separated from the solution which became warm as the addition was made. After stirring the suspension for 30 min. longer, the sodium chloride was filtered off (99% yield), and the filtrate was concentrated to 10 ml. by distilling the solvent through a Vigreux column at atmospheric pressure. The residue was dissolved in 60 ml. of ether, washed with 7 ml. of 20% sodium hydroxide and 7 ml. of water, and dried over sodium sulfate. The solvent was removed by distillation through a Vigreux column, the last of the solvent being removed carefully under slight vacuum. The residual solid was recrystallized by dissolving in a minimum amount of petroleum ether and chilling the solution in Dry Ice: yield 2.90 g. (96%), m.p. 55–56°, $\lambda_{\max}^{\mathrm{MeOH}}$ 257, 216 mμ (ϵ 5366, 9817), $\lambda_{\min}$ 236.5 mμ.

Anal. Calcd. for $C_7H_7F_3N_2O_2$: C, 40.39; H, 3.39; F, 27.39; N, 13.45. Found: C, 40.89; H, 3.06; F, 25.31; N, 13.29.

This compound sublimes readily even at room temperature, and must be kept in well-sealed containers.

2′,3′,5′-Tri-*O*-benzyl-1-β-D-arabinofuranosyl-4-methoxy-5-trifluoromethyl-2-(1*H*)pyrimidinone (X).—Methylene chloride (80 ml.), which had been dried over magnesium sulfate, was filtered directly into a dry flask containing 5.60 g. (0.0128 mole) of 2′,3′,5′-tri-*O*-benzylarabinofuranosyl chloride (I). A solution of 2,4-dimethoxy-5-trifluoromethylpyrimidine (IX, 2.66 g., 0.0128 mole) in 20 ml. of methylene chloride was dried over sodium sulfate and filtered directly into the reaction vessel. The solution was stirred gently for 3 days at room temperature, protected by a drying tube. After removal of solvent, the crude product, 7.5 g. (quant.), was used without purification in the following step.

1-β-D-Arabinofuranosyl-4-methoxy-5-trifluoromethyl-2(1*H*)-pyrimidinone (XI).—Two grams of the crude condensation product was dissolved in 90 ml. of dry methanol (Molecular Sieves) and added to 2 g. of palladium chloride which had been suspended and pre-reduced in 60 ml. of anhydrous methanol. The theoretical hydrogen absorption was observed after 3 min. shaking at room temperature. After removal of the catalyst by filtration the acidic solution was neutralized batchwise with Dowex 2-X8 (HCO_3^-) and filtered. When the solvent was removed *in vacuo*, spontaneous crystallization occurred. The product was triturated with water, filtered, and washed several times in order to remove contaminant arabinofuranose. Recrystallization was accomplished by dissolving in the minimum amount of methanol, adding an equal volume of ether and excess hexane, to yield 0.720 g. (66%) of pure product: m.p. 184–186°; $[\alpha]_D$ +133.4° (*c* 0.5, MeOH); ultraviolet spectra: pH 2, $\lambda_{\max}$ 270, 205 mμ (ϵ 5933, 18,006), $\lambda_{\min}$ 238 mμ; pH 12, $\lambda_{\max}$ 278, 217 mμ (ϵ 6390, 12,812), inflection at 225 mμ (ϵ 12,290), $\lambda_{\min}$ 255 mμ.

Anal. Calcd. for $C_{11}H_{13}F_3N_2O_6$: C, 40.50; H, 4.02; F, 17.47; N, 8.58. Found: C, 40.68; H, 3.80; F, 17.3; N, 8.52.

5-Trifluoromethyl-1-β-D-arabinofuranosyluracil (XII).—To 5 ml. of 1.1 *N* methanolic hydrogen chloride 160 mg. of 1-β-D-arabinofuranosyl-4-methoxy-5-trifluoromethyl-2(1*H*)-pyrimidinone (XI) was added. The solution, in a tightly stoppered flask, was kept at room temperature for 3 days. After concentration *in vacuo* the residue was dissolved in a minimum amount of methanol, diluted with ether, and crystallized by addition of hexane. After one recrystallization 125 mg. (82%) of the pure product was obtained: m.p. 225–227°; $[\alpha]_D$ +76° (*c* 0.5, water); ultraviolet spectra: pH 2, $\lambda_{\max}$ 262.5, 205 mμ (ϵ 10,296, 8923), $\lambda_{\min}$ 228 mμ; pH 12, immediately after dissolving, $\lambda_{\max}$ 262.5 mμ (ϵ 7020), $\lambda_{\min}$ 241 mμ; after 1 hr., $\lambda_{\max}$ 267.5 mμ (ϵ 7238), $\lambda_{\min}$ 247.5 mμ; after 24 hr., $\lambda_{\max}$ 272 mμ (ϵ 8170), $\lambda_{\min}$ 249.5 mμ.

Anal. Calcd. for $C_{10}H_{11}F_3N_2O_6$: C, 38.47; H, 3.55; F, 18.25; N, 8.89. Found: C, 38.11; H, 3.81; F, 19.4; N, 8.80.

Acknowledgment.—The authors wish to thank Dr. Arthur A. Patchett for his encouragement and Dr. Hewitt Fletcher for information on the synthesis of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride in advance of publication.

The Structure of Osazones[1]

H. El Khadem, M. L. Wolfrom,[2] and D. Horton

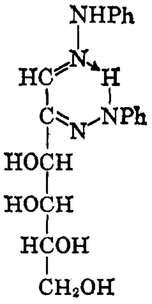
Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received August 17, 1964

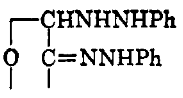
The n.m.r. spectra of D-*lyxo*-hexose phenylosazone (I) and its tetraacetate (IV) show two imino protons, indicating that both compounds have acyclic sugar chains. A range of mono-*N*-benzoylated poly-*O*-benzoylated osazones (IXa–f) described herein showed only one, low-field imino proton resonance, as did D-*arabino*-hexosulose 1-(methylphenylhydrazone) 2-(phenylhydrazone) tetraacetate (VI), indicating that the *N*-benzoyl group in (IXa–f) is attached to the hydrazone residue at C-1. For the same reason, structure X was assigned to *N*-acetyl-di-*O*-acetyl-3,6-anhydro-D-*ribo*-hexose phenylosazone.

Various cyclic structures have been suggested[3] for osazones to explain their mutarotation, the different reactivity of their two hydrazone residues,[4] and the difference in their behavior toward nitrous acid as compared with their acyclic acetates.[5] In the present work n.m.r. spectroscopy was used to determine whether osazones exist mainly in the acyclic form (I) which possesses two imino protons or in one of the two cyclic forms (II or III) which possess three.

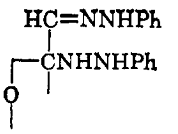
The n.m.r. spectrum of the acyclic D-*lyxo*-hexose phenylosazone tetraacetate (IV) in $CDCl_3$ was first determined by Wolfrom, Fraenkel, Lineback, and Komitsky[6] and provided direct evidence for the chelated structure originally proposed, without experimental evidence, by Fieser and Fieser.[7] The spectrum showed two peaks at τ −2.48 and 1.58 which were attributed[6] to the two imino protons and the aldimine proton of C-1, respectively. Since both peaks disappear on deuteration (Figure 1), we have now assigned them both to the



I



II



III

---

[1] Reported in part in Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964, p. 27D.

[2] To whom inquiries should be addressed.

[3] E. G. V. Percival, *Advan. Carbohydrate Chem.*, **3**, 23 (1948).

[4] F. Weygand, H. Grisebach, and K. D. Kirchner, *Ber.*, **88**, 487 (1955).

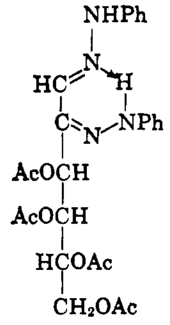
[5] M. L. Wolfrom, H. El Khadem, and H. Alfes, *J. Org. Chem.*, **29**, 2072 (1964).

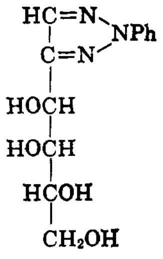
[6] M. L. Wolfrom, G. F. Fraenkel, D. R. Lineback, and F. Komitsky, Jr., *ibid.*, **29**, 457 (1964).

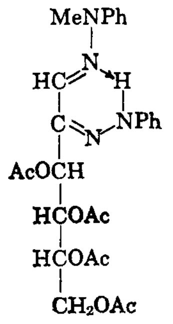
[7] L. F. Fieser and M. Fieser, "Organic Chemistry," D. C. Heath and Co., Boston, 1944, p. 351.

two imino protons of the hydrazone residues of C-2 and C-1, respectively.[8] Similarly the n.m.r. spectrum of the free D-*lyxo*-hexose phenylosazone in dimethyl sulfoxide (Figure 2) showed two imino protons as two one-proton peaks at τ -2.40 and -0.55 which disappeared on deuteration. The hydroxyl groups appeared as two peaks, a one-proton peak at τ 4.50 which was due to the hydroxyl group of C-3 and a three-proton peak at τ 5.50 which was due to the three hydroxyls of C-4, 5, and 6; both peaks disappeared on deuteration. These assignments were confirmed by a study of the n.m.r. spectrum of D-*lyxo*-hexose phenylosotriazole (V) in dimethyl sulfoxide. This compound has the same sugar residue as the osazone but lacks its imino groups. Its n.m.r. spectrum showed two hydroxyl groups at τ 4.70 and τ 5.30, in nearly the same positions as those of the osazone hydroxyls, but lacked the two peaks at τ -2.40 and -0.55.

The presence of only two imino protons in the n.m.r. spectrum of D-*lyxo*-hexose phenylosazone suggests that in dimethyl sulfoxide this compound exists mainly in the chelated acyclic structure I. If the cyclic structures II and III are present, they constitute a small and undetected proportion of the equilibrium mixture.


IV


V


VI

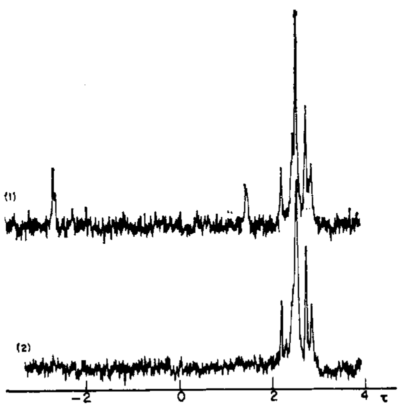


Figure 1.—N.m.r. spectrum of D-*lyxo*-hexose phenylosazone tetraacetate (IV) in CDCl$_3$: (1) before deuteration; (2) after deuteration.

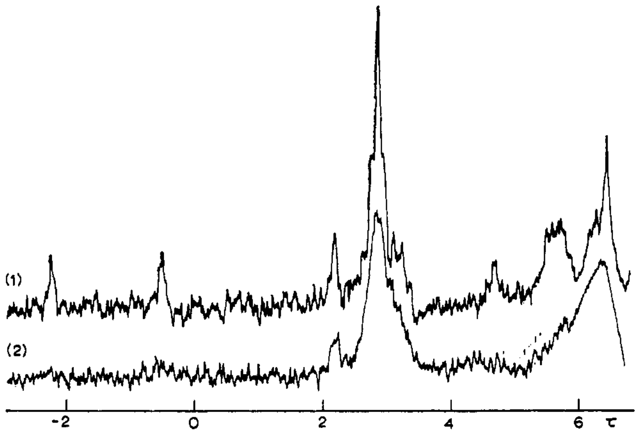


Figure 2.—N.m.r. spectrum of D-*lyxo*-hexose phenylosazone (I) in dimethyl sulfoxide: (1) before deuteration; (2) after deuteration.

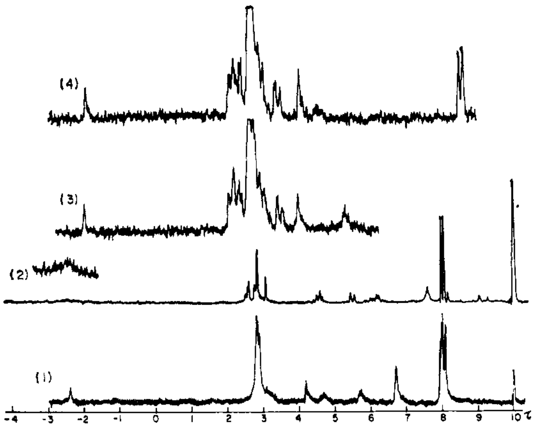


Figure 3.– N.m.r. spectra in CDCl$_3$: (1) D-*arabino*-hexosulose 1-(methylphenylhydrazone) 2-(phenylhydrazone) tetraacetate (VI); (2) *N*-acetyl-di-*O*-acetyl-3,6-anhydro-D-*ribo*-hexose phenylosazone (X); (3) *N*-benzoyl-tri-*O*-benzoyl-D-*erythro*-pentose phenylosazone (IXa); (4) *N*-benzoyl-tri-*O*-benzoyl-6-deoxy-L-*arabino*-hexose phenylosazone (IXc).

To determine which of the two imino proton bands in the n.m.r. spectrum of osazone I and acetate IV was due to the imino group of the hydrazone residue at C-1, the n.m.r. spectrum of the mixed osazone D-*arabino*-hexosulose 1-(methylphenylhydrazone) 2-(phenylhydrazone) tetraacetate (VI) was determined (Figure 3).[9a] This compound has been shown by Henseke and Hantschel[9b] to possess the methylphenylhydrazone residue on C-1, since reduction of the hexosulose 1-(methylphenylhydrazone), from which it is prepared, gives D-mannose methylphenylhydrazone. This mixed osazone VI consequently has only one imino proton, on the hydrazone residue of C-2. The spectrum showed a peak at τ -2.45 analogous to the low τ-value peak of IV. It was therefore concluded that the band in the spectrum of IV with the higher τ-value was due to the imino proton of the C-1 hydrazone residue, and the lower τ-value peak was due to that of the C-2 hydrazone residue. This is in agreement with the formulation of the osazone in the chelated form VII with the proton of the C-2 hydrazone chelated and hence of lower τ-value, rather than the tautomeric form VIII in which the proton of the C-1 hydrazone would be chelated. It should be noted that, whereas this chelated proton has nearly the same τ-value in the osazone I and its acetate IV, the imino proton of the C-1 hydrazone residue has a lower value in the free osazone than in the acetate, probably on account of hydrogen bond-

---

[8] After this work was completed, we noted that similar assignment of the two lowest field resonances in IV was made in an n.m.r. study at 100 Mc.p.s., by L. Mester, Abstracts, International Symposium on Carbohydrate Chemistry, Münster, Germany, 1964, p. 37; later detailed by L. Mester, E. Moczar, and J. Parello, *Tetrahedron Letters*, 3223 (1964); compare O. L. Chapman, R. W. King, W. J. Welstead, Jr., and T. J. Murphy, *J. Am. Chem. Soc.*, **86**, 4968 (1964).

[9] (a) This spectrum was also reported, after this work was submitted, by Mester and co-workers.[8] (b) G. Henseke and H. Hantschel, *Ber.*, **87**, 477 (1954).

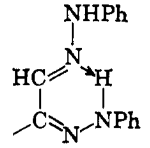
TABLE I

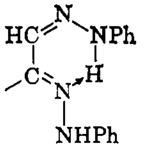
OSAZONE BENZOATES

Compd.	M.p., °C.	$[\alpha]^{25}\text{D}$,[a] deg.	Formula	Carbon, % Calcd.	Carbon, % Found[b]	Hydrogen, % Calcd.	Hydrogen, % Found[b]	Nitrogen, % Calcd.	Nitrogen, % Found[b]	Infrared maxima,[c] μ OBz	Infrared maxima,[c] μ NBz	Infrared maxima,[c] μ C=N
IXa	167	−24	$C_{45}H_{36}N_4O_7$	72.56	72.23	4.87	5.02	7.52	7.58	5.78	5.95	6.20
IXb	...	−0.5	$C_{45}H_{36}N_4O_7$	72.56	72.06	4.87	5.17	7.52	7.34	5.79	5.94	6.23
IXc	130	−62	$C_{46}H_{38}N_4O_7$	72.80	72.59	5.05	5.12	7.38	7.41	5.80	5.98	6.20
IXd	...	+26	$C_{53}H_{42}N_4O_9$	72.42	72.26	4.82	5.12	6.37	6.24	5.79	5.96	6.23
IXe	...	+84	$C_{53}H_{42}N_4O_9$	72.42	72.13	4.82	4.96	6.37	6.15	5.80	5.96	6.23
IXf	...	−190	$C_{53}H_{42}N_4O_9$	72.42	72.18	4.82	5.02	6.37	6.27	5.80	5.98	6.23

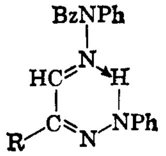
[a] *c* 1, $CHCl_3$, 2-dm. tube. [b] Made by W. N. Rond. [c] Infrared spectra were measured in potassium bromide pellets with a Perkin-Elmer Infracord infrared spectrophotometer. Tetra-*O*-benzoyl-D-*arabino*-hexose phenylosazone[11] showed the OBz band at 5.87 and the C=N at 6.23 μ.

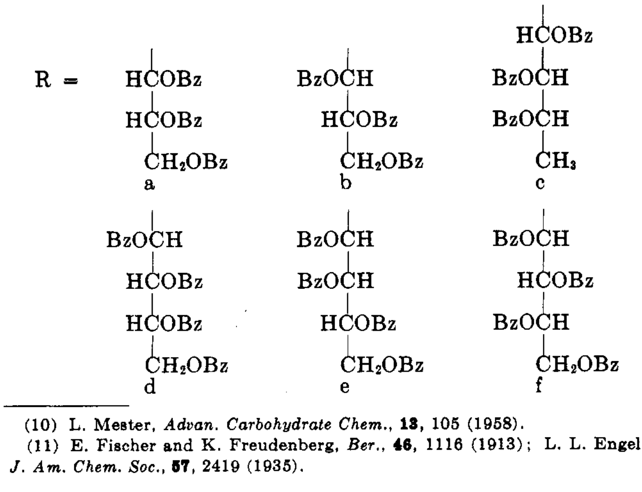
ing in the former, although the effect of the difference in solvent cannot be excluded.


VII

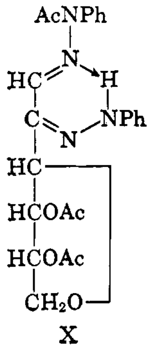

VIII

The formulation of osazones in the chelated structure VII is in agreement with Mester's[10] observation that the C-1 hydrazone is more reactive than that of C-2. It is also supported by our present work wherein different osazones were benzoylated (Table I) with benzoyl chloride in pyridine, yielding pentabenzoates having one *N*-benzoyl group. Fischer and Freudenberg[11] had obtained an amorphous tetrabenzoate of D-*arabino*-hexose phenylosazone by benzoylating the osazone with benzoyl chloride–quinoline diluted with chloroform. Our compounds showed in their infrared spectra both *O*-benzoyl and *N*-benzoyl carbonyl absorptions at λ 5.79 and 5.96 μ, respectively; the tetrabenzoate of Fischer and Freudenberg did not show the *N*-benzoyl absorption at 5.95 μ. The n.m.r. spectra of benzoates IXa and IXc (Figure 3) showed only the low-field imino proton resonance (C-2 hydrazone residue) at τ −2.05 and −1.97, respectively, denoting that one benzoyl group was attached on the C-1 hydrazone residue leaving the hydrazone residue of C-2 unbenzoylated. In no case was it possible to isolate a benzoate having two *N*-benzoyl groups, presumably because of the chelation of the imino proton of the C-2 hydrazone.


IX



It was also possible by means of n.m.r. spectroscopy to establish the position of the *N*-acetyl group in the *N*-acetyl-di-*O*-acetyl-3,6-anhydro-D-*ribo*-hexose phenylosazone obtained by boiling D-*arabino*-hexose phenylosazone with acetic anhydride.[12] This compound also showed (Figure 3) a single imino proton at τ −2.50, indicating the structure X, with the *N*-acetyl group attached to the hydrazone residue of C-1.


X

The spectroscopic and chemical evidence herein presented thus indicate that, in the light of present knowledge, the structure of the osazones is best represented by VII. The tautomeric form VIII and the cyclized forms II and III are evidently not significant components of the osazone in solution.

Experimental

Osazone Benzoates.—The osazones (5 g.) were dissolved in pyridine (50 ml.) and treated with benzoyl chloride (20 ml.). The temperature quickly rose and an abundant precipitate of pyridine hydrochloride separated. After standing overnight at room temperature the reaction mixture was poured onto crushed ice (1 kg.) and stirred for 6 hr. with frequent decantation and addition of water. The D-arabinose (IXa) and L-rhamnose (IXc) derivatives crystallized on addition of methanol and were recrystallized from methanol-benzene mixtures. The other benzoates (IXb from D-xylose, IXd from D-glucose, IXe from D-galactose, IXf from L-sorbose) were purified by repeated precipitation from hot methanol. In all cases the yields were above 90%; for analyses and infrared spectral data see Table I. All the benzoates were yellow solids.

X-Ray Powder Diffraction Data.[13]—Benzoate IXa had 11.95 s (1), 10.53 m, 6.92 vw, 5.99 m, 5.44 m, 5.10 w, 4.82 w, 4.55 m,

---

[10] L. Mester, *Advan. Carbohydrate Chem.*, **13**, 105 (1958).

[11] E. Fischer and K. Freudenberg, *Ber.*, **46**, 1116 (1913); L. L. Engel, *J. Am. Chem. Soc.*, **57**, 2419 (1935).

[12] H. El Khadem, Z. M. El-Shafai, and M. M. Mohammed-Ali, *J. Org. Chem.*, **29**, 1565 (1964).

[13] Interplanar spacings, Å., Cu Kα radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very. First few lines are numbered (1 strongest).

4.29 s (3), 4.17 vw, 3.80 s (2), 3.59 vw; benzoate IXc, 11.38 vs (1), 9.83 m, 8.04 w, 7.03 s, 6.56 w, 6.33 w, 5.75 w, 5.34 m, 4.50 s (2), 4.27 m, 3.95 s (3), 3.56 m, 3.29 w, 3.09 w.

Nuclear Magnetic Resonance Spectra.—Spectra were determined on a Varian A-60 n.m.r. spectrometer (Varian Associates, Palo Alto, Calif.). Tetramethylsilane (τ 10.00) was used as internal standard. Deuteration was performed by shaking the prepared sample with 1 drop of deuterium oxide for 30 min.

Acknowledgment.—The authors thank Mr. W. N. Turner for the n.m.r. data. H. El Khadem is indebted to the Educational and Cultural Exchange Program of the Department of State for a Fulbright Grant.

Synthesis of Amino Compounds in the Sugar Series by Reduction of Hydrazine Derivatives. Two Epimeric Pairs of 1,2-Diamino-1,2-dideoxyalditols[1-3]

M. L. Wolfrom and J. L. Minor

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received July 6, 1964

Hydrogenation of the hexosulose bis(phenylhydrazones) derived from D-glucose and D-xylose has afforded the two respective epimeric pairs of 1,2-diamino-1,2-dideoxyalditols. The products were isolated as their crystalline bis(salicylaldehyde Schiff base) derivatives. Structural identification of the former pair was effected by comparison with authentic samples, that of the latter by identification with the hydrogenation product of 2-amino-2-deoxy-D-lyxose phenylhydrazone, and that of 2-amino-2-deoxy-D-lyxose oxime hydrochloride. The dihydrohalide salts of three of the bases were characterized.

In earlier work reported from this laboratory,[4] 1,2-diamino-1,2-dideoxy-D-mannitol (**3**) was isolated from the reduction products of D-*arabino*-hexosulose bis(phenylhydrazone), "D-glucosazone" (**1**), as its crystalline bis(salicylaldehyde Schiff base) derivative. The yield, however, was quite low and it was postulated that the chelation of the osazone function[5-8] may have been responsible. Work by Mester[9] has indicated that 2 *N* ethanolic potassium hydroxide is required before "D-glucosazone" will undergo the formazan reaction. The diazo coupling fails in pyridine. Mester concluded that the strongly basic medium opened the chelate ring (**1**) and permitted the osazone to exhibit the anticipated chemical behavior.

Applying Mester's conditions to the hydrogenation of D-*arabino*-hexosulose bis(phenylhydrazone) and using Raney nickel as catalyst, we have found that the yield of 1,2-diamino-1,2-dideoxy-D-mannitol as its bis(salicylaldehyde Schiff base) is considerably improved, and in addition, an essentially equivalent amount of the epimeric 1,2-diamino-1,2-dideoxy-D-glucitol (**2**) is obtained as its bis(salicylidene) derivative, previously prepared only by reduction of the oxime of 2-amino-2-deoxy-D-glucose. The epimeric Schiff bases were identified by comparison with authentic samples.[4,10] Separation of the isomers could be effected by fractional recrystallization from 95% ethanol. The isomeric composition was determined by comparison of the optical rotation and optical rotatory dispersion curves of the crude product mixture with those of the pure epimers. The precision of the measurements was decreased in the former experiment by the color of the dissolved reaction mixture and in the latter by the ultraviolet absorption of the Schiff bases which necessitated the use of very dilute solutions with the accompanying decrease in the differences of observed optical rotation (Figure 1). However, both methods indicated approximately equimolar amounts of the two isomers.

The Schiff bases were hydrolyzed with dilute mineral acids to the corresponding amine salts.

D-*threo*-Pentosulose bis(phenylhydrazone), from D-xylose, was similarly hydrogenated and again two isomeric diaminoalditols were isolated as their bis(salicylidene) derivatives. Separation was effected by fractional recrystallization. Structural identification was achieved by a procedure analogous to that used previously.[4] 2-Amino-2-deoxy-D-lyxose hydrochloride was treated with phenylhydrazine and heated to initial formation of the osazone. After removal of the osazone, the reaction mixture, containing the phenylhydrazone (**4**) of the amino sugar, was hydrogenated. The product (**5**), isolated as its bis(salicylaldehyde Schiff base), was shown to be identical with the higher melting isomeric Schiff base from the osazone reduction. Hydrogenation of 2-amino-2-deoxy-D-lyxose oxime (**6**) hydrochloride gave the same results. Therefore, the higher melting product was 1,2-dideoxy-1,2-bis(salicylideneamino)-D-lyxitol and the low-melting isomer must be the epimeric 1,2-dideoxy-1,2-bis(salicylideneamino)-D-xylitol. The isomeric composition was determined by the optical rotatory dispersion procedure and again the crude reaction mixture was found to contain essentially equivalent amounts of the two epimers (Figure 2).

---

[1] Supported by Grant No. CY-3232(C6) from the Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Bethesda 14, Md. (Ohio State University Research Foundation Project 759).

[2] Preliminary communication: Abstracts, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, p. 14C.

[3] Previous publication on this subject: M. L. Wolfrom, J. Bernsmann, and D. Horton, *J. Org. Chem.*, **27**, 4505 (1962).

[4] M. L. Wolfrom, F. Shafizadeh, J. O. Wehrmüller, and R. K. Armstrong, *ibid.*, **23**, 571 (1958).

[5] L. F. Fieser and M. Fieser, "Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1944, p. 351; L. Mester, *Advan. Carbohydrate Chem.*, **13**, 105 (1958).

[6] G. Henseke and H. J. Binte, *Chimia*, **12**, 103 (1958).

[7] O. L. Chapman, R. W. King, and W. J. Welstead, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963, p. 36Q.

[8] M. L. Wolfrom, G. Fraenkel, D. R. Lineback, and F. Komitsky, Jr., *J. Org. Chem.*, **29**, 457 (1964).

[9] L. Mester, *J. Am. Chem. Soc.*, **77**, 4301 (1955).

[10] These compounds have recently been obtained by the alternate route of reduction of D-*arabino*-hexosulose 1-(*N*-methylphenylhydrazone) 2-oxime for the 1,2-diamino-1,2-dideoxy-D-mannitol derivative and by a modification of our procedure[4] for the epimeric 1,2-diamino-1,2-dideoxy-D-glucitol derivative: G. Henseke and R. Neinass, *Ber.*, **97**, 733 (1964).