Synthetic Nucleosides. LIX.[1,2] Studies on the Synthesis of *cis*-2,3-Diamino Sugars. II. The Thiourea Neighboring Group

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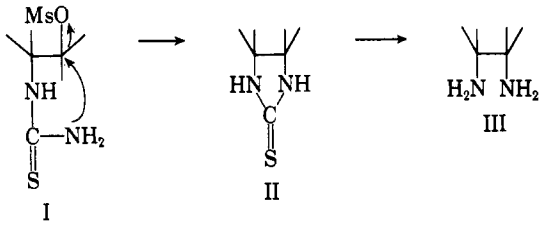
Neighboring group ring closure of the *N*-thiocarbamyl derivative (IX) of methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-2-*O*-mesyl-α,D-altropyranoside under acid acceptor conditions gave a thiazolino sugar (VIII). When the anion of IX was cyclized, an *N*-thiocarbamyl imine derivative (X) was obtained rather than the expected imidazoline (XIII). That the ring closure of IX to the imine (X) could not be attributed to the fixed *trans*-diaxial conformations of attacking and leaving groups was shown by the anionic ring closure of the same *N*-thiocarbamyl altroside without the *trans*-fused benzylidene blocking group (XV); since the participating groups in the anionic ring closure of XV can assume either *trans*-diaxial or *trans*-diequatorial conformations with little energy difference, the formation of the *N*-thiocarbamyl imine (XVIII) rather than an imidazoline (XVI) must be attributed to factors apparently more important than the conformational factors. The *N*-thiocarbamyl derivative (XXX) of methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-3-*O*-mesyl-β,D-glucopyranoside, which has *trans*-diequatorial participating groups, ring closed to a thiazoline (XXXII) under acid acceptor conditions. In contrast to IX, anionic ring closure of XXX did not lead to nitrogen attack to form either an imine or an imidazoline; sulfur attack took place to give the same thiazoline (XXXII) obtained under acid acceptor conditions.

In the previous paper of this series,[2] the rationale for synthesis of nucleosides derived from 2,3-diamino-2,3-dideoxy-D-ribofuranose was presented, and general methods for their synthesis by neighboring group reactions were discussed. Among the "complex neighboring groups" that might be suitable for synthesis of the necessary 2,3-diamino system (III) would be the thiourea group (I) *via* the imidazolidine (II). The



I II III

investigation of the thiocarbamyl derivatives of methyl 3-amino-3-deoxy-α,D-altropyranoside and methyl 2-amino-2-deoxy-β,D-glucopyranoside is the subject of this paper.

When methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α,D-altropyranoside (IV) in dilute alcohol was treated with potassium thiocyanate with or without the presence of one equivalent of acetic acid, mixtures were obtained from which the desired thiourea (VI) could not be isolated. In contrast, IV reacted smoothly with potassium cyanate and an equivalent of acetic acid in dilute alcohol to give the crystalline urea derivative (V) in 82% yield. Treatment of V with 3 moles of mesyl chloride in pyridine not only formed the 2-mesylate derivative, but, as could be predicted,[3] dehydrated the urea group to a cyanamide (VII) in 82% yield. When the cyanamide (VII) was treated with hydrogen sulfide in pyridine at ambient temperature, addition across the triple bond occurred with formation of the desired thiourea[4] (IX) in 73% yield (Scheme I).

Cyclization of IX in boiling pyridine gave a 70% yield of crystalline product that appeared to be the thiazoline (VIII), since it showed C=N absorption at 6.10 μ, whereas the imidazolidine (XIII) would not be expected to have absorption in this region. The structure, VIII, was confirmed by basic hydrolysis to the amino thiol (XI) which gave a noncrystalline, though pure *N*,*S*-diacetyl derivative (XII). The intermediate thiol (XI) could not be crystallized, but XI gradually formed a crystalline disulfide[5] by air oxidation.

Cyclization of the thiourea (IX) by conversion to the anion with methanolic sodium methoxide gave a crystalline product in 85% yield that was isomeric to the thiazoline (VIII) and had infrared spectral properties agreeing with either the aziridine structure, X, or the imidazolidine structure, XIII. That the former structure was correct was shown by basic hydrolysis to the imino sugar (XIV).[2,6] The anionic cyclization of IX to the thermodynamically labile aziridine (X), rather than the thermodynamically stable imidazoline, is indeed surprising; similar results were observed previously with the nitroguanidine[2] and dithiocarbomethoxy[6] neighboring groups.

Jeanloz, *et al.*,[7] have shown that the 4,6-*O*-benzylidene blocking group in the α,D-galactopyranoside system could negate a neighboring group reaction, whereas the same system without the benzylidene group would undergo neighboring group reaction. Therefore, an investigation of ring closure of a thiourea derivative without the benzylidene group (XV) was undertaken to determine whether or not the benzylidene group was controlling the ring closure to the thermodynamically unstable aziridine (X). Treatment of IX with Dowex 50W-X 8 (H^+) resin in boiling 80% methanol for 4 hr. gave the debenzylidenated glycol (XV) in

(1) This work was generously supported by Grant CY-5845 of the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper of this series, see B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1047 (1964).

(3) Primary amides can be converted to nitriles with sulfonyl chlorides in pyridine, presumably *via* the imino-*O*-sulfonate. Secondary amides have been converted to thioamides by formation of imino-*O*-sulfonates with a sulfonyl chloride in pyridine followed by treatment with hydrogen sulfide. *Cf.* P. Oxley, D. A. Peak, and W. F. Short, *J. Chem. Soc.*, 1618 (1948); J. Witte and R. Huisgen, *Chem. Ber.*, **91**, 1129 (1958).

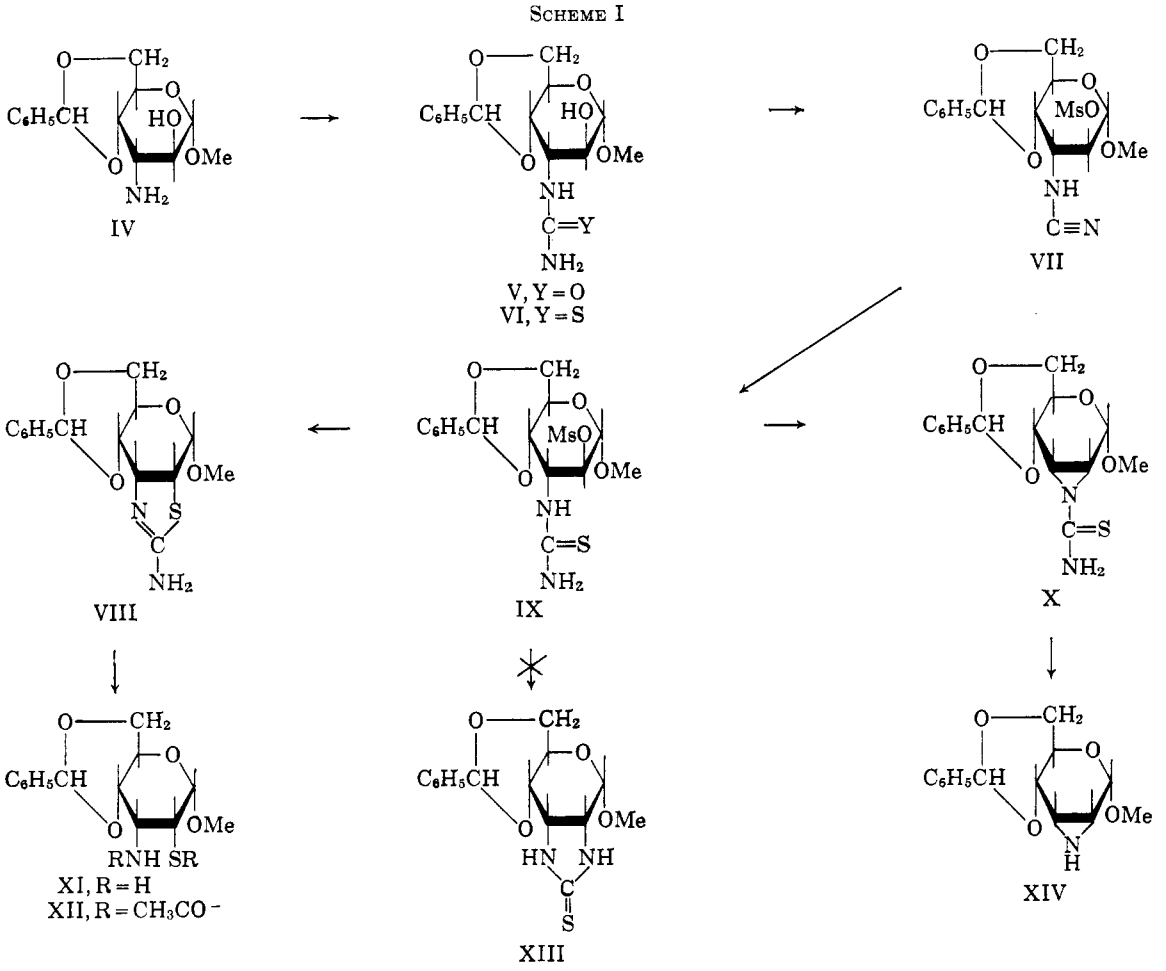
(4) The preparation of thioureas by addition of hydrogen sulfide to nitriles has been described by A. E. S. Fairfull, J. L. Lowe, and D. A. Peak, *J. Chem. Soc.*, 742 (1952); see also O. Wallach, *Ber.*, **32**, 1872 (1899), and *Org. Syn.*, **36**, 23 (1956).

(5) Ring closure of IX in pyridine to the thiazoline (VIII) could be expected in view of the similar cyclization of the corresponding dithiocarbomethoxy derivative (XXIV) to a thiazoline.[6] The melting point of the disulfide of XI is about 100° lower than that recorded,[6] probably because our sample crystallized as a solvate, whereas the disulfide has been reported[6] as solvent free.

(6) L. Goodman and J. E. Christenson, *J. Am. Chem. Soc.*, **83**, 3823 (1961); **82**, 4738 (1960).

(7) Z. Jarasiejska and R. W. Jeanloz, *ibid.*, **79**, 4215 (1957).

SCHEME I



95% yield as a glass; the ion-exchange resin[8] was found to give a cleaner product than methanolic hydrochloric acid or dilute sulfuric acid in aqueous acetic acid. Treatment of XV with ethanolic sodium ethoxide gave rapid formation of sodium methanesulfonate; the resultant cyclized product (XVI or XVIII) was a glass that gave a crystalline diacetate of structure XVII or XIX in 75% yield for the three steps (Scheme II). That this cyclization still had formed the aziridine XVIII was shown by chemical structure proof, as well as by infrared and n.m.r. studies.

Treatment of the benzylidene aziridine (X) with Dowex 50W-X8 (H^+) to give crude XVIII followed by acetylation with acetic anhydride and pyridine gave crystalline XIX in 46% over-all yield, which was identical with the cyclization product (XIX) from XV *via* XVIII. Basic hydrolysis of XIX gave XXI as a glass that was acetylated to pure XX, obtained as an oil; the lack of NH absorption in the infrared and combustion analyses confirmed the structure as the aziridine XX, rather than a di-*O*-acetyl-di-*N*-acetyl derivate of an alloside derived from XVII.

That XX was an aziridine was further confirmed by comparison of the n.m.r. spectra of XXII, XXIII,[2] XX, and XIV shown in Table I. The mean signal assigned to the protons of the epoxide ring of the anhydromannoside (XXII) was 196 c.p.s. in agreement with 190 c.p.s. usually attributed to the corresponding protons of an epoxide ring fused in a bicyclic structure. By use of the empirical rule that substitution of nitrogen for oxygen causes a shift of 50 c.p.s. upfield toward tetramethylsilane, it is reasonable to expect that XIV should give a signal near 146 c.p.s.; a signal at 158 c.p.s. was actually observed.

TABLE I

NUCLEAR MAGNETIC RESONANCE COMPARISONS

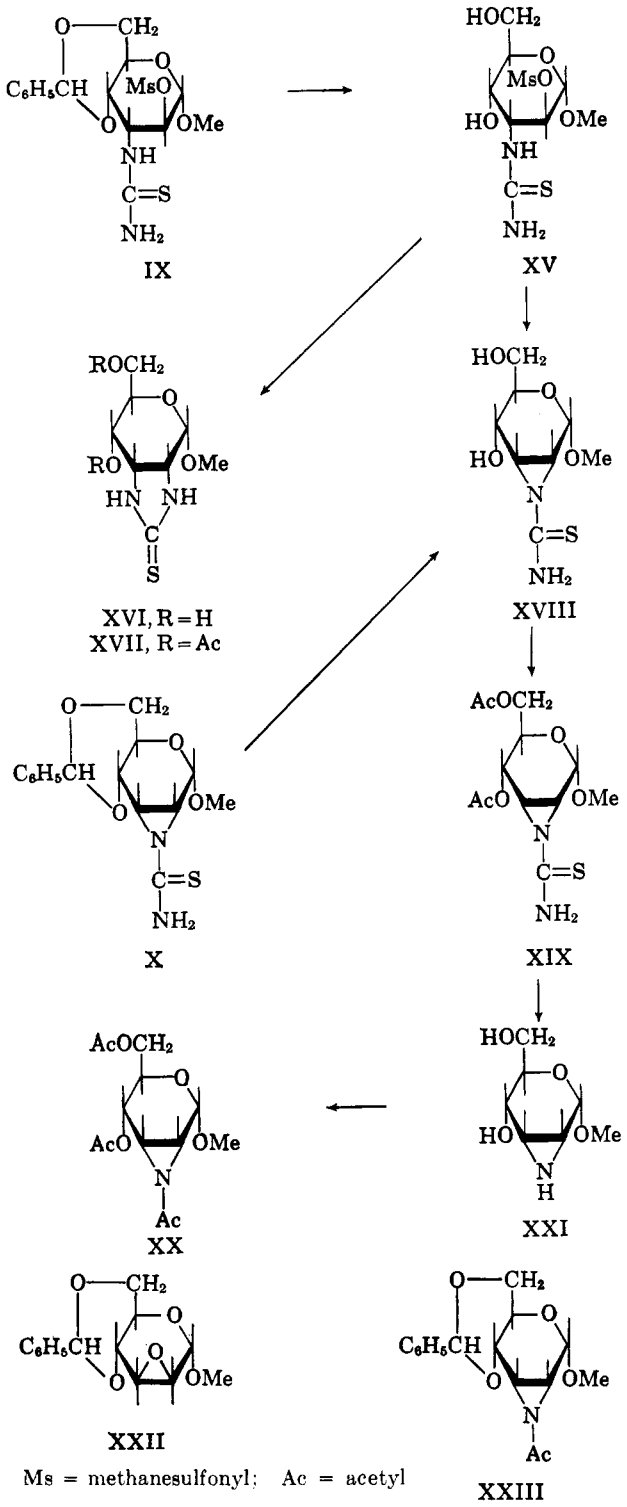
Compounds	Bands in c.p.s.	Half width in c.p.s.	Integration
XXII	187, 191, 201, 205	2 each	2H
XIV	158	10	2H
XXIII	185	8	2H
XX	192	5	2H

The vicinal proton for an amide, as demonstrated by the comparison of pyrrolidine with 2-pyrrolidone, shows a shift downfield. Hence the *N*-acetyl derivatives (XXIII and XX) could be expected to have aziridine ring proton signal near 196 − 50 + 40 = 186 c.p.s., in good agreement with the observed signals at 185 and 192 c.p.s., respectively.

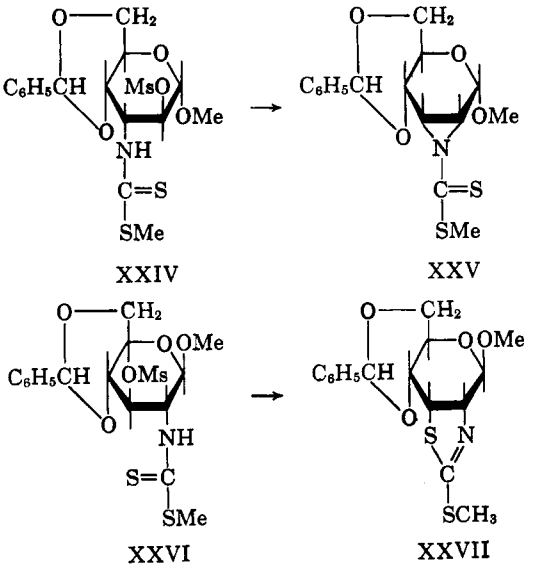
The anionic ring closure of IX and XV to the aziridines (X and XVIII), respectively, parallels the reported anionic ring closure of the dithiocarbomethoxy derivative (XXIV) to the aziridine derivative (XXV)[6] (Scheme III). However, it could not necessarily be anticipated that ionic ring closure of the thiourea neighboring group would follow a similar course; IX and XV have an additional possible mode of anionic

(8) See B. R. Baker, K. Hewson, L. Goodman, and A. Benitez, *J. Am. Chem. Soc.*, **80**, 6577 (1958), for removal of a 4,6-*O*-benzylidene group with a sulfonic type ion-exchange resin.

SCHEME II



SCHEME III



ring closure to the imidazolidines (VIII and XVI), respectively, not possible with XXIV. In contrast, Bonner, *et al.*,[9] have observed recently that the isomeric dithiocarbomethoxy derivative of 2-amino-D-glucopyranoside (XXVI) underwent anionic ring closure to the thiazoline (XXVII) rather than to the β anomer of XXV; the same ring closure occurred in aqueous pyridine. Bonner attributed this difference to the fact that the participating groups in XXVI are *trans*-diequatorial, whereas those of XXIV are *trans*-diaxial. Therefore, the mode of ring closure of the 2-thiourea derivative D-glucose configuration (XXX) was investigated.

Methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β,D-glucopyranoside (XXVIII) was synthesized from D-glucosamine essentially according to Bonner, *et al.*[10] The subsequent conversion of XXVIII to XXX paralleled the similar conversion of the 3-amino-D-altroside (IV) to IX. Reaction of XXVIII with potassium cyanate in dilute alcohol containing one equivalent of acetic acid gave the crystalline urea derivative (XXIX) in 90% yield. Treatment of XXIX with three equivalents of mesyl chloride in pyridine gave the mesylated cyanamide (XXXI) in 82% yield as a glass that had poor crystallizing properties. When crude XXXI was reacted with hydrogen sulfide in pyridine, the crystalline thiourea (XXX) was obtained in 42% yield (Scheme IV).

Surprisingly, either anionic ring closure of XXX or ring closure in the presence of an acid acceptor, pyridine, gave the same product in 71 and 66% yields, respectively, which was shown to have the thiazoline structure (XXXII). It is notable that the thiazoline (XXXII) and the isomeric thiazoline (VIII) had radically different infrared spectra in the 6.0–6.8-μ region, indicating that one of the compounds was a 2-aminothiazoline and the other a 2-iminothiazolidine. Since XXXII had a C=N band at 6.03 μ and VIII a C=N band at 6.10 μ, it is likely that XXXII is a 2-iminothiazolidine; an exocyclic C=N of a five-membered ring should show absorption at a lower wave length than an endocyclic C=N.

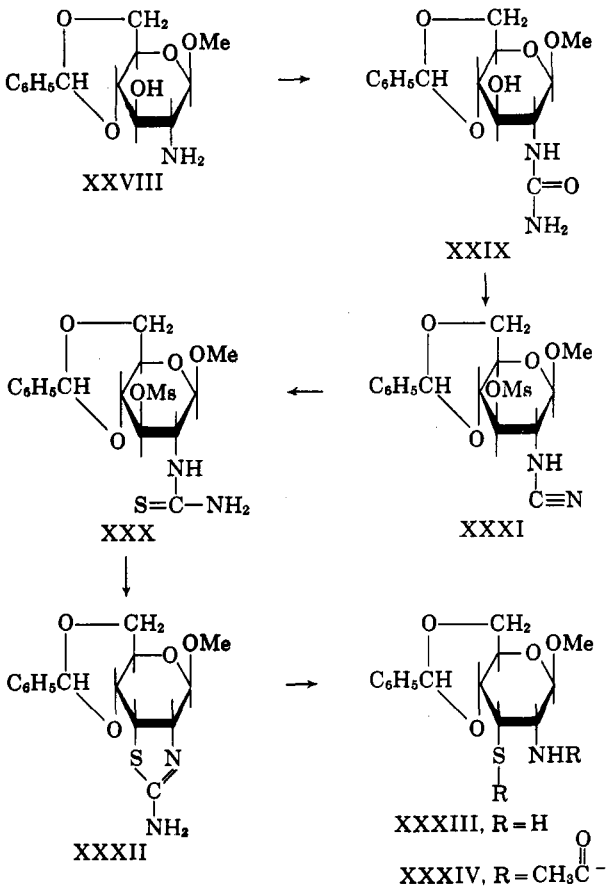
Hydrolysis of the thiazoline (XXXII) with 20% sodium hydroxide to XXXIII followed by acetylation gave the crystalline *N*,*S*-diacetate (XXXIV) in 62% yield that had physical properties agreeing with this same compound prepared previously from the methylthiothiazoline (XXVII) by Bonner.[10b]

Conformational aspects alone appear to be insufficient to explain the observed neighboring reactions in the anionic conversion of IX to X, XVa to XVIII,

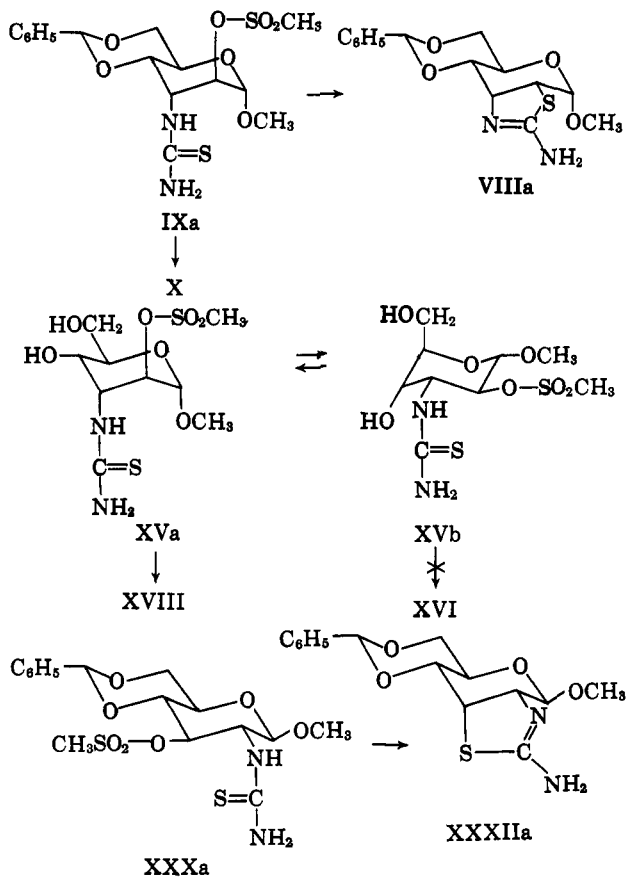
(9) (a) W. M. Reckendorf and W. A. Bonner, *Chem. Ind.* (London), 429 (1961); (b) *Tetrahedron*, **19**, 1711, 1721 (1963). We wish to thank Professor Bonner for sending us the latter manuscript prior to publication.

(10) W. M. Reckendorf and W. A. Bonner, *Chem. Ber.*, **94**, 3293 (1961).

SCHEME IV



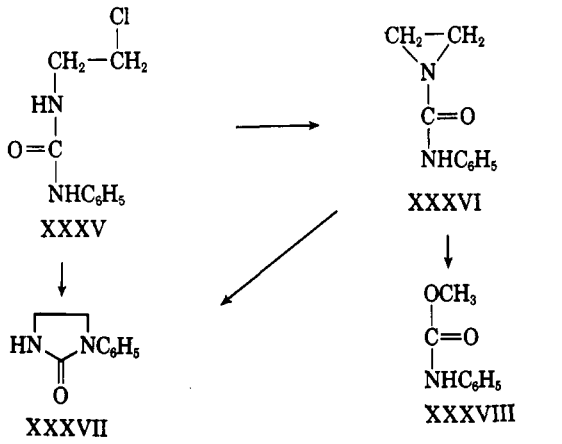
SCHEME V



and XXXa to XXXIIa. The 1-C and C-1 conformations of XVa and XVb appear about energetically equal; XVb has two axial groups and three equatorial groups, although the bulkiest group—the hydroxymethyl—being in an unfavorable axial position probably counterbalances the gain in more equatorial groups than axial groups. In contrast, XVa with three axial groups and two equatorial groups has the bulky hydroxymethyl group in a favorable equatorial conformation. With the assumption that XVa and XVb are readily interconvertible, then treatment of XV with methanolic sodium methoxide should have given the more thermodynamically stable imidazoline (XVI) or thiazoline (VIII) rather than the strained imine (XVIII) (Scheme V).

One possible explanation follows. If there were an equal conformational probability for formation of an imine (XVIII) or an imidazoline (XVI), the imine could be formed preferably, owing simply to a faster rate factor even though the imine was thermodynamically less stable than the imidazoline. If such were the case, then neighboring group reactions on an ethane system such as XXXV also should give an imine; this imine could be an intermediate in the known formation of a five-membered ring, but the sluggishly reacting pyranose system would stop at the imine stage. 1-(2-Chloroethyl)-3-phenylurea (XXXV) has been reported to form the imidazolone (XXXVII) when treated with ethanolic sodium hydroxide,[11] as did the corresponding bromide when treated with ethanolic sodium ethoxide.[12] If this reaction proceeded through

SCHEME VI



an imine (XXXVI) as the rate-limiting step, then XXXVI should be convertible to the imidazolone (XXXVII) when treated with an alkoxide. That this reaction did *not* proceed through the imine (XXXVI) was shown by treatment of XXXVI with methanolic sodium methoxide; the product was methyl-*N*-phenylurethane (XXXVIII), formed by methanolysis due to the imine activation of the carbonyl group[13] (Scheme VI).

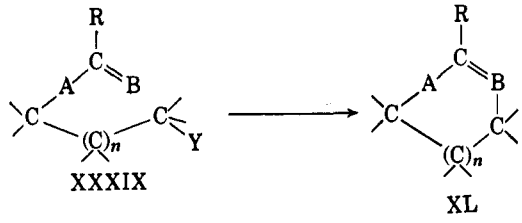
Further investigation will certainly be required to find an explanation for the differences in products in the anionic neighboring group reactions with IXa, XVa and b, and XXXa. Even the anionic attack by

(11) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).

(12) F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957).

(13) The higher reactivity of the carbonyl group in an acylaziridine compared to an ordinary *t*-amide has been reported previously; see H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **83**, 4549 (1961), and H. W. Heine, M. A. Fetter, and E. M. Nicholson, *ibid.*, **81**, 2202 (1959).

sulfur in the ring closure of XXXa to XXXIIa, contrasted to anionic attack by nitrogen in ring of IXa and XVa, resists suitable explanation with the currently available information. One precaution certainly can emerge from the above reactions with the thiourea neighboring group; one should hesitate at the present time to write a general mechanism, such as XXXIX to XL proposed by Winstein and Boschan,[14] since any one of the groups A, B, or R (if R is nucleophilic) may participate in a ring closure *the mode of which can be dependent on the carrier* $(>C)_{n+2}$ *for the participating groups.*



Experimental[15]

Methyl 4,6-*O*-Benzylicene-3-deoxy-3-ureido-α,D-altropyranoside (V).—To a hot solution of 18 g. of IV in 100 ml. of ethanol was added a solution of 7.5 g. of potassium cyanate in 100 ml. of water followed by 4.8 ml. of glacial acetic acid. After being heated on a steam bath for 15 min., the hot solution was filtered, then cooled. The product was collected on a filter and washed with 50 ml. of water to yield 15.9 g. (77%) with m.p. 229–230°; $[\alpha]_D$ + 111 ± 1°; λ_{max} 2.85, 2.98, 3.12 (NH), 5.98 (C=O), 6.25, 6.54 (amide II), and 12.93, 14.11 μ (C_6H_5—).

Anal. Calcd. for $C_{15}H_{20}N_2O_6$: C, 55.5; H, 6.24; N, 8.64. Found: C, 55.5; H, 6.46; N, 8.69.

An additional 1.0 g. (total 82%) was isolated by concentration of the mother liquor.

Methyl 4,6-*O*-Benzylidene-3-cyanamido-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (VII).—To a magnetically stirred suspension of 4.4 g. of V in 20 ml. of reagent pyridine cooled in an ice bath was added 3.5 ml. of methanesulfonyl chloride over a period of 30 min. with strict temperature control in the range of 0–5°. After being stirred an additional 15 min., the mixture was allowed to stand at 0–5° for about 18 hr. protected from moisture, then poured onto about 100 g. of ice. The mixture was extracted with two 100-ml. portions of chloroform; the combined extracts, washed with two 100-ml. portions of water and dried with magnesium sulfate, were spin evaporated to residue *in vacuo*. Traces of pyridine were removed from the residue by spin evaporation of toluene (two 25-ml. portions) *in vacuo*. Recrystallization from ethanol gave 4.2 g. (82%) of white needles, m.p. 154–155°; $[\alpha]^{22}_D$ + 61 ± 1° (1.13%); λ_{max} 3.13 (NH), 4.48 (C≡N), 7.30, 8.55 (sulfonate), and 13.3, 14.3 μ (C_6H_5—).

Anal. Calcd. for $C_{16}H_{20}N_2O_7S$: C, 50.0; H, 5.50; N, 7.29; S, 8.44. Found: C, 49.9; H, 5.45; N, 7.46; S, 8.57.

Methyl 4,6-*O*-Benzylidene-3-deoxy-2-*O*-mesyl-3-thioureido-α,D-altropyranoside (IX).—Through a solution of 1.00 g. of VII in 10 ml. of reagent pyridine was bubbled slowly hydrogen sulfide for 15 min. After standing about 18 hr., the solution was spin evaporated to residue *in vacuo;* traces of pyridine were removed from the residue by spin evaporation of toluene (two 5-ml. portions). Crystallization from ethyl acetate–petroleum ether gave 0.80 g. (73%) of white prisms, m.p. 160–161°; $[\alpha]^{22}_D$ + 60.5 ± 0.7° (1.02%); λ_{max} 2.85, 3.00, 3.15 (NH), 6.26, 6.45 (amide II), 7.30 (C=S), 7.45, 8.56 (sulfonate), 13.4, 14.3 (C_6H_5), and no C≡N near 4.5 μ.

Anal. Calcd. for $C_{16}H_{22}N_2O_7S_2$: C, 45.9; H, 5.30; N, 6.70; S, 15.3. Found: C, 46.2; H, 5.35; N, 6.72; S, 15.2.

2-Amino-4′,6′-*O*-benzylidene-1′-*O*-methyl-α,D-allopyrano[3′,-2′:4,5]-2-thiazoline (VIII).—A solution of 250 mg. of IX in 8 ml. of reagent pyridine was refluxed for 1 hr., then poured into 20 ml. of water, and extracted with two 20-ml. portions of chloroform. The combined extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Traces of pyridine were removed from the residue by spin evaporation with toluene (two 10-ml. portions) *in vacuo*. Crystallization from ethyl acetate–petroleum ether gave white prisms, m.p. 195–196°; $[\alpha]^{22}_D$ + 196 ± 2° (0.64%); λ_{max} 2.91 (NH), 6.10, 6.30 (NH, C=N), 13.35, 14.35 (C_6H_5—), and no C=S or sulfonate absorption near 7.4 μ.

Anal. Calcd. for $C_{15}H_{18}N_2O_4S$: C, 55.9; H, 5.64; N, 8.70; S, 9.96. Found: C, 56.1; H, 5.70; N, 8.79; S, 10.1.

Anal. Calcd. for $C_{15}H_{18}N_2O_4S$: C, 55.9; H, 5.64; N, 8.70; S, 9.96. Found: C, 56.1; H, 5.70; N, 8.79; S, 10.1.

Methyl 3-Acetamido-2-acetylthio-4,6-*O*-benzylidene-2,3-dideoxy-α,D-allopyranoside (XII).—A mixture of 1.00 g. of VIII and 25 ml. of 20% sodium hydroxide was refluxed for about 18 hr. The cooled solution was neutralized to pH 8–9 with glacial acetic acid, then immediately stirred with 2 ml. of acetic anhydride for 1 hr. The solution was extracted with three 30-ml. portions of chloroform; the combined extracts, washed with three 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo* to yield 0.91 g. (77%) of a glass that could not be crystallized, but was nearly pure. The sample showed $[\alpha]^{22}_D$ + 13.5 ± 1.7° (0.28%); λ^{film}_{max} 2.97, 3.03 (NH), 6.0 (broad) (ester and amide C=O), 6.65 (amide II), and 13.3, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{18}H_{23}NSO_6$: C, 56.7; H, 6.08; N, 3.67; S, 8.36. Found: C, 56.1; H, 6.09; N, 3.66; S, 8.06.

Disulfide of Methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-2-mercapto-α,D-allopyranoside (XI).—Treatment of 1.00 g. of VIII as in the previous experiment, except that the acetic anhydride was omitted, gave XI as a glass that showed SH absorption at 3.89 μ. When XI was allowed to stand in ethanol, the disulfide slowly crystallized as an ethanol solvate to yield 420 mg. (43%), m.p. 123–124° (gas); $[\alpha]^{22}_D$ + 47 ± 3° (0.17%); λ_{max} 2.85, 2.99, 6.31, 6.35 (NH_2), and 13.2, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{14}H_{17}NO_4S \cdot {}^2/_3C_2H_5OH$: C, 56.3; H, 6.78; N, 4.28; S, 9.78; mol. wt., 654. Found: C, 55.9; H, 6.85; N, 4.31; S, 9.88; mol. wt., 690.

The n.m.r. spectrum ($DCCl_3$) showed a CH_3 peak of ethanol at 70 c.p.s., the intensity of which was $^2/_3$ mole compared to the phenyl ring. The compound gave a negative nitroprusside test.

Goodman and Christensen[6] obtained this compound free of solvate by a different route; they recorded m.p. 228–236°, but did not record an optical rotation.

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2,3-imino-*N*-thiocarbamyl-α-D-allopyranoside (X).—To a warm solution of 2.00 g. of IX in 25 ml. of absolute ethanol was added 8.0 ml. of 1 *N* methanolic sodium methoxide. After being refluxed 10 min., during which time solid separated, the mixture was allowed to stand overnight at ambient temperature. The solids were collected on a filter and recrystallized from aqueous ethanol to give 1.30 g. (85%) of product as white needles, m.p. 177–178°; $[\alpha]_D$ + 132.4 ± 0.8° ± 0.8° (1.22%); λ_{max} 2.90, 3.04, 3.15, 6.15, 6.22 (NH), 7.35 (C=S), and 13.4 μ (C_6H_5—).

Anal. Calcd. for $C_{15}H_{18}N_2O_4S$: C, 55.9; H, 5.64; N, 8.70; S, 9.96. Found: C, 55.7; H, 5.89; N, 8.53; S, 9.66.

A solution of 300 mg. of X in 25 ml. of 0.2 *N* sodium hydroxide was refluxed for 2 hr. As previously described,[2] XIV was isolated in 85% yield (210 mg.) with m.p. 144–145°, that was identical with the earlier sample.[2]

Methyl 3-deoxy-2-*O*-mesyl-3-thioureido-α,D-altropyranoside (XV).—A magnetically stirred solution of 2.00 g. of IX in 200 ml. of 80% aqueous methanol was refluxed with 5 g. of sulfonic acid resin [Dowex 50W-X8 (H^+)] for 4 hr. The filtered solution was spin evaporated *in vacuo* leaving the product as a glass; yield 1.60 g. (95%); λ_{max} 2.92, 3.01, 3.13 (NH, OH), 6.25, 6.50 (amide NH), 7.40, 8.56 μ (sulfonate), and no C_6H_5– absorption in the 13–14.5-μ region.

Anal. Calcd. for $C_9H_{18}N_2O_7S_2$: C, 32.7; H, 5.47; N, 8.48; S, 19.4. Found: C, 32.6; H, 5.27; N, 8.30; S, 19.2.

Similarly, hydrolysis of X gave a quantitative yield of **methyl 2,3-dideoxy-2,3-imino-*N*-thiocarbamyl-α,D-allopyranoside (XVIII)** that was suitable for further transformation to XIX. Crystallization from ethanol gave only a 14% recovery of white crystals with m.p. 223–224°; $[\alpha]^{24}_D$ + 150 ± 1° (0.41%);

(14) S. Winstein and R. Boschan, *J. Am. Chem. Soc.*, **72**, 4669 (1950).

(15) Melting points were taken in capillary tubes in a Mel-Temp block and those below 230° are corrected. Infrared spectra were determined in Nujol mull with a Perkin-Elmer Model 137B spectrophotometer. Nuclear magnetic resonance spectra were determined in $DCCl_3$ with a Varian A-60 spectrometer using tetramethylsilane as the internal standard. Optical rotations were determined in a 1-dm. microtube in *N,N*-dimethylformamide unless otherwise indicated. Petroleum ether was a fraction boiling at 30–60°.

λ_{max} 2.92, 3.01, 3.15 (NH, OH), 6.25, 6.32 μ (NH), and no C_6H_5– peak in the 14-μ region.

Anal. Calcd. for $C_8H_{14}N_2O_4S$: C, 41.0; H, 6.02; N, 12.0; S, 13.7. Found: C, 41.0; H, 6.15; N, 11.8; S, 13.5.

Methyl 4,6-Di-*O*-acetyl-2,3-dideoxy-2,3-imino-*N*-thiocarbamyl α,D-allopyranoside (XIX). **A.**—To a solution of 400 mg. of XV in 10 ml. of absolute ethanol was added 2.0 ml. of 1 *N* methanolic sodium methoxide. The mixture was warmed to 40°, then allowed to cool to room temperature; sodium methanesulfonate separated. The mixture was spin evaporated to dryness *in vacuo*. To the residue of crude XVIII was added 5 ml. of acetic anhydride. After standing for about 18 hr., 10 ml. of ethanol was added; 1 hr. later, the mixture was spin evaporated *in vacuo*, then diluted with 20 ml. of water, and extracted with three 20-ml. partions of chloroform. The combined chloroform extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Crystallization from ethyl acetate–petroleum ether (30–60°) gave 290 mg. (75%) of white crystals, m.p. 139–140°; $[\alpha]^{24}D$ + 208 ± 3° (0.14%); λ_{max} 2.92, 3.02, 3.12 (NH), 5.78 (ester C=O), 6.22 (NH), 8.0–8.4 (ester C—O—C), and no sulfonate near 8.6 μ.

Anal. Calcd. for $C_{12}H_{18}N_2O_6S$: C, 45.3; H, 5.71; N, 8.80; S, 10.1. Found: C, 45.6; H, 5.92; N, 8.81; S, 10.2.

B.—To a solution of 500 mg. of crude XVIII, prepared *via* X, in 10 ml. of reagent pyridine was added 0.5 ml. of acetic anhydride. After 2 hr. at room temperature, the solution was diluted with 20 ml. of water and processed as in method A. Traces of pyridine in the crude product were removed by spin evaporation with toluene (two 10-ml. portions). Crystallization from ethyl acetate–petroleum ether gave 305 mg. (46%) of white needles, m.p. 139–140°, that were identical with preparation A.

Methyl *N*-Acetyl-4,6-O-acetyl-2,3-dideoxy-2,3-imino-α,D-allopyranoside (XX). **A.**—The crude XVIII, prepared from XV by method A, was hydrolyzed with boiling 0.2 *N* aqueous sodium hydroxide for 2 hr. Spin evaporation *in vacuo*, followed by acetylation as described for XIX, gave 282 mg. (77%) of the product as an oil; $[\alpha]^{24}D$ + 162 ± 1° (1.02%); λ_{max} 5.77 (ester C=O), 5.90 (amide C=O), 8.0–8.4 (ester C—O—C), and no NH near 3 or 6 μ.

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 63.0; H, 6.28; N, 4.59. Found: C, 63.1; H, 6.39; N, 4.56.

B.—Hydrolysis of 250 mg. of crystalline XIX with 0.2 *N* aqueous sodium hydroxide, followed by acetylation as in method A, gave 156 mg. (66%) of product as an oil that was identical with preparation A.

Methyl 4,6-*O*-benzylidene-2-deoxy-2-ureido-β,D-glucopyranoside (XXIX).—Methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside was prepared essentially according to the method of Reckendorf and Bonner[10] with the following notation. (1) In the formylation of D-glucosamine, sodium chloride was not removed by filtration prior to addition of methyl formate, since, in some runs, D-glucosamine base rapidly crystallized from the methanol and was rejected with the salt; the salt did not interfere with the benzylidenation step. The over-all yield, m.p. 236–237°, for the two steps was 26%; however, the first step did not work consistently unless the D-glucosamine hydrochloride was finely ground. (2) The insoluble material remaining prior to adding dimethyl sulfate to a basic solution of *N*-formyl-4,6-*o*-benzylidene-D-glucosamine was unchanged material and could be used again; thus, the yield of β anomer was 57%, m.p. 260–261°.

To a solution of 1.8 g. of crude XXVIII (free base)[10] in 15 ml. of warm ethanol was added a solution of 0.75 g. of potassium cyanate in 10 ml. of water followed by 0.48 ml. of glacial acetic acid. After being heated to about 80°, the mixture was allowed to cool to room temperature and the product was collected. A second crop was obtained by concentration of the mother liquor *in vacuo*. Recrystallization of the combined crops from ethanol gave 1.8 g. (90%) of product, m.p. 321–323°; $[\alpha]^{24}D$ −73 ± 3° (0.084%); λ_{max} 2.90, 2.95, 3.05 (OH, NH), 6.05 (amide C=O), 6.28, 6.40 (amide II), and 13.2, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{15}H_{20}N_2O_6$: C, 55.5; H, 6.24; N, 8.64. Found: C, 55.4; H, 6.22; N, 8.43.

Methyl 4,6-*O*-Benzylidene-2-thioureido-2-deoxy-3-*O*-mesyl-β,D-glucopyranoside (XXX).—XXX was prepared from 1.50 g. of crude XXXI as described for V → VII → IX. Crystallization from ethanol gave 0.71 g. (43%) of white needles, m.p. 223–224°; $[\alpha]^{24}D$ + 103 ± 1° (0.36%); λ_{max} 3.05, 3.19, 5.99, 6.21 (NH), 7.27, 8.62 (sulfonate), 8.43 (C=S), and 13.2, 14.3 (C_6H_5—).

Anal. Calcd. for $C_{16}H_{22}N_2O_7S_2$: C, 45.9; H, 5.30; N, 6.70; S, 15.3. Found: C, 46.1; H, 5.40; N, 6.54; S, 15.5.

2-Amino-4′,6′-*O*-benzylidene-1′-*O*-methyl-α,D-allopyrano-[2′,3′:4,5]-2-thiazoline (XXXII). **A.**—To a solution of 1.0 g. of XXX in 20 ml. of methanol was added 5 ml. of 1 *N* methanolic sodium methoxide. The mixture was warmed to 50° during which time sodium mesylate separated. The mixture was spin evaporated *in vacuo*, then diluted with 20 ml. of water, and extracted with three 25-ml. portions of chloroform. The combined chloroform extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Crystallization from ethanol gave 550 mg. (71%) of white needles, m.p. 235–237°; $[\alpha]D$ +54 ± 1° (0.30%); λ_{max} 2.91, 3.00 (NH), 6.03, 6.15, 6.30, 6.41 (C=N, NH), and 13.2, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{15}N_{18}N_2O_4S$: C, 55.9; H, 5.64; N, 8.70; S, 9.96. Found: C, 56.1; H, 5.71; N, 8.66; S, 9.70.

B.—A solution of 300 mg. of XXX in 10 ml. of reagent pyridine was refluxed for 2 hr., then processed as described for VIII. Crystallization from ethanol gave 153 mg. (66%) of product, m.p. 235–236°, that was identical with preparation A.

Methyl 2-Acetamido-3-acetylthio-4,6-*O*-benzylidene-2,3-dideoxy-β,D-allopyranoside (XXXIV).—Hydrolysis of 500 mg. of XXXII with 20% sodium hydroxide, then acetylation of the intermediate aminothiol (XXXIII), as described for the preparation of XII, gave, after recrystallization from ethanol, 370 mg. (62%) of white needles, m.p. 233–234°; $[\alpha]^{24}D$ −118 ± 3° (0.20% in chloroform); λ_{max} 3.05 (NH), 5.92 (thiol C=O), 6.08 (amide C=O), 6.58 (amide NH), and 13.2, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{18}H_{23}NSO_6$: C, 56.7; H, 6.08; N, 3.67; S, 8.36. Found: C, 56.9; H, 6.31; N, 3.77; S, 8.13.

Reckendorf and Bonner[9b] have recorded m.p. 231–232° (uncor.) and $[\alpha]^{23}D$ −122° (1.06% in chloroform).

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