(OH), 3.5–3.9 and 6.25–6.35 (NH_3^+), 3.9–4.0 (SH); these were broad bands and not well resolved; $[\alpha]^{23}D$ +103° (1% in methanol). On paper chromatography[25] in solvents A and B, the compound traveled as a single spot with R_{ad} 0.81 and 1.38, respectively.

Anal. Calcd. for $C_7H_{16}ClNO_4S$: C, 34.2; H, 6.56; Cl, 14.4; N, 5.70; S, 13.1. Found: C, 33.9; H, 6.66; Cl, 14.1; N, 5.24; S, 13.0.

3-Amino-1,6-anhydro-2,3-dideoxy-2-mercapto-D-allopyranose Hydrochloride (XIII).—A solution of 0.390 g. (1.59 mmoles) of the glycoside IX in 20 ml. of 6 *N* hydrochloric acid was heated at 120° (bath temperature) for 1.5 hours. The slightly yellow solution was decolorized with Norit, filtered through Celite and the filtrate evaporated to dryness *in vacuo* giving a partially crystalline pale yellow sirup. The residue was triturated with several portions of ether, then evaporated *in vacuo* affording 0.34 g. (100%) of a pale yellow crystalline solid, m.p. 175–190° dec., $[\alpha]^{22}D$ −112° (1% in water); $\lambda_{max(\mu)}^{Nujol}$ 3.07 (OH); 3.65–3.80, 6.32, and 6.59 (NH_3^+); 3.94 (SH). On paper chromatography in solvents A and B, the material moved as a single spot with R_{ad} 0.77 and 1.30, respectively, not cleanly separated from IX.

Anal. Calcd. for $C_6H_{12}ClNO_3S$: C, 33.7; H, 5.66; Cl, 16.6; S, 15.0. Found: C, 33.1; H, 6.24; Cl, 17.0; N, 6.12; S, 14.6.

Acetylation of the anhydride XIII with acetic anhydride and sodium acetate gave an amorphous solid whose infrared spectrum showed the O-acetyl, S-acetyl and N-acetyl carbonyl absorptions in an approximately 1:1:1 ratio. The material, however, could not be obtained as a crystalline solid.

(25) Paper chromatography was run by the descending technique on Whatman No. 1 paper using the solvent systems A, isopropyl alcohol–2 *N* hydrochloric acid (65:35) and B, 1-butanol–acetic acid–water (5:2:3). Spots were detected with the sodium azide–iodine spray[26] and were located relative to adenine (R_f adenine = 1.00).

(26) E. Chargaff, C. Levine and C. Green, *J. Biol. Chem.*, **175**, 67 (1948).

Acknowledgments.—The authors wish to thank Dr. Peter Lim for interpretation of the infrared spectra and his staff for the paper chromatography and rotation data; Mr. O. P. Crews and his staff for the large-scale preparation of certain intermediates; and Dr. Leonard T. Capell of "Chemical Abstracts" for help in assigning appropriate nomenclature to some of the compounds.

[CONTRIBUTION FROM LIFE SCIENCES DIVISION, STANFORD RESEARCH INSTITUTE, MENLO PARK, CALIF.]

Potential Antiradiation Drugs. III. β-Aminomercaptans Derived from D-Altrose[1,2]

BY JAMES E. CHRISTENSEN AND LEON GOODMAN

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Two methods were explored for the preparation of a glycoside of 3-amino-2,3-dideoxy-2-mercapto-D-altrose. In the first, unsuccessful approach, a synthesis for the unique sugar episulfide VI was developed. Ammonolysis of VI, however, afforded polymeric products containing amino and mercaptan groups. The successful approach employed a *trans*-benzylthiotosylate (XVII) which was converted to a *trans*-benzylthioazide (XIX). A change of blocking groups gave the *trans*-benzylthioazide XXIII, which, treated with sodium and liquid ammonia and the product XXII deblocked with methanolic hydrogen chloride, afforded the desired aminomercapto glycoside (XXI, R = CH_3).

The preceding article[3] described the synthesis as a potential antiradiation drug of a β-aminomercaptan derived from D-allose. It was of interest to study the effect, if any, of the sugar stereochemistry on the radiation protection properties of these sugar β-aminomercaptans; this report describes the synthesis of a β-aminomercapto glycoside derived from D-altrose which is closely related to the compounds described in the previous paper.[3]

Ammonolysis of a sugar episulfide was visualized as the first approach to the preparation of the desired *trans*-β-aminomercapto sugar system. The ring opening of aliphatic episulfides with primary and secondary amines has been reported by several groups[4,5] to give good yields of aminomercaptans. By analogy with the ammonolysis of epoxides, the aminomercaptans derived from cyclic episulfides should have the new functional groups in the *trans* configuration.

The synthesis of an appropriate sugar episulfide was accomplished starting from the available anhydromannoside I.[6] Reaction of I with ammonium thiocyanate in aqueous 2-methoxyethanol gave an excellent yield of a crystalline solid whose infrared spectrum showed the thiocyanate band at 4.66 μ. The initial reaction product had a wide melting range and required several recrystallizations to afford the narrowly melting analytical sample. However, a widely melting sample gave correct analyses for the expected thiocyanohydrin. These facts indicated that ring-opening of I had taken place at both C.2 and C.3 to give a mixture of two thiocyanohydrins. A fair yield of a sharply melting compound was easily obtained from the mixture by recrystallization and was assumed to be the thiocyanohydrin II by analogy with the predominant opening of I at C.3 by other nucleophiles.[7] The *trans*-diaxial structure II would be the product predicted by the Fürst–Plattner rule.[8] Proof of structure II was provided by desulfuri-

(1) This work was carried out under the joint auspices of the Office of the Surgeon General, Medical Research and Development Command, under Contract No. DA-49-193-MD-268 and of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, under Contract No. SA-43-ph-1892. The opinions expressed in this article are those of the authors and not necessarily those of either sponsoring agency.

(2) For a preliminary announcement of a part of this work, see J. E. Christensen and L. Goodman, *J. Am. Chem. Soc.*, **82**, 4738 (1960).

(3) L. Goodman and J. E. Christensen, *ibid.*, **83**, 3823 (1961).

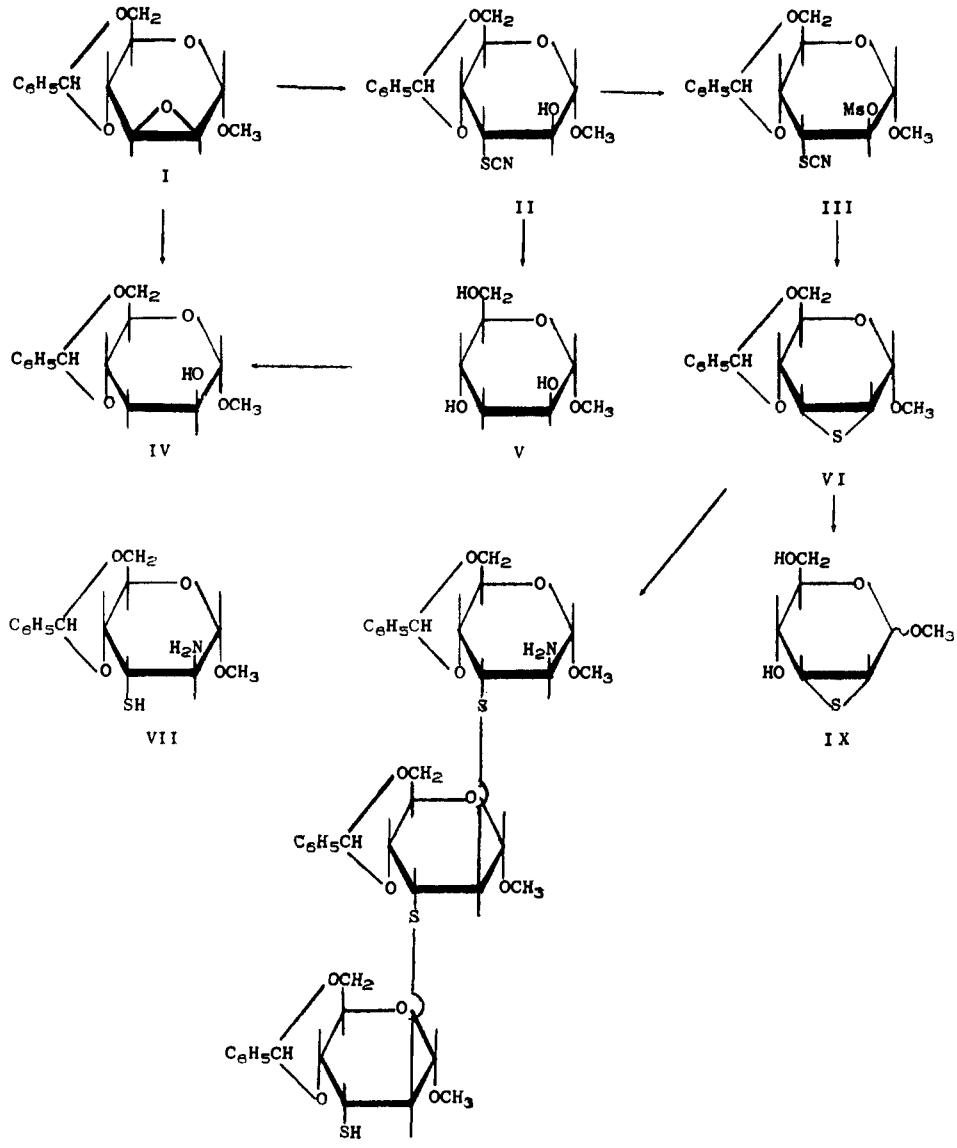
(4) H. R. Snyder, J. M. Stewart and J. B. Ziegler, *ibid.*, **69**, 2672 (1947).

(5) F. Iu. Rachinskii, N. M. Slavachevskaia and D. V. Ioffe, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*), **28**, 3027 (1958).

(6) H. R. Bolliger and D. A. Prins, *Helv. Chim. Acta*, **28**, 465 (1945).

(7) W. H. Myers and G. J. Robertson, *J. Am. Chem. Soc.*, **65**, 8 (1943).

(8) A. Fürst and Pl. A. Plattner, Abstracts of Papers, 12th International Congress of Pure and Applied Chemistry (New York), 1951, p. 409.



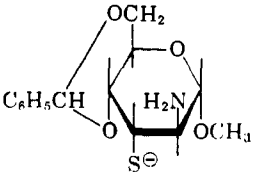
zation of the thiocyanohydrin with Raney nickel which was accompanied by loss of the benzylidene blocking group, affording the glycoside V as a sirup. The treatment of V with benzaldehyde and zinc chloride gave the crystalline IV identical with a sample prepared by the ring-opening of I with lithium aluminum hydride.[9] The reaction of many epoxides with thiocyanate ion gives the episulfide as the direct product,[10] but the rigidity imposed by the 4,6-benzylidene group obviously prevents the interaction of the hydroxy group at C.2 and the thiocyanate group at C.3 which is a necessary step in the direct epoxide–episulfide conversion.[10]

Conventional sulfonylation of II afforded an essentially quantitative yield of the mesylate III as a sirup whose infrared spectrum showed the absence of hydroxyl. Reaction of the sulfonate III, dissolved in 2-methoxyethanol, with aqueous sodium hydroxide[11] gave a fair yield of a crystalline solid whose elemental analyses and infrared spectrum were completely compatible with the episulfide structure VI.

Ammonolysis of VI, which might have been expected to yield some of the desired aminomercaptan VII, gave disappointing results. The low reactivity of VI made it necessary to carry out the reaction in a bomb. Under these conditions, the isolated product was a series of widely melting solids which gave positive nitroprusside reactions and whose infrared spectra showed weak evidence for amine and sulfhydryl groups. These compounds were obviously the result of the intervention of more than one molecule of VI in the ammonolysis. Indeed, the one fraction that was purified gave correct analysis for the three-sugar structure VIII.[12] This polymerization of VI, initiated by

(9) D. A. Prins, *J. Am. Chem. Soc.*, **70**, 3955 (1948).
(10) E. E. van Tamelen, *ibid.*, **73**, 3444 (1951).
(11) L. Goodman and B. R. Baker, *ibid.*, **81**, 4924 (1959).
(12) The wide melting range of the product is evidence that a mixture of isomers is present, but structure VIII is written on the assump-

the ion X, a much better nucleophile than ammonia, precluded any hope of preparing VII from VI.

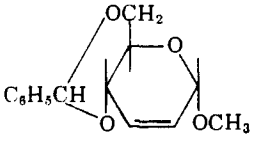


X

Attempts to open VI with dimethylamine in a sealed system at 100° were also unsuccessful, with only starting material VI isolated.

When the cyclic sulfide VI was heated in 80% aqueous methanol with an acid ion-exchange resin, the deblocked episulfide IX was isolated as a widely melting, crystalline solid, possibly as a mixture of anomers. It was hoped that IX would possess a reactivity that would permit its ammonolysis by the slow addition of IX to a large excess of ammonia under atmospheric conditions. However, the reaction of IX with ammonia again required the use of a sealed system and led to polymeric products.

The reaction of VI with triethyl phosphite under relatively mild conditions gave a good yield of the interesting sugar olefin XI. Compound XI rapidly decolorized aqueous potassium permanganate and bromine in carbon tetrachloride. The



XI

n.m.r. spectrum of XI showed the expected vinyl resonances centered at τ[13] 3.94 and 4.31, each of unit area. At least in this reaction with triethyl phosphite, compound VI then exhibited a reactivity comparable to that of a simple aliphatic episulfide.[14] The oxygen analog of VI, methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (XII),[15] however, under substantially more severe conditions than were used with VI, was recovered after treatment with triethyl phosphite. This latter reagent has been used previously to convert epoxides to olefins.[16]

The successful approach to the preparation of the desired *trans*-β-aminomercaptoaltroside XXI also utilized a sugar epoxide in the first step of the synthesis. Reaction of the anhydroalloside XII with sodium benzyl mercaptide afforded an excellent yield of a sharply melting, crystalline solid whose structure was assumed to be the 2-benzylthio glycoside XIII by analogy with other attacks of nucleophiles on XII.[7,8] Raney nickel desulfurization of XIII was accompanied by removal of the benzylidene blocking group, giving the 2-deoxy glycoside XIV as an oil which rapidly consumed one mole of periodate ion, confirming structures XIV and XIII.

Tosylation of XIII afforded a quantitative yield of crystalline solid that was not stable to storage at room temperature for more than a few days; its infrared spectrum showed the strong sulfonate ester band at 8.47 μ that would be expected for structure XVII. The isolation of the *trans*-tosylate XVII was surprising; the usual reaction product of a sulfonyl chloride and a *trans*-alkylthio alcohol is the *trans*-alkylthio chloride which is probably formed *via* the intervention of an episulfonium ion.[17] Evidently in the tosylation of XIII, conformational hindrance to formation of the episulfonium ion XVI permits the formation of XVII. At higher temperatures, however, the ion XVI probably is formed as an intermediate, since reaction of XVII with sodium azide at 100–115° in 2-methoxyethanol led to a good yield of a crystalline and sharply melting azide which could be reduced to a crystalline amine with lithium aluminum hydride. Raney nickel desulfurization of either the azide or the amine in aqueous dioxane formed qualitatively the same mixture of products. A low yield of a crystalline desulfurized amine, which is assigned structure XXIV, was isolated along with a mixture of deblocked glycosides whose low nitrogen analysis suggested that some elimination of ammonia had occurred in the course of the desulfurization reaction. The amino glycoside, presumably XVIII, was separated by means of an ion-exchange resin affording a crystalline solid. Periodate oxidation of the amino glycoside resulted in a rapid consumption of one mole of oxidant, as would be expected for the *cis*-aminoalcohol moiety of XVIII. Although these data do not exclude the isomeric methyl 3-amino-2,3-dideoxy-α-D-gluco(manno)pyranoside for the structure of the desulfurized and deblocked amino glycoside, the ease of displacement of the tosylate in XVII can only be reconciled with a displacement *via* the episulfonium ion XVI followed by the *trans*-diaxial opening at C.3 to give XIX (and therefore XV, XXIV and XVIII). Simple SN2 displacements of secondary sugar sulfonate esters (such as would be required to give eventually the (gluco)-mannoisomer of XVIII) require much more stringent conditions than were used in the formation of XIX.[18]

In the original sequence visualized for the preparation of the *trans*-aminomercaptans, removal of the benzyl group of XV with sodium and liquid ammonia was contemplated. In practice the conversion of XV to a mercaptan was successful, as determined by a positive nitroprusside test, but the simultaneous removal of the benzylidene blocking group made it virtually impossible to separate the very water-soluble and easily air-oxidized product from the inorganic salts. Application of the sodium–liquid ammonia reduction to the glycoside XIII also resulted in deblocking, affording a

tion that the predominant attack on the episulfide VI would occur at C.2 to give the *trans*-diaxial product.[7,8]

(13) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

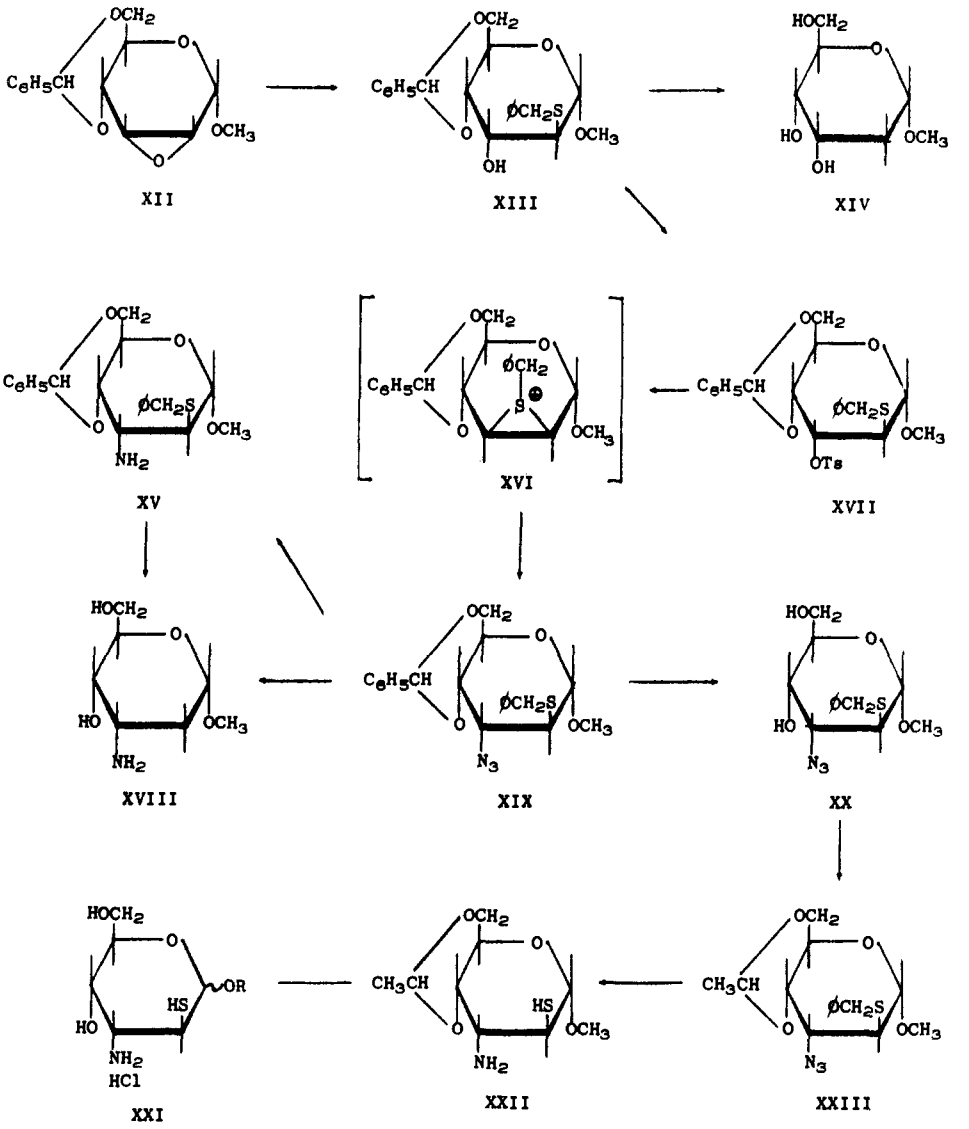
(14) N. P. Neureiter and F. G. Bordwell, *J. Am. Chem. Soc.*, **81**, 578 (1959).

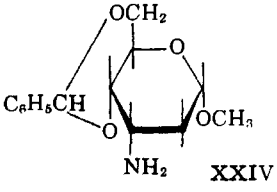
(15) N. K. Richtmyer and C. S. Hudson, *ibid.*, **63**, 1727 (1941).

(16) C. B. Scott, *J. Org. Chem.*, **22**, 1118 (1957).

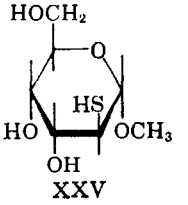
(17) (a) L. Goodman, A. Benitez and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 1680 (1958); (b) C. D. Anderson, L. Goodman and B. R. Baker, *ibid.*, **81**, 898 (1959).

(18) For a review of the subject, see R. S. Tipson, *Adv. in Carbohydrate Chem.*, **8**, 107 (1953).





fair yield of the crystalline mercaptan XXV, whose greater stability to air oxidation permitted its isolation from an aqueous solution by a lengthy continuous extraction with chloroform.



In order to provide a blocking group that would be stable to sodium and liquid ammonia, the azide XIX was treated with an acid ion-exchange resin in aqueous methanol, affording an excellent yield of a sirup that gave correct analysis for the deblocked glycoside XX, and that probably contained some of the β-anomer. The sirup then was treated with 1,1-dimethoxyethane in the presence of a trace of sulfuric acid,[19] giving an essentially quantitative yield of the blocked azido glycoside XXIII. The reaction of XXIII with sodium in liquid ammonia cleaved the benzylthio group and reduced the azide group, affording a nitroprusside-positive sirup that was easily extracted from aqueous solution and had good infrared evidence for amino and sulfhydryl groups, as would be expected for structure XXII. The mercaptan XXII was converted rapidly to the nitroprusside-negative disulfide, also a sirup, on exposure to air. Efforts to obtain crystalline derivatives of XXII or the disulfide derived from it were without success. Deblocking of XXII with methanolic hydrogen chloride afforded a gum (XXI, R = CH_3) which was dissolved in hot ethanol[20] and reprecipitated

(19) D. O'Meara and D. M. Sheperd, *J. Chem. Soc.*, 4232 (1955).

(20) When the precipitation of XXI (R = CH_3) was attempted from methanol it was very difficult to obtain a solid product.

with ether, yielding a nitroprusside-positive amorphous solid with correct analysis for a solvated form of the glycoside (XXI, R = CH_3) and which was chromatographically homogeneous. Alternatively, the deblocking of XXII with ethanolic hydrogen chloride afforded the same solid (XXI, R = CH_3). The analyses of various preparations of the glycoside (XXI, R = CH_3) showed the proper N:S:Cl ratios but indicated the presence of various amounts of diethyl ether. The n.m.r. spectrum of a solution of one of these preparations in deuterium oxide clearly showed the presence of the glycoside O-methyl group at τ = 6.60 with some indication of the O-methylene ether quadruplet in this region. The triplet attributable to the C-methyl group of ether was cleanly resolved at τ = 8.82. The integrated value of the peak areas in the n.m.r. spectrum also was in agreement with the presence of ether in the sample of XXI (R = CH_3). Attempts to characterize XXI (R = CH_3) as a crystalline derivative were unsuccessful. The attempted hydrolysis of XXI with aqueous hydrochloric acid to form the free sugar (XXI, R = H) gave a dark sirup which did not have the correct analysis for XXI (R = H); it may have contained the 1,6-anhydride of the free sugar. The analogous treatment of the related glycosides of 3-amino-D-altrose affords the 1,6-anhydride of the amino sugar.[21]

Experimental[22]

Methyl 4,6-O-Benzylidene-3-deoxy-3-thiocyano-α-D-altropyranoside (II).—A mixture of 0.50 g. (1.89 mmoles) of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (I),[6] 0.80 g. (10.5 mmoles) of ammonium thiocyanate, 10 ml. of 2-methoxyethanol and 1.5 ml. of water was heated at 105–110° for 7.5 hours. The pale yellow solution was cooled, water (25 ml.) was added, and the solution was chilled. The crystalline precipitate was collected, yielding 0.47 g. (89%) of product, m.p. 175–186°. Recrystallization from 5 ml. of absolute ethanol afforded two crops of crystals: (1) 0.28 g. (53%), m.p. 187–189°, and (2) 0.08 g. (15%), m.p. 180–187°. The first crop was recrystallized again from absolute ethanol to give 0.22 g. (42%) of the analytical sample, m.p. 188–190°; $\lambda_{max(\mu)}^{Nujol}$ 2.97 (OH), 4.66 (SCN), 13.08 and 14.20 (monosubstituted phenyl); there was no epoxide band near 11.8 μ; $[\alpha]^{28}D$ 0° (1% in chloroform).

Anal. Calcd. for $C_{15}H_{17}NO_5S$: C, 55.7; H, 5.30; S, 9.92. Found: C, 55.8; H, 5.30; S, 9.61.

From another run using 5.0 g. of the anhydromannoside, 4.11 g. (67%) of product, m.p. 181–188°, was isolated after one recrystallization from absolute ethanol.

Anal. Found: C, 56.0; H, 5.39; S, 10.0.

Proof of Structure of the Thiocyanohydrin (II).—A stirred mixture of 2.00 g. (6.19 mmoles) of the thiocyanohydrin II, approximately 20 g. of Raney nickel[23] and 100 ml. of ethanol was heated at reflux for 17 hours, then filtered through Celite. The filtrate was evaporated to dryness *in vacuo* affording 1.50 g. of a pale green sirup whose infrared spectrum showed the absence of the –SCN band at 4.66 μ and the essential absence of phenyl bands in the 13–15 μ region.

A portion of the sirup (1.1 g.) was dissolved in 4 ml. of freshly distilled benzaldehyde, 0.8 g. of freshly fused and powdered zinc chloride was added and the mixture, protected from moisture, was stirred for 2 hours at room temperature. Excess saturated aqueous sodium carbonate was added, then 10 ml. of chloroform and the mixture was transferred to a separatory funnel. The chloroform layer was separated and the aqueous layer was extracted with two 10-ml. portions of chloroform. The combined chloroform solutions were washed with water, dried over magnesium sulfate and evaporated *in vacuo* to dryness. The residue was triturated with three 10-ml. portions of Skellysolve B (b.p. 62–70°) leaving 0.42 g. (25%) of an orange sirup whose infrared spectrum indicated it to contain mainly the desired product. The combined Skellysolve B extracts, after evaporation to dryness and removal of benzaldehyde in high vacuum, left 0.79 g. (48%) of a sirup which crystallized on standing. Recrystallization of the combined crops from ether–pentane yielded 0.37 g. (22%) of crystalline solid, m.p. 95–108°. Two more recrystallizations of the solid afforded 0.17 g. of product IV, m.p. 108–109°; $\lambda_{max(\mu)}^{Nujol}$ 2.96 (OH), 13.11, 13.22 and 14.29 (monosubstituted phenyl).

The infrared spectrum was identical with that of IV from the lithium aluminum hydride reduction of the anhydromannoside (I)[9] and had a melting point of 108–110° when mixed with the latter material.

Methyl 4,6-O-Benzylidene-3-deoxy-2-O-methylsulfonyl-3-thiocyano-α-D-altropyranoside (III).—To a chilled (3–8°), stirred solution of 2.16 g. (6.69 mmoles) of crude thiocyanohydrin (II) in 20 ml. of reagent pyridine was added dropwise 1.14 ml. (14.7 mmoles) of methanesulfonyl chloride. The solution, protected from atmospheric moisture, was stirred for 1 hour at 0–3°, then kept at room temperature for 14 hours. The brown reaction mixture was poured into 100 ml. of ice and water and the organic product was extracted with two 40-ml. portions of dichloromethane. The combined extracts were washed with 40 ml. of saturated sodium bicarbonate solution and 40 ml. of water, then decolorized with Norit A and dried over magnesium sulfate. The dichloromethane solution was evaporated *in vacuo*, then twice dissolved in toluene and re-evaporated *in vacuo* to remove pyridine. The residue, 2.48 g. (95%), was a brown sirup; $\lambda_{max(\mu)}^{film}$ 4.64 (SCN), 7.37 and 8.49 (-OSO_2-), 13.1–13.3 and 14.26 (monosubstituted phenyl); there was no –OH band near 3.0 μ.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-2,3-epithio-α-D-allopyranoside (VI).—To a chilled (0°), stirred solution of 2.48 g. (6.33 mmoles) of the mesylate III in 75 ml. of 2-methoxyethanol was added dropwise during 5 minutes a solution of 13 ml. (13 mmoles) of 1 *M* aqueous sodium hydroxide. The solution was stirred at room temperature for 10 minutes, during which time it became dark red, then was poured into 100 ml. of water. The pink solid, 1.03 g. (58%), was collected and had m.p. 150–165°. The product was dissolved in 70 ml. of absolute ethanol, the solution decolorized with Norit A and filtered through Celite, and the filtrate concentrated to *ca.* 30 ml. and chilled to yield 0.67 g. (38%) of solid, m.p. 165–167°. From a previous run the analytical sample was obtained by recrystallization as above, m.p. 166–167°, $[\alpha]^{33}D$ +192° (1% in chloroform); $\lambda_{max(\mu)}^{Nujol}$ 13.31 and 14.40 (monosubstituted phenyl); there was no –OH band near 3.0 μ and no sulfonate band at 8.5 μ.

Anal. Calcd. for $C_{14}H_{16}O_4S$: C, 60.0; H, 5.75; S, 11.4. Found: C, 60.2; H, 5.79; S, 11.5.

From a large-scale run of 116.7 g. of the mesylate III there was isolated 71.4 g. (97%) of product, m.p. 154–164°.

Reaction of the Episulfide VI with Ammonia.—A mixture of 1.00 g. (3.57 mmoles) of episulfide VI and 20 ml. of methanolic ammonia (saturated at 7°) was heated in a stainless steel bomb at 100° for 24 hours. The bomb was cooled and the contents filtered to yield 0.42 g. of brown solid a, m.p. 180–210°. Evaporation of the filtrate *in vacuo* afforded 0.46 g. of brown solid b, m.p. 85–150°. The infrared spectra of the two samples were essentially identical and both samples gave weak nitroprusside tests. Solids a and b were recrystallized separately from 5 ml. of benzene with the addition of hexane to turbidity to yield 0.27 g. of solid c, m.p. 190–210°, and 0.27 g. of solid d, m.p. 156–175°, respectively. Recrystallization of c and d separately from the same solvent mixture gave 0.14 of solid e, m.p. 195–215°, and 0.10 g. of solid f, m.p. 172–190°, respectively. Both e and f had identical infrared spectra which were essentially the same as those of a and b; $\lambda_{max(\mu)}^{Nujol}$ 2.97, 3.01

(21) L. F. Wiggins, *J. Chem. Soc.*, 18 (1947).

(22) Melting points are uncorrected and were obtained with the Fisher–Johns apparatus. Optical rotations were measured with a Standard polarimeter model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions. The n.m.r. spectra were obtained using a Varian V-4311 spectrometer operated at 60 mc., with samples dissolved either in deuterium oxide or deuteriochloroform. Tetramethylsilane was used as a reference standard.

(23) Sponge nickel catalyst, Davison Chemical Co., Cincinnati 29, Ohio.

and 6.18 (NH_2, weak bands), 13.27 and 14.30 (monosubstituted phenyl).

Anal. Calcd. for $C_{28}H_{36}NO_8S_2$ (dimer): C, 58.2; H, 6.11; N, 2.42; S, 11.1. Calcd. for $C_{42}H_{51}NO_{12}S_3$ (trimer, VIII): C, 58.8; H, 5.99 N, 1.63; S, 11.2. Found: (e) C, 59.2; H, 6.08. Found: (f) C, 59.2; H, 6.20; N, 1.46; S, 10.9.

Methyl 2,3-Epithio-α-D-allopyranoside (IX).—A stirred mixture of 1.00 g. (3.56 mmoles) of the blocked episulfide VI, 100 ml. of 80% aqueous methanol and 8.5 g. of wet Amberlite IR-120 (H) resin (equivalent to 4.5 g. of dry resin) was heated at 50–55° for 55 hours, during which time the starting material slowly dissolved. The resin was removed by filtration and the filtrate evaporated *in vacuo* to afford 0.66 g. (96%) of a cream-colored solid, m.p. 90–100°. The residue was recrystallized from 30 ml. of benzene, filtering off 0.29 g. of an insoluble, brown solid to yield 0.22 g. (32%) of white crystals, m.p. 87–96°; $\lambda_{max(\mu)}^{Nujol}$ 3.10 (OH); there was no monosubstituted phenyl absorption in the 13.0–14.5 μ region.

Anal. Calcd. for $C_7H_{12}O_4S$: C, 43.7; H, 6.30; S, 16.7. Found: C, 43.6; H, 6.14; S, 17.1.

A sample of VI which had an identical infrared spectrum but m.p. 120–129° showed $[\alpha]^{24}D$ −126° (1% in chloroform) and a third sample with m.p. 114–131° had $[\alpha]^{19}D$ −124° (1% in chloroform).

Anal. Found: C, 43.4; H, 5.96; S, 16.9.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-α-D-allo(manno)-pyranoside-2-ene (XI).—A stirred mixture of 2.0 g. (7.12 mmoles) of the blocked episulfide VI and 10 g. of triethyl phosphite was heated for 10 minutes at 95° (bath temperature) during which time the starting material slowly dissolved. The mixture was heated gradually to 155° over a period of 30 minutes and was maintained at 155° for 5 minutes, then allowed to cool to room temperature. The cooled mixture contained a white precipitate, 0.95 g. (54%), m.p. 119–120°, which was separated by filtration and washed thoroughly with petroleum ether (30–60°). A second crop, 0.29 g. (16%), m.p. 114–118°, crystallized from the filtrate. The first crop was recrystallized twice from Skellysolve C (b.p. 88–99°) to afford 0.24 g. of the analytical sample, m.p. 117–119°, $[\alpha]^{20}D$ +126° (1% in chloroform); $\lambda_{max(\mu)}^{Nujol}$ 13.38 and 14.31 (monosubstituted benzene); surprisingly, there was no olefinic absorption in the 6.0–6.4 μ region.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.7; H, 6.50. Found: C, 67.9; H, 6.37.

Compound XI instantaneously decolorized 2% aqueous potassium permanganate with the production of brown manganese dioxide; compound VI did not react under the same conditions. The olefin XI dissolved in carbon tetrachloride decolorized a carbon tetrachloride solution of bromine but the product, on attempted isolation, decomposed to a black tar; the odor of benzaldehyde was noticeable.

Methyl 4,6-O-Benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside (XIII).—To a sodium benzyl mercaptide solution prepared from 2.03 g. (37.6 mmoles) of sodium methoxide, 4.42 ml. (37.6 mmoles) of benzyl mercaptan and 80 ml. of methanol was added 5.00 g. (18.9 mmoles) of the anhydroalloside XII.[11] The suspension was heated at reflux under nitrogen for 20 hours, during which time the solids dissolved. The solution was cooled, adjusted to *p*H 7 with glacial acetic acid, and poured into 200 ml. of ice-water. The white solid, 7.08 g. (96%), m.p. 120–134°, was collected and dried. Recrystallization from 60 ml. of absolute ethanol afforded 6.14 g. (84%) of white needles, m.p. 135–137°. From another experiment an analytical sample was obtained, m.p. 135–136°, $[\alpha]^{31}D$ −85.8° (1% in chloroform); $\lambda_{max(\mu)}^{Nujol}$ 2.87 (OH). 12.99, 14.10 and 14.26 (monosubstituted phenyl); there was no epoxide absorption at 11.09 μ.

Anal. Calcd. for $C_{21}H_{24}O_5S$: C, 64.9; H, 6.23; S, 8.24. Found: C, 64.8; H, 6.34; S, 8.02.

Proof of Structure of the 2-Benzylthioglycoside XIII.—Exactly the same conditions were used to desulfurize 2.00 g. of XIII as were used in the treatment of the thiocyanohydrin II (see above). The product XIV was a clear sirup, 0.85 g. (93%), whose infrared spectrum showed the essential absence of phenyl absorption in the 13–15 μ region.

Anal. Calcd. for $C_7H_{14}O_5$: C, 47.2; H, 7.92. Found: C, 48.9; H, 7.69.

On titration with periodate, the product showed the consumption of 1.0 mole/mole after 15 minutes, 1.2 moles/mole after 1 hour and 1.1 moles/mole after 2 hours.

Methyl 4,6-O-Benzylidene-2-benzylthio-2-deoxy-3-O-*p*-tolylsulfonyl-α-D-altropyranoside (XVII).—To a stirred, chilled (0–5°) solution of 6.14 g. (15.8 mmoles) of the 2-benzylthioglycoside XIII in 68 ml. of reagent pyridine was added, portionwise, 12.0 g. (63.0 mmoles) of *p*-toluenesulfonyl chloride. The solution was stirred at room temperature for 65 hours, then poured into 250 ml. of ice-water. The aqueous mixture was extracted with three 75-ml. portions of dichloromethane and the combined extracts were washed with two 75-ml. portions of water before being dried over magnesium sulfate. Evaporation *in vacuo*, followed by treatment with toluene and re-evaporation until the odor of pyridine had disappeared, yielded 9.1 g. (106%) of an orange solid, m.p. 120–128° dec.; $\lambda_{max(\mu)}^{Nujol}$ 8.47 ($-OSO_2-$), 12.33 (*p*-disubstituted phenyl), 13.24 and 14.31 (monosubstituted phenyl); there was no –OH band near 3.0 μ. The product was dried *in vacuo* at room temperature for analysis.

Anal. Calcd. for $C_{28}H_{30}O_7S_2$: C, 62.0; H, 5.57; S, 11.8. Found: C, 62.5; H, 5.94; S, 11.6.

The compound was unstable to prolonged storage at room temperature and slowly changed to a dark tar.

Methyl 3-Azido-4,6-O-benzylidene-2-benzylthio-2,3-dideoxy-α-D-altropyranoside (XIX).—A stirred mixture of 1.00 g. (1.84 mmoles) of the tosylate XVII, 3.00 g. (46.1 mmoles) of sodium azide and 20 ml. of dry 2-methoxyethanol under nitrogen was heated at 100–115° for 2 hours, then cooled. The mixture was evaporated to dryness *in vacuo* and the brown residue was partitioned between 30 ml. of dichloromethane and 50 ml. of water which contained 0.50 g. of sodium bicarbonate. The aqueous phase was extracted with three 10-ml. portions of dichloromethane and the combined dichloromethane solutions were washed with 20 ml. of saturated aqueous sodium chloride solution, then dried over magnesium sulfate. The solvent was evaporated *in vacuo* to afford 0.79 g. (104%) of an orange sirup which slowly solidified. The crude solid was recrystallized from 5 ml. of warm (50°) 2-methoxyethanol by the addition of water until crystals began to form. Chilling of the mixture yielded 0.39 g. (51%) of white crystals, m.p. 105–107°. From another run an analytical sample was obtained by recrystallization from Skellysolve C (b.p. 88–99°); m.p. 107–109°, $[\alpha]^{27}D$ +78.6° (1% in chloroform); $\lambda_{max(\mu)}^{Nujol}$ 4.77 (N_3), 12.99, 13.12, 14.05 and 14.21 (monosubstituted phenyl); there was no sulfonate absorption at 8.5 μ.

Anal. Calcd. for $C_{21}H_{23}N_3O_4S$: C, 61.0; H, 5.61; N, 10.2. Found: C, 61.0; H, 5.56; N, 9.96.

Methyl 3-Amino-4,6-O-benzylidene-2-benzylthio-2,3-dideoxy-α-D-altropyranoside (XV).—A solution of 1.46 g. (3.54 mmoles) of the 3-azide XIX in 20 ml. of dry tetrahydrofuran was added dropwise, and with stirring, to a suspension of 0.25 g. (6.58 mmoles) of lithium aluminum hydride in 40 ml. of dry tetrahydrofuran which was maintained at 20–25°. After the addition the mixture was heated with stirring at 70–75° for 6 hours, cooled and treated with 2 ml. of absolute ethanol, then with 7 ml. of 2 *M* aqueous sodium hydroxide. The hydrolyzed mixture was stirred for 30 minutes, allowed to settle and the solution was decanted from the white sludge. The solution was evaporated *in vacuo* and the residual solid partitioned between 25 ml. of dichloromethane and 15 ml. of water. The organic phase was dried over magnesium sulfate and evaporated *in vacuo* to leave 1.24 g. (90%) of a yellow sirup which crystallized on standing. Recrystallization from 30 ml. of heptane afforded 0.83 g. (61%) of yellow crystals, m.p. 137–141°, and a second such recrystallization gave the analytical sample, m.p. 140–142°, $[\alpha]^{28}D$ +96.2° (1% in chloroform); $\lambda_{max(\mu)}^{Nujol}$ 2.96 and 4.16 (NH_2), 13.10 and 14.29 (monosubstitituted phenyl); there was no azide absorption near 4.7 μ.

Anal. Calcd. for $C_{21}H_{25}NO_4S$: C, 65.1; H, 6.50; S, 8.27. Found: C, 65.9, 65.3; H, 6.72, 6.72; S, 7.96.

Desulfurization of the Amine XV and of the Azide XIX.—A stirred mixture of 2.00 g. (5.16 mmoles) of the amine XV, 70 ml. of 1,4-dioxane, 30 ml. of water and approximately 30 g. of wet Raney nickel[23] was heated at 90° (bath temp.) for 17 hours, then cooled and filtered through Celite. The filtrate and washings were evaporated *in vacuo*, affording 1.08 g. of a pale yellow sirup. This residue

was thoroughly triturated with two 15-ml. portions of hot (70°) Skellysolve B, leaving 0.67 g. of a yellow sirup (A) whose infrared spectrum showed weak phenyl absorptions in the 13–15 μ region.

Anal. Calcd. for $C_7H_{15}NO_4$ (XVIII): N, 7.91; S, 0. Found: N, 3.97; S, 0.

The Skellysolve B extracts deposited 0.15 g. (11%) of a white crystalline solid, m.p. 112–116°, which was recrystallized from Skellysolve B, affording 0.07 g. of the analytical sample of XXIV, m.p. 117–118°, $[\alpha]^{25}D$ + 132° (1% in chloroform); $\lambda_{max(\mu)}^{Nujol}$ 2.95, 3.00, 6.22 and 6.31 (NH_2), 13.31 and 14.27 (monosubstituted phenyl; the latter band was decreased in intensity as compared to XV.

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.4; H, 7.22; N, 5.28. Found: C, 63.4; H, 7.27; N, 5.35.

The yellow sirup A (see above) was dissolved in 8 ml. of water, Dowex 50(H), 2 g., was added and the mixture was stirred at room temperature for 2.5 hours, then filtered and the resin washed thoroughly with water. The resin was stirred with 6 ml. of 20% aqueous methylamine for 1.75 hours, then removed by filtration and washed with three 6-ml. portions of 20% aqueous methylamine. The combined amine filtrate and washings were decolorized with Norit A, filtered through Celite and the filtrate evaporated to dryness *in vacuo* affording 0.22 g. (24%) of an orange sirup, which crystallized on standing; $\lambda_{max(\mu)}^{film}$ 2.90–2.96 (OH, NH_2), 6.28 (NH_2); there was no phenyl absorption in the 12–15 μ region. The sirup consumed 1.0 mole of periodate per mole of compound after 30 minutes, 1.1 moles/mole after 1 hour and 1.1 moles/mole after 3 hours.

Anal. Calcd. for $C_7H_{15}NO_4$: N, 7.91. Found: N, 6.97.

When 4.00 g. (9.69 mmoles) of the azide XIX was treated with 60 g. of Raney nickel in aqueous dioxane as described above, 1.94 g. of a yellow sirup was obtained as the initial crude product. Extraction with Skellysolve C afforded 0.60 g. (23%) of the crude, blocked amine XXIV. The Skellysolve C-insoluble sirup, 1.25 g., furnished 0.56 g. (33%) of basic residue after separation with Dowex 50 (H) as described above. The residue crystallized on standing and after several recrystallizations from acetonitrile afforded the analytical sample XVIII, m.p. 152–156°, $[\alpha]^{21}D$ +138° (1% in methanol).

Anal. Calcd. for $C_7H_{15}NO_4$: C, 47.4; H, 8.53; N, 7.91. Found: C, 47.4; H, 8.76; N, 7.95.

Methyl 3-Azido-2-benzylthio-2,3-dideoxy-α-D-altropyranoside (XX).—A stirred mixture of 5.00 g. (12.1 mmoles) of the blocked azido glycoside XIX, 29 g. of wet Amberlite IR-120(H) (*ca.* 67 meq.) and 250 ml. of 90% aqueous methanol was heated 15 hours at 55°. The reaction mixture was filtered through a Celite pad and the filtrate evaporated to dryness *in vacuo*, leaving 3.99 g. (101%) of an orange sirup. The residue was dissolved in 30 ml. of hot methanol and water was added to cause the solution to become turbid. Upon being chilled, the solution deposited 0.18 g. (3.6%) of yellow needles, m.p. 103–105°, which had an infrared spectrum identical with that of the blocked glycoside XIX. Evaporation of the filtrate *in vacuo* afforded 3.43 g. (87%) of an orange sirup, $[\alpha]^{25}D$ +61° (1% in chloroform) $\lambda_{max(\mu)}^{film}$ 2.93 (OH), 14.21 (monosubstituted phenyl); there was no monosubstituted benzene near 13.2 μ which is characteristic of the benzylidene group.

Anal. Calcd. for $C_{14}H_{19}N_3O_4S$: C, 51.7; H, 5.89; S, 9.85. Found: C, 51.7; H, 6.11; S, 9.83.

Methyl 3-Azido-2-benzylthio-2,3-dideoxy-4,6-O-ethylidene-α-D-altropyranoside (XXIII).—A mixture of 3.10 g. (9.53 mmoles) of the deblocked glycoside XX, 21 ml. of 1,1-dimethoxyethane and 0.08 ml. of concentrated sulfuric acid was stirred at room temperature for 48 hours. Excess solid sodium bicarbonate was added and the reaction mixture was stirred for 0.5 hour, then evaporated *in vacuo*. The residue was partitioned between 100 ml. of water and 100 ml. of dichloromethane. The aqueous layer was extracted with 40 ml. of dichloromethane and the combined dichloromethane solutions were washed with 60 ml. of water. After being dried over magnesium sulfate and being decolorized with Norit A, the solution was evaporated *in vacuo* to leave 3.06 g. (91%) of an orange sirup; $\lambda_{max(\mu)}^{film}$ 14.22 (monosubstituted phenyl); there was no absorption of the benzylidene group near 13.2 μ or OH absorption near 3.0 μ; $[\alpha]^{24}D$ +71° (1% in chloroform). The rotation of different samples of XXIII showed considerable variation, probably dependent on the anomeric nature of XX.

Anal. Calcd. for $C_{16}H_{21}N_3O_4S$: C, 54.7; H, 6.02; S, 9.12. Found: C, 55.0; H, 6.21; S, 8.92.

Methyl 3-Amino-2,3-dideoxy-2-mercapto-D-altropyranoside Hydrochloride (XXI) (R = Me).—To 200 ml. of liquid ammonia was added 5.0 g. (0.218 g. atom) of clean sodium, cut into small pieces. To the resultant blue solution was added, dropwise and with stirring, a solution of 3.06 g. (8.71 mmoles) of the blocked benzylthio azide XXIII in 25 ml. of dry 1,2-dimethoxyethane. After the addition stirring was continued for 30 minutes, then solid ammonium chloride was added until the blue color had disappeared. The ammonia was allowed to evaporate, water (130 ml.) was added to the residue, and the aqueous solution was adjusted to *p*H 7 with glacial acetic acid. The solution was extracted with two 130-ml. portions of dichloromethane, then the combined extracts were washed with two 100-ml. portions of water and dried over magnesium sulfate while maintaining a nitrogen atmosphere. Evaporation *in vacuo* left 1.36 g. (66%) of an orange sirup (XXII) which gave a positive nitroprusside test. The sirup was dissolved immediately in 33 ml. of 1% methanolic hydrogen chloride (9.05 mmoles) and the solution was heated at reflux for 30 minutes, cooled, and evaporated *in vacuo* to leave 1.57 g. of a viscous, brown sirup. The residue was dissolved in 15 ml. of absolute ethanol and precipitated by the addition of a large volume of dry ether. The solid, 1.00 g. (44%), gave a positive nitroprusside test. It was dissolved in 8 ml. of 0.3% ethanolic hydrogen chloride and the solution was heated at 55° for 15 minutes, Norit A being added during the last 5 minutes of heating. The hot solution was filtered through Celite and dry ether added to the filtrate to precipitate 0.75 g. (30%) of the hygroscopic, solvated glycoside, m.p. 40–70° dec., $[\alpha]^{25}D$ +22° (1% in ethanol); $\lambda_{max(\mu)}^{Nujol}$ 2.98–3.05 (OH), 3.65–4.1 (NH_3^+ and SH), 6.20 and 6.65 (NH_3^+), 9.10 and 9.50 (C–OH); there was no phenyl absorption in the 11–15 μ region. The compound moved as a single spot on paper chromatography with R_{Ad} 1.51.[24]

Anal. Calcd. for $C_7H_{16}ClNO_4S \cdot 1/2[(C_2H_5)_2O]$: C, 38.2; H, 7.49; Cl, 12.5; N, 4.95; S, 11.3. Found: C, 38.0, 38.0; H, 7.25, 7.33; Cl, 12.6, 12.4; N, 4.89, 5.05; S, 10.8, 10.9.

From a second preparation carried out as above using 8.1 g. (23.1 mmoles) of the blocked azide XXIII was obtained 1.46 g. (22%) of XXI (R = Me).

Anal. Found: C, 38.7; H, 7.21, Cl, 12.1; N, 5.99, 5.70; S, 11.5.

Methyl 2-Deoxy-2-mercapto-α-D-altropyranoside (XXV).—Sodium metal (1.20 g., 0.0521 g. atom) was added in small pieces with stirring to 50 ml. of liquid ammonia. To the stirred blue solution was added dropwise a solution of 2.00 g. (5.15 mmoles) of the benzylthioglycoside XIII in 20 ml. of dry 1,2-dimethoxyethane. After the solution had been stirred for 20 minutes, 30 ml. of reagent chloroform was added slowly, causing the disappearance of the blue color. The ammonia was evaporated using a warm (50°) water-bath, then 40 ml. of water was added to the residue and the solution was adjusted to *p*H 7 with glacial acetic acid. The chloroform layer was separated and the aqueous layer was extracted with 40 ml. of chloroform. The combined organic layers were dried over magnesium sulfate, then evaporated *in vacuo* to leave 0.22 g. of an orange oil which gave a negative nitroprusside test. Infrared examination showed that the oil was mainly bibenzyl.

The aqueous phase was evaporated *in vacuo*, then redissolved in 10 ml. of water and continuously extracted with chloroform for 48 hours. The extract was dried over magnesium sulfate, then evaporated *in vacuo* to leave 0.76 g. (70%) of pale yellow crystals which gave a positive nitroprusside test. Recrystallization from 30 ml. of ethyl acetate yielded 0.46 g. (43%) of tan needles, m.p. 145–148°, and a second recrystallization from 15 ml. of ethyl acetate afforded 0.42 g. (39%) of the analytical sample, m.p. 145–

(24) Paper chromatography was done by the descending technique on Whatman No. 1 paper and the spots were located relative to adenine (R_f adenine = 1.00). The solvent system used was isopropyl alcohol-2*N* hydrochloric acid (65/35) and the sodium azide-iodine reagent[25] was used to detect the spots.

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148°, $[\alpha]^{24}D$ +88° (1% in water); $\lambda_{max(\mu)}^{Nujol}$ 2.93 (OH), 3.90 (SH); there was no monosubstituted phenyl in the 12.5–15 μ region.

Anal. Calcd. for $C_7H_{14}O_6S$: C, 40.0; H, 6.71; S, 15.3. Found: C, 40.2; H, 6.64; S, 14.9.

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[CONTRIBUTION FROM THE RICHARD B. WETHERILL LABORATORY OF PURDUE UNIVERSITY, LAFAYETTE, IND.]

Hydroboration. XI. The Hydroboration of Acetylenes—A Convenient Conversion of Internal Acetylenes into *cis*-Olefins and of Terminal Acetylenes into Aldehydes

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The treatment of internal acetylenes, such as 3-hexyne, with the theoretical quantity of hydroborating agent results in the formation of the corresponding trivinylborane. However, under the same conditions, terminal acetylenes, such as 1-hexyne, undergo dihydroboration predominantly. The use of hydroborating agents of large steric requirements, such as disiamylborane, permits the conversion of both internal and terminal acetylenes into the corresponding vinylboron compounds in essentially quantitative yields. These vinyl derivatives undergo rapid protonolysis with acetic acid at room temperature, forming *cis*-olefins of high purity from the internal acetylenes, and terminal olefins from the terminal acetylenes. Oxidation with alkaline hydrogen peroxide forms the ketone from the internal acetylene and the aldehyde from the terminal acetylene. Dihydroboration of acetylenes appears to place two boron atoms on the same carbon atom. Oxidation of these derivatives produces the alcohol predominantly. This result is attributed to the rapid hydrolysis of the dihydroboration intermediate. The same result is obtained with the dihydroboration product of dicyclohexylborane and 1-hexyne. However, the use of a large excess of diborane in the hydroboration stage reduces the amount of alcohol in the product and increases markedly the yield of the carbonyl derivative to be anticipated for a dihydroboration product containing two boron atoms on the same carbon atom.

The hydroboration of olefins provides a convenient new route to the aliphatic and alicyclic organoboranes[1,2] and to the numerous derivatives into which these organoboranes may be transformed.[3–7]

The synthesis of the vinylboranes *via* the Grignard reaction has offered difficulties[8] and their utilization as intermediates for organic synthesis has received relatively little attention. Accordingly, we undertook a study of the hydroboration of acetylenes as a possible route to the vinylboranes and to the utilization of these substances as intermediates in synthetic work.

Results

The Monohydroboration of 3-Hexyne and 1-Hexyne.—3-Hexyne and 1-hexyne were selected as typical representatives of acetylenes with an internal and a terminal triple bond.

The 3-hexyne was added to the usual hydroboration mixture of sodium borohydride in diglyme and the hydroboration accomplished at 0° by adding boron trifluoride etherate to the reaction mixture. The sodium borohydride utilized was sufficient to achieve the monohydroboration of the 3-hexyne (1).

$$12\ \mathrm{RC{\equiv}CR} + 3NaBH_4 + 4BF_3 \longrightarrow 4\ (\mathrm{RCH{=}CR})_3B + 3NaBF_4 \qquad (1)$$

After two hours at room temperature, ethylene glycol was added to convert residual hydride to hydrogen, and residual acetylene was estimated by gas chromatographic examination (adiponitrile column). Only traces of residual hydride were found, and 84% of the initial acetylene had reacted. Consequently, the reaction had proceeded largely as indicated (1), with approximately 16% of double hydroboration suggested.

Under similar experimental conditions, 44% of 1-hexyne was found in the reaction mixture, with complete utilization of the available hydride indicated. Consequently, the 1-hexyne undergoes dihydroboration preferentially. Only traces of hydrogen were evolved during the hydroboration. Consequently, the terminal hydrogen atom of the acetylene is not sufficiently acidic to react with the hydroborating reagent.

It was evident that the monohydroboration of 1-hexyne would require the use of a large excess of the acetylene to repress the second stage. However, a more convenient solution suggested itself. Bis-3-methyl-2-butylborane (disiamylborane) is a hydroborating agent of large steric requirements.[9] It appeared possible that the large steric requirements would hinder the second stage and permit

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