was worked up by deionization with cation[12] and anion exchange[9] resins. In this way, from 0.88 g. of IV there was obtained 0.22 g. of sirupy degradation product. The 3-*C*-(hydroxymethyl)-L-*glycero*-tetrose N^2-benzyl-N^2-phenylhydrazone was prepared, m.p. 136–137°, $[\alpha]^{20}_{5460}$ +94° and $[\alpha]^{20}_{5790}$ +79.5° (*c* 1, pyridine). For the enantiomorph,[8a] the m.p. was reported[8b] as 137–138° and $[\alpha]^{20}_{5460}$ −94° and $[\alpha]^{25}_{5790}$ −78.5°.

Anal. Calcd. for $C_{19}H_{24}N_2O_5$: C, 65.4; H, 6.7. Found: C, 65.6; H, 6.7.

The benzylphenylhydrazone was treated with benzaldehyde, to give L-apiose, $[\alpha]^{20}D$ −5° (*c* 8, water). For naturally occurring, sirupy D-apiose[8a,b] the following values are given: $[\alpha]^{20}D$ +3.8°, $[\alpha]^{15}D$ +5.6° and, for a synthetic[8c] D-apiose, $[\alpha]^{25}D$ +6.4°.

Preparation of II from 1,2-*O*-Isopropylidene-D-glucofuranose.—A solution of 50 g. of sodium metaperiodate in 400 ml. of water was treated with 50 g. of 1,2-*O*-isopropylidene-D-glucofuranose, then freeze-dried, extracted with chloroform, and concentrated as previously described.[3c] The sirupy product was dissolved in 500 ml. of water. The solution was treated with 45 g. of a 37% formaldehyde solution (aqueous) and then, after cooling, with 450 ml. of 1 *N* sodium hydroxide solution. After 6 days at room temperature, the mixture was treated for isolation of II as described above. The weight of product was 29 g. and its m.p. was 97–99°.

Acknowledgments.—The author expresses his appreciation to R. A. Paulson and E. R. Deardorff for the microanalyses, to Dr. Emma J. McDonald for certain of the optical rotatory measurements, and to Dr. H. S. Isbell for his interest in this work.

WASHINGTON 25, D. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

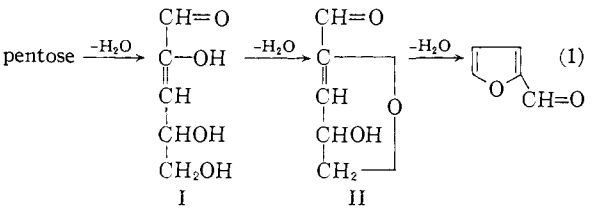
The Conversion of D-Xylose-1-C^{14} into 2-Furaldehyde-α-C^{14}

BY WILLIAM A. BONNER AND MAX R. ROTH[1]

RECEIVED MAY 1, 1959

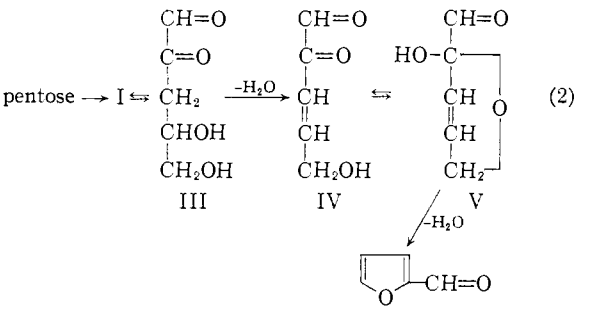
D-Xylose-1-C^{14} has been prepared and converted by acid into 2-furaldehyde-α-C^{14}. This product has been oxidized to 2-furoic-α-C^{14} acid, which was converted into 2-chloromercurifuran and $C^{14}O_2$. The latter furan derivative contained less than 2% of the radioactivity of its 2-furoic-α-C^{14} acid precursor, indicating that substantially all of Cl in the pentose starting material appeared as the aldehydic carbon in the 2-furaldehyde conversion product. These results accord with the predictions of speculative mechanisms for the pentose → 2-furaldehyde conversion, as well as with the results of a radiochemical investigation of the conversion of hexose to levulinic acid under similar acid conditions.

The world production of 2-furaldehyde (furfural) runs to the order of 100 million pounds per year,[2] ranking it about 67th[3] in annual volume among major organic chemicals. In view of this importance of 2-furaldehyde it is rather surprising that so relatively little has been established regarding the intimate mechanism of its production from pentoses and related substances under the usual acidic conditions. Arguing that the aldehyde group at C-1 in pentoses was essential to 2-furaldehyde production on the basis that *meso*-erythritol failed to yield furan under comparable conditions, Hurd and Isenhour, in 1932, proposed[4] the following mechanism for the pentose → 2-furaldehyde conversion.



(1)

Sixteen years later, on the basis of ultraviolet absorption spectra studies on solutions of D-glucose under acidic conditions, Wolfrom and co-workers arrived at an alternative explanation for the conversion of D-glucose to 4-hydroxymethyl-2-furaldehyde,[5] an explanation which was extended on the basis of similar evidence to the pentose → 2-furaldehyde conversion in 1949.[6] Wolfrom's mechanism for the latter conversion is illustrated in (2).



(2)

Similar intermediates have been postulated by Isbell[7] to explain the conversion of 2,3,4-tri-*O*-methylpentoses into 2-furaldehyde, as well as other related transformations.

While mechanisms 1 and 2 are plausible ones, they remain unsupported by way of isolation of any of the postulated intermediates as such, although Wolfrom and coworkers do report the isolation of the phenylosazone of the analog of IV formed during the related hydrochloric acid-catalyzed conversion of 2,3,4,6-tetra-*O*-methyl-D-glucose-en-1,2 into 5-(methoxymethyl)-2-furaldehyde.[8]

According to both mechanisms 1 and 2 the aldehydic carbon at C-1 in pentose does not change its oxidation state during the transformation to 2-furaldehyde and appears unaltered as the free alde-

(1) Quaker Oats Co. Post-doctoral Fellow, 1956–1958. The authors are indebted to the Quaker Oats Co. for its generous support of their research.

(2) H. R. Duffey and P. A. Well, Jr., *Ind. Eng. Chem.*, **47**, 1408 (1955).

(3) "Chemical Economics Handbook," Stanford Research Institute, Vol. VI, 600.10a, Sept., 1955.

(4) C. D. Hurd and L. L. Isenhour, THIS JOURNAL, **54**, 317 (1932).

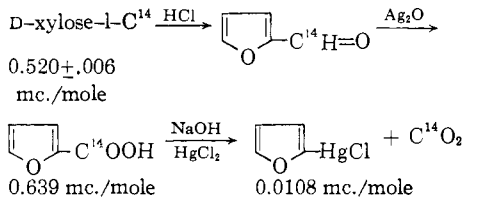
(5) M. L. Wolfrom, R. D. Schuetz and L. F. Cavalieri, *ibid.*, **70**, 514 (1948).

(6) M. L. Wolfrom, R. D. Schuetz and L. F. Cavalieri, *ibid.*, **71**, 3518 (1949).

(7) H. S. Isbell, *J. Research Natl. Bur. Standards*, **32**, 45 (1944); *cf.* also A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p. 289 ff.

(8) M. L. Wolfrom, E. G. Wallace and E. A. Metcalf, THIS JOURNAL, **64**, 265 (1942).

hyde group in the latter product. We have undertaken to test the validity of this prediction by conversion of D-xylose-1-C^{14} into 2-furaldehyde-C^{14}, followed by oxidation of the latter to 2-furoic-C^{14} acid and decarboxylation of this product to a furan derivative. The results of these experiments are summarized in (3).



(3)

The radiochemical data in (3), showing that less than 2% of the radioactivity of the furoic-α-C^{14} acid product was present in the furan nucleus, are in accord with both mechanisms 1 and 2 and indicate that for practical purposes all of the carbon atoms at C-1 in pentoses end up as the aldehydic carbon of 2-furaldehyde during this conversion. These observations confirm and extend those of Sowden in the hexose series, who found that D-glucose-1-C^{14} underwent clean conversion to formic-C^{14} acid and non-radioactive levulinic acid under similar acidic reaction conditions.[9]

Experimental

Tetra-O-acetyl-D-xylononitrile.—To a solution of sodium hydroxide (4 g.) dissolved in a minimum of water and diluted to 100 ml. with absolute ethanol was added a solution of hydroxylammonium chloride (6.9 g.) in a minimum of hot water. Sodium chloride was filtered from the chilled mixture, and the filtrate was treated with D-xylose (15 g.) while warming and stirring. After solution was complete the mixture was allowed to stand at 25° overnight, then evaporated *in vacuo* in a rotary evaporator at room temperature, producing 18 g. of oily D-xylose oxime which was used without purification. The crude oxime was mixed with acetic anhydride (100 ml.) and freshly fused sodium acetate (6 g.). After initial cautious heating an exothermic reaction commenced, whereupon external cooling was applied so as to maintain gentle refluxing. After the exothermic reaction was complete the mixture was refluxed for three minutes, then was poured slowly into ice-water (750 ml.). The tan crystalline precipitate was recrystallized twice from ethanol (Norit) to yield 14.5 g. of product having m.p. 80°. Deulofeu reports m.p. 82° for this substance.[10]

D-Threose was prepared by the general procedure of Hockett[11] employing the above nitrile. A mixture of the latter (14.5 g.) and ammonium hydroxide (100 ml.) was heated gently in an air stream until concentrated to a sirup. Additional ammonium hydroxide (50 ml.) was added and the process was repeated. The sirupy residue was dissolved in ethanol (50 ml.) and clarified with Norit. The D-threose-diacetamide which formed on concentration was recrystallized twice from ethanol, m.p. 163–167°. Hockett reports m.p. 165–167° for this substance.[11] The purified material was hydrolyzed by heating for 60 minutes at 80° with 50 ml. 0.1 *N* sulfuric acid. The solution was neutralized with sodium bicarbonate and passed through a mixed bed of Amberlite IR100 and IR45B to remove anions and cations. The eluate was concentrated to 40 ml., then lyophilized to 1.2 g. of colorless oil which was used below without further treatment.

Lead D-Xylonate.—A solution of iodine (9.5 g.) in methanol (160 ml.) was stirred at 40° and treated with a solution of D-xylose (4 g.) in water (6 ml.) and methanol (50 ml.). To the stirred mixture a solution of potassium hydroxide (5.2 g.) in methanol (130 ml.) was added over a 15-minute period. After 15 minutes stirring an additional 4 g. of potassium hydroxide in 100 ml. of methanol was added over a 10-minute period, maintaining the temperature at 40°. After cooling to room temperature the crystalline potassium D-xylonate was filtered and air-dried, 4.2 g. The above procedure is an adaptation of that of Moore and Link.[12] The potassium salt was dissolved in water (20 ml.) and the solution was deionized by passage through a column of Amberlite IR100, rinsing the bed well with water. The eluate was neutralized with lead carbonate and evaporated to dryness *in vacuo*. The residue was dissolved in 5 ml. of distilled water and the solution was added slowly to 50 ml. of methanol under vigorous stirring. The lead D-xylonate so precipitated weighed 3.5 g. and was used as carrier in the synthesis below.

Lead D-Xylonate-1-C^{14}.—A solution of the above D-threose (743 mg.) and sodium bicarbonate (690 mg.) in water (40 ml.) was chilled to 0° and treated with 20 ml. of a cold aqueous solution containing sodium cyanide-C^{14} (158 mg., 0.5 mc.) and sodium hydroxide (130 mg.). After one day at 0° and 4 days at 25° the reaction mixture was heated at 80° in an air stream, maintaining the water volume, until the evolution of ammonia had ceased. The solution was diluted with water and passed through a cation exchange bed (Amberlite IR100), rinsing the column thoroughly. The eluate was neutralized with lead carbonate, concentrated to a 100-ml. volume *in vacuo* and filtered. The above lead D-xylonate carrier (700 mg.) was added and the solution was reduced to 5 ml. *in vacuo*, whereupon methanol was added dropwise until the solution was strongly turbid. After 24 hours the microcrystalline lead D-xylonate-1-C^{14} was filtered and the filtrate was evaporated to dryness. Additional non-radioactive lead D-xylonate (500 mg.) was added and recrystallization was accomplished as above. This procedure was repeated with two additional 500-mg. portions of carrier lead D-xylonate, whereupon the four crops of salt were combined and recrystallized once from a methanol–water mixture, giving 2.560 g. of lead D-xylonate-1-C^{14} employed below. The above is an adaptation of the procedure of Isbell, Frush and Holt.[13]

D-Xylose-1-C^{14}.[13,14]—The above-mentioned lead D-xylonate-1-C^{14} was dissolved in water and passed through a cation exchange column, rinsing well. The eluate volume was adjusted to 50 ml. and divided equally among five test-tubes. These were heated to 60° in an air stream, and the sirupy residue in each was wetted with methyl Cellosolve and placed in a vacuum desiccator, repeating the treatment with methyl Cellosolve occasionally. After five days no crystalline material was obtained on repeated scratching and the combined (1.5 g.) crude D-xylonolactone-1-C^{14} was dissolved in ice-water (60 ml.) and mixed with sodium hydrogen oxalate (10.7 g.) and 3% sodium amalgam (25.5 g.). The mixture was stirred in an ice-bath for 45 minutes, separated from the mercury and filtered, rinsing and discarding the oxalate. The filtrate was concentrated *in vacuo* to a 25-ml. volume, then neutralized (phenolphthalein) with sodium hydroxide and diluted with two volumes of methanol. The precipitate was collected and rinsed with methanol. The filtrate was concentrated and passed through a bed of mixed anion and cation exchange resins. The effluent was concentrated to dryness and treated with carrier D-xylose. The total residue was recrystallized from methanol, yielding 5.5 g. of D-xylose-1-C^{14} showing a specific radioactivity of 0.520 ± 0.006 mc./mole.

Conversion of D-Xylose-1-C^{14} to Furoic-α-C^{14} Acid.—The above D-xylose-1-C^{14} (500 mg.) was dissolved in 12% hydrochloric acid (500 ml.) and the solution was steam distilled at a very slow rate for about 7 hours. The distillate was neutralized with sodium bicarbonate, saturated with sodium chloride and extracted continuously with ether during an 18-hour period. The ether layer was dried and freed of solvent through a small fractionating column. The resulting crude 2-furaldehyde-α-C^{14}, prepared essentially by the procedure of Hughes and Acree,[15] was oxidized directly to 2-furoic-α-C^{14} acid by a modification of the procedure of Asinger.[16] The entire product was treated with silver oxide (1.0

(9) J. C. Sowden, THIS JOURNAL, **71**, 3568 (1949).

(10) V. Deulofeu, *J. Chem. Soc.*, 2459 (1929).

(11) R. C. Hockett, THIS JOURNAL, **57**, 2267 (1935).

(12) S. Moore and K. P. Link, *J. Biol. Chem.*, **133**, 293 (1940).

(13) H. S. Isbell, H. L. Frush and N. B. Holt, *J. Research Natl. Bur. Standards*, **53**, 325 (1954); *cf.* also H. S. Isbell and co-workers, *ibid.*, **48**, 163 (1952); **50**, 133 (1953); **51**, 307 (1953); **53**, 217 (1954).

(14) N. Sperber, H. E. Zaugg and W. W. Standstrom, THIS JOURNAL, **69**, 915 (1947).

(15) E. E. Hughes and S. F. Acree, *J. Research Natl. Bur. Standards*, **21**, 327 (1938); **23**, 293 (1939).

(16) F. Asinger, *Ber.*, **75**, 656 (1942); *cf.* also J. Mitchell, Jr., and D. M. Smith, *Anal. Chem.*, **22**, 746 (1950).

g.) suspended in 10% sodium hydroxide solution (4 ml.). The mixture was heated at 95° during a 7-hour period with occasional shaking, then cooled to 70° and treated with concd. nitric acid (6 ml.), stirred for an hour while cooling and finally extracted with ether. After drying and solvent removal, the crude furoic-α-C^{14} acid was purified to constant m.p. by repeated sublimation at 80–90° (1 mm.). The purified product weighed 112 mg. (30% based on xylose-1-C^{14}) and showed a specific radioactivity of 0.639 mc./mole. The radioactivity assay of the 2-furoic-α-C^{14} acid was thus about 23% higher than that of its D-xylose-1-C^{14} precursor, an observation for which we have no definitive explanation. It is well known[4] that hydrochloric acid converts 2-furaldehyde into amorphous, polymeric "humins" under the conditions of the xylose-2-furaldehyde transformation. If the conversion of our 2-furaldehyde-α-C^{14} partially into humic materials were accompanied by a large kinetic isotope effect, favoring the C^{12}-species, the unconverted 2-furaldehyde-α-C^{14} and its resulting 2-furoic-α-C^{14} acid would be expected to show a higher specific radioactivity than their D-xylose-1-C^{14} precursor. The present 23% discrepancy in the radioactivity assays in question, however, seems rather large to be explained only as an isotope effect.

Decarboxylation of 2-Furoic-α-C^{14} Acid.—The above 2 furoic-α-C^{14} acid (13.65 mg.) was neutralized with 0.1 *N* sodium hydroxide (4.88 mg. of NaOH) and the solution was treated with mercuric chloride (33.09 mg.) after the procedure of Gilman and Wright.[17] The mixture was placed in the customary combustion apparatus for carbon-14 assay[18] and heated under gentle reflux while sweeping the apparatus with helium. After several minutes the reaction mixture was cooled, whereupon the 2-chloromercuri derivative of furan crystallized.[17] This was collected, recrystallized twice from ethanol, dried and assayed for radioactivity. The specific radioactivity proved to be 0.0108 mc./mole, or approximately 1.7% that of the 2-furoic-α-C^{14} acid precursor.

Radioactivity assays were conducted by wet combustion of the above labeled samples to carbon dioxide[19] followed by counting[20] the latter in an ionization chamber with the aid of a Cary model 31 vibrating reed electrometer.

(17) H. Gilman and G. F. Wright, THIS JOURNAL, **55**, 3302 (1933).
(18) J. G. Burr, *Anal. Chem.*, **26**, 1395 (1954).
(19) O. K. Neville, THIS JOURNAL, **70**, 3501 (1948).
(20) V. A. Raaen and G. A. Ropp, *Anal. Chem.*, **25**, 174 (1953).

STANFORD, CALIF.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

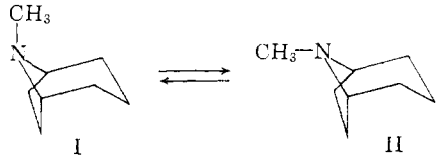
The Configurational Equilibrium of the N-Methyl Group in Some Tropane Deuteriohalides[1]

BY GERHARD L. CLOSS

RECEIVED APRIL 6, 1959

The non-equivalent methyl groups in pseudotropine methiodide give rise to proton magnetic resonance at slightly different fields and cause a doublet with a 6 c.p.s. separation. The occurrence of two doublets in the N-methyl region in the n.m.r. spectrum of an acidified aqueous solution of pseudotropine hydrochloride is interpreted as being caused by the presence of two isomers arising from the two possible configurations of the N-methyl group. As a consequence of rapid exchange of the nitrogen proton with the solvent, the two doublets coalesce into a single peak on adjusting the solution to *p*H 6. In acidified deuterium oxide solution two single peaks are obtained because of eliminated spin coupling. By measuring the ratio of the areas of the peaks, the equilibrium constant of the interconversion process is obtained in a semi-quantitative way. The resonance line at higher field is assigned to the isomer having the N-methyl group attached in an equatorial position relative to the piperidine ring. Equilibrium constants are reported for a number of deuteriohalides of tropane derivatives and the isomer with the equatorial methyl group was generally found to be the more stable one.

Because of the non-planar configuration of the nitrogen, tropane and its derivatives can exist in two stereoisomeric forms in which the methyl group is either oriented axial or equatorial relative to the piperidine ring (I and II). Since the inversion of



I II

substituents on trivalent nitrogen in relatively unstrained ring systems is known to be a process of low activation energy,[2] it can be expected that the two isomers exist in solution in a rapid equilibrium. Information about the position of this equilibrium and the magnitude of the equilibrium constant is of interest in connection with the recent observation of the stereoselective quaternization of tropane bases. In a series of publications Fodor and his group[3] have demonstrated that in nearly all cases they have studied, tropane derivatives yield on quaternization exclusively that isomer in which the entering substituent is located on the same side of the piperidine ring as the endoethylene bridge, or in other words occupies an equatorial position on the six-membered ring. In order to explain this stereospecificity the Hungarian workers argue that the amine with the methyl group axial relative to the piperidine ring is the more stable isomer because of smaller "Pitzer strain" in this configuration than in the isomer in which the methyl group is located in a quasi-axial position with regard to the pyrrolidine ring.

This argument does not seem to be a valid one because the stereochemical course of this rate-controlled alkylation does not give any information about the equilibrium of the much faster interconversion of the two isomeric amines.

Because of the fast rate of the inversion process no simple method is available to give direct information concerning this equilibrium. However, the conjugate acids of the tropane bases should exist in similar equilibria in which the interconversion of the two isomers proceeds *via* the free bases (III–VI). If one assumes in first approximation that this equilibrium is mainly determined by the difference of non-bonded interactions in the two isomers

(1) Presented in part at the 135th Meeting of the American Chemical Society, April, 1959, Boston, Mass.

(2) See, *e.g.*, A. T. Bottini and J. D. Roberts, THIS JOURNAL, **80**, 5203 (1958).

(3) For recent reviews see: G. Fodor, *Tetrahedron*, **1**, 87 (1957); G. Fodor, *Acta Chim. Acad. Sci. Hungar.*, **5**, 379 (1955); G. Fodor, *Experientia*, **11**, 129 (1955); compare also S. P. Findley, THIS JOURNAL, **75**, 3204 (1953); K. Zeile and W. Schulz, *Chem. Ber.*, **88**, 1078 (1955).