

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEPAUL UNIVERSITY]

## Degradation of DL-2-Hydroxymethyl-2,3-dihydro-4H-pyran, a Model Carbohydrate, to Racemic Mixtures Related to D-Glyceraldehyde<sup>1</sup>

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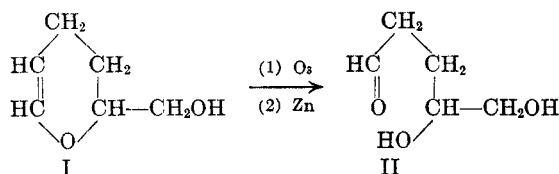
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DL-2-Hydroxymethyl-2,3-dihydro-4H-pyran (I), racemic 3,4-dideoxyglucal, has been degraded to racemic mixtures of which enantiomorphs can be configurationally related to D-glyceraldehyde. The procedures would preserve the configuration of the asymmetric carbon in the pyran ring.

The ready conversion of 2,3-dihydro-4H-pyran to polydeoxyaldopentoses<sup>3</sup> and of dl-2-hydroxymethyl-2,3-dihydro-4H-pyran (I) to polydeoxyaldohexoses<sup>4</sup> has demonstrated that these compounds are model carbohydrates. An optically active form of I would be the precursor for novel types of synthetic carbohydrates.

This paper describes the development of a model route for the degradation of the racemic 3,4-dideoxyglucal (I) to racemic mixtures of which enantiomorphs are known to be configurationally related to D-lactic acid and thus to D-glyceraldehyde and D-glucose. The procedures employed would preserve the configuration of the asymmetric carbon of I and allow the designation of an enantiomorphous form, not yet obtained, as D or L. Of the four degradation routes tested, two were successful, one was partially completed, and another failed because of isolation difficulties.

The shortest route appeared to be the ozonolysis of I to DL-dideoxyribose (II) and its conversion to



the dibenzylmercaptal since both L-2,3-dideoxyribose and its dibenzylmercaptal have been reported in the literature.<sup>5</sup> Unfortunately, our attempts to apply this scheme failed and neither II nor its mercaptal could be isolated.

(1) Abstracted from the master's thesis of Herman J. Eichel, DePaul University, 1956.

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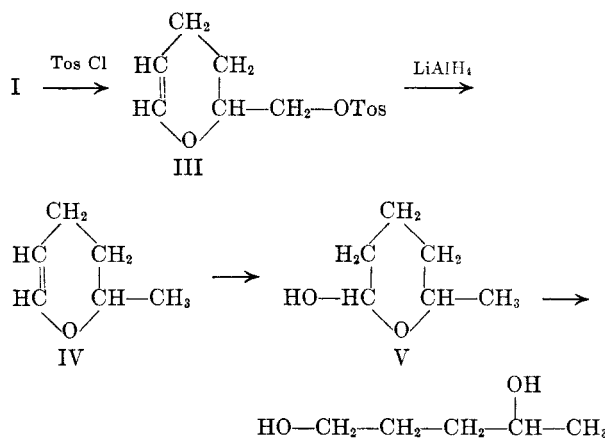
(3) (a) L. E. Schniepp and H. H. Geller, *J. Am. Chem. Soc.*, **68**, 1646 (1946); (b) C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.*, **70**, 1484 (1948); (c) C. D. Hurd and O. E. Edwards, *J. Org. Chem.*, **14**, 680 (1949); (d) C. D. Hurd, J. Moffat, and L. Rosnati, *J. Am. Chem. Soc.*, **77**, 2793 (1955).

(4) R. Zelinski, A. Verbiscar, and H. Eichel, *J. Org. Chem.*, **23**, 184 (1958).

(5) R. Allerton, W. G. Overend, and M. Stacey, *J. Chem. Soc.*, 255 (1952).

Levene and Haller<sup>6</sup> have demonstrated that L-(+)-4-hydroxypentanoic acid has the configuration of L-(+)-lactic acid<sup>7</sup> and that the lactone of its enantiomorph is reduced by sodium and acetic acid to D-(-)-1,4-pentanediol.<sup>8</sup> Therefore, the degradation of I to racemic 1,4-pentanediol was the goal of the second scheme.

This approach required the preparation of 2-methyl-2,3-dihydro-4H-pyran (IV) by lithium aluminum hydride reduction of the toluenesulfonate (III) of I. Hydration of IV to 6-methyltetrahydropyran-2-ol (V) and subsequent oxidation would yield 5-hydroxyhexanoic acid which might then be degraded to 1,4-pentanediol by the classical sequence developed by Levene and Haller.<sup>6</sup> However, although the pyran intermediates III, IV,



and V were obtained, the poor yields in the steps leading to V, together with length of the subsequent degradation scheme, legislated against this course.

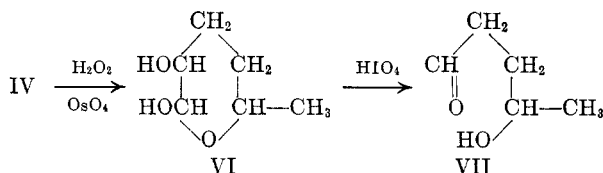
The third route proceeded with the dihydroxylation of 2-methyl-2,3-dihydro-4H-pyran (IV) to 6-methyltetrahydropyran-2,3-diol (VI), which was not isolated, according to the procedure used by Hurd<sup>3</sup> for the analogous hydroxylation of 2,3-di-

(6) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **69**, 165 (1926).

(7) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **65**, 49 (1925); **67**, 329 (1926).

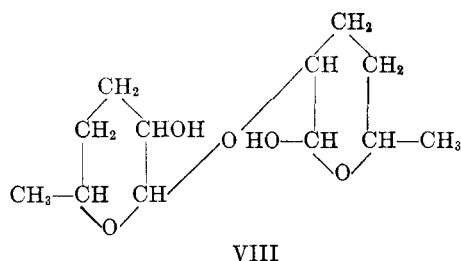
(8) P. A. Levene, H. L. Haller, and A. Walti, *J. Biol. Chem.*, **72**, 591 (1927).

hydro-4H-pyran. The diol VI was degraded by periodate oxidation to 4-hydroxypentanal (VII)



which was then reduced to 1,4-pentanediol by means of sodium borohydride.

The diol VI is a mixture of 3,4,6-trideoxyhexopyranoses probably in tautomeric equilibrium<sup>9</sup> with a small amount of 2,5-dihydroxyhexanal. It readily formed a 2,4-dinitrophenylosazone and showed the browning reaction reported for tetrahydropyran-2,3-diol.<sup>3b</sup> And in similar manner, an attempt to distill VI gave a reducing compound which had an elemental analysis in close agreement with that of a reducing disaccharide such as 2-(3,4,6-trideoxyhexopyranosyl)-3,4,6-trideoxyhexopyranose (VIII). This compound gave a positive



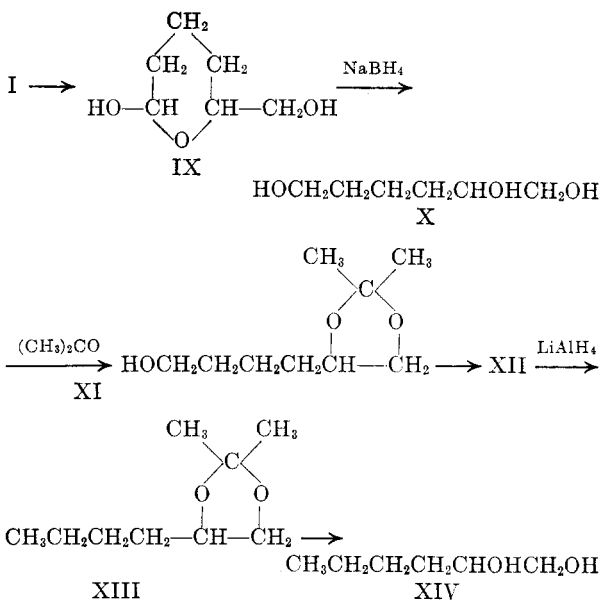
Fehling test and showed the browning reaction. Infrared analysis confirmed the presence of a carbonyl group. However, in acidic solution it formed the same 2,4-dinitrophenylhydrazone as the undistilled parent compound VI. Although it is possible that VIII was an impure form of 2,5-dihydroxyhexanal (VI), it is also possible that during derivative preparation a disaccharide such as VIII would be hydrolyzed. In fact, under the conditions used,<sup>10</sup> lactose did hydrolyze and form a product with 2,4-dinitrophenylhydrazine which was identical to that obtained from glucose.

Periodic acid oxidation of racemic 3,4,6-trideoxyaldohexoses VI went in low yield, but 4-hydroxypentanal (VII) was isolated. Infrared analysis showed the presence of the carbonyl group. In view of Hurd and Saunders' work<sup>9</sup> on the amounts of cyclic hemiacetals in equilibrium with hydroxy aldehydes, VII is probably a tautomeric mixture consisting largely of 5-methyltetrahydrofuran-2-ol. In demonstration of the greater stability of the six-membered ring, infrared analysis of 6-methyltetrahydropyran-2-ol (V) did not show the presence of a carbonyl group although the compound readily

reduced Fehling's solution. The amount of 5-hydroxyhexanal present in tautomeric equilibrium must, therefore, be small.

The fourth and last degradation route was also successful and required converting 2-hydroxymethyl-2,3-dihydro-4H-pyran (I) to 1,2-hexanediol (XIV). Enantiomorphs of the latter have been configurationally related to L-(+)-lactic acid by Levene and coworkers.<sup>11</sup>

In this scheme, compound I was converted to racemic 1,2,6-hexanetriol (X) by sodium borohydride reduction of the unisolated 6-hydroxymethyltetrahydropyran-2-ol (IX), a racemic 2,3,4-trideoxyaldohexose, obtained by hydrating I. The hexanetriol was then readily converted to 2,2-dimethyl-4-(4-hydroxybutyl)dioxolane (XI), a racemic 1,2-isopropylidene-3,4,5-trideoxyhexitol, and thence to the toluenesulfonate (XII). This was then reduced by lithium aluminum hydride to 4-butyl-2,2-dimethyldioxolane (XIII) which was subsequently hydrolyzed to 1,2-hexanediol (XIV). This scheme appears to be a satisfactory means of relating the configuration of optically active 2-hydroxymethyl-2,3-dihydro-4H-pyran (I) to D-glyceraldehyde.



#### EXPERIMENTAL<sup>12</sup>

*2-Hydroxymethyl-2,3-dihydro-4H-pyran* (I). This compound was conveniently prepared by reduction of 2,3-dihydro-4H-pyran-2-carboxaldehyde<sup>13</sup> (acrolein dimer) with sodium borohydride.<sup>4</sup>

*2,3-Dihydro-4H-2-pyranylmethyl p-toluenesulfonate* (III). A solution of 17 g. (0.15 mole) of the hydroxymethylpyran (I) and 38 g. (0.20 mole) of *p*-toluenesulfonyl chloride was prepared at  $-15^\circ$  in 35 ml. of anhydrous ether and 25 ml. of pyridine was added slowly. After 4 days at  $5^\circ$  the resultant

(11) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **79**, 475 (1928).

(12) Analyses by Micro Tech Laboratories, Skokie, Ill.

(13) A sample was generously supplied by the Shell Development Company, Emeryville, Calif.

(9) C. D. Hurd and W. H. Saunders, *J. Am. Chem. Soc.*, **74**, 5324 (1952).

(10) R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, Third Edition, John Wiley and Sons, Inc., New York, 1948, p. 171.

slurry was diluted with 2 volumes of ice water and chilled to 0–5° during acidification with 10% hydrochloric acid. The organic layer was separated and combined with two subsequent ether extracts of the water phase. The ether solution was washed with water and 10% sodium carbonate solution, dried, and evaporated to two thirds its volume. Storage at 5° for several days gave crystals which were washed with ether to give 13 g. (32%) of the *p*-toluenesulfonic ester (III), m.p. 44–45.5°. Recrystallization from ether shortened the range to 45–45.5°.

*Anal.* Calcd. for  $C_{13}H_{16}SO_4$ : C, 58.2; H, 6.01. Found: C, 58.0, 58.5; H, 6.3, 6.1.

*2-Methyl-2,3-dihydro-4H-pyran* (IV). A solution of 74 g. (0.28 mole) of the *p*-toluenesulfonate (III) in 350 ml. of anhydrous ether was added during 2 hr. with stirring to 11.4 g. (0.30 mole) of lithium hydride in 100 ml. of ether under a nitrogen blanket. The mixture was gently boiled for 4 hr., 50 ml. of water was slowly added, and the organic phase was separated by filtration. It was combined with two 50-ml. ether extracts of the aqueous phase, dried, and distilled through a 1 × 22 cm. column packed with clay saddles to give 8.5 g. (31%) of 2-methyl-2,3-dihydro-4H-pyran (IV), b.p. 76–80°/737 mm.,  $n_D^{25}$  1.4314. The infrared spectrum conformed with the expected structure.

*Anal.* Calcd. for  $C_6H_{10}O$ : C, 73.43; H, 10.27. Found: C, 74.35; H, 10.92.

*6-Methyltetrahydropyran-2-ol* (V). A mixture of 1.5 g. (0.015 mole) of 2-methyl-2,3-dihydro-4H-pyran (IV) and 7 ml. of 0.2*N* hydrochloric acid was refluxed for 2.5 hr., allowed to stand overnight, and adjusted to pH 7–8 with 0.5*N* sodium hydroxide. Three 2-ml. ether extracts were combined, washed with water, dried, and distilled to give 0.5 g. (30%) of 6-methyltetrahydropyran-2-ol (V), b.p. 61–62/6 mm.,  $n_D^{25}$  1.4482 (lit.<sup>14</sup> b.p. 71–78/11 mm.,  $n_D^{25}$  1.4452). The infrared spectrum did not show the presence of carbonyl absorption.

A high boiling viscous oil left from the distillation of IV was hydrolyzed in like manner to give a substance, b.p. 61–65/5 mm.,  $n_D^{25}$  1.4439 which had an infrared spectrum identical to that of V.

*Anal.* Calcd. for  $C_6H_{12}O_2$ : C, 62.02; H, 10.42. Found: C, 62.21; H, 10.49.

*6-Methyltetrahydropyran-2,3-diol* (VI). To 4.2 g. (0.043 mole) of 2-methyl-2,3-dihydro-4H-pyran (IV), cooled in an ice bath, there was added 1.2 ml. of a 0.5% solution of osmium tetroxide in *t*-butyl alcohol. Then 33 ml. of a solution of hydrogen peroxide in *t*-butyl alcohol<sup>15</sup> was added with shaking. After storage overnight at 5° the solution was stripped of solvent at 20° and 5 mm. pressure to leave a viscous oil. Continuous extraction for 9 hr. with cyclohexane and distillation of that solvent left 2.3 (41%) of crude 6-methyltetrahydropyran-2,3-diol (VI). It was characterized by conversion<sup>10</sup> to the racemic 2,4-dinitrophenylosazone, m.p. 243–245° (sintered at 226°).

*Anal.* Calcd. for  $C_{13}H_{18}O_3N_2$ : N, 22.85. Found: N, 22.11.

An attempt to distill VI gave a fraction,  $n_D^{25}$  1.4461, boiling above 56° at 5 mm. It reduced Fehling solution, gave the browning reaction<sup>3b</sup> with glycine in 1 min. at 100°, and formed<sup>10</sup> the same osazone as VI. The infrared spectrum showed the presence of carbonyl and hydroxyl absorption, but no carbon to carbon unsaturation. These data and the elementary analysis are in conformity with a disaccharide structure such as 2-(3,4,6-trideoxyhexopyranosyl) 3,4,6-trideoxyhexopyranose (VIII).

*Anal.* Calcd. for  $C_8H_{12}O_5$ : C, 54.60; H, 9.17. Calcd. for  $C_{12}H_{22}O_5$ : C, 58.50; H, 9.00. Found: C, 58.16; H, 8.79.

When glucose and lactose were similarly treated with the acidic 2,4-dinitrophenylhydrazine reagent,<sup>10</sup> each gave the same product, m.p. 126–127°, with no mixed melting point depression.

(14) B. Helferich and T. Malkemes, *Ber.*, **55**, 702 (1922).

(15) N. A. Milas and S. Sussman, *J. Am. Chem. Soc.*, **58**, 1302 (1936).

*4-Hydroxypentanal* (VII). A 2.0 g. (0.015 mole) sample of 6-methyltetrahydropyran-2,3-diol (VI) was allowed to stand overnight with 12.4 g. of periodic acid in 120 ml. of water. This was then made neutral to phenolphthalein with strontium hydroxide and filtered. About 0.8 g. of strontium carbonate was added to the filtrate which was concentrated to about 100 ml. volume at 70° and 25 mm. This mixture was extracted with three 60-ml. portions of ether which were combined and dried. Removal of the ether left 0.5 g. (32%) of 4-hydroxypentanal (VII) which was distilled to make a final 26% yield of product, b.p. 37–41°/5 mm.,  $n_D^{25}$  1.4352 (lit.<sup>16</sup> b.p. 63–65°/10 mm.,  $n_D^{17}$  1.4359). Infrared scanning showed the presence of both carbonyl and hydroxyl absorption.

Further identification of VII was made by reduction with sodium borohydride to 1,4-pentanediol, b.p. 220°/735 mm.,  $n_D^{25}$  1.4461, which had a satisfactory elemental analysis. Literature<sup>17,18</sup> values are b.p. 219–220°/713 mm.,  $n_D^{25}$  1.4452. A sample made<sup>19</sup> from  $\gamma$ -valerolactone had a refractive index of  $n_D^{25}$  1.4461.

*1,2,6-Hexanetriol* (X). Ten grams (0.088 mole) of 2-hydroxymethyl-2,3-dihydro-4H-pyran (I) was boiled for an hour with 50 ml. of 0.2*N* hydrochloric acid. The resultant solution of 2-hydroxymethyltetrahydropyran-2-ol (IX) was made slightly alkaline with potassium carbonate, stirred with 3.8 g. (0.10 mole) of sodium borohydride and allowed to stand overnight. It was brought to pH 7 by hydrochloric acid, concentrated to 10 ml. by vacuum distillation and cooled and filtered. Distillation of the filtrate gave 3.0 g. (25%) of 1,2,6-hexanetriol (X), b.p. 172°/3 mm.,  $n_D^{25}$  1.4754 (lit.<sup>20</sup> b.p. 170°/3 mm.).

*Anal.* Calcd. for  $C_6H_{14}O_3$ : C, 53.70; H, 10.50. Found: C, 53.91; H, 10.50.

The infrared spectrum was identical with that of a commercial sample,  $n_D^{25}$  1.4763.

*2,2-Dimethyl-4-(4-hydroxybutyl)dioxolane* (XI). This racemic 1,2-isopropylidene-3,4,5-trideoxyhexitol was prepared by shaking overnight a mixture of 2.0 g. (0.015 mole) of 1,2,6-hexanetriol, 1.2 g. of sodium sulfate and 15 ml. of a 1% solution of hydrogen chloride in anhydrous acetone. The decanted solution was neutralized with lead carbonate, filtered, and distilled to give 1.8 g. (67%) of XI, b.p. 118°/5 mm.,  $n_D^{25}$  1.4432.

*Anal.* Calcd. for  $C_9H_{18}O_3$ : C, 61.99; H, 10.42. Found: C, 61.81; H, 10.43.

Thirty grams of a commercial sample of the triol treated the same way gave 24.5 g. of XI, b.p. 119–120°/5 mm.,  $n_D^{25}$  1.4455, with an identical infrared spectrum.

*4-Butyl-2,2-dimethyldioxolane* (XIII). Fifteen grams (0.086 mole) of XI and 18 g. (0.095 mole) of *p*-toluenesulfonyl chloride was stirred in 30 ml. of pyridine at less than 40°. After the initial exothermic reaction, the slurry was stirred for 6 hr. at room temperature. Water was added and the oily layer was extracted into ether which was then dried. However, since attempts to distill or to crystallize the 2.7 g. of the *p*-toluenesulfonate (XII) were unsuccessful, the crude product was used in the next step.

The crude XII in 10 ml. of anhydrous ether was added in 10 min. to a solution of 1.0 g. (0.026 mole) of lithium aluminum hydride in 25 ml. of ether. This was boiled under reflux for 5 hr. and cautiously treated with 3 ml. of water. The ether layer was dried and distilled to give 0.5 g. of 4-butyl-2,2-dimethyldioxolane (XIII), b.p. 47–48°/5 mm.,  $n_D^{25}$  1.4349.

(16) B. Helferich, *Ber.*, **52**, 1128, 1802 (1919).

(17) A. Lipp, *Ber.*, **22**, 2567 (1889).

(18) L. E. Schniepp, H. H. Geller, and R. W. Von Korff, *J. Am. Chem. Soc.*, **69**, 672 (1947).

(19) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).

(20) H. Schulz and H. Wagner, *Angewandte Chem.*, **62**, 105 (1950).

*Anal.* Calcd. for  $C_6H_{12}O_2$ : C, 68.33; H, 11.47. Found: C, 68.48; H, 11.37.

In confirmation, XIII was prepared from 1,2-hexanediol (prepared from 1-hexene) by shaking 2.0 g. (0.017 mole) of the diol with 2 g. of sodium sulfate and 20 ml. of 1% hydrogen chloride in acetone for 6 hr. followed by standing overnight. Distillation gave 1.2 g. (45%) of XIII, b.p.  $62^\circ/15$  mm.,  $n_D^{25}$  1.4351.

*1,2-Hexanediol* (XIV). A mixture of 300 mg. (0.0019 mole) of XIII and 10 ml. of 2% sulfuric acid was refluxed for 2 hr., neutralized with barium hydroxide and centrifuged. Evaporation of the supernatant and distillation gave 150 mg. (67%) of 1,2-hexanediol, b.p.  $140^\circ/760$  mm.,  $n_D^{25}$  1.4400 (lit.<sup>11</sup> b.p.  $110-113^\circ/6$  mm.).

*Anal.* Calcd. for  $C_6H_{14}O_2$ : C, 60.96; H, 11.94. Found: C, 60.75; H, 11.79.

A sample prepared from 1-hexene by conditions described<sup>21</sup> for the hydroxylation of 1-octene gave a 29% yield of XIV, b.p.  $107-108^\circ/4$  mm.,  $n_D^{25}$  1.4414.

*Infrared results.* A Perkin-Elmer Model 21 Spectrophotometer was used with rock salt, variable thickness absorption cells for liquid compounds. Solids were examined by the pressed plate technique using potassium chloride as the carrier. The results are summarized in Table I.

(21) D. Swern, G. N. Billen, and J. T. Scanlan, *J. Am. Chem. Soc.*, **68**, 1504 (1946).

TABLE I

INFRARED ABSORPTION CHARACTERISTICS ( $Cm^{-1}$ )

Compound	C=O	C=C	OH
2,3-Dihydro-4 <i>H</i> -pyran-2-carboxaldehyde	1742	1653	Absent
2-Hydroxymethyl-2,3-dihydro-4 <i>H</i> -pyran (I)	Absent	1653	3367
2-Methyl-2,3-dihydro-4 <i>H</i> -pyran (IV)	Absent	1647	Absent
6-Methyltetrahydropyran-2-ol (V)	Absent	Absent	3367
4-Hydroxypentanal (VII)	1776	Absent	3401
Reducing "disaccharide" (VIII)	1718	Absent	3378
1,2,6-Hexanetriol (X)	Absent	Absent	3311
2,2-Dimethyl-4-(4-hydroxybutyl)dioxolane (XI)	Absent	Absent	3378
<i>p</i> -Toluenesulfonate (XII) of XI	Absent	Absent	Absent
4-Butyl-2,2-dimethyldioxolane (XIII)	Absent	Absent	Absent

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CHICAGO 14, ILL.

[CONTRIBUTION FROM RESEARCH AND DEVELOPMENT DEPARTMENT, U. S. NAVAL POWDER FACTORY]

## Effect of Aqueous Sulfuric Acid on Reducing Sugars. V. Infrared Studies on the Humins Formed by the Action of Aqueous Sulfuric Acid on the Aldopentoses and on the Aldehydes Derived from Them<sup>1</sup>

F. A. H. RICE

Received May 16, 1957

Studies on the infrared absorption spectra of the polymeric materials, formed by the treatment of aldopentoses with sulfuric acid, indicated that the chemical structure of the polymer did not depend on the conditions of acid concentration or temperature under which it was formed. The ethanol-soluble and -insoluble fractions into which the polymeric material could be separated were found, so far as could be determined from the infrared spectra, and by carbon and hydrogen analysis, to be identical.

A comparison between the infrared spectrum of the polymeric material obtained by the treatment of L-arabinose with sulfuric acid and the infrared spectra of the polymeric materials prepared by the sulfuric acid treatment of either furfural alone, or furfural admixed with crotonaldehyde, or mixtures of furfural, crotonaldehyde, acetaldehyde, and formaldehyde strongly suggested that furfural alone was not responsible for the insoluble material obtained when a pentose is treated with sulfuric acid. The polymeric material obtained by the treatment of mixtures of furfural, crotonaldehyde, acetaldehyde, and formaldehyde with sulfuric acid were almost identical with the polymers prepared by treating L-arabinose with sulfuric acid.

This finding can explain the fact that the ultraviolet absorbance of an aldopentose in sulfuric acid reaches a steady state after an interval of time that depends on the concentrations of aldopentose and acid and the temperature.

In previous communications on the effect of sulfuric acid on the aldoses<sup>2,2a</sup> it was shown that the ultraviolet spectrum which develops when an aldopentose or aldohexose is treated with sulfuric acid, depends on the formation of certain specific compounds, and that these compounds can be

extracted from aqueous acid into ether solution. It was found possible to isolate and identify the compounds in the ether solution by forming and chromatographing the mixture of their 2,4-dinitrophenylhydrazones. The separated hydrazones gave crystalline products which were identified. Furfuraldehyde, crotonaldehyde, acetaldehyde, and formaldehyde were found to be formed from the action of acid on the pentose series of reducing sugars.<sup>2</sup>

Examination of the ultraviolet spectra as they developed in acid solution of reducing sugars

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(2) F. A. H. Rice and L. Fishbein, *J. Am. Chem. Soc.*, **78**, 1005 (1956).

(2a) F. A. H. Rice and L. Fishbein, *J. Am. Chem. Soc.*, **78**, 3731 (1956).