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The Synthesis of Unsaturated Carbohydrates

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The review deals with modern achievements in the chemistry of unsaturated carbohydrates. The methods of synthesis of these compounds, their use for the preparation of compounds of other classes, and in a few cases their properties have been analysed. A systematic account is given of the available data on the basis of the method employed, i.e. on the basis of the reactions used to form multiple bonds. The methods for the elimination of various groups, Grignard syntheses, the Knoevenagel - Doebner condensation, and the Wittig reaction are analysed in succession. Considerable attention has been devoted to the discussion of conformational effects and reaction mechanisms.
The bibliography includes 204 references.

CONTENTS

I. Introduction 477
II. Structural types and structure of unsaturated carbohydrates 477
III. Methods of synthesis of unsaturated sugars 478

I. INTRODUCTION

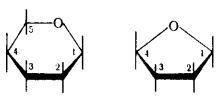
The chemistry of unsaturated monosaccharides has now become an extensive and fairly independent branch of carbohydrate chemistry. The interest in these sugar derivatives is due to the fact that their reactions constitute the basis of convenient methods for the synthesis of many biologically important compounds—deoxy- and amino-sugars, sialic acids, nucleosides, branched carbohydrates, sphingosines, etc.[1,2] Derivatives of unsaturated monosaccharides have been isolated from natural raw materials both in a free form (ascorbic and shikimic acids)[3] and as components of antibiotics (angustmycin[4], blasticidin[5]). Unsaturated carbohydrates are actively involved in the metabolism of the living cell, since the biosynthesis of aromatic compounds is associated with their various reactions[6]. Moreover, it has been shown recently that unsaturated monosaccharides play an important role in the acid and alkaline degradation of carbohydrates[7].

Many methods of synthesis of unsaturated monosaccharides are known at present. (We have covered the literature up to October, 1970, inclusive.) The aim of the present review is a systematic account of experimental data on the basis of reaction types and not the classes of unsaturated carbohydrates as in previous reviews[1,2]. This makes it possible to consider the problem from the standpoint of the general characteristics of organic synthesis.

The most modern carbohydrates nomenclature[8], proposed in 1963, is largely employed in the review, although trivial names are sometimes used.

II. STRUCTURAL TYPES AND STRUCTURE OF UNSATURATED CARBOHYDRATES

The unsaturated carbohydrates known at present can be divided into two independent groups in accordance with their structural features: cyclic and acyclic compounds. The first group has a greater variety of structures. It includes compounds with endo- and exo-cyclic double bonds. Pyranose (I) and furanose (II) structures are known with all possible types of location of the endocyclic double bond, i.e. $\Delta^{1,2}$-, $\Delta^{2,3}$-, $\Delta^{3,4}$-, and $\Delta^{4,5}$-derivatives (compounds of the last type are naturally only pyranose derivatives). $\Delta^{1,2}$-Derivatives are usually called glycals. $\Delta^{1/2}$-Derivatives of pyranoses and furanoses and also $\Delta^{3,4}$-derivatives of furanoses and $\Delta^{4,5}$-derivatives of pyranoses are essentially cyclic vinyl ethers. In compounds with an exocyclic double bond, the latter either adjoins directly the ring [compounds (III)] or is separated from it by one or several carbon atoms [compounds (IV)].

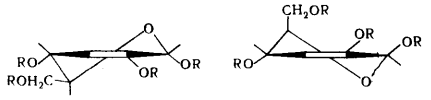


(I) (II)

R=CHR' (III) R = (I) or (II)
RCH=CHR' (IV) R' = H, Alk.

The following classes may be distinguished among unsaturated acyclic carbohydrate derivatives: polyols[1], aldehydo-forms[9], hydrazones[10], nitroalcohols[1], sulphones[11], keten dithioacetals[12], and aldonic[13] and glycaric acids[14].

Since unsaturated carbohydrates contain trigonal carbon atoms (sp^2-hybridisation), their conformations are distorted compared with the usual sugars. This is because the ethylene carbon atoms and two adjacent carbon atoms must be in the same plane. On the basis of general considerations[15], the half-chair conformations H1 and 1H are the most probable for the cyclic unsaturated carbohydrates of types (I) and (II). Recently NMR spectroscopic studies have been begun in order to establish the exact conformations of unsaturated sugars[16-19]. In particular, on the basis of the large coupling constant $I_{4,5}$ (6—10 Hz) for α-anomers of various derivatives of 3-deoxy-D-*erythro*-hex-2-enopyranose, Ferrier[18] suggested the occurrence of H-4 and H-5 diaxial interactions. From this it follows that the above compounds exist preferentially in the H1 conformation (V). β-Anomers of the same carbohydrate derivatives have low values of $I_{4,5}$ (1.5—2 Hz) and therefore are more likely to have the 1H conformation (VI):

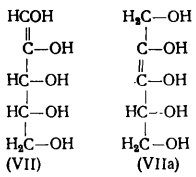


(V) (VI).

(R = Ac, Bz)

The results obtained are consistent with the general hypothesis[6] concerning the relative stabilities of the conformations of the α- and β-anomers (the anomer effect).

In a study and interpretation of the reactivities of unsaturated carbohydrates, account must be taken, together with steric factors, also of the distribution of electron density over their carbon atoms. The first attempt to perform a quantum-mechanical calculation of electron distribution in the molecules of unsaturated carbohydrates was made by Zhdanov and coworkers[20,21]. The results of calculations on endiols of types (VII) and (VIIa) show appreciable positive σ charges on the carbon atoms of the double bond. Structure (VII) may be regarded as analogous to that of a glycal for which attack by a proton on the second carbon atom is typical in electrophilic addition reactions. This may be explained by the fact that the π electron cloud, which interacts initially with the proton, is displaced to the $C_{(2)}$ atom with its high positive charge:



(VII) (VIIa)

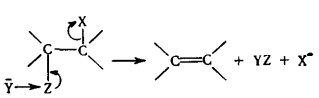
III. METHODS OF SYNTHESIS OF UNSATURATED SUGARS

There are two fundamentally different methods for synthesising unsaturated carbohydrates. These are firstly the elimination of various groups from substituted monosaccharides—the classical procedure for the formation of a double bond. Such reactions do not of course involve a rearrangement of the carbon skeleton of carbohydrates. The second method is based on a wide variety of condensations involving the carbonyl group of sugars which take place with a simultaneous increase in the length of the carbon chain.

1. ELIMINATION REACTIONS

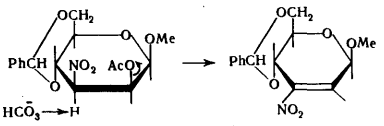
a. $\alpha\beta$-Elimination

Most elimination reactions leading to the formation of unsaturated sugars proceed via an $\alpha\beta$-elimination mechanism:

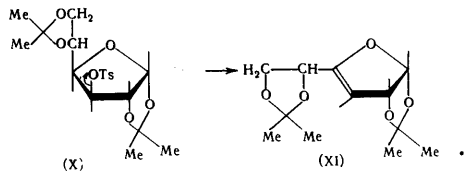


(X = OAc, OTs, OBz; Z = H, Hal).

The E_2 synchronous elimination mechanism, which reduces to a single-stage reaction of a base (Y^-) and the carbohydrate molecule, is the most probable. The most important condition for such eliminations is known to be a *trans*-diaxial disposition of the X and Z groups to be eliminated. Hence it follows that the E_2 mechanism occurs most frequently in rigid cyclic systems. Thus the elimination of acetic acid from the cyclic nitropyranoside (VIII) takes place readily[22,23] in the presence of a weak base such as sodium bicarbonate with a yield of 70—80%. In this case, elimination is evidently facilitated not only by the *trans*-diaxial disposition of the groups eliminated but also by the presence of the nitro-group which increases the acidity of the proton at $C_{(3)}$.

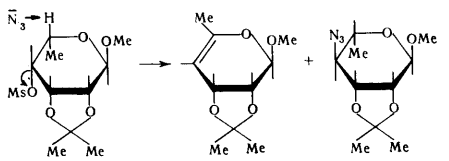


(VIII) (IX)



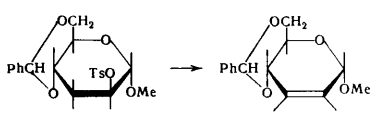
(X) (XI)

When there is no activation of this type, stronger bases are required: soda-lime, alkoxides, and azides. For example, on heating with soda-lime, the furanose (X) is converted[24] into 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-*erythro*-hex-3-eno-1,4-furanose (XI) and treatment of methyl 6-deoxy-1,2,3-*O*-isopropylidene-4-*O*-methanesulphonyl-α-L-talopyranoside (XII) with sodium azide yields[25] an unsaturated product (XIII) together with the azide (XIV) in proportions of 3:1 respectively:

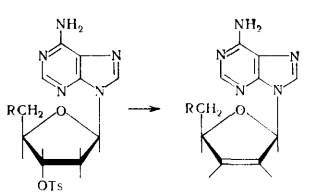


(XII) (XIII) (XIV)

In this case the deoxy-unit serves as the proton donor; other similar examples may be quoted[26,27]:



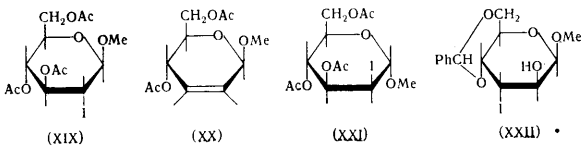
(XV) (XVI)



(XVII) (XVIII)

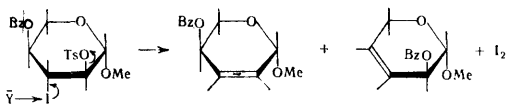
The elimination reaction where the first stage is the elimination of the halide ion (Z = Hal, left column) is also frequently used to form a double bond in the carbohydrate molecule. Thus when the pyranoside (XIX) was treated with $NaCo(CO)_4$, the product was methyl 4,6-di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranoside (XX). The analogous derivative of mannose (XXI) forms a $\Delta^{2,3}$-unsaturated compound under more severe conditions[28] owing to the *cis*-disposition of the groups eliminated. When an attempt was made to obtain the 2-*O*-methanesulphonyl derivative from the pyranoside (XXII) by treatment with

methanesulphonyl chloride in pyridine, methyl 4,6-*O*-benzylidene-β-D-*threo*-hex-2-enopyranoside was isolated[29]:



(XIX) (XX) (XXI) (XXII).

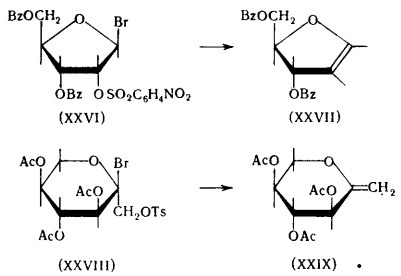
Sodium iodide in acetone is very often employed as the nucleophilic agent for the elimination reaction. Dimitrievich and Taylor[30] obtained by this procedure methyl 4-*O*-benzyl-2,3-dideoxy-β-L-glyceropent-2-enoside (XXIV) from the 3-iodo-derivative (XXIII) and also isolated the side product (XXV). The formation of two isomeric unsaturated sugars (XXIV) and (XXV) can be explained by the allyl rearrangement of the benzyl group in (XXIV) with formation of an equilibrium mixture of the $\Delta^{2,3}$- and $\Delta^{3,4}$-derivatives:



(XXIII) (XXIV) (XXV).

When tosyl derivatives of type (XXVI) are treated with sodium iodide in acetone, an unsaturated sugar (XXVII) and elemental iodine are also formed[31]. In this case the tosyl group is probably replaced by iodine and the resulting iodo-derivative undergoes elimination by the mechanism quoted above.

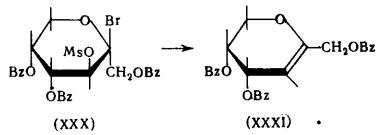
Using this possibility, Ness and Fletcher[31] obtained the furanal (XXVII) from the tosyl derivative (XXVI). Earlier attempts to synthesise (XXVII) by the usual methods for glycals (zinc in acetic acid) proved to be inapplicable owing to the lability of (XXVII) in acid media:



(XXVI) (XXVII)

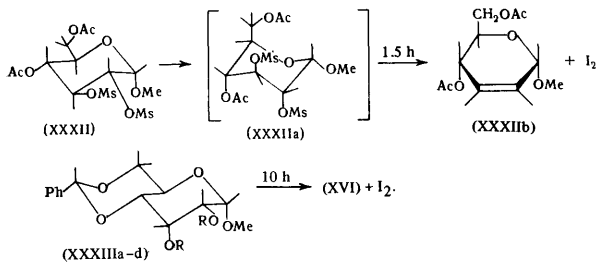
(XXVIII) (XXIX).

Using the method Ness and Fletcher, Tokuyama et al.[32] obtained 3,4,5-tri-*O*-acetyl-1,2-dideoxy-L-*xylo*-hex-1-enopyranose (XXIX) from 3,4,5-tri-*O*-acetyl-1-*O*-(*p*-tosyl)-α-L-sorbopyranosyl bromide (XXVIII). The glycal (XXXI) with an endocyclic double bond was obtained similarly from the bromide (XXX):



(XXX) (XXXI).

In this case, when both groups eliminated are identical (X = Z = OTs, OMs, *p*-$BrC_6H_4SO_2$, or *p*-$NO_2C_6H_4SO_2$), more severe conditions are required for the elimination process. Tipsom and Cohen[34] suggested that a 20% solution of sodium iodide in dimethylformamide (DMF) in the presence of zinc must be employed. The first step in this reaction is probably the replacement by iodine of one of the groups eliminated with formation of an iodide (see above). The latter is attacked by the nucleophilic agent, yielding an unsaturated derivative. Zinc is required to bind the iodine eliminated, which can add under the reaction conditions (boiling DMF) to the unsaturated carbohydrate formed, reducing its yield. Methyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (XXXIIIb) was obtained in this way from methyl 4,6-di-*O*-acetyl-2,3-di-*O*-methanesulphonyl-α-D-*gluco*-pyranoside (XXXII).[35] It is interesting to note that the elimination reaction with 4,6-*O*-benzylidine derivatives (XXXIII, a—d) is much slower[36] than with (XXXII), probably because the presence of the rigid *trans*-junction of two six-membered rings prevents the methanesulphonyl groups from occupying the *trans*-diaxial positions. The 4,6-diacetates (XXXII) can have the $C_{(1)}$-conformation (XXXIIa) at the instant of reaction, where both methanesulphonyl groups are *trans*-diaxial, which of course accelerates the elimination reaction.

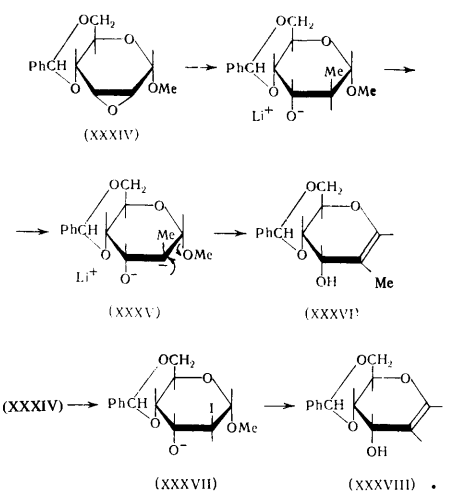


(XXXII) (XXXIIa) (XXXIIb)

(XXXIIIa-d) (XVI) + I_2.

(a) R = Ts; (b) R = Ms; (c) R = *p*-$NO_2C_6H_4SO_2$; (d) R = *p*-$BrC_6H_4SO_2$.

Epoxides are frequently used to synthesise unsaturated carbohydrates. *trans*-Diaxial ring-opening products (the Reichstein rule) are probably formed as intermediates in this process and subsequently undergo elimination by the mechanism described above (p. 478). For example, Horton and coworkers[36] treated the epoxide (XXXIV) with potassium ethylxanthate and obtained the $\Delta^{2,3}$-derivative (XVI). On the other hand, the use of methyl-lithium to open the ring of the epoxide (XXXIV) unexpectedly leads to the $C_{(2)}$-substituted glycal (XXXVI),[37-39] instead of the $\Delta^{2,3}$-derivative (XVI). The mechanism of this reaction has not been elucidated. The first stage is probably *trans*-diaxial opening of the epoxide ring with subsequent elimination of a proton from $C_{(2)}$. The resulting dianion (XXXV) is subsequently converted into the glycal (XXXVI) following the loss of a methoxide ion, as shown in the scheme below:

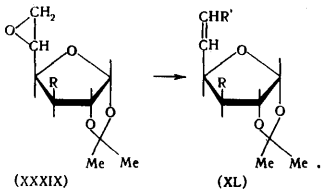


(XXXIV) (XXXV) (XXXVI)

(XXXVII) (XXXVIII).

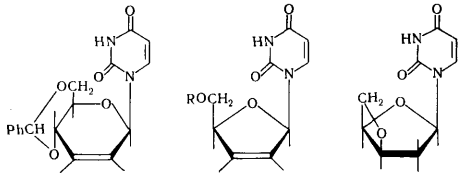
If the methyl-lithium solution contains lithium iodide, the initial epoxide (XXXIV) gives rise initially to the iodohydrin (XXXVII), with subsequent formation of the glycal (XXXVIII).

Methyl-lithium has been successfully used[40] also to open the terminal epoxy-ring of 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucose (XXXIX, R = OBz) to give the unsaturated furanoside (XL, R = OBz, R′ = H):



(XXXIX) (XL)

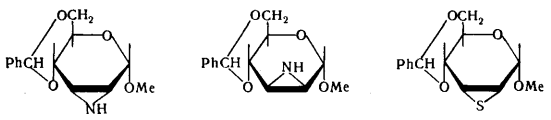
Unsaturated nucleosides (XLI) and (XLII, R = Bz, Tr, or H) have been synthesised by the reaction of epoxides with various nucleophilic agents[41,42]:



(XLI) (XLII) (XLIII)

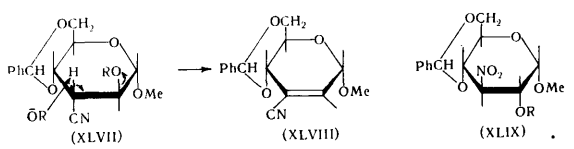
Horwitz et al.[43] described an interesting case of the ring opening of the anhydro-derivative (XLIII) by potassium t-butoxide in dimethyl sulphoxide (DMSO), which is also accompanied by the formation of the unsaturated nucleoside (XLII, R = H).

Together with the reactions of epoxides, the interaction of aziridine compounds of types (XLIV) and (XLV) and of the thi-iron (XLVI) with nucleophilic agents also gives rise to the corresponding unsaturated derivatives[36,44]:



(XLIV) (XLV) (XLVI)

All the reaction discussed above are examples of *trans*-elimination, characteristic of reactions proceeding via the E_2 mechanism. However, since, apart from steric conditions, the elimination reaction is controlled also by electronic factors, cases of *cis*-elimination are likewise possible. They occur mainly when the group eliminated (usually the proton) is activated by an electron-accepting substituent. For example, when an attempt was made to carry out epimerisation at the second carbon atom of the pyranoside (XLVII) with sodium methoxide, the cyanoolefin (XLVIII) was obtained instead of the expected epimer[45]:

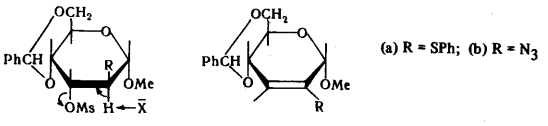


(XLVII) (XLVIII) (XLIX)

(R = H, Ac, Ts)

Despite the *cis*-disposition of the groups eliminated in the nitroglycoside (XLIX), the elimination process can nevertheless be carried out[46-50] albeit under more severe conditions (alumina in boiling toluene) than for the galactose derivative (VIII).

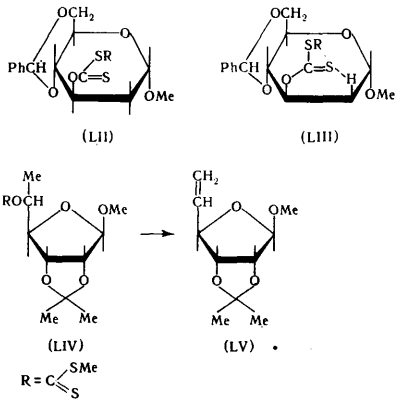
Hanessian[51] described the formation of the vinyl thioether (LIa) from compound (La) and an unsaturated azide (LIb) from (Lb) via *cis*-elimination under the influence of 1,5-diazabicyclo[4,3,0]nonene in dry DMSO. Owing to the large bulk of the nucleophilic agent employed, the competing nucleophilic substitution reaction was ruled out:



(a) R = SPh; (b) R = N_3

(L) (LI)

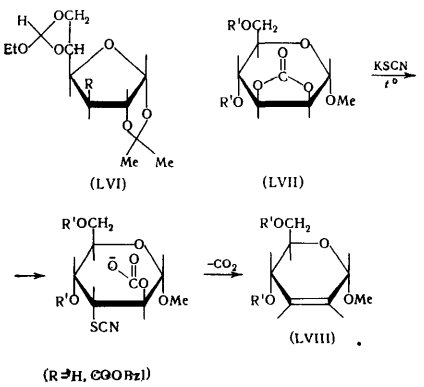
A classical example of *cis*-elimination in carbohydrates is the pyrolysis of sugar xanthate esters (the Chugaev reaction). Under these conditions, the hydrogen of the deoxy-units is as a rule involved in the elimination process. Thus the xanthates (LII) and (LIV) yield[52,53] methyl 4,6-*O*-benzylidene-α-D-*threo*-hex-2-enopyranoside (XVI) and methyl 2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranoside (LV). *cis*-Elimination can be readily accounted for by the formation of a six-membered intermediate transition state (LIII):



(LII) (LIII)

(LIV) (LV)

An unusual method for the conversion of a glycol group into a double bond involves the hydrolysis of cyclic orthoformates on heating the latter with acids. The furanoside (LVI) was converted in this way into an olefin (XL, R = OMe, or OCH_2Ph, R′ = H). Klemer and Mersmann[55] employed cyclic sugar carbonates to synthesise unsaturated carbohydrates. By treating methyl α-D-*manno*-pyranoside 2,3-carbonate (LVII) *in vacuo* at 120°C with potassium thiocyanate, they obtained the unsaturated methyl α-D-*manno*-pyranoside (LVIII). According to the mechanism proposed by the authors, in the first stage nucleophilic substitution takes place at $C_{(3)}$ with subsequent formation of (LVIII) and carbon dioxide:

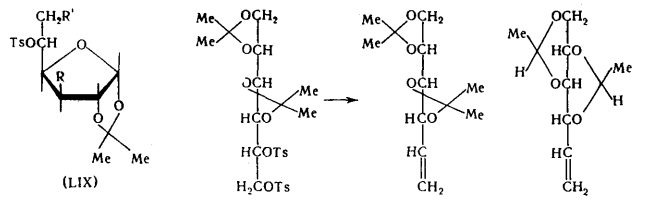


(LVI) (LVII)

(LVIII)

(R = H, COOBz)

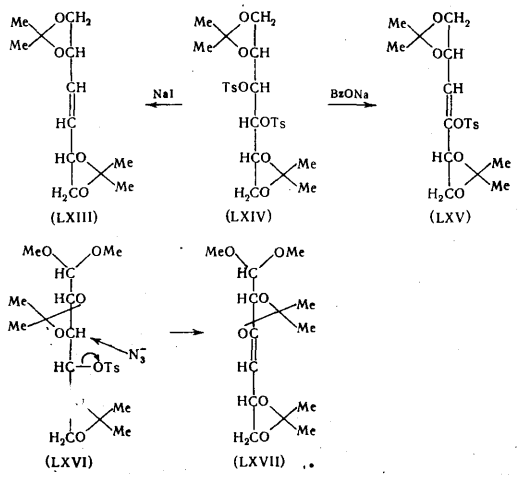
In cyclic systems, the *trans*-diaxial disposition of the groups eliminated, which is necessary for a successful elimination reaction, restricts the choice of the starting compound. Since in acyclic carbohydrate derivatives there is a possibility of free rotation of the substituents about the single carbon—carbon bond, this limitation is removed. In particular 5,6-dideoxy-1,2-*O*-isopropylidene-*α*-D-*xylo*-hex-5-enofuranose (XL, R = OH, R′ = H) and its 3-azido- and 3-*O*-methanesulphonyl derivatives are readily formed[56-58] when 5,6-ditosyl derivatives of type (LIX) are treated with sodium iodide in acetone. The mannitol (LXI) and sorbitol (LXII) derivatives have been synthesised similarly. According to the data of Foster and Overend[59], the reaction mechanism is similar to that quoted on p. 479.



(LIX) (R = OH, N_3, OMs; R′ = OTs, OMs) (LX) (LXI) (LXII).

When 1,3:2,4-di-*O*-ethylidenesorbitol 5,6-dinitrate is employed, an olefin (LXII) is also formed[60]. The initial reaction stage may be the replacement of the primary nitro-group by iodine but this intermediate has not been isolated. It is probably unstable and may be immediately converted into the olefin (LXII).

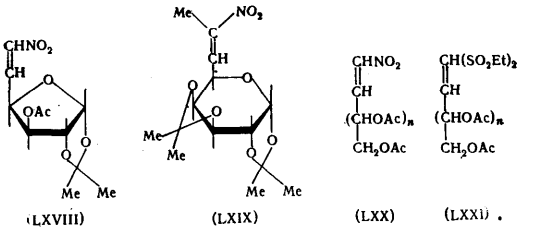
Since the secondary *p*-toluenesulphonyl group is replaced by iodine with considerable difficulty (p. 479), the synthesis of the polyol (LXIII) with a non-terminal double bond from compound (LXIV) requires more severe conditions of the kind used earlier for cyclic ditosyl derivatives of type (XXXIIIa). For example, Tipson and Cohen[34] converted 1,2:5,6-di-*O*-isopropylidene-D-mannitol 3,4-di(toluene-*p*-sulphonate) (LXIV) into 1,2:5,6-di-*O*-isopropylidene-*trans*-hex-3-ene-D-*threo*-1,2,5,6-tetrol (LXIII) by heating (LXIV) with a 20% solution of sodium iodide in DMF in the presence of zinc. Treatment of the product (XLIV) with sodium benzoate in DMF yields[61] an olefin (LXV) having a different structure, the formation of which can be accounted for by the classical E_2 mechanism.



(LXIII) (LXIV) (LXV) (LXVI) (LXVII).

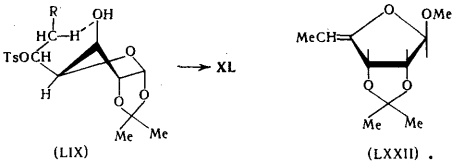
Paulsen[62,63] showed that, in the synthesis of the azide from the 4-*O*-tosyl derivative (LXVI), an unsaturated polyol (LXVII) is formed together with the expected product.

An increase of the acidity of the proton eliminated facilitates the elimination process. Thus the formation[64-71] of unsaturated nitro-compounds (LXVIII), (LXIX), and (LXX) proceeds equally readily regardless of the configuration of the initial carbohydrate. Acetic acid is eliminated even more readily[11,72], from sugar sulphone acetates with formation of a product of type (LXXI):



(LXVIII) (LXIX) (LXX) (LXXI).

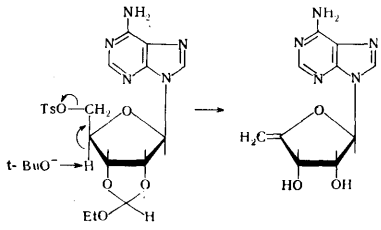
The elimination may be facilitated by the simultaneous involvement of adjacent groups[73-76]. For example, a number of workers[73,75] have shown that in the synthesis of olefins (XL, R = OH, R′ = OBz, H, or OTr) from 5-*O*-tosyl derivatives (LIX, R = OH, R′ = H, Bz, or OTr), the concentration of sodium methoxide employed as a base plays a significant role. In particular, an increase of the concentration of methoxide ions from one to four moles per mole of the initial tosyl derivative (LIX) increases sharply the yield of the olefin (XL). On the other hand, when the substituent at $C_{(3)}$ is resistant to alkalides, the corresponding olefin is hardly formed. All the above remarkable findings can be accounted for by the involvement in the elimination reaction of the hydroxyl at $C_{(3)}$ which facilitates the partial dissociation of the hydrogen atom at $C_{(6)}$, as shown in the scheme below:



(LIX) (LXXII).

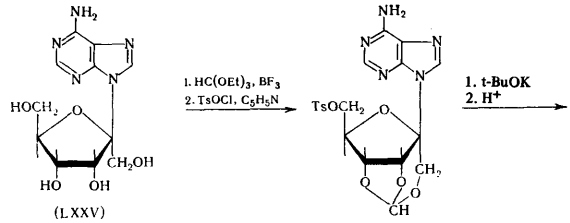
One should expect the elimination of the proton at $C_{(4)}$, but in this case the *trans*-orientation of the proton of the tosyl group is impossible owing to steric hindrance of the substituent at $C_{(3)}$. The reason for the formation[74] of the derivative (LXXII) on treating methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-tosyl-β-D-*allo*-furanoside (LIV, R = Ts) with alkoxides in hot alcohol is understandable from this standpoint. Here the simultaneous involvement of the hydroxy-group at $C_{(3)}$ is naturally impossible, while, on the other hand, the *trans*-orientation of the tosyl group and of the hydrogen atom at $C_{(4)}$ is quite likely, since the asymetric $C_{(3)}$ atom has the D-configuration. Compound (LXXII) is interesting because it is a structural analogue of the carbohydrate component of the nucleosidic antibiotic decoyinine[4] (XXVI). A closer analogue of decoyinine

(LXXIV) has been synthesised[77] from the 5-*O*-tosyl derivative (LXXIII):

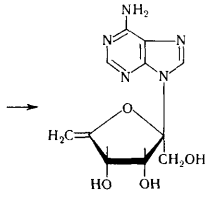


(LXXIII) (LXXIV)

On the basis of these preliminary studies, Robins and coworkers[77] achieved an elegant synthesis of decoyinine (LXXVI) from psicofuranine (LXXV):

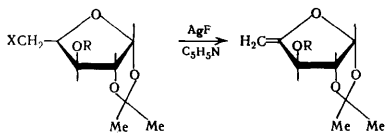


(LXXV)



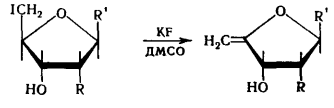
(LXXVI)

5-Halogeno-derivatives (LXXVII, a and b) and (LXXIX) can be employed[78-82], apart from tosyl derivatives, to introduce an exocyclic 4-methylene group:



(LXXVII) (LXXVIII)

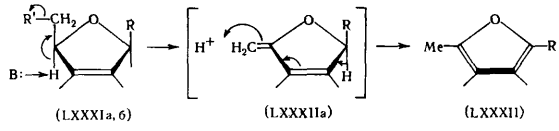
(LXXVIIa), L-configuration at $C_{(4)}$, X = I, R = H
(LXXVIIb), D-configuration at $C_{(4)}$, X = Br, R = Me



(LXXIX) (LXXX)

(a) R = H, R' = thymidyl
(b) R = OH, R' = uridyl

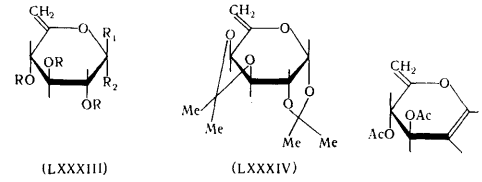
When an attempt was made to carry out a similar reaction[27,83] with unsaturated nucleosides of (LXXXI, a and b), only the furan derivatives (LXXXII) were obtained. Probably the product (LXXXIIa) formed initially readily loses a proton at $C_{(1')}$, yielding a stable nucleoside of type (LXXXII):



(LXXXIa, b) (LXXXIIa) (LXXXII)

(LXXXIa), R = thymidyl, R' = I
(LXXXIb), R = adenyl, R' = H or SEt.

The elimination of hydrogen halides under the influence of silver fluoride in pyridine has been used[1,84] also in the syntheses of numerous unsaturated derivatives of aldoses and aldosides of types (LXXXIII), (LXXXIV), and (LXXXV):

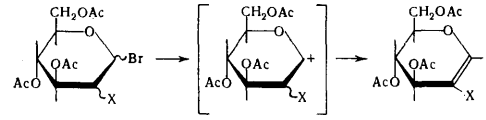


(LXXXIII) (LXXXIV)

(a) R = Ac; R_1 = H, R_2 = OMe;
(b) R = Ac; R_1 = OMe, R_2 = H

(LXXXV).

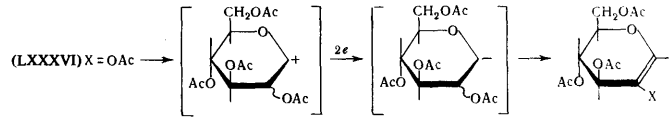
The well known derivatives of 2-hydroxyglycals (LXXXVIII) can be obtained by the elimination of hydrogen bromide from glycosyl bromides under the influence of diethylamine[1]:



(LXXXVI) (LXXXVII) (LXXXVIII).

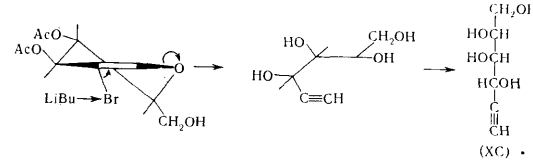
(X = OAc, NO, NO_2, Cl, SCN)

The rate of elimination of hydrogen bromide increases[85] following the addition of polar solvents. This finding is consistent with the E_1 mechanism via the intermediate sugar cation (LXXXVII), which the authors proposed. The elimination of hydrogen bromide from glycosyl bromides of 2-deoxy-sugars can yield an important class of unsaturated hydrocarbons—glycals (LXXXVIII, X = H). However, this reaction is of no preparative value, since the initial 2-deoxyglycosyl bromides are themselves obtained from glycals. The latter are usually synthesised by treating acetohalogenoses (LXXXVII, X = OAc) with zinc dust in acetic acid. As in the synthesis of 2-hydroxyglycals, the dissociation of the initial glycosyl bromide results in this case in the intermediate formation[1,86] of the sugar cation (LXXXVII, X = OAc). Subsequently a zinc atom transfers two electrons to this cation. The resulting carbanion (LXXXIX) is stabilised by the elimination of an acetate ion with formation of the glycal (LXXXVIII, X = H):



(LXXXVI) X = OAc (LXXXVII) (LXXXIX) (LXXXVIII).

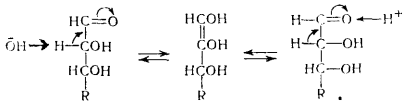
The 2-bromoglycal (LXXXVIII, X = Br) can be subjected[87] to a repeated elimination reaction by treatment with an excess of butyl-lithium. This results in the formation D-*lyxo*-hex-5-yno-1,2,3,4-tetritol (XC). The reaction constitutes a new method of synthesising carbohydrates with triple bonds:



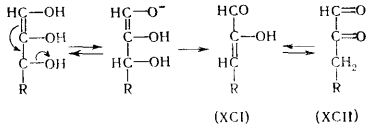
(XC).

b. β-Elimination

Many important unsaturated carbohydrates can be obtained as the result of 1,3-elimination reactions characteristic of all β-hydroxyaldehydes and β-hydroxyketones. These reactions, frequently referred to as β-elimination, are catalysed by both acids and bases. Their first stage is 1,2-enolisation, which accounts for the acid–base type of catalysis of these processes:

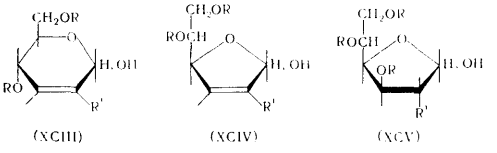


Next follows the elimination of the hydroxyl at $C_{(3)}$ with formation of the enol (XCI) which is in tautomeric equilibrium with the 3-deoxy-2-ketoglycose (XCII):



(XCI) (XCII)

The enol (XCI) can be isolated on a preparative scale only in the presence of a substituent at $C_{(2)}$, which prevents the conversion of (XCI) into (XCII). For example, in the presence of calcium hydroxide 2-*O*-methyl-D-glucose gave a high yield[88,89] of the 2-*O*-methyl ether of the enol, which exists, according to NMR spectroscopic data, as a mixture of the pyranose (XCIIIa) and furanose (XCIVa) forms, with the latter predominating:



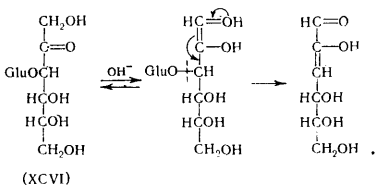
(XCIII) (XCIV) (XCV)

(a) R = H, R' = OMe; (b) R = Me, R' = OMe (c) R = Ac, R' = NHAc

(a) R = Me, R' = OMe (b) R = Ac, R' = NHAc.

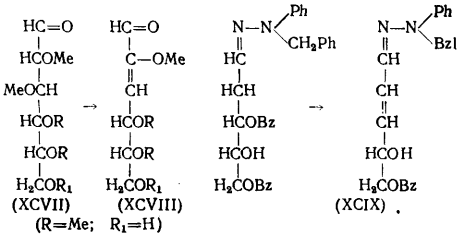
Under the influence of lime water, 2,3,5,6-tetra-*O*-methyl-D-glucose (XCVa) is rapidly converted[90,91] into the unsaturated derivative (XCIVb). On treatment with alkalies, the glucosamine derivative (XCVb) yields[92] the enamine (XCIVc).

The rate of β-elimination is determined by many factors. Thus, 2,3-di-*O*-methylglucose is converted into the enol much faster than 2-*O*-methylglucose. Hence, in order to accelerate β-elimination, it is necessary to have a substituent at the third carbon atom. Disaccharides, particularly 3-*O*-substituted derivatives, exhibit a similar behaviour. For example, 3-*O*-glucopyranosyl-D-fructose (XCVI) undergoes β-elimination in the presence of calcium hydroxide 23 times faster than D-fructose[93,94]. This also accounts for the extremely high sensitivity of such disaccharides to alkaline hydrolysis:



(XCVI)

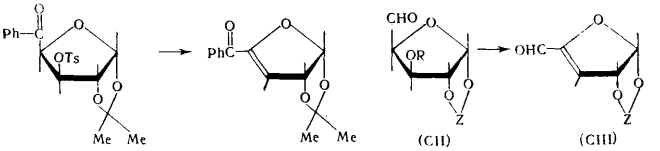
One of the factors controlling the rate of β-elimination is probably the concentration of the acyclic carbonyl form of the sugar, since this species is in fact involved in the enolisation reaction. Numerous experimental data confirming this hypothesis are now available. For example, 2,3,4,5-tetra-*O*-methylglucose (XCVII), which is distinguished by an enhanced content of the acyclic carbonyl form owing to the instability of the septanose ring, is very labile in alkalies. According to Anet's data[95], it is fully converted into the enol (XCVIII) after 2 min:



(XCVII) (R=Me; (XCVIII) R_1=H) (XCIX).

2-Deoxy-sugars and pentoses, in which the content of the aldehydo-form is higher than in hexoses, show a very high tendency[93] to undergo β-elimination. This explains the formation of unsaturated hydrazones of type (XCIX) when attempts are made to prepare the hydrazones of 2-deoxy-sugars.

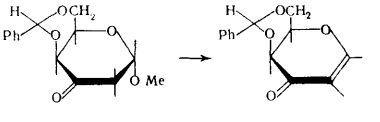
Naturally, fixed acyclic forms of hydrocarbons (the aldehydo-forms) undergo β-elimination most readily, which is sometimes employed for preparative purposes. For example, Anet[9] obtained the derivative (XCVIII, R = R_1 = Me) from the methylated aldehydo-form of glucose (XCVII, R = R_1 = Me) and Inch and Rich[96] synthesised the unsaturated ketone (CI) by heating the ketoaldose (C) with sodium carbonate in DMF. It was also shown that the dialdose derivative (CII) undergoes a similar reaction in the presence of alkalies with formation[97] of an αβ-unsaturated aldehyde (CIII):



(C) (CI) (CII) (CIII)

(R = Ts, Bzl; Z = CMe_2, C_6H_{10}).

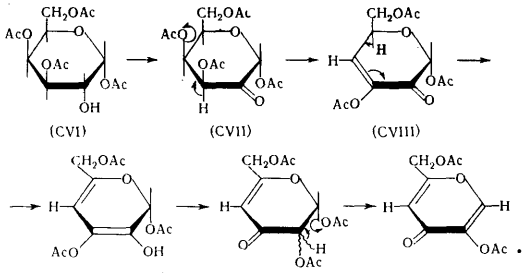
The group removed in the β-elimination reaction can also be the hydroxymethyl group at the glycosidic centre. Thus, in the presence of acids, the aldoketose (CIV) has been converted[98] into the derivative (CV):



(CIV) (CV).

Double β-elimination is possible in some cases. In particular, in the oxidation of the tetra-acetate (CVI) with DMSO in acetic anhydride in order to obtain the ketose (CVII), the diacetate of kojic acid (CXI) was obtained[99] in 84% yield. This unexpected result can be explained as follows. The ketone (CVII) formed initially undergoes β-elimination, yielding the acetate of the ketoenol (CVIII). The latter enolises further with formation of the acetate (CIX) in which the acetyl group undergoes intramolecular migration from $C_{(3)}$ to $C_{(2)}$. This results in the formation of the isomer (CX), which yields (CXI) after repeated

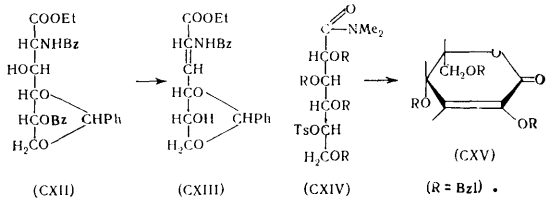
β-elimination. Since kojic acid does not contain an asymmetric carbon atom, any monosaccharide can be used to prepare it in this way:



(CVI) (CVII) (CVIII)

(CIX) (CX) (CXI)

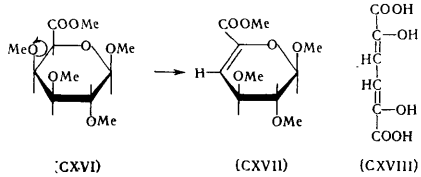
Apart from unsaturated aldoses and ketoses, unsaturated uronic, aldonic, and glycaric acid can be synthesised by the β-elimination reaction. The process proceeds via a mechanism analogous to that described above but is catalysed as a rule by bases (pyridine, sodium methoxide) or acetic anhydride. Thus methanesulphonation of ethyl 2-benzamido-4,6-*O*-benzylidene-5-*O*-benzoyl-2-deoxy-D-gluconate (CXII) led to the isolation of the unsaturated ether[1] (CXIII) instead of the expected 3-*O*-methyl derivative[1]:



(CXII) (CXIII) (CXIV) (CXV) (R = Bzl).

Treatment of the amide (CXIV) with potassium acetate in DMF gave[100] the product (CXV), which has the structure of an αβ-unsaturated lactone. A multistage mechanism has been proposed for this unusual reaction, but it requires further evidence.

It was shown above (see p. 483) that the hydrogen atom at $C_{(4)}$ in furanoses of types (C) and (CII) is acidic owing to the adjoining ring oxygen atom and an electron-accepting group. It is therefore not surprising that uronic acids can also undergo β-elimination in the presence of bases. Best results were obtained[101-103] by treating 2,3,4-tri-*O*-methyl derivatives of type (CXVI) with sodium methoxide in methanol:

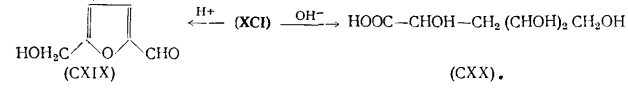


(CXVI) (CXVII) (CXVIII).

4,5-Unsaturated uronic acids of type (CXVII) have been isolated[104] following the enzymatic degradation of mucopolysaccharides. This is why conditions governing the synthesis of these interesting derivatives and the various related carbohydrates have been so carefully ascertained.

Naturally, in the deacetylation of the acetates of glycaric acids with alcoholic alkali[14], double β-elimination takes place with formation of a dienol (CXVIII).

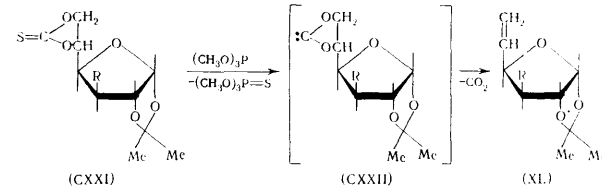
Thus a tendency towards β-elimination is characteristic of a wide variety of carbohydrates. Although frequently undesirable, this property of many sugars can be used for the preparative synthesis of unsaturated carbohydrates. However, the importance of β-elimination is not restricted to this factor. The concept of β-eliminations plays an important role in the explanations of processes such as acid and alkaline degradations of carbohydrates, which are at first sight different. As stated above (p. 483), in both cases the initial intermediate is the enol (XCI), subsequently converted either into furfural (CXIX) (or its derivatives) (acid medium) or into a glycaric acid (CXX) (alkaline medium):



(CXIX) (CXX).

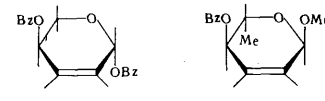
c. Elimination via the Carbene Mechanism

Among the wide variety of methods for synthesising unsaturated sugars, the formation of a double bond on stabilisation of various carbohydrate carbenes plays an important role. Sugar thiocarbonates can serve as a source of carbenes. According to the data of Horton and Turner[105,106], desulphuration of the thiocarbonate (CXXI) takes place under the influence of trimethyl phosphite. The resulting carbene (CXXII) is then stabilised by the elimination of carbonic acid, which yields 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (XL, R = OH):



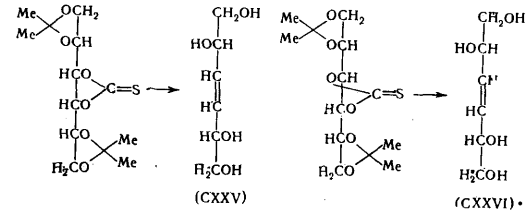
(CXXI) (CXXII) (XL)

Methyl 4,6-*O*-benzylidene-α-D-*threo*-hex-2-enopyranoside (XVI),[36] benzyl 4-*O*-benzyl-β-L-*glycero*-pent-2-enopyranoside (CXXIII), methyl 4-*O*-benzyl-6-deoxy-α-L-*threo*-hex-2-enopyranoside (CXXIV),[107] and even the Δ²,³-unsaturated nucleoside (XLII, R = Tr)[108] have been obtained similarly:



(CXXIII) (CXXIV).

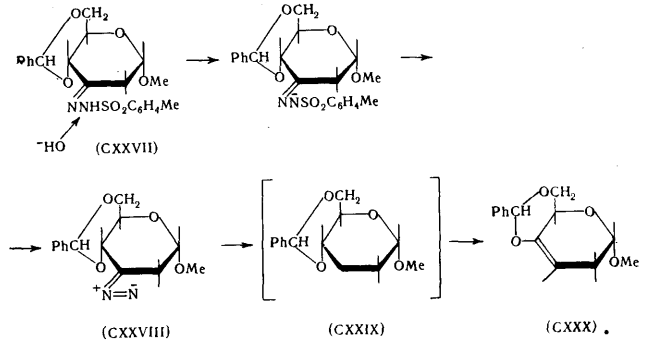
Haines[109] employed successfully the thionocarbonate method for the synthesis of the *cis*- and *trans*-isomers of 3,4-dideoxy-3,4-didehydro-D-*threo*-hexitol [compounds (CXXV) and (CXXVI)] which were isolated in the hydrolysis of substances characteristic of the blood groups:



(CXXV) (CXXVI).

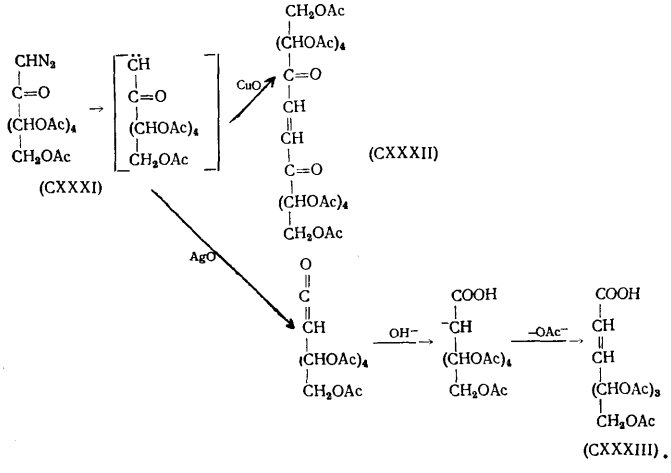
The thionocarbonate method is not the only example of the employment of carbenes for the conversion of carbohydrates into olefins. Ferrier[52] proposed a synthesis of unsaturated sugars based on the capacity of carbohydrates tosylhydrazones to yield olefins in the elimination reaction

catalysed by alkalies (the Wolff—Kishner reaction). The olefin (CXXX) was obtained in this way from the hydrazone (CXXVII). The mechanism of this elimination consists in the initial abstraction of a proton by the alkali and conversion into the diazo-compound (CXXVIII), which decomposes to the olefin (CXXX) via the intermediate carbene (CXXIX):



(CXXVII) (CXXVIII) (CXXIX) (CXXX).

The intermediate formation of a carbene has been observed[110] also in the decomposition of the acetates of 1-diazo-1-deoxyketoses (CXXXI) in the presence of copper(II) oxide, as shown by the isolation of the product (CXXXII). The decomposition of these diazoketoses in the presence of silver oxide (the Wolff rearrangement) yields[111] unsaturated acids (CXXXIII) via the mechanism



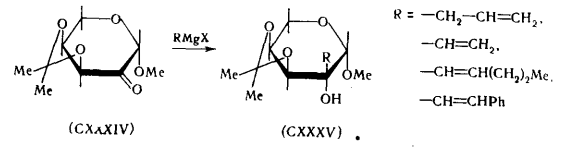
(CXXXI) (CXXXII) (CXXXIII).

2. NUCLEOPHILIC ADDITION VIA THE CARBONYL GROUP

The addition of nucleophilic agents via the carbonyl group of carbohydrates supplements significantly the methods described above for the conversion of sugars into olefins, since, apart from the introduction of a double bond, it involves an increase in the length of the carbon chain of the carbohydrate.

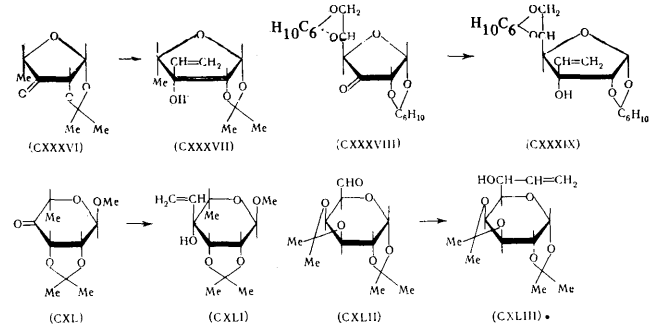
a. Interaction with Unsaturated Grignard Reagents

The condensation of the carbonyl forms of sugars with unsaturated Grignard reagents is as a rule stereospecific and therefore is frequently employed in the syntheses of carbohydrate derivatives; the method is applicable to the synthesis of streptose, 2-deoxyribose, and L-hamamelose. In their studies designed to develop the synthesis of L-hamamelose, Burton et al.[112] obtained a series of unsaturated sugar derivatives of type (CXXXV) by the condensation of methyl 3,4-*O*-isopropylidine-β-D-*erythro*-pentulopyranoside (CXXXIV) with unsaturated Grignard reagents. The preferential formation of isomers with the D-configuration at $C_{(2)}$ can be explained by the fact that the carbonyl group is screened below by the methoxy-group. Therefore only axial attack on the keto-group by the Grignard reagent is possible:



(CXXXIV) (CXXXV).

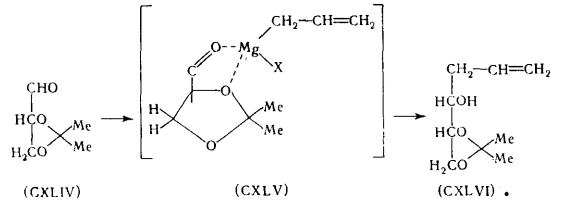
Unsaturated sugars of type (CXXXVII), (CXXXIX), and (CXLI) have been obtained by a similar procedure from the aldoketoses (CXXXVI), (CXXXVIII), and (CXL) respectively[113–115]:



(CXXXVI) (CXXXVII) (CXXXVIII) (CXXXIX)

(CXL) (CXLI) (CXLII) (CXLIII).

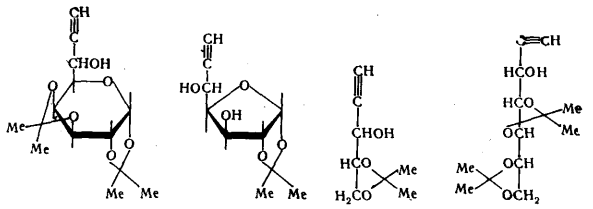
Apart from ketones, the aldehydo-forms of carbohydrates have been used for condensation with unsaturated organometallic compounds. The condensation of vinylmagnesium bromide and the dialdose (CXLII) yields[64,116] a mixture of isomeric unsaturated carbohydrates in which compound (CXLIII) predominates. Hough[3] obtained 1,2-*O*-isopropylidinehex-5-ene-1,2,3-triol (CXLVI) from isopropylidene-D-glyceraldehyde (CXLIV) and allylmagnesium bromide. The preferential formation of the isomer with the D-*ribo*-configuration becomes understandable if one postulates the existence of an intermediate magnesium complex (CXLV), proposed earlier[117,118] to account for similar reactions:



(CXLIV) (CXLV) (CXLVI).

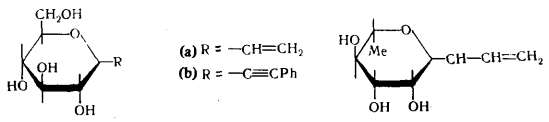
So far the Grignard reaction is the only general method for the introduction of a triple bond into the carbohydrate molecule. Thus the interaction of various aldehydo-forms of sugars with ethynylmagnesium bromide yielded[119–123] a

series of ethynyl derivatives of carbohydrates of the type (CXLVII)—(CL):



(CXLVII) (CXLVIII) (CXLIX) (CL)

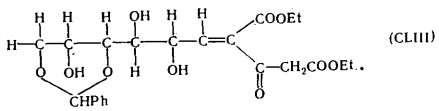
It is interesting to note the preferential formation of the product (CXLVIII) with the D-configuration at $C_{(5)}$, which can also be accounted for by the formation of a magnesium complex analogous to (CXLV). The interaction of acetohalogenoses with unsaturated organomagnesium compounds constitutes a remarkable complication of the Grignard reaction in carbohydrate chemistry. Compounds (CLI, a and b) and compound (CLII) were obtained respectively from acetobromoglucose[124,125] and acetobromorhamnose[126]:



(CLI, a and b) (CLII)

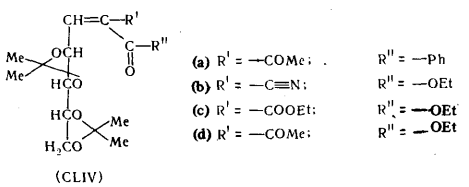
b. The Knoevenagel—Döebner Condensation

The reactivity of the carbonyl forms of sugar have also been used to synthesise unsaturated carbohydrates by the Knoevenagel—Döebner reaction. The interaction of 4,6-*O*-benzylidene-D-glucose with acetonedicarboxylic acid ester in the presence of piperidine yielded[127,128] the unsaturated ketoacid (CLIII):



(CLIII)

Zimmer et al.[129] investigated the reaction of a series of compounds with an active methylene group (benzoylacetone and malonic, cyanoacetic, and acetoacetic esters) with the al-form of 2,3:4,5-di-*O*-isopropylidene-D-arabinose. They isolated the unsaturated branched-chain sugars (CLIV, a—d):

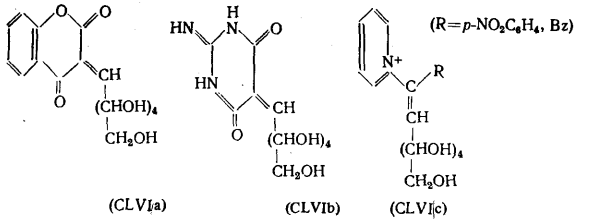


(CLIV)

When malonic acid was employed, unsaturated acids of type (CLV) were obtained similarly[130,131]:

R—CH=CHCOOH (CLV) (R = sugar residue).

A whole series of unsaturated sugars with heterocyclic groups (CLVI, a—c) have been synthesised by condensing the acetates of the aldehydo-forms of hexoses with the active methylene groups of 5-hydroxycoumarin[132], iminobarbituric acid[133,134], and Kröhnke [sic] salts[135]:

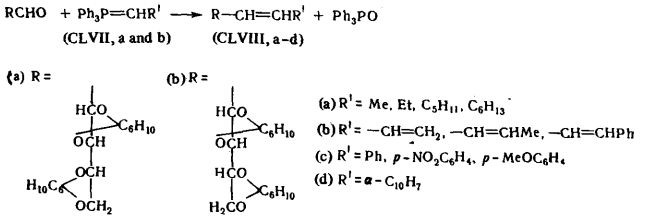


(CLVIa) (CLVIb) (CLVIc)

C-glycosylated 4-hydroxycoumarins (CLVIa) exhibit a high anticoagulant activity, surpassing somewhat heparin in the duration of its activity.

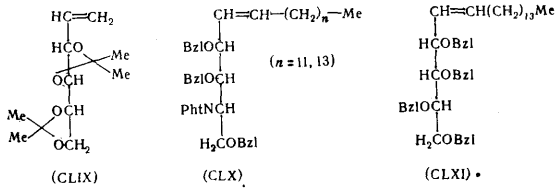
c. The Wittig Reaction

Among other condensation methods for synthesising unsaturated hydrocarbons, the most elegant and modern techniques involve the interaction of phosphoranes with the carbonyl forms of sugars (the Wittig reaction)[136]. The process is interesting because it is universal, takes place under mild conditions, and makes it possible to introduce a double bond into the monosaccharide molecules in a specific position. Intense studies on the conversion of carbohydrates into olefins by the Wittig reaction[137] showed the possibility of the synthesis of a wide variety of unsaturated sugar derivatives—*C*-glycosylated derivatives of aliphatic, aromatic, and heterocyclic compounds, and unsaturated aldoses, ketoses, and aldonic acids. Cyclic and acyclic aldehydo-forms of carbohydrates are usually employed as the carbonyl component. Free monosaccharides are inconvenient, since the products with a polyol residue obtained from them are unstable under the conditions of the Wittig reaction (p. 490). The choice of the aldehydo-form in each specific case depends on the reaction conditions and the reactivity of the phosphorane employed. For example, only the aldehydo-forms with acetal, methyl, and benzyl protecting groups can be employed for condensation[138] with reactive group I phosphoranes, since with acetylated aldehydo-forms of the sugars the phosphoranes are involved in side reactions with the protecting groups. In particular, condensation of 2,3:4,5-di-*O*-cyclohexylidene derivatives of the aldehydo-forms of L-arabinose and D-xylose with a wide variety of group I phosphoranes enabled Zhdanov and coworkers[139-144] to synthesise a series of unsaturated polyols with the general formula (CLVIII, a—d). Depending on the structure of the group R′, the products obtained can be assigned to various classes of organic compounds: *C*-glycosylated ethylenes (CLVIIIa), butadienes (CLVIIIb), styrenes (CLVIIIc), and vinylnaphthalenes (CLVIIId):



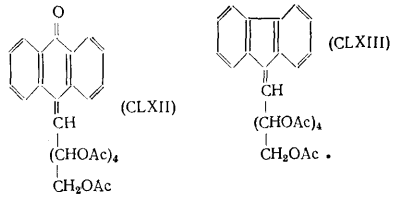
Tronchet et al.[145] synthesised similarly 1,2:3,4-di-*O*-isopropylidene-$C_{(1)}$-vinyl-L-*arabino*-tetritol (CLIX). The condensation of the aldehydo-forms of 2,3,5-tri-*O*-benzyl-4-phthalimido-L-ribose and of

2,3,4,5-tetra-*O*-benzyl-L-lyxose with triphenyl-, n-tridecylidene-, or n-pentadecylidene-phosphoranes yielded[146,147] unsaturated derivatives of the polyols (CLX) and (CLXI) used subsequently in the syntheses of phytosphingosines:



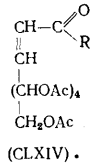
(CLIX) (CLX) (CLXI).

C-Substituted unsaturated polyols can be synthesised also with the aid of certain relatively inactive group III phosphoranes. In this case one can employ the aldehydo-forms of carbohydrate acetates; thus compound (CLXII), similar in structure to natural aloins, was obtained in this way from 10-anthronylidenetriphenylphosphorane and the penta-acetate of the aldehydo-form of D-galactose[148]. A fluorene derivative (CLXIII) was synthesised by a similar procedure[148]:



(CLXII) (CLXIII)

The Wittig reaction is particularly valuable as a method for the introduction into the carbohydrate molecule of active functional groups together with the double bond. One employs for this purpose phosphoranes of the second kind which are stable under the usual conditions and are fairly reactive. Thus the Wittig reaction has proved convenient for the synthesis of higher unsaturated $C_{(1)}$-substituted ketoses. According to the data of Zhdanov and coworkers[149-152], the interaction of the acetates of the aldehydo-forms of hexoses with acetyl-, aroyl-, and acyl (from heterocyclic acids) derivatives of methylene phosphoranes constitutes a preparative synthesis of these interesting carbohydrate derivatives having the general formula (CLXIV):



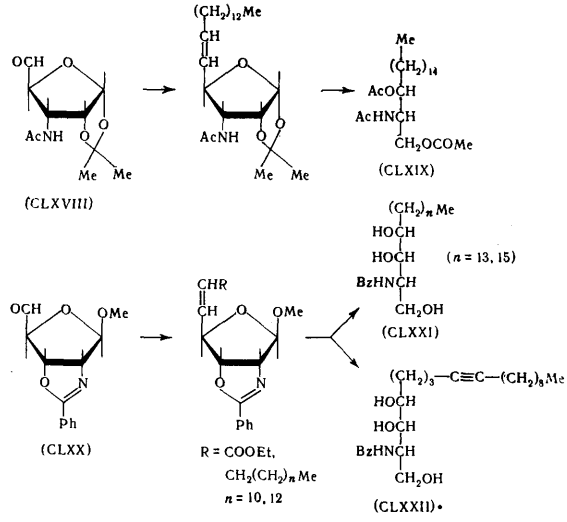
R=Me, Ph—NO_2-*p*, Ph—Br-*p*, Ph—(OMe)-*p*, $C_6H_2(OMe)_3$, $C_6H_3(OMe)_2$, α-thienyl or fury

(CLXIV).

The condensation of formylmethylenetriphenylphosphorane with the aldehydo-forms of (CII) and (CLVII) can serve as a general method of synthesising[142,153] unsaturated aldoses of type (CLXIV), which are difficult to obtain:

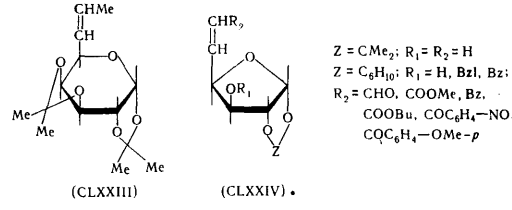
RCH=CH—CHO (CLXV) (R = carbohydrate residue)

The use of partly protected dialdoses and their derivatives greatly extends the scope of the Wittig reaction in the series of carbohydrates. One then introduces into the condensation with phosphoranes only one aldehyde group, while the second, which is temporarily protected, can be subsequently used for further reactions. The sphinogisines (CLXIX), (CLXXI), and (CLXXII) were synthesised in this way from the corresponding dialdoses (CLXVIII) and (CLXX):



(CLXVIII) (CLXIX) (CLXX) R = COOEt, $CH_2(CH_2)_nMe$, n = 10, 12 (n = 13, 15) (CLXXI) (CLXXII).

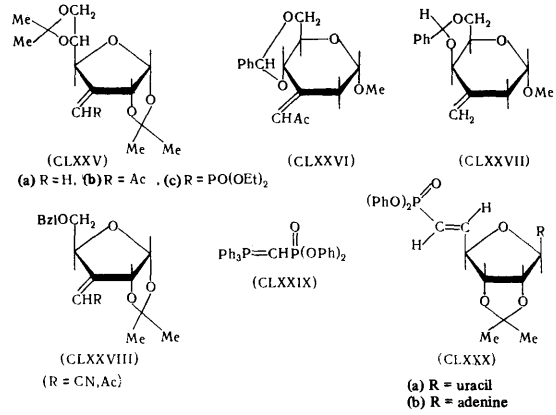
A series of unsaturated aldoses of types (CLXXIII) and (CLXXIV) were obtained also from dialdoses of a similar structure[150,157-159]:



Z = CMe_2; $R_1 = R_2 = H$
Z = C_6H_{10}; R_1 = H, Bzl, Bz;
R_2 = CHO, COOMe, Bz, COOBu, COC_6H_4—NO_2, COC_6H_4—OMe-*p*

(CLXXIII) (CLXXIV).

Branched-chain sugars (CLXXV)—(CLXXVIII), which are difficult to obtain, have been synthesised from ketoaldoses by the Wittig reaction[157,160-164]:

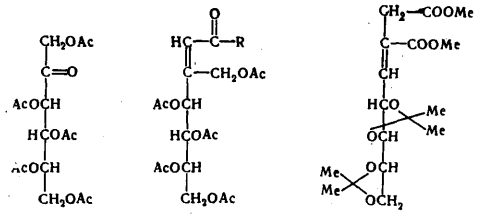


(CLXXV) (a) R = H, (b) R = Ac, (c) R = PO(OEt)$_2$ (CLXXVI) (CLXXVII) (CLXXVIII) (R = CN, Ac) (CLXXIX) (CLXXX) (a) R = uracil (b) R = adenine

The branched-chain monosaccharides with a C—P bond (CLXXV), synthesised[165] from 1,2:5,6-di-*O*-isopropylidene-D-*ribo*-3-hexulofuranose and tetraethyl methylenediphosphonate are of considerable interest. The unsaturated carbohydrate phosphonate (CLXXV) was used further to synthesise modified nucleotides. Jones and Moffatt[166] showed that the condensation of phosphonylmethylenephosphorane (CLXXIX) with $C_{(4)}$-formyl-2,3,-*O*-isopropylidene-derivatives of uridine and adenosine yields 5′-deoxy-5′-(*OO*-diphenylphosphonomethylene)uridine (CLXXXa) and the analogous adenosine derivative

(CLXXXb). Similar condensations lead to convenient pathways to the synthesis of modified nucleotides.

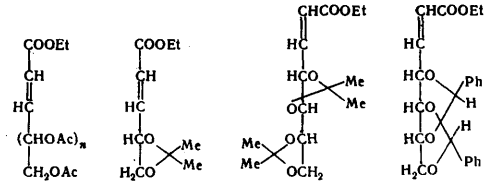
On treatment with an acylmethylenephosphorane, the penta-acetate of the keto-form of L-sorbose (CLXXXI) also yields[167] a sugar with an olefinic bond (CLXXXII):



(CLXXXI) (CLXXXII) (CLXXXIII).

The methyl ester of 3,4-dehydro-2,3,4-trideoxy-5,6:7,8-di-*O*-isopropylidene-3-methoxycarbonyl-L-*arabino*-octonic acid (CLXXXIII) was obtained by a similar procedure from phosphoranes with an iso-structure and the aldehydo-form of 2,3:4,5-di-*O*-isopropylidene-L-arabinose[167].

The bulk of the studies on the Wittig reaction in carbohydrate chemistry concern the synthesis of $\alpha\beta$-unsaturated acid esters. Kochetkov and Dmitriev[168] developed on the basis of these compounds a new and convenient method of synthesising higher sugars. Starting with a wide variety of aldehydo-forms of carbohydrates and alkoxycarbonylmethylenetriphenylphosphoranes, they obtained[169-175] a series of esters of *trans*-2,3-didehydro-2,3-dideoxyaldonic acids of types (CLXXXIV, a and b)—(CLXXXVII):

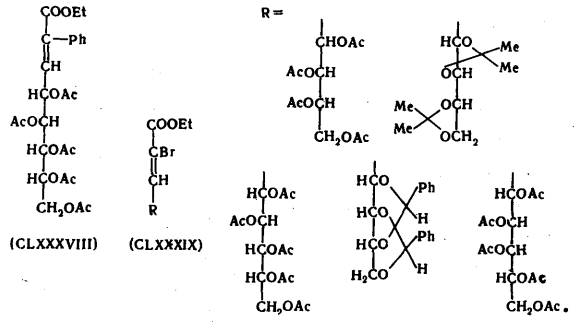


(CLXXXIV) (CLXXXV) (CLXXXVI) (CLXXXVII)

(a) n = 3, L-*arabino*-, D-*arabino*-

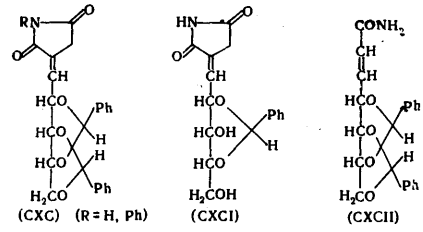
(b) n = 4, D-*gluco*-, D-*galacto*-

The employment of modified alkoxycarbonylmethylenetriphenylphosphoranes makes it possible to obtain[176,177] interesting derivatives of $\alpha\beta$-unsaturated acids (CLXXXVIII) and (CLXXXIX). The latter were used by Kochetkov and Dmitriev[177] to synthesise aziridine derivatives of carbohydrates:

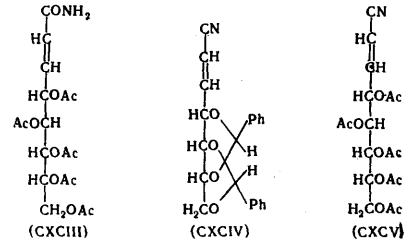


(CLXXXVIII) (CLXXXIX)

A series of unsaturated carbohydrates (CXC)—(CXCV) have been obtained from phosphoranes with maleimide, amide, and nitrile substituents[175,178]. The derivatives (CXC) and (CXCI) were synthesised for further use in the synthesis of the antibiotic Showdomycin[175]:

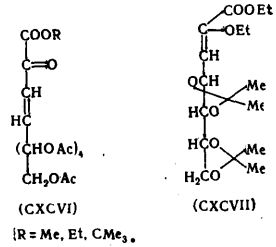


(CXC) (R = H, Ph) (CXCI) (CXCII)



(CXCIII) (CXCIV) (CXCV)

Interesting pathways to the synthesis of 3-deoxy-2-oxoaldonic acids and their amino-derivatives (sialic acids), which are widely distributed[6] in nature, have been outlined on the basis of the Wittig reaction. These acids are formed in the organism by the condensation of monosaccharides with phosphoenolpyruvic acid. Therefore it was natural to investigate the interaction of the aldehydo-forms of carbohydrates with alkoxycarbonyloxomethylenephosphoranes obtained from bromopyruvic acid esters. This led to the synthesis[179,180] of unsaturated ketoacids of the general formula (CXCVI). Further reactions of these products, investigated by Kochetkov and coworkers[181-183], led to the synthesis of 2-deoxy-3-oxoaldonic acids identical with the natural products:

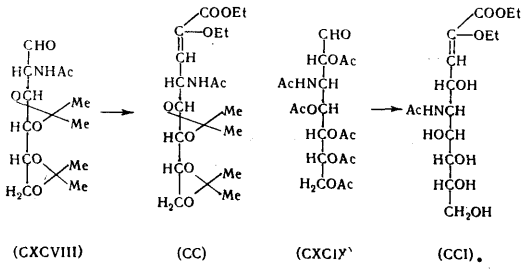


(CXCVI) (CXCVII)

(R = Me, Et, CMe_3).

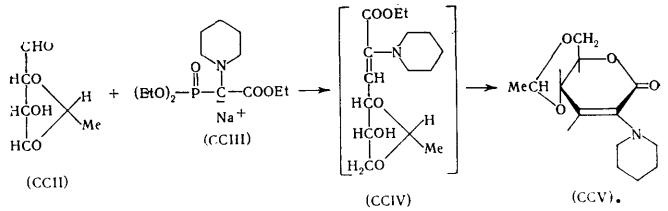
Samokhvalov and coworkers[184] obtained the fixed enolic forms (CXCVII) of an α-ketoacid from the aldehydo-forms of 2,3:4,5-di-*O*-isopropylidene-D-arabinose and ethoxycarbonylethoxymethylenetriphenylphosphorane. They demonstrated that the product (CXCVII) is also convenient for the synthesis of 2-deoxy-3-oxoaldonic acids. The use of derivatives of the aldehydo-forms of glucosamine (CXCVIII) and heptosamine (CXCIX) [185,186] for condensation with ethoxycarbonylethoxymethylenetriphenylphosphorane permits the synthesis of the starting materials (CC) and

(CCI) for the preparation of neuraminic acid and its analogues:



(CXCVIII) (CC) (CXCIX) (CCI).

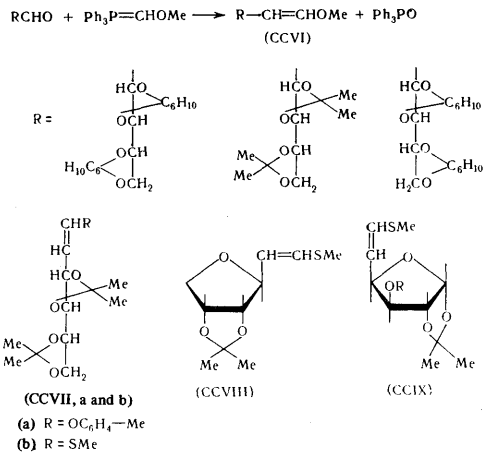
The simplest and novel synthesis of 3-deoxy-2-octoaldonic acids was proposed by Baschang and Tritz[187], who employed for this purpose the condensation of the sodium salt of ethyl *OO*-diethylphosphonopiperidinoacetate (CCIII) with 2,4-*O*-ethylidene-D-erythrose (CCII). They obtained as a result the enaminolactone (CCV) without isolating the intermediate enaminoester (CCIV):



(CCII) (CCIII) (CCIV) (CCV).

The enaminolactone (CCV) can be subsequently converted under mild conditions into the corresponding 3-deoxy-2-oxoaldonic acid. Further development of this reaction may lead to the elaboration of a convenient method of synthesising 3-deoxyhexulonic acids, including sialic acids.

The vinyl ethers employed in the syntheses of 2-deoxyaldoses are also unsaturated carbohydrate derivatives obtained by the Wittig reaction. The condensation of derivatives of the aldehydo-forms with methoxymethylenetriphenylphosphorane yielded[141,145,188-190] the vinyl ethers (CCVI) and the interaction of the aldehydo-form of 2,3:4,5-di-*O*-isopropylidene-L-arabinose with methylenetriphenyltolyloxyphosphorane gives[191] aromatic vinyl ethers of type (CCVIIa):



(CCVII, a and b)
(a) R = OC_6H_4—Me
(b) R = SMe

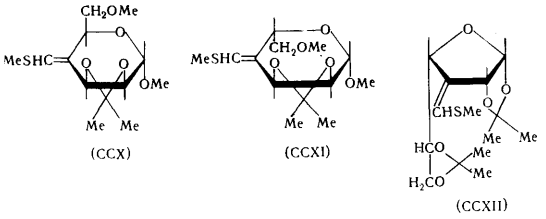
(CCVI)

(CCVIII) (CCIX)

In the search for other precursors of 2-deoxy-sugars, attention was turned to methylenemethylthiotriphenylphosphorane, which was employed by Tronchet and coworkers[190,192] for condensation with various aldehydo-forms.

The methylthio-derivative (CCVIIb) was prepared in this way[190] from the aldehydo-form of 2,3:4,5-di-*O*-isopropylidene-L-arabinose. A similar treatment of 2,5-anhydro-3,4-*O*-isopropylidene-D-ribose and 1,2-*O*-isopropylidene-3-*O*-methyl-(and 3-*O*-benzyl-)-α-D-*xylo*-pentodialdo-1,4-furanoses led[192] to the synthesis of the corresponding vinyl thioethers (CCVIII) and (CCIX).

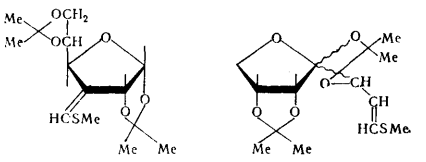
The interaction of methylenemethylthiotriphenylphosphorane with certain protected keto-sugars proved to be more complex. Thus 2,3-*O*-isopropylidene-6-*O*-methyl-α-D-*lyxo*-3-hexulopyranoside gives the vinyl thioethers[193] (CCX) and (CCXI) in a yield of only 20%:



(CCX) (CCXI) (CCXII)

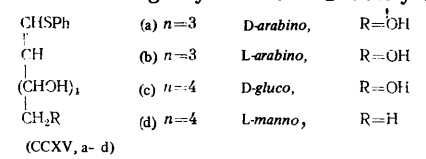
The formation of the side product (CCXI) is probably a result of the epimerisation of a similar ketose at $C_{(5)}$ in the course of enolisation induced by the basic medium.

It is interesting that epimerisation is not observed with 1,2:5,6-di-*O*-isopropylidene-α-D-*xylo*-3-hexulofuranose, since only the normal reaction product (CCXII) has been isolated[194]. The same reaction with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-3-hexulofuranose proved to be much more complicated[195,196], since, apart from the expected vinyl thioester (CCXIII), the $C_{(5)}$ epimer (CCXII) was isolated as well as the unexpected rearrangement product (CCXIV):



(CCXIII) (CCXIV)

Apart from methylenemethylthiotriphenylphosphorane, methylenephenylthiotriphenylphosphorane can be used to synthesise vinyl thioethers. Thus, according to the data of Bestmann and Angerer[197], this phosphorane reacts smoothly even with the free sugars in DMSO, forming the corresponding aryl vinyl thiovinyl ethers (CCXV, a—d). Since the products (CCXVa) and (CCXVb) were converted further into 2-deoxy-D-(and L-)-*arabino*-hexoses, it is a very convenient two-stage synthesis of 2-deoxy-sugars:



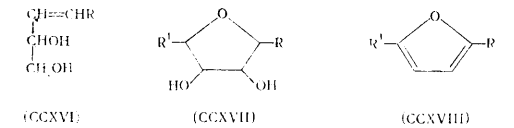
(CCXV, a-d)

(a) $n=3$	D-*arabino*,	R=OH
(b) $n=3$	L-*arabino*,	R=OH
(c) $n=4$	D-*gluco*,	R=OH
(d) $n=4$	L-*manno*,	R=H

A number of studies by Kochetkov and coworkers[189,199], who made a detailed investigation of the condensation of alkoxycarbonylmethylenetriphenylphosphoranes with D-arabinose, D-ribose, D-glucose, D-galactose, D-glycero-D-*gulo*-heptose, and 2-acetamido-2-deoxy-D-glucose, were devoted to the employment of free and partially protected sugars in the Wittig reaction. They obtained the corresponding esters of *trans*-2,3-didehydro-2,3-dideoxyaldonic acids in yields of 45%. The decrease of yield is probably due to the formation of cyclic side

products. To prevent such cyclisation, partly protected sugars were employed. For example, the use of 2,3,4,6-tetra-*O*-acetyl-D-galactose instead of free D-galactose increases the yield of the required product to 80%. Similarly when 2-acetamido-2-deoxy-D-glucose is replaced by its 4,6-*O*-benzylidene derivative, the yield of the normal product of the condensation with methoxycarbonylmethylenetriphenylphosphorane increases from 30 to 50%.

The problem of the employment of free and partly protected sugars in the Wittig reaction with alkoxycarbonylmethylenetriphenylphosphoranes was investigated in greater detail by Zhdanov and coworkers[200-204], who showed that the required product is formed only with DL-glyceraldehyde (CCXVI):



(CCXVI) (CCXVII) (CCXVIII)

(R = CO Me, COPh) (R = CH_2OH, $(CHOH)CH_2OH$ (R = Me, Ar; R^1 = CH_2COAr, CH_2COMe) R^1 = $(CHOH)_n CH_2OH$)

When various pentoses and hexoses were allowed to interact with group II phosphoranes, the anhydro-derivatives were isolated, compounds of type (CCXVII) being formed preferentially. During the reaction, these anhydro-derivatives are dehydrated, probably under the influence of the excess phosphorane, with formation of substituted furans (CCXVIII). Thus the results show that conformational factors, and particularly the preference for specific conformations in the opening of the cyclic forms of aldoses at the instant of reaction, play a decisive role in the formation of a particular product.

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