Neighboring-Group Participation across a Furanose Ring. Synthesis of 5-Acetamido-5-deoxy-D-lyxopyranose from D-Arabinose Precursors[1]

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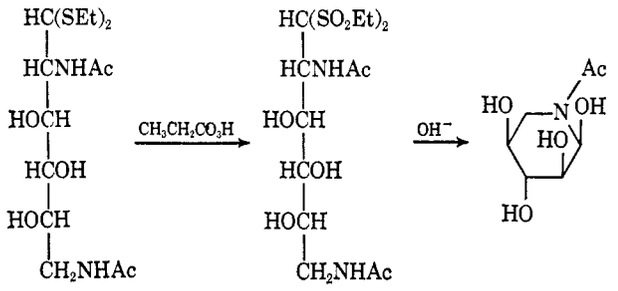
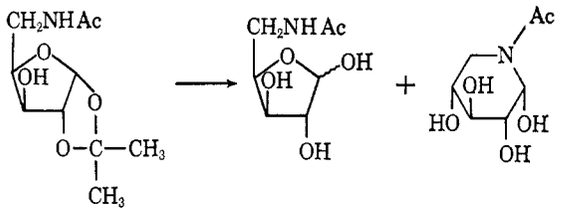
Displacement of 5-acetamido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-D-arabinofuranose with sodium benzoate in *N,N'*-dimethylformamide afforded 5-acetamido-5-deoxy-1,2-*O*-isopropylidene-D-lyxofuranose as the sole product. The reaction is an example of a 1,3 amide participation across the furanose ring and is highly dependent on the solvent and reagent used. The effectiveness of the C-5 acetamido function in the displacement reaction is compared with derivatives having other functionalities at that carbon atom. The synthesis of 5-acetamido-5-deoxy-D-lyxopyranose, the last of the D-pentoses containing nitrogen as the ring atom, is described. The mass spectral fragmentation pathways of 5-acetamido-5-deoxypentopyranose tetraacetates are compared with those of an analog containing oxygen in the ring.

In a prior publication[2] from these laboratories, the synthesis of 5-acetamido-5-deoxypentopyranoses having the D-*xylo*, L-*arabino*, and D-*ribo* configurations was described. The first two derivatives were reported shortly before.[3,5] The availability of this novel class of compounds enabled us to establish the configuration of paromose (neosamine B), a 2,6-diaminohexose in the antibiotics paromomycin, neomycin, and zygomycin.[6] Paromose was degraded by way of its *N,N*-diacetyl 1,1-bis(alkylsulfonyl) derivative to crystalline 5-acetamido-5-deoxy-L-xylopyranose,[7] thereby providing the configuration at C-3, C-4, and C-5



of the original diaminohexose. The successful adaptation of the MacDonald–Fischer degradation[8] to such uncommon amino sugar dithioacetals emphasized the utility of these N-heterocyclic sugars as model primary degradation products. Interest has also been extended to the biochemical field since these and other heteroses containing sulfur in the ring were recently found to be powerful inhibitors of glycosidase activities.[9] This paper describes the synthesis of the fourth and last members of this class of sugars in the pentose series, namely, 5-acetamido-5-deoxy-D-lyxopyranose (6). The availability of this crystalline compound, and several of its crystalline derivatives could assist in the elucidation of the partial configuration (C-3–C-5) of 2,6-diamino- or 6-aminohexoses in the *galacto* and *talo* series, through the application of the disulfone degradation reaction.

The available methods for the synthesis of 5-acetamido-5-deoxypentoses generally involve the generation of an aldehyde function in the presence of an existing amide group in the molecule. This procedure usually affords mixtures of the furanose and pyranose (containing N) products. One recent method relies



on the cyclization[10,11] of 5-amino-5-deoxypentose bisulfite addition compounds[12] and another[13] involves the reductive rearrangement[14] of terminal azidopentoses. Employing these methods, the N-heterocyclic pyranose form is formed selectively in the *xylo* series and preponderantly in the *arabino* and *ribo* series.[13]

Preliminary experiments were aimed at the selective sulfonylation at C-5 in various D-lyxose dithioacetals with the objective of replacing the sulfonate function by azide and proceeding from there as in the *arabino* analog.[2] Concurrent with these trials, Defaye[15] demonstrated the formation of 2,5-anhydro-D-lyxose diisobutyldithioacetal when D-lyxose diisobutyl dithioacetal was treated with 1 equiv of *p*-toluenesulfonyl chloride in pyridine. Anhydro ring formation also occurred in the D-ribose and D-xylose series.[15,16]

Attention was then turned to the more readily accessible arabinose derivatives and attempts were made to invert C-3 to provide the desired D-*lyxo* configuration. Reaction of 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-D-arabinose[17] (1) with sodium azide in *N,N'*-dimethylformamide at 100° gave the corresponding 5-azido derivative (2) as a pure liquid in good yield.

(1) Presented in part at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, Abstracts, p 15C.

(2) S. Hanessian and T. H. Haskell, *J. Org. Chem.*, **28**, 2604 (1963).

(3) H. Paulsen, *Angew. Chem.*, **74**, 901 (1962); *Ann.*, **670**, 121 (1963).

(4) (a) J. K. N. Jones and J. C. Turner, *J. Chem. Soc.*, 4699 (1962); (b) J. K. N. Jones and W. A. Szarek, *Can. J. Chem.*, **41**, 636 (1963).

(5) For a review on sugars containing nitrogen in the ring, see H. Paulsen, *Angew. Chem. Intern. Ed. Engl.*, **5**, 495 (1966).

(6) For reviews, see K. L. Rinehart, Jr., "The Neomycins and Related Antibiotics," John Wiley and Sons, Inc., New York, N. Y., 1964, p 36; J. D. Dutcher, *Advan. Carbohydrate Chem.*, **18**, 259 (1963).

(7) T. H. Haskell and S. Hanessian, *J. Org. Chem.*, **28**, 2598 (1963).

(8) D. L. MacDonald and H. O. L. Fischer, *J. Am. Chem. Soc.*, **74**, 2087 (1952).

(9) M. Claeyssens and C. K. DeBruyne, *Naturwissenschaften*, **18**, 515 (1965).

(10) H. Paulsen, K. Todt, and F. Leupold, *Tetrahedron Letters*, 567 (1965); H. Paulsen, F. Leupold, and K. Todt, *Ann.*, **692**, 200 (1966).

(11) D. L. Ingles, *ibid.*, 1317 (1965).

(12) D. L. Ingles, *Chem. Ind.* (London), 927 (1964).

(13) S. Hanessian, *ibid.*, 1296 (1965).

(14) S. Hanessian and T. H. Haskell, *J. Heterocyclic Chem.*, **1**, 55 (1964).

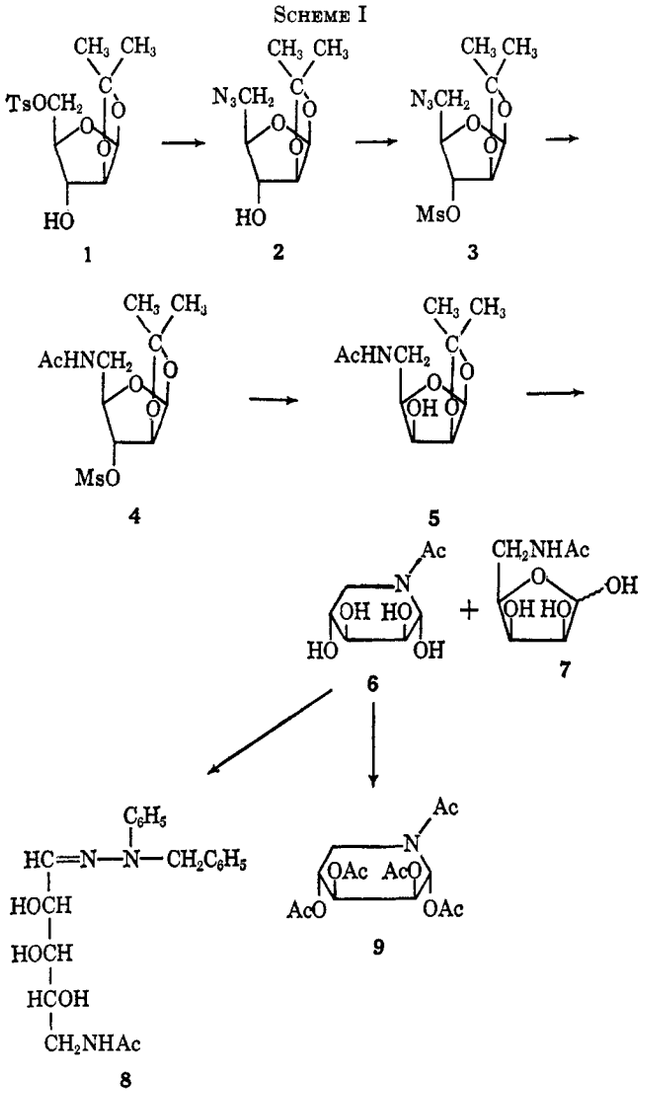
(15) J. Defaye, *Bull. Soc. Chim. France*, 2686 (1964).

(16) H. Zinner, H. Brandhoff, H. Schmandke, H. Kristen, and R. Hann, *Chem. Ber.*, **92**, 3151 (1959).

(17) E. L. Hirst, J. K. N. Jones, and E. Williams, *J. Chem. Soc.*, 1062 (1947).

Treatment of **2** with methanesulfonyl chloride in pyridine in the usual way afforded crystalline 5-azido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-D-arabinose (**3**) in 96% yield. This product was hydrogenated over Pd–C and hydrogen and the resulting 5-amino derivative was N-acetylated to give crystalline 5-acetamido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-D-arabinose (**4**). When **4** was refluxed overnight in *N,N'*-dimethylformamide containing excess sodium benzoate, the major product was that resulting from inversion at C-3, namely, 5-acetamido-5-deoxy-1,2-*O*-isopropylidene-D-lyxofuranose (**5**). Mild acid hydrolysis with dilute sulfuric acid (pH 1–1.5) during 3 days at room temperature gave a mixture of **6** and the corresponding furanose isomer (**7**) in an approximate ratio of 1:1. Compound **6** was obtained in pure crystalline form by direct crystallization from this mixture; the furanose isomer remained as a syrup and was not investigated further. By standard procedures, **6** was converted into crystalline 5-acetamido-5-deoxy-D-lyxose benzylphenylhydrazone (**8**), and into crystalline 5-acetamido-5-deoxy-D-lyxose tetraacetate (**9**) (Scheme I).

SCHEME I



Compound **6** had all the characteristic properties expected of its structure. Its infrared spectrum exhibited a band at 1620 cm^{-1} (amide I) but showed no amide II band. It displayed negligible mutarotation in aqueous solution and could be isomerized[2] partially to **7** when treated with acids or bases or when heated. Its nmr spectrum in deuterium oxide, with tetramethylsilane as external standard, showed a singlet at τ 7.82 for the acetyl hydrogens. The usual splitting of this peak due to rotational isomerism about the C–N bond[18] was not observed at *ca.* 35°. That this phenomenon was operating in solution, however, was indicated by the appearance of two doublets centered at τ 4.05 and 4.48, respectively, owing to the anomeric hydrogen atoms of the rotational isomers. Compound **6** is most probably the α anomer in analogy with the D-*xylo*, D-*ribo*, and L-*arabino* isomers.[2,19]

Previously, the position of the amide absorption bands in the infrared spectra of the benzylphenylhydrazones[2] of 5-acetamido-5-deoxy-D-xylose, -D-ribose, and -L-arabinose was found to differ appreciably. The D-ribose derivative showed a band at 1627 cm^{-1} (amide I), with evidence of strong hydrogen bonding in the hydroxyl absorption region, while the D-xylose and L-arabinose derivatives had peaks at 1645 and 1640 cm^{-1}, respectively. The amide I peak in the infrared spectrum of **8** was at 1656 cm^{-1}; the amide II band at 1563 cm^{-1} could be clearly seen as in the case of the *xylo* and *arabino* isomers, but contrary to that of the D-*ribo* analog.[2] The acyclic nature of all these hydrazones has been established by nmr studies.[2] The physical constants of the 5-acetamido-5-deoxypentoses and their benzylphenylhydrazones are compiled in Table I.

TABLE I

PHYSICAL PROPERTIES OF 5-ACETAMIDO-5-DEOXYPENTOSES AND THEIR BENZYLPHENYLHYDRAZONES

Pentose	Mp, °C	$[\alpha]_D$ (H_2O), deg	Mp,[a] °C	$[\alpha]_D$ (MeOH),[a] deg
L-*arabino*[b]	145–146	18.5	151–152	−12.2
D-*lyxo*[b]	166–167	−71.0	155–156	+23.4
D-*ribo*[b]	Syrup	...	143–144	−36.4
D-*xylo*[b]	163–164	−21.8	132–133	0 ± 1.7
L-*xylo*[c]	160–162	...	128	0 ± 2

[a] Benzylphenylhydrazone. [b] Reference 2. [c] Reference 7.

The structure of the acetate **9** was confirmed by infrared and mass spectral data. The behavior of this compound upon electron impact[20] was investigated in order to study its preferred modes of fragmentation and to compare the stability of the different fragments with those from an analog containing oxygen in the ring (D-ribopyranose tetraacetate).[21] The mass spectrum of the isomeric 5-acetamido-5-deoxy-D-xylopyranose tetraacetate[1,3] was also recorded and is shown in Figure 1. Except for minor relative intensity differences and the fact that a molecular ion

(18) W. A. Szarek, S. Wolfe, and J. K. N. Jones, *Tetrahedron Letters*, 2743 (1964).

(19) The α form is produced by topside attack of the C-5 nitrogen function on C-1. The absence of mutarotation precludes anomerization at that carbon atom and the original anomeric integrity is preserved. This has also been corroborated by nmr data which will be discussed in a subsequent publication.

(20) The mass spectra were determined with an Atlas CH4 mass spectrometer at an ionizing potential of 70 ev and an ionizing current of 20 ma (18 ma for **9**). The samples were introduced through a direct inlet and were vaporized with the use of little (compound **9**) or no heat.

(21) K. Biemann, D. C. DeJongh, and H. K. Schnoes, *J. Am. Chem. Soc.*, **85**, 1763 (1963).

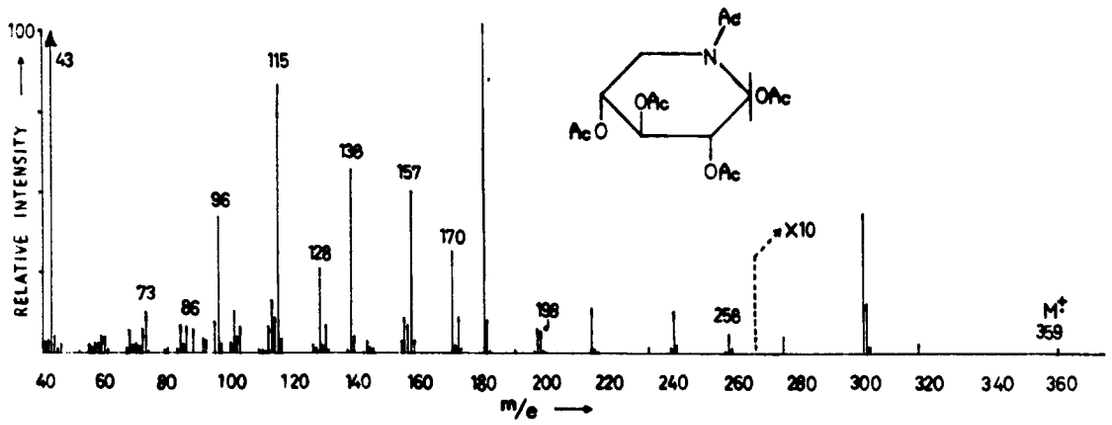
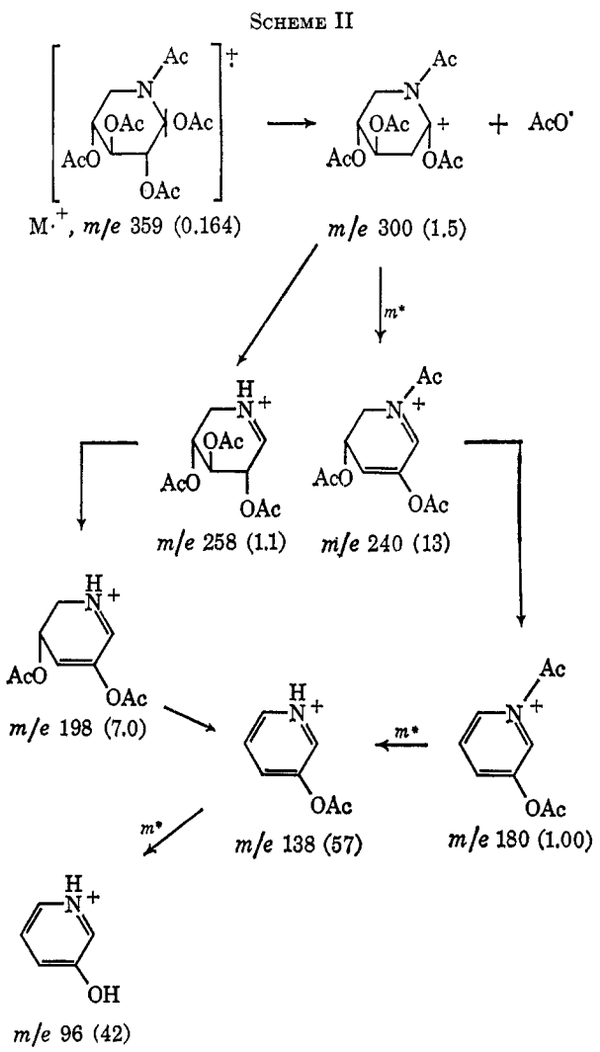


Figure 1.—Mass spectrum of 5-acetamido-5-deoxy-D-xylopyranose tetraacetate. Peak intensities are based on the *m/e* 180 peak (100% intensity), although the *m/e* 43 peak is the most intense, 211%.

peak cannot be seen in **9**, the spectra were identical. The position of the metastable ion peaks were also identical, indicating that both compounds fragment by identical pathways.

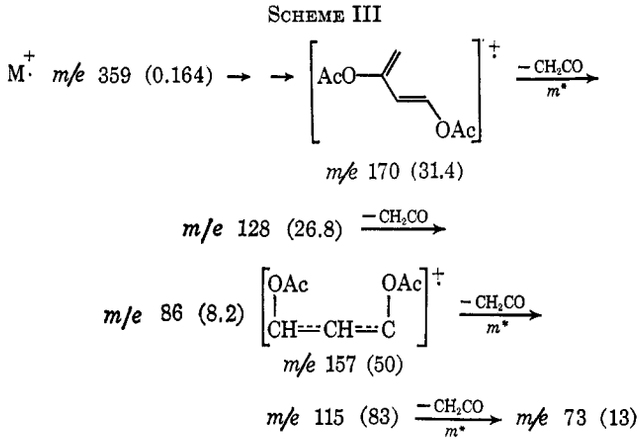
The primary fragmentation pathway (designated as series A[21]) was as expected, different from that in the case of D-ribopyranose tetraacetate, and is depicted in Scheme II. Minor fragmentation pathways[21] similar to series A are also present and involve the loss of acetyl radical, followed by ketene and acetic acid.

SCHEME II



The 3-hydroxypyridinium ion at *m/e* 96 is also formed in the fragmentation of 1-acetyl-D-xylo-3,4,5-triacetoxypiperidine.[1,22] Two other major fragmentation sequences follow the same course as in the case of D-ribopyranose tetraacetate[21] and are depicted in Scheme III (series B and C). The fragmentation of a related derivative, methyl 5-acetamido-5-deoxy-2,3,4-tri-*O*-methyl-D-xylopyranoside, was recently reported by Heyns and Müller.[23]

SCHEME III



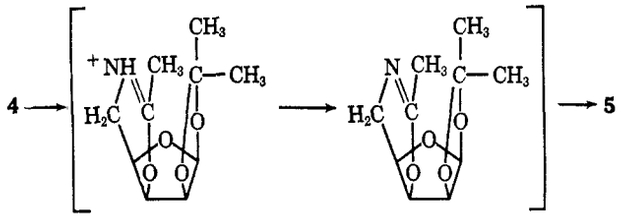
The direct replacement of a secondary sulfonate group in a furanose or furanoside derivative by nucleophiles has been generally unsuccessful.[24,25] In order to invert such secondary carbon atoms, use has been made in many cases of the participating ability of a neighboring amide or ester function at the site of nucleophilic displacement, through the formation of acylonium or oxazolinium intermediates, respectively. The inverted carbon would then carry a hydroxyl group originating from the participating carbonyl oxygen function as a result of attack of hydroxyl ion from the medium on the charged intermediate. In the strict absence of moisture, the inverted carbon atom would bear the attacking nucleophile. The nature of the reaction product(s) in such displacement reactions depends, among other things, on the choice of

(22) H. Paulsen, *Ann.*, **688**, 187 (1965).
(23) K. Heyns and D. Müller, *Tetrahedron*, **21**, 3151 (1965).
(24) K. J. Ryan, H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Am. Chem. Soc.*, **86**, 2497 (1964).
(25) (a) N. A. Hughes and P. R. H. Speakman, *J. Chem. Soc.*, 2236 (1965); (b) N. A. Hughes and P. R. H. Speakman, *Carbohydrate Res.*, **1**, 341 (1966).

nucleophile or reagent, the solvent, steric considerations, and the electronic disposition of the participating function. The selection of suitable conditions in solvolysis reactions of this type could be of prime importance in many cases.

The advantages of the sodium benzoate and *N,N'*-dimethylformamide system[26] in effecting inversions of secondary carbon atoms in the presence of a vicinal participating function have been discussed.[24] In the present study, this reagent was found to effect the desired inversion of C-3 in compound **4** decidedly better than others. Under the same conditions, the system of sodium acetate in *N,N'*-dimethylformamide was also effective, but gave a more heterogeneous product. In the time required for most of the starting material to react, noticeable amounts of demesylation occurred owing to the basic nature of the reagent (compared with sodium benzoate). The separation of demesylated product from the expected product **5** proved difficult. The system of sodium acetate in refluxing ethyl alcohol afforded only unchanged starting material even after 48 hr. When sodium acetate in refluxing Methyl Cellosolve was used instead (with or without water added), a period of 40 hr was required to produced appreciable amounts of **5**. This material was, however, contaminated with demesylated **4**, resulting from O–S bond cleavage due to the prolonged heating in the basic medium.

The transformation of **4** → **5** is an example of a 1,3 participation of an amide function across the ring in a furanose derivative *via* the intermediate oxazolinium ion–oxazoline system **10**. The oxazoline was not



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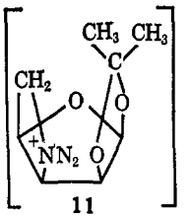
isolated, which implies its relative instability and ready hydrolysis by traces of water; another possibility would be the attack of the hydroxyl ion on the oxazolinium ion itself before its eventual transformation to the hypothetical oxazoline. A related example involves the inversion of C-4 by the C-6 benzamido group in methyl 2,6-dibenzamido-2,6-dideoxy-3-*O*-methyl-4-*O*-methylsulfonyl-β-D-glucopyranoside,[27] where the six-membered oxazoline intermediate was actually isolated.

It is noteworthy that a compound much related to **4**, 5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-L-arabinofuranose, was recovered unchanged when treated with tetrabutylammonium benzoate in *N*-methylpyrrolidone at 105° for 20 hr.[25b] The resistance of the C-3 sulfonyloxy group to replacement was explained on the basis of its unfavorable *exo* position as well as the steric effect of a *trans* C-5 benzoate function. It seems, however, that this resistance to displacement is the consequence of the nature of the C-5 participating function. The presumed unfavorable steric features are also present in compound **4**, but are evidently surmounted by the superior participating ability of the C-5 acetamido function.

In order to further test the effectiveness of the C-5 acetamido function in assisting the removal of the C-3 mesylate in **4**, the displacement reaction was attempted under the same conditions, but with compound **3**. Investigation of the 24-hr reaction product by thin layer chromatography indicated the presence of starting material (subsequently recovered in over 90% yield), demesylated product **2**, and some by-products having slower mobility. The identity of **2** was confirmed by converting it into 5-acetamido-5-deoxy-1,2-*O*-isopropylidene-D-arabinofuranose, known in the L series.[4a] Two other products were formed (<1% yield) on prolonged reaction times (60–72 hr) and had faster mobilities on thin layer chromatograms compared with **3**. These were isolated by preparative thin layer chromatography and were obtained as homogeneous syrups. Infrared spectral data showed the presence in both components of azide and benzoate ester absorptions, and the absence of hydroxyl, sulfonate, and unsaturated functions. It is conceivable that these products could correspond to the C-3 benzoate (D-*lyxo*) arising from direct SN2 attack and to an isomer formed by participation[28,29] of the azide group at C-3 *via* the azidonium intermediate **11**. Un-



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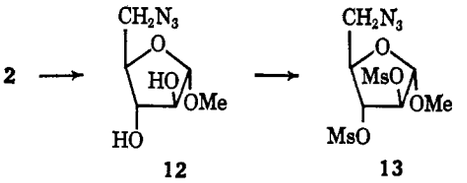
fortunately, attempts to enrich these products by prolonged reaction times were not successful owing to the competing demesylation reaction. Consequently insufficient amounts of these compounds were available for their complete characterization.

The furanoside derivative **13**, which is conformationally less rigid than **3**, was also subjected to displacement by benzoate ion in *N,N'*-dimethylformamide. Compound **13** was obtained by methanolysis of **2**, followed by mesylation of the resulting glycoside **12**.



12 **13**

When **13** reacted under the same conditions employed for **3**, extensive darkening resulted even after refluxing for 2 hr. Examination of the processed oily product from an overnight reaction by thin layer chromatography revealed the presence of several

(26) E. J. Reist, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5775 (1958).

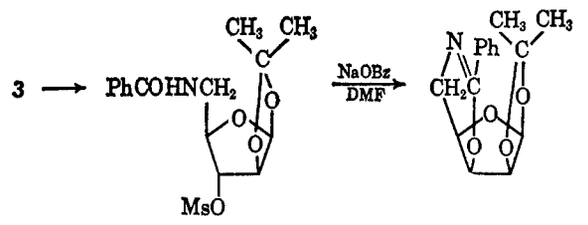
(27) W. Meyer zu Reckendorf, *Chem. Ber.*, **96**, 2019 (1963).

(28) Participation by an azide group has been recently suggested in a comparable displacement in the acyclic series: S. Hanessian, *Carbohydrate Res.*, **1**, 178 (1965); see also A. Streitweiser, Jr., and S. Pulver, *J. Am. Chem. Soc.*, **86**, 1587 (1964), for an example in the cyclohexane series.

(29) The formation of 3,5-oxetane derivatives in the *xylo* series and in certain pyrimidine nucleosides, is well established: P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, **102**, 331 (1933); J. P. Horwitz, J. Chua, M. A. DaRooge, and M. Noel, *Tetrahedron Letters*, 2725 (1964).

components. Infrared spectral examination showed that much of the sulfonate functions was absent.

A final objective in this research was to compare the efficacy of a 5-benzamido group *vs.* the 5-acetamido group as a participating function in the solvolysis of the C-3 mesylate. Reduction of **3** and benzoylation of the resulting 5-amino derivative gave crystalline 5-benzamido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-D-arabinofuranose (**14**). Compound **14** was subjected to solvolysis in the presence of sodium benzoate in *N*,*N*′-dimethylformamide as in the case of **4**. The preponderant product from such a reaction was the crystalline oxazoline **15**. Traces of starting material and some demesylated **14** were also present.



Thus, whereas the 5-acetamido derivative **4** afforded an inverted product **5**, by initial participation at C-3 and subsequent collapse of the oxazolinium ion–oxazoline intermediate **10**, the corresponding 5-benzamido analog **14** underwent preferential proton expulsion to yield a presumably stabilized product **15**. That oxazoline formation was somewhat general and characteristic of compound **14** was evidenced by its identical behavior in the system sodium acetate–*N*,*N*′-dimethylformamide. Although this resistance to ring opening by the traces of water present could be explained in terms of steric hindrance, previous reports have indicated the unusual resistance to ring opening of such aromatic oxazolines even under forcing conditions.[30] The oxazoline **15** was found to be stable to methanolic sodium methylate at room temperature for 18 hr.

Experimental Section

Melting points are uncorrected. Silica gel for thin layer chromatography was type G obtained from Brinkmann Instruments, New York, N. Y. Components were detected with a spray containing 5% each of ammonium molybdate, sulfuric acid, and phosphoric acid after heating the plate for 5–10 min at 110°.[27] Paper chromatography was carried out on Whatman No. 1 paper in the solvent system, 1-butanol–ethanol–water (3:1:1), and spots were detected with alkaline silver nitrate (reducing compounds) and potassium permanganate in 0.1 *N* sulfuric acid (nonreducing compounds).

5-Azido-5-deoxy-1,2-*O*-isopropylidene-D-arabinofuranose (2).—A solution containing 16.1 g of **1** and 20.4 g of sodium azide in 500 ml of *N*,*N*′-dimethylformamide was stirred at 85–90° for 8 hr. The solvent was removed by codistillation with 1-butanol under reduced pressure in a rotary evaporator. The residue was suspended in acetone, the salts were filtered, and the filtrate was evaporated to a mobile yellow liquid. The last traces of salts were removed by filtration from acetone and the latter was evaporated to give 9.295 g (93%) of crude **2**. An ether solution of this product was washed briefly with a small quantity of water, the ether was evaporated, and the resulting liquid was distilled at 131–133° and *ca.* 0.6 mm to afford the pure product as a very pale yellow liquid which was homogeneous on silica gel plates (benzene–methanol, 10:1): infrared spectral data ($CHCl_3$) 2100 cm^{-1} (azide).

5-Azido-3-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-D-arabinofuranose (3).—A solution of **2** (3.26 g) in 30 ml of dry pyridine was treated dropwise with stirring at −30°, with 2.1 ml of methanesulfonyl chloride. The mixture was stored overnight at −5° and poured into ice–water. The crystalline product was filtered and washed with cold water then with pentane to give 3.755 g of product. An additional crop (575 mg) was obtained by processing the mother liquors, total yield 4.33 g (96%). A portion was crystallized from ether–pentane to give an analytical sample: mp 61–62°; $[\alpha]^{24}D$ 44.5° (*c* 1.72, methanol); infrared spectral data (KBr) 2100 (azide), 1190 cm^{-1} (sulfonate).

Anal. Calcd for $C_9H_{15}N_3O_6S$: C, 36.88; H, 5.16; N, 14.31; S, 10.94. Found: C, 37.17; H, 5.17; N, 14.53; S, 10.98.

5-Acetamido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-D-arabinofuranose (4).—A solution containing **3** (1.2 g) and 6% palladium on carbon (0.2 g) in 60 ml of methanol was stirred for 1 hr in the presence of hydrogen. The filtered solution was treated with 5 ml of acetic anhydride and evaporated to dryness after 3 hr. The crystalline residue was recrystallized from a mixture of acetone–ether and pentane to give the pure product: 1.23 g (97%); mp 127–128°; $[\alpha]^{25}D$ 6.5° (*c* 1.16, methanol); infrared spectral data (KBr) 1648 (amide I), 1565 (amide II), 1190 cm^{-1} (sulfonate).

Anal. Calcd for $C_{11}H_{19}NO_7S$: C, 42.80; H, 6.20; N, 4.53; S, 10.35. Found: C, 43.05; H, 6.11; N, 4.50; S, 10.58.

5-Benzamido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-D-arabinofuranose (14).—A solution containing 1.27 g of **3** was hydrogenated as with **4**, the catalyst was filtered, and the filtrate was evaporated to dryness. The syrupy residue was dissolved in 20 ml of pyridine and was treated dropwise with 0.5 ml of benzoyl chloride at −10°. After standing at 5° overnight the reddish solution was poured into ice–water and the crystalline product was filtered (1.46 g, 94%). Recrystallization from a mixture of acetone–ether and pentane afforded pure material: mp 117–118°; $[\alpha]^{25}D$ 9° (*c* 0.545, methanol); infrared spectral data (KBr) 1655 (amide I), 1535 (amide II), 1178 cm^{-1} (sulfonate).

Anal. Calcd for $C_{16}H_{21}NO_7S$: C, 51.85; H, 5.72; N, 3.77; S, 8.52. Found: C, 52.27; H, 6.19; N, 3.60; S, 8.74.

5-Acetamido-5-deoxy-1,2-*O*-isopropylidene-D-lyxofuranose (5).—To 140 ml of *N*,*N*′-dimethylformamide were added 1.25 g of **4** and 2 g of sodium benzoate, and the mixture was stirred at reflux temperature for 24 hr in an atmosphere of nitrogen. Evaporation of the solvent gave 0.9 g (94%) of **5** as a semicrystalline syrup which showed essentially one spot on silica gel plates (benzene–methanol 10:2). On paper chromatograms it moved as a single component, R_f 0.36; 5-acetamido-5-deoxy-1,2-*O*-isopropylidene-D-arabinofuranose had R_f 0.27. This material was suitable for the next step.

When **4** (0.3 g) was refluxed in 50 ml of 95% aqueous ethanol, containing 0.2 g of anhydrous sodium acetate, it was recovered unchanged after 24 hr. This reaction was repeated using 95% aqueous Methyl Cellosolve and refluxing was continued for a total of 40 hr. Thin layer chromatography (benzene–methanol, 10:2) showed the presence of **4** and **5**. Compound **4** was subsequently isolated in crystalline form (180 mg). Paper chromatographic examination of the fraction corresponding to **5** showed the presence of demesylated **4** in addition to the product **5**. When the reaction was repeated in *N*,*N*′-dimethylformamide and anhydrous sodium acetate was used instead of sodium benzoate (see above), thin layer chromatography (benzene–methanol, 10:2) indicated the formation of **5** as the major component, in addition to starting material, demesylated **4**, and several slow-moving by-products.

5-Acetamido-5-deoxy-α-D-lyxopyranose (6).—A portion of **5** (0.80 g) was dissolved in dilute sulfuric acid (pH 1.0) and the solution was left at room temperature for 3 days. Neutralization with Amberlite IR-45 (OH^-) and evaporation of the filtered solution afforded a pale yellow syrup. This was dissolved in methanol, decolorized with Darco G-60, and filtered, and the solution was evaporated to an almost colorless syrup, (625 mg, 95%). Examination of this syrup by paper, and thin layer chromatography (benzene–methanol, 2:1) showed the presence of two reducing components. The nmr spectrum of this mixture in deuterium oxide using tetramethylsilane as external standard showed two methyl peaks at τ 7.85 and 8.03 owing to the pyranose (**6**) and furanose (**7**) acetyl hydrogens, respectively. On

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standing the syrup crystallized. Trituration with acetone and filtration gave the pure, crystalline product **6** (320 mg). A portion (100 mg) was recrystallized from methanol–acetone to give an analytical sample (85 mg): mp 166–167°; $[\alpha]^{25}D$ −71° (*c* 1, water), no appreciable change after 3 hr; infrared spectral data (KBr) 1620 cm^{-1} (amide I), no amide II band; nmr data (D_2O, external TMS) τ 7.82 (acetyl hydrogens, singlet) 4.05 (J = 2.5 cps), and 4.48 (J = 2.3 cps, C-1 hydrogen).

Anal. Calcd for $C_7H_{13}NO_5$: C, 43.97; H, 6.85; N, 7.32. Found: C, 44.01; H, 7.04; N, 7.24.

The tetraacetate **9** was prepared by usual acetylation of **6**, mp 121–122°. Mass spectral data corroborated its structure and homogeneity.

5-Acetamido-5-deoxy-D-lyxose benzylphenylhydrazone (8).—An amount (35 mg) of **6** in a mixture of isopropyl alcohol and water containing 60 mg of sodium acetate and 45 mg of benzylphenylhydrazine hydrochloride was left at room temperature for 4 days. The solution was evaporated to dryness, and the residue was dissolved in chloroform and washed with water. Evaporation of the chloroform solution afforded a crystalline residue which was recrystallized from acetone and ether to give 22 mg of pure **8**: mp 155–156°; $[\alpha]^{23}D$ 23.4° (*c* 0.17, methanol); infrared spectral data (KBr) 1656 (amide I), 1563 cm^{-1} (amide II).

Anal. Calcd for $C_{20}H_{25}N_3O_4$: N, 11.31. Found: N, 10.98.

Methyl 5-azido-5-deoxy-α-D-arabinofuranoside (12).—A mixture of methyl α- and β-D-arabinoside[17] (20.9 g) in 157 ml of dry pyridine was treated dropwise at 0° with a solution of *p*-toluenesulfonyl chloride (24.2 g) in 40 ml of pyridine. After stirring at room temperature overnight, the solvent was removed under reduced pressure and the syrupy residue was evaporated several times from toluene and finally from ether. The residue was dissolved in chloroform, washed successively with 1 *N* sulfuric acid and sodium bicarbonate solution and dried over sodium sulfate. Filtration and evaporation gave a colorless syrup (20.1 g) which consisted predominantly of methyl 5-*O*-*p*-tolylsulfonyl-α-D-arabinofuranoside, $[\alpha]^{24}D$ 72° (*c* 1.72, methanol).

The preceding compound (5 g) was dissolved in 125 ml of *N*,*N*′-dimethylformamide containing 6.5 g of sodium azide and the mixture was stirred at 85–90° for 8 hr. The solution was evaporated in the presence of 1-butanol under reduced pressure at 60–70° and the dark residue was extracted with a mixture of acetone–ether (2:1). The extract was decolorized with charcoal and evaporated to a pale yellow syrup (2.7 g, 90%), $[\alpha]^{24}D$ 132° (*c* 1.77, methanol). Examination of this product on thin layer plates (benzene–methanol, 10:0.5) confirmed its homogeneity except for some impurities at the origin. This material was suitable for the next step.

Methyl 5-azido-5-deoxy-2,3-di-*O*-methanesulfonyl-α-D-arabinofuranoside (13).—A solution of **12** (0.7 g) in 10 ml of dry pyridine was cooled to −20° and treated dropwise with 0.62 ml of methanesulfonyl chloride. The solution was stored at 0° overnight, then poured into ice–water to give crystalline **13**, (0.80 g, 62%). Recrystallization from a mixture of acetone, ether, and pentane gave colorless crystals (0.75 g), mp 69–70°, $[\alpha]^{25}D$ 140° (*c* 0.556, methanol).

Anal. Calcd for $C_8H_{15}N_3O_8S_2$: C, 27.83; H, 4.38; N, 12.17; S, 18.55. Found: C, 28.30; H, 4.42; N, 12.00; S, 18.12.

1′,2′-*O*-Isopropylidene-D-lyxofurano[3′.5′:6.5]-Δ²-dihydro-1,3-oxazine (15).—A suspension of **14** (0.1 g) and 0.2 g of sodium benzoate in 25 ml of *N*,*N*′-dimethylformamide was refluxed with stirring for 18 hr. The pale yellow suspension evaporated to dryness and the residue was filtered from a mixture of ether and acetone. The filtrate was evaporated to dryness, extracted with ether, and evaporated again. The crystalline residue was triturated with cold methanol and filtered to give pure **15**: yield 60 mg; mp 137–138°; $[\alpha]^{25}D$ 30° (*c* 1.06, $CHCl_3$); infrared spectral data (KBr) 1660 cm^{-1} (C=N), no sulfonate; nmr data ($CDCl_3$) τ 4.1 ($J_{1,2}$ = 3–4 cps), C-1 hydrogen, 8.65, 8.52 (CH_3), ring and C-5 hydrogens, formed a series of multiplets between 6.1 and 5.1.

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 64.98; H, 6.22; N, 4.56.

The same product was obtained when sodium acetate was used instead of sodium benzoate.

Compound **15** was recovered unchanged after standing for 36 hr in a solution of methanol containing a catalytic amount of sodium methoxide.

Attempted Displacement of 3 with Sodium Benzoate in *N*,*N*′-Dimethylformamide.—An amount of **3** (220 mg) was refluxed for 24 hr in 15 ml of *N*,*N*′-dimethylformamide containing 0.4 g of sodium benzoate. Processing of the reaction mixture produced a syrup which crystallized on standing overnight. The starting material **3** was subsequently recovered (0.2 g). Thin layer chromatography in the solvent system (benzene–2,2,4-trimethylpentane–methanol 100:30:1) of the crude reaction product showed the presence of some demesylated **3**.

The above reaction was repeated and the refluxing time was extended to a total of 73 hr. Thin layer chromatography showed, in addition to **3** and **2**, two faster moving spots (14 and 11.5 cm, from the origin, respectively) designated as A and B. Separation by preparative thin layer chromatography afforded A and B as homogeneous syrups (about 1 mg each). Infrared spectral data for compound A and B (microliquid film) showed 2100 (azide), 1727 cm^{-1} ester, no OH, unsaturation, or sulfonate. Compound A had the same mobility as 5-azido-3-*O*-benzoyl-5-deoxy-1,2-*O*-isopropylidene-D-arabinofuranose (obtained as homogeneous semicrystalline syrup by benzoylating **2**) and a very similar infrared spectrum.

Compound B, $[\alpha]^{25}D$ 18° (*c* 0.1, MeOH), when debenzoylated in methanol–sodium methoxide afforded a product which had a mobility on thin layer chromatograms (benzene–methanol 10:2), similar to that of **2**.

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