The top of the condenser was connected in series to a 0° trap, a U-tube filled with calcium sulfate, and a three-necked reaction flask fitted with a magnetic stirrer, an addition funnel, and a Dry Ice cooled reflux condenser which was vented to the atmosphere through a trap filled with aqueous potassium iodide. A stream of nitrogen was continually passed through the system.

Difluorourea solution was placed in the generator flask and concentrated sulfuric acid (20 ml/100 ml of difluorourea solution) was added from the dropping funnel. The solution was heated to 90° to liberate difluoramine, which was swept by the nitrogen stream to the reaction flask, where it refluxed. The yield of difluoramine was 4.5–5 g/100 ml of difluorourea solution. The system must be flushed thoroughly with nitrogen before difluoramine is generated. Difluoramine is a very sensitive explosive and adequate barriers must be used.

Difluoraminocyclohexane.—Cyclohexene (4.12 g, 0.05 mole) was placed in the reactor flask and difluoramine generated from 200 ml of difluorourea solution was refluxed over it. Boron trifluoride complex of phosphric acid[4] (2 ml) was added dropwise and the mixture was stirred for 2 hr. The excess difluoroamine was flushed out of the reactor by allowing the Dry Ice condenser to warm to room temperature. The mixture was poured onto 50 ml of crushed ice and the product was extracted with two 15-ml portions of pentane. The pentane solution was dried over sodium sulfate and distilled to give 2.3 g (34% yield) of difluoraminocyclohexane, bp 34° (11–12 mm).

Anal. Calcd for $C_6H_{11}NF_2$: C, 53.33; H, 8.15; N, 10.37. Found: C, 53.03; H, 7.90; N, 10.40.

The infrared spectrum consisted of peaks at 3.55 (s), 3.45 (m), 6.83 (m), 7.3 (w), 9.5 (w), 10.3 (s), 10.6 (m), 10.85 (m), 11.3 (m), 11.8 (s), 12.0 (m), 12.7 (w), 13.8 (w), and 14.7 μ (w).

1-Difluoramino-1-methylcyclohexane.—To a mixture of difluoramine (generated from 400 ml of difluorourea solution) and 2 ml of the boron trifluoride complex of phosphoric acid, 20 g (0.209 mole) of 1-methyl-1-cyclohexene was added dropwise, with stirring. Stirring was continued for 3 hr and then 200 ml of pentane was added and unreacted difluoramine was vented off. The insoluble catalyst layer was discarded and the pentane layer was dried over sodium sulfate and was distilled. After the solvent was removed, the residue was vacuum distilled to yield 25.8 g (83% yield) of 1-difluoramino-1-methylcyclohexane, bp 44° (14 mm).

Anal. Calcd for $C_7H_{13}NF_2$: C, 56.37; H, 8.72; N, 9.40; F, 25.5. Found: C, 55.93; H, 9.10; N, 9.15; F, 25.2.

The proton nmr spectrum of a carbon tetrachloride solution of the compound consisted of a triplet (J = 1.9 cps) at δ 1.26 for the methyl group and a broad multiplet at δ 1.59 for the methylenes. The F^{19} spectrum contained only a broadened singlet at ϕ −22.17. The infrared spectrum consisted of peaks at 3.38 (s), 3.48 (m), 6.8 (sh), 6.9 (m), 7.23 (m), 7.4 (m), 8.65 (w), 10.15 (w), 10.5 (s), 10.97 (w), and 11.5–11.9 μ (s).

***t*-Butyldifluoramine.**—To a refluxing mixture of 13 g of isobutylene (0.232 mole) and difluoramine (from 600 ml of difluorourea solution), 1 ml of the boron trifluoride complex of phosphoric acid was added. An additional 1 ml of the catalyst was added after 1 hr and the mixture was allowed to reflux for an additional 3-hr period. *n*-Decane (100 ml) was then added and the excess difluoramine was removed. Distillation of the decane solution gave 15.9 g (0.146 mole, 63% yield) of *t*-butyldifluoramine, bp 54°.[5]

Reaction of Alkyldifluoramines with Acids.—Sulfuric acid solutions for the nmr spectra were prepared as described previously.[2] The product from fluorosulfonic acid and 1,2-bis(difluoramino)cyclohexane was prepared by adding 0.2 ml of the NF compound to 1 ml of the acid, cooled in a Dry Ice bath. The mixture was agitated until a homogeneous solution was formed. This solution was stable at room temperature. When the addition was conducted with the acid at 0°, a fume-off occurred when the first drop was added.

Registry No.—Difluoraminocyclohexane, 14182-78-6; 1-difluoramino-1-methylcyclohexane, 14182-79-7; difluoraminocyclopentane, 14182-80-0; *cis*-1,2-bis(difluoramino)cyclohexane, 14182-81-1; *trans*-1,2-bis(difluoramino)cyclohexane, 14182-82-2; N-fluoroimonium ion from 1-difluoramino-1-methylcyclohexane, 14182-83-3; N-fluoroimonium ion from difluoraminocyclohexane, 14182-84-4; N-fluoroimonium ion from difluoroaminocyclopentane, 14182-85-5; N-fluoroimonium ion from 1,2-bis(difluoramino)cyclohexane, 14182-86-6.

Acknowledgment.—The author is indebted to Mr. F. J. Gerhart for assistance in the synthesis work, to Dr. H. M. Nelson and Mr. L. A. Maucieri for nmr analysis, and to Mr. K. Inouye for elemental analysis.

The Conversion of Acylic Carbohydrates to Tetrahydrofuran Derivatives. The Acid-Catalyzed Dehydration of Tetritols and Pentitols[1]

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The acid-catalyzed dehydration of tetritols and pentitols leads primarily to the formation of tetrahydrofuran derivates without inversion of configuration. The process appears to involve the intramolecular displacement of water. The rate of cyclization is strongly influenced by the inductive effects of groups adjacent to the leaving group and to the entering group. The rate is also influenced by changes in the configuration of hydroxyl groups not directly involved in the reaction. This effect is attributed to interactions of the C–O dipoles. There is a strong interaction possible between a hydroxyl group adjacent to the leaving group and the leaving group which strongly influences the rate of cyclization. When these groups are *gauche*, the leaving group is effectively restrained from leaving by hydrogen bonding to the adjacent hydroxyl group.

The acid-catalyzed conversion of alditols to anhydroalditols has been the subject of numerous investigations,[2–5] none of which has been primarily concerned with the mechanism of the reaction or with the effect of configuration and substitution on its rate and course.

The acid-catalyzed ring closure of alditols, such as ribitol, has been proposed to be a nucleophilic displacement from C-1 of a protonated leaving group by a suitably situated hydroxyl group, usually at C-4[5,6] (Scheme I, route 2). Similar displacement reactions

(1) 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.

(2) L. F. Wiggins, *Advan. Carbohydrate Chem.*, **5**, 191 (1950).

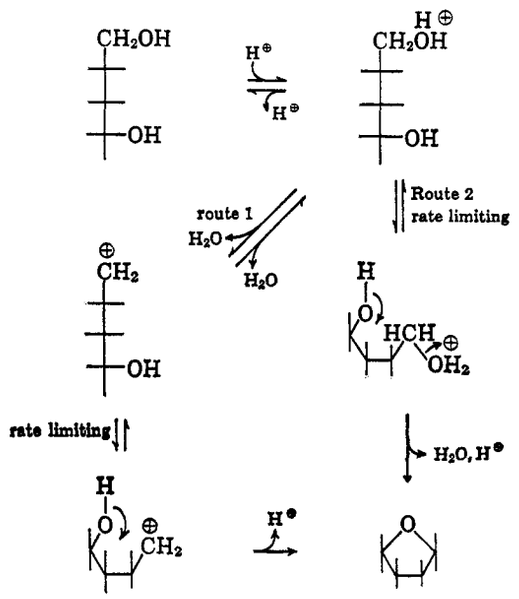
(3) J. Baddiley, J. G. Buchanan, B. Carss, and A. P. Mathias, *J. Chem. Soc.*, 4583 (1956).

(4) J. Baddiley, J. G. Buchanan, and B. Carss, *ibid.*, 4138 (1957).

(5) J. Baddiley, J. G. Buchanan, and B. Carss, *ibid.*, 4058 (1957).

(6) F. Shafizadeh, *Advan. Carbohydrate Chem.*, **13**, 59 (1958).

SCHEME I

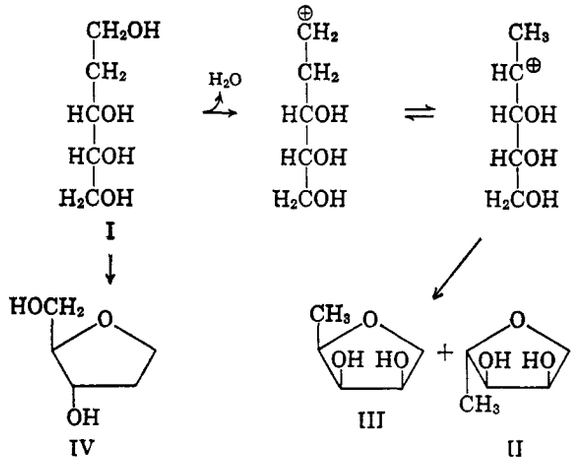


have been proposed to occur in glycoside formation from diacetals,[7] tetrahydrofuran-ring formation from polyol phosphates,[5,8] and nitrous acid deaminations leading to ring closure,[5] but in no case has the possible occurrence of carbonium ions (Scheme I, route 1) been ruled out.

The effects of acid concentration, temperature, and substitution on the rate of cyclization of a series of alditols have now been examined, and the products have been isolated and characterized in an attempt to decide between these mechanistic possibilities.

The major and frequently the only product in the cases reported in this study is that which would be formed by ring closure, without inversion, between a hydroxyl at C-4 and C-1. Of the two mechanisms shown in Scheme I, that involving a carbonium-ion intermediate seems the least likely to produce this result. For example, the configuration of substituents would not be expected to have a profound effect on the rate of carbonium-ion formation but configurational changes produce marked changes in the rate of tetrahydrofuran ring formation. If a carbonium ion is generated, the rate-limiting process would have to be its conversion to a cyclic transition state to explain the effects of configuration which are observed. A primary carbonium ion which did not cyclize could, instead, react with water to regenerate the starting material, react with a neighboring hydroxyl to form an epoxide, rearrange to a secondary carbonium ion, or undergo elimination reactions. Products which could be due to the last reaction have not been observed. The products isolated which could not have arisen by attack of the C-4 hydroxyl on C-1 all could have arisen by the formation of 1,2-epoxides formed by a displacement reaction. No inversions were observed in situations where epoxide could not be formed, but where carbonium-ion rearrangement would be possible. For example, 2-deoxy-D-ribitol (2-deoxy-D-*erythro*-pentitol) (I) could give 1,4-anhydro-5-deoxy-L-ribitol (II) and 1,4-anhydro-5-deoxy-D-lyxitol (III) if carbonium-ion rearrangement occurred, but the only product obtained was 1,4-anhydro-2-deoxy-D-ribitol (IV) (Scheme II). Additional strong evidence against a carbonium-

SCHEME II



ion intermediate is the finding that the position of a substitutent at C-2 relative to a leaving group at C-1 is the most important factor in determining the rate of cyclization in a series of isomeric pentitols (see below).

For these reasons in the remainder of this manuscript the cyclization of alditols will be considered as an SN2 displacement reaction as depicted in Scheme I, route 2, as proposed by Baddiley, *et al.*[5]

The Effect of Acid Concentration.—All of the compounds tested undergo a second-order, acid-catalyzed loss of water with the formation of tetrahydrofuran derivatives. The reaction is first order with respect to alditol and H_0.[9] Plots of log k_ψ *vs.* H_0 were found to give straight lines with slopes between 0.69 and 0.99 (Table I). This direct relationship implies that the reaction proceeds *via* a protonated intermediate rather than an intermediate involving addition of a hydronium ion to the substrate.[9]

The deviation of this line from a slope of 1.0, which would be expected if the reaction proceeds as shown in Scheme III, might be due either to the fact that H_0

SCHEME III

$$ROH + H^{\oplus} \underset{}{\overset{\text{rapid and reversible}}{\rightleftharpoons}} ROH_2^{\oplus} \xrightarrow{\text{slow}} P + H_2O + H^{\oplus}$$

determined at 25° cannot be used without correction at 100° or to the fact that the mechanism proposed is incorrect, and that some factors other than proton activity, of which H_0 is presumably a measure, play a role and are affected by changes in the concentration of acid. The first possibility has not been tested although if it was the cause of the differences all of the slopes should be similar. The second possibility can be evaluated to some extent by use of the Bunnet equation.[10] The term w, which is the slope of the line obtained when log $k_\psi + H_0$ is plotted against log a_{H_2O}, has been empirically related to the degree to which water is involved in the reaction. Negative values of w signify no involvement of water (*i.e.*, reaction *via*

(7) E. Fischer, *Ber.*, **28**, 1145 (1895).
(8) D. A. Applegarth, J. G. Buchanan, and J. Baddiley, *J. Chem. Soc.*, 1213 (1965).
(9) F. A. Long, and M. A. Paul, *Chem. Rev.*, 935 (1957).
(10) J. F. Bunnet, *J. Am. Chem. Soc.*, **82**, 499 (1960); **83**, 4956, 4968, 4973, 4978 (1961).

TABLE I

VALUES OF SLOPES OF LOG k *vs.* $-H_0$, w, k_2, ΔS^*, E_a, ΔF^*, AND RELATIVE RATE OF TETRITOL AND PENTITOL DEHYDRATIONS

	Slope[a]	w[b]	k_2[c]	$\Delta S^* \pm 2$, eu	$E_a \pm 0.8$, kcal	ΔF^*, kcal/mole	Relative[d] rate
1,4-Butanediol	0.79	+3.0	105	+0.24	30.9	30.1	256
1,2,4-Butanetriol	0.83	+20.0	27.9	+0.35	30.0	31.4	68
Erythritol	0.89	+2.05	5.9	+0.26	32.9	32.1	14
D-Threitol	0.76	+2.6	13.6	+0.64	32.6	31.7	33
2-*O*-Methyl-1,2,4-butanetriol	...	...	23.2	...	...	...	68
2-Methyl-1,4-butanediol	...	...	327	...	...	...	800
1,4-Pentanediol	0.74	+3.1	339	−1.0	29.9	29.6	830
erythro-1,2,4-Pentanetriol / *threo*-1,2,4-Pentanetriol	0.99	+0.2	102	...	...	...	250
1,2,5-Pentanetriol	0.77	+4.35	70.5	...	...	...	172
Ribitol	0.69	+4.4	20.4[e]	−2.4	31.5	31.7	50
Xylitol	0.74	+3.8	11.7[e]	−0.3	32.7	32.1	29
Arabinitol	0.92	+0.35	3.7[f]	+1.1	33.9	32.7	10
Lyxitol	...	...	0.4[f]	−2.8	33.9	34.2	1
2-Deoxy-D-ribitol	0.76	+3.3	84.4	−1.5	30.8	30.6	207
1-Deoxy-D-arabinitol	0.88	+1.5	23.8	+1.2	32.7	31.6	58

[a] Slopes of plot of log k *vs.* $-H_0$ at 99°; at least four acid concentrations were used and the data were analyzed by linear least-squares analysis. Standard deviations in all cases are less than ±0.10. [b] Slope of plot of log $k + H_0$ *vs.* log a H_2O. [c] Second-order rate constant k_2 (l. mole^{-1} sec^{-1}) × 10^7 calculated from data obtained at 99° using 2 *N* HCl ($k_2 = k/h_0 = k/4.9$). [d] Compared to lyxitol, relative rate = 1. [e] Experimental values corrected (divided by 2) because substrate is *meso* and has two equal opportunities to form the same product. [f] Calculated from the proportion of products having this configuration in the dehydration of arabinitol.

Scheme III); positive values of w seem to be associated with nucleophilic attack by water at some site in the protonated molecule. The values of w obtained in this study are given in Table I. An exceptionally wide variation is observed and no consistent pattern is apparent although the values are all positive, which might indicate the involvement of water as a nucleophile. It is unlikely that the different values of w indicate that different mechanisms are involved for the various dehydrations.

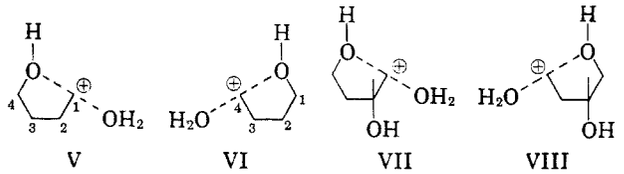
The Effect of Temperature.—The rate of tetrahydrofuran-ring formation from a number of polyols was measured at temperatures from 90 to 123° in 2 *N* hydrochloric acid. Plots of log k, the pseudo-first-order rate constant, *vs.* $1/T$ were all linear, and from their slopes values of E_a were calculated.[11] The values of E_a, ΔS^*, and ΔF^* are given in Table I. The products of the reaction are the same at different temperatures.

A cyclic transition state has fewer degrees of freedom than an acyclic reactant and ΔS^* for a reaction proceeding through a cyclic transition state is expected to be negative, however, all values of ΔS^* observed were close to zero. Differences in solvation between the transition state and the ground state affect the values of ΔS^*, and the release of tightly bound water in the formation of the transition state,[12] which would produce an increase in entropy, might be the cause of the observed values of ΔS^*.

The Effect of Substituents and Their Configuration.—In the following discussion the relative rates of the processes are used rather than the values of ΔF^*.

The simplest compound that can dehydrate to a tetrahydrofuran is 1,4-butanediol. It does so readily. The effect on the rate of replacement of a hydrogen at C-2 by hydroxyl, methoxyl, or methyl is pronounced and can be ascribed entirely to the inductive effects of these groups. There is a strong correlation between the logarithm of the second-order-rate constant and σ^*[13] for the substituents hydrogen, hydroxyl, methoxyl, and methyl; the values of k (l. mole^{-1} sec^{-1}) and σ^* are 10.5×10^{-6}, 0.00; 2.79×10^{-6}, +0.56; 2.82×10^{-6}, +0.64; 32.7×10^{-6}, −0.10.

A substituent in the butanediol system influences the development of the cyclic transition state by affecting both the nucleophilic entering group and the electrophilic group being attacked. For example, butanediol has two equivalent transition states, V and VI, whereas 1,2,4-butanediol has two nonequivalent transition states, VII and VIII. Electron withdrawal



V VI VII VIII

by the 2-hydroxyl should decrease the ease of formation of both of these transition states. In VII a diffusion of positive charge over the reaction site is taking place which would be inhibited by electron withdrawal. In VIII the hydroxyl would decrease the nucleophilic nature of the entering group. The threefold decrease in rate observed is of the order to be expected of such effects.

As expected 2-*O*-methyl-1,2,4-butanetriol dehydrates at a similar rate since the *O*-methyl group has an inductive effect similar to that of a hydroxyl group.

A threefold increase in rate is found with 2-methyl-1,4-butanediol. Two transition states, resembling VII and VIII, are possible, and electron donation by the methyl group would be expected to facilitate their formation (σ^* for OH = 0.55; σ^* for CH_3 = −0.100).

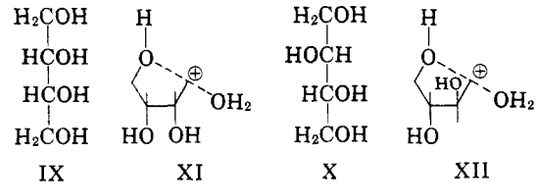
When erythritol IX and threitol X are dehydrated a further decrease in rate would be expected since only

(11) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1961, pp 22, 98.

(12) J. F. Lane and H. W. Heine, *J. Am. Chem. Soc.*, **73**, 1348 (1951).

(13) R. W. Taft, Jr., "Steric Effect in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

one transition state is possible for each (XI and XII, respectively). In each case the inductive effect of the

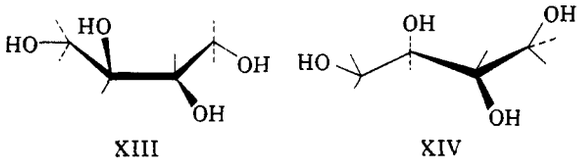


IX XI X XII

hydroxyls would affect both the nucleophilicity of the entering group and the ease of charge distribution in the transition state.

Although the inductive effects in these two isomers are comparable, their rates of cyclization are not, indicating that the configuration of substituents is as important as the kinds of substituents in determining rates. Buchanan, Baddiley, and Carss[4] have shown that, in the pentitol and hexitol series, the presence of *cis*-hydroxyls facilitates ring formation, and the same effect might have been expected in this case if *cis*-hydroxyls stabilize the transition state as they suggested. However, the fact that threitol cyclizes 2.3 times faster than erythritol indicates that the presence of *cis*-hydroxyls decreases the rate of ring formation. This may be due to differences in the transition states and, if it is, can be ascribed to the requirement that the C–O dipoles must be eclipsed in XI but not in XII.

The possibility that the rate differences might be due to differences in the ground states has been considered. If the ground-state conformation is that in which there is a maximum separation between *all* hydroxyl groups (*i.e.*, hydroxyl groups on adjacent and nonadjacent carbons are considered) then the carbon chain in the ground state for threitol (XIII) would be disposed almost as in the transition state. The ground state for erythritol (XIV) would have an extended carbon chain. Reaction of the latter requires rotation about the C-2–C-3 bond in addition to the events which are common to both reactions. These are protonation and rotation about the C-3–C-4 bond to bring the 4-OH into position to attack at C-1.



XIII XIV

It is not possible to explain the rate difference observed on the basis of hydrogen bonding in either the ground states or the transition states. In the ground states both isomers can exist with all hydroxyls *gauche* having either two or three intramolecular hydrogen bonds and the carbon chain disposed much as it is in the product. To achieve the transition state in the *erythro* isomer the hydroxyls as 2 and 3 must approach each other thus improving their situation with respect to hydrogen bonding; whereas the *threo* isomer moves to a conformation in which hydrogen bonding is less favored. These considerations predict that if hydrogen bonding is important the *erythro* isomer would be most easily dehydrated, which is not the case.

It is probable that differences in both the ground states and the transition state are important in determining the rates of these reactions. The relative energies for the ground states cannot be evaluated but most of the rate differences observed in this study can be rationalized on the basis of C–O dipole repulsions in the transition state and for this reason the effect of ground state energies on most of the rates will not be considered.

When the formation of a tetrahydrofuran derivative from a five-carbon acyclic precursor takes place, a substituent is present at C-4 which can give rise to strong nonbonded interactions which are not present in a four-carbon compound. The presence of a substituent at C-4 also designates a direction of ring closure (*i.e.*, the hydroxyl at C-4 is the entering group) and conclusions can be drawn which cannot be drawn from the four-carbon system where the identity of the leaving group and the entering group cannot be established.

The simplest member of the five-carbon series is 1,4-pentanediol which cyclizes much more readily than does 1,4-butanediol. The substitution of methyl for hydrogen at C-4 produces a sixfold increase in the rate of cyclization. (Comparisons should be based on the relative rate of 1,4-butanediol divided by two since two equivalent transition states are possible for this compound but not for the pentane derivatives.) When a hydroxymethyl group is present at C-4 there is a slight increase in rate as compared to hydrogen, but a fivefold decrease as compared to the methyl group. The σ^* values for these groups are hydrogen +0.49, hydroxymethyl +0.56, and methyl 0.00.[12] It appears that the rate of cyclization is strongly affected by the inductive effects of substituents at C-4 altering the nucleophilic nature of the hydroxyl group at C-4.

As expected, and in agreement with the observations in the four-carbon series, the presence of a hydroxyl group at C-2 causes a decrease in the rate of cyclization. This can be seen by comparing the rate of anhydrization of ribitol with that of 2-deoxyribitol and the 1,2,4-pentanetriols with 1,4-pentanediol (Table I).

That there is an effect of configuration on the rate of cyclization is apparent when the relative rates of anhydrization of the pentitols are compared (Table I). Since erythritol (*cis*-hydroxyls) cyclizes slower than threitol (*trans*-hydroxyls) the pentitols having *trans* arrangements of substituents would be expected to cyclize most readily. As has been previously observed by Baddiley, *et al.*,[5] this is not the case; ribitol, with all *cis*-hydroxyls, cyclizes most rapidly, and xylitol, with all *trans*-hydroxyls, cyclizes almost as readily. The dominant factor appears to be the relationship between the hydroxyl group at C-2 and the hydroxymethyl group at C-4. When these are *cis* in the product, the reaction proceeds slowly; when they are *trans*, it is rapid. The differences in rate between ribitol and xylitol on one hand and arabinitol and lyxitol on the other is best explained in terms of interactions occurring in the transition state for cyclization.

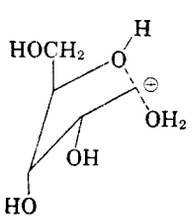
One aspect of the reactant that is changing rapidly along the reaction coordinate is the length of the bond between O-4 and C-1. If, in the transition state, the length of this bond is approximately the same as in the product then the interactions between nonreacting groups will be the same as those in the product. However, it seems probable that in the transition state the newly forming bond will be longer than it is in the

TABLE II
PRODUCTS FROM THE ACID-CATALYZED ANHYDRIZATION OF TETRITOLS AND PENTITOLS

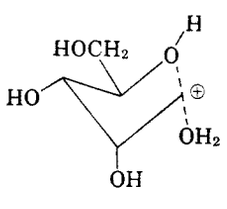
Compound	Product
1,4-Butanediol	Tetrahydrofuran
1,2,4-Butanetriol	3-Hydroxytetrahydrofuran
Erythritol	1,4-Anhydroerythritol
D-Threitol	1,4-Anhydro-D-threitol
2-*O*-Methyl-1,2,4-butanetriol	3-*O*-Methyl-3-hydroxytetrahydrofuran
2-Methyl-1,4-butanediol	3-Methyltetrahydrofuran
1,4-Pentanediol	2-Methyltetrahydrofuran
DL-*erythro*-1,2,4-Pentanetriol	DL-*erythro*-2-Methyl-4-hydroxytetrahydrofuran
DL-*threo*-1,2,4-Pentanetriol	DL-*threo*-2-Methyl-4-hydroxytetrahydrofuran
L-1,2,5-Pentanetriol	L-2-Hydroxymethyltetrahydrofuran (9% D)
Ribitol	1,4-Anhydro-DL-ribitol
Xylitol	1,4-Anhydro-DL-xylitol
D-Arabinitol	1,4-Anhydro-D-arabinitol (62.6%); 1,4-anhydro-L-ribitol (7.6%); 1,4-anhydro-D-ribitol (3.3%); 1,4-anhydro-L-xylitol (11.7%); 1,4-anhydro-D-xylitol (4.3%); 1,4-anhydro-D-lyxitol (6.2–6.9%) 1,4-anhydro-L-lyxitol (0.7%); 1,5-anhydro-D-arabinitol (4.6%)
2-Deoxy-D-ribitol	1,4-Anhydro-2-deoxy-D-ribitol
1-Deoxy-D-arabinitol	1,4-Anhydro-5-deoxy-D-lyxitol

product. Similarly, the bond being broken will be longer than it is in the reactant. In this case the interactions between substituents approach those found in cyclohexane systems and the atoms of the forming ring are disposed as if they occupied five of the positions of a cyclohexane ring. There are two strain-free arrangements for these atoms which produce quite different interactions between substituent groups.

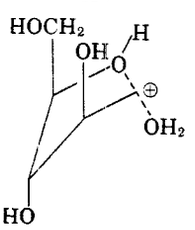
The four possible transition states for ribitol (XV and XVI) and arabinitol (XVII and XVIII) show the differences in interactions between substituents at C-2 and C-4 in these compounds. Of the four conformers,



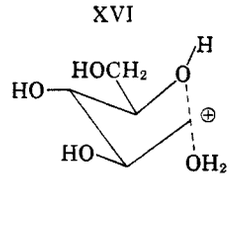
XV



XVI

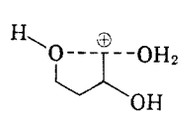


XVII

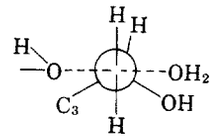


XVIII

XVIII has the fewest nonbonded interactions and would be expected to be the most stable although the single axial hydroxyl in XVI could not destabilize that transition state by more than a fraction of a kilocalorie. Conformer XVII is obviously the least stable. This evaluation is based on the assumption that the bond between O-4 and C-1 is long (~2.4 A), however a shorter bond makes little difference. The transanular



XIX



XX

interactions in XVII would be reduced but the conformer having that interaction would still be least stable. Clearly, the cyclization of arabinitol *via* conformer XVIII should proceed more rapidly than that of ribitol through conformers XV and XVI. The fact that the reverse is found indicates that interactions between nonreacting substituents do not adequately account for the effect of configuration on the rate of cyclization.

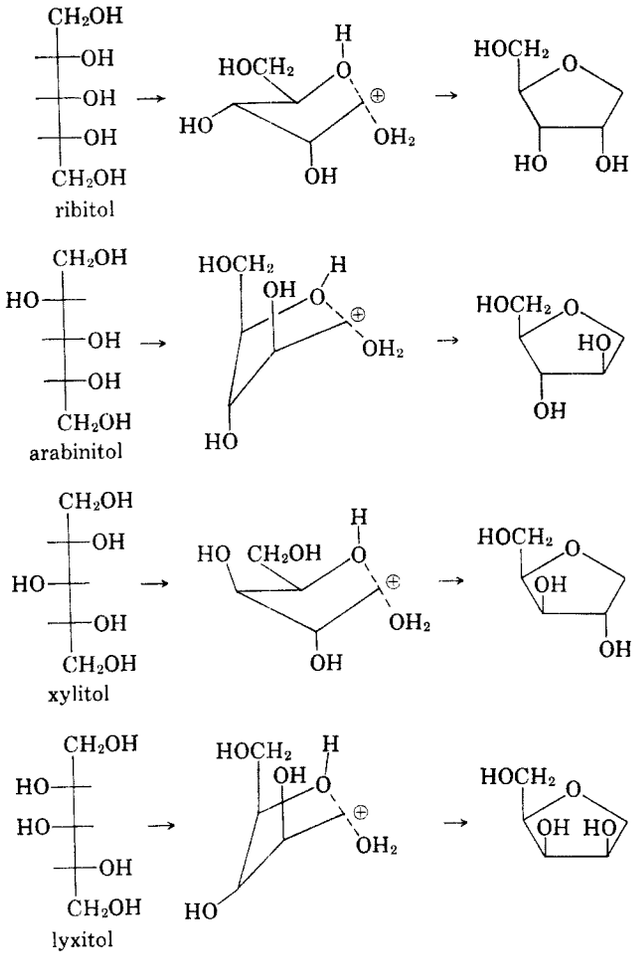
A rationalization of the observed rate differences can be developed if interactions between the leaving group and the hydroxyl at C-2 are considered. If conformers XV and XVIII are viewed from above (XIX) and in Newman projection (XX) then it can be seen that the leaving group is within 3 A of the hydroxyl group at C-2. The leaving group is positively charged and would be expected to form a hydrogen bond with the oxygen at C-2. To the extent that hydrogen bonding occurs the leaving group will have lost its ability to leave. It is proposed that conformers in which the leaving group and the hydroxyl group at C-2 are oriented as in XIX–XX cannot serve as transition states for cyclization because of stabilization of the leaving group.

When the involvement of the leaving group at C-2 is considered, it is apparent that the cyclization of ribitol must proceed *via* XVI and that of arabinitol *via* XVII. The difference in steric interactions in these two conformers could easily explain the fivefold rate difference observed.

When the four pentitols are considered it is clear that ribitol should cyclize faster than arabinitol and xylitol faster than lyxitol, and a question remains regarding the relative rates of cyclization of ribitol and xylitol, and arabinitol and lyxitol. The other factors which influence the ease of cyclization are the interactions of the C–O dipoles of the hydroxyl groups at carbons 2 and 3 with each other and with the hydroxymethyl group at C-4. It appears that hydroxyls at 2 and 3 can approach an eclipsed condition more easily than a hydroxyl at 3 and a hydroxymethyl at 4. The transition states and the products of the four pentitols are shown in Scheme IV.

In summary, there are four interactions between substituents which retard ring closure. The most effective is the interaction between the leaving group and the hydroxyl group at C-2. The next strongest is between an axial hydroxymethyl at C-4 and an axial hydroxyl at C-2, and the next between a hydroxymethyl at C-4 and a hydroxyl at C-3 which are *cis* in the product. The weakest is due to the presence of hydroxyl groups at C-2 and C-3 which become *cis* in the product. The hydroxymethyl group is important in determining the ease of ring formation. Its inductive effect has been discussed above and its steric effect

SCHEME IV



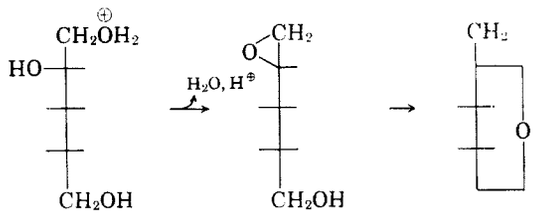
is considered important in determining the difficulty with which arabinitol and lyxitol cyclize. Verification of its importance is obtained when the rates of dehydration of lyxitol and 1-deoxy-D-arabinitol (5-deoxy-D-lyxitol) are compared. The relative rates are 1 and 58. When a methyl is replaced by a hydroxymethyl the reaction rate is decreased by a factor of 5 (compare 1,4-pentanediol and 1,2,5-pentanetriol), the 58-fold increase in rate observed when the 4-hydroxymethyl of lyxitol is replaced by a methyl indicates the importance of the steric interactions of the former with hydroxyls in the 2 and 3 positions of the ring. The methyl group does not seem to have an important steric interaction with these hydroxyls. (Compare 1,4-butanediol to erythritol and 1,4-pentanediol to 1-deoxy-D-arabinitol. The adjacent *cis*-hydroxyls in erythritol decrease the rate by a factor of 18, the adjacent *cis,cis* arrangement of hydroxyls and methyl in 1-deoxy-D-arabinitol decrease the rate by a factor of 14).

The lack of steric effect of a methyl group at C-4 is also shown by comparison of the *erythro* and *threo* isomers of 1,2,4-pentanetriol. These compounds were produced in an approximately equimolar mixture by formylation of 1-penten-4-ol and subjected to anhydrization without further purification. The reaction is first order until 80% complete when measured by periodate oxidation. The last 15% of periodate oxidizable material disappears at a fivefold-slower rate which is also first order. These findings were interpreted initially as indicating that the two isomers are dehydrated at significantly different rates. However, examination of the reaction mixture at intervals by gas chromatography and by nmr spectroscopy indicates that both isomers react at approximately the same rate. The deviation of kinetic data obtained by the periodate procedure is due to the fact that the reaction reaches an equilibrium in which approximately 5% of the starting material is present (estimated from the nmr spectrum of a sample heated 150 hr).

Participation by Adjacent Hydroxyl Groups.—In most of the cases described there is little evidence for the occurrence of reactions other than displacement reactions at C-1 involving the hydroxyl group at C-4. Only in the case of arabinitol has the participation of a hydroxyl at C-5 been demonstrated; although in some anhydrizations of substituted alditol systems, the formation of six-membered rings predominates.[14]

Participation of a hydroxyl group at C-2 is possible with the formation of an epoxide as an intermediate. In the dehydration of L-1,2,5-pentanetriol 8.5% of the product undergoes inversion in the course of the reaction, most probably *via* the 1,2-epoxide which can be opened intramolecularly by the 5-hydroxyl (Scheme V).

SCHEME V

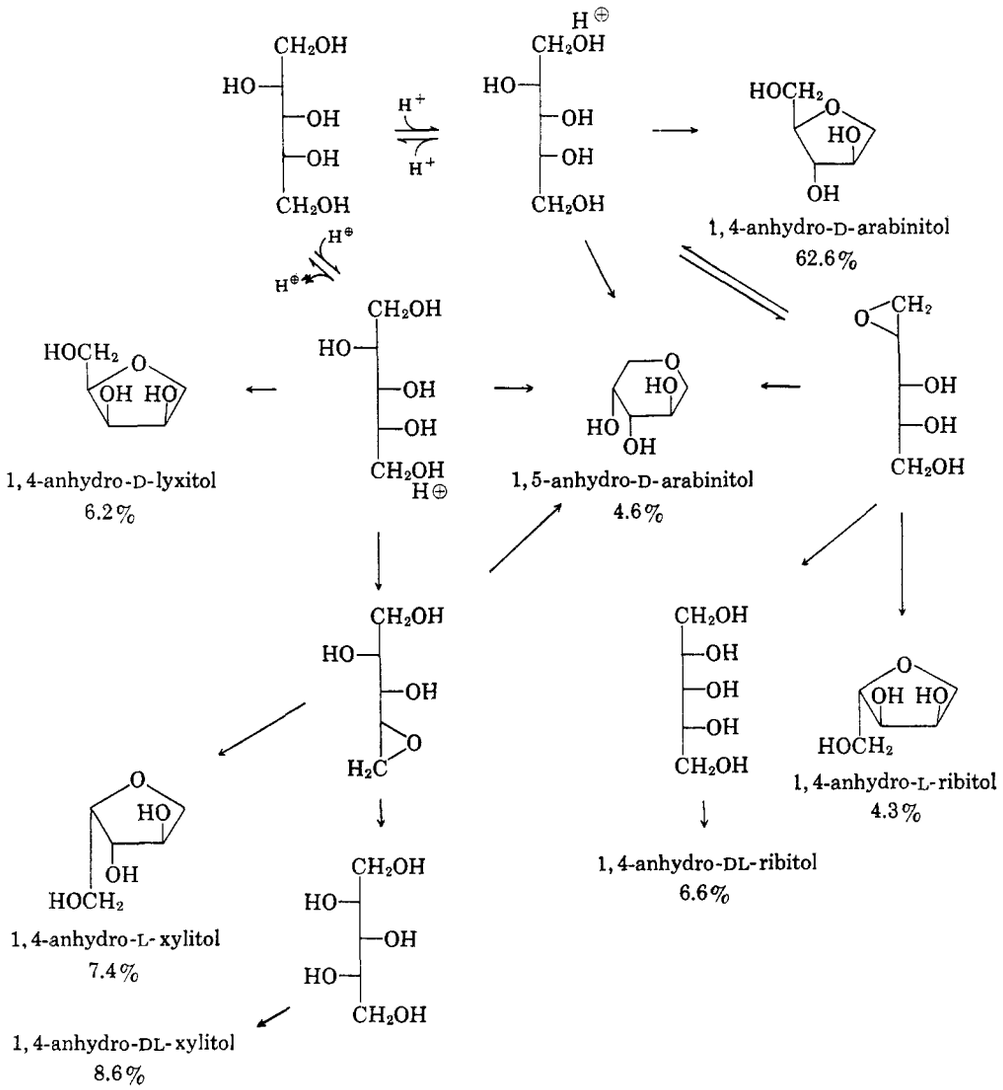


The dehydration of arabinitol is more complex than the dehydration of the other pentitols (Table II). In addition to the products of ring closure without inversion there is a relatively large proportion of products showing inversion at carbons 2 and 4, and a small proportion of 1,5-anhydroarabinitol. Apparently the requirements of the transition state for tetrahydrofuran-ring formation in this case are sufficiently restrictive to allow the formation of transition states which are not achieved by the other pentitols. The various products, their proportions, and possible pathways for their production are shown in Scheme VI.

The methods used to separate the products of arabinitol dehydration are described in detail in the Experimental Section. Using relatively small columns of a strong-base resin in the borate form, it is possible to separate compounds having *cis*-hydroxyl groups (either vicinal or 1,3) from those having only *trans*-hydroxyls. For example, 1,4-anhydro-D-arabinitol is not retarded and 1,5-anhydro-D-arabinitol is only slightly retarded by a column containing IRA-400 (borate) whereas all of the other compounds of the anhydrization mixture are held quite strongly. These anhydrides can be eluted with solutions containing borate or acetate to achieve a separation which is adequate to establish the enantiomeric forms present.

(14) (a) John C. Sowden and M. L. Oftedahl, *J. Org. Chem.*, **26**, 1974 (1961); (b) L. Hough and N. I. Taha, *J. Chem. Soc.*, 3564 (1957), and earlier papers in the series; (c) R. Barker and D. L. MacDonald, *J. Am. Chem. Soc.*, **82**, 2297 (1960). The anhydrizations reported appear to involve the intermediate formation of an olefin.

SCHEME VI



Experimental Section

Melting points are corrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were obtained on a Varian A-60 spectrometer and chemical shifts are reported relative to 3-(trimethylsilyl)propanesulfonic acid sodium salt or TMS as an internal standard.

Pentitols were prepared by the method of Abdel-Akher, *et al.*,[15] with a slight modification. To 5 g of aldose in 50 ml of water at 4° was added 500 mg of sodium borohydride in 5 ml of 0.001 *N* sodium hydroxide. After 18 hr at room temperature, 50% aqueous acetic acid was added to destroy excess borohydride. The mixture was passed through a column of 25 ml of IR-120-(H^+) and the eluate was concentrated to dryness *in vacuo* at 60°. The residue was taken up in 25 ml of methanol and concentrated to dryness *in vacuo* at 60°; this procedure was repeated six times. The crystalline alditol was then recrystallized from methanol until the physical properties agreed with literature values.

2-Deoxy-D-*erythro*-pentitol was prepared from 2-deoxy-D-*erythro*-pentose by the above procedure and purified by formation of the known tetrabenzoyl derivative which was crystallized to a constant melting point and specific rotation (129° and $[\alpha]^{25}D$ −15.2°; *c* 1.64 in $CHCl_3$).[16] Debenzoylation by sodium methoxide in methanol and removal of ions and materials soluble in methylene chloride gave a clear syrup which was free of carbonyl absorption in the infrared, yield 87%.

1,4-Pentanediol.—To 100 ml of ethyl acetate were added 10 g of 1-pentanol-4-one and 1 g of platinum oxide and the mixture was hydrogenated at room temperature and atmospheric pressure for 21 hr. The mixture was filtered through Celite and concentrated to dryness *in vacuo* at 60°. A clear syrup was obtained which was contaminated with ethyl acetate, yield 11.7 g. The di-*p*-nitrobenzoyl derivative was prepared and recrystallized from methanol to a constant melting point of 149°.[17] The alcohol was regenerated by catalytic deacylation using sodium methoxide in a mixture of methylene chloride and methanol. After removal of the inorganic materials by ion exchange and of the methyl-*p*-nitrobenzoate by partition between water and methylene chloride, a clear syrup of the alcohol was obtained.

1-Deoxy-D-arabinitol was prepared by the method of Lukes and Jary.[18]

1,2,5-Pentanetriol and 1,2,4-pentanetriols were prepared by previously reported procedures.[19]

2-*O*-Methyl-1,2,4-butanetriol was prepared from 1,2,4-butanetriol by tritylation in pyridine with 2 molar equiv of triphenylchloromethane followed by methylation of the 1,4-ditrityl derivative with an excess of dimethyl sulfate in dioxane in the presence of solid potassium hydroxide. Removal of the trityl groups in dioxane–aqueous hydrochloric acid gave the desired product in 71% overall yield. The material did not consume periodate. It had an nmr spectrum with a multiplet

(15) M. Abdel-Akher, J. K. Hamilton, and F. Smith, *J. Am. Chem. Soc.*, **73**, 4691 (1951).

(16) E. Hardegger, H. Gempeler, and Z. Zust, *Helv. Chem. Acta*, **40**, 1819 (1957).

(17) E. Hanschke, *Ber.*, **88**, 1043 (1955).

(18) R. Lukes and J. Jary, *Collection Czech. Chem. Commun.*, **24**, 3223 (1959).

(19) F. C. Hartman and R. Barker, *J. Org. Chem.*, **29**, 873 (1964).

due to two protons at τ 8.29 (7.84–8.50), a singlet due to three protons at 6.58, to five protons at 6.4 (6.10–6.68), and a singlet due to two protons at 5.25. These absorptions are assigned, respectively, to the methylene protons at C-3, to the $-OCH_3$, to the protons at C-1, C-2, and C-4, and to the OH protons.

Anal. Calcd for $C_5H_{12}O_3$ (120.14): C, 49.9; H, 10.08. Found: C, 49.7; H, 10.21.

2-Methyl-1,4-butanediol was prepared from 2-methyl succinic anhydride by reduction with lithium aluminum anhydride in dioxane. The product was recovered by the method of Woodward, *et al.*,[20] and purified by passage through a column of IRA 400 (OH^-). The material had an nmr spectra compatible with it being the desired product with a doublet due to three protons at τ 9.05, a multiplet due to three protons centered at 8.4, a doublet due to two protons at 6.58, a triplet due to two protons at 6.38, and a singlet due to two protons at 4.9. These were assigned to the protons of the methyl group, the protons at C-2 and C-3, C-1, C-4, and of the hydroxyl groups, respectively.

Anal. Calcd for $C_5H_{12}O_2$ (104.14): C, 57.6; H, 11.6. Found: C, 57.4; H, 11.40.

Cyclization of the Alditols.—A 1-ml portion of a 4% solution of the alditol in the appropriate concentration of hydrochloric acid was placed in each of a series of tubes which were sealed and maintained in a well-stirred constant-temperature bath controlled within $\pm 0.05°$ with a YSI Thermistemp Model 71 temperature controller.

Kinetic Studies. A. Periodate Oxidizable Alditols.—Most periodate oxidizable alditols consume at least 1 molar equiv of periodate more than the corresponding anhydro product. Sealed tubes were removed from the bath at intervals and opened, and duplicate 0.2-ml aliquots were removed and added to 1 ml of 0.108 *M* sodium metaperiodate. After sufficient time had elapsed to ensure complete oxidation (5 min for products with adjacent *cis*-hydroxyl group and 18 hr for products with adjacent *trans*-hydroxyl groups), 10 ml of 2 *N* sulfuric acid, 10 ml of 20% potassium iodide, and the iodine liberated was titrated with 0.02 *N* sodium thiosulfate to a starch end point. The accuracy of the procedure was checked in all cases by oxidation of the purified products under the conditions used to follow the reaction.

B. Gas–Liquid Partition Chromatography.—The relative amounts of reactants and products in the case of the pentitols were determined by neutralizing samples with 2 *N* sodium hydroxide, concentrating them to dryness under a stream of hot, dry air, forming the tetramethysilyl esters in the presence of the salt, and injecting a suitable aliquot of the reaction mixture into the gas chromatograph. All components could be separated at 110° on a 5 × ⅛ in. column of polyethyleneglycol sebacate on Chromosorb Q using helium at 30 cc per min as the carrier gas. Under these conditions the retention times for the various pentitols and their anhydrides were ribitol, 81; D-arabinitol, 76.5; xylitol, 71.0; 1,4-anhydro-DL-ribitol, 63.2; 1,4-anhydro-DL-xylitol, 68.4; 1,4-anhydro-D-lyxitol, 100; 1,4-anhydro-D-arabinitol, 53.4; 1,5-anhydro-D-arabinitol, 49.0 min. The detector response to each compound was established using authentic materials and was used with measurements of peak areas to calculate the proportions of the various components.

C. 1,4-Pentanediol and 1,4-Butanediol.—A colorimetric assay was developed based on the fact that alcohols give a yellow color with ceric ammonium nitrate.[21] The cyclization products of these diols also give colors with this reagent but of much lower intensities. A standard curve was obtained for each diol by measuring the absorbancy at 480 mμ of mixtures containing varying amounts of the diol and its cyclization product. The analysis procedure consisted of withdrawing sealed tubes at intervals and adding aliquots of the reaction mixture to 3 ml of 0.25 *M* ceric ammonium nitrate. After 1 min the absorbancy was measured at 480 mμ. The amount of diol reacted in the time interval was calculated from the standard curve.

Identification of Products. A. Arabinitol.—The rate of disappearance of arabinitol during the cyclization procedure can be determined readily using sodium metaperiodate as described above. The nature and proportion of the products formed was established by gas-liquid partition chromatography, but it was not possible to translate the separation obtained on the analytical column into a preparative procedure. For this reason a rather complicated separation was devised to obtain fractions of each of the components of the mixture to establish their enantiomeric purity.

A sample of D-arabinitol (20 g) was heated in 500 ml of 2 *N* hydrochloric acid under reflux for 45 days ($15 \times t_{1/2}$). The hydrochloric acid was removed by repeated concentration *in vacuo* followed by passage of an aqueous solution of the products over a column containing 100 ml of IR 45 in the free-base form. Concentration of the eluate gave 17.4 g of syrup. The syrup was dissolved in water (200 ml) and passed over a column of IRA-400 (borate form). Elution with water was continued and four 500-ml fractions of the eluate were collected. The fractions were concentrated to dryness; the residue so obtained was concentrated five times from 100-ml portions of methanol to remove traces of boric acid. Analysis of the fractions by gas chromatography showed that each contained 1,4-anhydroarabinitol and 1,5-anhydroarabinitol. The combined yield was 11.4 g. Elution of the column with 700 ml of 20% aqueous acetic acid gave, after removal of the boric acid with methanol *in vacuo*, 4.65 g of syrup which by gas chromatography was shown to contain 1,4-anhydroribitol, 1,4-anxydrocylitol, 1,4-anhydrolyxitol, and arabinitol in the same proportions as the initial mixture.

The separation of 1,5-anhydroarabinitol and 1,4-anhydroarabinitol was achieved by passing a solution of the mixture over a column of IRA-400 (OH^-) and eluting it with water. 1,5-Anhydroarabinitol is not retarded by the column whereas the 1,4-anhydride is. From 10.6 g of the mixture, by passage over 250 ml of resin, was obtained 650 mg of 1,5-anhydro-D-arabinitol in the first 240 ml of eluent. Further elution with 5 l. of water gave 9.5 g of 1,4-anhydro-D-arabinitol mainly in the first 2 l. of eluent.

The 1,5-anhydro-D-arabinitol so obtained had $[\alpha]^{29}D$ −97° (*c* 1.0, H_2O) before and after crystallization and one crystallization from ethyl alcohol gave 210 mg of material, mp 96–97° in agreement with the values of $[\alpha]^{20}D$ −98° and mp 96–97° reported by Fletcher and Hudson.[22] The material also gave a quantitative yield of benzoate having mp 120–121° and $[\alpha]^{30}D$ −223° (*c* 4.0, $CHCl_3$) in good agreement with the reported values.[22]

1,4-Anhydro-D-arabinitol crystallized spontaneously. Although very hygroscopic it could be recrystallized from a minimal amount of isopropyl alcohol on the addition of ethyl acetate. The compound has mp 53° and $[\alpha]^{29}D$ +23.7° (*c* 1.5, H_2O). The compound gave a syrupy benzoate with $[\alpha]^{25}D$ −76.9° (*c* 2.16, $CHCl_3$), −77.4° (*c* 2.14, CH_2Cl_2) in good agreement with the value reported by Bhattacharya, *et al.*[23] The mother liquors from the crystallization of 1,4-anhydro-D-arabinitol were also converted to a benzoate with $[\alpha]^{25}D$ −79° (*c* 2.1, CH_2Cl_2) indicating that the material is enantiomerically pure in the reaction mixture.

A crystalline tri-*O*-*p*-nitrobenzoate was also prepared in quantitative yield having mp 80–81° and $[\alpha]^{28}D$ −86.2° (*c* 1.0, $CHCl_3$) in good agreement with the values reported for the L-isomer.[24]

It was not possible to obtain a clean, quantitative separation of the anhydrides eluted from the borate column with acetic acid, however, a partial separation was achieved which gave small amounts of the pure materials. The mixture (0.98 g) was placed on a column containing 25 ml of IRA-400 (borate) and elution with increasing concentrations of boric acid was performed. Elution with 500 ml of 0.1 saturated boric acid (50 ml of saturated boric acid + 450 ml of water) gave 160 mg of 1,4-anhydro-D- and -L-xylitol, which gave a single peak on gas chromatography and which gave a benzoate with $[\alpha]^{25}D$ −33° (*c* 2.82, $CHCl_3$) indicating by comparison with authentic 1,4-anhydro-D-xylitol benzoate, which has $[\alpha]^{25}D$ +72° (*c* 4.5, $CHCl_3$),[25] that the mixture contains 73% of the L and 27% of the D isomer.

Elution with 100-ml volumes of eluent having increasing

(20) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLemore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(21) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p 96.

(22) H. G. Fletcher, Jr. and C. S. Hudson, *J. Am. Chem. Soc.*, **69**, 1672 (1947).

(23) A. K. Bhattacharya, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 428 (1963).

(24) R. Barker and H. G. Fletcher, Jr., *ibid.*, **26**, 4605 (1961).

(25) D. D. Heard, B. G. Hudson, and R. Barker, unpublished observation.

levels of saturation with boric acid (0.2, 0.3, 0.4, etc.) up to full saturation and finally with 5, 10, and 20% aqueous acetic acid displaced 1,4-anhydroribitol, followed by arabinitol and finally 1,4-anhydrolyxitol. All of these components overlapped but pure 1,4-anhydroribitol (210 mg) was obtained from the 0.3 and 0.4 times saturated boric acid eluents, and pure 1,4-anhydrolyxitol (115 mg) was obtained from the 5% acetic acid eluents. The syrupy benzoate had $[\alpha]^{25}D$ −42° indicating that the ribitol anhydride was 70% L and 30% D isomer; $[\alpha]^{25}D$ +107° (*c* 1.71, $CHCl_3$) for the D isomer has been reported.[23] From the syrup used to obtain the optical rotation 40 mg of crystalline 1,4-anhydro-DL-ribitol tribenzoate was isolated, mp 113–114°, undepressed on admixture with authentic material,[26] $[\alpha]^{26}D$ 0.0 ± 0.4° (*c* 2.0, $CHCl_3$). The lyxitol anhydride was at least 90% D isomer, its benzoate before purification had $[\alpha]^{25}D$ −32.2 (*c* 2.8, $CHCl_3$). The reported value for the crystalline 1,4-anhydro-D-lyxitol tribenzoate is −36.1° (*c* 1.73, $CHCl_3$), mp 117–118.[28] Crystalline material was obtained in good yield which had mp 115–116° and $[\alpha]^{25}D$ −34.0° (*c* 1.9, $CHCl_3$) in agreement with the reported values.

B. Ribitol and Xylitol.—The products present at 10 × $t_{1/2}$ were identified by gas chromatography of their trimethylsilyl ethers by comparison with known compounds. The product from ribitol gave a quantitative yield of a crystalline benzoate which was shown by comparison with authentic material to be 1,4-anhydro-DL-ribitol tribenzoate. The product from xylitol was shown to be the 1,4-anhydride by periodate oxidation (1 molar equiv of periodate consumed) and by conversion to a monotrityl derivative, mp 135–137°.[27]

1,4-Butanediol, 1,2,4-Butanetriol, 2-*O*-Methyl-1,2,4-butanetriol, 2-Methyl-1,4-butanediol, and 1,4-Pentanediol.—The products formed from these alcohols were identified by carrying out the dehydration using a 10% solution of the alcohol in D_2O–2 *N* sulfuric acid at 100° for 10 × $t_{1/2}$, the solutions were examined by nmr spectroscopy and the spectra obtained were compared with those obtained from known samples of the suspected product in similar solutions. In all cases the spectra were identical except for weak absorptions due to the small proportion of starting material still present.

***erythro*- and *threo*-1,2,4-Pentanetriol.**—The product was examined by nmr spectroscopy as described above and its identity inferred from the similarity of the absorptions to those observed for similar compounds such as 3-hydroxytetrahydrofuran and 2-methyltetrahydrofuran. A comparison of the spectra is presented in Table III.

Erythritol and Threitol.—That the product in each case was the 1,4-anhydride was established by preparation of the di-*O*-*p*-nitrobenzoyl derivative for comparison with authentic materials.[28]

1-Deoxy-D-arabinitol.—The product from the dehydration rapidly consumed 1 mole of periodate per mole of starting material. It contained only one component when examined as the acetate or trimethylsilyl derivative by gas chromatography.

2-Deoxy-D-ribitol.—The product did not consume periodate and appeared as a single component when examined as the acetate or trimethylsilyl derivative by gas chromatography.

First-order rate constants were calculated using the equation, $k = 2.303 \times$ slope. The slopes were calculated using the method of least squares.

Activation energy (E_a) was determined from the Arrhenius equation, $k = Se^{-E_a/RT}$, by plotting the logarithm of the first-order rate constant (k) against the reciprocal of the absolute temperature ($1/T$). The energy of activation was then calculated by use of the equation $E_a = -2.303R$ (slope). A hydrochloric acid strength of 2 *N* was used in obtaining these data.

The entropy of activation (ΔS^*) was calculated from the transition state theory[11] using the data obtained at 99° in 2 *N* hydrochloric acid. The second-order rate was used in calculating ΔS^*; it was derived from the experimental pseudo-first-order rate constant using the expression $K = k/H_0$ where K = second-order rate constant, k = pseudo-first-order rate constant, and H_0 = Hammett acidity function.

In calculating ΔS^* for ribitol and xylitol cyclization, their corresponding pseudo first-order rate constants were corrected by multiplying by one-half.

The free energy of activation (ΔF^*) was determined from the transition state theory using the data obtained at 99° in 2 *N* acid, and the equation $\Delta F^* = \Delta H^* - T\Delta S^*$, where $\Delta H^* = E_a - RT$.

TABLE III
CHEMICAL SHIFTS (τ VALUES) IN D_2O, 2 *N* WITH RESPECT TO H_2SO_4

Compound	Value for protons[a] C_2	C_5	C_3	C_4	CH_3
Tetrahydrofuran	6.20–6.60(m)		8.10–8.42(m)		
2-Methyl THF	5.72–6.57(m)		7.72–8.78(m)		1.22(2)
3-Hydroxy THF	5.88–6.32(m)		5.30–5.61(6)	7.46–8.25(m)	
Product from 1,2,4-pentanetriols	5.65–6.52(m)		5.40–5.65(6)	7.28–8.59(m)	1.25(2) 1.30(2)

[a] Numbers in parentheses indicate numbers of peaks; m indicates multiple peaks.

Registry No.—1,4-Butanediol, 110-63-4; 1,2,4-butanetriol, 3068-00-6; erythritol, 149-32-6; D-threitol, 2418-52-2; 2-*O*-methyl-1,2,4-butanetriol, 13942-68-2; 2-methyl-1,4-butanediol, 2938-98-9; 1,4-pentanediol, 626-95-9; DL-*erythro*-1,2,4-pentanetriol, 13942-71-7; DL-*threo*-1,2,4-pentanetriol, 13942-72-8; L-1,2,5-pentanetriol, 13942-73-9; ribitol, 488-81-3; xylitol, 87-99-0; D-arabinitol, 488-82-4; lyxitol, 13942-75-1; 2-deoxy-D-ribitol, 13942-76-2; 1-deoxy-D-arabinitol, 13942-77-3.

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Constituents of *Iva* Species. X. Ivangulin, a Novel *seco*-Eudesmanolide from *Iva angustifolia* Nutt.[1,2]

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The structure of two new sesquiterpene lactones from *Iva angustifolia* Nutt. has been elucidated. One of these, ivangustin, is the double bond isomer **2a** of asperilin. The second, ivangulin (**6**), represents a new structure type and is the methyl ester of a ring A *seco*-eudesmanolide.

In the course of our systematic study of the genus *Iva*,[1] we examined several collections of *Iva angustifolia* Nutt. (section *Linearbractea*), a species which is found mainly in Oklahoma and Texas.[3] This has led to the isolation of two new sesquiterpene lactones whose structure is discussed in the present paper.

(1) Previous paper, L. Farkas, M. Nogradi, V. Sudarsanam, and W. Herz, *Tetrahedron*, **23**, 3557 (1967).

(2) Supported in part by grants from the U. S. Public Health Service (GM-05814) and the National Science Foundation (GP-1962).

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