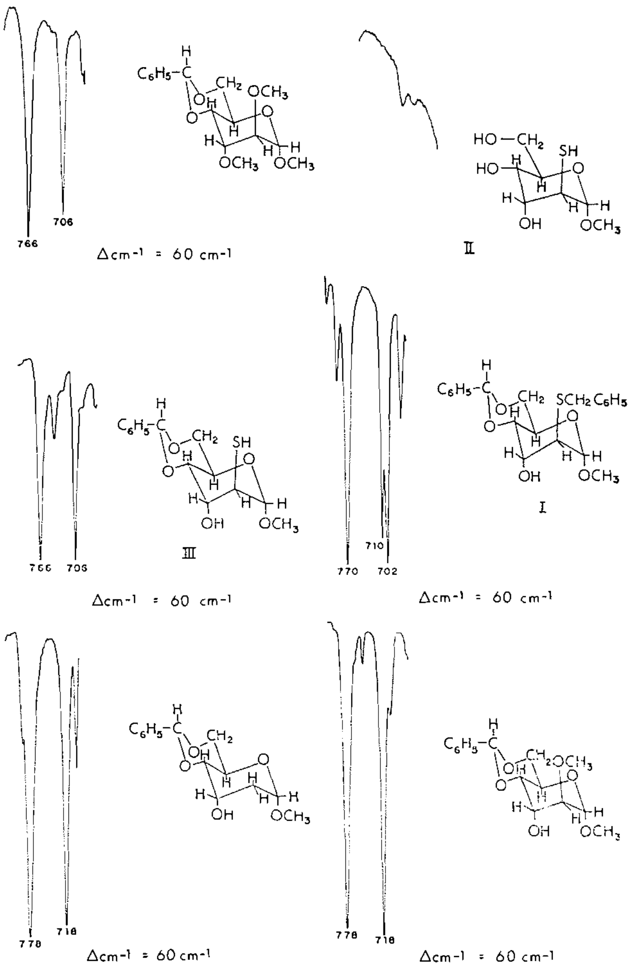

FIG. 1. Infrared absorption in Nujol of a number of altropyranosides in the region of 700 to 780 cm^{-1}.

ether (60–80°) to faint turbidity, gave 42.3% of methyl 4,6-*O*-ethylidene-2-*O*-(*p*-toluenesulfonyl)-α-D-glucopyranoside, m.p. 151° (lit. m.p. 150–151° (12)). (*e*) The mother liquors from the precipitated mono- and di-*p*-toluenesulfonyl compounds, freed from solvent and the residue acetylated (12), gave 11% of methyl 3-*O*-acetyl-4,6-*O*-ethylidene-2-*O*-(*p*-toluenesulfonyl)-α-D-glucopyranoside as long needles, m.p. 171° (lit. m.p. 169–171° (12)).

Methyl 2,3-Anhydro-4,6-O-ethylidene-α-D-mannopyranoside

The following modifications of the published procedure (12) greatly simplified the preparation of pure product. Methyl 4,6-*O*-ethylidene-2-*O*-(*p*-toluenesulfonyl)-α-D-glucopyranoside (or its acetate) was treated with a 25% rather than 100% excess of sodium methoxide in refluxing methanol for 4 h. The cooled mixture (needles separated) was poured into ice water. The water mixture was extracted with chloroform and the extract dried (Na_2SO_4) and freed from solvent. The residual solid was crystallized from methanol to give needles (84%) melting at 100° (lit. m.p. 100–100.5° (12)).

Methyl S-Benzyl-4,6-O-ethylidene-3-thio-α-D-altropyranoside (Va)

Published directions (12) were followed for most of this preparation. However, the isolation and crystallization procedures were modified advantageously. The precipitate obtained when the reaction mixture was poured into ice water was washed with water and petroleum ether as described (12), dissolved in diethyl ether, and dried (Na_2SO_4). The filtered ethereal solution was diluted with an equal volume of petroleum ether (60–80°) and the resulting solution gently refluxed on a water bath. When much of the ether had been removed and the boiling point of the solvent had reached 50°, the flask and contents were allowed to cool to room temperature, whereupon V*a* separated as long colorless needles, yield 93%, m.p. 133° (lit. m.p. 132–133° (12)).

*Methyl S-Benzyl-4,6-O-ethylidene-2-O-methyl-3-thio-α-*D*-altropyranoside (Vb)*

To a solution of 16.3 g (0.05 mole) of V*a* in 90 ml of methyl iodide was added 24 g of silver oxide. The mixture, first stirred for 1.5 h at room temperature and then for 1.5 h at reflux, was filtered (cold) and the silver salts were washed with 50 ml of dry ether. The combined methyl iodide and ether solutions were freed from solvent under vacuum. The viscous oily residue showed no absorption for OH in the infrared spectrum. Chromatography on neutral alumina, activity grade I (Alupharm Chemicals, New Orleans, Louisiana), gave, by benzene elution, 11.1 g (65.3%) of an oil which solidified when cooled. Crystallization from cold hexane gave a compound melting at 84–85°; $[\alpha]_D^{24}$ −91° (*c*, 0.5 in chloroform). The infrared spectrum in Nujol showed bands at 710 cm^{-1} (phenyl) but none for OH.

Anal. Calcd. for $C_{17}H_{24}O_5S$: C, 59.97; H, 7.11; S, 9.42. Found: C, 59.84; H, 6.88; S, 9.68.

Ether elution of the column gave 2.5 g (25%) of a compound melting at 98–99° (from methanol). The infrared spectrum in Nujol was identical with that of authentic methyl 2,3-anhydro-4,6-*O*-ethylidene-α-D-mannopyranoside (ref. 12; see also above). No absorption for OH was evident. A mixed melting point was undepressed.

*Methyl S-Benzyl-4,6-O-benzylidene-2-thio-α-*D*-altropyranoside (I)*

This compound was prepared by an improved variation of the literature directions (3). Commercial sodium methoxide (Fisher Scientific Co.) (21.9 g, 0.115 mole) was dissolved in 200 ml of pure, dry methanol. A continuous current of nitrogen was passed through the apparatus, and benzyl mercaptan (67.9 g, 0.58 mole) was then added. When the solution had been stirred for 15 min, 26.4 g (0.1 mole) of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (14, 17) was added and the solution refluxed for 24 h (N_2). When cooled and poured with stirring into 1 l of ice water, the solution gave a precipitate of I. The solid was separated by filtration and dissolved in chloroform; this was combined with chloroform extracts (2 × 250 ml) of the filtrate. After the organic solution had been washed with water, it was dried (Na_2SO_4), separated from the drying agent, and freed from solvent under vacuum in a rotary evaporator. The semisolid residue was triturated with 500 ml of petroleum ether (60–80°), whereupon solidification occurred, yield (crude) 39 g (~100%). Recrystallization from 250 ml of absolute ethanol gave needles (35 g, 90%) melting at 136–137°; $[\alpha]_D^{25}$ +94.7° (*c*, 1 in chloroform) (lit. m.p. 136–137°; $[\alpha]_D^{24}$ +90.6° (*c*, 1.668 in chloroform) (3)). The infrared spectrum in Nujol showed absorption at 3 505 cm^{-1} (OH), 770 cm^{-1} and 710 cm^{-1} (phenyl of the benzylidene group), and 702 cm^{-1} (phenyl of the benzyl group).

Sodium – Liquid Ammonia Reduction

*Methyl 4,6-O-Ethylidene-2-O-methyl-3-thio-α-*D*-altropyranoside (VIIb) from Methyl S-Benzyl-4,6-O-ethylidene-2-O-methyl-3-thio-α-*D*-altropyranoside (Vb) (a Typical Procedure for Estimation of the Consumption of Sodium by Reaction in Liquid Ammonia)*

A dry, 500 ml, three-necked, round-bottomed flask (A) was fitted with a gas inlet tube (C), mercury seal stirrer, and dry ice condenser (B) whose outlet accommodated a tube containing sodium hydroxide pellets as protection against moisture from the atmosphere. The apparatus (A and B) was gently heated with a free flame for 5 min while a current of dry nitrogen was passed through via C to drive out surface moisture. When the system had been cooled (under a constant flow of dry nitrogen) gaseous ammonia from a cylinder of commercial anhydrous liquid ammonia was collected (150 ml) in a dry ice – acetone cooled receiver (D) fitted with a dry ice – acetone condenser (E) whose outlet was protected by a sodium hydroxide pellet tube. Metallic sodium was added to the liquid in D to destroy moisture, and then the ammonia was distilled, by using a cold water bath gradually warmed to 50°, into the dried vessel (A) previously cooled in a dry ice – acetone bath. A few milligrams of metallic sodium were added at intervals to A until the blue color persisted (for about 1 h). To this flask was then added 3.4 g (0.01 mole) of V*b*. A clear solution was obtained. Freshly cut sodium (0.46 g) was weighed in dry toluene, and from this four small pieces of about 100 mg each were added to the reaction mixture in A, one at a time only when the blue color caused by each preceding piece of metal had disappeared. Then the size of each subsequent piece of metal was reduced to ~10 mg and these were added until the blue color persisted for at least 15 min. In all, 440 mg was necessary, over a total reaction time of about 20 min.

The reaction mixture was then decomposed with excess ammonium chloride (5 g) and the ammonia allowed to evaporate in a current of nitrogen. The residue was dissolved in chloroform, and filtered free of solid; then the solvent was removed under vacuum. The remaining solid, when crystallized from cold ether, gave 2.35 g (98%) of VII*b*, m.p. 103–104°, $[\alpha]_D^{24}$ +113.7° (*c*, 1 in chloroform). Absorption in the infrared (Nujol) occurred at 2 600 cm^{-1} (SH) but none between 700 and 800 cm^{-1} for phenyl.

Anal. Calcd. for $C_{10}H_{18}O_5S$: C, 47.98; H, 7.25; S, 12.81. Found: C, 48.13; H, 6.96; S, 12.72.

The residual ethereal filtrate was evaporated and the residue triturated with 20 ml of petroleum ether (60–80°) to dissolve bibenzyl. The petroleum ether extract was freed from solvent to give 80 mg (8.3%) of bibenzyl, m.p. 51° (mixed melting point undepressed).

Methyl 4,6-O-Ethylidene-3-thio-α-D-altropyranoside (VIIa) from Methyl S-Benzyl-4,6-O-ethylidene-3-thio-α-D-altropyranoside (Va)

Method A: with sodium and liquid ammonia.—The reduction of this compound was carried out by using the apparatus and typical procedure described above. The 3.26 g (0.01 mole) of V*a* required 440 mg (0.02 mole) of sodium over a 15 to 20 min period. The reaction mixture was worked up accordingly to the preceding description to give a solid, after removal of the chloroform solvent, which, when dissolved in ether and diluted with petroleum ether (60–80°) to slight turbidity, gave 2.26 g (95.5%) of VII*a* as needles melting at 106–107°; $[\alpha]_D^{24}$ −123° (*c*, 1 in chloroform).

Anal. Calcd. for $C_9H_{16}O_5S$: C, 45.75; H, 6.83; S, 13.57. Found: C, 45.83; H, 6.91; S, 13.72.

Infrared absorption occurred at 3 465 cm^{-1} (OH) and 2 600 cm^{-1} (SH). There was no absorption for phenyl.

The residual ethereal filtrate, worked up as before, gave 80 mg of bibenzyl.

Method B: with sodium and liquid ammonia and modification to isolate the product toluene.—The preparation of the system and the reduction of the thioether V*a* (3.26 g, 0.01 mole) were carried out exactly as in the typical procedure above, except that the sodium was weighed and cut up in Skellysolve B. The work-up differed as follows. After the decomposition of the reaction mixture with ammonium chloride, the condenser (B) was filled with an ice–salt freezing mixture to retain the toluene but permit vaporization of the ammonia. The stream of nitrogen that was passed through the solution was discontinued, since it might promote loss of toluene by entrainment. The ammonia was allowed to volatilize and escape through B, without the use of a warmed water bath, by allowing the apparatus to remain overnight exposed to room temperature conditions. The residue in A was stirred with dry ether (200 ml) for half an hour and the solution then filtered. Careful fractionation removed the ether (which showed no peak for toluene by gas–liquid chromatography) until the residue was concentrated to about 15 ml. To this residue was added 0.499 g of ethylbenzene as internal standard; the resulting solution was analyzed by gas–liquid chromatography. An authentic mixture of known amounts of toluene and ethylbenzene was used for comparison. A total of 540 mg (58%) of toluene was thus determined. Removal of the ethylbenzene, toluene, and ether by distillation *in vacuo* gave a residue which was washed with water to eliminate the water-soluble VII*a*. The solid remaining (100 mg, 11%) was bibenzyl, m.p. 51°.

Method C: with sodium and liquid ammonia diluted with 1,2-dimethoxyethane.—A quantity of dry ammonia (250 ml) was put into a 1 l, three-necked, round-bottomed flask according to the typical procedure above. To this was added, via a dried dropping funnel, 100 ml of dry 1,2-dimethoxyethane (distilled from potassium metal) followed by a solution of 3.26 g (0.01 mole) of V*a* in 100 ml of dry 1,2-dimethoxyethane. An additional 50 ml of 1,2-dimethoxyethane was used to rinse the funnel, thus giving a 1:1 mixture (by volume) of ammonia and 1,2-dimethoxyethane in the reaction flask. To this solution was added freshly cut sodium (230 mg, 0.01 mole) in four pieces, one at a time, according to the typical procedure. The time required for this sodium to react was 45 min. The mixture was then decomposed with ammonium chloride as usual and the ammonia allowed to escape overnight, without the use of a warmed water bath, by using a constant current of dry nitrogen gas. About 150 ml of chloroform was then added and the mixture stirred for 1 h. This process eliminated the rest of the ammonia (pH paper test). The material was filtered, and chloroform (100 ml) was used to rinse the flask and to wash the collected solid. Removal of the chloroform and 1,2-dimethoxyethane on a rotary evaporator under vacuum left a semisolid. Trituration with water dissolved the mercaptan, and unreacted V*a* and bibenzyl remained as a solid. The mixture was filtered, and the aqueous filtrate concentrated *in vacuo* until the residue solidified. The crude yield was 1.59 g (67.3%). Crystallization from a mixture of ether and petroleum ether (60–80°) gave 1.55 g (66%) of material melting at 106–107°. The infrared spectrum and mixed melting point showed this to be identical with VII*a*.

Anal. Calcd. for $C_9H_{16}O_5S$: C, 45.75; H, 6.83; S, 13.57. Found: C, 46.00; H, 6.87; S, 13.66.

The mixture of unreacted material and bibenzyl left after removal of the aqueous solution was heated in 50 ml of refluxing petroleum ether (60–80°). The cooled mixture was filtered, leaving 1.07 g (32.6%) of solid melting at 132–133° and identical (infrared, mixed melting point) with starting material (V*a*). The petroleum ether filtrate was freed from solvent, leaving 300 mg (32%) of solid bibenzyl melting at 51°.

When the solvent was composed of 250 ml of ammonia and 200 ml of 1,2-dimethoxyethane, and 3.26 (0.01 mole) of V*a* and 0.31 g (0.0134 mole) of sodium were used, an 86% yield of VII*a*, 0.451 g (14%) of unchanged V*a*, and 400 mg (42%) of bibenzyl were obtained.

Table III illustrates the influence of solvent composition and amount of metal on the proportion of products in the ammonia–1,2-dimethoxyethane–sodium reduction of V*a* to VII*a*.

Methyl 4,6-O-Benzylidene-2-thio-α-D-altropyranoside (III) from Methyl S-Benzyl-4,6-O-benzylidene-2-thio-α-D-altropyranoside (I)

Method A: with sodium and liquid ammonia.—Details of the procedure followed those in method A for the reduction of the 3-benzylthioaltroside V*a* described above. The 19.4 g (0.05 mole) of I in 600 ml of ammonia consumed a total of 6.7 g (0.29 mole) of sodium in 200 mg pieces over a period of 15 min. The solution, after decomposition with excess ammonium chloride, was extracted with hot chloroform (4 × 250 ml). The solid left after removal of the chloroform from these extracts was triturated with 100 ml of petroleum ether (60–80°) to remove any bibenzyl, and the residue was dissolved in 50 ml of hot ethanol. When cooled overnight in a refrigerator, the solution yielded II as long colorless needles (8.4 g). A second crop (1.37 g) was obtained upon concentration of the mother liquor. The total yield was 9.87 g (94%) of material melting at 146–147° (lit. m.p. 145–146° (3), 145–148° (4)). The infrared spectrum in Nujol showed absorption at 3 415 cm^{-1} (OH) and 2 570 cm^{-1} (SH) but no phenyl absorption.

Method B: with sodium and liquid ammonia and modifications to isolate toluene and bibenzyl.—The procedure used in method B for the reduction of the 3-benzylthioaltroside V*a* was followed here. A total of 1.34 g (0.058 mole) of sodium was required by 3.88 g (0.01 mole) of compound I in 150 ml of ammonia. After decomposition of the reaction mixture with ammonium chloride, 250 ml of dry ether was added to the flask and the ammonia allowed to evaporate through the condenser B cooled by a salt–ice freezing mixture. The residual ethereal mixture was filtered and the solid residue extracted with 200 ml of hot chloroform. Removal of the chloroform from this extract and crystallization of the resulting material from ethanol gave II as colorless needles (1.822 g, 87%), m.p. 146–147°. The ethereal extract was reduced in volume and ethylbenzene added as internal standard according to the details of method B for compound V*a*; 1.02 g (~56%) of toluene and 0.163 g (~9%) of solid bibenzyl, m.p. 51–52°, were obtained.

Method C: with sodium and liquid ammonia diluted with 1,2-dimethoxyethane.—The apparatus and the procedure used for the preparation of the ammonia–1,2-dimethoxyethane solution and subsequent reduction were the same as those in method C described for the reduction of V*a*.

To a mixture of 300 ml of ammonia and 250 ml of 1,2-dimethoxyethane containing 7.76 g (0.02 mole) of I was added 0.69 g (0.03 mole) of sodium cut into seven pieces, each piece being added in accordance with previous directions. The time required for total addition was 2.5 h. The decomposition and solvent elimination also followed cited directions. The solid that was obtained was dissolved in 50 ml of hot ethanol (rather than being triturated with water), and the solution was cooled to room temperature to give 2.3 g of the selectively reduced compound III as needles, m.p. 167–169°. The ethanol was removed from the filtrate with a rotary evaporator under vacuum, and the residue was dissolved in benzene and subjected to chromatography on 100 g of neutral alumina, activity grade II (Alupharm Chemicals, New Orleans, Louisiana). Initial benzene elution gave bibenzyl and unreacted I. With continued elution by benzene the mercaptan III began to appear, as shown by infrared absorption at 2 500 cm^{-1}, whereupon ether replaced benzene as the eluant to hasten the exit of the rest of component III still on the column (1.9 g). The total yield of III was 4.2 g (70.5%). Crystallization of the combined material from ethanol raised the melting point slightly to 168–169°; $[\alpha]_D^{21}$ +80.5° (*c*, 1 in chloroform).

Anal. Calcd. for $C_{14}H_{18}O_5S$: C, 56.37; H, 6.08; S, 10.74. Found: C, 56.23; H, 6.04; S, 10.76.

The infrared spectrum in Nujol showed absorption at 3 483 cm^{-1} (OH), 2 540 cm^{-1} (SH), and 766 cm^{-1} and 706 cm^{-1} (monosubstituted phenyl for the benzylidene group), but none at 702 cm^{-1} (monosubstituted phenyl for benzyl group). The integrated nuclear magnetic resonance spectrum in $CDCl_3$, with tetramethylsilane as reference, agreed with the structure assigned. Signals appeared at $\tau = 2.35$ to 2.75 (multiplet for five phenyl protons), $\tau = 6.58$ (singlet for three methyl protons), and $\tau = 7.95$ and 8.15 ($J = 10$ c.p.s.) (doublet for SH proton).

The combined benzene eluates, freed from solvent, gave a solid which was heated with 50 ml of refluxing petroleum ether (60–80°). Separation by filtration left 1.61 g (21%) of unreacted I (undepressed melting point and identical infrared spectrum). From the petroleum ether filtrate was obtained, upon solvent removal, 0.87 g (48%) of bibenzyl, m.p. 51°.

Final methanol elution of the column above gave 0.47 g of unidentified oil which showed absorption for SH (2 540 cm^{-1}).

Table II illustrates the effect on product yield of different proportions of mixed solvent and starting materials with compound I as the reducible substance.

Selective Reduction of I with Lithium in Liquid Ammonia – 1,2-Dimethoxyethane

A solution of compound I in ammonia–1,2-dimethoxyethane, with the same quantities of materials as in the preceding experiment for method C, was treated with 0.208 g (0.03 mole) of lithium according to the detailed directions in method C. The solid obtained upon decomposition of the reaction mixture and removal of the 1,2-dimethoxyethane and chloroform used for extraction was heated with benzene to permit separation of the lithium chloride by filtration. The benzene was removed from the filtrate and the solid residue was dissolved in 100 ml of hot ethanol. When cooled, the solution deposited 2.7 g of III as needles, m.p. 168–169°. Chromatography of the residue as described above (method C) gave a further 1.81 g of III. The total yield of the mercaptan was 4.51 g (75.7%). Unreduced starting material amounted to 1.248 g (16%), and bibenzyl to 1.09 g (59%). Here again the same unidentified oil (420 mg) was obtained via the final methanol elution.

Reduction of Methyl 4,6-O-Benzylidene-α-D-glucopyranoside (IV)

Method A: with sodium in liquid ammonia.—Details of the procedure were the same as those in method B for the reduction of I to obtain the products II, toluene, and bibenzyl. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (11) (5.64 g, 0.02 mole) in 300 ml of ammonia required 1.785 g (0.0776 mole) of sodium over a period of about 15 min. The ethereal extract obtained after removal of the solid by filtration gave, by gas–liquid chromatographic analysis, 1.14 g (62%) of toluene and 0.053 g (~3%) of bibenzyl.

Methanol extraction of the solid obtained after separation of the ether filtrate gave 3.08 g (79%) of methyl α-D-glucopyranoside melting at 164–165° (lit. m.p. 165° (11)).

Method B: with sodium and liquid ammonia containing 1,2-dimethoxyethane.—Details for this experiment followed those in method C for the reduction of I to obtain III. A solution of 5.64 g (0.02 mole) of IV in 300 ml of ammonia diluted with 200 ml of 1,2-dimethoxyethane consumed 1.770 g (0.0756 mole) of sodium over a period of 4 h. After evaporation of the ammonia, however, the residue was extracted with ether to remove bibenzyl.[4] This amounted to 0.30 g (16%). The glycoside that was produced was not isolated in this case and was believed to be only methyl α-D-glucopyranoside. We were concerned in this experiment only with the amount of bibenzyl formed in an ammonia–1,2-dimethoxyethane mixture compared with the amount produced in ammonia alone under otherwise identical conditions.

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[4] *No attempt was made to isolate or to estimate toluene on the assumption that it must have been present as part of the product. Its amount was assumed to be equal to that portion of the benzylidene group which did not form bibenzyl. The latter compound was readily obtained almost quantitatively.*