Thermal Reactions of α-D-Xylopyranose and β-D-Xylopyranosides[1]

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Thermal analysis and chemical studies have shown that crystalline α-D-xylopyranose on melting equilibrates with the β-D form. Heating of this mixture and a variety of β-D-xylopyranosides at steadily increasing temperatures resulted in the cleavage of the glycosidic group, polymerization of the glycosyl moiety, and decomposition within a narrow range. When $ZnCl_2$ was added as a catalyst, the cleavage and polymerization reactions occurred at a much lower temperature than decomposition of the polymer, and there was considerable charring. Esr spectroscopy and isothermal kinetic investigations indicate a heterolytic mechanism for the initial glycosidic cleavage.

Thermal analysis provides a valuable method for investigating the sequence of transformations and reactions which take place on heating carbohydrate compounds. Some of these transformations, such as the solid-state transition of 1,6-anhydrohexopyranoses,[3-5] have escaped detections by conventional methods and other reactions such as polymerization of free sugars[6,7] and pyrolysis of the cellulosic materials[8,9] have received sporadic attention because of academic or technological interest. However, little is known about the sequence and nature of the thermal reactions which eventually lead to the decomposition of the carbohydrate compounds and the suggested free-radical or ionic mechanisms[8] are based mainly on speculation rather than chemical data. In this study the sequence and nature of these reactions have been investigated by combining thermal analysis of crystalline α-D-xylopyranose, methyl β-D-xylopyranoside, and several phenyl β-D-xylopyranosides with parallel chemical investigation. These materials were used with the idea of determining the stability of the anomeric form as the free sugar is heated, how various glycosidic groups affect the thermal cleavage of the D-xylopyranosyl moiety, whether the cleavage is homolytic or heterolytic, and what are the conditions for condensation or further degradation of the glycosyl moiety. It has been shown that under acid conditions D-xylose undergoes thermal condensation to provide a polymeric material with a wide variety of links.[6,10] Zinc chloride was used as a catalyst to determine the effect of the acidic conditions on the expected polymerization and other pyrolytic reactions.

Results and Discussion

α-D-Xylopyranose.—The thermogram of crystalline α-D-xylopyranose is shown in Figure 1. In this figure the dta (differential thermal analysis), tga (thermogravimetric analysis), and dtg (derivative thermal gravimetry) curves reflect the sequence of physical transformations and chemical reactions as the sugar is heated at a constant rate.

The dta curve contains an endotherm at 155°, corresponding to the melting point of the sugar. However, the melting endotherm of pure organic compounds is generally very sharp (see Figures 2 and 3) and the rather wide and unsymmetrical appearance of this peak indicates the presence of some impurity (the amount of which could be calculated by established methods[11]) or the occurrence of another simultaneous transformation. In this case the situation is complicated because of the possibility for conversion of α-D-xylopyranose to the β-D form as well as the preexistence of the latter form in the crystalline material. This possibility was investigated by heating the sugar for a short period at several temperatures before, during, and after the melting point to obtain a series of products corresponding to different stages in the development of the endotherm. The products containing different ratios of the α- and β-D-xylopyranoses were silylated and analyzed by glc. The resulting data shown in Table I indicate that melting is accompanied by thermal anomerization of the α-D-xylopyranose. The crystalline sugar contains about 10% of the β-D anomer up to about 125° when the endotherm begins. It then continues to equilibrate until the melting is completed and the ratio of the anomers becomes constant. Broido and associates[12] who studied D-glucose near its melting point found that mutarotation occurs more readily than condensation, and Liskowitz and Carroll[13] have reported differences in condensation behavior of aldo-

TABLE I

RATIO OF D-XYLOPYRANOSE ANOMERS AT VARIOUS TEMPERATURES

Temp, °C	α-D-Xylopyranose, %	β-D-Xylopyranose, %
25	90.6 ± 4.0	9.4 ± 4.0
127	91.7 ± 0.6	8.3 ± 0.6
131	85.9 ± 2.1	14.1 ± 2.1
140	83.0 ± 0.4	17.0 ± 0.4
149	73.0 ± 0.7	27.0 ± 0.7
154	47.9 ± 0.3	52.1 ± 0.3
200[a]	48.0	52.0

[a] This sample showed 5.3% weight loss due to condensation. The ratio of anomeric forms was determined by the analysis of the remaining free sugar.

(1) Presented in part before the Division of Carbohydrate Chemistry of the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970.

(2) Established through a grant from the Hoerner-Waldorf Corp. of Montana.

(3) F. Shafizadeh, G. D. McGinnis, C. W. Philpot, and R. A. Susott, *Carbohyd. Res.*, **13**, 184 (1970).

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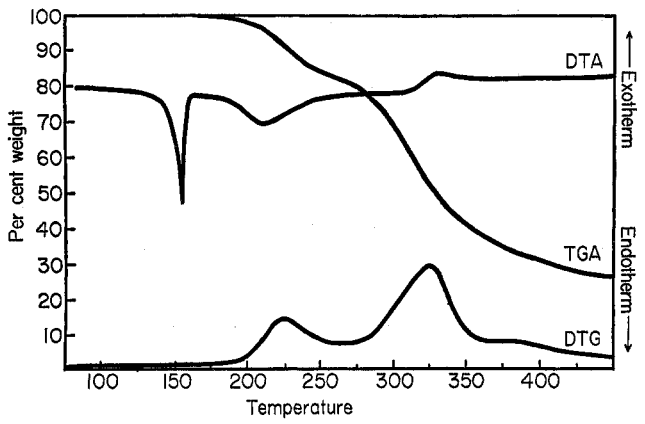

Figure 1.—Thermogram of α-D-xylopyranose.

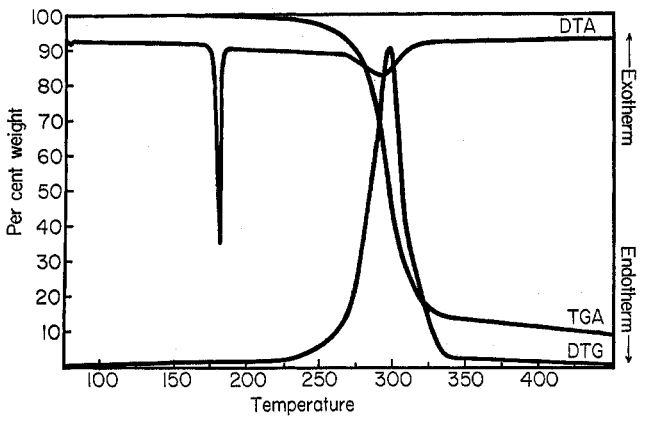

Figure 2.—Thermogram of phenyl β-D-xylopyranoside.

hexoses that could be attributed to different anomeric forms of the sugar at temperatures considerably above the melting point. The above data, however, show that the molecular rearrangement and equilibration of the sugar takes place on melting, starting with formation of microscopic liquid pockets in the solid phase.[14]

The next reaction in Figure 1 is indicated by a broad endotherm (dta curve) centered at 210°, a weight loss of about 13% (tga curve) and a corresponding increase in the rate of weight loss (the minor dtg peak). This reaction was investigated by isothermal heating of D-xylose at 200° to different levels of weight loss controlled and recorded by tga. The heated materials were analyzed for D-xylose before and after acid hydrolysis. The results shown in Table II indicate that the reaction

TABLE II

ANALYSIS OF THE MIXTURE FORMED ON HEATING D-XYLOSE AT 200°

Weight loss, %	D-Xylose, %	
	Before hydrolysis	After hydrolysis
5.3	50.3	68
10.7	10.7	63
20.0[a]	0.0	

[a] Although D-xylose was the major compound liberated by acid hydrolysis, glc analysis showed the formation of other minor products.

involves loss of water and condensation of the sugar. This was further established by elemental analysis and

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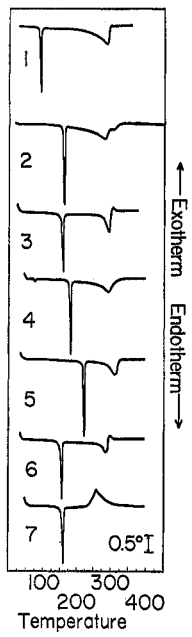

Figure 3.—Dta signals of the following xylosides: 1, methyl α-D-xylopyranoside; 2, methyl β-D-xylopyranoside; 3, *p*-methoxyphenyl β-D-xylopyranoside; 4, phenyl β-D-xylopyranoside; 5, *p*-phenylphenyl β-D-xylopyranoside; 6, *p*-chlorophenyl β-D-xylopyranoside; 7, *p*-nitrophenyl β-D-xylopyranoside.

tlc of a heated sample. The latter experiment showed several slow-moving spots on tlc which formed a trail streaking between the starting point and the location of D-xylose. However, when the heated material was subjected to acid hydrolysis the trail disappeared and the substrate gave only a spot for D-xylose. This indicated the formation of a heterogeneous polymer, which separates to a number of spots because of the variation in the relationship between the molecular weight and the number of the hydroxyl groups as well as other fundamental properties of the molecules in solution.[13,15] After hydrolysis the trail disappears, because the polymeric material is converted to the free sugar. The isolation and investigation of the polymeric product will be described later.

Before completion of the condensation reaction, decomposition of the sugar molecule begins and accelerates on further heating until evaporation of the decomposition products leaves a residue of about 30% at 400°. The decomposition is recorded by a minor exotherm on dta, a rapid weight loss on tga, and a major peak on dtg indicating the maximum rate of weight loss at about 325°. Further information on this reaction could be obtained by analysis of the decomposition products which will be reported in the following paper.

As seen from Figure 4 when $ZnCl_2$ is added to the free sugar the melting endotherm becomes much broader and the condensation and decomposition process takes place at considerably lower temperatures. It is also significant to note that the amount of charred residue at 400° increases to about 45%.

β-D-Xylopyranosides.—The thermogram of phenyl β-D-xylopyranoside, shown in Figure 2, provides a different pattern. In the dta curve, the sharp melting point endotherm at 178° is followed by only one wide endotherm at 290°. The weight loss begins at 230°

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TABLE III
THERMAL ANALYSIS FEATURES OF THE β-D-XYLOPYRANOSIDES

β-D-Xylopyranoside		Dta peaks		Dtg peaks		Tga data	
Aglycone	Mp, °C	Mp, °C	Dec, °C	Aglycone evap, °C	Glycosyl dec, °C	Threshold temp, °C	Residue at 400°, %
Before Treatment with $ZnCl_2$							
Methyl	156	159	287[a]	286		170	0
p-Methoxyphenyl	157	156	290	296		220	12
Phenyl	178	178[b]	288	297		230	12
p-Phenylphenyl	221	221	310	318		262	7
p-Chlorophenyl	156	156	285	290		220	12
p-Nitrophenyl	158	158	255	260		221	30
After Treatment with $ZnCl_2$							
Methyl		143[c]	221	168	220	150	42
p-Methoxyphenyl		128	213	179	212	136	44
Phenyl		131	214	152	212	116	46
p-Phenylphenyl		160	220		207	151	37
p-Chlorophenyl		129	211	168	205	130	33
p-Nitrophenyl		133	212		210	154	39

[a] Decomposition of the methyl β-D-xylopyranoside is not meaningful due to simultaneous evaporation. [b] Phenyl β-D-xylopyranoside also has a small but reproducible transition of unknown origin at 73°. [c] Fusion of treated samples is accompanied by cleavage of the glycoside and polymerization.

and proceeds very rapidly leaving a residue of only 12% at 400° and the dtg shows a single peak for the rate of weight loss corresponding to the wide dta endotherm. A similar thermal behavior is also shown by a variety of other β-D-xylopyranosides except for the *p*-nitrophenyl β-D-xylopyranoside which gives a wide exotherm instead of an endotherm at the elevated temperatures and leaves a considerably greater residue (see Figure 3 and Table III).

Comparison of the thermogram of α-D-xylopyranose with those of β-D-xylopyranosides indicates that in the latter compounds complete degradation of the molecule takes place within a narrow temperature range and the loss of the glycosidic group could not be differentiated from the decomposition and volatilization of the carbohydrate moiety. However, glc analysis of phenyl β-D-xylopyranoside heated at 250° to different levels of weight loss (see Table IV) shows that the decomposition takes place through closely occurring consecutive reactions. The initial weight loss mainly involves cleavage of the glycosidic group and evaporation of the aglycone as free phenol that could be detected among the pyrolysis products. The fate of the glycosyl moiety was detected by tlc analysis of the partially decomposed material. This showed a small amount of starting glycoside followed by the characteristic trail of a heterogeneous polymer, which on hydrolysis gave D-xylose. The later stages of the reaction progressively reflect decomposition of the glycosyl unit ultimately leaving a charred residue.

TABLE IV
ANALYSIS OF PHENYL β-D-XYLOPYRANOSIDE PARTIALLY DEGRADED AT 250°

Total wt loss, %	Remaining glycoside, %	Calcd wt loss[a]	
		Aglycone, %	Glycosyl, %
15	65	14	1
30	38	25	5
50	11	36	14

[a] Assuming complete evaporation of phenol derived from cleavage of the glycoside at 250°. All data are based on the original weight of the glycoside.

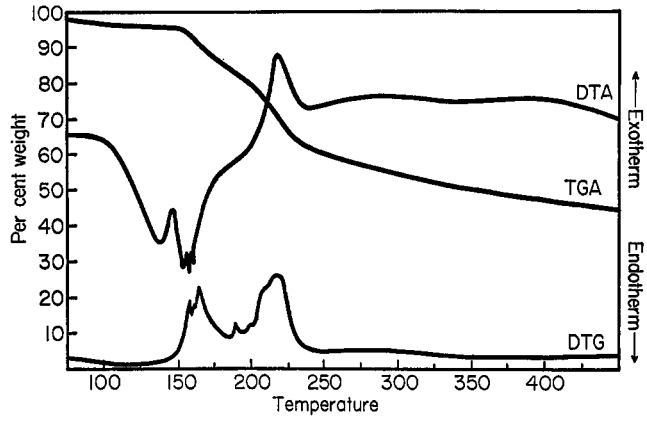

Figure 4.—Thermogram of $ZnCl_2$ treated α-D-xylopyranose.

According to these data the decomposition endotherm of the phenyl β-D-xylopyranoside and the rapid weight loss at elevated temperatures show the net effect produced by cleavage of the glycoside, evaporation of the aglycone, polymerization of the glycosyl group, and decomposition and volatilization of the sugar moiety. Since the glycosidic group is cleaved at relatively high temperatures, the other reactions and transformations could follow readily and give the physical appearance of simultaneous reactions.

Addition of $ZnCl_2$ which facilitates the cleavage of the glycosides and polymerization of the glycosyl moiety drastically alters the thermograms of the phenyl β-D-xylopyranoside (see Figure 5) and other xylopyranosides (see Figure 6 and Table III). In these thermograms the first endotherm is considerably wider than those observed for the melting of the untreated materials. This may be attributed to the presence of $ZnCl_2$ as an impurity. However, chemical analysis showed that this endotherm represents not only the fusion of the treated xylopyranosides but also their cleavage and polymerization. Heating of the treated glycoside through the endotherm and tlc and glc analysis of the products formed on melting (see Table V) showed almost total disappearance of the glycosides, production of free phenols, and formation of a polymer which on

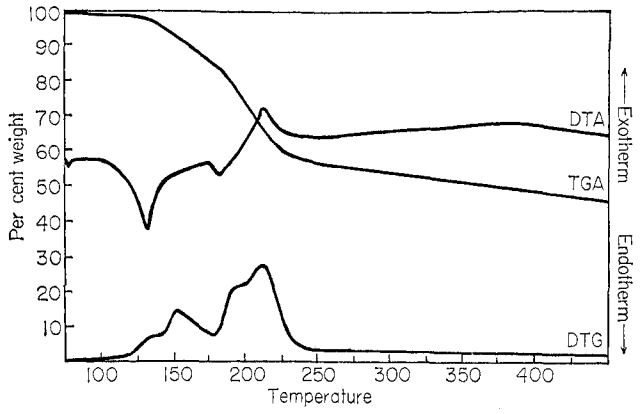

Figure 5.—Thermogram of $ZnCl_2$ treated phenyl β-D-xylopyranoside.

TABLE V
ANALYSIS OF MIXTURE FORMED ON MELTING TREATED PHENYL β-D-XYLOSIDES

β-D-Xylopyranoside		Products after heating[a]		
Aglycone	Temp, °C	Free phenol, %	Remaining[b] glycoside, %	D-Xylose on hydrolysis, %
p-Methoxyphenyl	175	87	2.0	91.0
Phenyl	150	100	0.0	91
p-Phenylphenyl	172	95	3.0	88
p-Nitrophenyl	145	85	3.0	58

[a] Yields are given in per cent of theoretical amounts. [b] This value represents the total of both α-D and β-D anomers.

acid hydrolysis gave high yields of D-xylose. It is interesting to note that cleavage of the β-D-xylopyranosides was also accompanied by the formation of small amounts of the corresponding α-D-xylopyranoside.

Since cleavage takes place at a relatively low temperature, the phenolic aglycone remains in solution until evaporation at a higher temperature. As seen in Figure 5 for β-D-xylopyranosides, this gives rise to the initial weight loss on tga and a peak on the dtg at 155°. On further heating the glycosyl moiety, which is stabilized by condensation, decomposes with a gradual weight loss that leaves a charred residue of about 45% at 400°. The decomposition is also signalled by a dta exotherm and a dtg peak at ~210°.

The nature of the $ZnCl_2$-catalyzed polymerization and decomposition products will be discussed in a forthcoming publication. However, it should be noted here that condensation of the glycosyl moiety at lower temperatures as shown for both untreated D-xylose and the $ZnCl_2$-treated D-xylopyranosides results in the formation of relatively heat-resistant products that are charred at elevated temperatures, whereas the cleavage of untreated D-xylopyranosides at higher temperatures results in a rapid decomposition and evaporation of the carbohydrate moiety. This is of technical interest in flame proofing of wood and cellulosic materials which contain substantial amounts of xylan. In such compounds decomposition of the D-xylose units in xylan yields combustible volatile products which propagate the fire.[8,9] Catalytically induced cleavage of the glycosidic bonds at lower temperatures should result in charring and suppress the evolution of flammable volatile degradation products.

Cleavage of the Glycosidic Group.—Both ionic and free-radical mechanisms have been suggested for the

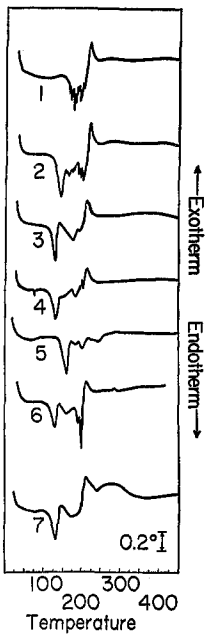

Figure 6.—Dta signals of the following xylosides treated with $ZnCl_2$: 1, methyl α-D-xylopyranoside; 2, methyl β-D-xylopyranoside; 3, *p*-methoxyphenyl β-D-xylopyranoside; 4, phenyl β-D-xylopyranoside; 5, *p*-phenylphenyl β-D-xylopyranoside; 6, *p*-chlorophenyl β-D-xylopyranoside; 7, *p*-nitrophenyl β-D-xylopyranoside.

pyrolysis of the sugar units in cellulosic materials.[8] The above data show that the first step in the pyrolysis of β-D-xylopyranosides, with or without the addition of $ZnCl_2$, involves cleavage of the glycosidic group. The fact that the reaction is strongly catalyzed by addition of a Lewis acid and yet gives the same general products indicates that it proceeds through a heterolytic mechanism. The almost quantitative recovery of the phenolic aglycones as free phenols also supports this contention because homolytic cleavage of the phenolic glycosides is expected to provide a variety of products derived from condensation of aryloxy free radicals.[16] Further information on mechanism of thermal cleavage of the xylopyranosides was gained through esr spectroscopy and isothermal kinetic studies.

On several occasions esr spectroscopy has been used to follow the formation of free radicals in irradiated cellulose[17] and D-glucopyranosides[18] and to determine the kinetics of the pyrolysis[19] of these materials. In this study it was found that the pyrolysis is accompanied by the formation of free radicals. A typical esr signal obtained from phenyl β-D-xylopyranoside is shown in Figure 7. Although the observed simple, single spectrum could be reconciled with the formation of a glycosyl free radical,[18] the rate of formation of the free radicals listed in Table VI showed that they are not derived from homolytic cleavage of the β-D-xylopyranosides. As seen in Table VI, the relative rates of formation of the free radicals are more consistant with the electron density of the glycosidic oxygen rather than the resonance system and stability of the expected phenolic free radicals. It is therefore assumed that the

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(19) J. C. Arthur, Jr., and O. Hinojosa, *Text. Res. J.*, **36**, 385 (1966).

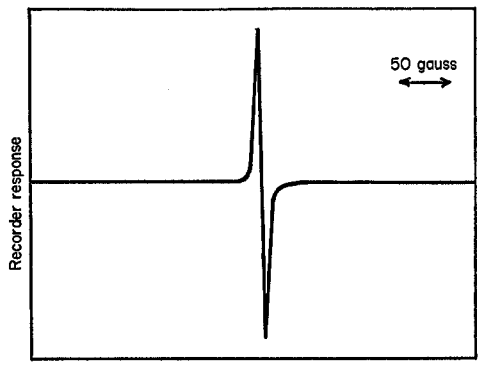

Figure 7.—The esr signal of phenyl β-D-xylopyranoside heated at 270°.

TABLE VI

RELATIVE ISOTHERMAL GROWTH RATES FOR FREE-RADICAL SIGNALS OF SUBSTITUTED PHENYL β-D-XYLOPYRANOSIDES

Aglycone	Relative rate at 270°
p-Methoxyphenyl	0.9
Phenyl	1.0
p-Phenylphenyl	1.3
p-Bromophenyl	1.8
p-Nitrophenyl	3.7

pyrolytic reactions involve initial heterolytic cleavage of the D-xylopyranosides, which on further degradation give free radicals. Figure 8 shows a set of closely similar data obtained for the rate of isothermal weight loss resulting from cleavage of the glycosidic bond and evaporation of the phenolic aglycone of several β-D-xylopyranosides.

It should be noted here that acid hydrolysis of glycosides has been shown to proceed through a mechanism involving initial protonation of the glycosidic oxygen, followed by heterolytic cleavage of the conjugated glycoside.[20] The net substituent effect that has been observed for these compounds are highly complex and could be manifested in opposite directions.[21] Kinetic studies of a few phenyl β-D-xylopyranosides[22] and a large number of phenyl β-D-glucopyranosides[23] show a small substituent effect opposite to that observed for pyrolysis of the phenyl β-D-xylopyranosides. This is attributed to opposing effects of electron-withdrawing substituents on protonation and on heterolytic cleavage, which tend to almost cancel each other, leaving a residual net effect that indicates the higher sensitivity of the protonation equilibrium constant to the substituent effect. For the pyrolytic reaction, however, the substituents exert a more direct influence on the heterolytic cleavage of the β-D-xylopyranosides. A more exact interpretation of the results and closer analogy with acid hydrolysis is not possible because of the unknown role of the molten glycosides as the solvent.

Experimental Section

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Tlc was performed on silica gel 1B-F (Bakerflex) using methanol–ethyl acetate–ethylene chloride

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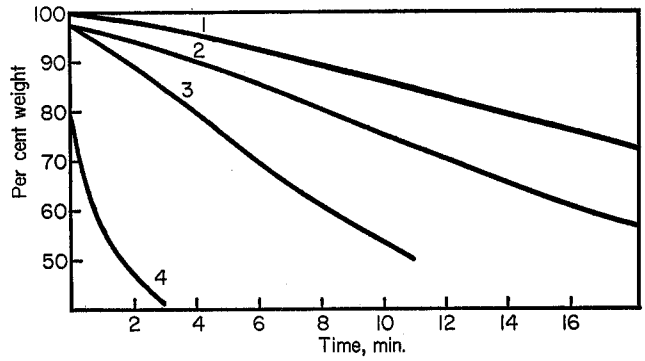

Figure 8.—The relative rates of isothermal weight loss at 250°: 1, *p*-phenylphenyl β-D-xylopyranoside (0.34); 2, *p*-methoxyphenyl β-D-xylopyranoside (0.53); 3, phenyl β-D-xylopyranoside (1.00); 4, *p*-nitrophenyl β-D-xylopyranoside (5.23).

(1:1:4) as eluting solvent. The spots were detected by spraying with 10% sulfuric acid in methanol. Glc was performed with a Varian Model 1800 instrument equipped with hydrogen flame detectors. The column used to separate the carbohydrate compounds after silylation was a 6 ft × 0.25 in. aluminum tubing packed with Varaport 30 as the support and 3% SE-30 as the stationary phase. Phenols were analyzed with a column containing 10% Carbowax 20M supported on Fluropak 80. Quantitative data were obtained by using a Varian Model 475–470 digital integrator calibrated with standard samples.

Sample Preparation.—Commercial D-xylose was recrystallized three times from ethyl alcohol, mp 149–151° (lit.[24] gives melting points ranging from 141 to 154°). Methyl α- and β-D-xylopyranosides were prepared following the method of Hudson.[25] The β-D form was isolated by crystallization from the reaction mixture and purified by recrystallization from 1-butanol, mp 156–157° (lit.[25] mp 156–157°). The α-D form was isolated from the reaction mixture by formation of the phenylboronate derivative. The compound was recrystallized three times from a mixture of ligroin and benzene mp 169–172° (lit.[26] mp 175–176°). Decomposition of the ester with 1,3-propanediol gave pure methyl α-D-xylopyranoside, mp 87–88° (lit.[27] mp 90–92°).

The substituted phenyl β-D-xylopyranosides listed in Table III were prepared by the method originally developed by Helferich[28] and modified by De Bruyne and Van Wijnendaele.[29]

The free sugar and the glycosides were ground to a fine powder prior to the thermal analysis. Treated samples were prepared by dissolving 50 mg of the above compounds in 5 ml of methanol containing 1.11 mg of $ZnCl_2$/ml and removing the solvent under vacuum at room temperature to produce a solid residue.

Thermal Analysis.—The dta data were obtained with a Du Pont Model 900 thermal analyzer equipped with a calorimeter cell accessory. All experiments were carried out using 2-mg samples in covered 6-mm aluminum pans with an empty pan as the reference. The cover was used to reduce vaporization of starting material and ensure temperature uniformity throughout the sample. Samples were heated at a programmed rate of 15°/min in a 70 ml/min flow of nitrogen. Under these conditions the recorded fusion temperatures of benzoic acid and lead standards were within 2° of the literature values.

For tga a Cahn RG electrobalance was used, and programmed heating of samples was carried out with a Research Incorporated Thermac 6000 temperature controller coupled with an elliptical radiant heater. Temperature was measured with a chromel–alumel thermocouple positioned 1 mm below the sample. The sample size, configuration, atmosphere, and heating rate was the same as in dta so that the two methods would be comparable. The derivative of the tga signal (dtg) was taken with a Cahn time derivative computer (Mark II). The isothermal kinetic data were obtained from the dtg curves with the tga held at

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250 ± 0.5°. The results obtained are summarized in Figures 1–6 and 8 and Table III.

Thermal Anomerization of α-D-Xylopyranose.—Samples (3 mg) of the sugar were placed in small aluminum pans. The pans were sealed and heated isothermally for 12.5 min, at several temperatures ranging from 127 to 200°, in a Fisher-Johns melting point apparatus. The heated samples were silylated and analyzed for the α- and β-D-xylopyranose forms by glc.[30] Each experiment was repeated four times to determine the reproducibility of the data. The results obtained are given in Table I.

Condensation of D-Xylose.—Samples of free sugar (3 mg) were heated in the tga instrument at 200° to several levels of weight loss. The heated samples were analyzed by glc and tlc methods before and after hydrolysis with 1 *N* HCl at 100° following the method described by Laver and associates.[31] The glc results are given in Table II.

A heated sample of D-xylose (weight loss 9.5%) had C, 42.67; H, 6.36 [$C_5(H_2O)_{4.5}$ requires C, 42.55; H, 6.38].

Cleavage of Phenyl β-D-Xylopyranosides.—Samples of phenyl β-D-xylopyranoside were heated at 250° and analyzed as in the previous experiment. This gave the amounts of glycoside remaining intact and the lost aglycone. The loss of the carbohydrate moiety was calculated by difference from the total weight loss recorded by tga. The results are shown in Table IV.

For the $ZnCl_2$-treated phenyl β-D-xylopyranosides, the samples were heated under flowing nitrogen in a small test tube, at temperatures just above their first endotherm and analyzed for the carbohydrates as before and for the free phenols by direct glc. The data obtained are given in Table V.

Esr Spectroscopy.—Samples of the glycosides (one part) were mixed with ground glass (nine parts) and ground together thoroughly to ensure uniform mixing. The ground samples (4–7 mg) were accurately weighted into a 2-mm capillary tube. The tube was placed into the cavity of a Varian E-3 esr spectrometer equipped with a specially designed variable temperature accessory, which was previously heated to 270 ± 0.5°. Temperature was controlled by means of a Research Incorporated Thermac series 6000 temperature controller employing a copper–constantan thermocouple feedback.

The intensity of the esr signal was plotted against time. The relative rates were measured at the inflection points of the resulting sigmoid curves, which correspond to the maximum rate of increase in signal amplitude. The resulting data are presented in Figure 7 and Table VI.

Registry No.—α-D-Xylopyranose, 6763-34-4; methyl β-D-xylopyranoside, 612-05-5; *p*-methoxyphenyl β-D-xylopyranoside, 13299-09-7; phenyl β-D-xylopyranoside, 4756-31-4; *p*-phenylphenyl β-D-xylopyranoside, 13299-14-4; *p*-chlorophenyl β-D-xylopyranoside, 3325-47-1; *p*-nitrophenyl β-D-xylopyranoside, 2001-96-9.

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Potential Folic Acid Antagonists. VI. The Syntheses of 1- and 3-Deazamethotrexate[1,2]

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The reaction of ethyl 6-amino-4-chloro-5-nitro-2-pyridinecarbamate (**4a**) and ethyl 4-amino-6-chloro-5-nitro-2-pyridinecarbamate (**4b**), respectively, with the oxime of methyl *p*-[(3-aminoacetonyl)methylamino]benzoate gave the corresponding 4- and 6-(acetonylamino)pyridine oximes **6a** and **6b**. Reductive cyclization of these compounds with Raney nickel gave the 1,2-dihydropyrido[3,4-*b*]pyrazine (**9a**) and 3,4-dihydropyrido[2,3-*b*]-pyrazine (**9b**) ring systems. Oxidation of **9a** and **9b** with $KMnO_4$ in acetone and DMAC gave the heteroaromatic compounds **10a** and **10b**, which were hydrolyzed with ethanolic KOH to give *p*-[[(5,7-diaminopyrido-[3,4-*b*]pyrazin-3-yl)methyl]methylamino]benzoic acid (**13a**) and *p*-[[(6,8-diaminopyrido[2,3-*b*]pyrazin-2-yl)-methyl]methylamino]benzoic acid (**13b**). The amino groups of **13a** and **13b** were acetylated with Ac_2O to give **14a** and **14b**, which were coupled with diethyl L-glutamate to give **11a** and **11b**. Treatment of **11a** and **11b** with aqueous NaOH hydrolyzed both the ester and acetyl groups to give 1-deazamethotrexate {*N*-[*p*-[[(5,7-diaminopyrido[3,4-*b*]pyrazin-3-yl)methyl]methyloamino]benzoyl]-L-glutamic acid} (**12a**) and 3-deazamethotrexate {*N*-[*p*-[[(6,8-diaminopyrido[2,3-*b*]pyrazin-2-yl)methyl]methylamino]benzoyl]-L-glutamic acid} (**12b**).

Previously, we reported unambiguous methods for the preparation of 6-substituted 2,4-diamino-1- and -3-deazapteridines[3] and, recently, the synthesis of 2,4-diaminopteridines by a method involving the construction of the pyrazine ring containing the *p*-(methyleneamino)benzoyl moiety of folic acid and its antagonists, aminopterin and methotrexate (**12**, X = Y = N).[4] We now wish to report the preparation of both 1- and 3-deazamethotrexate by these methods.

Initially, studies were directed toward the preparation of 1-deazaaminopterin. Ethyl *p*-[(3-aminoacetonyl)amino]benzoate oxime[4] was alkylated with **4a**[5] to give the nitropyridine **1**, which was hydrolyzed in HCl to give the corresponding ketone **2**. The nitro group of **2** was hydrogenated in the presence of Raney nickel and the resulting 5-aminopyridine cyclized *in situ* to give the dihydro-1-deazapteridine **3**. Careful oxidation of **3** with a dilute solution of $KMnO_4$ in acetone and DMAC gave the heteroaromatic 1-deazapteridine **5**. However, hydrolysis of the ester and urethane groups of **5** with KOH in refluxing EtOH under N_2 resulted in extensive decomposition, and no further work was carried out on this compound.

The instability of **5** was attributed to the lability of the CH_2–NH bond under basic conditions.[4,6] The

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