

CHEMISTRY *of the* CARBOHYDRATES

BY

WILLIAM WARD PIGMAN

The Institute of Paper Chemistry, Appleton, Wisconsin

AND

RUDOLPH MAXIMILIAN GOEPP, JR.

The Atlas Powder Co., Wilmington, Delaware

PREFACE

It is hoped that this monograph will fill the urgent need for an introductory survey of the broad field of the carbohydrates including sugars, derived products, and polysaccharides from organic, physical, analytical, biological, and industrial chemical aspects. In any case, this book brings together much hitherto unassembled material and considers many subjects both from the standpoint of products and of the reactions involved. The latter approach may make this work of interest to organic and physical chemists who are not specialists in the carbohydrate field. In general, the intention has been to write this monograph for the use of research workers and graduate students, but it is hoped that generally the style is such that the book can be used to advantage by readers not having an extensive acquaintance with organic and physical chemistry.

The preparation of a specialized monograph of this type presents many problems for the author; two of the most difficult are the selection of material and the proper balance between various subjects. The number of published researches is so great that only a small part of the material can be presented in a single volume, and it would appear that the complete summation of researches in special fields requires new publication media. For the carbohydrates, it is hoped that the "Advances in Carbohydrate Chemistry" in time will bridge the gap between the publication of original papers and passage of the data and concepts into texts and the general body of scientific knowledge. Certainly there is no conflict of purpose between the present book and the "Advances," for the former represents a brief summary of a broad field, whereas the latter gives detailed discussions of restricted scope.

Numerous subjects of considerable importance such as carbohydrate metabolism, fermentations and photosynthesis have been omitted or covered only briefly. The discussion of cellulose and starch is inadequate in terms of the amount of material available, but it was felt that a book purporting to cover carbohydrates must include something on these important subjects; in any case there are numerous more extensive works on the subject. Perhaps only the author's privilege and the particular interest of the writer can justify the depth of the discussion of several other subjects. Within these limitations, it is hoped that this monograph presents a fair view of the subject of carbohydrates in its broad aspects.

The problem of the proper citation of old work is often very difficult, particularly when reviews are not available or when old work has lost its significance. The citation of original work by the author refers only to the specific statements involved. When a statement may involve work prior to the reference actually given, the word "See" may be inserted before the actual citation. Practically all the references were inspected in the

original; in most of the remaining instances, the secondary references employed are also given. The literature covered comprises the period to early 1946, but some later work is included.

In spite of extensive attempts to avoid errors, undoubtedly additional ones will be found. It will be greatly appreciated if such instances are called to the attention of the writer.

The current status of nomenclature in the carbohydrate field, in spite of the excellent work of the Nomenclature Committee of the Division of Sugar Chemistry and Technology of the American Chemical Society, has created many difficulties in the preparation of this book. With but few exceptions, the recommendations of this committee have been followed, but the scope of the recommendations is extremely limited. Attempts have been made to point out difficulties and possible improvements in nomenclature without completely accepting or standardizing the usage in the book. The most radical changes are in the names of the dibasic or "aric" acids, but even here old and new names are intermingled with the hope of a gradual introduction of the more systematic nomenclature. The preparation of the index required that a definite stand be made on many questions of nomenclature, and, in general, represents the nomenclature favored by the writer. To reduce difficulties in the use of the index, an extensive system of cross entries and multiple headings including synonyms is used. Undoubtedly, no one, including the writer, will be completely satisfied with the nomenclature, but there seems to be no better solution until progress is made by national or international agreement.

Active work on the present book commenced in 1940 while the writer was associated with the National Bureau of Standards and was continued subsequently at the Corn Products Refining Co. and the Institute of Paper Chemistry. Originally, Dr. H. S. Isbell was to participate as co-author. The pressure of other duties prevented active collaboration on his part, but the writer is deeply indebted to Dr. Isbell for suggestions of the general organization of material and for the use of his valuable file of reference cards.

In 1943, Dr. R. Max Goeppe, Jr., decided to participate as co-author. Dr. Goeppe's contribution to the present book is very significant, although his actual written contributions are limited to the Introduction (Chapter I) and the section on anhydrides in Chapter VIII. His death on October 3, 1946, as a result of an airplane accident while traveling to Germany under the authority of the Office of Technical Services, U. S. Department of Commerce, ended a brilliant and promising career and prevented the completion of his assignment as co-author. His notes were used by Drs. Green and Soltzberg and the present writer in the preparation of Chapters VI and VII. Dr. Goeppe, however, had devoted much time to critical evaluations of the other chapters, and his suggestions were found to be of the utmost value.

Dr. Sol Soltzberg and Dr. John W. Green were mainly responsible for the preparation of Chapters VI and VII, respectively. The present writer is deeply grateful for their help. Dr. Green also undertook the principal responsibility for the preparation of the subject index, an extremely difficult and time-consuming task.

The assistance of many other individuals has been of the greatest importance. Professor C. S. Hudson read many of the chapters and gave many valuable critical comments. His comments, as well as those of persons mentioned hereafter, added much to the present book, but the statements made therein are the sole responsibility of the writer and are not to be blamed on any of the co-operating individuals. Others who have read one or more chapters are:

Drs. R. S. Tipson, H. K. Rutherford, A. M. Sookne, Sol Soltzberg, L. E. Wise, Harriet Frush, D. H. Brauns, H. G. Fletcher, Jr., E. Anderson, N. K. Richtmyer and T. J. Schoch.

The advice and aid with proof reading on the part of Dr. C. J. West were of great help. Drs. Hewitt G. Fletcher, Jr., Sol Soltzberg and Charles J. Pedersen devoted much time to the reading of the page proofs and suggested important changes. Their help is deeply appreciated.

The editorial work in connection with a project of this type is a grueling but essential task. Particular gratitude for help in this connection is due Dr. Mary Grace Blair and Dr. Elizabeth Osman; both revised or wrote several sections and contributed valuable suggestions. The assistance of Miss Marilyn Podest, Mrs. John W. Green and Mrs. W. Bruce Weber is also gratefully acknowledged.

The author index was prepared by Miss Hannah Bergman of the Academic Press. Her help, as well as that of the Academic Press, generally, was of great value. Miss Mary Ann Zastrow and Miss Marilyn Podest cooperated in this work.

Valuable sustaining assistance was provided by Mr. John G. Strange, Mr. Westbrooke Steele and Dr. H. F. Lewis (of the Institute of Paper Chemistry), Drs. E. W. Reid, H. F. Cox, A. L. Elder and S. M. Cantor (of Corn Products Refining Co.), Mr. F. J. Bates (of the National Bureau of Standards), and Mr. K. R. Brown and Dr. R. S. Rose, Jr. (of Atlas Powder Co.). The organizations represented by these individuals provided important encouragement for this project.

To the authors of reviews and books in the carbohydrate field, the present writer is deeply indebted, for these reviews were used extensively in the preparation of this book.

WARD PIGMAN

Appleton, Wisconsin
April 1, 1948

CONTENTS

CHAPTER	PAGE
PREFACE	v
I. Introduction	1
1. Development of Carbohydrate Chemistry	1
2. General Chemistry	5
A. Stereoisomerism	5
B. Activation by Carbonyl Groups	5
C. Intermolecular Reactions	8
D. The Glycosidic Hydroxyl and Polymeric Carbohydrates	10
3. Nomenclature and Definitions	13
A. Scope and General Definitions	13
B. Configurational and Trivial Names	18
C. D- and L-Series	21
D. Alpha-Beta Designations	21
II. Structure and Stereochemistry of the Monosaccharides	23
1. Structures of Glucose and Fructose	23
2. Stereochemistry	24
A. General Principles	24
B. Establishment of the Configuration of Glucose and Some Other Sugars	27
C. D, L Nomenclature	35
3. Ring Structures of the Sugars	42
A. Necessity for Ring Structures	42
B. Proof of Ring Structure	44
C. Configuration of the Anomeric Carbon Atom	48
D. The Representation of the Ring Structures of the Sugars	50
E. Nomenclature of Anomers (α - β Non-enclature)	55
4. Homomorphous Sugars	56
A. Homomorphology	56
B. Nomenclature of the Higher Sugars	60
5. The Sugars in Solution	62
A. In the Absence of Strong Acids or Alkalies; Mutarotation	62
B. In the Presence of Acids	69
C. In the Presence of Alkalies	71
a. Isomerizations	72
b. Fragmentation	77
D. Behavior of the Sugars with Short Carbon Chains	79
6. Optical Superposition, the Isorotation Rules, and the Influence of Structure on Optical Rotation	80
III. Occurrence, Properties, Synthesis and Analysis of the Monosaccharides	89
1. Naturally Occurring Monosaccharides	89
A. Introduction	89
B. Properties, Identification, Origin and Preparation of Naturally Occurring Monosaccharides	90
a. Hexoses	91

CHAPTER

PAGE

D-Fructose	91
D-Galactose	93
L- and D, L-Galactose	96
D-Glucose	96
D-Mannose	99
L-Sorbose	101
b. Pentoses:	102
L-Arabinose	102
D-Arabinose	103
D-Ribose	103
D-Xylose	104
L-Xylulose	105
c. Methyloses:	106
6-Desoxy-D-glucose	106
L-Fucose	107
D-Fucose	107
L-Rhamnose	108
d. Heptoses:	109
D-Mannoheptulose	109
Sedoheptulose	110
2. Synthetic Sugars	111
A. Complete Synthesis of the Sugars	111
B. Methods for Lengthening the Carbon Chains of the Sugars	116
C. Methods for Shortening the Carbon Chains of Sugars	121
D. Methods for the Synthesis of Sugars with Terminal Methyl Groups (Methyloses)	125
E. Synthetic Methods Based on Changing the Configuration of Other Sugars	126
F. Preparation of Ketoses by Biochemical Oxidation of Alcohols	131
G. Aldose to Ketose Conversion Utilizing the Osones	132
3. The Identification and the Quantitative Determination of Carbohy- drates	133
A. Qualitative Identification	133
a. Separation of Sugar Mixtures	133
b. Color Reactions	134
c. Derivatives	135
B. Quantitative Determination	137
a. Optical Rotation	137
b. Reducing Sugar Methods	139
Oxidation by Metallic Salts in Alkaline Solution	139
Oxidation with Potassium Ferricyanide	143
c. Colorimetric Procedures Using Orcinol or Carbazole	143
d. Special Methods	144
Determination of Aldoses by Hypiodite	144
Determination of Pentoses and Pentosans	145
Determination of Sugars as Hydrazones and Osazones	145
Fermentation Methods	146
IV. Esters	149

CHAPTER	PAGE
1. Acetyl Derivatives.....	150
A. Cyclic Acetates.....	150
B. Acyclic Sugar Acetates (Aldehyde Derivatives).....	152
C. Acetates with a Heptanose Ring.....	155
D. Derivatives of Orthoacetic Acid.....	156
E. Acetyl Migration.....	159
2. Acetylglycosyl Halides (Halogeno Acetyl Sugars).....	159
A. Cyclic Forms.....	159
B. Optical Rotation and Atomic Dimension.....	164
C. Acyclic Analogs of the Acetylglycosyl Halides.....	164
3. Benzoyl Derivatives.....	165
4. Galloyl Derivatives and Tannins.....	167
5. Other Organic Esters.....	169
6. Tosyl and Mesyl Derivatives.....	170
1. Nitric Acid Esters.....	170
2. Sugar Carbonates.....	177
3. Phosphate Esters.....	178
4. Esters of Arsenous Acids.....	182
5. Sulfate Esters.....	182
6. Boric Acid Esters.....	183
7. Halogeno Esters.....	184
V. Glycosides, Full Acetals and Thioacetals.....	186
1. Glycosides.....	187
A. Methods for Synthesis.....	188
a. Fischer Method.....	189
b. Michael Synthesis.....	193
c. Koenigs-Knorr Reaction.....	193
d. Helferich Method.....	194
e. Use of Sugar Mercaptals.....	195
f. Direct Alkylation Method.....	196
g. From Glycols.....	197
h. Furanoid Glycosides and Sugars from Carbonates.....	197
i. Enzymic Synthesis.....	197
j. Transglycosidation.....	198
B. Properties of Glucosides.....	199
a. Stability to Alkaline Hydrolysis.....	199
b. Hydrogenation.....	201
c. Ease of Hydrolysis by Acids.....	202
C. Determination of the Structures of Glycosides.....	207
a. Pyranoid Structure of Fischer's Crystalline Methyl Glycosides.....	207
b. Furanoid Structure of "γ" Methyl Glucosides.....	208
c. Pyranoid Nature of the Methyl Fructosides.....	208
d. Periodic Acid Oxidation.....	209
2. Glycosans (Inner Glycosides).....	214
A. Preparation.....	214
B. Difructose Anhydrides.....	216
C. Structures.....	217
D. Reactions.....	218

CHAPTER

PAGE

3. Acetal and Mercaptal Derivatives of Acyclic Sugars	218
A. Mercaptals	218
B. Acetals	220
4. Reactions of Carbohydrates with Aldehydes and Ketones	222
A. Methylene (Formal) Derivatives	224
B. Benzylidene Derivatives	224
C. Condensation with Acetaldehyde and Furfuraldehyde	226
D. Isopropylidene (Acetone) Derivatives	228
E. Acetoacetic Ester Derivatives	231
VI. The Polyols	232

PART I. ACYCLIC POLYOLS (GLYKITOLS)

1. Configurations, Occurrence and Preparation	233
A. Tetritols	233
B. Pentitols	234
C. Hexitols	236
D. Heptitols	242
E. Octitols, Nonitols and Decitols	245
2. Proofs of Structure and Configuration	247
3. Synthesis	250
4. Reactions	252
A. Esterification	252
B. Oxidation	254
C. Reduction	255
D. Etherification	256
E. Qualitative and Quantitative Determination	256
F. Biochemistry	257
5. Desoxy Polyols	257
A. Synthesis and Properties of Monodesoxy Polyols	259
B. Synthesis and Properties of Didesoxy Polyols	261
C. Proofs of Structure and Configuration	263

PART II. THE INOSITOLS AND RELATED COMPOUNDS

1. Isomerization and Representation of Configuration	264
2. Occurrence and Synthesis	266
3. Proofs of Structure and Configuration	271
A. <i>meso</i> -Inositol	271
B. <i>d</i> - and <i>l</i> -Inositol	273
C. <i>d</i> -Quercitol	273
D. Conduritol	275
E. Mytilitol	276
F. Quinic Acid	277
G. Shikimic Acid	278
4. Reactions	279
A. Behavior with oxidizing agents	279
a. Nitric Acid	279
b. Alkaline Permanganate	280
c. Hypobromite and Bromine	280
d. Tetravalent Lead	280
e. Bacterial Oxidation	280

CHAPTER	PAGE
B. Reaction with Halogen Acids	281
a. Halohydrin Formation	281
b. Aromatisation	283
C. Esterification	283
D. Alkylidene Formation	284
E. Metallic Complexes	284
F. Miscellaneous Reactions	284
5. Biochemistry	286
VII. Acids and Oxidation Products of Carbohydrates	288
1. Preparation and Reactions	290
A. Aldonic Acids	290
a. Preparation	291
b. Equilibrium in Solution	292
c. Epimerization	295
d. Optical Rotatory Relationships	296
e. Reactions of the Aldonic Acids	297
B. Saccharic (Aric) Acids	299
a. Tartronic and Malic Acids	299
b. Tetraric Acids (Tartaric Acids)	300
c. Pentaric and Hexaric Acids	301
C. Uronic Acids	303
a. Preparation and Occurrence	303
b. Aldobiuronic Acids	306
c. Reactions of Uronic Acids	308
D. Keto Aldonic Acids	310
E. Ascorbic Acids	313
a. General Properties and Reactions	313
b. Vitamin C (L-Xyloascorbic Acid)	316
F. Osones	318
2. Oxidation Agents	319
A. Halogen Oxidations	319
a. Halogens and Hypohalites	320
b. Halic Acids (HXO_3)	327
c. Chlorous Acid (HClO_2)	328
B. Reagents Cleaving Glycols	328
C. Nitric Acid and Nitrogen Oxides	332
D. Oxygen in Alkaline or Neutral Solution	335
E. Hydrogen Peroxide	336
F. Relatively Unspecific Oxidants	339
a. Chromic Acids and Ceric Sulfate (Acid Conditions)	339
Wet Combustions	339
b. Neutral and Alkaline Permanganate	341
c. Silver Oxide	342
d. Copper Salts in Alkaline Solution	342
G. Microbial Oxidations	343
VIII. Ethers, Anhydrides and Unsaturated Derivatives	345
1. Ether Derivatives (External)	345
A. Alkylation Methods	346
B. Trityl Derivatives	348

CHAPTER	PAGE
2. Carbohydrate Inner Ethers (Anhydrides).....	350
A. Five-membered Rings. 1,4 and 3,6 Types.....	351
B. Isohexides (1,4-3,6-Hexides).....	354
C. 2,5-Anhydro Compounds.....	354
D. 1,5-Ether Rings.....	359
E. Epoxy Derivatives.....	361
F. Biochemistry and Reactions of Sugar Alcohol Anhydrides (Glykitans).....	362
a. Biochemistry.....	362
b. Reactions with Inorganic Reagents.....	363
c. Reactions with Organic Reagents.....	366
3. Unsaturated Sugars (Glycals and Glycoseens).....	369
A. Glycals.....	369
B. Glycoseens.....	372
IX. Nitrogenous Derivatives.....	375
1. Glycosylamines.....	376
A. Osimines or Primary Glycosylamines.....	376
B. N-Glycosides.....	377
a. Preparation.....	379
b. Reactions of N-Glycosides.....	385
c. Amadori Rearrangement.....	386
d. Nucleosides.....	388
2. Nucleotides.....	390
A. Preparation and Structure.....	390
B. Adenosine Di- and Tri-phosphoric Acids.....	392
C. Biologically Important Substances Related to the Nucleotides.....	393
3. Nucleic Acids.....	396
A. Thymus Desoxyribonucleic Acid.....	398
B. Yeast Ribonucleic Acid.....	399
4. Reactions of the Sugars with Substituted Hydrazines and Hy- droxylamine.....	401
A. Hydrazones and Osazones.....	401
B. Oximes.....	410
5. Derivatives in Which an Amino Group Replaces a Primary or Secondary Hydroxyl Group.....	412
A. Amino Sugars (Glycosamines).....	412
B. Glycamines and Desoxy Amino Glykitols.....	419
6. Combinations of Sugars with Amino Acids and Proteins.....	420
A. Preparation.....	421
B. Protein-Carbohydrate Compounds as Synthetic Antigens.....	425
X. Oligosaccharides.....	427
1. Individual Oligosaccharides and Their Classification.....	430
2. Synthesis of Oligosaccharides.....	430
A. From Naturally Occurring Oligosaccharides.....	430
B. Condensation of Two Monosaccharide Molecules.....	432
3. Determination of Structure.....	435
4. Ease of Acid Hydrolysis.....	437
5. Preparation, Properties and Structures of Some Natural Oligosac- charides.....	438

CHAPTER	PAGE
A. Disaccharides.....	438
B. Tri- and Tetrasaccharides.....	455
XI. Naturally Occurring Glycosides and Glycosidases.....	459
1. Anthocyanidin and Flavanol Glycosides.....	460
2. Indican.....	462
3. Aglycons Related to Phenanthrene.....	463
A. Cardiac glycosides.....	463
B. Saponins.....	465
4. Substituted-Phenyl Glycosides.....	466
5. Vanillin and Coumarin Glucosides.....	467
6. Cyanogenetic Glycosides.....	468
7. Hydroxyanthraquinone Glycosides.....	469
8. Sugar Components of Natural Plant Glycosides.....	470
9. Thioglycosides and thiosugars.....	472
10. Streptomycin.....	474
1. Introduction and Classification.....	474
2. Mechanism of Action.....	476
A. Kinetic Equations and Effect of Substrate Concentrations.....	476
B. Mechanism.....	481
C. Influence of Hydrogen Ion Concentration.....	483
D. Measurement of Activity and Influence of Enzyme Concentration.....	484
E. Temperature Influences.....	485
3. Chemical Composition of Glycosidases.....	487
A. β -Glucosidase.....	487
B. Yeast Invertase.....	488
4. Enzymes of Almond Emulsin.....	488
A. Preparation and Purification.....	488
B. Optimal pH.....	489
C. Enzymes Present.....	489
D. Specificity of the β -Glucosidase.....	492
5. Occurrence and Specificity of Other β -Glucosidases.....	499
6. Alfalfa and Coffee Emulsins.....	502
7. Yeast Glycosidases.....	503
8. Enzymic Synthesis of Glycosides.....	507
9. In Vivo Synthesis of Glycosides.....	509
10. Bourquelot Biochemical Determination of Glycosides and Oligosaccharides in Plant Materials.....	510
XII. Classification and Determination of Structure of the Polysaccharides.....	512
1. Structural Classification of the Polysaccharides.....	513
2. Classification Based on Biological Function.....	514
3. General Procedures for the Determination of the Structures of the Polysaccharides.....	514
A. End Group Analysis.....	515
B. Structure of a Bacterial Dextran (an Example of Structural Analysis).....	519

CHAPTER	PAGE
4. General Procedures for the Determination of the Molecular Weight of High Polymers.....	521
A. Osmotic Pressure Method.....	522
B. Ultracentrifuge.....	523
C. Viscosity Measurements.....	525
D. Light Scattering Method.....	527
E. Other Methods.....	528
XIII. Cellulose.....	529
1. Occurrence and Structure.....	529
A. Occurrence.....	529
B. Chemical Evidence for Structure.....	530
C. Molecular Weights of Cellulose and Derivatives.....	532
D. Crystalline Structure.....	536
a. Unit Cell.....	537
b. Spatial Molecular Model.....	538
c. Micellar Structure of Native Cellulose Fibers.....	539
d. Regenerated Cellulose.....	542
2. Reactions of Cellulose.....	542
A. Reactions with Bases, Acids and Salts.....	543
a. Ammonia, Amines, Quaternary Bases, etc.....	543
b. Action of Inorganic Acids and Salts.....	545
B. Cellulose Xanthate.....	546
C. Oxycellulose.....	547
D. Cellulose Esters.....	548
a. Cellulose Nitrates.....	549
b. Cellulose Acetates.....	552
c. Other Esters.....	553
E. Cellulose Ethers.....	554
a. Methyl and Ethyl Ethers.....	555
b. Other Ethers.....	556
F. Methylene Derivatives.....	557
G. Hydrolysis by Enzymes.....	558
XIV. The Starches and Starch Substances.....	560
1. Introduction.....	560
2. Composition.....	561
A. General Composition of Starch Granules.....	561
B. Amylose and Amylopectin.....	564
C. Soluble Starches.....	569
D. Chemical Evidence for Structure.....	569
E. Molecular Weight of Starches.....	570
F. End Group Assay and Molecular Structure.....	572
G. X-Ray Diffraction Studies of Starch.....	576
3. Starch Esters.....	577
4. Ether Derivatives.....	579
5. Oxidation Products.....	580
6. The Action of Enzymes on Starch.....	582
A. Saccharogenic or β -Amylases.....	586
B. Liquefying Amylases.....	589
C. Schardinger Dextrins.....	592
D. "Synthetic" Starches and Phosphoamylases.....	594

CHAPTER	PAGE
7. Industrial Preparation and Utilization of Starch and Starch Products	597
8. Glycogen	599
XV. Polyuronides, Hemicelluloses, Plant Gums, Microbial Polysaccharides and Related Substances	602
1. Homopolysaccharides	602
A. Glucose Polymers	602
B. Fructose Polymers	604
C. Galacturonic Acid Polymers (Pectins)	607
D. Polymers of Other Hexoses, Pentoses and Uronic Acids	614
E. Polymers of Glucosamine (Chitin)	619
2. Heteropolysaccharides Derived from Several Sugar Types	620
A. Hemicelluloses and Cell-wall Polysaccharides	620
B. Mucilages, Gums and Gel-forming Substances	630
C. Polysaccharides Associated with Proteins and/or Micro-organisms	639
D. Mucopolysaccharides	640
E. Bacterial and Fungal Polysaccharides	642
F. Glycoproteins	646
AUTHOR INDEX	649
SUBJECT INDEX	669

CHAPTER I

INTRODUCTION*

1. Development of Carbohydrate Chemistry¹

The culture of sugar cane and the use of the juices as a sweetening agent appear to have originated in northeastern India. As early as 300 A.D., the crystalline sugar was known and used. Sugar cane culture was extended to China around 400 A.D. and to Egypt around 640 A.D.; from Egypt, the culture and use of the sugar spread gradually over North Africa to Spain and Sicily. The introduction into North America is ascribed to Columbus who brought the plant to Santo Domingo on his second voyage. Sugar cane cannot be grown well in Europe because it requires a tropical or semi-tropical climate, but the sugar was known in Europe during the fourteenth and fifteenth centuries and used as a costly sweetening agent. However, by 1600 many sugar refineries had been erected in Europe, and the use of cane sugar had become widespread.

The necessary restriction of the culture of sugar cane to tropical or semi-tropical lands stimulated the search for sweetening materials which could be obtained from plants native to the temperate region. This search led to the technical development on the European continent of the sugar beet during the latter part of the eighteenth century and especially in the early years of the nineteenth because of the continental blockade during the Napoleonic wars.

The desire to find sweetening agents stimulated the study of known products and of new sources. Honey, grape juice, and raisins were known to contain material which crystallized under some conditions. Marggraf in 1747 described a type of sugar which occurs in raisins. Lowitz (1792) isolated a sugar from honey which he indicated to be different from cane sugar. Proust (1802) claimed that grapes contain a sugar which is different from sucrose. The action of acids on starch was shown to produce a sweet sirup from which a crystalline sugar was isolated by Kirchoff in 1811. Later workers established that the sugar contained in grapes is identical with that in honey, in diabetic urine, and in the acid-hydrolyzates of starch and cellulose; it was given the name of glucose by Dumas (1838) and of dextrose by Kekulé (1866). Emil Fischer revived the name glucose, and it is now used generally in scientific work.

* The principal portion of this chapter was prepared by the late R. Max Goepf, Jr.

¹ For more details of the history and earlier work, the reader is referred to the following references from which the present discussion was abstracted:

a. E. O. von Lippmann, "Geschichte des Zuckers"; 2nd Ed., Berlin (1929).

b. "Beilsteins Handbuch der organischen Chemie," Vol. 31; J. Springer, Berlin (1938).

Our present knowledge of carbohydrate chemistry is an outgrowth of scientific inquiry into the composition of such common substances as sugar, honey, milk, starch, cotton, wood, vegetable gums, crabshells, and also the less familiar sweet principles, acids, pigments, and pharmacological extractives of numerous plants.

Due to their ease of isolation and purification, sucrose, lactose (milk sugar), starch, cotton cellulose, glucose and fructose were among the first to be studied, and their empirical composition was found to correspond to the general formula $C_n(H_2O)_x$. Since structural chemistry and the existence of hydroxyl groups and hydrogen as structural elements was unknown at the time, the substances were looked upon quite naturally as compounds of carbon and water, and were termed carbohydrates (French, *hydrates de carbone*).

It was soon learned that acid hydrolysis converted starch and cellulose, $[C_6(H_2O)_5]_x$, into glucose, $C_6(H_2O)_6$, with the uptake of one mole of water per C_6 unit. Cane sugar, $C_{12}(H_2O)_{11}$, took up one mole of water to give two $C_6(H_2O)_6$ sugars (hexoses), glucose and fructose. Lactose, another $C_{12}(H_2O)_{11}$ compound, gave glucose and galactose, both $C_6(H_2O)_6$. Hydrolysis of cherry gum yielded arabinose, $C_5(H_2O)_5$, a pentose. Another C_6 sugar, sorbose, was discovered in an old, fermented sample of sorb apple juice. Hence some of the carbohydrates came to be considered as anhydride polymers of the simpler sugars. Further work showed that arabinose, glucose, and galactose were polyhydroxy aldehydes (aldoses) while fructose and sorbose were polyhydroxy ketones (ketoses). Somewhat later a third C_6 aldose (aldohexose), mannose, was synthesized from mannitol, and subsequently found in nature. The actual structure of the three natural C_6 aldoses was unknown, but after the development of the Le Bel-van't Hoff theory it was evident that they were stereoisomers, since all were straight-chain compounds.

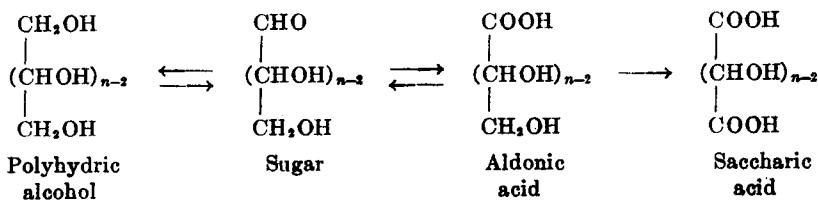
Meanwhile, the series of naturally occurring, homologous, straight-chain polyhydric alcohols: glycol, glycerol, erythritol (C_4), arabitol (C_5), mannitol, dulcitol, sorbitol, and iditol (C_6), and perseitol (C_7), had been discovered. They had the general formula $C_n(H_2O)_nH_2$, (in modern terms, $HOCH_2(CHOH)_{n-2}CH_2OH$). Erythritol and the higher members were crystalline, sweet-tasting and water-soluble. The four hexitols were known to be isomeric, but their relationship to each other and to the five natural C_6 sugars was not known until Emil Fischer's classical work in the early nineties.

Three dibasic acids of the series $HOOC(CHOH)_{n-2}COOH$ were likewise discovered very early, the C_4 tartaric acid from wine lees, and the isomeric C_6 mucic and saccharic acids from the nitric acid oxidation of lactose and of cane sugar.

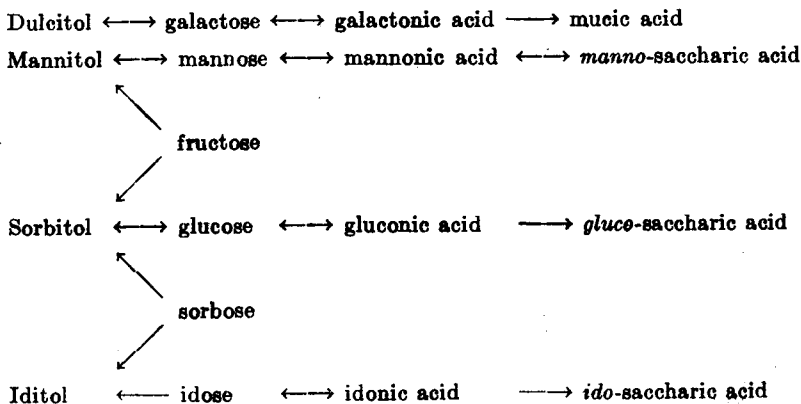
Similarly, a few monobasic or aldonic acids corresponding to the oxida-

tion of one end of a polyhydric alcohol or the aldehyde group of a sugar—hence of the formula $\text{HOCH}_2(\text{CHOH})_{n-2}\text{COOH}$ —were found. The first was glyceric acid, from glycerol and nitric acid, the next gluconic acid, from glucose. Subsequently gluconic acid was found to be a common product of the bacterial oxidation of glucose.

Application of established organic chemical reactions to these compounds demonstrated that the simple sugars, as aldehydes or ketones, could be reduced to alcohols, oxidized to mono- or dibasic acids, and reacted, under suitable conditions, with carbonyl reagents, such as phenylhydrazine, hydroxylamine, and hydrocyanic acid. The hydrocyanic addition reaction led to Kiliani's proof of a 2-keto structure for fructose, and also allowed the conversion of a C_5 aldehyde sugar to a C_6 sugar acid. Fischer showed that phenylhydrazine could be used for isolating various sugars, and that glucose, mannose and fructose had the same stereochemical configuration on carbons 3, 4 and 5. Similarly the alcohols could be oxidized to mixtures of sugars and sugar acids by nitric acid, and the acids, in the form of their lactones, could be reduced to the aldehyde sugars, and ultimately to the alcohols, by sodium amalgam.

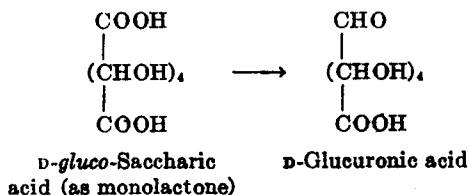


These interconversions, applied to the naturally occurring sugars, sugar alcohols, and derived acids, played an essential part in elucidating their structure, so that the chemistry of all four groups had a parallel development. The following family relationships were discovered.



It is noteworthy that sorbitol, glucose, and gluconic acid are all readily fermented, or utilized as a carbon source, by numerous species of molds and bacteria.

The sodium amalgam reduction of a saccharic acid monolactone to an aldonic acid goes by way of an intermediate, aldehyde acid. In this way glucuronic acid was first synthesized from a *gluco*-saccharic monolactone acid. It had been discovered previously in urine, hence the name.



Somewhat later, it was found that the C_6 aldehyde acids, or uronic acids, are widely distributed (citrus pulp, beet pulp, seaweed, cartilage, mucin, agar-agar) as polymers, known as polyuronides, analogous to starch and cellulose. Here again the glucuronic, mannuronic, and galacturonic acids were the only representatives found in nature.

Glucose, mannose and galactose residues likewise appear in epirhamnose, rhamnose, and fucose, six-carbon sugars in which the hydroxyl on carbon 6 is replaced by hydrogen, giving the 6-desoxy sugars or methylsoses.

Two other natural sugar types have been found, the 2-desoxy sugars, represented by the C_5 sugar, 2-desoxyribose, $\text{HOCH}_2(\text{CHOH})_2\text{CH}_2\text{CHO}$, present in many cell nuclei, and the 2-amino sugar, glucosamine, $\text{HOCH}_2(\text{CHOH})_2\text{CHNH}_2\text{CHO}$, obtained by the acid hydrolysis of chitin, a structural polymer in the shells of insects and crustaceans. Neither of these biologically important sugars has the empirical composition $\text{C}_6(\text{H}_2\text{O})_6$.

The glycamines, 1-desoxy-1-amino glykitols $\text{CH}_2\text{OH}(\text{CHOH})_n\text{CH}_2\text{NH}_2$, are another class of straight chain, polyhydroxylic compounds, wherein the characteristic functional group is NH_2 . They do not occur naturally, but ribamine, $\text{HOCH}_2(\text{CHOH})_3\text{CH}_2\text{NH}_2$ is a starting material for one of the riboflavin syntheses. The glycamines and their N-substituted derivatives are obtainable by pressure hydrogenation of sugars in the presence of ammonia, primary, or secondary amines.

A series of naturally occurring compounds having the carbohydrate formula $\text{C}_6(\text{H}_2\text{O})_6$ is known, which are not sugars, but cyclic polyhydric alcohols, or cyclitols, $\text{C}_6\text{H}_6(\text{OH})_6$, of which meso-inositol, possibly a provitamin, is the most important.

The simple carbohydrate formula $\text{C}_n(\text{H}_2\text{O})_n$ is also shared by a class of saccharinic acids, $\text{C}_{n-1}\text{H}_{n+1}(\text{OH})_{n-2}\text{COOH}$, obtainable by the alkaline isom-