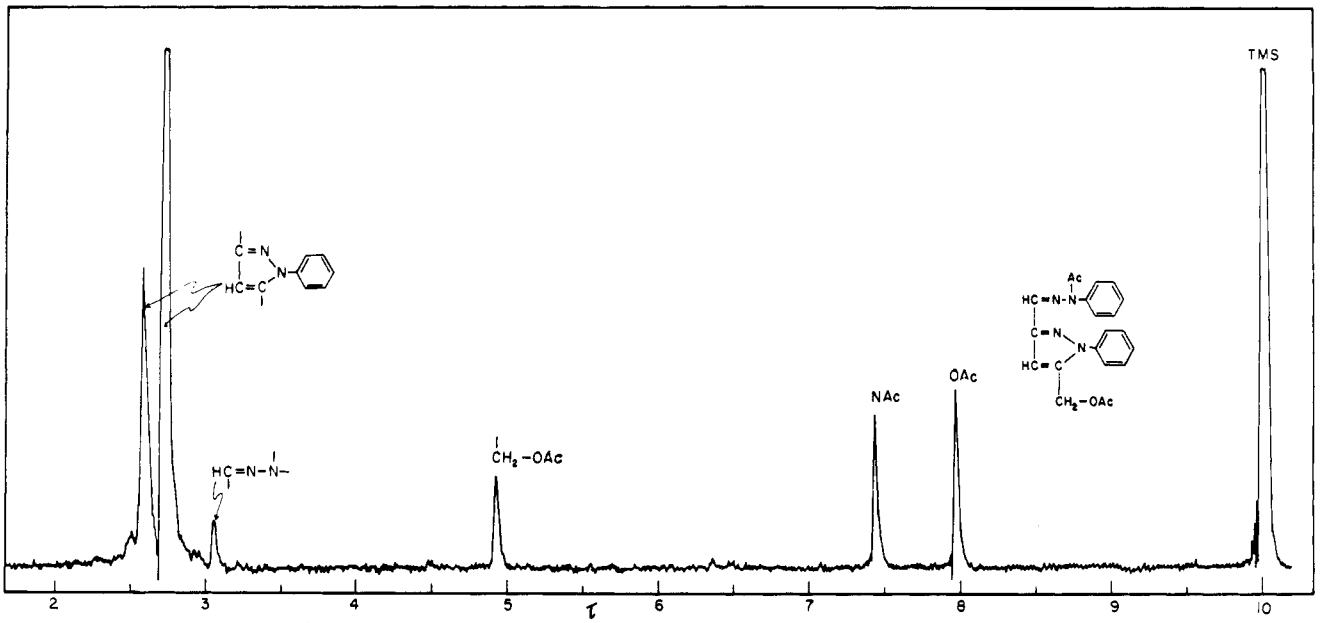

Fig. 3.—N.m.r. spectrum of 5-acetoxymethyl-3-formyl-1-phenylpyrazole *N*-acetylphenylhydrazone (III).

Anal. Calcd. for $C_{36}H_{40}N_4O_{13}$: C, 58.69; H, 5.47; N, 7.60; total Ac, 35.06; O-Ac, 29.21. Found: C, 59.19; H, 5.93; N, 8.17; total Ac, 34.18; OAc, 28.34.

Dianhydrophenylosazone Hexaacetate (III) from Gentiobiose Phenylosazone.—The osazone[8] (2.3 g.) was refluxed with acetic anhydride (50 ml.) for a period for 1 hr., then poured onto crushed ice (0.5 kg.). The aqueous solution was decanted and the oily residue crystallized on trituration with ethanol. 2-(3-Formyl-1-phenylpyrazol-5-yl)-2*S*-2-acetoxyethyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside acetylphenylhydrazone recrystallized from 50% aqueous ethanol in colorless needles: yield 2.2 g. (68%); m.p. 178°; $[\alpha]^{20}D$ +31.6° (*c* 0.475, chloroform); λ_{max}^{EtOH} 282 mμ (log ε 4.46); ν_{max}^{KBr} 1790 (O-Ac), 1685 (N-Ac), 1595 cm.$^{-1}$ (C=N); X-ray powder diffraction pattern[7]: 11.79 m, 10.78 s, 10.04 m, 7.76 s, 5.86 w, 5.40 w, 5.18 w, 4.82 vs, 4.17 m, 4.02 s, 3.86 m, 3.66 w, 3.48 m, and 3.23 m.

Anal. Calcd. for $C_{36}H_{40}N_4O_{13}$: C, 58.69; H, 5.47; N, 7.60; total Ac, 35.06; O-Ac, 29.21. Found: C, 58.63; H, 5.26; N, 8.01; total Ac, 34.38; O-Ac, 29.64.

Acknowledgment.—The author is indebted to the Educational and Cultural Exchange Program for a Fulbright Grant to visit the Ohio State University; to Professor M. L. Wolfrom, Dr. D. Horton, and Mr. F. Komitsky for their counsel; to The Ohio State University for the laboratory facilities provided; to Dr. A. Sato who kindly made available the isomaltose and gentiobiose used; to Dr. R. D. Nelson of Chemical Abstracts who helped in the nomenclature of the compounds.

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Amidino and Carbamoyl Osazones of Sugars

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1,2-Bis(amidinohydrazone) salts[2,3] are known[4] to be active against some forms of leukemia but have the disadvantage of producing toxic effects. It was considered that saccharide bis(amidinohydrazone) salts might be less toxic. These compounds can be considered as amidinoosazones but attempts to synthesize them according to the method used by Fischer[5] to prepare sugar osazones proved unsuccessful. We have therefore prepared them from aldosuloses ("osones") and 1-aminoguanidine sulfate. Thus, D-*arabino*-hexosulose bis(amidinohydrazone) monosulfate (Ia) was obtained from D-*arabino*-hexosulose ("D-glucosone"), L-*xylo*-hexosulose bis(amidinohydrazone) monosulfate (Ic) from L-*xylo*-hexosulose (from L-sorbose), and D-*threo*-pentosulose bis(amidinohydrazone) monosulfate (Id) from D-*threo*-pentosulose (from D-xylose). These compounds exist as slightly yellow crystals, soluble in hot water, from which they crystallize on cooling.

Although sugar disemicarbazones can be considered as carbamylosazones, they cannot be prepared by treating aldoses with semicarbazide as the reaction does not proceed beyond the semicarbazone stage; we have therefore prepared these from aldosuloses ("osones") and semicarbazide also. Thus, D-*arabino*-hexosulose disemicarbazone (IIa) was obtained from D-*arabino*-hexosulose ("D-glucosone"), D-*lyxo*-hexosulose disemicarbazone (IIb) from D-*lyxo*-hexosulose ("D-galactosone"), L-*xylo*-hexosulose disemicarbazone (IIc) from L-*xylo*-hexosulose ("L-gulosone"), and D-*threo*-pentosulose disemicarbazone (IId) from D-*threo*-pentosulose ("D-xylosone"). Unlike arylosazones these compounds were colorless and their ultraviolet spectra were characterized by a single maximum at 292 mμ instead of consecutive maxima stretching from 256 to 399 mμ in the case of the phenylosazones.[6] Furthermore, they possessed greater solubility in water than in organic solvents, excluding pyridine.

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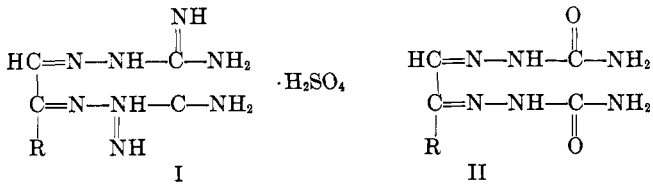
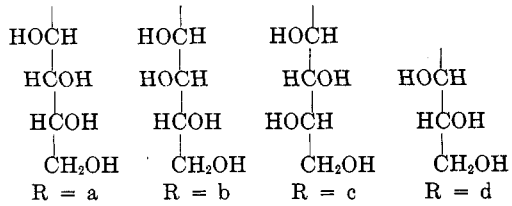
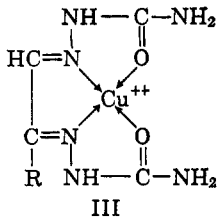


I

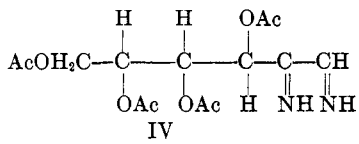
II



R = a R = b R = c R = d



III



IV

Like the sugar semicarbazones studied earlier,[7] the disemicarbazones formed green complexes with copper salts; these, however, were deeper in color and possessed greater stability, probably owing to the contribution of the second semicarbazone residue in the formation of tetradentate ligands as in III.

Nitrous acid is known to react with semicarbazones[8] and osazones,[9] liberating the free sugar or aldosulose ("osone"). Nitrous acid readily reacted with D-*arabino*-hexosulose disemicarbazone to yield D-*arabino*-hexosulose ("D-glucosone"), which was characterized by conversion to the quinoxaline derivative.

Acetylation of saccharide semicarbazones has been shown[8,10] to result in the formation of several isomeric acetates; the same difficulty was encountered with disemicarbazones where eight isomers could be detected on thin layer chromatograms. However, it was possible to isolate a chromatographically homogeneous compound from acetylated D-*arabino*-hexosulose disemicarbazone after treatment with nitrogen trioxide. This compound now possessed two nitrogen atoms and four acetyl groups and its infrared spectrum showed the *O*-acetyl band at 1755 and the C=N band at 1590 cm.$^{-1}$. Furthermore, it reacted with phenylhydrazine yielding 3,4,5,6-tetra-*O*-acetyl-D-*arabino*-hexosulose bis(phenylhydrazone)[11] and the latter was converted to Percival's anhydroosazone.[12] It was therefore tentatively ascribed the structure IV of tetra-*O*-acetyl-D-*arabino*-hexosulose diimine.

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Experimental[13]

D-*arabino*-Hexosulose Bis(amidinohydrazone) Monosulfate (Ia).—To a suspension of aminoguanidine bicarbonate in water sulfuric acid (diluted 1:1) was added slowly until the pH was between 4 and 5. This solution was diluted with water so that 1 ml. of the diluted solution contained 360 mg. of 1-aminoguanidine sulfate.

Dry D-*arabino*-hexosulose[14] powder (5 g.) was added to a solution of 9 g. of 1-aminoguanidine sulfate (25 ml. of the above prepared solution, 30% excess) and 7.5 ml. of glacial acetic acid. The mixture was heated at 100° for 10 min. and cooled to room temperature. Crystallization began after 20 min. On standing for 2 days at room temperature and 1 day in the refrigerator, the product was filtered and washed with water, methanol, and ether; yield 3.5 g. The substance was recrystallized twice from boiling water to yield light yellow needles: m.p. 220° dec.; $[\alpha]^{24}D$ +9° (*c* 0.5, water, no mutarotation observed in 48 hr.); λ_{max}^{EtOH} 289 mμ (log ε 4.56); λ_{max}^{KBr} 3.0 (OH, NH), 5.9, 6.0 (HN:CNH$_2$), 6.3 (C=N), 8.8–9.4 μ (SO_4^{-2}); X-ray powder diffraction data[15]: 10.50 w, 7.80 m, 6.81 w, 6.15 m, 5.75 s, 5.30 s (2), 4.97 s, 4.25 m, 4.05 w, 3.87 w, 3.75 w, 3.54 s (3), and 3.39 vs (1).

Anal. Calcd. for $C_8H_{20}N_8O_8S$: C, 24.74; H, 5.19; N, 28.86; S, 8.26. Found: C, 24.61; H, 5.63; N, 28.89; S, 8.21.

L-*xylo*-Hexosulose Bis(amidinohydrazone) Monosulfate (Ic).—Attempts were made to prepare the title compound according to the procedure mentioned above. A few crystals formed after 4 months. These were filtered and recrystallized from hot water to be used as nuclei. The procedure was repeated. Dry L-*xylo*-hexosulose powder (5 g.) was added to a solution of 1-amidinoguanidine sulfate (9 g.) and 7.5 ml. of glacial acetic acid. After standing 1 day at room temperature the solution was seeded with the above nuclei. After 24 hr., crystallization began. The solution was allowed to stand at room temperature for 5 days, then in the refrigerator for 1 day. The crystals were filtered and washed with water, methanol, and ether; yield 2 g. Two recrystallizations from boiling water gave slightly yellow crystals: m.p. 214° dec.; $[\alpha]^{23}D$ −46° (*c* 0.41, water); λ_{max}^{EtOH} 289 mμ (log ε 4.42); λ_{max}^{KBr} 3.0 (OH, NH), 5.9, 6.0 (HN:CNH$_2$), 6.3 (C=N), 8.8–9.4 μ (SO_4^{-2}); X-ray powder diffraction data[15]: 7.73 m, 6.68 w, 5.96 vw, 5.70 m, 5.44 w, 5.17 s, 4.84 s, 4.58 w, 4.27 s, 4.01 s (3), 3.72 m, 3.62 w, 3.48 vs (1), 3.37 vs (2), and 3.20 m.

Anal. Calcd. for $C_8H_{20}N_8O_8S$: C, 24.74; H, 5.19; N, 28.86; S, 8.26. Found: C, 24.84; H, 5.17; N, 28.60; S, 8.26.

D-*threo*-Pentosulose Bis(amidinohydrazone) Monosulfate (Id).—D-*threo*-Pentosulose (5 g.) was treated as above with 10.7 g. of 1-aminoguanidine sulfate; yield, 3 g. of Id. Pure material was obtained as light yellow needles on two recrystallizations from boiling water: m.p. 211–212° dec.; $[\alpha]^{21}D$ −17° (*c* 0.34, water, no mutarotation observed in 4 days); λ_{max}^{EtOH} 289 mμ (log ε 4.57); λ_{max}^{KBr} 3.0 (OH, NH), 5.9, 6.0 (HN:CNH$_2$), 6.3 (C=N), 8.8–9.4 μ (SO_4^{-2}); X-ray powder diffraction data[15]: 10.28 m, 7.53 m, 7.03 m, 5.42 m, 4.93 w, 4.63 m, 4.43 vs (1), 3.88 m, 3.75 m, 3.56 s (3), 3.46 s (2), 3.28 w, 3.18 w, 3.05 w, and 2.99 s.

Anal. Calcd. for $C_7H_{18}N_8O_7S$: C, 23.46; H, 5.06; N, 31.28; S, 8.95. Found: C, 23.19; H, 5.28; N, 31.46; S, 8.87.

D-*arabino*-Hexosulose Disemicarbazone.[16]—The sirupy D-*arabino*-hexosulose[14] prepared from 10 g. of phenylosazone was taken up in 10 ml. of water, and semicarbazide hydrochloride (3 g.) and sodium acetate (3 g.) in the least amount of water were added. The mixture was allowed to stand at 0° for 5 days and the crystalline product formed was filtered, washed with water and ethanol, and recrystallized from 50% ethanol: yield 1.2 g.; m.p. 215° dec.; $[\alpha]^{24}D$ +55° (*c* 0.34, water); λ_{max}^{EtOH} 292 mμ (log ε 4.31); λ_{max}^{KBr} 3.0 (OH), 5.9, 6.0 (CONH), 6.3 μ (C=N);

(13) Infrared spectra were obtained on a Perkin-Elmer Infracord spectrometer and ultraviolet spectra on a Bausch and Lomb model 505 spectrophotometer. Microanalytical determinations were made by W. N. Rond.

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(15) Interplanar spacing, Å., Cu Kα radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak v, very; three strongest lines numbered (1, strongest).

(16) Experimental work by E. G. Wallace.

X-ray powder diffraction data[15]: 7.80 m, 6.89 m, 5.97 w, 5.57 w, 5.21 m, 4.92 vs (1), 4.18 m, 3.86 m, 3.46 s (2), 3.30 s, 3.06 s (3), 2.78 w, and 2.69 w.

Anal. Calcd. for $C_8H_{16}N_6O_6$: C, 32.87; H, 5.52; N, 28.75. Found: C, 32.84; H, 5.65; N, 28.79.

Absorption Spectrum of the Copper Complex.—A solution of D-*arabino*-hexosulose disemicarbazone (292 mg.) in water (10 ml.) was treated with a solution of cupric chloride (133 mg.) in ethanol (10 ml.) and the volume was brought to 25 ml. with ethanol. The absorbance of the green solution [λ_{max}^{EtOH} 740 mμ, (log ε 1.69)] remained constant for 24 hr.

D-*lyxo*-Hexosulose Disemicarbazone.—D-*lyxo*-Hexosulose sirup (1.0 g.) was treated as above and the product was isolated in the same manner: yield, 0.25 g. of disemicarbazone which was recrystallized from water; m.p. 235° dec.; $[\alpha]^{21}D$ −2° (*c* 1.9, water); λ_{max}^{EtOH} 292 mμ; λ_{max}^{KBr} 3.1 (OH), 5.9, 6.0 ($CONH_2$), 6.3 μ (C=N); X-ray powder diffraction data[15]: 4.78 m, 4.25 s (3), 3.99 s (2), 3.65 m, 3.24 vs (1), 3.15 w, 2.85 w, 2.48 w, and 2.33 w.

Anal. Calcd. for $C_8H_{16}N_6O_6$: C, 32.87; H, 5.52. Found: C, 32.35; H, 5.47.

L-*xylo*-Hexosulose Disemicarbazone.—L-*xylo*-Hexosulose sirup (10 g.) was treated as above: yield, 0.75 g. of disemicarbazone which was recrystallized from water; m.p. 225° dec.; $[\alpha]^{20}D$ −16° (*c*, 0.45, water); λ_{max}^{EtOH} 292 mμ (log ε 4.69); λ_{max}^{KBr} 3.0 (OH), 5.95, 6.05 ($CONH_2$), 6.33 μ (C=N); X-ray powder diffraction data[15]: 7.38 m (3), 5.91 w, 5.32 w, 4.86 m, 4.23 w, 3.67 s (2), 3.45 vs (1), 3.14 m, 3.02 vw, 2.50 w, and 2.29 w.

Anal. Calcd. for $C_8H_{16}N_6O_6$: C, 32.87; H, 5.52; N, 28.75. Found: C, 32.86; H, 5.98; N, 28.66.

D-*threo*-Pentosulose Disemicarbazone.—D-*threo*-Pentosulose sirup (1.0 g.) yielded 0.15 g. of disemicarbazone which was recrystallized from water: m.p. 232° dec.; $[\alpha]^{22}D$ +3° (*c* 1.5, water); λ_{max}^{EtOH} 292 mμ; λ_{max}^{KBr} 2.9 (OH), 5.9, 6.0, ($CONH_2$), 6.33 μ (C=N); X-ray powder diffraction data[15]: 10.92 m, 7.34 m, 5.47 w, 5.07 m, 4.21 s, 4.05 w, 3.88 s (2), 3.55 s (3), 3.46 s, 3.30 vs (1), 2.99 m, and 2.97 m.

Anal. Calcd. for $C_7H_{14}N_6O_5$: C, 32.05; H, 5.38. Found: C, 31.62; H, 5.61.

Action of Nitrous Acid on D-*arabino*-Hexosulose Disemicarbazone.—A solution of the disemicarbazone (0.5 g.) in water (25 ml.) was treated at 50° with sodium nitrite (5.5 g.) in 25 ml. of water followed by the dropwise addition of 15% hydrochloric acid (12 ml.). After 30 min. the hexosulose solution was neutralized and refluxed for 10 min. with *o*-phenylenediamine (0.2 g.) and 1 ml. of acetic acid. The quinoxaline derivative separated on cooling and was recrystallized from ethanol: m.p. 188°, $[\alpha]^{22}D$ −76.6° (*c* 1.84, 5 *N* hydrochloric acid) (lit.[17] m.p. 187–188°, $[\alpha]D$ −75.2°).

Acetylation of D-*arabino*-Hexosulose Disemicarbazone and Reaction with Nitrogen Trioxide.—The disemicarbazone (3.5 g.) was acetylated by stirring with a mixture of 15 ml. of acetic anhydride and 30 ml. of pyridine until complete dissolution occurred (4 days). Since the acetylated disemicarbazone was water soluble, the reaction mixture was evaporated to dryness and the acetate, which could not be obtained in a crystalline form, was subjected to thin layer chromatography [silica gel G, methanol–benzene (1:9)] to reveal eight spots on spraying with sulfuric acid. The crude acetate was taken up in acetic acid and a stream of nitrogen trioxide was passed into the solution for 5 hr. at 5° after which the mixture was left overnight at room temperature. The reaction mixture was then evaporated, taken up in chloroform, washed with water and then with aqueous sodium hydrogen carbonate, and evaporated to dryness, yielding a nearly colorless, hygroscopic sirup which distilled at 140° (0.5 mm.): it appeared as a single spot (R_F 0.88) on a paper chromatogram developed with 1-butanol–ethanol–water (4:1:5); $[\alpha]^{22}D$ +28° (*c* 3.8, chloroform); λ_{max}^{KBr} 5.7 (O-Ac), 6.29 μ (C=N).

Anal. Calcd. for $(C_{14}H_{20}N_2O_8)_2 \cdot H_2O$: C, 47.59; H, 5.99; N, 7.93; CH_3CO, 48.73. Found: C, 47.13; H, 5.63; N, 7.82; CH_3CO, 48.67.

The above substance yielded with phenylhydrazine and acetic acid 3,4,5,6-tetra-*O*-acetyl-D-*arabino*-hexose phenylosazone[11] which was converted with sodium hydroxide in acetone to Percival's dianhydrophenylosazone,[12] m.p. and m.m.p. 238°.

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Reduction Potential and Effect of *ortho* Substituents on Dimerization of Aromatic Nitroso Compounds

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It has been known for many years that *ortho* groups larger than hydrogen favor dimerization of aromatic nitroso compounds.[1-3] For example, in a 0.1 *M* benzene or chloroform solution at 20°, nitrosomesitylene is[4,5] about 70% dimer, whereas *p*-bromonitrosobenzene,[4,5] *p*-methylnitrosobenzene,[5] and nitrosobenzene itself[4,5] are close to 100% monomer. Various explanations have been offered.[3,6-8] Luttke[7] has presented a detailed theory in which he attributes increased dimerization of *ortho*-substituted compounds to steric inhibition of resonance in the dimers. It is the purpose of the present Note to show that di-*ortho*-substituted nitroso *monomers* are subject to a sizeable steric effect and to suggest that steric inhibition of resonance *in the monomers* is the cause of the greatly increased dimerization of these compounds.

Some years ago, Lutz and Lytton[9] measured the reduction potentials, $E°$, of a number of monosubstituted nitrosobenzenes. The effect of a substituent in *meta* or *para* position varied with the electronic nature of the group, but every substituent in the *ortho* position made reduction take place more readily. This observation suggests a steric effect. It was of interest, therefore, to measure polarographically the reduction potentials of some di-*ortho*-substituted nitrosobenzenes and, for comparison, of related compounds with one substituent in the *para* position only. The results are presented in Table I.

The second column lists observed half-wave potentials, the third the difference between the potential and that for nitrosobenzene itself. A more positive potential means that the compound is more easily reduced. Although the absolute values of the reduction potentials listed are not directly comparable to those reported by Lutz and Lytton,[9] since the latter authors' values refer to acidic solutions and were obtained by the more accurate potentiometric titration method,

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