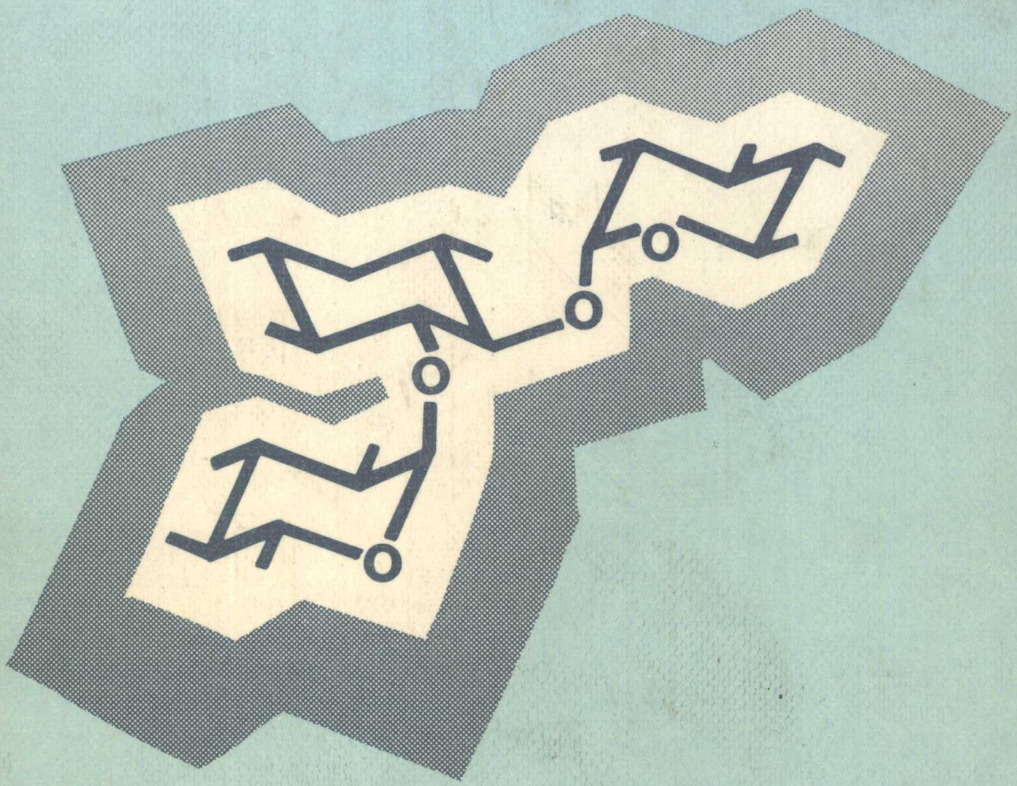
# Chemistry of the O-Glycosidic Bond:

## *Formation & Cleavage*



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# CHEMISTRY OF THE *O*-GLYCOSIDIC BOND

## *Formation and Cleavage*

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# CHEMISTRY OF THE *O*-GLYCOSIDIC BOND

## *Formation and Cleavage*

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As no better man advances to take this matter in hand, I hereupon offer my own poor endeavours. I promise nothing complete; because any human thing supposed to be complete must for that very reason infallibly be faulty.

(from *Moby Dick,* HERMAN MELVILLE)

# Preface

Carbohydrates can be considered from two distinct points of view. They are a class of organic compounds, which can be a subject of pure organo-chemical study — independent of their sources and role in the living cell. In this sense, for example, $C_4$, $C_5$, $C_6$, $C_7$ monosaccharides are of equal importance and septanose derivatives are no less interesting than pyranose. In other words, the development of study in these respects is determined by intrinsic logic of organic chemistry as such rather than bioorganic chemistry. On the other hand, carbohydrates are components of living systems with a great variety of important functions. The final aim of their studies from this viewpoint is an understanding of the function of carbohydrates in relation to their structures, and rational control of this function by man. Such an approach creates a definite hierarchy of problems, subordinated to the more general biological problem. In this sense, continuing the above examples, septanose rings are of negligible interest, being an unnatural form of sugar, whereas pyranose and furanose are of the greatest importance.

This book is written from the latter point of view. We have taken as a subject for treatment the chemistry of the *O*-glycosidic bond, which seems to be the most universal structural element of all carbohydrate-containing biopolymers and of low molecular weight natural compounds including monosaccharide residues. Consequently, the choice of material for this book was controlled by its relative importance for bio-organic chemistry first of all. On the other hand, progress in this field seems to be proportional to the contribution of the most recent methods and ideas of general organic chemistry. Therefore, the bio-organic viewpoint is reflected here in the choice of topics but not in the organo-chemical level of treatment.

Chemistry of the *O*-glycosidic bond has attracted the interest of investigators during the entire history of carbohydrate chemistry. Almost all leading laboratories have made important contributions to this field. In the last 3 to 5 years an even greater increase of interest has taken place. Numerous new names appear in the literature on the subject. In this book we have attempted to give systematic information both for experienced investigators and for those who are just beginning their work in this field.

Chapter 1 contains elemental data on *O*-glycosidic bond and plays an introductory role. It is addressed mainly to beginners.

The chemical formation of the *O*-glycosidic bond, and particularly the synthesis of oligosaccharides, is the most developed and extensively developing aspect of the field. Consequently, Chapters 2 and 3 are the most fundamental and comprehensive.

We have attempted to collect carefully not only the data on final results of investigations, but also promising new ideas and approaches. The synthesis of regular polysaccharides, being the most complex and difficult part of carbohydrate synthetic chemistry, is in the beginning of its development now. Therefore in Chapter 4 we have attempted to analyse a series of works of little success, the failures of which seem to be instructive for the future, and to discuss in detail the rare successful ones.

Chapters 5 and 6 are more fragmentary. The former contains illustrations of various other aspects of *O*-glycoside synthesis. The latter discusses a field which, in our opinion, is not developed enough for monographic treatment. On the other hand, the subject of Chapter 6 is covered by few recent reviews and it it did not seem reasonable to repeat them.

We want to thank Professor C. Schuerch and Professor N.S. Zefirov, who presented us with manuscripts of their work in the press, and Dr. M.I. Artsis and Dr. S.N. Senchenkova for technical assistance in the preparation of the manuscript.

We deeply thank Professor C. Schuerch, who took the not easy task of scientific editing of this book, and Academician N.M. Emanuel for his interest, help, and advice.

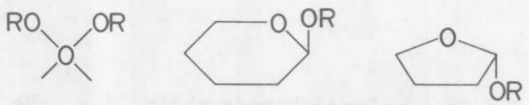
October 1977.

# Contents

Chapter 1

# General Characteristics of the *O*-glycosidic Bond

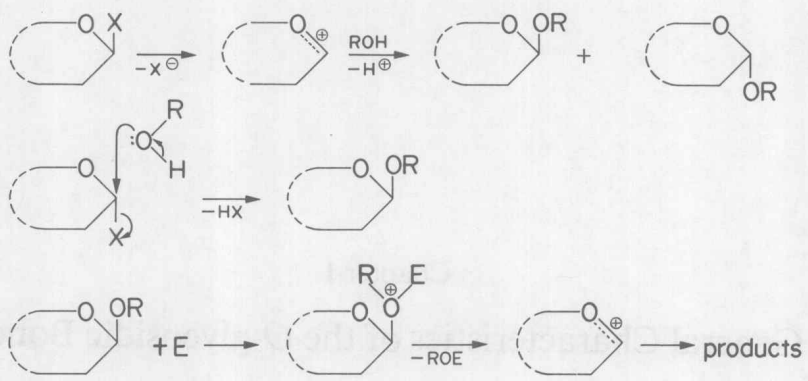
The *O*-glycosidic bond is an example of the acetal bond[1,2] and has the same set of fundamental properties. However, a series of structural features imparts to the *O*-glycosidic bond an inimitable chemical peculiarity which allows this structural unit to be distinguished as a separate chemical class. Actually, whereas ordinary acetals (as 1) are symmetric systems formed by condensation of two moles of an alcohol with a carbonyl compound (or by a chemically equivalent reaction), the sharp non-equivalence of the two alkoxyl groups attached to the glycosidic centre is characteristic of the *O*-glycosidic bond (as in 2 or 3).

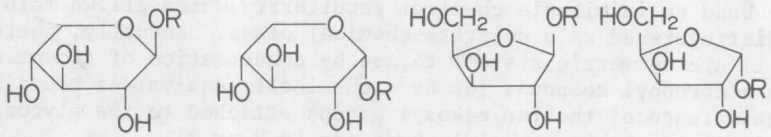



1 2 3

One of these groups is included in the cyclic system, whereas another is exocyclic and is much more reactive than the former. So the typical reactions of formation and cleavage of the *O*-glycosidic bond proceed by exchange of exocyclic residues of the acetal system in which the oxygen heterocycle remains unreacted. Therefore the chemistry of these reactions can be considered mainly as a chemistry of nucleophilic substitution at the glycosidic centre, which occurs with retention of the cycle by the following generalized schemes (see the next page).

Another fundamental feature of the glycosidic bond is related to cycle isomerism and chirality of the glycosidic centre. Both pyranosides (4 and 5) and furanosides (6 and 7), as well as glycosides with opposite configurations (4 and 5, 6 and 7), represent four different compounds from the formal point of view. Practically, however, they are derivatives of the same monosaccharide (D-xylose in the particular case) related to parent sugar both in metabolic pathways and in synthetic chemistry. Therefore in structural studies the following question normally arises: With what type of glycosidic bond (of four possible ones) is this particular monosaccharide unit included into more complex molecule? Similarly, the typical synthetic problem in the field can be formulated as follows: How can a compound with a definite type of glycosidic structure (one of four possible) be obtained from the particular monosaccharide and the particular aglycone?




A monosaccharide residue in a polysaccharide chain, i.e. the principal structural unit of carbohydrate-containing biopolymers, has a number of alcoholic hydroxyl groups. Any of them can be linked with another monosaccharide unit with an *O*-glycosidic bond, which, in turn, can be of any of four types mentioned above. Taking into consideration the great variety of monosaccharides found up to now in biopolymers, one can easily see the wide variety of glycosidic units which are the subject of attention in the synthetic or structural study of these classes of biopolymers and related compounds.

The basic methods for the synthesis of each of four types of glycosides are often quite different. The rates and even mechanism of acid-catalysed solvolysis (as hydrolysis) of different glycosides vary widely as well. Therefore the reactions of formation and cleavage of *O*-glycosidic bonds can hardly be described in a simplified generalized form.

The problem of *glycoside synthesis* in its narrow sense would seem to be solved with the creation of methods for making glycosidic bonds of any particular sugar with definite configurations of the glycosidic centre and definite ring size. In the light of such a definition, however, a synthesis of methyl-α-D-glucopyranoside (which has been successfully carried out at the end of the last century) and a synthesis of branched D-glucan of glycogen or amylopectin type (which can hardly be expected in the near future), seem to be of the same level of difficulty. Obviously such an estimate cannot be right. Therefore the problem of glycoside synthesis should be discussed in the wider context of related problems of modern

carbohydrate chemistry.† Among them should be mentioned first of all the synthesis of oligosaccharides as fragments of carbohydrate-containing biopolymers, the synthesis of natural polysaccharides and their models, as well as the synthesis of natural glycosides and their analogues. The solution of such problems requires a body of synthetic methods which are not limited to those providing the formation of a glycosidic bond of a particular monosaccharide of appropriate configuration and ring size. In addition the methods used should lead to regiospecific building of the linkage towards a definite hydroxyl group of a polyfunctional aglyconic component (of carbohydrate or non-carbohydrate nature). Self-condensation of the glycosylating derivative via its own hydroxyl groups (self-glycosylation) also has to be excluded by some method. A definite sequence of monosaccharide residues should be provided in the synthesis of oligo- and polysaccharide chains, as well as definite structure of branch points, etc.

Therefore the problem of glycoside synthesis in its wide sense includes a series of more particular problems, none of which can be sufficiently solved independently from others, and which create rather contradictory requirements. So, for example, the choice of a particular method of glycosylation for some synthesis determines the conditions of the main reaction and, therefore, the required properties of protecting groups used to provide its regiospecificity. The protective system in turn determines the possibilities and limitations of the creation of some monosaccharide sequences, which are usually achieved by means of selective removal and commutation of protecting groups. On the other hand, the course and features of glycosylation reactions are often dependent on the kind of substituents in reacting carbohydrate derivatives etc.

Because of the above considerations only very few of many glycoside-forming reactions can serve as general synthetic methods. In fact, these reactions should be effective, general, compatible with the use of appropriate protective groups, regiospecific (ring size), and stereospecific. The latter requirement is of special importance. A separation of anomers (i.e. glycosides with opposite configuration) can present difficulties even in the case of the simple glycosides. It becomes a serious problem in the case of compounds with complicated aglycones, which can appear to be almost insoluble when one operates with higher oligosaccharides. In the synthesis of polysaccharides, a non-stereospecific glycoslyation reaction leads to incorporation of anomalous linkages into the chain. Contrary to the synthesis of low molecular compounds, these linkages are not a removable contaminant but a part of the main chain that cannot be removed without destruction of the macromolecule.

A number of features of the *cleavage of O-glycosidic bond* are interesting. First of all this reaction provides one of the most universal methods of structural analysis of oligo- and polysaccharide chains and of low molecular glycosides (e.g. acid-catalysed hydrolysis and acetolysis). In this respect a knowledge of relative rates of cleavage of glycosidic linkages of different types is of importance. Moreover, methods providing selective (or, ideally, specific) splitting of one type of glycosidic bond increase immeasurably the information available from destructive analysis (cf. reviews[9,10]) and are especially desirable here (enzymic hydrolysis, incomparable in its specificity,[11,12] is outside our scope).

Hydrolytic cleavage is also of industrial importance with cellulose[13,14] and some other polysaccharides. The partial degradation of cellulose is one of the technological stages of its manufacture and as such is a desirable process. On the

†For general carbohydrate chemistry see, for example, monographs 3-7, the series of modern and informative reviews,[8] as well as the periodic issues *Advances in Carbohydrate Chemistry and Biochemistry* (Academic Press) and *Methods in Carbohydrate Chemistry* (Academic Press).

other hand, in a variety of treatments and uses of polysaccharides a cleavage of their glycosidic bonds is a harmful phenomenon. For example, in preparation of cellulose acetates the acetolysis of glycosidic bonds is one of the main side reactions resulting in a decrease of molecular weight and quality of the product.

In addition to the above-mentioned sources of interest in glycosidic bond splitting, these reactions attract the attention of investigators from the theoretical point of view. Historically, hydrolysis of glycosides is a traditional reaction for kinetic study, and the acid hydrolysis of sucrose is the first classical example of an A-1 reaction. The mechanism of these and related reactions remains up to now a series of unsolved problems which have a general interest due to just that very textbook character of these reactions.

Finally, the chemistry of reactions at the glycosidic centre, and particularly reactions related to the *O*-glycosidic bond, provoke modern organic theory to explain their surprising features and to solve a series of mechanistic problems which are not made more simple by the fact that all events occur around just a few atoms.

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Chapter 2

# Formation of the *O*-glycosidic Bond: General Discussion

## 2.1. Introduction

The previous chapter shows that the problem of glycoside synthesis has a complex character and cannot be limited solely to reactions leading to glycosidic bond formation. In this chapter we shall discuss the problem only in its narrow sense, i.e. the chemistry of reactions at the glycosidic centre irrespective of their application to syntheses of particular classes of compounds. The specific complications appearing in the synthesis of basic types of derivatives with glycosidic linkages and the ways of overcoming them will be outlined in the following chapters. An exception in this chapter will be made only for synthesis of lower glycosides, which occupies a peculiar position in this area.

Obviously there is no *fundamental* difference between synthesis of some glycoside from, say, methanol and from a more complicated alcohol, as, for example, cholesterol. There is, however, an important *technical* non-equivalence of these cases with a series of consequences. Usually lower alcohols are more reactive and, in addition, can be used in large excess or even as a solvent in a reaction with a glycosylating reagent. These conditions cannot be obtained with alcohols of complicated structure. Therefore a glycosylation of lower alcohols can be successful even by means of relatively slow reactions or by reversible ones with unfavourable equilibrium constants, or by reactions complicated by side processes. On the contrary application of such reactions to complex aglycones can provide only quite impractical results. Thus these reactions cannot serve as general synthetic methods.

Synthesis of lower glycosides has always been a conventional model system for investigation of regularities and mechanism of known glycosylation reactions and for a search for new or improved synthetic methods in the field. In view of the preceding considerations, one can consider, however, that such a principle of study is not indisputable. Therefore most generalizations concerning glycoside formation were derived from the results of detailed study of lower glycoside synthesis. In addition, an appreciable contribution to an understanding of the regularities and mechanisms of these reactions was made on the basis of experimental data accumulated during preparations of complex glycosides and especially oligosaccharides. So the general description of reactions at the glycosidic centre made in this chapter is based on the whole complex of data on glycoside synthesis, whereas attention is concentrated on the reactions at the glycosidic centre.

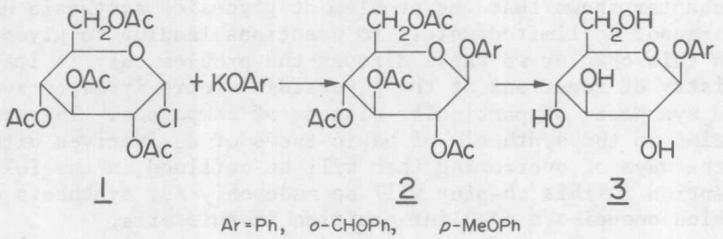
## 2.2. Literature

Various aspects of the problem of *O*-glycoside synthesis are covered by a number of reviews and monographs. Nucleophilic substitution at the glycosidic centre is discussed in reviews 1 and 2 and monograph 3. Aspects of the glycoside synthesis as such are reflected in monographs 3-5 and reviews 6-13; the related topics, particularly chemistry of glycosylating reagents, in reviews 13-16.

## 2.3. Historical background

The first synthesis of an *O*-glycoside was carried out by Michael[17] about 100 years ago. Although this work already demonstrated many features of methods applicable for complex glycoside synthesis, the further development of the field had to wait until the fifties or in part even the sixties before a clear understanding of specific problems in this area had been achieved and the basic principles for preparative synthetic methods had been formulated. The following principal advances should be mentioned first of all.

In the work by Michael[17] the simplest natural aryl glycosides 3 were synthesized by condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride 1 with potassium phenoxides via acetates 2 by the scheme:

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Ar = Ph, *o*-CHOPh, *p*-MeOPh

A few fundamental synthetic approaches were introduced in this pioneering study, which later became of almost universal application. They are:

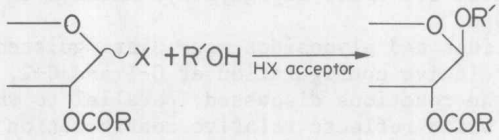
(1) The use of a glycosylating derivative with a fixed cyclic system providing the formation of a glycoside with a definite ring size.
(2) Activation of the glycosidic centre by an anionic leaving group (halogen).
(3) The use of acetyl protecting groups on the glycosylating reagent, which prevented its self-condensation and provided a convenient synthesis of starting material as well as an easy removal of protection from the product.† In addition, the introduction of acyl groups resulted in the effective stereochemical control of substitution at C-1. To understand this effect, 60 further years had to pass until Isbell's works were published (see below).

In 1893 Emil Fischer, one of the creators of scientific carbohydrate chemistry,[18] proposed a synthesis of lower glycosides, now known by his name, based on acid-catalysed alcoholysis of monosaccharides.[19,20] This reaction was convenient from a preparative point of view due to its simplicity but gives rise to a mixture of isomeric glycosides. Thus it is not able to solve the problem of glycoside synthesis on the whole.

In 1901 Koenigs and Knorr[21] extended the approach of Michael for glycosylation of

†Under the particular conditions used by Michael the removal of acetyl groups occurred in the reaction mixture. (Absolute ethanol was used as a medium.) This imperfection was improved by further investigators.

alcohols. In contrast to condensation with phenoxide ion, which leads to splitting off a neutral salt, glycosylation of alcohol by halide of type 1 proceeds with a liberation of hydrogen halide, which has to be removed to prevent side processes. For this purpose Koenigs and Knorr used silver oxide added to the mixture as a hydrogen halide acceptor (a point quite clear to the authors) and as a catalyst of condensation as well (a point that became clear only 30-40 years later). The reaction described is widely used with only limited improvements up to the present as one of the main general methods for synthesis of complex glycosides according to the scheme†




Until the sixties, the further development of methods of glycosylation proceeded almost exclusively along the lines of the Koenigs-Knorr reaction - its investigation, improvement, and synthetic utilization. In the late twenties, in the series of works by Helferich††[23-27] and Freudenberg with their colleagues,[28,29] the Koenigs-Knorr method was applied to the synthesis of oligosaccharides. The reaction conditions in these works were not far from the original procedure.

In the early thirties two important features of the reaction were recognised mainly due to investigations by Helferich *et al.*[30,31] The first was that formation of water by reaction of hydrogen halide with the acceptor used lead to hydrolysis of the starting material and a decrease in yield. Therefore the necessity of adding to the mixture as a third component a desiccant had become clear. The second was the catalytic function of acceptor silver ions, which promote splitting off halide ion. The clear understanding of this function was finally formulated later in works by Isbell and Frush.

The observation on the promoting role of traces of iodine added was made simultaneously.[30] Later, after 30 years, it was recognized that iodine is not a catalyst of the main reaction but rather an inhibitor of side processes,[32,33] although the mechanism of its effect is still unknown. By empirical optimization of reaction conditions appreciable successes were achieved in this period. For example, Reynolds and Evans[34] described the synthesis of the disaccharide gentiobiose in the record yield of 74%.

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†This synthetic method is well known as the Koenigs-Knorr method. It is far less known that a few months after publication of the work by Koenigs and Knorr the quite similar (and obviously independent) paper by Fischer and Armstrong appeared,[22] where the authors also proposed a synthesis of alkyl glycosides from derivatives of type 1. Therefore the name Koenigs-Knorr-Fischer-Armstrong method would seem to be more just.

††We should like to underline the role of B. Helferich in the development of the field. For 50 years various aspects of glycoside synthesis and reactions at C-1 have been fruitfully studied by this investigator and his co-workers. In particular they proposed a series of synthetic methods known as the Helferich method for the synthesis of aliphatic glycosides, the Helferich method for synthesis of aryl glycosides, and the Helferich method for the synthesis of sugar orthoesters.

Beginning in 1940 the series of excellent works by Isbell† and Frush[36-39] raised and partly solved fundamental problems of nucleophilic substitution at the glycosidic centre. From the viewpoint of glycosidic synthesis the main achievements of these investigations are as follows:

(1) For the first time in organic chemistry, before Winstein, the concept of neighbouring group participation in nucleophilic reactions was suggested.
(2) On the basis of this concept a logical view was developed which allowed one to explain uniformly the stereospecific formation of 1,2-*trans*-glycosides from 1,2-*cis*-acylglycosyl halides, the formation of orthoesters from 1,2-*trans*-acylglycosyl halides, and hindrance in the formation of 1,2-*cis*-glycosides from 1,2-*trans*-acylglycosyl halides in reactions of the Koenigs-Knorr type.
(3) Acylglycosyl halides and glycosides were distinguished and classified on the basis of their relative configuration at C-1 and C-2, which is of fundamental importance for the reactions discussed, parallel to the traditional α,β-classification, which reflects relative configuration of the glycosidic centre and C-4 in pentoses or C-5 in hexoses. The latter classification is not related to chemical features of reactions at C-1 and earlier could lead to confused interpretations, when compounds, classified as closely related, displayed a rather different reactivity.

In other words, this study provided the chemistry of the glycoside centre with a solid theoretical basis.

The next important step in the theoretical interpretation of reactions at the glycosidic centre were the studies by Lemieux and co-workers[1,40-45] and by Fletcher *et al*,[46-50] which were carried out in the next decade. In these works the concept of neighbouring group participation and its consequences underwent detailed treatment in the case of sugar acetates (Lemieux) and benzoates (Fletcher). Finally, in more recent studies[11] data on the fine mechanism of the reactions and the precise optimization of their conditions are accumulated.

The low yields and inconvenience of heterogeneous reaction mixtures that characterized the original version of the Koenigs-Knorr reaction have stimulated searches for improved modifications. Omitting numerous frail variations we shall consider here only the application of mercury(II) derivatives as hydrogen halide acceptors.

In the thirties Zemplen[51] proposed using mercury(II) acetate, soluble in organic solvents, as an acid acceptor that does not produce water and that in solvents of low polarity can promote preferential formation of 1,2-*cis*-glycosides in reactions of the Koenigs-Knorr type. The modification of Helferich *et al*.[52,53] appeared much more effective. Their procedure includes condensation of acylglycosyl halides with alcohols in aprotic polar media (in nitromethane or acetonitrile) with mercury(II) cyanide as a catalyst and an acceptor of hydrogen halide. The method usually provides high yields of glycosides and therefore has had a wide application, especially recently. The reaction under these conditions proceeds with low stereospecificity, unfortunately, and can lead to both 1,2-*trans*- and, more rarely, 1,2-*cis*-glycosides.

Recognition of two side reactions of glycosyl halides with acid acceptors was of practical interest for application of the Koenigs-Knorr reaction. Their condensation with silver oxide gives rise to orthoesters of complicated structure[32,33] (as 4), whereas reaction with mercury(II) cyanide leads to nitriles of anhydro-

†In addition to the discussion here, the theoretical contributions of Isbell[35] in the chemistry of the glycosidic centre and carbohydrate chemistry in general cannot be overestimated.