Routes of Conversion of D-Xylose, Hexuronic Acids, and L-Ascorbic Acid to 2-Furaldehyde[1]

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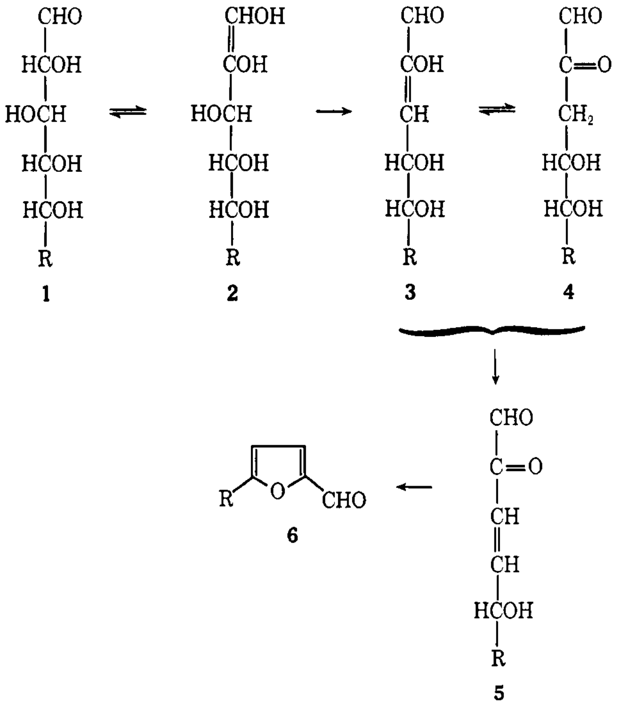
Investigations into the mechanism by which a number of carbohydrates are converted to 2-furaldehyde were undertaken by performing the conversions in acidified, tritiated water followed by a determination of the carbon-bound tritium incorporated into the product. The 2-furaldehyde derived from D-xylose contained essentially no carbon-bound tritium while that obtained from L-ascorbic acid and the related 2-oxo-D-*arabino*-hexonic acid had about 60% the radiochemical activity of the solvent. In the latter two cases, further degradation studies showed that nearly all of the activity was situated at the aldehyde carbon atom of the 2-furaldehyde. The 2-furaldehyde derived from L-sorburonic acid contained 17% the activity of the solvent and that from D-glucuronic acid 19%. In both cases none of the activity is located at the aldehyde carbon atom, and further degradation of the D-glucuronic acid derived 2-furaldehyde showed that the activity resides at either position 3 or 4 or a combination of both positions on the furan ring. The data are discussed in terms of mechanisms which are now in print. 2-Amino-2-deoxy-D-glucose was also investigated as a potential source of 2-furaldehyde but, in both cases, none was produced in detectable amounts.

The acid-catalyzed production of 2-furaldehyde from pentoses, hexuronic acids, and ascorbic acid and of 5-(hydroxymethyl)-2-furaldehyde from hexoses represent well-known dehydration reactions in the field of carbohydrate chemistry. The mechanism of carbohydrate dehydration reactions has been the subject of a number of studies in recent years, and it has been concluded[2] that for hexoses (R = CH_2OH, Chart I) and pentoses (R = H, Chart I) the pathway involves an initial conversion of the aldose **1** or related 2-ketose to the 1,2-enediol **2** in a reversible reaction followed by a dehydration of **2** to the enolic form **3** of a 3-deoxyglycosulose **4** which further dehydrates to **5** and thence to the 2-furaldehyde **6**. Evidence for such a mechanism rests on the isolation of **4** and **5** (R = CH_2OH) from D-fructose after treatment with acid[3] and further studies of these compounds. Kinetic studies indicate[4] that **4** is not a necessary intermediate in the dehydration reaction, but as much as 40% of the reaction involves this intermediate with the remaining 60% proceeding directly *via* **3**. Recent studies[5] involving deuterium exchange experiments are not consistent with this conclusion, however, and indicate a pathway involving only **1**, **2**, **3**, **5**, and **6**.

CHART I



It is noteworthy that an analog of **4**[6,7] has been suggested as an intermediate in the decarboxylation of hexuronic acids during which 2-furaldehyde is produced, and 3-deoxy-D-pentosulose[8] (**3**, R = H) has been reported produced during the acid-catalyzed degradation of ascorbic acid, which also produces carbon dioxide and 2-furaldehyde.

Thus, for a number of dehydration reactions involving a variety of reactants, structurally similar reaction intermediates have been proposed.

The purpose of the present study was to evaluate a number of carbohydrates as potential sources of 2-furaldehyde and to determine the importance of the reversible equilibration between compounds having the general structures **1** and **2**, and the importance 3-deoxyglycosuloses (**4**) as reaction intermediates during such dehydration reactions. The compounds investigated were D-xylose (**7**), D-glucuronic acid (**8**), L-sorburonic acid (**9**), L-ascorbic acid (**10**), 2-oxo-D-*arabino*-hexonic acid (**11**), and 2-amino-2-deoxy-D-glucose (**12**). Compounds **7** through **11** were readily converted to 2-furaldehyde in yields in excess of 20% on treatment with aqueous acid.

Zimmerman and Cosmatos[9] have reported that 2-furaldehyde is the product of dehydration of **12** when the reaction is performed at a pH near neutrality in a sodium borate solution and that the 2-furaldehyde so produced can be distilled from the solution. Spectrophotometric measurements of distillates of such a reaction, which was repeated under these conditions, did not verify this and indicated that only small amounts of volatile ultraviolet-absorbing materials are produced.

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[1] Journal Paper No. 6210 of the University of Missouri Agricultural Experiment Station.

[2] E. F. L. J. Anet, *Advan. Carbohyd. Chem.*, **19**, 181 (1964).

[3] E. F. L. J. Anet, *Chem. Ind. (London)*, 262 (1962).

[4] E. F. L. J. Anet, *Aust. J. Chem.*, **18**, 240 (1965).

[5] (a) M. S. Feather and J. F. Harris, *Tetrahedron Lett.*, 5807 (1968). (b) M. S. Feather and J. F. Harris, *Carbohyd. Res.*, **15**, 304 (1970).

[6] D. M. W. Anderson and S. Garbutt, *J. Chem. Soc.*, 3204 (1963).

[7] E. Stutz and H. Deuel, *Helv. Chim. Acta*, **41**, 1722 (1958).

[8] T. Kurata and Y. Sakurai, *Agr. Biol. Chem.*, (*Tokyo*), **31**, 170 (1967).

[9] H. K. Zimmerman and A. Cosmatos, *Z. Physiol. Chem.*, **326**, 73 (1961).

Assuming that all the ultraviolet-absorbing material was 2-furaldehyde, the maximum yield was less than 0.24% under these conditions.

The importance of the suggested reaction intermediates was examined by converting the compounds to 2-furaldehyde in acidified, tritiated water followed by a determination of the distribution of carbon-bound tritium in the product. For **7**, **8**, and **9** an equilibration between the reactant and 1,2-enediol would be expected to involve aldose, ketose, and enediol and would involve the acquisition of carbon-bound tritium at C-1 which ultimately would reside on the α carbon atom of 2-furaldehyde. The participation of **4** (or an analog thereof) in the reaction would involve tritium incorporation at C-3, which would ultimately reside at position 3 of the furan ring.

In the case of ascorbic acid (**10**) and the related 2-oxo-D-*arabino*-hexonic acid (**11**) it is presumed[8] that C-1 is lost as carbon dioxide during the conversion and that C-2 corresponds to the α carbon atom of 2-furaldehyde. Thus, for these cases, an incorporation at the α carbon of 2-furaldehyde represents an evaluation of the extent of reversible 2,3 enolization of the starting material with its 3-keto form, and an incorporation at position 3 of the furan ring represents an evaluation of the importance of 3-deoxypentosulose as a reaction intermediate.

The tritium content and distribution (Table I) was determined by isolating and counting 2-furaldehyde as its phenylhydrazone, a procedure which allowed the determination of the total amount of isotope incorporated, followed by a similar determination of 2-furoic acid, which allowed a determination of the combined activity at position 3, 4, and 5 of the furan ring.

TABLE I

SPECIFIC ACTIVITIES OF 2-FURALDEHYDE DERIVATIVES PREPARED FROM SUGARS IN ACIDIFIED, TRITIATED WATER

	2-Furaldehyde phenylhydrazone		2-Furoic acid	
Sugar	Specific activity, μCi/mmol	Activity of solvent, %	Specific activity, μCi/mmol	Activity of solvent, %
D-Xylose	0.03[a]	4.3	0.009[b]	0.5
D-Glucuronic Acid	0.14[a]	19.4	0.34[b]	18.9
L-Sorburonic Acid	0.30[b]	16.7	0.25[b]	13.9
L-Ascorbic Acid	0.42[a]	58.3	0.056[b]	3.1
2-Oxo-D-*arabino*-hexonic acid	0.41[a]	56.9	0.067[b]	3.7

[a] Prepared in tritiated water having a specific activity of 0.72 μCi/mmol. [b] Prepared in tritiated water having a specific activity of 1.80 μCi/mmol.

The possibility of solvent and primary isotope effects must be considered when the collected data are used to interpret mechanisms. For isotope exchange experiments, such effects will affect the validity of a direct comparison of reactions in water with similar ones in tritiated water. Thus, the extent of equilibration of starting material or intermediates might be substantial in water and less so as evidenced by tritium incorporation. The results as obtained, however, are consistent with a direct conversion of D-xylose to 2-furaldehyde involving only **1**, **2**, **3**, and **5** (R = H) and, in this respect, the data is identical with that obtained for the conversion of D-glucose and D-fructose to 5-(hydroxymethyl)-2-furaldehyde in deuterium oxide solution.[5]

The 2-furaldehyde derived from the hexuronic acids (compounds **8** and **9**) is interesting in that only negligible amounts of the tritium incorporated during the reaction is located at the α carbon atom (Table I). A further conversion of the 2-furoic acid obtained from D-glucuronic acid to methyl 5-nitro-2-furoate with retention of all the radiochemical activity indicates that the isotope is located at position 3 or 4, or both positions. It thus appears possible, at least in a portion of the reaction pathway, that analogs of **4** could participate in the reaction. It is interesting to note that existing mechanism proposals predict, aside from proton exchange[6] at C-3 (corresponding to position 3 of the furan ring), that exchange would occur at C-5 (corresponding to position 5 of the furon ring)[8] and no exchange would necessarily occur during the reaction.[10]

In an earlier report[11] on the conversion of D-glucuronic acid to 2-furaldehyde, we reported that the conversion in tritiated water (0.49 μCi/mmol) resulted in only an 8% incorporation of tritium relative to the solvent and the conversion in deuterium oxide resulted in no measurable incorporation on the furan ring, as evidenced by nmr measurements. While the absence of deuterium relative to tritium incorporation can be explained on the basis of isotope effects, we cannot, at present, explain the discrepancy between the radiochemical measurements except to point out that the measurements made herein used much higher activity water and hence would constitute a more accurate measurement.

Kurata and Sakurai[8] in a recent investigation of ascorbic acid decarboxylation considered two possible mechanisms, one which involved a dehydration sequence followed by decarboxylation and 2-furaldehyde formation, and another which involved a rearrangement to the 3-keto form followed by a β-keto acid decarboxylation to give a pentose 1,2-enediol which is then converted to 2-furaldehyde. These investigators preferred the former mechanism, which predicts solvent proton exchange at C-4 of the ascorbic acid (corresponding to position 3 of the furan ring). In the case of the 2-furaldehyde derived from **10** and **11**, the labeling distribution is consistent only with the latter pathway, however. It is interesting to note that the predicted product of L-ascorbic acid decarboxylation is the pentose 1,2-enediol, which would be expected to dehydrate with no further isotope exchange. Such a mechanism explains the reported isolation of pentosuloses (**4**, R = H) during ascorbic acid dehydration since, although the reaction apparently proceeds *via* **3** (R = H), this compound would be isolated as its more stable keto form **4** (R = H). It is also noteworthy that the results relative to the L-ascorbic acid reaction are entirely consistent with the Isbell mechanisms[10,12] which also predict isotope exchange corresponding to acquisition at the α carbon atom of the 2-furaldehyde.

Experimental Section

Materials and Methods.—Radiochemical determinations were performed in Brays solution using a tritiated toluene internal standard. At least 10,000 total counts were obtained for each sample. Thin layer chromatography was performed using silica

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(10) H. S. Isbell, *J. Res. Nat. Bur. Stand.*, **33**, 45 (1944).

(11) M. S. Feather, *Tetrahedron Lett.*, 4143 (1970).

(12) H. S. Isbell, *Ann. Rev. Biochem.*, **12**, 205 (1943).

gel HF supports with benzene–methanol (99:1) as an irrigant for phenylhydrazones and chloroform–acetic acid (9:1) for furoic acid samples. Spots were visualized by uv light or by spraying with 10% ethanolic sulfuric acid followed by heating at 110° for 10 min.

Carbohydrates were commercially obtainable samples, with the exception of L-sorburonic acid, which was obtained from Northern Regional Research Laboratories, Peoria, Ill., as a gift.

Ultraviolet spectra were obtained on a recording Coleman Model 124 double beam grating spectrometer.

Preparation of 2-Furaldehyde.—Essentially the same procedure was followed for the preparation of 2-furaldehyde for all sugars tested. In a typical experiment 2.0 g of carbohydrate was placed in a 1-l. round-bottom flask containing 500 ml of 6 *N* sulfuric acid. The solution was brought to boiling, an operation which required about 30 min, and 250 ml of distillate was then collected over a 3-hr period. The 2-furaldehyde contained by the distillate was readily identified by its ultraviolet spectrum, which showed maxima at 227 and 278 mμ[13] and which was identical with the spectrum of an authentic sample. Yields of 2-furaldehyde in the distillate were estimated by a spectrophotometric measurement at 278 mμ based on a molar absorptivity of 2-furaldehyde of 18,000. The 2-furaldehyde was further identified by conversion to the phenylhydrazone and to 2-furoic acid in radiochemical experiments described below.

Reaction of 2-Amino-2-deoxy-D-glucose (12) in Borate Buffer.—The procedure of Zimmerman and Cosmatos[9] was repeated in this experiment. **12** (2.15 g), boric acid (9.27 g), and sodium hydroxide (6.0 g) were dissolved in 1 l. of water and held at 25° for 30 hr. The solution was then adjusted to pH 7 with concentrated hydrochloric acid and distilled as described above. The distillate contained a small amount of uv-absorbing material which showed maxima at 235 and 265 mμ. Assuming that all the absorbance at 265 mμ was due to 2-furaldehyde the total yield was 0.24%.

Preparation of 2-Furaldehyde-^{3}H Phenylhydrazone.—In a typical experiment, 2-furaldehyde was obtained from 3.0 g of D-xylose by distillation as described above with the exception that the solution contained 20 mCi of tritiated water. An equimolar amount of phenylhydrazine hydrochloride in 20 ml of water was added and the resulting precipitate was collected on a filter. This material was recrystallized from ethanol–water (1:1) to constant radiochemical activity. The 2-furaldehyde phenylhydrazone had mp 94° (lit.[14] mp 97°) and had a thin layer chromatographic flow rate identical with that of an authentic sample. Identical procedures were used in subsequent experiments using compound **8**, **9**, **10**, and **11**.

Preparation of 2-Furoic Acid-^{3}H.—A solution of 2-furaldehyde-^{3}H was obtained from D-xylose in tritiated water as described above. To the distillate was added 2.0 g of freshly prepared silver oxide and the pH was adjusted to 10 with sodium hydroxide solution. The suspension was stirred for 30 min with aeration and filtered, and the filtrate was passed through a column of Dowex 50 (hydrogen form). The eluate was evaporated to dryness and alternately sublimed at 110° (0.3 mm) and reevaporated from water until constant radiochemical activity was reached. The final product had mp 131° (lit.[15] mp 133°) and had a chromatographic mobility identical with that of an authentic specimen. Identical results were obtained using compounds **8**, **9**, **10**, and **11** as starting materials.

Preparation of Methyl 5-Nitro-2-furoate-^{3}H from 2-Furoic Acid-^{3}H.—A sample (12 mg) of 2-furoic acid-^{3}H derived from D-glucuronic acid as described above was diluted with inert material and recrystallized to give a sample having a specific activity of 0.357 μCi/mmol. This sample (936.8 mg) was esterified with diazomethane and the resulting ester was converted to methyl 5-nitro-2-furoate as described by Freure and Johnson.[16]

This compound after two recrystallizations from methanol and one from hexane had mp 79.5° (lit.[16] mp 81.6°) and ran as a single spot on thin layer chromatograms.

Anal. Calcd for $C_6H_5O_5N$: N, 8.18. Found: N, 7.90.

The specific activity of this derivative was 0.353 uCi/mmol and was not changed on further purification.

Registry No.—**7**, 58-86-6; **8**, 6556-12-3; **9**, 488-34-6; **10**, 50-81-7; **11**, 669-90-9; **12**, 3416-24-8; 2-furaldehyde, 98-01-1.

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[13] A. P. Dunlop and F. Peters, "The Furans," Wiley, New York, N. Y., 1953, p 13.

[14] Reference 13, p 364.

[15] Reference 13, p 489.

[16] B. T. Freure and J. R. Johnson, *J. Amer. Chem. Soc.*, **53**, 1142 (1931).

New Route to Branched-Chain Sugars. Photoamidation and Photohydroxyalkylation of 3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose

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The acetone-initiated photochemical addition of formamide to 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**1**) afforded trans 1:1 adducts, namely, 3-*C*-carbamoyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**), 3-carbamoyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**3**), and 3-deoxy-3-*C*-(1-hydroxy-1-methylethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**4**) in 16, 15, and 7% yields (after chromatography), respectively. Irradiation of **1** in the presence of isopropyl alcohol and acetone gave the hydroxyisopropyl 1:1 adduct **4** in 31% yield and, in addition, a novel 1:2 adduct **6** which is tentatively assigned the structure of 3-deoxy-3,4-*C*-bis(1-hydroxy-1-methylethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose in 8% yield. The proton magnetic resonance and high-resolution infrared spectra of these substances are described. Lithium aluminum hydride reduction of the carbamoyl sugar **3** afforded 3-*C*-aminomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose, isolated as its trifluoroacetamido derivative **7**.

In continuation of our studies on the chemistry of branched-chain sugars[1] we now wish to report a different approach to the synthesis of these novel sugars by photoaddition of formamide and of isopropyl alcohol to unsaturated carbohydrates.

Formamide has been shown to undergo acetone-initiated photochemical addition to terminal[2] and nonterminal olefins[3] to yield 1:1 carbamoyl adducts. In the case of norbornene the reaction has been found to be stereospecific, leading exclusively to the exo isomer. This reaction, termed photoamidation, has also been

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[1] (a) A. Rosenthal, *Advan. Carbohyd. Chem.*, **23**, 59 (1968); (b) A. Rosenthal and M. Sprinzl, *Carbohyd. Res.*, **16**, 337 (1971); (c) A. Rosenthal, K. S. Ong, and D. A. Baker, *ibid.*, **13**, 113 (1970); (d) A. Rosenthal and G. Schöllnhammer, *ibid.*, **15**, 421 (1970); (e) A. Rosenthal, and D. A. Baker, *Tetrahedron Lett.*, 397 (1969).

[2] (a) D. Elad and J. Rokach, *J. Org. Chem.*, **29**, 1855 (1964); (b) D. Elad and J. Rokach, *J. Chem. Soc.*, 800 (1965).

[3] D. Elad and J. Rokach, *J. Org. Chem.*, **30**, 3361 (1965).