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AMERICAN CYANAMID COMPANY]

PUROMYCIN. SYNTHETIC STUDIES. III. SYNTHESIS OF 3-AMINO-D-RIBOSE, AN HYDROLYTIC FRAGMENT

B. R. BAKER AND ROBERT E. SCHAUB

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One of the hydrolysis products of puromycin is a 3-aminopentose, $C_5H_{11}NO_4$, the first example of the occurrence of a 3-amino sugar and an aminopentose in a natural source (1).[1] Since this sugar gives a *meso* form on reduction to the pentitolamine, it must be a 3-aminoribose or 3-aminoxylose.[2] The constitution of this $C_5H_{11}NO_4$ moiety has now been established to be 3-amino-D-ribose by synthesis from L-arabinose.

Of the few methods described in the literature (3) for the synthesis of amino sugars, the most useful is the ring opening of the epoxide ring of an anhydro sugar. For example, the action of ammonium hydroxide on methyl 2,3-anhydro-4,6-benzylidene-α-D-mannopyranoside (I) takes place on the oxide by rear attack and Walden inversion to give predominantly methyl 3-amino-4,6-benzylidene-α-D-altropyranoside (II) with traces of methyl 2-amino-4,6-benzylidene-α-D-glucopyranoside (III) (4).[3]

The requisite anhydropentose necessary for the potential synthesis of a 3-aminopentose, namely methyl 2,3-anhydro-β-L-ribopyranoside (IX), has been synthesized (6, 7) in five steps from L-arabinose as shown on the Flow Sheet. Treatment of the oxide (IX) with ammonium hydroxide at 100° gave a crystalline aminopentoside in 63% yield which could be either methyl 3-amino-β-L-xylopyranoside (XII) or methyl 2-amino-β-L-arabinopyranoside (VIII).[3] This crystalline aminopentoside formed an N-acetyl derivative, m.p. 194–195°, which could be either XI or XIV. That the N-acetyl derivative had structure XIV was proven by its failure to consume periodate, a reaction characteristic of the glycol system present in XI (8). In contrast the non-acetylated xyloside (XII) rapidly consumed two moles of periodate, as expected, under the same conditions.

Hydrolysis of the methyl xyloside (XII) to 3-amino-L-xylose hydrochloride with 1 *N* hydrochloric acid at 100° caused a slow loss of the methoxyl group

[1] The only aminopentose described in the literature is 2-amino-D-xylose, recently synthesized by removal of carbon 6 from D-glucosamine by Wolfrom and Anno (2).

[2] Private communication from Dr. C. W. Waller of these laboratories.

[3] It should be noted that in this type of synthesis the hydroxyl and amino groups resulting from the oxide opening are necessarily *trans* since Walden inversion takes place at the carbon accepting the amide ion. There are no examples of *cis* or "allo" type amino sugars in the literature. The bimolecular reaction of ammonia with 1,2:5,6-diisopropylidene-3-tosyl-D-glucofuranoside takes place only with difficulty in low yield and does not take place with a single Walden inversion to form a 3-amino-D-alloside as might be expected. 1,2:5,6-Diisopropylidene-3-amino-D-glucofuranoside is formed (5) by either a frontal attack or by a double Walden inversion involving a possible neighboring group effect by the adjacent oxygen at the 2-position.

with formation of a reducing sugar, but did not afford a crystalline product. The glass obtained had only 57% of reducing sugar present and appeared to be contaminated with the anhydro sugar (XIII) or polymeric products since it contained no methoxyl. The formation of a free sugar-anhydro sugar mixture has been observed in the hexose series, particularly on acid treatment of methyl α-D-altropyranoside (9) or methyl 3-amino-α-D-altropyranoside (10). This

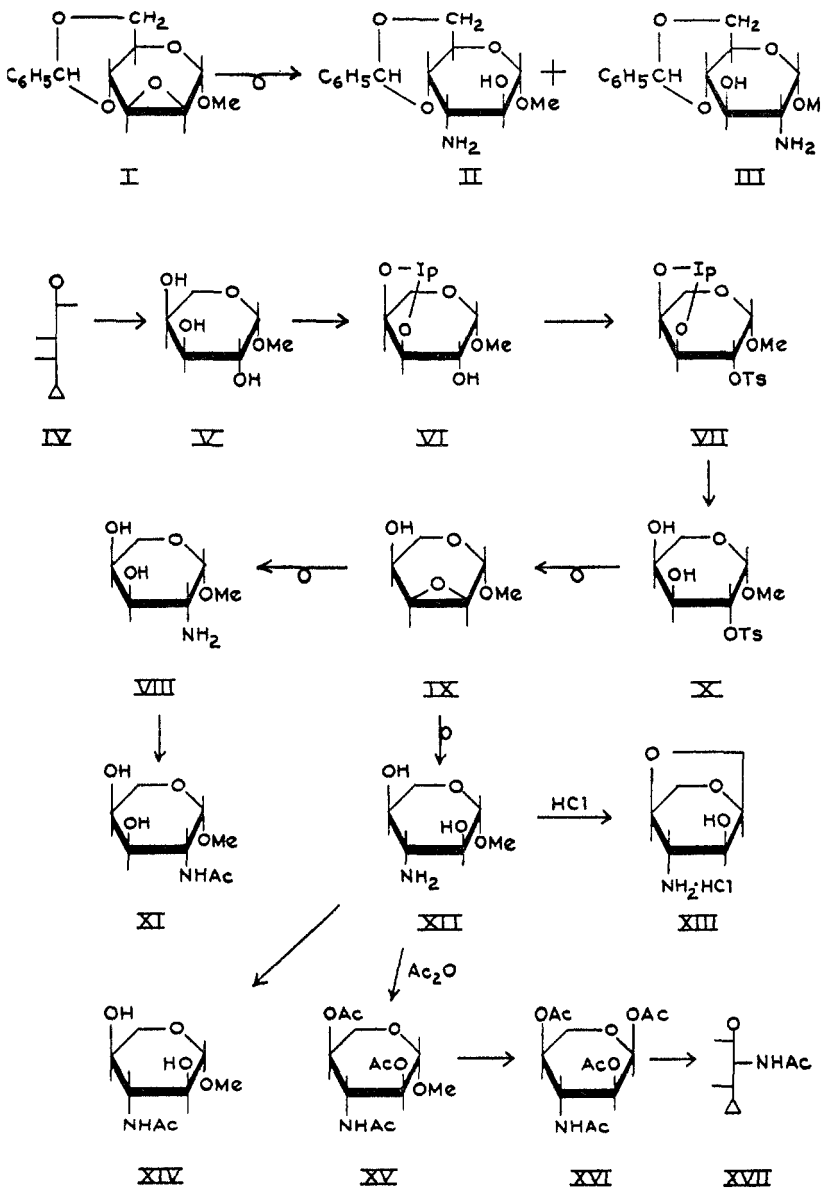

CHART I

difficulty of anhydro formation in the D-altrose series was circumvented by Richtmeyer and Hudson (11) by acetolysis of methyl α-D-altropyranoside to D-altropyranoside pentaacetate followed by ammonolysis to D-altrose. Methyl 3-amino-β-L-xyloside triacetate (XV) underwent acetolysis of the methyl ether with acetic anhydride-sulfuric acid (11) at a much slower rate than methyl α-D-altropyranoside. From the reaction mixture there could be isolated one crystalline anomer of 3-amino-L-xylopyranoside tetraacetate (XVI), probably the α-form, in 12% yield. Deacetylation with methanolic sodium methoxide gave 3-acetamino-L-xylose (XVII) as a strongly reducing glass. Attempts to obtain a crystalline osazone under a variety of conditions failed, including the conditions employed for preparation of the crystalline osazone of the N-acetyl derivative of the $C_5H_{11}NO_4$ moiety from puromycin.[2] This gave strong evidence, but not proof, that the $C_5H_{11}NO_4$ moiety was not a 3-aminoxylose, but a 3-aminoribose. Unfortunately, infrared spectra were unsatisfactory for comparison since suitable films or mulls for good resolution could not be obtained. These compounds were insoluable in solvents ordinarily used for I. R. spectra.

It is conceivable that methyl 3-amino-β-L-xylopyranoside (XII) could be converted to methyl 3-amino-β-L-ribopyranoside (XXI) by inversion of the amine group or to methyl 3-amino-α-D-ribopyranoside by inversion of both hydroxyl groups. Although there is precedent for these type inversions, as will be discussed, they have not been applied in the carbohydrate field.

The amine group of XII readily reacted with benzaldehyde to form an anil, XVIII. Treatment with hot methanolic sodium methoxide followed by hydrolysis did not give any of the L-riboside (XXI) but the L-xyloside was recovered unchanged. The epimerization of the 3-amine group was expected to take place *via* an intermediate destroying asymmetry at the 3-position such as XIX, since this type of equilibration has been used successfully in the colchicine series with benzyltrimethylammonium hydroxide as a catalyst by Rapoport (12). However, in the latter case the amine group was on a benzyl position so that shift of the double bond to cause equilibration at the asymmetric center could probably take place more easily.

Although methyl 3-acetamino-β-L-xylopyranoside (XIV) reacted with thionyl chloride, inversion of one of the hydroxyl groups to an oxazoline such as XXII could not be established with certainty. This reaction has been successful with N-benzoylthreonine (13) and in the cyclohexane and cyclopentane series (14).

The mixture of products was hydrolyzed with base to convert any mono- or bis-chlorosulfinate of XIV or cyclic sulfite (XX)[4] back to XIV and to hydrolyze either of the two possible oxazolines (XXII) or their chlorosulfinates to the corresponding 3-acetaminopyranosides. Acetylation gave 55% of methyl 3-amino-β-L-xylopyranose triacetate (XV) which could arise only from non-inversion products. The corresponding methyl arabinoside or lyxoside triacetates, if present, could not be crystallized from the mother liquor. The infrared spec-

[4] The formation of a cyclic sulfite rather than an oxazoline has been observed when *d-threo*-3-*p*-nitrophenyl-2-benzamido-1,3-propanediol was treated with thionyl chloride (15).

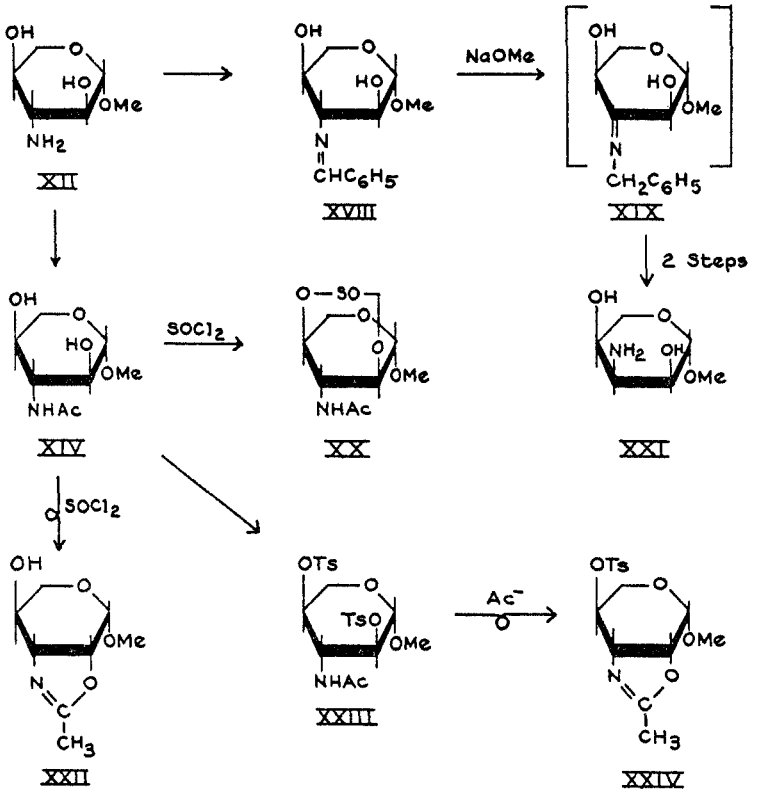

CHART II

trum of the crude thionyl chloride reaction product showed the generation of a new peak at 5.80 μ which could be assigned to the $>C{=}NH^+$ band of an oxazoline hydrochloride.

Another type of inversion found useful in the cyclohexane series has been the attack of an acetamino group on a neighboring *trans*-tosylate to give *cis*-acetamino-2-cyclohexanol *via* *cis*-cyclohexanoöxazoline (16). Treatment of methyl 3-acetamino-β-L-xylopyranoside (XIV) with *p*-toluenesulfonyl chloride in pyridine gave a crude tosylate (XXIII) in 80 % yield which could not be crystallized. When XXIII was treated with sodium acetate in boiling alcohol, 0.84 mole of sodium *p*-toluenesulfonate was formed by displacement, presumably to XXIV if the 2-tosylate was ejected or to the *arabino*-isomer if the 4-tosylate was ejected. Sodium acetate in boiling Methyl Cellosolve[5] gave 1.49 moles of sodium *p*-toluenesulfonate which could be explained if both tosylates were being displaced. Unfortunately, from neither reaction could a crystalline product be isolated.

Since one or both hydroxyls could be involved in these reactions, it seemed probable that a system involving only one hydroxyl group would be less com-

[5] 2-Methoxyethanol.

plicated and might offer a better chance to establish proper experimental conditions for these inversions. Methyl 3-amino-4,6-benzylidene-α-D-altropyranoside (II) is a readily available amino sugar derivative (4) with the desired qualifications for an extensive study.

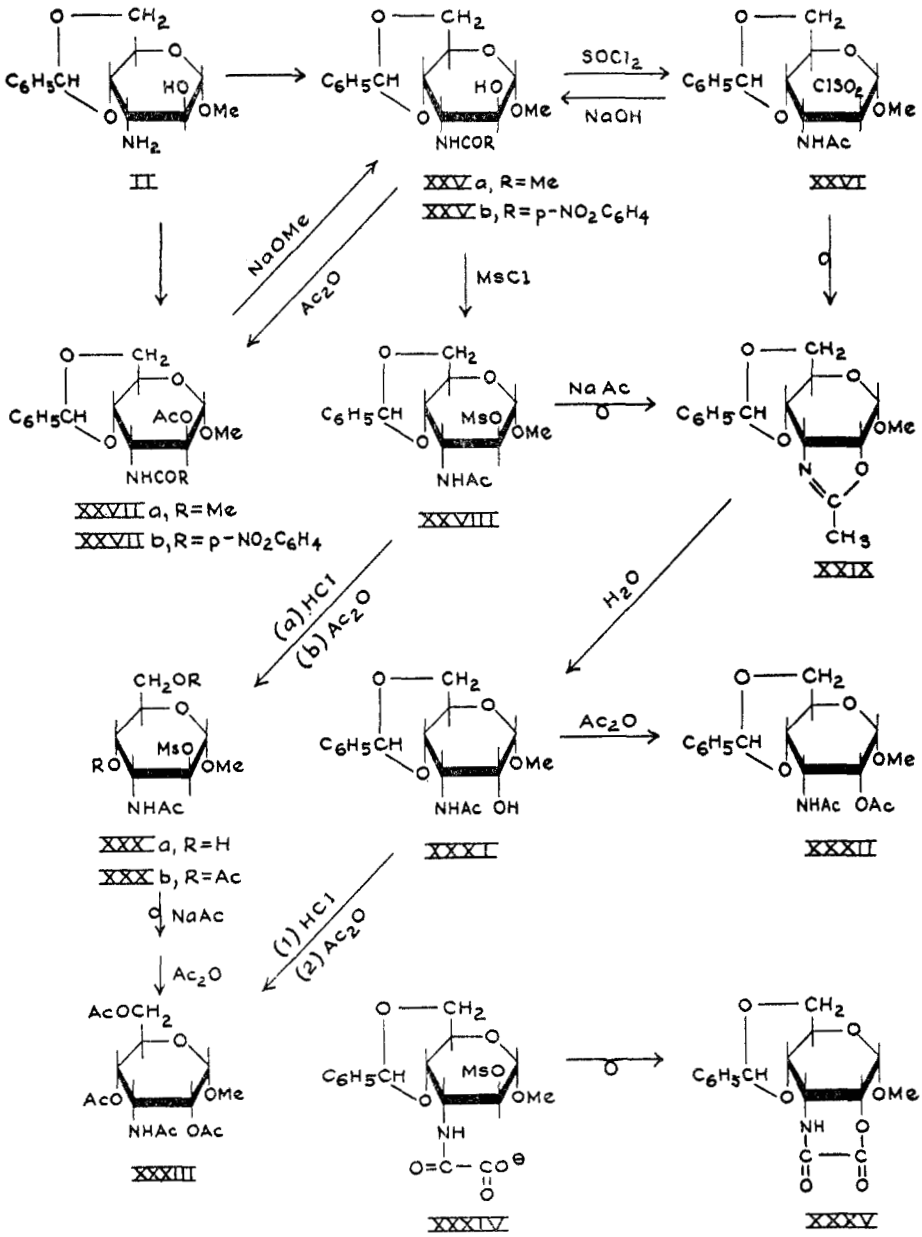

CHART III

Acetylation of II with acetic anhydride in pyridine gave the known (4) diacetate (XXVIIa), a valuable reference compound for this study. Acetylation of II with acetic anhydride in water gave the N-monoacetyl derivative (XXVa) in quantitative yield, as a glass. This same compound could be obtained by O-deacetylation of the diacetate (XXVIIa) with methanolic sodium methoxide. The amine group of II could also be selectively *p*-nitrobenzoylated in chloroform-aqueous sodium carbonate in quantitative yield. Although this product (XXVb) was a glass, it gave a crystalline acetate (XXVIIb).

When the N-monoacetylaltroside (XXVa) was treated with thionyl chloride reaction readily took place. The expected oxazoline (XXIX) was not formed by inversion, but a crude chlorosulfinate (XXVI) was obtained as a glass. As a check to show that inversion had not taken place, the glassy product was treated with base to open any of the oxazoline to the alloside (XXXI) and to hydrolyze any sulfinate back to the starting material (XXVa). The crude product was acetylated giving the unepimerized crystalline altroside diacetate (XXVIIa) in 94% yield instead of the desired alloside derivative (XXXII). Although pyridine is known to catalyze the elimination of sulfur dioxide from chlorosulfinates with displacement (17), the use of pyridine-thionyl chloride also led to unepimerized altroside diacetate (XXVIIa) after hydrolysis and acetylation. Similar unfavorable results were obtained with boron trifluoride-etherate.

The tosylation of the free hydroxyl group of the N-monoacetylaltroside (XXVa) proceeded sluggishly and although a crude product containing about 80% of the required sulfur for a tosylate was obtained, it could not be crystallized. The *m*- or *p*-nitrobenzenesulfonyl chlorides were even less reactive and also did not give crystalline sulfonates. Helferich and Gnüchtel (18) have shown that methanesulfonyl chloride will react more rapidly with an hydroxyl group and give higher yields of sulfonate than *p*-toluenesulfonyl chloride. The resulting methanesulfonates are also displaced more rapidly than tosylates. When this reagent was tried with the N-monoacetylaltroside (XXVa), the reaction proceeded at 3° in pyridine to give an 85% yield of crystalline 2-mesylate (XXVIII), m.p. 161°.

When methyl 2-mesyl-3-acetamino-4,6-benzylidene-α-D-altropyranoside (XXVIII) was treated with sodium acetate in boiling 95% alcohol, the mesylate was ejected with Walden inversion to form the non-crystalline N-acetylalloside (XXXI) in 79% yield, the reaction presumably proceeding *via* the oxazoline (XXIX), which is hydrolyzed by the water present (16). Acetylation of XXXI gave the diacetylalloside (XXXII) as an analytically pure glass, $[\alpha]_D$ +32.7° ($CHCl_3$). If no inversion had taken place, then the product would have been the diacetylaltroside, m.p. 195–196°, $[\alpha]_D$ +14.6° ($CHCl_3$) (4).

The inversion was also successful with another altroside derivative. Selective hydrolysis of the benzylidene group of methyl 2-mesyl-3-acetamino-4,6-benzylidene-α-D-altropyranoside (XXVIII) with 0.5% hydrochloric acid in 95% methanol followed by acetylation gave the crystalline 2-mesylaltroside triacetate, XXXb in 71% yield. When the intermediate glassy XXXa was treated with sodium acetate in boiling 95% alcohol, the mesyl group was displaced with

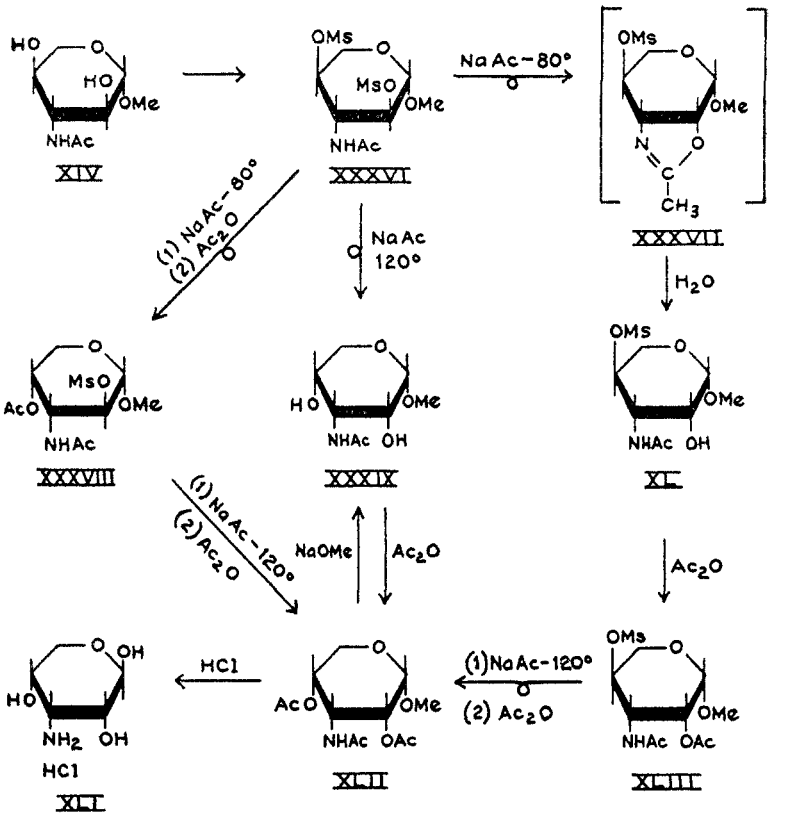

CHART IV

Walden inversion. Acetylation gave methyl 3-amino-α-D-allopyranoside tetraacetate (XXXIII) as an analytically pure glass in 84% yield. This material crystallized after several months and after recrystallization melted at 128–129° and had $[\alpha]_D^{25}$ +85.3° ($CHCl_3$),[6,7] thus being definitely epimeric to methyl 3-amino-α-D-altroside tetraacetate, m.p. 177°, $[\alpha]_D$ +34.7° ($CHCl_3$) (4). The non-crystalline benzylidene alloside (XXXI) was then characterized by selective removal of the benzylidene group followed by acetylation to the same crystalline methyl 3-amino-α-D-allopyranoside tetraacetate (XXXIII).

In view of the success in obtaining crystalline mesyl derivatives and their subsequent inversion in the D-altrose series, these reactions were reinvestigated with methyl 3-acetamino-β-L-xylopyranoside (XIV). Mesylation of XIV in

[6] The use of neighboring group inversions should be useful for the synthesis of some difficultly available sugars. For example, reaction of the readily available methyl 2-benzoyl-3-tosyl-4,6-benzylidene-α-D-glucopyranoside (9) with sodium acetate (19) followed by alkaline hydrolysis should give methyl 4,6-benzylidene-α-D-allopyranoside. This could in turn be converted to D-allose in the usual hydrolytic fashion or by the method used for conversion of methyl-α-D-altropyranoside to D-altrose (11).

[7] Although the carboxylate ion is considered a stronger nucleophilic reagent than the carbonyl group of an amide, no cyclization to XXXV took place with displacement of the mesylate when the sodium salt of XXXIV was refluxed in alcohol.

pyridine at 25° gave a crystalline dimesyl xyloside (XXXVI) in 83% yield. When the latter was treated with sodium acetate in boiling 95% alcohol, one mole of sodium methanesulfonate was formed. The crude product was acetylated and a crystalline monomesylate acetate was obtained in 66% yield which could be either the L-lyxoside (XLIII) or the D-arabinoside (XXXVIII), formed by displacement of the 2- or 4-mesylate *via* an oxazoline, respectively, by the adjacent acetamido group. The second mesylate group would not displace on further treatment with sodium acetate in boiling 95% alcohol. The geometric identity of the groups on positions 1, 2, and 3 on XXXVI to the corresponding groups in methyl 2-mesyl-3-acetamino-α-D-altropyranoside (XXXa), where displacement of the mesyl group did take place, suggests that the product obtained was the L-lyxoside, XLIII.[8]

The second mesylate group displaced slowly with sodium acetate in 95% Methyl Cellosolve[5] by heating at 100°, but when the temperature was raised to the b.p., one mole of sodium methanesulfonate was formed during 24 hours. Subsequent acetylation of the crude product gave a 69% yield of methyl 3-amino-α-D-ribopyranoside triacetate (XLII), m.p. 117°. Displacement of both mesylate groups of the xyloside (XXXVI) occurred when the reaction with sodium acetate was carried out in boiling 95% Methyl Cellosolve.[5] The crude product, XXXIX, which probably formed *via* the 2,3-oxazoline (XXXVII), the monomesyl-L-xyloside (XL), and finally a 3,4-oxazoline, gave the D-riboside triacetate (XLII) in 70% over-all yield after acetylation. Hydrolysis of the triacetyl-D-riboside (XLII) with 1% hydrochloric acid at 100° formed 3-amino-D-ribose hydrochloride (XLI), m.p. 160°, in 83% yield, which probably has the β-configuration. This synthetic amino sugar was proven to be identical with the natural aminopentose obtained by hydrolysis of puromycin (1) by comparison of their infrared spectra, optical rotations, and melting points.

It is interesting to note that this synthesis of 3-amino-D-ribose proceeds through substances which possess all four pentose configurations in the order *arabino*, *ribo*, *xylo*, *lyxo*, and *ribo*.[9]

Acknowledgement. The authors wish to thank Messrs. L. Brancone, W. Fulmor, and W. McEwen and their staffs for the microanalyses, physical measurements, and large scale preparation of some intermediates, respectively.

EXPERIMENTAL

Methyl 2,3-anhydro-β-L-ribopyranoside (IX). A mixture of 46 g. of VII (7) and 440 cc. of 1 *N* acetic acid was refluxed for 2 hours, solution being essentially complete in 20 minutes. The solution, decanted from a little insoluble gum, was evaporated to dryness *in vacuo*. The residual crude X was dissolved in 100 cc. of chloroform and the solution was evaporated *in vacuo* leaving 42.2 g. of a gum.

To a solution of the crude X in 150 cc. of methanol cooled to 3° was added 135 cc. of 1 *N* methanolic sodium methoxide. After standing at room temperature for about 16 hours in a stoppered flask, the solution was neutralized with 9 cc. of glacial acetic acid and evaporated

[8] A structure proof is currently under investigation and, if successful, will be the subject of a future communication.

[9] A preliminary announcement of this synthesis appeared in *J. Am. Chem. Soc.*, **75**, 3864 (1953).

to a paste *in vacuo*. The residue was dissolved in 55 cc. of water and 100 cc. of chloroform. The separated aqueous layer was extracted twice more with 50-cc. portions of chloroform. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo*. Distillation of the residue (13.7 g.) gave 11.1 g. (59%) of product, b.p. 69–70° (0.1 mm.), which solidified in the receiver and had a m.p. 51–52°.

This procedure is a considerable simplification of that described by Kent, Stacey, and Wiggins (7) who crystallized the intermediate X and recorded an over-all yield of 50% of product, b.p. 110° (bath) at 0.05 mm. and m.p. 46°.

*Methyl 3-amino-β-*L*-xylopyranoside* (XII). A solution of 12.1 g. of IX in 90 cc. of concentrated ammonium hydroxide was heated in a steel bomb at 100° for 21 hours. The solution was clarified with Norit by filtration through Celite. Evaporation to dryness *in vacuo* gave a semi-crystalline solid which was recrystallized from 120 cc. of 3A[10] alcohol; yield, 8.1 g. (65%), m.p. 191–192° dec. Recrystallization from the same solvent gave white crystals, m.p. 192–193° dec., $[\alpha]_D^{24}$ +61.4° (1% in H_2O).

Anal. Calc'd for $C_6H_{13}NO_4$: C, 44.2; H, 8.03; N, 8.60.
Found: C, 44.2; H, 8.07; N, 8.93.

This compound consumed 2.1 mole-equivalents of periodate in aqueous sodium bicarbonate in less than 2 minutes, then consumed no additional oxidant in 3 hours.

No attempt was made to isolate the isomeric β-methyl 2-amino-L-arabinopyranoside (VIII) which may have been in the filtrate.

The *hydrochloride* of XII was prepared by solution of XII in hot absolute alcohol, addition of excess absolute alcoholic hydrogen chloride, then ether to turbidity; white crystals, m.p. 169° dec., $[\alpha]_D^{26}$ +58° (1% in H_2O).

Anal. Calc'd for $C_6H_{13}NO_4 \cdot HCl$: N, 7.02. Found: N, 7.08.

*Methyl 3-acetamino-β-*L*-xylopyranoside* (XIV). To a solution of 1.00 g. of XII in 5 cc. of water was added 0.87 cc. of acetic anhydride. The mixture was shaken for 5 minutes, then evaporated to dryness *in vacuo* leaving 1.22 g. (97%) of product, m.p. 184–187°. Recrystallization from ethyl acetate gave white crystals, m.p. 194–195°, $[\alpha]_D^{24}$ +64.4° (2% in H_2O).

Anal. Calc'd for $C_8H_{15}NO_5$: C, 46.8; H, 7.36; N, 6.83.
Found: C, 46.4; H, 7.53; N, 6.74.

This compound failed to consume any periodate in aqueous sodium bicarbonate after 3 hours, thus proving the structure to be XIV and not XI.

*Methyl-3-amino-β-*L*-xylopyranoside triacetate* (XV). To a mixture of 5.0 g. of XII and 18 cc. of reagent pyridine was added 32 cc. of acetic anhydride portionwise with ice-cooling at such a rate that the temperature was 20–25°. After 20 hours at room temperature in a stoppered flask, the solution was diluted with 150 cc. of iced-water and extracted with three 75-cc. portions of chloroform. The combined extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo*. The residue was dissolved in 50 cc. of toluene and again was evaporated *in vacuo*; yield, 8.4 g. (95%), m.p. 163–165°. Recrystallization of a similar preparation (98% yield) from toluene-heptane gave white crystals, m.p. 170–171°, $[\alpha]_D^{23}$ +60.7° (2% in $CHCl_3$).

Anal. Calc'd for $C_{12}H_{19}NO_7$: C, 49.8; H, 6.62; N, 4.85.
Found: C, 50.2; H, 6.87; N, 4.79.

*1,4-Anhydro-3-amino-*L*-xylopyranoside hydrochloride* (XIII) (?) and *3-amino-*L*-xylose hydrochloride*. A solution of 500 mg. of XII and 10 cc. of 1 *N* hydrochloric acid was refluxed for 18 hours, then clarified by Norit by filtration through acid-washed Celite. The water-white filtrate was evaporated to a syrup *in vacuo* (bath 40–45°). Further drying over potassium hydroxide and concentrated sulfuric acid in a vacuum desiccator gave a light amber glass; yield, 560 mg., $[\alpha]_D^{23}$ −46° (1.2% in H_2O).

Anal. Calc'd for $C_5H_{11}NO_4 \cdot HCl \cdot 1\frac{1}{2}\ H_2O$: C, 28.2; H, 7.10; N, 6.60; MeO, 0.0.
Found: C, 28.3; H, 6.59; N, 6.86; MeO, 0.8.

The product contained 57% of reducing sugar (22) calculated as a sesquihydrate. The remaining 43% in the mixture is assumed to be the anhydro sugar hydrochloride (XIII)

[10] A denatured ethyl alcohol.

(10), but could be polymeric in nature. As a check glucosamine hydrochloride gave 101% reducing sugar.

3-Amino-L-xylopyranoside tetraacetate (XVI). A solution of 8.4 g. of XV in 42 cc. of acetic anhydride containing 0.84 cc. of 96% sulfuric acid (11) was allowed to stand for 24 hours in a stoppered flask. The mixture was diluted with 250 cc. of water and, after the acetic anhydride had hydrolyzed, was extracted with three 100-cc. portions of chloroform. After drying with magnesium sulfate the combined extracts were evaporated to dryness *in vacuo*. The residue (6.2 g.) still contained about ¼ of the original methoxyl content. Crystallization from 30 cc. of ethyl acetate gave 1.02 g. of crude product, m.p. 188–193°. One more recrystallization from ethyl acetate afforded 0.79 g. (9.3%) of nearly pure product, m.p. 206–208°. The combined filtrates were evaporated to dryness *in vacuo* and were retreated with acetic anhydride-sulfuric acid to give an additional 3% of product. In a trial run the product was recrystallized several times from ethyl acetate giving white crystals, m.p. 209–211°, $[\alpha]_D^{24}$ 0.0°, $[\alpha]_{Hg}^{24}$ 0.0° ($CHCl_3$).

Anal. Calc'd for $C_{13}H_{19}NO_8$: C, 49.2; H, 6.03; N, 4.46; MeO, 0.0.
Found: C, 49.2; H, 6.30; N, 4.24; MeO, 0.0.

The considerably more levo rotation of XVI than XII indicates that the former has the α-configuration.

3-Acetamino-L-xylose (XVII). To a suspension of 900 mg. of pure XVI in 18 cc. of methanol was added 0.36 cc. of 1 *N* methanolic sodium methoxide. Solution took place immediately. After being refluxed for 30 minutes, the solution was evaporated to dryness *in vacuo* leaving a glass which could not be crystallized, but which gave a strong Benedict's test; yield, 530 mg. (98%), $[\alpha]_D^{24}$ 0.0° (2% in H_2O).

Anal. Calc'd for $C_7H_{13}NO_5$: C, 44.0; H, 6.85.
Found: C, 44.4; H, 6.77.

Attempts to obtain a crystalline osazone under a variety of conditions failed, including those conditions used for preparation of the osazone of the N-acetyl derivative of the $C_5H_{11}NO_4$ moiety from puromycin.[2]

Methyl N-benzylidene-3-amino-β-L-xylopyranoside (XVIII). A solution of 300 mg. of XII and 0.3 cc. of benzaldehyde in 3 cc. of alcohol was refluxed for 15 minutes, then evaporated to dryness *in vacuo*. Trituration of the residue with petroleum ether gave 425 mg. (92%) of product, m.p. 147–148°. Recrystallization from ethyl acetate-heptane gave white crystals of unchanged m.p.

Anal. Calc'd for $C_{13}H_{17}NO_4$: C, 62.1; H, 6.81; N, 5.58.
Found: C, 61.8; H, 7.24; N, 5.42.

When XVIII was refluxed for 19 hours with methanolic sodium methoxide, then hydrolyzed, XII was recovered in near quantitative yield, showing no appreciable inversion took place.

Action of thionyl chloride on methyl 3-acetamino-β-L-xylopyranoside (XIV). To 500 mg. of XIV was added 2.5 cc. of thionyl chloride with ice-cooling. Solution was complete immediately with the evolution of gases. After 18 hours at room temperature protected from moisture, the solution was evaporated to dryness *in vacuo*, leaving 750 mg. of a hygroscopic residue. The mixture had absorption in the infrared at 5.80 μ indicating $\rangle C{=}NH^{\oplus}$ had been formed.

Anal. Found: C, 38.7; H, 6.07; N, 5.19; Cl, 11.3; S, 7.18.

A solution of 680 mg. of this solid in 5 cc. of absolute alcohol and 2.9 cc. of 10% sodium hydroxide was allowed to stand for 1 hour, then was neutralized with 0.6 cc. of acetic acid and was evaporated to dryness *in vacuo*. The residue was heated with 5 cc. of pyridine and 5 cc. of acetic anhydride on the steam-bath for 1 hour, then diluted with 25 cc. of iced-water. The mixture was extracted with three 15-cc. portions of chloroform. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo*, leaving 560 mg. of residue. Crystallization from toluene-heptane gave 350 mg. (55%) of XV, m.p. and mixture m.p. 165–167°. No other compound could be crystallized from the filtrate.

Methyl 3-amino-4,6-benzylidene-α-D-altropyranoside (II). Reaction of methyl α-D-glucopyranoside with benzaldehyde and zinc chloride (20) gave a 69% yield of 4,6-benzylidene

derivative, m.p. 154–157°, providing the reaction mixture was diluted with water before addition of heptane. Reaction with *p*-toluenesulfonyl chloride and treatment of the crude tosylate with sodium methoxide as described by Bolliger and Prins (21) gave methyl 2,3-anhydro-4,6-benzylidene-α-D-mannopyranoside, m.p. 140–142°, in 66% yield.

A mixture of 6.7 g. of the anhydro-D-mannoside and 60 cc. of concentrated ammonium hydroxide was heated in a rocking autoclave at 100° for 20 hours. The cooled mixture was filtered and the solid was washed with water. The dried crude solid (6.1 g., 86%) was recrystallized from ethyl acetate; yield, 5.16 g. (72%), m.p. 183–185°. Similar yields were obtained with 250 g. of anhydro sugar.

The procedure of Myers and Robertson (4) was not considered satisfactory for preparative purposes since it employed a larger volume of ammonia water. The smaller ratio described above was satisfactory only with agitation of the heterogeneous reaction mixture, otherwise reaction was incomplete. Myers and Robertson (4) record a quantitative crude yield and a purified m.p. of 188°.

Methyl 2-acetyl-3-acetamino-4,6-benzylidene-α-D-altropyranoside (XXVIIa). To a solution of 5.0 g. of II in 25 cc. of reagent pyridine was added 5.0 cc. of acetic anhydride with cooling so that the temperature was 20–23°. After 3 days in a stoppered flask, the solution was diluted with 100 cc. of water, then cooled in an ice-bath for 35 minutes. The product was collected and washed with ice-water; yield, 6.03 g. (93%), m.p. 193–195°.

Myers and Robertson (4) record m.p. 201° and a yield of 60%.

Methyl 3-acetamino-4,6-benzylidene-α-D-altropyranoside (XXVa). (*A*) To a solution of 5.0 g. of II in 25 cc. of 50% acetic acid was added 2.5 cc. of acetic anhydride. After being shaken for 5 minutes, the solution was evaporated to dryness *in vacuo* leaving 5.7 g. (99%) of a white amorphous glass which could not be crystallized. Material used for subsequent steps was prepared in this way.

Anal. Calc'd for $C_{16}H_{21}NO_6$: N, 4.34; N-Ac, 13.3.

Found: N, 4.32; N-Ac, 12.7.

(*B*) To a suspension of 200 mg. of XXVIIa in 5 cc. of methanol was added 0.07 cc. of 1 *N* methanolic sodium methoxide. Solution rapidly took place. After being refluxed for 30 minutes, the solution was evaporated to dryness *in vacuo* leaving 175 mg. (99%) of an amorphous white glass which could not be crystallized.

Anal. Calc'd for $C_{16}H_{21}NO_6$: N, 4.34; N-Ac, 13.3.

Found: N, 4.10; N-Ac, 13.0.

Methyl 3-p-nitrobenzamido-4,6-benzylidene-α-D-altropyranoside (XXVb). To a stirred solution of 1.00 g. of II in 10 cc. of chloroform was added a solution of 0.57 g. of anhydrous sodium carbonate in 6 cc. of water followed by 0.66 g. of *p*-nitrobenzoyl chloride. After being stirred for one hour, the layers were separated and the aqueous phase was extracted with 10 cc. of chloroform. Washed with water and dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo* leaving a light yellow glass which could not be crystallized; yield, 1.51 g. (99%).

Anal. Calc'd for $C_{21}H_{22}N_2O_8$: C, 58.6; H, 5.15; N, 6.51.

Found: C, 58.9; H, 5.37; N, 6.26.

Acetylation in acetic anhydride-pyridine overnight at room temperature gave 94% of the *O-acetyl derivative* (XXVIIb), m.p. 182–184°. Recrystallization from ethanol afforded white crystals, m.p. 193–194°, $[\alpha]_D^{26}$ +74.3° (1.7% in $CHCl_3$).

Anal. Calc'd for $C_{23}H_{24}N_2O_9$: C, 58.4; H, 5.11; N, 5.93.

Found: C, 58.2; H, 5.34; N, 5.73.

Methyl 2-mesyl-3-acetamido-4,6-benzylidene-α-D-altropyranoside (XXVIII). To a solution of 20.5 g. of XXVa in 150 cc. of reagent pyridine cooled in an ice-bath was added dropwise 6.5 cc. of methanesulfonyl chloride at such a rate that the temperature was 3–5°. After 21 hours at 3° in a stoppered flask, the mixture was diluted with 750 cc. of water. The product was collected and washed with water; yield, 18.8 g. (74%), m.p. 160–161°. An additional 2.7 g. (11%), m.p. 156–158°, was obtained by concentration of the filtrate *in vacuo*. Recrystallization of a similar preparation (85% yield) gave white crystals, m.p. 160–161°, $[\alpha]_D^{26}$ +30.1° (1.5% in $CHCl_3$).

Anal. Calc'd for $C_{17}H_{23}NO_8S$: C, 50.9; H, 5.77; N, 3.49; S, 7.98.
Found: C, 50.7; H, 5.86; N, 3.69; S, 8.09.

Under similar conditions *p*-toluenesulfonyl chloride gave the corresponding tosylate in 71% yield which was not pure and could not be crystallized.

Anal. Calc'd for $C_{23}H_{27}NO_8S$: S, 6.70. Found: S, 5.62.

Crystalline products were not obtained by reaction of XXVa with *m*- or *p*-nitrobenzenesulfonyl chloride or XXV*b* with *p*-toluenesulfonyl chloride.

*Methyl 3-acetamino-4,6-benzylidene-α-*D*-allopyranoside* (XXXI). A solution of 9.0 g. of XXVIII and 7.4 g. of anhydrous sodium acetate in 90 cc. of 95% ethanol was refluxed for 22 hours during when sodium methanesulfonate separated. The cooled, filtered solution was evaporated to dryness *in vacuo*. The residue was warmed with 90 cc. of water which dissolved the product and left 27% of unchanged XXVIII, m.p. and mixture m.p. 160–161°. The filtrate was extracted with three 100-cc. portions of chloroform. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo* leaving 4.2 g. (79% based on XXVIII not recovered) of a glass which could not be crystallized.

This alloside on treatment with 3,5-dinitrobenzoyl chloride in pyridine at 25° gave an 84% yield of 3,5-dinitrobenzoate which could not be crystallized. Similarly, methanesulfonyl chloride gave 89% of a 2-mesylate which failed to crystallize.

Attempts to prepare XXXI by treatment of XXV with thionyl chloride were unsuccessful. After 18 hours at room temperature an amorphous product could be isolated from ether which contained nearly one atom each of sulfur and chlorine per molecule and which appeared to be the chlorosulfinate (XXVI). Treatment of the whole reaction product remaining after removal of the thionyl chloride with alcoholic sodium hydroxide, then with acetic anhydride-pyridine gave the unepimerized altroside diacetate (XXVIIa), identified by mixture m.p.

The same altroside was obtained with thionyl chloride-pyridine at 25° for one hour followed by basic hydrolysis and acetylation.

*Methyl 2-acetyl-3-acetamino-4,6-benzylidene-α-*D*-allopyranoside* (XXXII). A solution of 200 mg. of XXXI in 2 cc. of reagent pyridine and 0.5 cc. of acetic anhydride was allowed to stand for 20 hours, then was diluted with 10 cc. of water and extracted with chloroform to give 210 mg. (93%) of product, $[\alpha]_D^{24}$ +32.7° (2.4% in $CHCl_3$) which could not be crystallized.

Anal. Calc'd for $C_{18}H_{23}NO_7$: C, 59.2; H, 6.35; N, 3.84; N-Ac, 23.6.
Found: C, 59.6; H, 6.80; N, 3.64; N-Ac, 23.5.

*Methyl 2,4,6-triacetyl-3-acetamido-α-*D*-altropyranoside.* Hydrolysis of 2.0 g. of XXVIIa in 0.5% methanolic hydrogen chloride, then acetylation with acetic anhydride-pyridine essentially as described by Myers and Robertson (4) gave 1.03 g. (53%) of product, m.p. 166–169°. Several recrystallizations from absolute alcohol gave white crystals of constant m.p. 171–172° and $[\alpha]_D^{26}$ +42.2° (1.2% in $CHCl_3$).

Anal. Calc'd for $C_{15}H_{23}NO_9$: C, 49.9; H, 6.41; N, 3.88.
Found: C, 50.3; H, 6.62; N, 3.67.

Myers and Robertson (4) record m.p. 177° and $[\alpha]_D^{18}$ +34.1° (1.2% in $CHCl_3$), but give no yield.

*Methyl 2-mesyl-3-acetamido-α-*D*-altropyranoside* (XXXa). A mixture of 5 g. of XXVIII and 250 cc. of 0.5% hydrochloric acid in 95% methanol was refluxed for 30 minutes, solution being complete at the b.p. The solvent was removed *in vacuo*, and the residue was dissolved in 50 cc. of absolute alcohol and evaporated again to give 3.9 g. (100%) of a glass which could not be crystallized.

*Methyl 2-mesyl-3-acetamino-4,6-diacetyl-α-*D*-altropyranoside* (XXXb). A solution of 1.53 g. of XXXa in 10 cc. of pyridine and 5 cc. of acetic anhydride was heated on the steam-bath for one hour, then diluted with 50 cc. of water and extracted with three 25-cc. portions of chloroform. The combined extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo*. Crystallization by solution in 7 cc. of hot methanol, addition of 7 cc. of water, and chilling gave 1.4 g. (71%) of product, m.p. 166–167°. Recrystallization from absolute alcohol afforded white crystals, m.p. 168–169°, $[\alpha]_D^{24}$ +41.6° (2% in $CHCl_3$).

Anal. Calc'd for $C_{14}H_{23}NO_{10}S$: C, 42.3; H, 5.83; N, 3.53.

Found: C, 42.3; H, 5.60; N, 3.37.

The direct preparation of this compound by acetolysis of XXVIII with acetic anhydride-sulfuric acid (11) was unsuccessful.

Methyl 2,4,6-triacetyl-3-acetamido-α-D-allopyranoside (XXXIII) (*A*). A solution of 5.0 g. of XXXa and 5.3 g. of anhydrous sodium acetate in 50 cc. of 95% alcohol was refluxed for 21 hours, during which time sodium methanesulfonate (1.49 g., 79%) separated. The filtered solution was evaporated to dryness *in vacuo* and the evaporation was repeated with 30 cc. of absolute alcohol. The mixture was heated with 25 cc. of reagent pyridine and 25 cc. of acetic anhydride on the steam-bath for 1 hour. After dilution with 125 cc. of iced-water, the solution was extracted with three 50-cc. portions of chloroform. The combined, magnesium sulfate-dried extracts were evaporated to dryness *in vacuo*. The evaporation was repeated with 25 cc. of toluene to remove traces of pyridine. The residue was heated to boiling with 10 cc. of ethyl acetate leaving some insoluble solid. The mixture of solid and solution was diluted with 10 cc. of heptane and allowed to stand a few hours. Filtration gave 0.90 g. (14%) of the 2-mesyl altroside (XXXb), m.p. 163–165°. Evaporation of the filtrate left 4.08 g. of a glass which resisted attempts at crystallization from solvents.

Anal. Calc'd for $C_{15}H_{23}NO_{10}$: C, 49.9; H, 6.41; N, 3.88.

Found: C, 50.2; H, 6.70; N, 3.88.

After several months the glass crystallized and then melted at 112–115°. Recrystallization from ethyl acetate-heptane afforded white crystals, m.p. 128–129°, $[\alpha]_D^{25}$ +85.3° (2% in $CHCl_3$).

Anal. Found: C, 49.9; H, 6.58; N, 3.85.

(*B*). Hydrolysis and acetylation of the benzylidene alloside (XXXII) as described for XXXb gave white crystals, m.p. and mixture m.p. with preparation *A*, 126–127°.

Methyl 3-ethoxalylamino-4,6-benzylidene-α-D-altropyranoside. A mixture of 5.0 g. of II and 15 cc. of ethyl oxalate was heated on the steam-bath with occasional shaking for 30 minutes when solution was complete. Heating was continued for 2.5 hours more. The oil was extracted with three 35-cc. portions of heptane to remove excess ethyl oxalate. Crystallization of the residue from 20 cc. of ether gave 3.6 g. (53%) of product, m.p. 139–141°. Retreatment of the filtrate residue with ethyl oxalate failed to give any additional product. A similar preparation was recrystallized from ethyl acetate-heptane forming white crystals, m.p. 140–141°, $[\alpha]_D^{24}$ +34.3° (1.2% in abs. alc.).

Anal. Calc'd for $C_{18}H_{23}NO_8$: C, 56.7; H, 6.08; N, 3.68.

Found: C, 56.8; H, 6.46; N, 3.58.

The *2-O-acetyl derivative* was obtained in the usual manner in 98% yield, but could not be crystallized.

Anal. Calc'd for $C_{20}H_{25}NO_9$: C, 56.7; H, 5.95; N, 3.31.

Found: C, 56.6; H, 6.26; N, 3.17.

Methyl 2-mesyl-3-ethoxalylamino-4,6-benzylidene-α-D-altropyranoside. Mesylation of 9.3 g. of methyl 3-ethoxalylamino-4,6-benzylidene-α-D-altropyranoside as described for XXVIII gave 10.5 g. (96%) of product, m.p. 130–132°. Recrystallization from methanol afforded white crystals, m.p. 132–133°, $[\alpha]_D^{26}$ +21.0° (2.7% in $CHCl_3$).

Anal. Calc'd for $C_{19}H_{25}NO_{10}S$: C, 49.7; H, 5.49; N, 3.05; S, 6.97.

Found: C, 49.8; H, 5.74; N, 3.19; S, 7.43.

Although the ethyl ester rapidly saponified with 1.1 equivalents of alcoholic sodium hydroxide, further reflux failed to displace the mesylate group with concurrent formation of XXXV. The ring closure also failed when the benzylidene group was first removed with ethanolic hydrochloric acid.

Methyl 2,4-dimesyl-3-acetamino-β-L-xylopyranoside (XXXVI). To a solution of 29.5 g. of XIV in 500 cc. of reagent pyridine was added 29.5 cc. of methanesulfonyl chloride portionwise with shaking and ice-cooling at such a rate that the temperature was 25–30°. When the reaction mixture was no longer exothermic it was allowed to stand in a stoppered flask at room temperature for 20 hours. Sufficient water was added to dissolve the pyridine hydrochloride, then the solution was concentrated *in vacuo* (bath 50°) to about 150 cc. Dilution with 300 cc. of water and cooling to 15° gave a buff solid which was collected, washed with

water, and dried on the steam-bath; wt., 31.7 g., m.p. 149–150°. Concentration of the filtrate gave an additional 11.2 g. (total 83%), m.p. 149–150°.

In a pilot run the product was isolated by chloroform extraction and after recrystallization from absolute alcohol had m.p. 139–140°. During a second recrystallization from absolute alcohol, solution was almost complete at the b.p. when crystals separated which would not redissolve until almost three times the original amount of alcohol was added. On cooling the solution deposited crystals, m.p. 149°, $[\alpha]_D^{23}$ +18.8° (2% in pyridine). The low-melting dimorph was not encountered in any subsequent preparations.

Anal. Calc'd for $C_{10}H_{19}NO_8S_2$: C, 33.2; H, 5.30; N, 3.88.

Found: C, 33.7; H, 5.61; N, 4.06.

Tosylation was sluggish and a 54% yield of crude gum was obtained after 24 hours at 34°. After 72 hours the ditosylate was obtained as a dark red gum in 80% yield, but could not be crystallized.

Methyl 2-acetyl-3-acetamino-4-mesyl-β-L-lyxopyranoside (XLIII) *or methyl 2-mesyl-3-acetamino-4-acetyl-α-D-arabinopyranoside* (XXXVIII). A mixture of 14.8 g. of XXXVI, 16.8 g. of anhydrous sodium acetate, and 178 cc. of 95% ethanol was refluxed for 22 hours. Cooling gave 5.1 g. (106%) of insoluble sodium methanesulfonate, m.p. > 250°. The filtrate was evaporated to dryness *in vacuo* and the evaporation was repeated with 50 cc. of absolute alcohol. After the addition of 75 cc. of reagent pyridine and 75 cc. of acetic anhydride, the mixture was heated on the steam-bath for one hour. After dilution with 375 cc. of iced-water the clear solution was extracted with three 100-cc. portions of chloroform. The combined extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo*. Trituration of the residue with 50 cc. of toluene gave 8.0 g. (60%) of product, m.p. 172–173°. From the filtrate there was isolated an additional 0.80 g. (6%), m.p. 171–172°. Recrystallization from absolute alcohol afforded white crystals, m.p. 171–172°, $[\alpha]_D^{24}$ −11.0° (1.4% in pyridine).

Anal. Calc'd for $C_{11}H_{19}NO_8S$: C, 40.6; H, 5.89; N, 4.31.

Found: C, 40.9; H, 5.78; N, 4.22.

Methyl 2,4-diacetyl-3-acetamido-α-D-ribopyranoside (XLII) (*A*). A mixture of 3.0 g. of monomesylate (XXXVIII or XLIII), 3.1 g. of anhydrous sodium acetate, and 30 cc. of 95% aqueous Methyl Celloslove[5] was refluxed on a heating mantle for 24 hours. The cooled solution was filtered from sodium methanesulfonate, then evaporated to dryness *in vacuo*. The residue was heated on the steam-bath with 30 cc. of pyridine and 30 cc. of acetic anhydride for one hour. After dilution with 150 cc. of water, the mixture was extracted with three 50-cc. portions of chloroform. The combined magnesium sulfate dried extracts were evaporated *in vacuo*. The residue was twice dissolved in 10 cc. of toluene and was evaporated to dryness *in vacuo* to remove pyridine; wt., 2.5 g. of a glass. Crystallization from 10 cc. of absolute alcohol gave 1.85 g. (69%) of product in three crops, all melting at 116–117°. Further recrystallization gave white crystals of unchanged m.p. $[\alpha]_D^{24}$ +93.7° (1.6% in $CHCl_3$).

Anal. Calc'd for $C_{12}H_{19}NO_7$: C, 49.8; H, 6.62; N, 4.85.

Found: C, 49.8; H, 6.84; N, 4.73.

When the reaction was run at 100° for 66 hours, less sodium methanesulfonate was formed and the product, partially melting at 117–120°, appeared to be a mixture of XLII and XLIII.

(*B*). A mixture of 18 g. of XXXVI, 20.5 g. of anhydrous sodium acetate, and 215 cc. of 95% aqueous Methyl Cellosolve[5] was refluxed for 24 hours, then processed as in part *A* by acetylation with 54 cc. of pyridine and 54 cc. of acetic anhydride; yield, 10.0 g. (70%), m.p. and mixture m.p. with preparation *A*, 116–117°.

Deacetylation of XLII with methanolic sodium methoxide as described for XXVa gave methyl 3-acetamino-α-D-ribopyranoside (XXXIX) in quantitative yield as a glass which could not be crystallized.

3-Amino-D-ribose hydrochloride (XLI). A solution of 2.27 g. of XLII in 45 cc. of 1% hydrochloric acid and 0.67 cc. of 12 *N* hydrochloric acid was refluxed for 18 hours. The solution was clarified with Norit and was evaporated to a syrup (bath 40°) which crystallized on cooling. Trituration with 5 cc. of glacial acetic acid gave 1.21 g. (83%) of product, m.p. 151° dec., $[\alpha]_D^{24}$ −24.6° (2% in H_2O).

Recrystallization was affected by solution of 100 mg. in 0.10 cc. of water and addition of

0.30 cc. of concentrated hydrochloric acid to give heavy white plates, m.p. 160° dec., $[\alpha]_D^{24}$ −25.0° (2% in H_2O). The infrared curve was identical with the 3-aminopentose hydrochloride obtained from puromycin (1) when recrystallized in the same fashion.

Anal. Calc'd for $C_5H_{11}NO_4 \cdot HCl$: C, 32.4; H, 6.52; N, 7.55.
Found: C, 32.6; H, 6.82; N, 7.79.

This compound forms a number of crystal modifications depending upon the solvent added to its 50% aqueous solution. All have the same rotation with no observable mutarotation, but can be differentiated by their infrared spectra in a Nujol mull, the intensity of peaks in the 7–11 μ region differing. From concentrated hydrochloric acid the same heavy plates, m.p. 160° dec., are obtained every time. Water-acetic acid gives one of two other crystal forms. One form crystallizes rapidly as heavy finely divided crystals, m.p. 162° dec., and another more slowly as voluminous plates, m.p. 156° dec.

Water-alcohol sometimes gives a fourth form, m.p. 172° dec., and at other times gives the form obtained from concentrated hydrochloric acid. The negative rotation compared to the strong positive rotation of the α-methyl ether (XLII), indicates a β configuration for this amino sugar.

In one run where no precautions were taken to avoid overheating the solution during removal of the 1% hydrochloric acid, the product was amorphous and could not be crystallized. No difficulty has been experienced in crystallizing this sugar in five other runs where the bath temperature was maintained at 40° during concentration.

PEARL RIVER, NEW YORK

SUMMARY

The synthesis of 3-amino-D-ribose in nine steps from L-arabinose proceeding through derivatives of L-ribose, L-xylose, and L-lyxose has been described. This amino sugar is identical with the 3-aminopentose obtained on hydrolysis of the antibiotic, puromycin.

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