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The Reaction of Methyl 2,3-Anhydro-D-ribofuranosides with Thiocyanate Ion¹

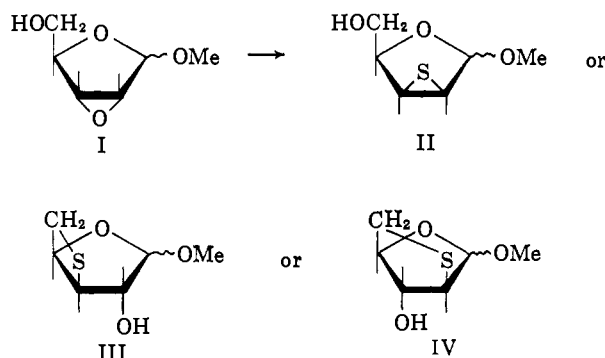
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The reactions of methyl 2,3-anhydro- α - or - β -D-ribofuranosides (Ia and Ib) with thiocyanate ion yield methyl 3,5-thioanhydro- α - or - β -D-xylofuranosides (IIIa and IIIb), both of which compounds were characterized by several crystalline derivatives. The n.m.r. spectra of the 3,5-thioanhydrides and of their crystalline derivatives were useful in elucidation of the structures of these epoxide thiocyanate ion products. Desulfurization of the phenylurethans of IIIa and IIIb afforded the phenylurethans (VIIa and VIIb) of methyl 3,5-dideoxy- α - and - β -D-erythro-pentofuranosides. Compound VIIb was also synthesized by two other routes that utilized methyl 2,3-anhydro-5-O-(*p*-tolylsulfonyl)- β -D-ribofuranoside (XVI) as a starting material. An attempt to prepare VIIa starting from methyl 2,3-anhydro-5-O-(*p*-tolylsulfonyl)- α -D-ribofuranoside (VIII) resulted instead in the synthesis of the phenylurethan (XIII) of methyl 2,5-dideoxy- α -D-erythro-pentofuranoside as a result of epoxide opening at C-2. Some observations on the opening of 2,3-anhydropentofuranosides with nucleophiles are presented.

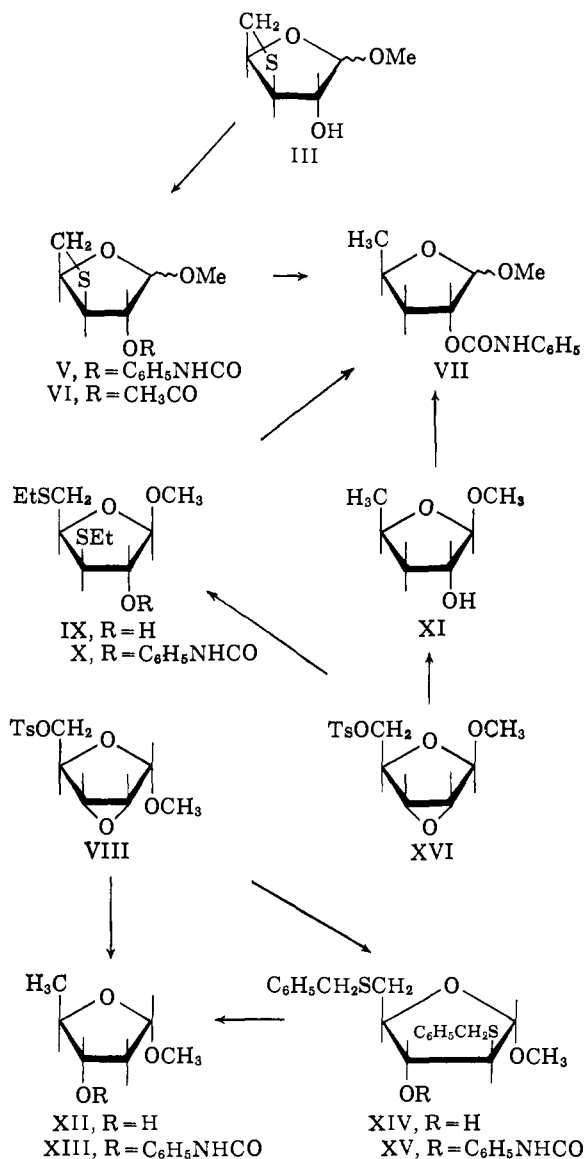
Previous papers² from this laboratory have pointed out the reasons for the interest in the synthesis of 2,3-thioanhydropentofuranosides, the sulfur analogs of the 2,3 anhydropentofuranosides that have proved so useful in nucleoside syntheses. One of the most convenient general methods for preparing episulfides is the reaction of an epoxide with thiocyanate ion³ but, as has been pointed out by van Tamelen,⁴ the method is unattractive for the transformation of cyclopentene oxide to cyclopentene sulfide; a similar unfavorable situation would be expected in the direct conversion of a 2,3-anhydropentofuranoside to a 2,3-thioanhydropentofuranoside. Since, however, cyclopentene oxide could be converted to cyclopentene sulfide, albeit in low yield, with thiocyanate ion,⁵ it appeared of interest to study the reaction of a 2,3-anhydropentofuranoside with thiocyanate ion.

Both anomers of methyl 2,3-anhydro-D-ribofuranoside (I) were available from previous work⁶ and were used in the present studies. Analysis of the generally



accepted mechanism⁴ for the epoxide-thiocyanate reaction suggests that any or all of the compounds II, III, and IV might be expected from the reaction of I with thiocyanate ion. When the reaction of Ib with ammonium thiocyanate (potassium thiocyanate gave

a series are (α anomers), b series are (β anomers))



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(2) (a) L. Goodman, A. Benitez, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 1680 (1958); (b) C. D. Anderson, L. Goodman, and B. R. Baker, *ibid.*, **81**, 898 (1959).

(3) A. Schönberg in Houben-Weyl, "Methoden der Organischen Chemie," Band IX, Georg Thieme Verlag, Stuttgart, 1955, p. 149.

(4) E. E. van Tamelen, *J. Am. Chem. Soc.*, **73**, 3444 (1951).

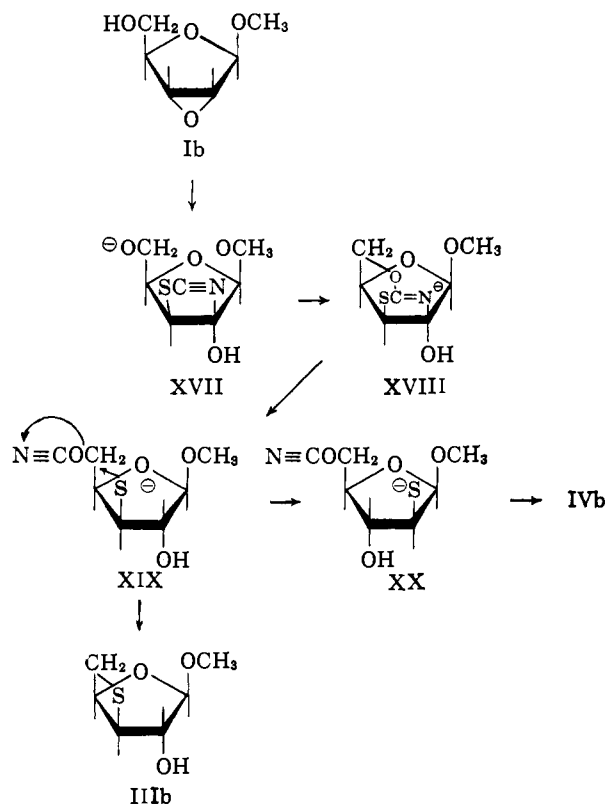
(5) L. Goodman and B. R. Baker, *ibid.*, **81**, 4924 (1959).

(6) C. D. Anderson, L. Goodman, and B. R. Baker, *ibid.*, **80**, 5247 (1958).

qualitatively similar results) was carried out in water, a sulfur-containing liquid was obtained which gave a crystalline *p*-nitrobenzoate and a crystalline phenylurethan. The n.m.r. spectra of the crystalline *p*-nitrobenzoate and of the hydroxyl-containing liquid that is the direct reaction product showed the C₁-proton as a singlet which suggested that the reaction product

was IIIb where the C₁- and C₂-protons had a *trans*-relationship⁷ and were not appreciably spin-coupled. However, this assignment could only be tentative since the bicyclic system present in IIIb might lead to conformations of the pentofuranoside ring in which the generally found⁷ coupling constants for *cis*- and *trans*-C₁-, C₂-protons in the ordinary pentofuranoside systems would not be applicable. Raney nickel desulfurization of the crystalline phenylurethan yielded a crystalline deoxysugar whose n.m.r. spectrum showed the doublet characteristic of a CH₃-C-H system and whose C₁-proton appeared as a clean singlet. Thus the n.m.r. spectrum of the desulfurized phenylurethan was only compatible with that of structure VIIb and the epoxide-thiocyanate ion reaction product therefore was IIIb.

It was desirable to provide a chemical proof of structure for IIIb and for this purpose Ib was converted to its crystalline tosylate XVI. Reaction of XVI with lithium aluminum hydride furnished, in low yield, a liquid whose n.m.r. spectrum showed the C₁-proton as a singlet and which contained only a trace contaminant according to gas chromatography. This liquid therefore was XI resulting from very predominant hydride attack at C-3 of the epoxide XVI. Conversion of XI to its phenylurethan afforded the same crystalline solid that was obtained by desulfurization of Vb. Alternatively, the reaction of XVI with sodium ethyl mercaptide gave a high yield of IX, the acetate of which showed one symmetrical peak on gas chromatography, and that was converted to the sirupy phenylurethan (X). Raney nickel desulfurization of X also furnished crystalline VII. Since Anderson^{2b} had previously shown that Ib was attacked exclusively at C-3 with sodium ethyl mercaptide, it seems safe to assume that



(7) See G. Casini and L. Goodman, *J. Am. Chem. Soc.*, **86**, 1427 (1964), for a discussion of this point and for previous references.

the reaction product of XVI with sodium ethyl mercaptide was essentially pure IX.

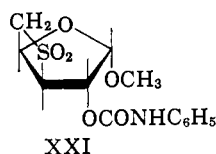
The conversion of Ib to IIIb may be rationalized in terms of the sequence Ib → XVII → XVIII → XIX → IIIb which is completely analogous to the accepted mechanism for the epoxide-episulfide transformation.⁴ The Ib-IIIb transformation represents a unique case of cyclic sulfide formation in which the participating alkoxide is one already present in the molecule rather than the one formed in the epoxide opening by thiocyanate ion. Interaction of the functional groups at C-2 and C-3 in XVII would lead to a highly strained system of two *trans*-fused five-membered rings. The rearrangement of XIX to XX *via* a C₂-alkoxide ion is not implausible and would lead to the more stable fused system of IV.

The reaction of the α -epoxide Ia with ammonium thiocyanate also gave a sulfur-containing liquid, but the yield of product was much lower. Reaction with potassium thiocyanate gave essentially the same results as ammonium thiocyanate. The reaction product could be converted to a crystalline acetate, *p*-nitrobenzoate, and phenylurethan. Again the n.m.r. spectra suggested that the isolated reaction product was IIIa since the C-1 proton appeared as a doublet with a coupling constant of 3.9 c.p.s. and as a doublet with *J* 4.5 c.p.s. in the crystalline acetate derived from the alcohol, as might be predicted for the *cis* coupling of the C₁- and C₂-protons in IIIa. Oxidation of the phenylurethan of the cyclic sulfide gave a crystalline sulfone which provided good evidence that the Ia-thiocyanate ion product was not IIa; episulfides are not smoothly oxidized to sulfones.³ Desulfurization of the crystalline phenylurethan of the reaction product gave a crystalline solid in whose n.m.r. spectrum, however, the C₁- and C₂-proton absorptions overlapped and it was not possible to assign a structure to the desulfurized phenylurethan simply on the basis of its n.m.r. spectrum.

In an attempt to provide a chemical structure proof for the desulfurized phenylurethan, the epoxide Ia was converted to its crystalline tosylate VIII. Reaction of VIII with sodium benzyl mercaptide gave a liquid that was converted to a crystalline phenylurethan. At the time this work was begun, the opening of 2,3-anhydro-pentofuranosides by nucleophiles was assumed always to occur predominantly at C-3; while the work was in progress, the first exception to that rule was noted.⁸ Thus the product from the reaction of VIII and sodium benzyl mercaptide was originally assumed to be methyl 3,5-di-S-benzyl-3,5-dithio- α -D-xylofuranoside and the crystalline phenylurethan to be the derivative of that sugar. However, the n.m.r. spectrum showed the C₁-proton of the phenylurethan as a singlet which strongly suggested that it was the arabinose derivative XV and therefore that the predominant product from VIII and sodium benzyl mercaptide was XIV. Desulfurization of the dibenzylthiophenylurethan XV gave an analytically pure and chromatographically homogeneous, unstable oil whose n.m.r. spectrum was in accord with that of structure XIII; the C₁-proton of this desulfurization product appeared as a pair of doublets. Further, the desulfurization product from the dibenzylthiourethan could be distinguished from the desulfuriza-

(8) G. Casini and L. Goodman, *ibid.*, **85**, 235 (1963).

tion product of the phenylurethan of the Ia-thiocyanate ion reaction product by thin layer chromatography. All these data indicate that IIIa was the structure of the Ia-thiocyanate ion reaction product, that desulfurization of its phenylurethan gave the 3-deoxy sugar VIIa, and that the sulfone derived from the phenylurethan of the cyclic sulfide had structure XXI.



The epoxide VIII was reduced with lithium aluminum hydride and it gave a liquid whose n.m.r. spectrum indicated that it was largely the 2-deoxy sugar XII accompanied by a small amount of methyl 3,5-dideoxy- α -D-erythro-pentose (the α -anomer of XI) from opening of VIII at C-3. Thus the major C₁-proton absorption consisted of a pair of doublets with $J_{cis-1,2}$ 4.5 and $J_{trans-1,2}$ 1.5 c.p.s. accompanied by a minor doublet with J 4.0 c.p.s., the latter doublet characteristic of the *cis*-C-1, C-3 coupling in the α -anomer of XI. Gas chromatography indicated a mixture of 89% of XII and 11% of a second component, presumably the α -anomer of XI; this is another example of predominant opening of a 2,3-anhydropentofuranoside at C-2. Conversion of the lithium aluminum hydride reduction product of VIII to its phenylurethan gave an analytically pure oil whose thin layer chromatographic behavior was compatible with that of a mixture of XIII and VIIa. The lithium aluminum hydride reduction product was separated into its components by gas chromatography and the minor component, derivatized with phenyl isocyanate, furnished crystalline VIIa, thus establishing the nature of the hydride opening of VIII.

These studies provide additional examples of openings of 2,3-anhydropentofuranosides with nucleophiles and emphasize the difficulty of predicting at which epoxide carbon predominant nucleophilic attack will occur. The ring openings of VIII and XVI reported in this paper suggest that steric factors determine the point of attack. The higher yield of IIIb from Ib as compared with that of IIIa from Ia is in accord with this idea; presumably IIIa results from a minor reaction of thiocyanate ion at C-3 while the major attack at C-2 gives products which have not yet been characterized. There are several examples of nucleophilic attack on these furanose epoxides, however, which cannot be rationalized on the basis of steric effects,⁹ and in these cases electronic effects in the furanose ring and/or the nature of the attacking nucleophile seem to be the determining factors.

Experimental¹⁰

Methyl 3,5-Thioanhydro- β -D-xylofuranoside (IIIb), Its Acetate VIb and Its *p*-Nitrobenzoate.—A stirred mixture of 3.10 g. (21.2

mmoles) of the β -epoxide Ib,⁸ 8.1 g. (0.107 mole) of ammonium thiocyanate, and 50 ml. of water was heated at reflux for 24 hr., then evaporated *in vacuo* to leave a dark viscous residue. Water (25 ml.) was added to the residue and the aqueous solution was extracted with four 25-ml. portions of chloroform. The dried extracts were evaporated *in vacuo* leaving 1.8 g. of a light colored sirup whose infrared spectrum suggested that it contained an appreciable quantity of the epoxide Ib.

The sirup was dissolved in 2 ml. of pyridine and the solution chilled and treated with 2 ml. of acetic anhydride. The acetylation mixture was allowed to stand at room temperature for 14 hr., then was evaporated *in vacuo*. Water (25 ml.) was added to the residue and the aqueous mixture was extracted with two 25-ml. portions of dichloromethane. The combined extracts were washed with 15 ml. of cold 1 *N* hydrochloric acid, with 15 ml. of saturated aqueous sodium bicarbonate, and with 15 ml. of water, affording, after drying, 2.30 g. of residue. On vapor phase chromatography using a 5 ft., 3/8 in. 20% butanediol succinate on Chromosorb W column at 200° and 200 ml./min. of helium, the mixture was resolved into two peaks of which 90% appeared at a retention time of 14 min. while 10% was contained in a peak at 8 min. The major peak was the thioanhydride VIb and the minor peak was the acetate of Ib. The yield of VIb from Ib was 46%. Pure VIb was obtained by preparative gas chromatography using the same column and conditions. The collected fraction was evaporatively distilled at 80–90° (bath temperature) and 0.8–1.5 mm. to give the analytical sample of VIb, $[\alpha]_D^{24} -36^\circ$ (2.7%); $\lambda_{max}^{24}(\mu)$ 5.70 (acetate C=O), 8.09 (acetate C—O—C). The n.m.r. spectrum showed τ 4.57 (3m, C-1, C-2, and C-4), 6.20 (1d, C-3), 6.44 (1s, OCH₃), 6.62 (2m, C-5), 7.95(3s, CH₃CO).

Anal. Calcd. for C₈H₁₂O₄S: C, 47.0; H, 5.92; S, 15.7. Found: C, 47.2; H, 6.21; S, 15.9.

A solution of 0.40 g. of VIb, 10 ml. of methanol, and about 0.01 g. of sodium methoxide was stored at 0° for 18 hr., adjusted to pH 7 with glacial acetic acid, and evaporated *in vacuo*. The residue was dissolved in 3 ml. of water, the solution was extracted with four 10-ml. portions of chloroform, and the combined extracts were dried and evaporated *in vacuo* leaving 0.25 g. of a viscous sirup that crystallized on standing. The solid, m.p. 47–50°, had $[\alpha]_D^{25} -73^\circ$ (0.98%); $\lambda_{max}^{25}(\mu)$ 2.89, 2.92 (OH); 9.10 and 9.52 (C—O). The n.m.r. spectrum showed τ 4.65 (1m C-4), 4.85 (1s, C-1), 5.60 (1s, C-2), 6.30 (1d, C-3, J 6.8), 6.50 (3s, OCH₃), 6.78 (3m, C-5 and OH).

To a solution of 0.60 g. (3.7 mmoles) of IIIb in 8 ml. of dry pyridine was added 1.50 g. (8.1 mmoles) of *p*-nitrobenzoyl chloride and the mixture was warmed gently on the steam bath for 10 min. to effect solution. The solution was allowed to stand at room temperature for 3 hr., then was poured over 25 g. of ice. After the ice had melted, the mixture was extracted with 50 ml. of dichloromethane, the extract was washed with 100 ml. of cold 1 *N* hydrochloric acid, with 50 ml. of saturated aqueous sodium bicarbonate, and with 50 ml. of water, dried, and evaporated leaving a brown sirup that crystallized on standing. The crude solid was dissolved in a large volume of boiling Skellysolve B (b.p. 62–70°), decanting from an insoluble gum. The solution, after being chilled, deposited white crystals, 0.65 g. (57%), m.p. 79.5–82.5°. A second recrystallization from 100 ml. of Skellysolve B gave the analytical sample, m.p. 79–80°, $[\alpha]_D^{21} 0^\circ$ (1%); $\lambda_{max}^{21}(\mu)$ 5.78 (ester C=O), 6.52 and 7.40 (NO₂), 7.85 (ester C—O—C), 13.90 (strong, unassigned). The n.m.r. spectrum showed τ 1.79 (4m, aromatic), 4.53 (1s, C-2), 4.71 (1s, C-1), 4.6 (1m, C-4); 6.17 (1d, J 7.0, C-3), 6.43 (3s, OCH₃), 6.65 (2m, C-5). *Anal.* Calcd. for C₁₃H₁₃N₂O₆S: C, 50.2; H, 4.21; S, 10.3. Found: C, 50.3; H, 4.26; S, 10.2.

Methyl 2-O-(*N*-Phenylcarbamoyl)-3,5-thioanhydro- β -D-xylofuranoside (Vb).—A mixture of 0.31 g. (1.9 mmoles) of crystalline alcohol IIIb, 0.38 g. (3.2 mmoles) of phenyl isocyanate, 1 drop of triethylamine, and 10 ml. of carbon tetrachloride was allowed to stand at room temperature, protected from atmospheric moisture, for 48 hr., then was warmed at 70–85° for 5 hr. The mixture was evaporated *in vacuo* leaving a sirup that crystallized after being seeded. The solid was recrystallized from benzene–Skellysolve B, affording 0.50 g. (94%) of product, m.p. 89–94°. From a previous run the analytical sample was obtained, m.p. 92–94°, $[\alpha]_D^{23} -15^\circ$ (1.06%); $\lambda_{max}^{23}(\mu)$ 3.03, 6.40

the n.m.r. peaks, the peaks are reported as xs (singlet), xd (doublet), xt (triplet), xq (quartet), or xm (multiplet) where x refers to the number of protons represented in the peak.

(9) (a) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Am. Chem. Soc.* **77**, 7 (1955); (b) W. W. Lee, A. Benitez, L. Goodman, and B. R. Baker, *ibid.*, **82**, 2648 (1960).

(10) Boiling points and melting points are uncorrected; the latter were obtained with the Fisher–Johns apparatus. Magnesium sulfate was used as the drying agent unless otherwise noted. Optical rotations refer to the sodium D line and were determined in chloroform at the stated concentration unless otherwise noted. The n.m.r. spectra were mainly run in deuteriochloroform using either the Varian V-4311 spectrometer operated at 60 Mc. or the A-60 instrument; the chemical shifts are expressed as τ -values using tetramethylsilane as the reference standard. In describing

(NH), 5.80 (urethan C=O), 13.10 (phenyl). The n.m.r. spectrum showed τ 2.7 (5m, aromatic), 2.89 (m, NH), 4.7 (3m, C-1, C-2, C-4), 6.13 (1d, J 7.2, C-3), 6.45 (3s, OCH₃), 6.65 (2m, C-5).

Anal. Calcd. for C₁₃H₁₅NO₄S: C, 55.5; H, 5.37; S, 11.4. Found: C, 55.4; H, 5.41; S, 11.4.

Methyl 3,5-Dideoxy-2-O-(N-phenylcarbamoyl)- β -D-erythro-pentofuranoside (VIIb). A. From the Thietane Vb.—A stirred suspension of 0.50 g. (1.8 mmoles) of Vb, about 7 g. of Raney nickel,¹¹ and 35 ml. of absolute ethanol was heated at reflux for 5 hr., then was filtered through Celite using four 30-ml. portions of boiling absolute ethanol to wash the catalyst. The combined filtrate and washings were evaporated *in vacuo* affording 0.27 g. (60%) of an oil that crystallized after being seeded. Two recrystallizations from Skellysolve B gave material, m.p. 105.5–108.0° and a mixture melting point 105–107° with the product obtained from XVI (see below); $[\alpha]_D^{25} -49^\circ$ (0.98%); infrared spectrum identical with that of the solid derived from XVI.

B. *Via Reduction of the Epoxide XVI.*—To a chilled (0°), stirred solution of about 0.50 g. (13.2 mmoles) of lithium aluminum hydride in 25 ml. of dry ether was added a solution of 2.0 g. (6.7 mmoles) of the epoxide XVI dissolved in 50 ml. of dry ether. The resulting solution, under nitrogen, was heated with stirring at reflux for 24 hr. Wet ether was added cautiously to decompose the excess hydride and the ether was decanted from the inorganic solids, dried, and distilled through a 12-in. Widmer column. The residue was evaporatively distilled at 70–80° (bath temperature) and 30 mm. to give about 150 mg. of a colorless liquid (XI); $\lambda_{\text{max}}^{\text{film}}(\mu)$ 2.86, 2.92 (OH, NH), 6.00–6.15 (weak, probably due to water). On gas chromatography using a 10-ft. 20% butanediol succinate column at 180° with 200 ml./min. of helium there was a symmetrical peak with a retention time of 12.1 min. that constituted more than 99% of the material; a trace component with a retention time of 8.3 min. was also present. The n.m.r. spectrum showed τ 5.30 (1s, C-1), 5.67 (3m, C-2, C-4, and OH), 6.71 (3s, OCH₃), 8.18 (2m, C-3), 8.73 (3d, J 6.3, C-5).

The alcohol XI was treated with 0.20 g. of phenyl isocyanate using the procedure described for the preparation of Vb. The diphenylurea was separated from the product by extracting the latter with hot Skellysolve B. Recrystallization of the Skellysolve B-soluble residue from Skellysolve B gave crystals, m.p. 105.5–108°, $[\alpha]_D^{25} -48^\circ$ (1.08%); $\lambda_{\text{max}}^{\text{Nujol}}(\mu)$ 3.05 and 6.41 (NH), 5.73 (urethan C=O), 13.10 (phenyl). The n.m.r. spectrum showed τ 1.81 (6m, aromatic and NH), 4.80 (1q, $J_{2,3-cis}$ 5, $J_{2,3-trans}$ ~ 1, C-2), 5.08 (1s, C-1), 5.55 (1m, C-4), 6.64 (3s, OCH₃), 7.99 (2m, C-3), 8.66 (3d, J 6, C-5).

Anal. Calcd. for C₁₃H₁₇NO₄: C, 62.1; H, 6.82; N, 5.58. Found: C, 62.4; H, 6.98; N, 5.75.

C. *From the Phenylurethan X.*—Desulfurization of 0.80 g. of the phenylurethan X (see below) using the Raney nickel procedure described for the preparation of VIIb from Vb gave an incompletely desulfurized product, 0.38 g. Repetition of the Raney nickel treatment afforded 0.21 g. of a brown oil that still contained some sulfur. This was extracted with about 5 ml. of hot Skellysolve B and the extract on chilling deposited a small amount of crystalline solid, m.p. 102–105°, whose infrared spectrum was identical with that of the analytical sample of VIIb.

Methyl 2,3-Anhydro-5-O-(*p*-tolylsulfonyl)- β -D-ribofuranoside (XVI).—To a chilled (0°), stirred solution of 2.0 g. (13.7 mmoles) of the epoxide (Ib)⁶ in 10 ml. of dry pyridine was added dropwise, over a period of 15 min., a solution of 4.0 g. (20.9 mmoles) of *p*-toluenesulfonyl chloride in 15 ml. of dry pyridine. The solution was maintained at 0–10° for 20 hr., then was poured into 200 ml. of ice-water. The crystalline solid, 4.05 g. (98%), m.p. 58–67°, was recovered by filtration and was recrystallized from 300 ml. of Skellysolve C (b.p. 88–89°), affording 3.06 g. of solid, m.p. 66.5–67.0°. The analytical sample, obtained from Skellysolve C, had m.p. 67–68°, $[\alpha]_D^{25} -80^\circ$ (1%); $\lambda_{\text{max}}^{\text{Nujol}}(\mu)$ 7.36, 8.39, and 8.51 (–OSO₂–), 6.26 (phenyl); there was no absorption near 3.0.

Anal. Calcd. for C₁₃H₁₆O₆S: C, 52.0; H, 5.37; S, 10.7. Found: C, 51.9; H, 5.59; S, 10.7.

Methyl 2,5-Di-S-ethyl-2,5-dithio- β -D-xylofuranoside (IX) and Its Phenylurethan X.—A stirred mixture of 2.50 g. (8.3 mmoles) of the epoxide XVI, 4.2 g. (68 mmoles) of ethanethiol, 3.4 g. (63 mmoles) of sodium methoxide, and 90 ml. of dry methanol was heated at reflux, under nitrogen, for 23 hr., then cooled. The solution was adjusted to pH 7 with glacial acetic acid, evapo-

rated *in vacuo*, and the residue dissolved in 25 ml. or water. The aqueous solution was extracted with three 35-ml. portions of dichloromethane and the combined extracts were washed with 20 ml. of water and dried. Evaporation *in vacuo* afforded 1.90 g. (91%) of IX, $\lambda_{\text{max}}^{\text{film}}(\mu)$ 2.92 (OH); there was no sulfonate ester absorption at 8.5.

A small quantity of the liquid IX was acetylated conventionally with pyridine and acetic anhydride. The product was a liquid whose infrared spectrum showed the expected acetate absorptions and the lack of absorption near 3.0 μ . The liquid was evaporatively distilled at 90–100° (bath temperature) and 0.1 mm. The distillate on vapor phase chromatography on a 5-ft. 20% butanediol succinate column at 210° using 400 ml./min. of helium showed a single symmetrical peak with a retention time of 17.6 min. On a 5-ft. 3% silicone column at 187° and 60 ml./min. of helium, the main peak appeared at 3.4 min. and was accompanied by a trace peak at 0.8 min. The acetate had $[\alpha]_D^{24} -94^\circ$ (2.7%). The n.m.r. spectrum showed τ 4.82 (1d, J 2.2, C-2), 5.13 (1s, C-1), 5.50 (1q, C-4), 6.61 (3s, OCH₃), ~6.5 (1m, C-3), 7.3 (6m, C-5 and CH₂), 7.90 (3s, CH₃CO), 8.73 (6t, CH₃).

Anal. Calcd. for C₁₂H₂₂O₄S₂: C, 49.0; H, 7.53; S, 21.8. Found: C, 49.3; H, 7.67; S, 21.9.

The alcohol IX, 0.50 g., as obtained from the reaction, was treated with 0.33 g. of phenyl isocyanate as described for the preparation of Vb. The product was obtained free of diphenylurea by extraction into boiling Skellysolve B. Evaporation of the Skellysolve B left a yellow sirup, $[\alpha]_D^{25} -47^\circ$ (1.25%); $\lambda_{\text{max}}^{\text{film}}(\mu)$ 3.02 and 6.49 (NH), 5.73 (urethan C=O), 13.21 (phenyl). The n.m.r. spectrum showed τ 2.7 (6m, aromatic and NH), 5.74 (1d, J 2.1, C-2), 5.04 (1s, C-1), 5.54 (1m, C-4), 6.25 (1m, C-3), 6.60 (3s, OCH₃), 7.3 (6m, C-5 and CH₂), 8.73 (6t, CH₃).

Anal. Calcd. for C₁₇H₂₃NO₄S₂: C, 55.0; H, 6.78; N, 3.77; S, 17.3. Found: C, 54.7; H, 6.39; N, 4.07; S, 16.5.

Methyl 3,5-Thioanhydro- α -D-xylofuranoside (IIIa), Its Acetate VIa, and Its *p*-Nitrobenzoate.—Using exactly the quantities of reagents and conditions with the α -epoxide Ia⁶ that were described for the reaction of Ib and ammonium thiocyanate, there was obtained 0.85 g. (25%) of crude IIIa whose infrared spectrum indicated it to be essentially free of the starting epoxide Ia.

Conventional acetylation of crude IIIa with pyridine and acetic anhydride afforded, after recrystallization of the crude product from *n*-hexane, 0.65 g. (61%) of crystalline acetate VIa, m.p. 53–65°. Two recrystallizations from *n*-hexane afforded the analytical sample, m.p. 64.5–65.5°, $[\alpha]_D^{24} +256^\circ$ (1.01%); $\lambda_{\text{max}}^{\text{Nujol}}(\mu)$ 5.78 (ester C=O), 8.00 (ester C–O–C), 9.50, 9.69 (C–O). The n.m.r. spectrum showed τ 4.39 (1d, J 4.5, C-1), 4.59 (1t, C-2), 4.79 (1q, C-4), 6.11 (1q, $J_{2,3}$ 3.5, $J_{3,4}$ 6.8, C-3), 6.49 (3s, OCH₃), ~6.4 and 6.88 (two one-proton multiplets, $J_{6,5}$ 11, C-5), 7.86 (3s, CH₃CO).

Anal. Calcd. for C₈H₁₂O₄S: C, 47.0; H, 5.92; S, 15.7. Found: C, 46.8; H, 5.94; S, 15.9.

Deacylation of 0.301 g. of VIa with methanolic sodium methoxide using the procedure described for the preparation of IIIb afforded 0.23 g. of IIIa as a light yellow oil, $[\alpha]_D^{24} +222^\circ$ (3.45%); $\lambda_{\text{max}}^{\text{film}}(\mu)$ 2.88 (OH), 9.10, and 9.7 (C–O). The n.m.r. spectrum showed τ 4.63 (1d, J 3.9, C-1), 4.91 (1, triplet of doublets, $J_{3,4}$ 6.5, C-4), 5.60 (1q, $J_{1,2}$ 3.9, $J_{2,3}$ 2.9, C-2), 6.31 (1q, $J_{2,3}$ 2.9, $J_{3,4}$ 6.5, C-3), 6.49 (3s, OCH₃), 6.78 (1s, OH), 6.57 and 7.01 (two one-proton quartets, $J_{5,5'}$ 10.5, C-5).

Anal. Calcd. for C₈H₁₀O₃S: C, 44.4; H, 6.21; S, 19.8. Found: C, 44.0; H, 6.71; S, 19.8.

Crude IIIa was treated with *p*-nitrobenzoyl chloride in pyridine using the procedure described for preparation of the *p*-nitrobenzoate of IIIb to afford, after several recrystallizations from Skellysolve B, crystals, m.p. 78.5–79.5°, $[\alpha]_D^{27} +207^\circ$ (1%); $\lambda_{\text{max}}^{\text{Nujol}}(\mu)$ 5.60 (ester C=O), 6.60 and 7.38 (NO₂), 7.75 (ester C–O–C), 13.80 (strong, unassigned).

Anal. Calcd. for C₁₃H₁₃NO₆S: C, 50.2; H, 4.21; S, 10.3. Found: C, 50.0; H, 4.23; S, 10.3.

Methyl 2-O-(N-Phenylcarbamoyl)-3,5-thioanhydro- α -D-xylofuranoside (Va).—The reaction of crude IIIa with phenyl isocyanate was carried as in the preparation of Vb. The crystalline solid was recrystallized several times from 50% aqueous methanol to give the analytical sample, m.p. 125.0–127.5°, $[\alpha]_D^{24} +178^\circ$ (1.1%); $\lambda_{\text{max}}^{\text{Nujol}}(\mu)$ 3.04 and 6.48 (NH), 5.83 (urethan C=O), 8.02 (urethan C–O–C), 13.48 and 14.43 (phenyl). The n.m.r. spectrum showed τ 2.75, 2.97, and 3.16 (three multiplets totaling 6 protons, representing aromatic and NH); 4.59, 4.78, and 4.97 (three multiplets totaling 3 protons representing C-1,

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

C-2, and C-4, $J_{1,2}$ 3.8); 6.28 (1q, C-3); 6.62 (3s, OCH₃); 6.8 (2m, C-5).

Anal. Calcd. for C₁₃H₁₅NO₄S: C, 55.5; H, 5.37; S, 11.4. Found: C, 55.2; H, 5.29; S, 11.8.

Methyl 3,5-Dideoxy-2-O-(N-phenylcarbamoyl)- α -D-erythro-pentofuranoside (VIIa).—The phenylurethan Va, 0.70 g., was desulfurized as described for the preparation of VIIb, yielding 0.43 g. (69%) of sirup that crystallized on standing. Recrystallization, once from Skellysolve C and a second time from water, gave the analytical sample, m.p. 109.5–110.5°, $[\alpha]^{24} +101^\circ$ (1.39%); $\lambda_{\text{max}}^{\text{Nujol}}$ (μ) 3.03 and 6.51 (NH), 5.91 (urethan C=O), 8.06 (urethan C—O—C), 13.59 and 14.41 (phenyl). The n.m.r. spectrum showed τ 2.74 and 3.00 (two multiplets representing 6 protons, aromatic and NH), 5.0 (2m, C-1 and C-2), 5.75 (1q, C-4), 6.69 (3s, OCH₃), 8.02 (2m, C-3), 8.71 (3d, J 6, C-5).

Anal. Calcd. for C₁₃H₁₇NO₄: C, 62.1; H, 6.82; N, 5.58. Found: C, 62.0; H, 6.82; N, 5.70.

Methyl 2,3-Anhydro-5-O-(*p*-tolylsulfonyl)- α -D-ribofuranoside (VIII).—To a chilled (0°), stirred solution of 3.60 g. (24.6 mmoles) of the epoxide Ia⁹ in 20 ml. of pyridine was added dropwise, while the internal temperature was maintained below 10°, a solution of 5.1 g. (26.7 mmoles) of *p*-toluenesulfonyl chloride in 14 ml. of dichloromethane. The mixture was stirred at 0° for 3 hr., allowed to stand at 0–5° for 48 hr., then poured into 100 ml. of ice-water. The dichloromethane layer was separated and the aqueous phase was extracted with two 50-ml. portions of dichloromethane. The combined dichloromethane solutions were washed with four 30-ml. portions of water, dried, and evaporated *in vacuo*, yielding 6.67 g. of partially crystalline solid. Recrystallization from isopropyl alcohol afforded 3.5 g. (47%) of crystalline solid, m.p. 92.5–95°. Two more recrystallizations from isopropyl alcohol furnished the analytical sample, m.p. 93.5–95.0°, $[\alpha]^{24} +7.0^\circ$ (1.2%); $\lambda_{\text{max}}^{\text{Nujol}}$ (μ) 6.25 and 12.25 (phenyl), 7.37 and 8.48 (—OSO₂—), 11.58 (epoxide).

Anal. Calcd. for C₁₃H₁₅O₆S: C, 52.0; H, 5.37; S, 10.7. Found: C, 51.8; H, 5.33; S, 11.0.

Methyl 2,5-Di-S-benzyl-2,5-dithio- α -D-arabinofuranoside (XIV) and Its Phenylurethan XV.—A stirred mixture of 3.00 g. (10.0 mmoles) of the epoxide VIII, 2.72 g. (21.9 mmoles) of benzyl mercaptan, 2.38 g. (44.0 mmoles) of sodium methoxide, and 60 ml. of methanol was heated at reflux under nitrogen for 19 hr., then adjusted to pH 7 with glacial acetic acid, and evaporated *in vacuo*. The residue was dissolved in 60 ml. of water, the aqueous solution was extracted with two 100-ml. portions of dichloromethane, and the combined extracts were washed with three 60-ml. portions of water, then dried. Evaporation *in vacuo* gave 3.60 g. (96%) of liquid, $\lambda_{\text{max}}^{\text{Nujol}}$ (μ) 2.93 (OH), 13.0 and 14.25 (phenyl); there was no sulfonate ester absorption near 8.5.

Treatment of 3.00 g. of the above alcohol with 1.10 g. of phenyl isocyanate in 5 ml. of dry carbon tetrachloride that contained a small amount of triethylamine gave, after filtration of some diphenylurea and evaporation, an oil that largely crystallized on standing. Recrystallization of the material was difficult, but about 1.5 g. of crystalline solid, m.p. 55–60°, was obtained by recrystallization from a large volume of Skellysolve B. An analytical sample of XV was obtained after several recrystallizations from Skellysolve B; m.p. 58–61°, $[\alpha]^{24} +112^\circ$ (1.11%); $\lambda_{\text{max}}^{\text{Nujol}}$ (μ) 2.98, 3.03, 6.50 (NH), 5.77 (urethan C=O), 8.21 (urethan C—O—C), 13.20 and 14.25 (phenyl). The n.m.r. spectrum showed τ 2.77 (5m, aromatic), 3.42 (1s, broad, NH), 5.00 (1q, J 3.9 and 2.6, C-3), 5.28 (1s, C-1), 5.89 (1m, C-4), 6.15 (2s, benzyl CH₂ on C-2), 6.25 (2s, benzyl CH₂ on C-5), 6.73 (3s, OCH₃), 6.95 (1m, C-2), 7.29 (2d, J 5.9, C-5).

Anal. Calcd. for C₂₇H₂₉NO₄S₂: C, 65.4; H, 5.90; N, 2.82; S, 12.9. Found: C, 65.7; H, 5.96; N, 2.75; S, 13.1.

Methyl 2,5-Dideoxy-3-O-(N-phenylcarbamoyl)- α -D-erythro-pentofuranoside (XIII).—Desulfurization of 0.40 g. of XV with about 16 g. of Raney nickel in absolute ethanol as described for the preparation of VIIb afforded 0.12 g. (59%) of a transparent sirup that turned to a black tar when it was maintained at room temperature for several weeks. In the infrared the sirup had $\lambda_{\text{max}}^{\text{Nujol}}$ (μ) 3.02 and 6.49 (NH), 5.78 and 5.81 (urethan C=O), 8.16 (urethan C—O—C), 13.25 and 14.40 (phenyl). The n.m.r. spectrum showed τ 2.73 and 2.95 (two multiplets representing 5 aromatic protons), 3.29 (1s, broad, NH), 5.28 (1q, J_{cis} 4.5, J_{trans} 1.0, C-1), \sim 5.3 (1m, C-3), 5.92 (1m, C-4), 6.69 (3s, OCH₃)

\sim 7.7 and 7.9 (two 1 proton multiplets, C-2), 8.68 (3d, J 6.5, C-5).

Anal. Calcd. for C₁₃H₁₇NO₄: C, 62.1; H, 6.82; N, 5.58. Found: C, 62.5; H, 7.08; N, 5.48.

On thin layer chromatography on alumina using benzene as the developer and iodine or potassium permanganate for detection, XIII and VIIa moved as single spots with $R_{\text{XIII}}/R_{\text{VIIa}} = 1.4$, easily distinguished from one another.

Reduction of the 5-O-Tosyl Epoxide VIII with Lithium Aluminum Hydride.—To a stirred suspension of 0.75 g. (19.8 mmoles) of lithium aluminum hydride in 70 ml. of dry ether was added, dropwise, a solution of 3.00 g. (10.0 mmoles) of the epoxide VIII in 20 ml. of dry tetrahydrofuran. The mixture was stirred at reflux, under nitrogen, for 24 hr., then was treated cautiously with wet tetrahydrofuran, then with enough water to coagulate the inorganic salts. The mixture was filtered and the filter cake was washed well with ether. The filtrate was dried and distilled through a 12-in. Widmer column until about 4 ml. of liquid remained in the distilling flask. Vapor phase chromatography on this residue using a 10 ft. $\frac{3}{8}$ in. 20% butanediol succinate on Chromosorb W column at 180° with 200 ml./min. of helium showed two peaks, the major one (89%) with a retention time of 7.8 min. and the minor peak (11%) with a retention time of 5.4 min. The residue was evaporatively distilled at 65–85° (bath temperature) and 45–48 mm. affording 0.90 g. (68%) of a colorless liquid, $\lambda_{\text{max}}^{\text{Nujol}}$ (μ) 2.90 (OH), 6.0 (broad, probably represents water). The n.m.r. spectrum showed τ 4.99 (0.89 q, J_{cis} 4.5, J_{trans} 1.5, C-1 of XIII), 5.17 (0.12 d, J 4.0, C-1 of alcohol derived from VIIa), 5.9 (1m, C-4), 6.2 (1m, C-3 of XIII), 6.67 (3s, OCH₃), 7.87 and 8.0 (C-2 of XIII and C-3 of alcohol derived from VIIa), 8.60 (3d, J 6.5, C-5).

The product from the lithium aluminum hydride reduction, 0.15 g., was treated with phenyl isocyanate in the manner described for the preparation of Vb. The product was an oil, 0.21 g., whose infrared spectrum was in good agreement with that of XIII as was its n.m.r. spectrum. The latter did not permit a definite assignment of the presence of any of VIIa. However, thin layer chromatography on alumina using benzene for elution and sulfuric acid for detection showed the mixture as a major spot and a minor spot with R_f major/ R_f minor = 1.3, agreeing reasonably well with the data for pure XIII and VIIa. The mixture had $[\alpha]^{26} +112^\circ$ (1.32%).

Anal. Calcd. for C₁₃H₁₇NO₄: C, 62.1; H, 6.82; N, 5.58. Found: C, 62.1; H, 6.90; N, 5.87.

Preparative gas chromatography of the lithium aluminum hydride reduction product of VIII gave a small amount of the minor component which was converted to its phenylurethan conventionally. The product, recrystallized from Skellysolve B, had m.p. 104–107°; there was no melting point depression when mixed with authentic VIIa. Its infrared spectrum compared well with that of VIIa, but contained two extraneous bands indicating an impurity that probably is responsible for the low melting point. Lack of material prevented further purification.

Methyl 2-O-(N-Phenylcarbamoyl)-3,5-thioanhydro- α -D-xylofuranoside S,S-Dioxide (XXI).—A mixture of 0.102 g. of the phenylurethan Va, 1.0 ml. of 30% hydrogen peroxide, and 2.0 ml. of glacial acetic acid was heated on the steam bath for 15 min., then diluted with 8 ml. of water. Within a few minutes a white precipitate formed. The precipitate, 0.82 g. (72%), m.p. 175–177°, was recrystallized from 35 ml. of carbon tetrachloride, affording 0.077 g. of the analytical sample, m.p. 176–178°, $[\alpha]^{27} +145^\circ$ (1%); $\lambda_{\text{max}}^{\text{Nujol}}$ (μ) 3.02 and 6.44 (NH), 5.82 (urethan C=O), 7.53 and 8.79 (SO₂), 8.07 (urethan C—O—C), 14.40 (phenyl).

Anal. Calcd. for C₁₃H₁₅NO₆S: C, 49.8; H, 4.83; N, 4.47; S, 10.2. Found: C, 49.8; H, 4.82; N, 4.42; S, 10.1.

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