

ADVANCES IN CARBOHYDRATE CHEMISTRY

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EDITORS' PREFACE

The increasing tempo of research and the consequent increased specialization of research workers make it desirable to provide frequent reviews of important developments in carbohydrate chemistry, not only for carbohydrate chemists, but also for research workers in other fields and industrial chemists and teachers. With this book there is begun the publication of a series of annual volumes entitled "Advances in Carbohydrate Chemistry." For each volume invitations will be extended to selected research workers to prepare critical reviews of special topics in the broad field of the carbohydrates, including the sugars, polysaccharides, and glycosides. It is also the intention to cover, as far as the available space will permit, biochemical, industrial, and analytical developments. It is our plan to have the individual contributors furnish *critical*, integrating reviews rather than mere literature surveys and to have the articles presented in such a form as to be intelligible to the average chemist rather than only to the specialist. Although the usual rules of the assignment of proper credit for developments will be followed, we do not believe it necessary to quote all past work done in a particular field and the contributions of a particular laboratory or group may be emphasized.

It may be found desirable to present several reviews of controversial subjects, particularly of those in fields undergoing a rapid state of development. In this way different points of view will find expression. In addition to the presentation of topics covering recent advances, we are providing occasional articles which will review thoroughly special fundamental topics in carbohydrate chemistry. These articles will cover fields which have matured and will be quite complete from the historical standpoint. After a number of years, it is hoped that the aggregate of these articles will provide a fairly complete summary of carbohydrate researches.

The general policies of the "Advances" have been formulated by an Executive Committee consisting of W. L. Evans, H. O. L. Fischer, R. Max Goepf, Jr., W. N. Haworth, C. S. Hudson and the two editors. It is a pleasure to announce that, beginning with the second volume, Dr. Stanley Peat of Birmingham University, England, will act as Associate Editor to solicit and edit contributions from the British Isles. It seems probable that an enlargement of the organization may be expected in the future.

Because the present volume is the first to be presented, we trust that the readers will not be too critical and will remember that the attainment of uniformity and the establishment of permanent policies will require some time and much consideration. The present international conflict has made the solicitation of manuscripts difficult and has provided many other difficulties. The cooperation shown by the contributors to the first volume is greatly appreciated.

We hope that the "Advances" will receive the whole hearted support of carbohydrate chemists in particular and of the chemical profession as a whole. Such support is necessary for the successful continuation of our work. We would be very glad to receive suggestions from the readers, of better ways in which we can serve the needs of carbohydrate chemists and of fields in need of review.

The support and encouragement given by the publishers in this undertaking are gratefully acknowledged. The index has been compiled by Dr. L. T. Capell. Mr. J. V. Karabinos has rendered valuable editorial assistance.

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Errata

Page 24, line 3 under section 4. For "z-propanol" read "2-propanol."

Page 25, footnote 73. For "Diehls" read "Diels."

Page 35, line 3 from bottom. For "D-Manno-L-manno-octitol" read "Manno-manno-octitol" since the structure is meso.

Page 59, last line. For "trihydroxypyrazole" read "5-(D-erythro-1, 2, 3-trihydroxypropyl)pyrazole."

Page 111, line 2 below formula. Reference number 56 should be 5, 6.

Page 231, formula XI. Insert bond between P and OH at bottom.

Page 275, line 13. For "hydroxymethyl" read "hydroxyethyl."

Page 276, line 10 from bottom. For "carbonyl" read "carboxyl."

THE FISCHER CYANOHYDRIN SYNTHESIS AND THE CONFIGURATIONS OF HIGHER-CARBON SUGARS AND ALCOHOLS

BY C. S. HUDSON

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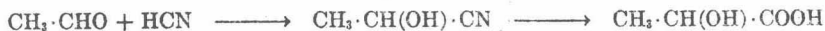
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INTRODUCTION

Demonstrations of the chemist's art in changing one sugar to another never fail to excite wonder, even among the initiated. Starting with either of the two most abundant carbohydrates in nature, starch or cellulose, he makes D-glucose by the very old and simple process of acid hydrolysis. From this D-glucose he can make today in the laboratory by other processes in yields that are actually practical, D-mannose (epimerization through the glycol), D-fructose (alkaline enolization), D-altrose (Walden inversions), D-arabinose and L-xylose (oxidative degradations) and D-ribose. In addition, a considerable number of sugars can be made from the sugars of the list by a process which is the subject of this review, namely, Emil Fischer's cyanohydrin synthesis of higher-carbon sugars. The importance of this synthesis in the historical development of the theoretical chemistry of the carbohydrates places it in the first rank of that field; the major role that its experimental results have played in the establishment of the van't Hoff-Le Bel theory of the asymmetric carbon atom extends its significance far beyond the carbohydrate group.

I. THE CYANOHYDRINS AND THE CORRESPONDING ACIDS AND LACTONES

The synthesis of α -hydroxy acids from carbonyl compounds by way of the cyanohydrin was an early discovery in organic chemistry.¹ In 1867 Simpson and Gautier,² working in Wurtz' laboratory, described the cyanohydrin from acetaldehyde and hydrocyanic acid, and its conversion to racemic lactic acid by strong hydrochloric acid.



¹ Mandelic acid from benzaldehyde cyanohydrin: F. W. Winckler, *Ann.*, 4, 246 (1832); 18, 310 and 319 (remarks by J. Liebig) (1836).

² M. Simpson and A. Gautier, *Compt. rend.*, 65, 414 (1867); J. Wislicenus had accomplished the synthesis from acetaldehyde, hydrocyanic acid and hydrochloric acid without isolating the cyanohydrin, *Ann.*, 128, 22 (1863).

The analogous reaction with a ketone is illustrated from the work of Staedeler³ in 1859, who prepared α -hydroxy-isobutyric acid from acetone, hydrocyanic acid and hydrochloric acid, without isolating the intermediate acetone cyanohydrin.



In a series of researches Kiliani⁴ succeeded in applying this cyanohydrin reaction to reducing sugars; the resulting polyhydroxy acids, which contained one more carbon atom than the sugar from which each was derived, were then reduced by hydriodic acid and phosphorus to homologs of acetic acid, which were accurately identified. The results of this pioneering work are summarized below, using the names that were current then and appending the present ones.

Summary of Kiliani's Cyanohydrin Results

Arabinose [L-Arabinose]	————→	Arabinosecarboxylic acid [L-Mannonic acid]	————→	normal hexylic acid
Dextrose [D-Glucose]	————→	Dextrosecarboxylic acid [D-Gluc-D-gulo-heptonic acid] ⁵	————→	normal heptylic acid
Galactose [D-Galactose]	————→	Galactosecarboxylic acid [D-Gala-L-manno-heptonic acid]	————→	normal heptylic acid
Levulose [D-Fructose]	————→	Levulosecarboxylic acid [Full configuration unknown]	————→	methyl- <i>n</i> -butyl-acetic acid

Kiliani accomplished the purpose of his plan of research; he established the aldopentose structure for arabinose and proved that glucose and galactose are aldohexoses and fructose a 2-keto-hexose. His discovery that these polyhydroxy acids lose water readily and pass to stable lactones of crystalline habit soon became of great significance.

II. EMIL FISCHER'S DISCOVERY AND APPLICATION OF THE SYNTHESIS

In 1889 Fischer⁶ discovered that the lactones of the acids of the sugar group can be reduced by sodium amalgam to yield the corresponding carbonyl compound, an aldose. The addition of this reaction to the cyanohydrin procedure of Kiliani made possible the first synthesis of

³ Staedeler, *Ann.*, 111, 320 (1859) and W. Markownikoff, *ibid.*, 146, 339 (1868).

⁴ H. Kiliani, (a) (fructose) *Ber.*, 18, 3066 (1885); 19, 221, 772 (1886); (b) (glucose) *ibid.*, 19, 767, 1128; (c) (arabinose) *ibid.*, 19, 3029 (1886); 20, 282, 339 (1887); (d) (galactose) *ibid.*, 21, 915 (1888); 22, 521 (1889).

⁵ It is recommended that the reader refer at this point to p. 28, where this nomenclature is explained.

⁶ E. Fischer, *Ber.*, 22, 2204 (1889). ["Untersuchungen über Kohlenhydrate und Fermente," vol. 1, p. 315. Verlag Julius Springer, Berlin (1909).]

higher-carbon sugars. Apparently the extent to which the sugar chain might be lengthened by successive applications of this synthesis would be limited only by experimental factors such as yield and crystallization of products. In the same year Fischer and Passmore⁷ discovered that the phenylhydrazides of the aldonic acids crystallize well, a development which proved of fundamental importance for the isolation and purification of such acids. At that time Fischer was beginning to use the van't Hoff-Le Bel theory of the asymmetric carbon atom in the interpretation of experimental results, and in 1891, in the introduction to his classical proof of the configuration of glucose and related substances, he stated: "all previous observations in the sugar group are in such complete agreement with the theory of the asymmetric carbon atom that the use of this theory as a basis for the classification of these substances seems justifiable."⁸ The theory predicts that two diastereoisomers should result from the addition of hydrocyanic acid to a reducing sugar; Fischer found that such is the case. Arabinose yielded in addition to Kiliani's arabinosecarboxylic acid [L-mannonic acid] also some L-gluconic acid, the isolation of which was accomplished through its phenylhydrazide.⁹ From D-xylose there were prepared the new synthetic diastereoisomeric hexoses D-gulose¹⁰ and D-idose.¹¹ In the continuation, such diastereoisomers will be designated "epimers," following usual practice. When two acids are found to result from the application of the cyanohydrin synthesis to a sugar it is naturally assumed that they are epimers. Fischer⁸ established several methods for proving the relationship: (1) the acids are interconvertible through heating with aqueous pyridine; (2) the epimeric aldoses which result from the reduction of the lactones of the epimeric acids yield one and the same osazone; (3) each epimeric aldose reduces to a polyhydroxy alcohol, both of which alcohols are obtained in mixture when the related 2-ketose is reduced. This ketose can be recognized also through the observation that it yields the same osazone.

Using the van't Hoff-Le Bel theory as a guide, Fischer extended his cyanohydrin syntheses from the work with xylose and arabinose to researches on all the other aldoses that were available in quantity at that time; the list consisted of glucose, mannose, galactose, rhamnose, lactose and maltose. The experimental results with the disaccharides

⁷ E. Fischer and F. Passmore, *Ber.*, 22, 2728 (1889). ["Untersuchungen," p. 222.]

⁸ E. Fischer, *Ber.*, 24, 1836, 2683 (1891). ["Untersuchungen," pp. 417, 427.]

The writer has reviewed the subject in the *Journal of Chemical Education*, 18, 353 (1941).

⁹ E. Fischer, *Ber.*, 23, 2611 (1890). ["Untersuchungen," p. 362.]

¹⁰ E. Fischer and R. Stahel, *Ber.*, 24, 528 (1891). ["Untersuchungen," p. 389.]

¹¹ E. Fischer and I. W. Fay, *Ber.*, 28, 1975 (1895). ["Untersuchungen," p. 526.]

were meager, due to the failure of the synthetic substances to crystallize.¹² The monoses led to brilliant developments.

1. Higher-carbon Sugars from D-Mannose

From D-mannose there was synthesized¹³ one mannoheptose [it is D-manno-D-gala-heptose], the cyanide addition seeming to proceed so much in one direction that the epimer was not detected; the reduction of this mannoheptose gave an alcohol *which proved to be identical with natural perseitol*. Continuing the synthesis from the mannoheptose a mannooctose [it is D-manno-L-manno-octose], and from the latter a mannnononose, were prepared. It was reported at that time that this mannnononose was fermented readily by yeast; subsequently Fischer¹⁴ mentioned that a research which Dr. Hagenbach had carried out under his direction confirmed the data concerning mannooctose but led to different results in the nonose series, in consequence of which he expected to study the subject again in order to determine the reason for the difference. As there is no later statement, it seems probable that Fischer's extensive activities in other lines of research left no opportunity for the resumption. Hermann O. L. Fischer has preserved most of his father's records, among which he has found Dr. Hagenbach's notebook, and he has kindly loaned it to the writer for study. With Dr. Fischer's permission the following data from the notebook are published in the belief that they can be helpful to future investigators.

Data from R. Hagenbach's Research on D-Mannnononose under the Direction of Emil Fischer. The mannooctonic lactone of Fischer and Passmore was obtained again (m. p. 165–170°, $[\alpha]_D^{20}$ -42° in water, m. p. of the phenylhydrazide of the acid, 252°, the corresponding values from the older work being 167–170°, -44° and 243°). The reduction of this lactone yielded an amorphous octose which formed a crystalline phenylhydrazone of low solubility, that appeared to be identical (m. p. 218–220°) with Fischer and Passmore's phenylhydrazone (212°). The two researches appear to be in agreement so far. In Hagenbach's first trial of the addition of hydrocyanic acid to his octose, he used 15 g. of octose that had been made from its phenylhydrazone by the usual benzaldehyde process. At room temperature the precipitation of amide began after three hours. The usual treatment with barium hydroxide was made eight days later. A nononic acid was isolated as a readily crystallizing phenylhydrazide, which began to appear even in the hot solution. The yield was small, about 5 g., m. p. 249°. This phenylhydrazide was converted to a lactone in the usual way (barium hydroxide) and crystallization took place on the water bath when high concentration was

¹² O. Reinbrecht, *Ann.*, **272**, 197 (1892). ["Untersuchungen," p. 661.]

¹³ E. Fischer and F. Passmore, *Ber.*, **23**, 2226 (1890). ["Untersuchungen," p. 569.]

¹⁴ E. Fischer, "Untersuchungen," p. 582.

reached. The crystals were washed with alcohol and showed m. p. 178° , yield 2.8 g. They were recrystallized from 200 cc. 95% alcohol, as small needles, m. p. $177-178^{\circ}$ and $[\alpha]_D^{20} +42^{\circ}$. The m. p. and magnitude of rotation agreed with the data of Fischer and Passmore ($175-177^{\circ}$, -41°), but the direction of rotation was opposite. After two more recrystallizations this sample melted at 185° , but there is no record of a rotation; Hagenbach thought it probable that this lactone sample was an impure preparation of the higher melting lactone that was obtained in all later experiments. This first sample of lactone was reduced with sodium amalgam to an amorphous sugar not free of ash, which rotated $[\alpha]_D -10.9^{\circ}$ (i.e. levorotatory) and was not fermented by yeast at 26° during 24 hours. The yeast fermented both glucose and galactose vigorously. In all later syntheses from the octose, a nononic lactone of much higher m. p. was obtained as needle crystals. It is much less soluble (12 parts of hot water) than the mannoheptonic and mannooctonic lactones and it forms a barium salt of low solubility; it is recrystallized best from solution in hot alcohol, in which it is difficultly soluble, and subsequent concentration. The best product showed $[\alpha]_D +60^{\circ}$ (dextrorotation), m. p. 199.5° corr., and the carbon and hydrogen analyses were correct for a nononic lactone. The phenylhydrazide from it showed correct percentages of carbon, hydrogen and nitrogen, m. p. 254° , and was difficultly soluble in hot water, from which it crystallized as "mikroskopische Krystalle sechsseitig, fast rund." Twelve separate syntheses from the octose were made, varying the temperature (12° to 35°) and the concentration of hydrocyanic acid; the lower temperatures gave better yields and cleaner products. In total, 60 g. of octose was used, from which 40.9 g. of nononic phenylhydrazide was obtained; the lactone from every experiment except the first, always melted with decomposition at some point between 192° and 202° ; the rotations of two samples are recorded ($[\alpha]_D +55^{\circ}$ and $+57^{\circ}$, once recrystallized material). The reduction of this high melting lactone yielded an amorphous mannononose. It rotated $[\alpha]_D^{20} -35^{\circ}$ (levorotatory) and it was not fermentable by yeast. It formed a phenylhydrazone which was only slightly soluble in water, m. p. 209° corr. (dec.); carbon, hydrogen and nitrogen percentages were correct. The nonose which Fischer and Passmore described formed a phenylhydrazone (m. p. $195-200^{\circ}$ uncorr. (dec.)) of low solubility in water, but their nonose was a crystalline sugar, could be recrystallized from hot 96% alcohol (m. p. about 130°), showed an initial rotation $[\alpha]_D$ about $+50^{\circ}$ (mutarotation not recorded), and it was readily fermentable by yeast. There is no record of a nonose osazone in Hagenbach's notebook.

The writer makes the following comments. The mannooctonic lactone that Fischer, Passmore and Hagenbach had in hand was certainly D-manno-L-manno-octonic lactone; it was later made by Peirce (ref. 23, p. 8) and also by workers in the writer's laboratory in connection with the research of ref. 55 (p. 18). Our data, not published before, are m. p. $169-172^{\circ}$, and $[\alpha]_D^{20}$ in water -44.8° (initial) which did not change in 24 hours. The absence of any rapid mutarotation suggests that it is a γ -lactone. The phenylhydrazide of the acid showed m. p. 257° ; it is so slightly soluble in cold water that its rotation could not be measured. Concerning the substances of the mannonononic series, if the same nononic phenylhydrazide was obtained in the two researches, the lactone from it may have crystallized in the earlier research as a levorotatory δ -lactone and in the later as a dextrorotatory γ -lactone, or mixture of the two. Since the nononic acid probably has the L-galactonic acid end