V was reduced with 14.5 g. (0.38 mole) of lithium aluminum hydride to yield 20.5 g. (79%) of (−)-VI, which had b.p. 58–59° (22 mm.), $n^{25}D$ 1.4410, $[\alpha]^{26}D$ −12.0° (0.248 g./5 ml. of benzene), $[\alpha]^{26}D$ −11.6° (neat); lit.,[10] b.p. 53–54° (15 mm.), $n^{25}D$ 1.4442, $[\alpha]^{25}D$ +23.9° (neat), calculated for optically pure (+)-VI; lit.,[14] $n^{25}D$ 1.4410 for (±)-VI.

(+)-2-Ethyloxirane (VII).—To a vigorously stirred solution of 22.2 g. (0.56 mole) of sodium hydroxide and 40 ml. of water at 100° was added dropwise 20.0 g. (0.184 mole) of (−)-VI. The distillate that resulted was collected over a few pellets of sodium hydroxide and then distilled from fresh sodium hydroxide pellets. (+)-2-Ethyloxirane (10.1 g., 76%) was collected at 62–63°. It had $n^{25}D$ 1.3813, $[\alpha]^{30}D$ +10.7° (0.325 g./5 ml. of benzene) and an infrared spectrum superimposable on that of redistilled (±)-VII obtained from Farchan Laboratories.[17]

(+)-s-Butanol.[18]—2-Ethyloxirane (3.6 g., 0.05 mole) dissolved in 15 ml. of anhydrous ether was added dropwise to a well stirred mixture of 1.1 g. (0.05 mole) of lithium borohydride[19] in 30 ml. of ether. When the addition was complete, the mixture was heated at reflux for 2 hr. and allowed to stand overnight at room temperature. Water (10 ml.) was added slowly to the reaction mixture, and the phases were separated. The aqueous phase was saturated with sodium chloride and extracted twice with 15-ml. portions of ether. The ether extracts were combined and dried over potassium carbonate. Distillation yielded 2.70 g. (75%) of a fraction boiling at 88–91°. This fraction was dried over calcium oxide and then distilled to yield 1.6 g. of s-(+)-2-butanol, b.p. 97–99°, $n^{26}D$ 1.3922, d_4^{25} 0.8033, $[\alpha]^{26}D$ +6.3° (neat); lit.,[11] b.p. 99°, $n^{20}D$ 1.3954, d_4^{27} 0.8025, $[\alpha]^{27}D$ 13.52° (neat).

(±)-1-Propylamino-2-butanol Acid Oxalate (IV). A. From 2-Ethyloxirane (VII) and *n*-Propylamine.—(±)-2-Ethyloxirane (21.6 g., 0.30 mole) was added dropwise to a stirred, ice-cold solution of 35.4 g. (0.60 mole) of *n*-propylamine and 5.4 ml. of water. The solution was allowed to stand overnight at room temperature. The excess *n*-propylamine and water were removed by distillation, and the residual oil was distilled to yield 28.5 g. (73%) of 1-propylamino-2-butanol, b.p. 72–74° (7 mm.), $n^{25}D$ 1.4390.

Anal. Calcd. for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.68. Found: C, 64.13; H, 13.12; N, 10.54.

(17) Levene and Walti[3] reported the preparation of (+)-VII, which had a specific rotation of $[\alpha]^{26}D$ +8.75° (neat), from (−)-1-bromo-2-butanol.

(18) Reduction of (±)-VII with lithium borohydride was reported by R. Fuchs and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76**, 1631 (1954).

(19) The lithium borohydride was prepared as described by H. I. Schlesinger, H. C. Brown, and E. K. Hyde, *ibid.*, **75**, 209 (1953).

The amino alcohol (1.3 g., 0.010 mole) was dissolved in 5 ml. of absolute ethanol, and the resulting solution was added to a solution of 1.26 g. (0.010 mole) of oxalic acid dihydrate in 10 ml. of absolute ethanol. The precipitate that formed was dissolved by warming the mixture. The white plates that separated when the solution was allowed to stand at room temperature for 3 hr. weighed 1.4 g. (64%) and melted at 159–160°. After one recrystallization from absolute ethanol, the acid oxalate melted at 159.5–160.0°.

Anal. Calcd. for $C_9H_{19}NO_5$: C, 48.86; H, 8.65; N, 6.33. Found: C, 49.07; H, 8.49; N, 6.27.

B. From III.—A mixture of 2.5 g. (0.020 mole) of 93% (±)-1-(2-methylene-1-aziridinyl)-3-buten-2-ol (III) and 7% (±)-2-(2-methylene-1-aziridinyl)-3-buten-1-ol[3] in 100 ml. of absolute ethanol to which had been added 0.20 g. of platinic oxide was shaken under 30–35 p.s.i. of hydrogen for 5 hr. The reduction appeared to be complete within 1 hr. The catalyst was removed by filtration, and 2.5 g. (0.020 mole) of oxalic acid dihydrate was dissolved in the filtrate by warming. The solution was concentrated to a volume of 25 ml. and cooled. The first crop of crystals that separated (2.3. g., 52%) melted at 132–137°. After three recrystallizations from ethanol, the acid oxalate (1.7 g.) melted at 157–158°, and the melting point was not depressed by the addition of (±)-IV prepared from (±)-2-ethyloxirane (VII) and *n*-propylamine.

Anal. Calcd. for $C_9H_{19}NO_5$: C, 48.86; H, 8.65; N, 6.33. Found: C, 48.58; H, 8.25; N, 6.10.

(−)-IV. A. From (+)-VII and *n*-Propylamine.—Using the same procedure described for the preparation of (±)-IV from (±)-VII, 3.6 g. (0.050 mole) of (+)-2-ethyloxirane and 5.9 g. (0.10 mole) of *n*-propylamine, in the presence of 1 ml. of water, were converted to 3.3 g. (50%) of (−)-1-propylamino-2-butanol, b.p. 74–76° (9 mm.), $n^{25}D$ 1.4388. The first crop of acid oxalate melted at 157.5–158.5°. After one recrystallization from absolute ethanol, the acid oxalate melted at 158.5–159.0° and had a specific rotation of $[\alpha]^{26}D$ −9.6° (0.220 g./5 ml. of 50% aqueous ethanol by weight).

B. From (+)-III and (+)-1-(2-Propynylamino)-3-buten-2-ol.—The fourth fraction (4.6 g. 0.037 mole) was hydrogenated as described for (±)-III. The first crop of acid oxalate (4.2 g., 51%) melted at 157–158°. After one recrystallization from absolute ethanol, the acid oxalate had a melting point of 158.5–159.0° and a specific rotation of $[\alpha]^{26}D$ −16.8° (0.211 g./5 ml. of 50% aqueous ethanol by weight). Admixture of the acid oxalate with (−)-IV obtained from (+)-VII did not depress its melting point.

Preparation of a Glycoside of 2-Amino-2,3-dideoxy-3-mercaptoaltrose[1]

LEON GOODMAN AND JAMES E. CHRISTENSEN

Life Sciences Research, Stanford Research Institute, Menlo Park, California

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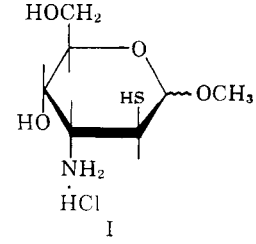
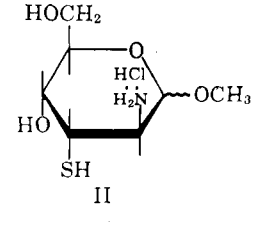
The synthesis of methyl 2-amino-2,3-dideoxy-3-mercapto-D-altropyranoside hydrochloride (II) is described.

An earlier paper in this series[2] described the synthesis of methyl 3-amino-2,3-dideoxy-2-mercapto-D-altropyranoside hydrochloride (I), prepared as a possible antiradiation drug. This synthesis utilized the conversion of a benzylthio group to the mercaptan function with sodium in liquid ammonia and required that the sugar blocking group be changed from the labile benzylidene to the stable (to sodium–liquid ammonia) ethylidene group prior to the debenzylation in order to permit



I



II

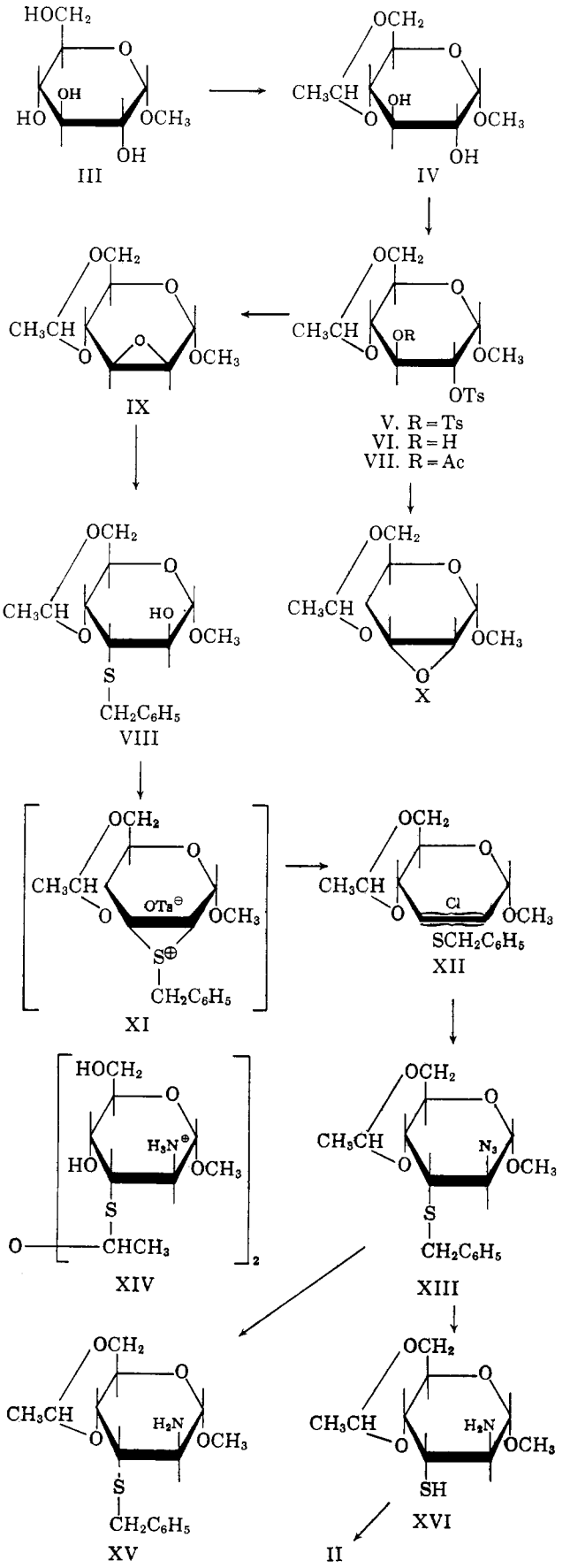
an easy isolation of the derived β-mercaptoamine. In order to circumvent this awkward deblocking-reblocking sequence, it was desirable to use an appropriate ethylidene-blocked sugar as the starting material. This manuscript describes the conversion of methyl 2,3-anhydro-4,6-O-ethylidene-α-D-mannopyranoside (IX) to the title compound (II).

(1) The work reported in this paper (no. 4 of the series) 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-2068 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.

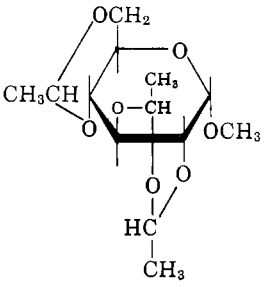
(2) J. E. Christensen and L. Goodman, *J. Am. Chem. Soc.*, **83**, 3827 (1961).

Methyl α-D-glucopyranoside (III) was converted to the blocked glycoside (IV) with 1,1-dimethoxyethane and an acid catalyst, using the procedure of O'Meara and Shepherd[3] for the β-anomer of IV. Crude IV, with the appropriate proportions of *p*-toluenesulfonyl chloride, formed the crystalline ditosylate (V)[4] and the crystalline monotosylate (VI), the latter best isolated as the acetate (VII). Treatment of V with refluxing sodium methoxide gave a good yield of the anhydroalloside (X),[4] the reaction taking place in the same manner as with the 4,6-benzylidene analog of V[5] although requiring much more stringent conditions. Similarly, the monotosylate (VI) and the tosylate acetate (VII) with methanolic sodium methoxide at reflux furnished good yields of an isomeric epoxide that must be the anhydromannoside (IX), not previously described.

Ring-opening of IX with sodium benzyl mercaptide furnished an excellent yield of VIII, whose structure is assumed as resulting from transdiaxial ring opening according to the considerations elaborated in paper III of this series.[2] Treatment of VIII with tosyl chloride in pyridine afforded either a mixed chloride, tosylate (according to infrared evidence) or a pure, sirupy chloroglycoside, depending on the length of time the reaction was allowed to proceed. The formation of the chloride can be rationalized by assuming the episulfonium ion intermediate (XI). The reaction of XII with sodium azide afforded an excellent yield of a crystalline, sharply melting azide (XIII) whose structure is written on the assumption of *trans*-diaxial episulfonium ion opening at C-2.[2] The azide (XIII) was reduced to the crystalline amine (XV) with sodium borohydride in refluxing isopropyl alcohol,[6] although this was not a necessary step in the preparation of II. Treatment of XIII with sodium in liquid ammonia directly afforded the blocked aminomercaptan (XVI) as a nitroprusside-positive sirup. When XVI was treated with methanolic hydrogen chloride either at room temperature or at reflux, hygroscopic solids were obtained whose n.m.r. spectra in deuterium oxide showed varying amounts of a doublet centered at $\tau = 8.36$. Since the doublet attributable to the O-ethylidene methyl group in XIII was found at $\tau = 8.62$, it was apparent that the secondary methyl group of the supposedly deblocked product from XVI was in a different environment and, indeed, under the proper conditions it was possible to isolate from treatment of XVI with methanolic acid a material that gave excellent analytical agreement with structure XIV. It seems probably that the proximity of the C-4 hydroxyl and the C-3 thiol group is responsible for the formation of XIV, since such a difficulty was not noted in the deblocking step that gave compound I. Structure XIV bears a relationship to methyl 4,6-O-ethylidene-2,3-oxidodiethylidene-α-D-glucoside (XVII), which is formed when methyl α-D-glucoside (III) is treated with paraldehyde and acid.[7] Attempts to complete the conversion of XIV to II by more vigorous acid treatment or by reaction with mercuric chloride were fruitless. When the deblocking of XVI was conducted in the presence of excess ethanedithiol, however, the formation of XIV was prevented and compound II was isolated as a hygroscopic, amorphous solid that could be purified by precipitation from a methanol solution



(3) D. O'Meara and D. M. Shepherd, *J. Chem. Soc.*, 4232 (1955).
(4) E. G. Ansell and J. Honeyman, *ibid.*, 2778 (1952).
(5) F. H. Newth, *Quart. Rev.* (London), **13**, 30 (1959).
(6) P. A. S. Smith, J. H. Hall, and R. O. Kan, *J. Am. Chem. Soc.*, **84**, 485 (1962).
(7) H. Appel and W. N. Haworth, *J. Chem. Soc.*, 793 (1938).



XVII

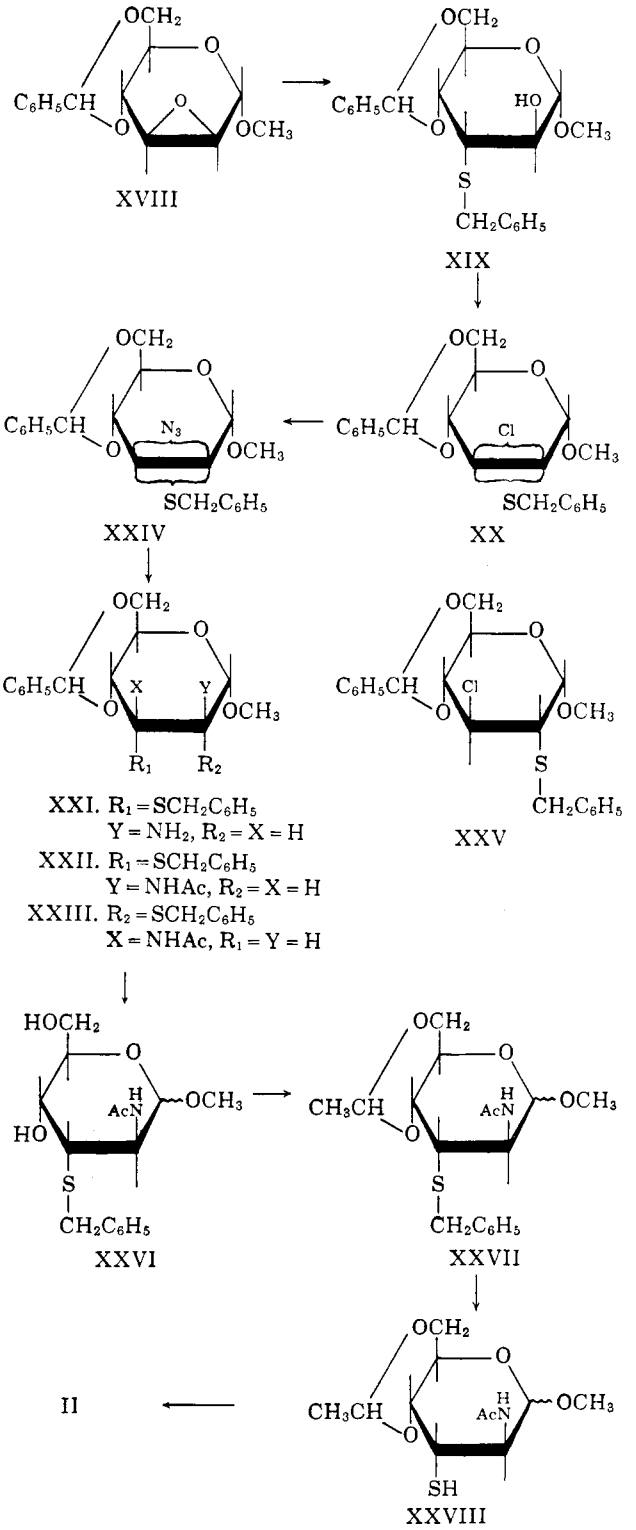
with ether. Similarly to I,[2] it tenaciously retained ether as evidenced both by analyses and by the ether C-methyl triplet n.m.r. resonance at τ = 8.78. Attempts to hydrolyze II to the free sugar with aqueous hydrochloric acid were not encouraging; the reaction mixtures darkened rapidly. There is a strong probability of 1,6-anhydride formation from the hydrolysis of an altroside such as II,[8] a similar situation was noted with I.[2]

Prior to the preparation of IX, some attempts were made to prepare II from the 4,6-O-benzylidene-blocked epoxide (XVIII).[9] The reaction of XVIII with sodium benzyl mercaptide gave an excellent yield of XIX,[10] tosylation of which afforded a sirupy chloride (XX) whose formation can be rationalized in the same way as that of XII. Treatment of XX with sodium azide gave a widely melting solid which was predominantly the azide mixture (XXIV).

The reaction of XX with azide did not go to completion under the conditions used; lithium aluminum hydride reduction of the product permitted, after fractional crystallization of the reduction product, the separation of an amine (XXI) and a small amount of a chloride. The chloride must be compound XXV, whose C-2, C-3 diequatorial substituents would resist episulfonium ion formation. The 2-chloro-3-benzylthio isomer of XXV, where these substituents would occupy diaxial positions, would readily undergo azide displacement *via* the episulfonium ion intermediate, with the predominant cleavage of that ion occurring by *trans*-diaxial opening at C-2 to give XXI as the predominant amine after reduction of the azide mixture (XXIV).

When the reaction product from XX and sodium azide was reduced directly with hydride, then acetylated, two amides were isolated by recrystallization. The lower melting, very predominant compound gave the amine (XXI), on basic hydrolysis, and is assigned structure XXII; the higher melting amide than should be XXIII.

An attempt to provide a more definitive structure proof for XXII and XXIII was not successful. Both amides were desulfurized with Raney nickel, affording from the high melting amide a quantitative yield of XXXII as a crystalline solid, resulting from the concurrent hydrogenolysis of the benzylidene group. The lower melting amide gave a small amount of the crystalline, blocked amide (XXIX) along with the crude deblocked amide (XXX) which was not obtained analytically pure. Cleavage of the deblocked amides with methanolic hydrogen chloride afforded the hydrochlorides, XXXI as an impure, hygroscopic solid and XXXIII as an analytically pure solid. Periodate determinations on these two solids gave perplexing results; compound XXXI, which should not consume



XXI. $R_1 = SCH_2C_6H_5$, $Y = NH_2$, $R_2 = X = H$

XXII. $R_1 = SCH_2C_6H_5$, $Y = NHAc$, $R_2 = X = H$

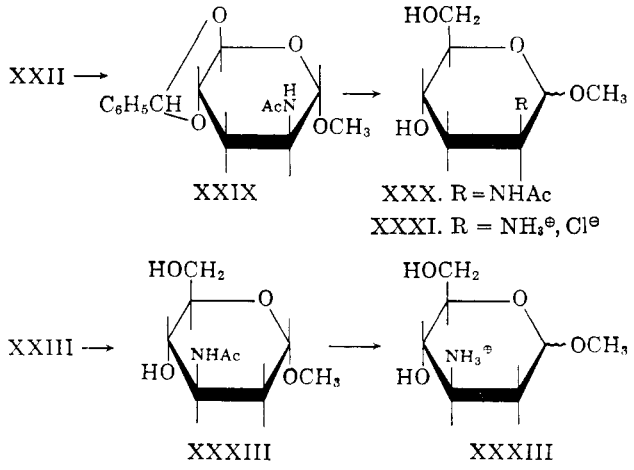
XXIII. $R_2 = SCH_2C_6H_5$, $X = NHAc$, $R_1 = Y = H$

periodate, took up approximately one mole of oxidant and XXXIII took up about two moles of periodate, with both compounds rapidly consuming most of the oxidant after one hour, then giving a slow but steady

(8) R. J. Ferrier and W. G. Overend, *Quart. Rev.* (London), **13**, 265 (1959).

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

(10) N. C. Jamieson and R. K. Brown, *Can. J. Chem.*, **39**, 1765 (1961), reported compound XIX while this work was in progress.



consumption of additional periodate.[11] In view of the ambiguous periodate results, structures XXII and XXIII are assigned on the basis of the episulfonium ion formation and opening discussed above.

The predominant amide (XXII) was deblocked with an acid ion-exchange resin to give XXVI as a sirup, which was reblocked with 1,1-dimethoxyethane and acid to afford XXVII as a widely melting, crystalline solid. Sodium and liquid ammonia treatment of XXVII yielded the crystalline thiol (XXVIII), which was converted to II, in low yield, by treatment with methanolic hydrogen chloride, separation of the insoluble mercuric mercaptide, and regeneration of II with hydrogen sulfide.

Experimental[12]

Methyl 4,6-O-Ethylidene-α-D-glucopyranoside (IV).—A suspension of 10.0 g. (51.4 mmoles) of methyl α-D-glucoside (III) in 40 ml. of 1,1-dimethoxyethane containing 0.40 ml. of concentrated sulfuric acid was stirred at room temperature for 18 hr., then adjusted to pH 7 with saturated aqueous sodium bicarbonate solution and evaporated *in vacuo*. The residue was extracted with three 40-ml. portions of boiling carbon tetrachloride, the combined extracts were filtered and dried over potassium carbonate, then evaporated *in vacuo*, leaving 12.46 g. of pale yellow, solid foam. The foam was triturated with two 50-ml. portions of petroleum ether (b.p. 30–60°), leaving 10.55 g. (98%) of a white solid, which was suitable for further conversion (lit.,[4] m.p. 76–77°).

Methyl 4,6-O-Ethylidene-2,3-di-O-(*p*-tolylsulfonyl)-α-D-glucopyranoside (V).—To a chilled (0°), stirred solution of 6.00 g. (27.2 mmoles) of the crude diol in 30 ml. of pyridine was added, dropwise, a solution of 30.0 g. (0.157 mole) of *p*-toluenesulfonyl chloride in 150 ml. of pyridine. The solution was stirred at room temperature for 4 days, then was poured into 500 ml. of ice–water. The brown solid, 15.74 g. (109%), was collected and recrystallized from 180 ml. of absolute ethanol to give 6.83 g. (47.4%) of tan plates, m.p. 155–156°. A previous preparation gave a 50% yield of V, m.p. 156–157° (lit.,[4] m.p. 154–155°); $\lambda_{max(\mu)}^{Nujol}$ 8.49 (OSO_2), 12.25 (phenyl); there was no —OH absorption near 3.0 μ; $[\alpha]^{24}D$ +59° [lit.,[4] $[\alpha]^{20}D$ +57.2° (0.6% in chloroform)].

Methyl 4,6-O-Ethylidene-2-O-(*p*-tolylsulfonyl)-α-D-glucopyranoside (VI) and Methyl 3-O-Acetyl-4,6-O-ethylidene-2-O-(*p*-tolylsulfonyl)-α-D-glucopyranoside (VII).—To a stirred solution of 5.73 g. (26.0 mmoles) of the crude diol (IV) in 30 ml. of pyridine was added 7.30 g. (38.3 mmoles) of *p*-toluenesulfonyl chloride, the temperature being maintained at 20–25°. The solution was stirred for 20 hr. at room temperature, then was poured, with stirring, into 200 ml. of ice–water. The mixture was extracted with four 25-ml. portions of chloroform and the combined extracts were washed with 50 ml. of saturated aqueous sodium bicarbonate solution and with two 50-ml. portions of water, then dried over magnesium sulfate, simultaneously decolorizing with Norit. The chloroform solution was evaporated *in vacuo*, the last traces of pyridine being removed by evaporation with toluene to afford 9.90 g. (102%) of a brown sirup. The sirup was crystallized from 50 ml. of absolute ethanol, affording 2.53 g. (26%) of leaflets, m.p. 147–155°, which were recrystallized from ethanol to give 2.18 g. of solid ditosylate (V) m.p. 154–156°. The mother liquors were evaporated to give 6.03 g. of sirup which, after two recrystallizations from isopropyl alcohol, afforded 1.26 g. (13%) of the analytical sample of monotosylate (VI), m.p. 150–151°; $\lambda_{max(\mu)}^{Nujol}$ 2.91 (OH), 8.52 (OSO_2), 12.36 (phenyl); $[\alpha]^{23}D$ +91° (1% in methanol).

Anal. Calcd. for $C_{16}H_{22}O_8S$: C, 51.3; H, 5.92; S, 8.56. Found: C, 51.4; H, 6.04; S, 8.53.

In another run, 7.06 g. (32.0 mmoles) of the crude diol (IV) was converted to 9.85 g. (82%) of the crude monotosylate (VI), using the above procedure with 7.60 g. (39.9 mmoles) of *p*-toluenesulfonyl chloride. A stirred solution of 9.66 g. of the sirup in 25 ml. of pyridine was treated with 25 ml. of acetic anhydride and stirred at room temperature for 18 hr. while protected from atmospheric moisture, then was poured into 500 ml. of ice–water. The aqueous mixture was stirred at room temperature for 30 min. and the brown solid, 9.12 g. (85% from IV), was collected by filtration. Recrystallization from 65 ml. of absolute ethanol gave 5.15 g. (48%) of crystals, m.p. 155–171°, and two more recrystallizations from absolute ethanol afforded 3.53 g. (33%) of the analytical product, m.p. 169–171°; $\lambda_{max(\mu)}^{Nujol}$ 5.86 (C=O), 8.09 (C—O—C), 12.19 (phenyl); there was no —OH absorption near 3.0 μ; $[\alpha]^{23}D$ +76°.

Anal. Calcd. for $C_{18}H_{24}O_9S$: C, 51.9; H, 5.81; S, 7.70. Found: C, 51.9; H, 5.49; S, 7.63.

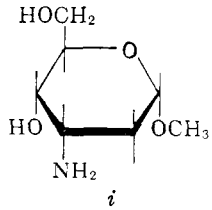
Methyl 2,3-Anhydro-4,6-O-ethylidene-α-D-allopyranoside (X).—A suspension of 20.0 g. (37.9 mmoles) of ditosylate (V), 6.00 g. (0.111 mmole) of sodium methoxide, and 300 ml. of methanol was heated at reflux for 18 hr. then cooled and filtered through Celite. The filtrate was diluted with 500 ml. of water, then extracted with two 300-ml. portions of chloroform. The combined extracts were washed with 300-ml. of water, dried over magnesium sulfate, and evaporated *in vacuo*. The white residue, 9.19 g., was sublimed at 80° and 0.7–0.9 mm., affording 5.01 g. (65.3%) of crystalline solid, m.p. 126–129° (lit.,[4] m.p. 125–126°); $\lambda_{max(\mu)}^{Nujol}$ 11.30 (epoxide). In a previous run, a melting point of 128–129° was obtained.

Methyl 2,3-Anhydro-4,6-O-ethylidene-α-D-mannopyranoside (IX).—A suspension of 1.29 g. (3.10 mmoles) of the acetate (VII), 0.34 g. (6.30 mmoles) of sodium methoxide, and 40 ml. of ethanol was heated at reflux for 18 hr. The cooled mixture was adjusted to pH 7 with glacial acetic acid, then evaporated *in vacuo* to give 1.48 g. of white solid. The solid was sublimed at 65° and 0.9 mm. to afford 0.54 g. (84%) of product, m.p. 98–100°. Recrystallization of the sublimate from 55 ml. of isopropyl alcohol gave a first crop of 0.41 g. (64%) of white needles, m.p. 100.0–100.5°, and a second crop of 0.05 g. (7.8%) of needles, m.p. 98.0–100.5°. The first crop was used as the analytical sample, and had $\lambda_{max(\mu)}^{Nujol}$ 11.16 (epoxide), $[\alpha]^{26}D$ + 108°.

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.5; H, 6.98. Found: C, 53.4; H, 6.98.

On a large scale it was advantageous to partition the crude product between water and chloroform before the sublimation.

(11) M. J. Weiss, J. P. Joseph, H. M. Kissman, A. M. Small, R. E. Schaub, and F. J. McEvoy, *J. Am. Chem. Soc.*, **81**, 4050 (1959), reported on the anomalous overoxidation of aminofuranosides with periodate but found normal oxidant uptake with 2- and 3-aminopyranosides. However, J. B. Lee *J. Chem. Soc.*, 1474 (1960), reported on overoxidation with certain deoxyfuranosides and pyranosides and the combination of amino and deoxypyranosides in compounds XXXI and XXXIII may be responsible for the strange periodate results. However, compound *i*, which was reported in an earlier paper of this series[2] and which has the same general features as XXXI and XXXIII, was run as a control and took up precisely one mole of periodate as had been described previously.[2]



i

(12) Melting points are uncorrected and were obtained with the Fisher–Johns apparatus. The n.m.r. spectra were obtained using a Varian V-4311 spectrometer operated at 60 Mc. with samples dissolved in deuterium oxide and with tetramethylsilane as the reference standard. Optical rotations are for 1% solutions in chloroform unless otherwise noted.

Methyl 3-Benzylthio-3-deoxy-4,6-O-ethylidene-α-D-altropyranoside (VIII).—A solution of 8.00 g. (39.6 mmoles) of IX, 2.60 g. (48.2 mmoles) of sodium methoxide, 6.03 g. (48.5 mmoles) of benzyl mercaptan, and 200 ml. of methanol was stirred at reflux under nitrogen for 18 hr., cooled, and adjusted to pH 7 with glacial acetic acid, then poured into 400 ml. of ice–water. The product slowly solidified and was collected by filtration, washed with water and petroleum ether (b.p. 62–70°) and dried, affording 12.53 g. (97%) of solid. Recrystallization of the solid from 800 ml. of petroleum ether (b.p. 62–70°) gave 11.41 g. (89%) of product, m.p. 132–133°. From a previous run an analytical sample was obtained with m.p. 132.0–132.5°; $\lambda_{max(\mu)}^{Nujol}$ 3.03 (OH), 14.00 (phenyl); $[\alpha]^{20}D$ −108°.

Anal. Calcd. for $C_{16}H_{22}O_5S$: C, 58.9; H, 6.80; S, 9.82. Found: C, 59.1; H, 6.51; S, 9.98.

Methyl 3(2)-Benzylthio-2(3)-chloro-2,3-dideoxy-4,6-O-ethylidene-α-D-altro(gluco)pyranoside (XII).—When 1.23 g. (3.77 mmoles) of VIII was treated with 2.8 g. (14.7 mmoles) of *p*-toluenesulfonyl chloride in 13 ml. of dry pyridine, initially at 0° for 1 hr., then at room temperature for 48 hr., 0.85 g. (*ca.* 65%) of sirupy product was isolated after a conventional work-up. The infrared spectrum showed no —OH absorption hear 3.0 μ but did show some sulfonate ester absorption at 8.5 μ. Analysis verified the presence of some sulfonate ester.

Anal. Calcd. for $C_{16}H_{21}ClO_4S$ (XII): Cl, 10.28; S, 9.30. Found: Cl, 8.19; S, 9.98.

When the sulfonylation time was extended to 90 hr., an essentially quantitative yield of XII was isolated.

Anal. Calcd. for $C_{16}H_{21}ClO_4S$: C, 55.7; H, 6.14; Cl, 10.3; S, 9.30. Found: C, 56.8; H, 6.20; Cl, 10.6; S, 9.29.

Methyl 2-Azido-3-benzylthio-2,3-dideoxy-4,6-O-ethylidene-α-D-altropyranoside (XIII).—A stirred mixture of 11.9 g. (34.5 mmoles) of crude XII, 27 g. (0.42 mole) of sodium azide, and 300 ml. of 95:5 2-methoxyethanol–water was heated at 100–110° under nitrogen for 18 hr., then evaporated *in vacuo*. The residue was partitioned between dichloromethane and water to yield, after drying, decolorizing with Norit A, and evaporating, 12.1 g. of a partially crystalline sirup. Recrystallization of the crude product from 150 ml. of petroleum ether (b.p. 88–99°) gave 7.09 g. (58%) of crystalline solid, m.p. 137–138°. The analytical sample from another run had m.p. 137–138°; $\lambda_{max(\mu)}^{Nujol}$ 4.59, 4.70, and 4.78 (N_3); $[\alpha]^{28}D$ −99°.

Anal. Calcd. for $C_{16}H_{21}N_3O_4S$: C, 54.7; H, 6.02; N, 12.9; S, 9.12. Found: C, 54.6; H, 6.09; N, 12.2; S, 9.30.

Methyl 2-Amino-3-mercapto-2,3-dideoxy-D-altropyranoside hydrochloride (II). Method A.—A solution of 2.00 g. (5.7 mmoles) of the azide (XIII) in 12 ml. of 1,2-dimethoxyethane was added dropwise, with stirring, to a solution of 0.80 g. (0.0348 g.-atom) of sodium in 35 ml. of liquid ammonia. The resulting mixture was stirred at reflux, with exclusion of moisture, for 30 min., then the blue color was discharged with excess solid ammonium chloride. The ammonia was evaporated under a nitrogen atmosphere, the residue was dissolved in 10 ml. of water, and the solution was adjusted to pH 7 with glacial acetic acid then extracted with two 20-ml. portions of dichloromethane while maintaining a nitrogen atmosphere. The combined extracts were washed with 17 ml. of water, decolorized with Norit A, and dried over magnesium sulfate. Evaporation of the dried extract afforded 0.68 g. of a yellow sirup whose infrared spectrum showed absorptions at 2.97 μ (NH_2) and 3.87 μ (SH). To the sirup was immediately added 3 ml. of ethanedithiol followed by 20 ml. of a 2% solution of hydrogen chloride in methanol, and the mixture was stirred at room temperature for 1 hr., then evaporated *in vacuo* to a semisolid residue which solidified when triturated with ether. The residue was reprecipitated from methanol–ether to yield 0.61 g. (44%) of cream-colored solid whose n.m.r. spectrum still showed some of the O-ethylidene methyl doublet centered at τ = 8.62. The solid was re-treated with methanolic hydrogen chloride and ethanedithiol at 50° for 5 hr., then worked up as before to give 0.49 g. (33% as the etherate) of solid, which had a wide decomposition range and showed essentially no ethylidene methyl resonance in the n.m.r. spectrum but which did show the ether C-methyl triplet centered at τ = 8.78. The analytical sample was dried *in vacuo* at 100°. On paper chromatography[13] in system A it gave a major spot with R_{Ad} 1.31 with some material staying at the origin.

Anal. Calcd. for $C_7H_{16}ClNO_4S \cdot 1/8(C_2H_5)_2O$: C, 35.3; H, 6.82; N, 5.49. Cl, 13.9; S, 12.6. Found: C, 35.6; H, 6.82; N, 5.53; Cl, 13.8; S, 12.8.

When deblocking of XVI was conducted in 2% methanolic hydrogen chloride at room temperature for 1 hr., the product (55% yield) was a hygroscopic solid, m.p. 124–146° dec.; $\lambda_{max(\mu)}^{Nujol}$ 2.99 (OH weak), 4.92 and 6.25 ($NH_3^{\oplus}$); $[\alpha]^{27}D$ +27° (1% in methanol); it gave good elemental analyses for structure XIV and its n.m.r. spectrum showed the prominent S,O-ethylidene methyl doublet centered at τ = 8.36.

Anal. Calcd. for $C_{13}H_{33}Cl_2N_2O_9S_2$: C, 38.5; H, 6.82; N, 4.99; Cl, 12.6; S, 11.4. Found: C, 38.6; H, 6.71; N, 5.06; Cl, 12.5; S, 11.4.

Method B.—A solution of 0.44 g. (1.58 mmoles) of the blocked thiol (XXVIII) (see below) and 23 ml. of 5% methanolic hydrogen chloride was heated at reflux for 20 hr., then cooled and decolorized with Norit. The mixture was filtered and evaporated *in vacuo*, leaving a residue, which was washed with several portions of ether and evaporated again. The final residue, an orange foam, 0.46 g. (118%), was dissolved in 3 ml. of methanol and the solution treated with 5 ml. of a saturated solution of mercuric chloride in methanol. Water (about 15 ml.) was added to precipitate the mercaptide, which was collected by filtration. The gummy solid was suspended in methanol, and hydrogen sulfide was bubbled through the stirred mixture for 20 min. Filtration through Celite removed the mercuric sulfide, leaving a pale yellow filtrate, which was evaporated *in vacuo*. The resultant sirup was washed several times with ether and dried *in vacuo* to leave 0.10 g. (26% from XXVIII) of a hygroscopic, nitroprusside-positive, solid foam.

Anal. Calcd. for $C_7H_{16}ClNO_4S$: C, 34.2; H, 6.56; Cl, 14.4; N, 5.70. Found: C, 34.4; H, 6.84; Cl, 13.1; N, 5.32.

Methyl 2-Amino-3-benzylthio-2,3-dideoxy-4,6-O-ethylidene-α-D-altropyranoside (XV).—A mixture of 1.00 g. (2.84 mmoles) of XIII, 0.25 g. (6.6 mmoles) of sodium borohydride, and 10 ml. of isopropyl alochol was stirred at reflux for 16 hr., then evaporated *in vacuo*. The residue was partitioned between dichloromethane and water, and the organic phase, after washing with water and drying, was evaporated *in vacuo* to afford 0.89 g., (96%) of white solid. Recrystallization from petroleum ether (b.p. 88–99°) gave 0.67 g. (72%) of the analytical sample, m.p. 123–124°; $\lambda_{max(\mu)}^{Nujol}$ 3.00 and 3 05 (NH_2), weak; $[\alpha]^{25}D$ −106°.

Anal. Calcd. for $C_{16}H_{23}NO_4S$: C, 59.1; H, 7.12; N, 4.30; S, 9.85. Found: C, 59.1; H, 7.24; N, 4.31; S, 9.93.

Methyl 4,6-O-Benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside (XIX).—Compound XIX was prepared from XVIII,[8] using essentially the same conditions as in the preparation of VIII. The crude product (88%), m.p. 104–105°, was recrystallized from 60% aqueous ethanol to give the analytical sample, m.p. 105–106°; $\lambda_{max(\mu)}^{Nujol}$ 2.93 (OH); 13.28, 13.82, and 14.25 (phenyl); $[\alpha]^{31}D$ −108° [lit.,[10] m.p. 105–106°, $[\alpha]D$ −112°].

Anal. Calcd. for $C_{21}H_{24}O_5S$: C, 64.9; H, 6.23; S, 8.24. Found: C, 64.8; H, 6.10; S, 8.49.

Methyl 4,6-O-Benzylidene-3(2)-benzylthio-2(3)-chloro-2,3-dideoxy-α-D-altro(gluco)pyranoside (XX).—Compound XIX was converted to XX, using essentially the conditions described for the preparation of XII. The yield of orange sirup was slightly more than theoretical; the infrared spectrum showed no —OH absorption near 3.0 μ and essentially no sulfonate ester absorption at 8.5 μ.

Anal. Calcd. for $C_{21}H_{23}ClO_4S$: Cl, 8.72. Found: Cl, 9.15.

Reaction of XX with Sodium Azide.—A stirred mixture of 0.50 g. (1.23 mmoles) of the crude glycoside (XX), 0.85 g. (13.1 mmoles) of sodium azide, and 10 ml. of 2-methoxyethanol that contained 5% water was heated at reflux for 3 hr. in a nitrogen atmosphere, then evaporated *in vacuo*. The brown residue was partitioned between 40 ml. of water and 25 ml. of dichloromethane. The aqueous phase was extracted with two 10-ml. portions of dichloromethane and the combined dichloromethane solutions were washed with 15 ml. of saturated aqueous sodium chloride solution, then dried over magnesium sulfate. Evaporation *in vacuo* left 0.53 g. (104%) of a tan solid, which was recrystallized once from 10 ml. of hexane and again from 5 ml. of hexane to yield 0.29 g. (57%) of pale yellow needles, m.p. 107–118°; $\lambda_{max(\mu)}^{Nujol}$ 4.73 (N_3), 13.19 and 14.31 (phenyl).

(13) Paper chromatography was run by the descending technique on Whatman no. 1 paper using the following solvent systems: A, isopropyl alcohol–2 *N* hydrochloric acid (65:35); B, *n*-butylalcohol–water; and C, *n*-butyl alcohol–acetic acid–water (4:1:5). Spots were detected with the sodium azide–iodine spray[14] and were located relative to adenine (R_f adenine = 1.00).

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

Anal. Calcd. for $C_{21}H_{23}N_3O_4S$: C, 61.0; H, 5.61; N, 10.2. Found: C, 61.4; H, 5.63; N, 9.22.

Subsequent work showed that the above sample contained an appreciable quantity (*ca.* 18%) of a chlorobenzylthio glycoside.

Methyl 2-Amino-4,6-O-benzylidene-3-benzylthio-2,3-dideoxy-α-D-altropyranoside (XXI) and Methyl 4,6-Benzylidene-2-benzylthio-3-chloro-2,3-dideoxy-α-D-glucopyranoside (XXV).—A stirred mixture of 5.00 g. (12.1 mmoles) of the crude azido glycoside (XXIV), 1.00 g. (26.3 mmoles) of lithium aluminum hydride, and 200 ml. of dry ether was heated at reflux for 17 hr. Absolute ethanol (4 ml.) was added dropwise to the cooled solution, followed by 100 ml. of 2 *M* aqueous sodium hydroxide. The mixture was stirred for 0.5 hr., then let stand until the inorganic salts had settled. The ether layer was decanted and the remaining mixture was filtered through Celite, the filter pad being washed well with ether. The layers of the filtrate were separated and the ether layer was combined with the ether reaction solution. The ethereal solution was washed with 50 ml. of water, then dried over magnesium sulfate. Evaporation *in vacuo* left 3.23 g. (69%) of a white solid, which was recrystallized from 150 ml. of heptane to yield 1.99 g. (42%) of white needles, m.p. 137–140°.

From a previous reaction an analytical sample was obtained that had m.p. 137–139°; $\lambda_{max(\mu)}^{Nujol}$ 3.01, 3.05, 3.09, 6.25 (NH_2); $[\alpha]^{24}D$ −86°.

Anal. Calcd. for $C_{21}H_{25}NO_4S$: C, 65.1; H, 6.50; S, 8.27. Found: C, 65.4; H, 6.66; S, 8.30.

The mother liquors from the separation of XXI were evaporated to dryness to yield 1.09 g. of solid, m.p. 95–115°. One recrystallization from 20 ml. of absolute ethanol yielded 0.40 g. (8.5%) of white solid, m.p. 135–150°. Three more recrystallizations from hexane afforded 0.18 g. (3.8%) of XXV as white needles, m.p. 154–156°; $\lambda_{max(\mu)}^{Nujol}$ 13.20, 14.08 and 14.35 (phenyl); there was no OH or NH_2 absorption at 3.0 μ; $[\alpha]^{24}D$ −106°.

Anal. Calcd. for $C_{21}H_{23}ClO_4S$: C, 62.0; H, 5.70; Cl, 8.72; S, 7.88. Found: C, 62.3; H, 5.86; Cl, 8.93; S, 7.90.

The amine (XXI) was also prepared by hydrolysis of the amide XXII (see below) with potassium hydroxide in aqueous 2-methoxyethanol; the product had m.p. 139–140° and an infrared spectrum identical to that of the amine from XXIV.

Methyl 3-Acetamido-4,6-O-benzylidene-2-benzylthio-2,3-dideoxy-α-D-glucopyranoside (XXIII) and Methyl 2-Acetamido-4,6-O-benzylidene-3-benzylthio-2,3-dideoxy-α-D-altropyranoside (XXII).—The crude mixed amine (XXI) 12.8 g., containing some XXV, was mixed with 80 ml. of acetic anhydride and 12 g. of anhydrous sodium acetate and stirred at 50° for 3 hr., then poured into 1 l. of ice water. The solid was collected and recrystallized from acetonitrile to afford 11.3 g. (80%) of material, m.p. 180–190°. The product was dissolved in 1500 ml. of 95% ethanol and chilled, yielding 2.7 g. (19%) of XXIII, m.p. 297–301° dec., $[\alpha]^{28}D$ −29° (1% in N,N-dimethylformamide). The infrared spectrum showed the same functional groups as that of XXII (see below), but the absorptions were somewhat displaced and of different intensities.

Anal. Calcd. for $C_{23}H_{27}NO_5S$: C, 64.3; H, 6.34; N, 3.26; S, 7.46. Found: C, 64.9; H, 6.51; N, 3.30; S, 7.66.

The filtrate from XXIII was evaporated *in vacuo* and the residue was recrystallized from 200 ml. of ethanol to give 5.7 g. (40%) of solid, m.p. 196–198°, and a second crop, 2.3 g. (16%), m.p. 185–195. The analytical sample, obtained in a previous run had m.p. 197–198°; $\lambda_{max(\mu)}^{Nujol}$ 2.95 (NH), 5.94 (amide C=O), 13.10 and 14.25 (phenyl); $[\alpha]^{27}D$ −38° (1% in N,N-dimethylformamide) and $[\alpha]^{27}D$ −20°.

Anal. Found: C, 64.8; H, 6.08; N, 3.64; S, 7.45.

Methyl 2-Acetamido-3-benzylthio-2,3-dideoxy-D-altropyranoside (XXVI).—A suspension of 0.91 g. (2.12 mmoles) of the blocked glycoside (XXII), 5.1 g. of Amberlite IR-120(H) resin, and 35 ml. of 90% aqueous methanol was stirred at 50° for 18 hr., then filtered through Celite. The filtrate was evaporated *in vacuo* and the residue washed with several portions of hot petroleum ether (b.p. 62–70°) to leave 0.69 g. (95%) of tan foam; $\lambda_{max(\mu)}^{film}$ 2.90–3.08 (NH, OH), 6.02 (amide C=O), 13.0 and 14.2 (phenyl).

Methyl 2-Acetamido-3-benzylthio-2,3-dideoxy-4,6-O-ethylidene-D-altropyranoside (XXVII).—A mixture of 4.7 g. (13.8 mmoles) of the crude glycoside (XXVI), 20 ml. of 1,1-dimethoxyethane, and 0.10 ml. of concd. sulfuric acid was stirred at room temperature for 65 hr., while protected against atmospheric moisture. Dichloromethane (100 ml.) was added and the solution was washed with 40 ml. of saturated aqueous sodium bicarbonate solution, then with two 40-ml. portions of water. After being dried over magnesium sulfate and filtered, the solution was evaporated *in vacuo*, affording 4.81 g. (95%) of a pale yellow, viscous sirup; $\lambda_{max(\mu)}^{film}$ 3.05 (NH), 6.02 (amide C=O), 13.0 and 14.2 (phenyl); $[\alpha]^{25}D$ −81° (1% in methanol).

Anal. Calcd. for $C_{18}H_{25}NO_5S$: C, 58.8; H, 6.86; N, 3.81; S, 8.72. Found: C, 58.6; H, 6.90; N, 3.60; S, 8.40.

From another preparation, run only 21 hr., 1.02 g. (94%) of crude product was obtained as a yellow sirup. This material partially solidified on standing and was recrystallized from petroleum ether (b.p. 88–99°) to give 0.23 g. of solid, then recrystallized again from petroleum ether (b.p. 88–98°), yielding 0.10 g. of crystalline material, m.p. 110–121°. Two more recrystallizations from petroleum ether (b.p. 88–99°) gave 0.05 g. of probably quite pure α-anomer, m.p. 120–135°, $[\alpha]^{25}D$ +200° (0.7% in methanol).

Anal. Found: C, 58.6; H, 7.05; N, 3.58; S, 8.75.

Methyl 2-Acetamido-2,3-dideoxy-4,6-O-ethylidene-3-mercapto-D-altopyranoside (XXVIII).—To a solution of 0.61 g. (26.5 mg.-atoms) of clean, dry sodium in 20 ml. of dry liquid ammonia was added, dropwise and with stirring, 1.19 g. (3.23 mmoles) of the sirupy, but analytically pure, glycoside (XXVII) dissolved in 5 ml. of 1,2-dimethoxyethane. When the addition was complete, the mixture was stirred for 30 min., then the excess sodium was decomposed by the cautious addition of solid ammonium chloride. Ammonia was slowly evaporated from the white mixture, then the residue was dissolved in 20 ml. of water and the solution adjusted to pH 6–7 with glacial acetic acid. The aqueous solution was extracted with two 15-ml. portions of dichloromethane, the combined extracts were washed with 20 ml. of water, then dried over magnesium sulfate, and, after filtration, evaporated *in vacuo*, giving 0.72 g. (80%) of a pale yellow, crystalline, nitroprusside-positive solid. The solid was recrystallized from 6 ml. of isopropyl alcohol to give 0.09 g. of white crystals, m.p. 130–132°, and a second crop of 0.23 g. of product, m.p. 130–132°, but containing a small amount of material, probably disulfide, which remained unmelted at 200°. The first crop of solid was recrystallized from benzene, affording 0.05 g. of product, m.p. 129–132°; $\lambda_{max(\mu)}^{Nujol}$ 3.05 (NH), 3.85 (SH), 6.06 (amide C=O); there was essentially no phenyl absorption at 13.0 and 14.2 μ; $[\alpha]^{27}D$ +72° (1% in methanol).

Anal. Calcd. for $C_{11}H_{19}NO_5S$: C, 47.6; H, 6.91; N, 5.05; S, 11.6. Found: C, 47.9; H, 6.99; N, 5.01; S, 11.7.

From a similar reduction of 2.73 g. of XXVII was obtained 1.79 g. (87%) of crude thiol (XXVIII), m.p. 105–131°, $[\alpha]^{33}D$ +60° (1% in methanol). The material was homogeneous on paper chromatography[13] in solvent systems B and C, with R_{Ad} 3.55 and 1.79, respectively, the spots also being detectable with ultraviolet light.

Anal. Found: C, 47.4; H, 6.74; N, 4.81; S, 10.4, 11.0.

Metyl 3-Acetamido-2,3-dideoxy-α-D-glucopyranoside (XXXII).—A mixture of 1.50 g. of the amide (XXIII), *ca.* 20 g. of Raney nickel[15] (washed thoroughly with dioxane to replace the water), and 90 ml. of dioxane was stirred at reflux for 6 hr., then filtered through Celite and evaporated *in vacuo*. The residue was a viscous sirup, 0.85 g. (110%), which crystallized on standing. The material was recrystallized by dissolving it in a large volume of dichloromethane, filtering the solution, and concentrating the filtrate to a small volume. The chilled solution deposited material of analytical purity, m.p. 132–135°; $\lambda_{max(\mu)}^{Nujol}$ 3.00, 3.10 (NH, OH), 6.10 (amide C=O); no phenyl absorption in the 14–15-μ region.

Anal. Calcd. for $C_9H_{17}NO_5$: C, 49.3; H, 7.82; N, 6.39. Found: C, 49.2; H, 8.01; N, 6.31.

Methyl 3-Amino-2,3-dideoxy-D-glucopyranoside hydrochloride (XXXIII).—A solution of 0.300 g. of XXXII in 40 ml. of saturated methanolic hydrogen chloride was heated at reflux with exclusion of moisture for 20 hr., then filtered and evaporated *in vacuo*, finally at 60° and 1 mm., leaving 0.20 g. (69%) of a yellow foam. The residue was dissolved in 20 ml. of methanol, the solution filtered, and the salt precipitated by the addition of excess ether. The very hygroscopic solid was collected by centrifugation and was washed with ether by centrifuging and decanting. It had $\lambda_{max(\mu)}^{Nujol}$ 3.0 (OH), 4.95, 6.23 ($NH_3^{\oplus}$).

Anal. Calcd. for $C_7H_{16}ClNO_4$: C, 39.4; H, 7.55; N, 6.56. Found: C, 39.4; H, 7.67; N, 6.61.

On titration with periodate, the product showed the consumption of 1.68 moles/mole after 1 hr., 1.81 moles/mole after

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

3 hr., 1.94 moles/mole after 6 hr., and 2.33 moles/mole after 24 hr.

Methyl 2-Acetamido-4,6-O-benzylidene-2,3-dideoxy-α-D-mannopyranoside (XXIX).—The blocked amide (XXII), 2.54 g. (5.91 mmoles), was desulfurized with 25 g. of Raney nickel[15] according to the procedure described for the preparation of XXXII. The residue was extracted with hot petroleum ether (b.p. 88–90°) and the insoluble portion was partitioned between 15 ml. of benzene and 15 ml. of water. The aqueous extract was evaporated *in vacuo*, affording 0.96 g. of a colorless sirup (XXX) whose infrared spectrum showed the amide carbonyl at 6.02 μ and essentially no phenyl absorption in the 13–14.5-μ region.

The methanolysis of 0.74 g. of crude XXX, carried out as described for the preparation of XXXIII, gave 0.29 g. of the very hygroscopic salt (XXXI) which showed essentially no infared amide absorption.

Anal. Calcd. for $C_7H_{16}ClNO_4$: C, 39.4; H, 7.55; N, 6.56; Cl, 16.6. Found: C, 39.2; H, 8.27; N, 5.66; Cl, 14.7.

On titration with periodate, the product showed the consumption of 0.74 mole/mole after 1 hr. and 3 hr., 0.81 mole/mole after 6 hr., and 1.12 moles/mole after 24 hr.

The benzene extract from the XXII desulfurization residue was evaporated *in vacuo* affording 0.63 g. of a white foam which was crystallized from isopropyl alcohol–petroleum ether (b.p. 30–60°) to give 0.24 g. of white needles, m.p. 162–173°. Two recrystallizations from ethyl acetate–petroleum ether (30–60°) yielded 0.15 g. of the analytical sample of XXIX, m.p. 169–171°; $\lambda_{max(\mu)}^{Nujol}$ 3.07 (NH), 6.10 (amide C=O).

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.5; H, 6.88; N, 4.56. Found: C, 63.1, H, 7.29; H, 4.47.

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The Reaction of 9-Chloro-*trans*-1-decalone with Methoxide Ion[1]

HERBERT O. HOUSE AND HUGH W. THOMPSON

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts

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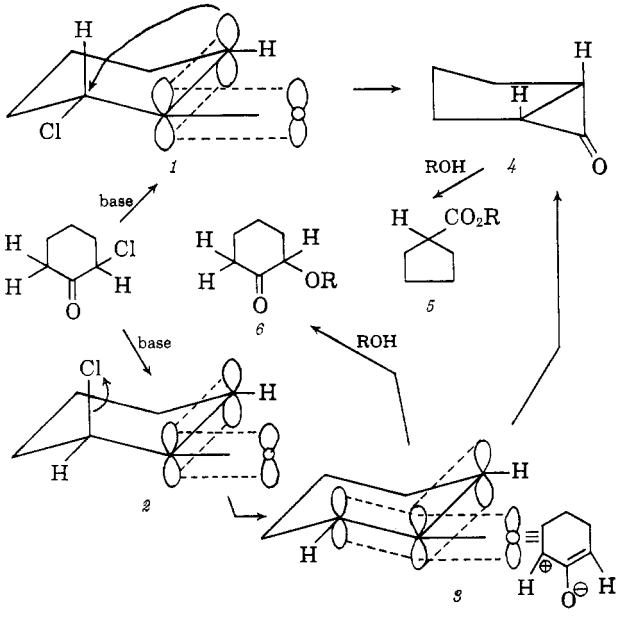
The reaction of 9-chloro-*trans*-1-decalone (**12**) with methanolic sodium methoxide yielded as the major products a mixture of 9-methoxy-*trans*-1-decalone (**14**), 9-methoxy-*cis*-1-decalone (**13**), and 2-methoxy-*trans*-1-decalone (**15**). The relationship of this reaction to the Favorskii rearrangement is discussed.

Previous studies of the Favorskii rearrangement[2] suggested that the reaction of α-halo ketones with bases to remove an α′-hydrogen atom could be followed either by an intramolecular S_N2 displacement (as in **1**) with inversion of configuration at the α-carbon atom[3] or by loss of halide ion (as in **2**) to form a zwitterionic intermediate **3** Although intervention of an intermediate such as **3** did not preclude a subsequent nonstereospecific Favorskii rearrangement—*e.g.*, the formation of **5**—in cases previously studied,[2a] it was clear that conditions favoring this intermediate **3** also favored the formation of solvolysis products such as **6**. In considering the applicability of these observations to the α-halocyclohexanone system, we have been led to the hypothesis that in order to maintain continuous *pi* orbital overlap the ionization **2** should be favored by an axial halogen atom and the displacement **1** should be favored by an equatorial halogen atom. Thus, the ionization process **2** should be enhanced not only by an increase in solvent polarity,[2a] but also by the presence of a halogen atom fixed in an axial conformation. Support for this idea is found in the reaction of several 9-α-halo-11-keto steroids (partial structure **7** necessarily containing an axial halogen atom) with alcoholic bases to yield 12-α-alkoxy ketones **8** rather than Favorskii rearrangement products.[4] The corresponding reaction with a 5-α-halo-6-keto steroid (partial structure **9**) was also reported to yield not a Favorskii product, but rather the 5-β-hydroxy ketone **10**.[5] The reported[3,6] failure of 2-chloro-2-methylcyclohexanone (**11**) to undergo a Favorskii rearrangement, only 2-hydroxy-2-methylcyclohexanone being isolated, may well be attributable to the same stereoelectronic effect since in this ketone both conformational factors[7] and dipole repulsion between the C=O bond and the C—Cl bond should favor the conformation **11** containing an axial chlorine atom.



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