Synthetic Nucleosides. LX.[1,2] Studies on the Synthesis of *cis*-2,3-Diamino Sugars. III. The Urea Neighboring Group

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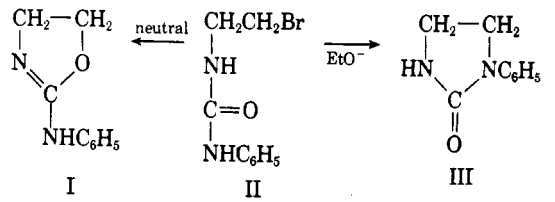
Anionic cyclization of methyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-mesyl-3-ureido-α,D-altropyranoside (VII) occurred by nitrogen attack to form an *N*-carbamyl imino alloside (VIII), rather than the desired imidazolidone. Cyclization of VII under acid acceptor conditions proceeded by oxygen attack with formation of an imino-oxazoline (XVII). In order to block imine formation, the addition of water or methanol to the C≡N of methyl 3-benzylamino-4,6-*O*-benzylidene-*N*-cyano-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (XXVI) with concurrent cyclization was investigated. Treatment of XXVI with sodium hydroxide in boiling 2-methoxyethanol gave only 3% yield of the expected imidazolone (XXVII) formed by anionic nitrogen attack; most of the intermediate urea derivative cyclized by oxygen attack to give an oxazolidone (XXVIII). However, when XXVI was treated with methanolic ammonia at 130–150° under pressure, the desired imidazolone (XXVII) was formed in 73% yield. Vigorous basic hydrolysis at 150–170°, followed by acetylation, gave 82% of a crystalline derivative of a *cis*-2,3-diamino sugar, namely methyl 2-acetamido-3-benzylamino-4,6-*O*-benzylidene-2,3-dideoxy-α,D-altropyranoside (XXX).

Among the neighboring groups that have the potential[3] for introduction of nitrogen on a vicinal carbon is the urea group. The phenylurea neighboring group has been investigated previously by Winstein, *et al.*, in an acylic system.[4] Under neutral conditions, the bromide of II was eliminated by oxygen attack to give



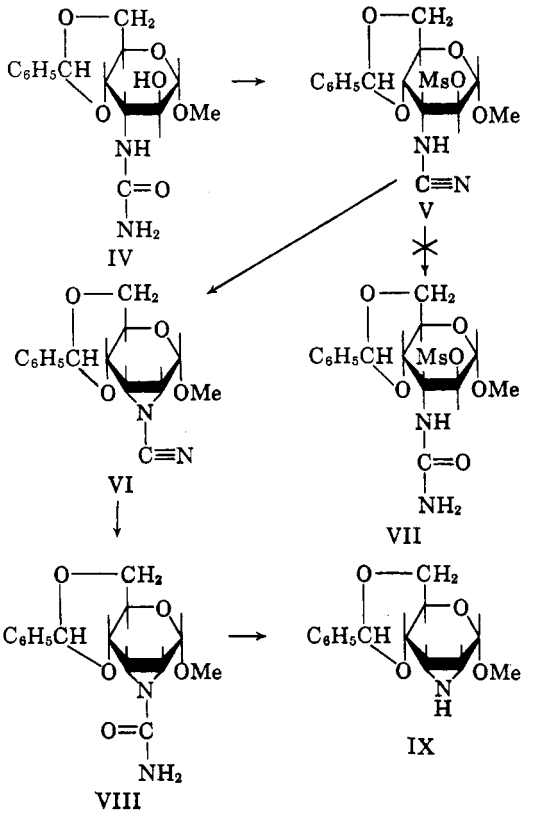
I II III

the 2-anilino-2-oxazoline (I); in contrast, when II was treated with ethanolic sodium ethoxide, nitrogen attack—presumably as an anion—took place to give the cyclic urea (III). Although they did not investigate the simple ureido neighboring group without a phenyl, it might be anticipated that similar results would be obtained.

As previously described,[2] mesylation of the urea (IV) did not give the urea mesylate (VII), but further elimination of the elements of water with formation of a cyanamide group (V) occurred; such a dehydration would be expected under these conditions.[2] The availability of the cyanamido mesylate (V) suggested that attempts be made to hydrate the cyanamido group in order to regenerate a ureido mesylate (VII). Since acidic conditions can remove the benzylidene group, it would be necessary to do such a hydration under neutral or basic conditions.

In boiling water, the benzylidene group of V underwent cleavage. When V was refluxed with 0.2 *N* aqueous sodium hydroxide solution for 2 hr., the desired ureido mesylate (VII) was not obtained; instead the aziridino sugar (IX)[2,3,5] was obtained in 90% yield

SCHEME I



(Scheme I). That the aziridine (IX) was formed by the sequence V → VI → VIII → IX was shown as follows.

Treatment of an ethanolic solution of the cyanamide (V) with methanolic sodium methoxide at room temperature caused almost instantaneous ring closure to the cyano imine (VI) in 88% yield. Further treatment of VI with 0.25 *N* alcoholic sodium hydroxide at 60–70° led to hydration of the cyanamido group and the carbamyl imine (VIII) was obtained in 74% yield. Finally, hydrolysis of VIII with boiling 0.2 *N* sodium hydroxide for 2 hr.—the conditions used for the conversion of V to IX—gave IX in 91% yield. The failure of this approach for the preparation of the ureido mesylate (VII) from the cyanamide (V) clearly can be

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

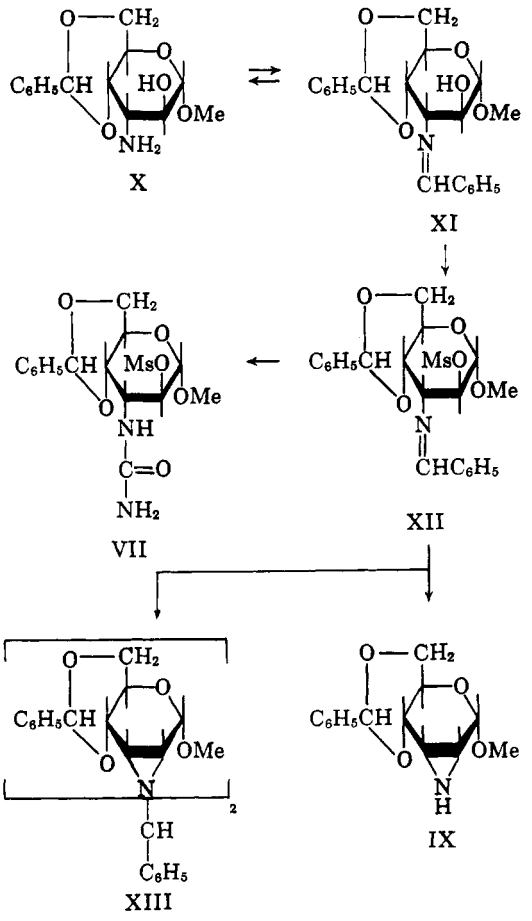
(2) For the previous paper of this series, see B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1051 (1964).

(3) B. R. Baker and T. Neilson, *ibid.*, **29**, 1047 (1964), paper LVIII of this series.

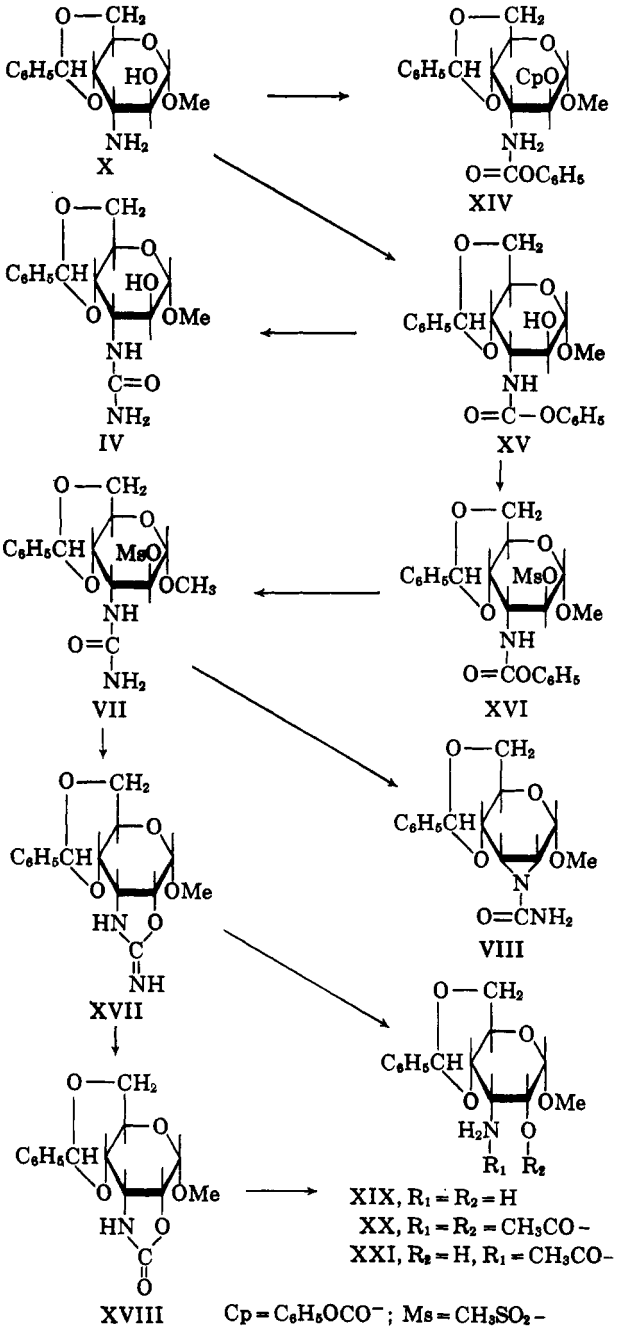
(4) (a) F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957); (b) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).

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

SCHEME II



SCHEME III



attributed to the faster rate of ring closure of V → VI, than the hydration of the triple bond of V → VII (compare VI → VIII).

Since substituted cyanamides such as V are more acidic than ureas such as VII, it could be anticipated that V would ring close more rapidly to an aziridine (VI) than VII would cyclize to VIII under basic conditions. Therefore, alternate routes for the preparation of the ureido mesylate (VII) were sought. The amino altroside (X) smoothly reacted with benzaldehyde to give the crystalline *N*-benzylidene derivative (XI) in 87% yield (Scheme II); that this protecting group for the amine was readily removed under mild conditions was shown by the hydrolysis of XI back to X in 89% yield when heated in aqueous alcohol for 2 hr. Mesylation of XI with methanesulfonyl chloride in pyridine at 0° gave a quantitative yield of XII as a glass that could not be crystallized, but had the proper infrared spectrum; its structure was verified by treatment with 0.2 *N* sodium hydroxide, when 20% of the aziridine IX and 32% of benzylidene diaziridine (XIII) were formed. When XII was treated with potassium cyanate in 50% alcohol containing acetic acid, the benzylidene group was removed and the resultant amine reacted with cyanic acid to give the urea VII as a glass; under these conditions the intermediate amino mesylate reacts more rapidly with cyanic acid than it ring closes to IX.

Earlier, an alternate route to the ureido mesylate (VII) utilizing a latent ureido group was investigated. *O*-Phenylurethanes have been found to be excellent intermediates for synthesis of mixed ureas[6,7] and usually are prepared by the reaction of an amine with phenyl chloroformate. Carefully controlled conditions—that is, addition of the amine to the acid chloride or total immediate mixing—must be used to avoid formation of the symmetrical urea.[7] Unfortunately, in addition to formation of the desired *N*-carbophenoxy derivative (XV), these conditions led to formation of considerable *N,O*-dicarbophenoxy derivative (XIV), probably due the insolubility of X and the solubility of XV in the reaction medium. The *N*-carbophenoxy derivative (XV) was best prepared by fusion of the amino altroside (X) with excess diphenyl carbonate; XV was obtained as a glass in 96% yield that was characterized by conversion to the crystalline urea (IV)[2] in 65%

(6) D. G. Crosby and C. Niemann, *J. Am. Chem. Soc.*, **76**, 4458 (1954).
(7) B. R. Baker and R. P. Patel, *J. Pharm. Sci.*, **52**, 927 (1963).

yield with ammonia in aqueous alcohol. Mesylation of XV in pyridine gave a 92% yield of XVI, which could not be crystallized but contained the proper infrared absorption bands. Further reaction of XVI with ammonia in dilute alcohol at room temperature afforded the desired VII as a glass in 92% yield; this compound could not be crystallized but was estimated to be at least 80% pure by combustion analyses.

When the ureido mesylate (VII) was heated with ethanolic sodium ethoxide, the desired imidazolidone was not obtained, but again cyclization to an aziridine (VIII)[2,3] took place in good yield; VIII was further characterized by basic hydrolysis to the imino alloside (IX). Cyclization of the ureido mesylate in boiling 2-methoxyethanol in the presence of sodium acetate as an acid acceptor gave 92% of a glass that had the spectral properties for a mixture of a cyclic iminourethane (XVII), formed by neighboring oxygen attack, and the cyclic urethane (XVIII), formed by hydrolysis of the imino group of XVII. Basic hydrolysis of XVIII gave the crystalline 3-amino alloside (XIX), further characterized by conversion to the authentic acetyl derivatives XX and XXI[8] (Scheme III).

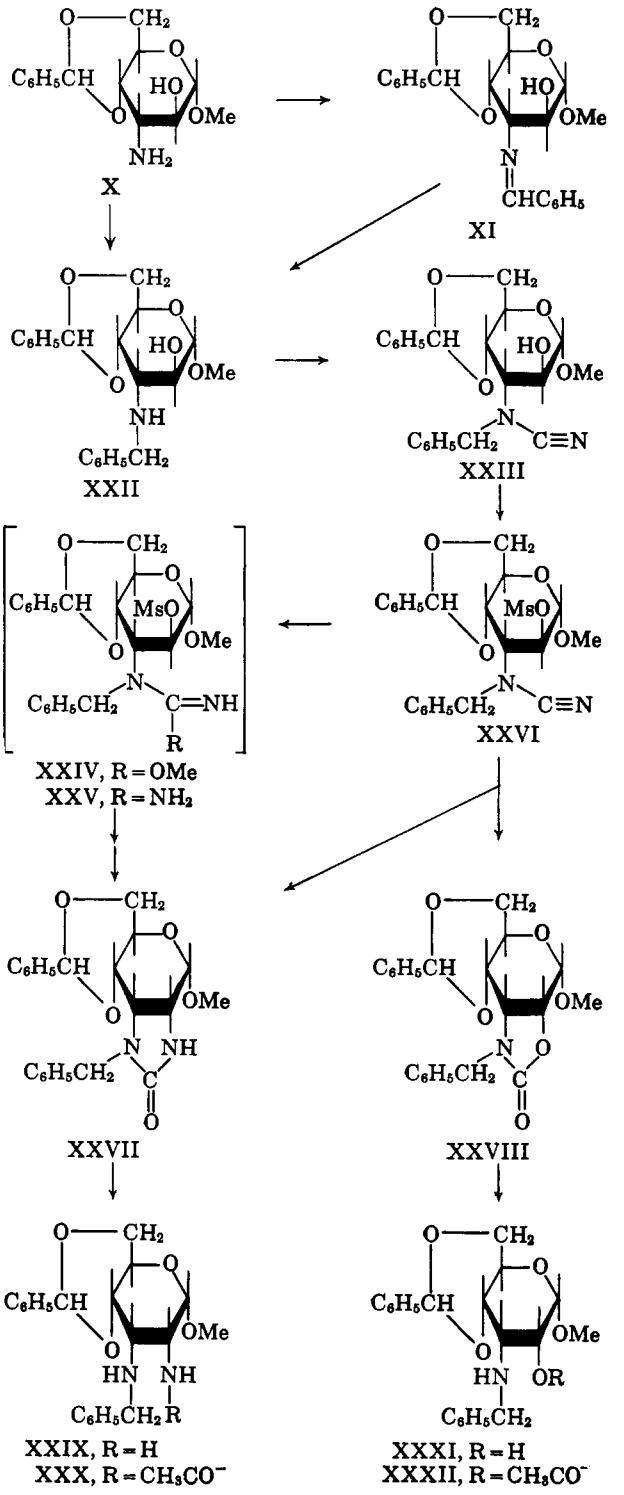
Similarly, when VII was refluxed in pyridine, oxygen attack to an iminocarbonate (XVII) took place in 84% yield; XVII also was characterized by conversion to XIX, XX and XXI.

Thus, the urea neighboring group of VII behaved in participation reactions exactly the same as the corresponding thiourea neighboring group[2]; reaction in the presence of an acid acceptor led to oxygen or sulfur attack, respectively, whereas conversion to an anion resulted in attack by the secondary amide group to give aziridine derivatives in both cases. It was concluded that the secondary amide NH would have to be blocked in order that the slower reacting primary amide group could attack to give a five-membered imidazolidone ring; the blocking group should be stable to the ring-closure conditions, yet should be removable at the proper time. The *N*-benzyl blocking group was selected for this purpose.

Sodium borohydride reduction of the anil (XI) gave the 3-benzylamino altroside (XXII) in 82% yield, 71% over-all for the two steps from the amino altroside (X). Direct reaction of 2 moles of X with 1 mole of benzyl bromide in ethanol gave a 91% yield of the benzylamino altroside (XXII), and most of the second mole of X used as an acid acceptor could be recovered. Treatment of XXII with cyanogen bromide in alcohol gave XXIII in 94% yield. Mesylation of XXIII in pyridine gave the cyanamido mesylate (XXVI) in 91% yield as a glass that could not be crystallized, but was analytically pure. Repetition of the sequence X → XXII → XXIII with *p*-nitrobenzyl bromide also failed to give crystalline compounds.

The *N*-benzylcyanamide (XXVI) was considerably less reactive towards hydroxide ion and hydrogen sulfide than were the corresponding nonbenzylated cyanamides (V and VI); XXIII was recovered unchanged under conditions where the nitrile group of V and VI underwent addition reactions. When the *N*-benzylcyanamide (XXVI) was refluxed with 0.4 *N* sodium hydroxide in 2-methoxyethanol for 3 days, the C≡N absorption finally disappeared. The product was mainly the cyclic urethane (XXVIII); a small amount (3%) of cyclic urea (XXVII) could be isolated after the crude XXVIII was hydrolyzed further with boiling 0.2 *N* sodium hydroxide for 2 hr. (Scheme IV). Neither the resultant benzylamino alloside (XXXI) nor its *O*-acetyl derivative (XXXII) could be crystallized. Although the evidence is good that the mesylate was ejected by neighboring group reaction to give an alloside *via* the oxazoline (XXVIII), it is also possible that some alloside was formed by direct SN2 displacement of the mesylate and that some altroside also could be present by cleavage of the O–S

SCHEME IV



(8) B. R. Baker and R. E. Schaub, *J. Org. Chem.*, **19**, 646 (1954).

group of the mesylate.[9] In view of the relatively good yield of the imidazolone (XXVII) obtained under the conditions described later and the apparent oxygen participation in ring closure to XXVIII under basic conditions, this sequence was not investigated further. However, it is notable that under these basic conditions oxygen attack rather than the expected nitrogen attack took place. Since it has been shown[4] that nitrogen attack would be preferred over oxygen attack when the urea neighboring group is converted to sufficient quantity of anion, it is probable that the disubstituted urea is so weakly acidic that insufficient anion is formed to complete with oxygen attack. In contrast, the ureido group of VII must be ionized sufficiently in aqueous sodium hydroxide to allow N^- attack to give VIII. In fact, the much more acidic cyanamido mesylate (V) is converted to the anion in dilute ammonia, thus causing rapid nitrogen attack with formation of the cyanoimine (VI).[10]

When the *N*-benzylcyanamide (XXVI) was heated in a steel bomb at 130–150° with saturated methanolic ammonia, slow reaction took place. After 7 days, 42% of the crystalline imidazolone (XXVII) had separated and 40% of the starting mesylate (XXVI) could be recovered unchanged. Since the imidazolone (XXVII) was isolated, rather than the corresponding aminoimidazoline, several steps must be involved in this transformation. The rate-limiting step must be the first step since only starting material and imidazolone (XXVII) are obtained. Thus, the first step could be the addition of methanol or ammonia to give the *O*-methylurea (XXIV) or the amidine (XXV) which could cyclize to a 2-methoxy or 2-aminoimidazoline, respectively; the 2-methoxy or 2-amino group could then be displaced by traces of water in the reaction or, less likely, the 2-methoxyimidazoline could react further with ammonia to give XXVII and methylamine. The odor of methylamine was noticeable when the bomb was opened. Although at first glance this might seem to be evidence for the conversion of a methoxyimidazoline to methylamine and XXVII, it also could be evidence for the first mechanism, since ammonia and methyl alcohol could give small amounts of methylamine and water under these conditions. Further evidence for the addition of methanol to a cyanamido group in the presence of ammonia is presented in the following paper.[10]

The imidazolone (XXVII) was extremely resistant to basic hydrolysis, again indicating the steric crowding caused by the *N*-benzyl group; however, after being heated with 30% potassium hydroxide in 50% aqueous ethanol at 150–170° for 7 days, the cyclic urea group was hydrolyzed. Work-up by acetylation in aqueous acetic acid gave a crystalline monoacetyl derivative (XXX) in 82% yield for the two steps; that the monoacetyl group was on the primary amine group as expected was shown by the amide-NH band at 6.57 μ.

Although it should be possible to remove the *N*-benzyl group from either XXVII or XXX by hydrogenolysis or by sodium–ammonia reduction to give the desired 2,3-diamino-D-alloside derivative, these reactions have not yet been investigated.

(9) R. W. Jeanloz and D. A. Jeanloz, *J. Am. Chem. Soc.*, **80**, 5692 (1958).

(10) B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1063 (1964), paper LXI of this series.

Experimental[11]

Methyl 4,6-*O*-Benzylidene-*N*-cyano-2,3-dideoxy-2,3-imino-α,D-allopyranoside (VI).—To a solution of 500 mg. of V[2] in 10 ml. of absolute ethanol at room temperature was added 2 ml. of 1 *N* methanolic sodium methoxide. A yellow coloration immediately formed that bleached in a few minutes as the product separated. The product was collected on a filter and washed with water. Recrystallization from ethanol gave 360 mg. (88%) of white needles, m.p. 183–184°; $[\alpha]^{22}D$ +135 ± 1° (1.1%); λ_{max} 4.53 (C≡N), 13.2, 14.3 (C_6H_5—), and no NH near 3 and no sulfonate near 7.4 or 8.5 μ.

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.5; H, 5.61; N, 9.73; S, 0.0. Found: C, 62.4; H, 5.66; N, 9.88; S, 0.0.

Methyl 4,6-*O*-Benzylidene-*N*-carbamyl-2,3-dideoxy-2,3-imino-α,D-allopyranoside (VIII). A.—A solution of 500 mg. of VI in 20 ml. of 0.25 *N* sodium hydroxide in 90% ethanol was warmed on a steam bath for 10 min., then spin evaporated *in vacuo*. The residue was extracted with two 20-ml. portions of chloroform. The combined extracts, washed with two 2-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Recrystallization from ethanol gave 390 mg. (74%) of white needles, m.p. 197–198°; $[\alpha]D$ + 141 ± 1° (0.94%); λ_{max} 2.92, 3.02, 3.13 (NH), 5.90, 6.05 (C=O), 6.30 (amide II), and 13.4, 14.5 μ (C_6H_5—).

Anal. Calcd. for $C_{15}H_{18}N_2O_5$: C, 58.8; H, 5.94; N, 9.15. Found: C, 58.6; H, 5.77; N, 8.90.

B.—To a solution of 1.00 g. of VII (prepared *via* XVI) in 10 ml. of absolute ethanol was added 1 ml. of 1 *N* methanolic sodium methoxide. After being refluxed for 1 hr., the mixture was processed as in method A to yield 520 mg. (68%) of recrystallized product, m.p. 199–200°, that was identical with preparation A. Similarly, VII prepared *via* XII gave 73% yield of VIII.

Anal. Found: C, 58.9; H, 5.83; N, 8.95.

Methyl 4,6-Benzylidene-2,3-dideoxy-2,3-imino-α,D-allopyranoside (IX). A.—A solution of 500 mg. of V[2] in 25 ml. of 0.2 *N* aqueous sodium hydroxide was refluxed for 2 hr., then cooled, and extracted with two 25-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*. Recrystallization from ethyl acetate–petroleum ether (b.p. 30–60°) gave 310 mg. (90%) of product, m.p. 143–144°, that was identical with an authentic sample.[3,5]

B.—Treatment of 500 mg. of VI as in method A gave 350 mg. (75%) of recrystallized product, m.p. 143–144°, identical with an authentic sample.[3,5]

C.—Treatment of 230 mg. of VIII (prepared from VI) as in method A gave 180 mg. (91%) of recrystallized product, m.p. 143–144°, identical with an authentic sample.[3,5] Similarly VIII, prepared *via* VII gave 68% of recrystallized product, m.p. 143–144°.

Methyl 3-Amino-*N*-benzylidene-4,6-*O*-benzylidene-3-deoxy-α,D-altropyranoside (XI).—A mixture of 1.5 g. of X,[18] 10 ml. of absolute ethanol and 0.75 g. of benzaldehyde was refluxed for 30 min. After being cooled overnight at 0–3°, the mixture was filtered and the white prisms were washed with ethanol to yield 1.7 g. (87%), m.p. 188–189°; $[\alpha]D$ + 129 ± 1° (1.1%); λ_{max} 2.92 (OH), 6.10 (C=N), 6.35 (C=C), and 13.2, 14.2, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.4; H, 6.27; N, 3.80. Found: C, 68.5; H, 6.18; N, 3.92.

When this anil was refluxed in 50% ethanol for 2 hr., 89% of X was regenerated.

Methyl 3-Amino-*N*-benzylidene-4,6-*O*-benzylidene-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (XII).—To a stirred solution of 1.7 g. of XI in 8 ml. of pyridine cooled in an ice bath was added dropwise 0.4 ml. of methanesulfonyl chloride over a period of 15 min., the temperature being maintained at 0–10°. After standing at 0–3° for about 18 hr. in a stoppered flask, the mixture was diluted with 40 ml. of chloroform and poured onto 50 g. of ice. The separated aqueous layer was extracted with two more 30-ml. portions of chloroform. The combined chloroform solutions, washed with two 40-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Traces of pyri-

(11) Melting points were taken in capillary tubes in a Mel-Temp block and those below 230° were corrected. Infrared spectra were determined in Nujol mull (unless otherwise indicated) with a Perkin-Elmer 137B recording spectrophotometer. Optical rotations were run in a 1-dm. microtube in *N,N*-dimethylformamide. Petroleum ether was a fraction boiling at 30–60°.

dine in the residue were removed by spin evaporation *in vacuo* with toluene (two 15-ml. portions) to yield 1.7 g. (97%) of a gum that could not be crystallized; λ_{max}^{film} 6.11 (C=N), 6.35 (C=C), 7.50, 8.53 (sulfonate), 13.25, 14.35 (C_6H_5—), no OH or NH absorption near 3 μ.

This compound was characterized as follows. A mixture of 2.0 g. of XII and 30 ml. of 0.2 *N* aqueous sodium hydroxide was refluxed for 2 hr., during which time the gum gradually changed to a solid. The cooled mixture was extracted with two 30-ml. portions of chloroform. The combined extracts, washed with two 30-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Crystallization of the residue from ethyl acetate gave 500 mg. (32%) of the benzylidenebisaziridine (XIII), m.p. 211–212°; λ_{max} 13.38, 14.43 (C_6H_5—), no NH or OH near 3, and no C=O or C=N near 6 μ.

Anal. Calcd. for $C_{35}H_{38}N_2O_8$: C, 68.4; H, 6.24; N, 4.57; S, 0.0. Found: C, 68.3; H, 5.89; N, 4.63; S, 0.0.

Addition of petroleum ether to mother liquor gave 240 mg. of the aziridine (IV), m.p. 143–144°, that was identical with an authentic sample.[3,5]

Methyl 4,6-*O*-Benzylidene-2-*O*-carbophenoxy-3-carbophenoxyamino-3-deoxy-α,D-altropyranoside (XIV).—To a stirred mixture of 1.00 g. of X[8] and 10 ml. of dichloromethane cooled in an ice bath was added in one portion a mixture of 0.55 g. of phenyl chloroformate, 10 ml. of dichloromethane, and 5 ml. of pyridine precooled to 0°. After being stirred in an ice bath for 1 hr., the mixture was diluted with 25 ml. of ice–water. The separated aqueous layer was extracted with additional dichloromethane (two 25-ml. portions). The combined dichloromethane extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo*. Crystallization from ethanol gave 390 mg. (21%) of white crystals, m.p. 140–141°; $[\alpha]_D$ + 37 ± 1° (1.44%); λ_{max} 2.90 (NH), 5.72 (broad, C=O of ester and amide), 6.30 (amide II), 8.10, 8.40 (ester C—O—C), and 13.3, 14.3 μ (C_6H_5—).

Anal. Calcd. for $C_{28}H_{27}NO_9$: C, 64.5; H, 5.22; N, 2.69. Found: C, 64.5; H, 4.93; N, 2.72.

The mother liquor upon evaporation gave crude XV, as shown by its infrared spectrum.

Methyl 4,6-*O*-Benzylidene-3-carbophenoxyamino-3-deoxy-α,D-altropyranoside (XV).—A mixture of 3.0 g. of X[8] and 6.75 g. of diphenyl carbonate was heated on a steam bath for 3 hr. Phenol and excess diphenyl carbonate were removed by extraction with three 50-ml. portions of hot petroleum ether (b.p. 30–60°) to yield 4.1 g. (96%) of a colorless oil which could not be crystallized; λ_{max}^{film} 2.93 (OH, NH), 5.8 (broad C=O), 6.32 (amide II), 8.33 (ester C—O—C), and 13.3, 14.5 μ (C_6H_5—).

This oil was characterized as follows. To a solution of 500 mg. of XV in 10 ml. of ethanol was added 5 ml. of concentrated ammonia water. After being heated on a steam bath for 1 hr., the solution was cooled to give 265 mg. (65%) of IV, m.p. 230–231°, that was identical with an authentic sample[2]; no attempt was made to obtain a second crop.

Methyl 4,6-*O*-Benzylidene-3-carbophenoxyamino-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (XVI).—To a magnetically stirred solution of 4.1 g. of XV in 25 ml. of reagent pyridine cooled in an ice bath was added dropwise 1.6 ml. of methanesulfonyl chloride at such a rate that the temperature was 0–5° (about 15 min.). After standing overnight at 0–3° in a stoppered flask, the mixture was diluted with 100 ml. of iced water and extracted with three 25-ml. portions of chloroform. The combined extracts, washed with two 30-ml. portions of water and dried with magnesium sulfate, were spin evaporated *in vacuo;* the last traces of pyridine were removed by spin evaporation *in vacuo* of toluene (two 20-ml. portions) to yield 4.5 g. (92%) of an oil that could not be crystallized; λ_{max}^{film} 2.92 (NH), 5.78 (C=O), 6.31 (amide II), 7.39, 8.52 (sulfonate), and 13.3, 14.5 μ (C_6H_5—).

Methyl 4,6-*O*-Benzylidene-3-deoxy-2-*O*-mesyl-3-ureido-α,D-altropyranoside (VII). A.—To a solution of 4.5 g. of XVI in 20 ml. of ethanol was added 30 ml. of concentrated ammonia water. After standing about 18 hr. at ambient temperature, the mixture was spin evaporated *in vacuo*. The residue was dissolved in 50 ml. of chloroform, washed with two 25-ml. portions of water, dried with magnesium sulfate, and spin evaporated *in vacuo* to yield 3.5 g. (92%) of a colorless glass containing some phenol that could not be crystallized but was estimated from the combustion values to be at least 80% pure; λ_{max}^{film} 2.87, 2.93, 3.10 (NH), 5.91 (broad C=O), 6.27, 6.50 (broad amide II), 7.35, 8.50 (sulfonate), and 13.2, 14.3 μ (C_6H_5—).

Anal. Calcd. for $C_{16}H_{22}N_2O_8S$: C, 47.8; H, 5.52; N, 6.97; S, 7.96. Found: C, 50.6; H, 5.51; N, 5.59; S, 7.81.

The conversion of VII to crystalline VIII can be considered as additional characterization of VII.

B.—To a solution of 2.0 g. of XII in 10 ml. of ethanol was added a solution of 0.71 g. of potassium cyanate in 10 ml. of water followed by 0.53 ml. of glacial acetic acid. The mixture was warmed on a steam bath for 15 min., then spin evaporated *in vacuo* to about 10 ml. The mixture was then processed by chloroform extraction as in method A. Benzaldehyde was removed by spin evaporation of water (two 20-ml. portions) *in vacuo* leaving 1.4 g. (78%) of a glass that had an infrared spectrum essentially identical with preparation A. From the combustion values, this material was estimated to be at least 85% pure.

Anal. Found: C, 47.2; H, 5.37; N, 7.28; S, 6.87.

Methyl 3-Amino-4,6-*O*-benzylidene-3-deoxy-α,D-allopyranoside (XIX).—A mixture of 1.00 g. of VII, 0.80 g. of anhydrous sodium acetate, and 15 ml. of 2-methoxyethanol was refluxed for 20 hr., during which time some sodium methanesulfonate separated. The reaction mixture was diluted with 20 ml. of water and extracted with three 20-ml. portions of chloroform. The combined extracts, washed with two 20-ml. portions of water and dried with magnesium sulfate, were spin evaporated to dryness *in vacuo* to yield 0.63 g. (82%) of a glassy mixture of XVII and XVIII; λ_{max}^{film} 2.95 (NH), 5.73, 5.90 (C=O), 6.05 (C=N), 6.30 (amide II), 13.2, 14.4 (C_6H_5—), and no sulfonate absorption near 7.4 or 8.6 μ.

A solution of 600 mg. of this mixture in 5 ml. of ethanol and 0.2 *N* aqueous sodium hydroxide was refluxed for 4 hr., then cooled, and extracted with two 25-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* leaving 430 mg. (78%) of glassy residue. When 200 mg. of this material was allowed to stand in ethanol, white crystals of XIX separated slowly with poor recovery to yield 80 mg. (31%), m.p. 231–233°; $[\alpha]^{22}_D$ + 133 ± 1.5° (0.44%); λ_{max} 2.85, 2.95 (NH, OH), 6.05, 6.55 (NH_2), and 13.3, 14.2 μ (C_6H_5—).

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.8; H, 6.82; N, 4.97. Found: C, 59.7; H, 6.97; N, 5.06.

This compound is clearly isomeric to X which has been reported[12] to have m.p. 188° and $[\alpha]_D$ +90° (chloroform). Acetylation of XIX in 50% aqueous acetic acid with acetic anhydride gave XXI, while acetic anhydride in pyridine[8] gave XX as a glass; both had infrared spectra identical with respective authentic samples.[8]

Methyl 3-Acetamido-4,6-*O*-benzylidene-3-deoxy-α,D-altropyranoside.—Treatment of X with acetic anhydride in 50% acetic acid gave the *N*-acetyl derivative as a glass, as previously described.[8] This compound has now been crystallized from ethyl acetate–petroleum ether (b.p. 30–60°) as white crystals, m.p. 136–137°; $[\alpha]_D$ + 102 ± 1° (1.1%); λ_{max} 2.92 (NH, OH), 6.03 (amide C=O), 6.62 (amide II), and 13.0, 14.2 μ (C_6H_5—).

Anal. Calcd. for $C_{16}H_{21}NO_6$: C, 59.5; H, 6.54; N, 4.34. Found: C, 59.4; H, 6.55; N, 4.52.

A mixture with the alloside (XXI) melted at 90–95°.

Methyl 3-Acetamido-4,6-*O*-benzylidene-3-deoxy-α,D-allopyranoside (XXI). A.—By treatment of methyl 3-acetamido-4,6-*O*-benzylidene-3-deoxy-2-*O*-mesyl-α,D-altropyranoside[8] with sodium acetate in boiling ethanol 700 mg. (79%) of glassy XX was obtained by the previously described method.[8] This compound has now been crystallized from ethyl acetate–petroleum ether (b.p. 30–60°) as white crystals to yield 350 mg. (40%), m.p. 120–121°; $[\alpha]_D$ + 107 ± 1°; λ_{max} 2.97, 3.13 (NH, OH), 6.08 (amide C=O), 6.60 (amide II), and 13.3, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{16}H_{21}NO_6$: C, 59.5; H, 6.54; N, 4.34. Found: C, 59.4; H, 6.41; N, 4.46.

B.—A solution of 1.00 g. of VII in 10 ml. of reagent pyridine was refluxed for 3 hr., diluted with 50 ml. of water, and extracted with three 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 residual pyridine were removed by spin evaporation of toluene (two 10-ml. portions) *in vacuo* to yield 0.65 g. (84%) of XVII as a glass; λ_{max} 2.88, 2.95 (NH), 6.00, 6.32 (NH, C=N), 13.25, 14.45 (C_6H_5—), and no sulfonate near 7.4 or 8.5 μ.

When XVII was stirred with 0.2 *N* aqueous sodium hydroxide at room temperature, the infrared spectrum shifted to that of the

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

cyclic urethane (XVIII). When XVII was refluxed with 0.2 *N* aqueous sodium hydroxide as described for the conversion of XVIII to XIX, XIX was obtained as a glass in 72% yield that had an infrared spectrum identical with glassy XIX prepared from XVIII. Instead of crystallization at this point, XIX was acetylated in 50% acetic acid with acetic anhydride to give, in poor yield, XX as crystals identical with those of preparation A.

Methyl 3-Benzylamino-4,6-*O*-benzylidene-3-deoxy-α,D-altropyranoside (XXIII). **A.**—To a warm solution of 5.0 g. of X in 50 ml. of ethanol was added 1.0 ml. of benzyl bromide in 5 ml. of ethanol. The solution was heated to boiling, then allowed to stand at ambient temperature for about 20 hr. After removal of the solvent by spin evaporation *in vacuo*, the residue was partitioned with 50 ml. of chloroform and 30 ml. of water. The separated aqueous layer was neutralized immediately for recovery of the excess X. The chloroform solution, washed further with water (three 30-ml. portions) and dried with magnesium sulfate, was evaporated *in vacuo* to yield 3.9 g. (91% based on benzyl bromide) of an oil that could not be crystallized; λ_{max}^{film} 2.9–3.0 (broad, NH, OH), 6.33 (C=C), 13.3, 13.6, 14.4 μ (C_6H_5—).

B.—To a solution of 1.00 g. of XI in 10 ml. of ethanol was added a solution of 0.50 g. of sodium borohydride in 2 ml. of water. After standing for about 18 hr. at ambient temperature, the solution was processed as in method A to yield 0.88 g. (82%) of an oil that had an infrared spectrum identical with preparation A, including no C=N absorption near 6.1 μ.

Methyl 3-Benzylamino-4,6-*O*-benzylidene-*N*-cyano-3-deoxy-D-altropyranoside (XXIII).—To a solution of 2.0 g. of XXII in 20 ml. of absolute ethanol was added a solution of 0.30 g. of cyanogen bromide in 5 ml. of absolute ethanol. After 2 hr. at 50–60°, the solution was allowed to stand overnight. Solvent was removed *in vacuo* and the residue was dissolved in 25 ml. of chloroform and 25 ml. of water. The separated chloroform layer was washed once more with water. The combined aqueous extracts were made strongly alkaline with 2 *N* sodium hydroxide and the recovered XXII (0.80 g.) was isolated by chloroform extraction.

The chloroform solution of XXIII, dried with magnesium sulfate, was evaporated *in vacuo* to yield 1.0 g. (94% based on cyanogen bromide or 79% based on XXII not recovered) of a gum that could not be crystallized; λ_{max}^{film} 2.95 (OH), 4.54 (C≡N), and 13.3, 13.8, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{22}H_{24}N_2O_3$: C, 66.7; H, 6.11; N, 7.07. Found: C, 66.7; H, 6.11; N, 6.92.

Methyl 3-Benzylamino-4,6-*O*-benzylidene-*N*-cyano-3-deoxy-2-*O*-mesyl-α,D-altropyranoside (XXVI).—Mesylation of 1.1 g. of XXIII in 10 ml. of reagent pyridine with 0.30 ml. of methanesulfonyl chloride as described for the preparation of XVI gave 1.20 g. (91%) of product as a glass; λ_{max}^{film} 4.53 (C≡N), 7.40, 8.55 (sulfonate), 13.3, 13.8, 14.4 μ (C_6H_5—), and no OH or NH near 3 μ.

Anal. Calcd. for $C_{23}H_{26}N_2O_7S$: C, 58.2; H, 5.53; N, 5.91; S, 6.74. Found: C, 58.4; H, 5.54; N, 5.74; S, 6.43.

4′,6′-*O*-Benzylidene-1-benzyl-1′-*O*-methyl-2-oxo-α,D-allopyrano[2′,3′:4,5]imidazolidine (XXVII).—To 2.0 g. of XXVI was added 30 ml. of methanol previously saturated with ammonia. When solution was complete, it was transferred to a steel bomb and heated at 130–150° for 7 days. On being cooled and opened, the bomb contained crystals suspended in the solution and some fastened to the side; an odor of methylamine was noticeable. The product was collected on a filter and washed with methanol to yield 0.70 g. (42 or 70% based on XXVI not recovered), m.p. 250–258°, suitable for further transformation. Recrystallization from ethanol gave white needles, m.p. 258–260°; $[\alpha]^{24}_D$ + 72 ± 1° (0.83%); λ_{max} 3.05 (NH), 5.91, 6.05 (C=O, NH), 6.78, 13.1, 13.3, 14.4 (C_6H_5), and no C≡N near 4.5 or sulfonate near 7.5 or 8.5 μ.

Anal. Calcd. for $C_{22}H_{24}N_2O_5$: C, 66.6; H, 6.11; N, 7.08. Found: C, 66.5; H, 6.21; N, 7.06.

The methanolic ammonia mother liquor was concentrated to give an additional 50 mg. (3%) of product. The filtrate was further processed for recovery of starting material by evaporation *in vacuo*. The residue was extracted with chloroform. The combined extracts, washed with water, dried with magnesium sulfate, and clarified with decolorizing carbon, gave on evaporation 0.80 g. (40%) of starting material (XXVI) that was recycled to XXVII.

Methyl 2-Acetamido-3-benzylamino-4,6-*O*-benzylidene-2,3-dideoxy-α,D-allopyranoside (XXX).—A solution of 10 g. of potassium hydroxide in 10 ml. of water and 10 ml. of ethanol was added to 350 mg. of XXVII. The mixture was heated in a steel bomb at 150–170° for 7 days. The cooled solution was transferred from the bomb with the aid of water. The solution containing XXIX was spin evaporated *in vacuo* until most of the ethanol was removed, then neutralized to about pH 9 with glacial acetic acid. To the stirred solution at 25° was added 1 ml. of acetic anhydride. After being stirred for 1 hr. at ambient temperature, the mixture was extracted with three 25-ml. portions of chloroform. Washed with three 20-ml. portions of water and dried with magnesium sulfate, the combined extracts were spin evaporated *in vacuo* to a crystalline residue, m.p. 142–143°, yield 300 mg. (82%). Recrystallization from a small volume of ethanol gave white needles, m.p. 142–143°; $[\alpha]^{24}_D$ + 27 ± 1° (0.09%); λ_{max} 3.00 (NH), 6.13 (amide C=O), 6.57 (amide II), and 6.75, 13.3, 13.6, 14.4 μ (C_6H_5—).

Anal. Calcd. for $C_{23}H_{28}N_2O_5$: C, 67.9; H, 7.00; N, 6.61. Found: C, 67.9; H, 7.00; N, 6.61.

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