methanol until their physical properties agreed with literature values.

Kinetic Studies.—One milliliter portions of a 4% solution of the hexitol in the appropriate concentration of hydrochloric acid were placed in a series of tubes which were sealed and submerged in a boiling water bath. The variation in temperature observed over a period of several weeks was less than 1°. Samples were withdrawn at intervals and neutralized with sodium hydroxide. They were then concentrated to dryness under a stream of hot, dry air and the acetate derivatives were formed in the presence of the residual salts. It was shown by subjecting known mixtures of hexitols and their anhydrides to this procedure that the salt does not interfere with the derivatization. A suitable aliquot (usually 1 to 5 μl) of the reaction mixture was injected into the gas chromatograph.

All separations were performed on a 5 ft × 1/8 in. column of polyethylene glycol sebacate on Chromosorb Q using helium at 30 ml/min as the carrier gas. The column was maintained at 110–140° for the separation of silyl derivatives and at 200–225° for the separation of acetates. In most cases either derivative could be used to follow the progress of the anhydrization reaction. The detector response to each compound was established when possible using authentic materials and was used with measurements of peak areas to calculate the proportions of the various components present.

In Table II are presented the relative retention times and the molar responses for the hexitols and anhydrohexitols used as standards in this study.

Registry No.—Allitol, 488-44-8; D-talitol, 22576-99-4; L-iditol, 488-45-9; D-glucitol, 50-70-4; galactitol, 608-66-2; D-mannitol, 69-65-8.

Conversion of Acyclic Carbohydrates into Tetrahydrofuran Derivatives. Deamination of 1-Amino-1-deoxypentitols[1a]

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The 1-amino-1-deoxypentitols were prepared from the corresponding oximes by hydrogenation over platinum. The products of deamination with nitrous acid at 0° were examined by gas chromatography. In each case, the 1,4-anhydropentitol having the configuration of the starting material was the major product. The amounts of pentitol with the parent configuration and anhydropentitol formed by ring closure with inversion at position 2 increased through the series *xylo* < *ribo* = *arabino* ≪ *lyxo*. Bis(1-deoxypentitol)amines are also formed during the reduction of the oximes. The D-*arabino* isomer has been characterized.

Other reports in this series describe the acid-catalyzed formation of the tetrahydrofuran rings of methyl pentofuranosides,[2] 1,4-anhydropentitols,[3] and 1,4-anhydrohexitols.[4] Similar effects of configuration on the rates of these reactions were observed and explained on the basis of interactions between substituents in the transition states. In particular, interactions between groups which were forced to occupy 1,3-diaxial orientations and between a 2-hydroxyl or methoxyl group and the group leaving C-1 appeared to be important.

The 1-amino-1-deoxyalditols have been shown to deaminate readily and to give rise to 1,4-anhydroalditols as major products.[5] The deamination reaction differs from the displacement reactions cited above in that it takes place at lower temperatures, and may therefore be influenced by conformations of the ground states. Further, the reaction is not reversible, and, unlike the dehydration of the alditols, reaction with the solvent produces a stable product. Finally, the transition state for the formation of a tetrahydrofuran derivative in the deamination does not contain a leaving group, or contains one which cannot have the kinds of interaction that a protonated leaving group can have with adjacent hydroxyls. Because of these differences we wished to determine whether the effect of configuration in the acid-catalyzed reactions was observed in this ring-closure reaction.

The deamination of the 1-amino-1-deoxypentitols with nitrous acid is rapid and leads to the formation of various amounts of 1,4-anhydropentitol, pentitol, and anhydrides formed by ring closure between C-5 and C-2, which have inversion at C-2. The proportions of these products are given in Table I.

TABLE I
MOLAR PROPORTIONS OF PRODUCTS FROM DEAMINATION OF 1-AMINO-1-DEOXYPENTITOLS[a]

1-Amino-1-deoxypentitol	1,4 anhydride	2,5 anhydride, inverted	Alditol
ribo	78	15	7
arabino	78	9	14
xylo	89	9	2
lyxo	55	24	20

[a] Values are averages of three separate deamination experiments and duplicate analyses.

The deamination reaction leading to 1,4 anhydrides and alditols having the configuration of the starting amine probably proceeds by one of the routes shown in Scheme I. For convenience, the *ribo* configuration is represented; however, the following discussion is concerned with the general case. It is not possible to distinguish between the two routes, but, to rationalize the differences in proportion of products observed with differences in configuration, it is not necessary to do so.

That the rate of formation of the diazo compound **2** was not influenced by changes in the configuration of the amine **1** was shown by measuring the rates of disappearance of the latter (see Experimental Section). However, the reactant for the formation of 1,4 anhydrides is either the diazo compound **2** or the carbonium ion **3**, and differences in rate of formation of **2** or **3** would not influence the proportion of **7** formed in the

(1) (a) This investigation was supported in part by a Public Health Service Research Grant (GM 11,963) and by a Public Health Service Research Career Program Award (GM 24,808) to R. B. from the Institute of General Medical Sciences; (b) to whom inquiries should be addressed.

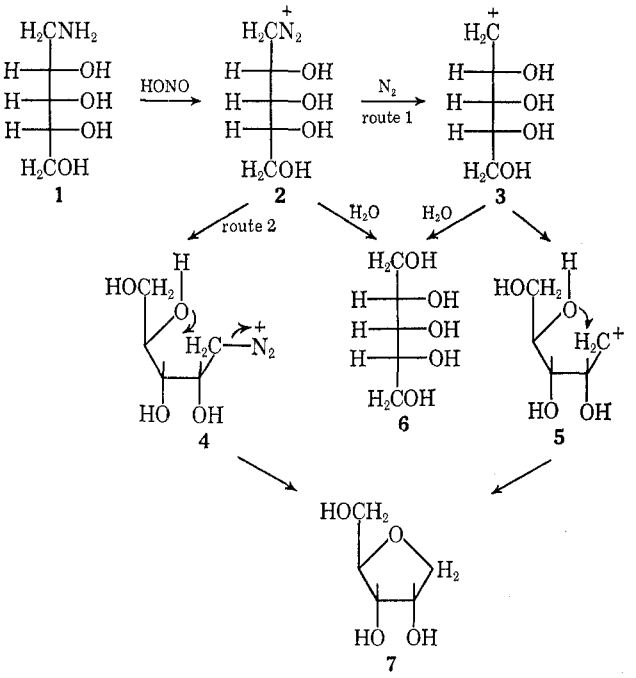
(2) D. Dennis Heard and R. Barker, *J. Org. Chem.*, **33**, 740 (1968).

(3) B. G. Hudson and R. Barker, *ibid.*, **32**, 3650 (1967).

(4) R. Barker, *ibid.*, **35**, 461 (1970).

(5) L. F. Wiggins, *Advan. Carbohyd. Chem.*, **5**, 191 (1950); V. G. Bashford and L. F. Wiggins, *Nature*, **165**, 566 (1950).

SCHEME I



reaction. This proportion should depend only on the relative rates of the intramolecular reaction (forming **7**) and reaction with solvent (forming **6**).

If the formation of the 1,4 anhydride is a displacement reaction,[6] then the ease of assumption of conformation **4** should affect the rate of the process and the rate would be sensitive to changes in configuration. The same effect would be expected if **5** were the intermediate in the process. On the other hand, neither the rate of conversion of the diazo compound **2** nor of the carbonium ion **3** into the alditol **6** would be expected to be as strongly influenced by configurational changes in the reactant as the ring-closure reaction.

The rates of reaction of the intermediate **2** or **3** cannot be measured. However, the relative rates of cyclization and solvolysis can be estimated from the relative proportions of products at any time in the reaction and, if it is assumed that solvolysis is unaffected by changes in configuration, the effect of configuration on the rate of the cyclization reaction can be estimated from the ratio of pentitol to 1,4 anhydride.

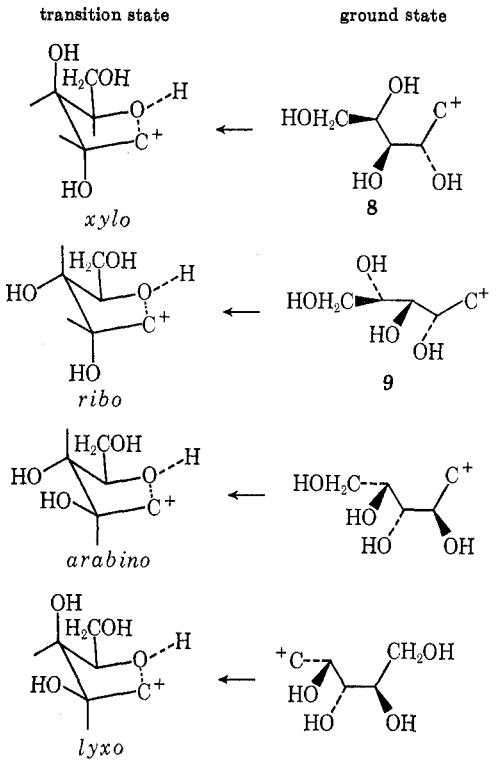
From the data in Table I and on the basis of the assumptions discussed above, it appears that ring formation becomes increasingly more difficult through the series *xylo*, *ribo*, *arabino*, and *lyxo*. However, the differences in rate are small. Probable transition states for the various configurations are shown in Scheme II.

In the acid-catalyzed formation of 1,4-anhydropentitols from the pentitols the rates were found to decrease through the series *ribo* (50), *xylo* (29), *arabino* (10), and *lyxo* (1).[7] In this case, the differences in rates between the pairs of isomers differing in configuration at C-2 were attributed largely to interaction of the hydroxyl group at C-2 with the leaving group in one of them. For example, arabinitol is much slower to

(6) J. Baddiley, J. G. Buchanan, and B. Carss, *J. Chem. Soc.*, 4058 (1957).

(7) Relative rates given in parentheses are corrected for the statistical factor in the case of ribitol and xylitol, and were calculated from the proportion and 1,4 anhydrides of arabinitol and lyxitol formed in the dehydration of arabinitol.[8]

SCHEME II



cyclize than is ribitol, primarily because of the interference of the C-2 hydroxyl group of the former with the leaving group in the transition state having fewest nonbonded interactions between substituents at C-2, C-3, and C-4. This interaction is proposed to involve hydrogen-bond formation with, or proton transfer to, the 2-OH group. In the deamination reaction, no such interaction can occur and the other effects of configuration (those due to interactions between groups at C-2, C-3, and C-4) should still be apparent. On this basis, the proportion of 1,4 anhydride would be expected to decrease through the series *arabino*, *xylo*, *ribo*, and *lyxo* as was found in an earlier study of the cyclization of benzylated pentitols.[8] This is not the case. It is possible that, in the deamination reaction which is carried out at or below room temperature, the conformations of the ground states are important in determining the ease of cyclization. It has been proposed earlier[8,9] that the ground-state conformations of the pentitols have their hydroxyl groups *gauche*, producing a maximum separation of the C–O dipoles. The ground state for xylitol would then have the conformation **8** and that of ribitol the conformation **9**. The former would be much more likely to give rise to a cyclic product. Alternatively, the ground-state conformers may be extended chains with a zig-zag conformation.[10] In this case the proportion of 1,4 anhydride will reflect the energy difference between the extended chain and the "cyclic" transition state. Such ground-state conformations are less likely to determine the rate of cyclization in the acid-catalyzed dehydration at 100°.

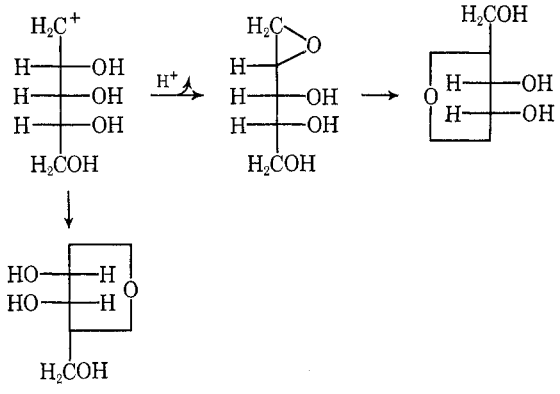
(8) G. R. Gray, F. C. Hartman, and R. Barker, *J. Org. Chem.*, **30**, 2020 (1965).

(9) F. C. Hartman and R. Barker, *Biochemistry*, **4**, 1068 (1965).

(10) H. S. Khadem, D. Horton, and T. F. Page, Jr., *J. Org. Chem.*, **33**, 734 (1968).

In addition to 1,4 anhydrides and alditols, varying proportions of products involving ring closure at C-2 by the hydroxyl at C-5 are found. These products could arise from the intermediate formation of 1,2 epoxides, which would rearrange to form stable tetrahydrofuran derivatives (Scheme III). It is improbable that 1,2

SCHEME III



epoxides are intermediates in the formation of the 1,4 anhydrides, since it has been shown that 1,2-epoxy-4-butanol does not give rise to 3-hydroxyfuran under mildly alkaline conditions.[11] The possibility that these products are formed from a rearranged carbonium ion can be discounted, since only products having inversion at C-2 are found. If a C-2 carbonium ion intermediate was involved, then products should be present having inversion and retention at this center.

A bis(1-deoxy-D-arabinitol)amine was isolated from the reduction of D-arabinose oxime, which was prepared by the neutralization of the acid released during oxime formation with sodium hydroxide. The reduction of the neutral solution followed by the usual work-up gave an amine, which, when treated with nitrous acid, gave an insoluble N-nitroso derivative. The derivative was characterized by molecular weight, elemental analysis, and conversion back into the amine. It gives an atypical Liebermann test and has a strong absorption band at 237 mμ. The occurence of secondary amines in the reduction of oximes has been described previously,[12a] and secondary amines are also formed in the reduction of glycosylamines.[12b]

Experimental Section

Melting points are corrected. Gas chromatography was performed with an Aerograph HY-FI 600-D, equipped with a 5 ft × 1/8 in. column of 10% polyethylene glycol sebacate on Chromosorb Q using helium as the carrier gas. Constant temperature for deamination experiments was maintained using a Haake Ultrathermostat NBS water bath. Absorbancies were measured using a Beckman DU with a Gilford attachment and absorption spectra were obtained using a Cary 15.

Reductions were performed at room temperature at low pressure (50 lb/in.²) using a Parr pressure reaction apparatus. Molecular weights were determined using a Mechrolab vapor phase osmometer. Analyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn.

Preparation of 1-Amino-1-deoxypentitol Hydrochlorides.—The 1-amino-1-deoxypentitols were obtained from the parent pentoses by catalytic reduction of freshly prepared pentose oxime. The amines were purified by preparation and recrystallization of the *N*-salicylidene-1-amino-1-deoxypentitols and the 1-amino-1-deoxypentitol hydrochlorides were generated by acid hydrolysis of the salicylideneamines.

A. 1-Amino-1-deoxy-D-arabinitol Hydrochloride.—To 5.6 g of hydroxylamine sulfate in 40 ml of water at room temperature was added 10 g of D-arabinose. The pH of the solution immediately dropped from 2.6 to 1.8. A solution of 3 *N* ammonium hydroxide was added dropwise to the reaction mixture to maintain a pH of 4.6. The pH reached this constant value in 1.5 hr, indicating the reaction had reached completion.[13]

The reaction mixture was transferred to a 500-ml Parr reduction bottle and 10 ml of glacial acetic acid and 1 g of platinum oxide were added. The mixture was reduced for 18 hr during which time the theoretical amount of hydrogen was taken up. The mixture was filtered through a Celite pad to remove the platinum, and passed over a column containing 150 ml of Dowex 50W × 8 (H^+). The column was washed with water until the eluate was neutral, and these washings were discarded. The column was then eluted with 250 ml of 5 *N* ammonium hydroxide, and the eluate concentrated to dryness at 30°. The residue was taken down to dryness several times from absolute ethanol, leaving the crude amine as a clear syrup (8 g, 80%).

The amine was purified by conversion into the salicylidene derivative. To a solution of 7.5 g of the amine syrup in 7.5 ml of water were added 22.5 ml of absolute ethyl alcohol and 5.25 ml of salicylaldehyde.[14] The mixture was refluxed for 30 min and then concentrated. The resulting crystalline *N*-salicylidene-1-amino-1-deoxy-D-arabinitol (6.0 g, 51%), after recrystallization from absolute ethyl alcohol, had mp 183–185°. Wolfrom, *et al.*, report mp 184–185°. 1-Amino-1-deoxy-D-arabinitol hydrochloride was obtained by acid hydrolysis of the salicylidene derivative and extraction of the salicylaldehyde with methylene chloride. The material obtained by concentration of the aqueous phase was recrystallized from aqueous methanol to a constant melting point of 135–135.5°. Jones, *et al.*, report mp 136.5–137.5°.[15]

Anal. Calcd for $C_5H_{14}NO_4Cl$: C, 32.01; H, 7.52; N, 7.46; mol wt, 187.6. Found: C, 32.24; H, 7.61; N, 7.30; mol wt, 180 ± 5.

1-Amino-1-deoxy-D-ribitol, -D-xylitol, and -D-lyxitol Hydrochlorides.—The crude amine hydrochlorides, the salicylidene derivatives, and the purified hydrochlorides of the 1-deoxypentitols were prepared as described for the *arabino* isomer. They had the properties listed in Table II.

TABLE II

	N-Salicylidene-1-amino-1-deoxypentitol		1-Amino-1-deoxypentitol hydrochloride			
	Mp, °C	Lit.[b] mp, °C	Mp, °C	C, %	H, %	N, %
ribo	124	126	126–128[c]	31.84	7.59	7.45
xylo	128–129	128–129	139–140[e]	32.19	7.42	7.37
lyxo	184–186[a]			28.28	7.85	6.47[d]

[a] *N*-Salicylidene-1-amino-1-deoxy-D-lyxitol: *Anal.* Calcd for $C_{12}H_{17}NO_5$: C, 56.5; H, 6.67; N, 5.48; mol wt, 255. Found: C, 56.4; H, 6.61; N, 5.47. Registry no. 22566-19-4. [b] See ref 14. [c] Lit. value 132.5–134° (ref 15). Registry no. 22566-17-2. [d] 1-Amino-1 deoxy-D-lyxitol hydrochloride could not be crystallized; however, the material was chromatographically pure, and the analysis obtained agrees closely with that expected of a monohydrate $C_5H_{14}NCl\cdot(H_2O)$. [e] Registry no. 22566-18-3.

Deamination Reactions.—Samples of 1-deoxy-1-aminopentitol hydrochlorides (180 mg) were dissolved in water (3 ml). Glacial acetic acid (1 ml) was added and the mixture cooled to 0°. Sodium nitrite (140 mg) was added to the solution in milligram amounts during 1 hr, while the temperature of the reaction mixture was maintained at 0°.

The reaction mixture was then kept at room temperature for 1 hr, degassed by alternately warming and applying a vacuum by means of a water aspirator, and passed over a column (6 ml) of Dowex 50W × 8 (H^+). The eluate was concentrated to dryness, and the residue taken up in water (1 ml) and passed over a column

(11) F. C. Hartman and R. Barker, *J. Org. Chem.*, **28**, 1004 (1963).

(12) (a) R. Paul, *Bull. Soc. Chim. Fr.*, [5] **4**, 1121 (1937); P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press Inc., New York, N. Y., 1967, p 139; (b) F. Kagan, M. A. Rebensdorf, and R. V. Heinzelman, *J. Amer. Chem. Soc.*, **79**, 3541 (1957).

(13) J. W. Haas, Jr., and R. E. Kadunce, *ibid.*, **84**, 4910 (1965).

(14) M. L. Wolfrom, F. Shafizadeh, J. O. Wehrmuller, and R. K. Armstrong, *J. Org. Chem.*, **23**, 571 (1958).

(15) J. K. N. Jones, M. B. Perry, and J. C. Turner, *Can. J. Chem.*, **40**, 503 (1962).

(6 ml) of Rexyn 203 (OH^-). The eluate was concentrated to dryness, to give 100 mg (60–70%) of a mixture of alditol and anhydrides.

The products of the deamination reactions were investigated by paper, thin layer, and gas chromatography. Aqueous solutions of the reaction products were applied to Whatman No. 1 filter paper or to plates of microcrystalline cellulose[16] and were developed in ethyl acetate–pyridine–water (10:4:3) and in methyl ethyl ketone–water (92:8). Carbohydrate components were located by their reaction with periodate/benzidene spray.[17] R_f values were compared with those of authentic alditols and 1,4-anhydroalditols.

Quantitative analysis of the reaction mixtures was performed by gas chromatographic analysis of the acetate and silyl derivatives using 10% polyethylene glycol sebacate on Chromosorb Q. The acetates were formed by treatment of samples (20 mg) with pyridine (0.2 ml) and acetic anhydride (0.1 ml) and separation was achieved at a column temperature of 220°. The silyl ethers were prepared by treatment of samples (50 mg) with pyridine (0.2 ml), trimethylchlorosilane (0.2 ml), and hexamethyldisilazane (0.1 ml), and separation was achieved at a column temperature of 130°. The retention times of the products were compared with those of authentic materials. The molar responses of the alditols and their 1,4 anhydrides were established using authentic materials. The compositions of the deamination mixtures were calculated from the molar responses and are shown in Table I.

To determine the reliability of the procedure, deaminations were performed in the presence of a known proportion of a pentitol which would not be formed in the reaction. (For example, ribitol was added to 1-amino-1-deoxy-D-arabinitol hydrochloride prior to deamination.) The reaction was processed as described and analyzed by gas chromatography. The proportion of ribitol in the products was used as an index of recovery of the alditol and anhydrides. In all cases it was found that at least 80% of the amine had been converted into alditol or anhydrides.

N-Nitrosobis(1-deoxy-D-arabinitol)amine.—In the experiments involving deamination of 1-amino-1-deoxy-D-arabinitol, which had not been purified *via* the salicylidene derivative, the formation of a polyhydroxy compound which strongly absorbed in the uv was observed. This component is fairly insoluble in water, and in one experiment crystallized from the deamination mixture. After several recrystallizations, it had mp 210° and $[\alpha]_D$ +39.2° (*c* 1.84, H_2O).

(16) Avicel F. M. C. Corp., Newark, Del.

(17) J. A. Cifonelli and F. Smith, *Anal. Chem.*, **26**, 1132 (1954).

The compound had E^{M}_{237} 8.75 × 10^2 and E^{M}_{346} 22.6. It gave an atypical Liebermann nitroso test in which the first color obtained was royal blue. The compound consumed 1.0 mmol of periodate/53.0 mg of sample.

Anal. Calcd for $C_{10}H_{22}N_2O_9$: C, 38.2; H, 7.06; N, 8.86; mol wt, 314.3. Found: C, 38.02; H, 7.03; N, 8.94; mol wt, 340 ± 40.

A benzoate, prepared in the usual fashion, had mp 80° and $[\alpha]^{25}_D$ +58.2 (*c* 1.77, $CHCl_3$).

Anal. Calcd for $C_{66}H_{54}N_2O_{17}$: C, 69.2; H, 4.70; N, 2.44; mol wt, 1147. Found: C, 69.8; H, 4.84; N, 2.54; mol wt, 1260 ± 100.

Bis(1-deoxy-D-arabinitol)amine.—Catalytic reduction of the nitroso compound over platinum gave an amine, mp 173.6, $[\alpha]_D$ −10° (*c* 1, H_2O), and pK_a' 7.75, which did not react with salicaldehyde, but which gave a crystalline hydrochloride, mp 199–201 and $[\alpha]_D$ +23° (*c* 2, H_2O). This amine could be quantitatively converted into the nitroso compound.

Kinetics of Deamination.—Attempts were made to estimate the rates of deamination of the 1-amino-1-deoxypentitol hydrochlorides by measurement of the evolution of nitrogen during reaction; however, reproducible results could not be obtained.

Reproducible results were obtained using a modification of Sorensen's formaldehyde titration as described by Taylor for the measurement of the deamination of aliphatic amino acids.[18]

A solution containing 1 ml of 0.1 *N* 1-amino-1-deoxypentitol hydrochloride and 0.5 ml of 0.2 *N* hydrochloric acid at 25° was mixed with 0.5 ml of 0.4 *N* sodium nitrite. Aliquots (100 μl) were withdrawn at intervals and were immediately mixed with 2 ml of 0.005 *N* sodium hydroxide and 1 ml of water. The pH of the solution was adjusted to 8.5. This solution was mixed with 1 ml of a 20% solution of formaldehyde, which had also been adjusted to pH 8.5. The solution was then purged with argon to prevent absorption of carbon dioxide and was titrated in a 3-min period with 0.001 *N* hydroxide to pH 8.5. All of the 1-amino-1-deoxypentitols were deaminated at approximately the same rate, $k = 0.253 \pm 0.04$ sec^{-1}.[19]

Registry No.—*N*-Nitrosobis(1-deoxy-D-arabinitol)-amine, 22566-20-7; *N*-nitrosobis(1-deoxy-D-arabinitol-amine) benzoate, 22566-21-8; bis(1-deoxy-D-arabinitol)-amine, 22566-22-9; bis(1-deoxy-D-arabinitol)amine hydrochloride, 22566-23-0.

(18) T. W. J. Taylor, *J. Chem. Soc.*, 1897 (1928).

(19) T. W. J. Taylor, *ibid.*, 1099 (1928).