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METHODS FOR CONVERTING CARBOHYDRATES TO CARBOCYCLIC COMPOUNDS

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INTRODUCTION

Among the various reactions undergone by carbohydrates an important place is occupied by processes in which the carbon framework of the monosaccharide is rearranged. The changes produced in the carbohydrate-carbon chain differ in character and may be reduced to three basic reaction types.

Reactions in which isomerisation and rearrangement of the carbon chain lead to the formation of branched-chain compounds, for example, saccharinic, isosaccharinic, and parasaccharinic acids, belong to the first type. Reactions of the second type include various processes that lead to a change in the number of carbon atoms in the carbohydrate molecule. To this type belong well-known methods of lengthening the carbon chain of sugars by addition of a molecule through the aldehyde group, organo-metallic, catalytic and condensation methods of synthesis of carbon-substituted carbohydrates with aliphatic, aromatic, and some heterocyclic aglycones [1,2], and also numerous methods in which the carbon chain is cleaved into smaller fragments.

Reactions of the third type, the literature on which is scanty, are of great theoretical and practical interest; in these the carbon framework of the monosaccharide or its derivatives cyclises to form various carbocyclic and heterocyclic compounds.

Because of a marked tendency to form cyclic compounds under the action of chemical agents or enzyme systems of living organisms, natural hexoses and pentoses and their derivatives are easily converted to mono- and poly-hydric phenols and to compounds containing furan, pyran, pyrrole, imidazole, and other ring systems.

The tendency of carbohydrates to cyclise and form carbocyclic compounds is of exceptional importance in elucidating the part played by sugars in the biosynthesis of various carbocyclic (particularly aromatic) compounds in plants and animal organisms. The concept developed in recent years that carbohydrates are the probable precursors in the biosynthesis of the aromatic nucleus in compounds of exceptional importance for the normal biological functioning of plants and animals, such as phenols, phenylglycosides, hydroxyacids, tannins, catechins, and amino-acids, has received fresh experimental confirmation.

The results of recent research work have shown that it is possible in principle to convert carbohydrates to aromatic and hydroaromatic compounds by chemical methods.

Cyclisation reactions are used in the preparation of many heterocyclic compounds. The conversion of carbohydrates to furfural by dilute acids [3] is well known. In the laboratory, carbohydrates and their derivatives are used for the preparation of many furan [4,5], pyran [6,7], pyrrole [8,9], and imidazole [10,11] compounds. Data are available on possible syntheses from carbohydrates of thiophene [12], pyridine [13], and pyrazine [14] derivatives. The preparation of heterocyclic compounds from monosaccharides and their derivatives is dealt with, although not completely covered, in several reviews [3-9], but information on methods of preparing carbocyclic compounds from carbohydrates is widely scattered. Micheel's monograph [15] contains isolated data on conversions of this type, and there is a more detailed, but less readily accessible, discussion by Dansi and Brocca [16].

In this review an attempt is made to generalise and systematise the information in the literature on the cyclisation of the carbohydrate-carbon chain, in the belief that this is of undoubted interest for synthetic organic chemistry, the chemistry of natural compounds, and biochemistry.

1. THERMAL CARBOCYCLISATION OF CARBOHYDRATES

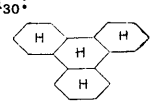
The thermal decomposition of carbohydrates, especially cellulose, has received detailed treatment in the chemical literature, because of the industrial applications of this process [17-20].

It is known that on dry distillation cellulose forms a complex mixture consisting of gaseous, liquid, and solid (carbon) products. The liquid decomposition products consist of an aqueous distillate and a resin, formic acid, acetic acid, and acetone being present in small amounts; formaldehyde, methylglyoxal, furfural, 5-hydroxymethylfurfural, di-, tri-, and tetra-methylfuran, maltol, γ-valerolactone, phenol, traces of toluene, and many other compounds have also been found. The separation of aromatic compounds (toluene, phenol [21], cresol [22], and others) from the distillate is of particular interest; cellulose tar contains as much as 2-4% of these.

Smith and Howard [23] oxidised and decarboxylated the liquid fraction from the thermal decomposition of cellulose and obtained benzene and diphenyl. Their results indicate that various alkyl homologues of benzene and diphenyl are present in the pyrolysis products.

When cellulose is reduced at high temperature, cyclisation of the carbon chain also occurs and aromatic and alicyclic compounds are formed. When cellulose is hydrogenated in the presence of a nickel catalyst at 400°-440°, gaseous and liquid products are formed. A tar is obtained in 23% yield, the main constituent of which is an oxygen-containing compound of unknown composition; phenol is formed in 2% yield [24].

Willstätter and Kalb have shown [25] that, when xylose, glucose, and cellulose are reduced by phosphorus and hydriodic acid in sealed tubes at 250°, a mixture of hydrocarbons is formed with the mean composition $CH_{1.6}$ and molecular weights from 167 to 842. Schrauth [26], who made a detailed examination of Willstätter's hydrocarbon fraction, showed it to be identical with perhydro-9,10-benzophenanthrene, $C_{18}H_{30}$:



It is very significant that compounds with the perhydrophenanthrene skeleton, for example, abietic acid, fichtelite, etc., are constituents of brown-coal, peat, and resin acids. These compounds may be products of extensive chemical transformations of carbohydrates of various plant remains from remote geological epochs.

The literature contains many other reports on the isolation of aromatic compounds from the products of the pyrolysis of carbohydrates. All this evidence undoubtedly indicates that acyclic carbohydrate compounds form carbocyclic compounds during pyrolysis.

It has been suggested that the formation of aromatic compounds in the pyrolysis of carbohydrates is due to the catalytic action of incandescent carbon, ash, or the walls of the retort on the glucose residues of cellulose or their cleavage products [19].

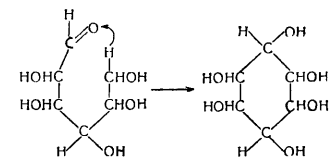
2. BIOSYNTHESIS OF ALICYCLIC AND AROMATIC COMPOUNDS FROM CARBOHYDRATES

According to Shorygin and Shorygina [27], in living animal organisms and plants there is a continual conversion of carbohydrates, the primary products of assimilation of atmospheric carbon dioxide, into various cyclic compounds widely distributed in the plant world, such as resins, terpenes, essential oils, tannins, dyes, sterols, etc. These workers consider that the genetic relation of these cyclic compounds to carbohydrates is evident — they are all formed in the plant organism by the biochemical conversion of carbohydrates, probably through a series of intermediate processes.

Recently two fundamental ideas on the biosynthesis of the aromatic nucleus have become widely current in biochemistry. According to the first, the main precursors of cyclic compounds in plants and living organisms are acyclic compounds with six carbon atoms in the molecule (most probably glucose or other carbohydrate compounds), which are converted by ring closure to cyclohexane derivatives (inositol, quercitol, etc.); these are then dehydrated to polyphenols and phenols. According to the second hypothesis, other initial compounds (possibly sedoheptuloses and other higher sugars) with longer carbon chains are present, and these cyclise to form various aromatic compounds with side chains of different lengths.

It may be that both these hypotheses correctly reflect the biosynthesis of the aromatic nucleus and are not contradictory. This is confirmed by the immense variety of aromatic compounds isolated from natural materials, which are probably formed from several types of alicyclic precursors. Both hypotheses have received experimental confirmation and are beginning to form the subject of modern monographs [28-32] and reviews [33,34].

Thanks to the Soviet workers Bach, Oparin, Kursanov, and others, the essential features of many biochemical processes occurring in the tea plant have been elucidated, and the problem of the conversion of carbohydrates to aromatic compounds and tannins is being successfully solved. Kursanov and his coworkers have recently developed a theory, supported by convincing experimental evidence, according to which the first conversion product of carbohydrates in the tea leaf is *meso*-inositol, formed from hexoses by ring closure of the aldol condensation type [31,36,37]:

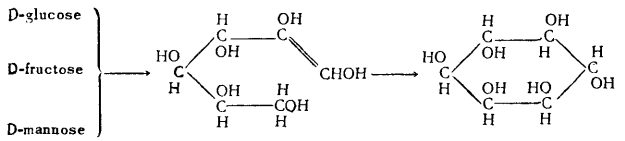


meso-Inositol, both free and combined, is widely distributed in the plant and animal world, being encountered in all tissues of plant and animal organisms. In animals *meso*-inositol has been found in muscle, kidney, liver, brain (as cephalin), and other organs.

In plants *meso*-inositol occurs free and as the hexaphosphate (phytin), first discovered by Palladin [35] in cereal grains. The high content of inositol in bran, oranges, peaches, strawberries, cabbage, tomatoes, carrots, and

tea leaves is noteworthy. It has been shown that *meso*-inositol is a growth factor for some cultivated species of yeast; it acts as a vitamin in mice and it stimulates the microbiological synthesis of many vitamins, for example, biotin.

Kursanov and his coworkers found[36,37] that inositol can be synthesised experimentally in tea leaves by introducing glucose, sucrose, or some glucosides into the tissue. The amount of *meso*-inositol in tea leaves increases by 10 to 12% an hour after glucose has been injected. *meso*-Inositol is formed at the same rate from fructose and mannose, which are related to glucose in their spatial configuration and have an enolic form in common with it. Sugars of different configuration (galactose, rhamnose, arabinose), hydroxyacids (glycollic and glyceric), and pyruvic acid are not converted to *meso* or other forms of inositol in tea leaves. From this, it can be concluded that the process is specific; it depends on the stereochemical configuration of the sugar and proceeds through a stage in which the enol form, common to D-glucose, D-fructose, and D-mannose, reacts



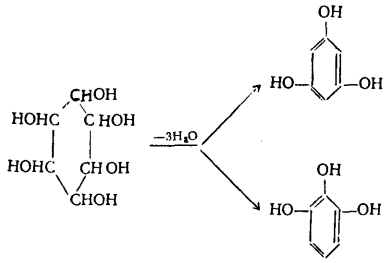
It has been shown experimentally[36,37] that the rate of *meso*-inositol synthesis increases several times when some α- and β-glucosides are injected instead of glucose. Compounds which are rapidly converted to inositol in tea leaves include sucrose, glucose 1-phosphate, and the plant glucosides arbutin and saligenin. From these facts, the hypothesis may be put forward that cyclisation of carbohydrates to inositol is preceded by activation of the hexose by the formation of a glucoside linkage, which facilitates ring closure[31].

The carbocyclisation of carbohydrates in plants is an enzymic process; up to the present it has not been possible to synthesise *meso*-inositol in one step by chemical means. In 1944, the enzyme cyclase, which converts glucose into inositol[38], was isolated from *Lactica virosa* L. When a 2% aqueous solution of glucose was maintained at 37° (pH 5.8) in the presence of cyclase, small quantities of *meso*-inositol were formed.

Further detailed studies of the biochemical conversion of sugars in tea leaves showed that the accumulation of polyphenols and tannins is closely connected with the synthesis of *meso*-inositol. The more active the biosynthesis of *meso*-inositol, from whatever precursor, the greater the amount of polyphenols (phloroglucinol and pyrogallol) that are produced in the tea plant[39,40].

As would be expected, the synthesis of phloroglucinol in the tea leaf proceeds most readily when *meso*-inositol is injected; the introduction of compounds which do not promote the synthesis of inositol does not lead to the formation of polyphenols[40].

Kursanov concludes from these experiments that polyphenols are formed in the tea plant from inositol, which in turn is produced from carbohydrates by cyclisation of the carbon chain by an aldol condensation. When inositol is dehydrated, three molecules of water are split off and the trihydric phenols pyrogallol and phloroglucinol are formed[31,40]:



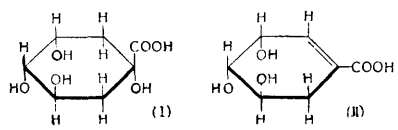
Nick[41] has obtained interesting results that confirm Kursanov's theory: he found that immersion of half-leaves of snakeweed in glucose or sucrose solution leads to the active production of tannins.

The first report on the biosynthesis of inositol in the living organism was made by Needham[42] in 1924. New proofs of the direct conversion of glucose to inositol in the living organism have been obtained quite recently by the tracer method. Glucose labelled with ^{14}C was introduced into the abdominal cavity of mice[43]. After some time, the experimental animals were killed and *meso*-inositol labelled with ^{14}C was isolated from the livers and other organs; it was purified by recrystallisation and paper chromatography. The amount of inositol in the tissues of mice varied between 0.08 and 1.8 mg per gramme of live weight. Similar results were obtained when glucose labelled with ^{14}C was introduced into the chick embryo shell, radioactive inositol being found 64 h after the injection.

The reversibility of the inositol biosynthesis has been demonstrated in a number of investigations[44,45]. Thus, when *meso*-inositol deuterated in position 2 was administered to mice, the glucose separated from the urine was found to be labelled mainly in the 6-position[44]. When deuterium-labelled inositol was injected into mice, 7% was converted to glucose after 24 h.[45]

The isolation from mouse kidney of an enzyme system that converts inositol to D,L-glucuronic acid has recently been reported[46,47].

Recent work has shown that an exceptionally important part in the biosynthesis of aromatic compounds from carbohydrates is played by quinic acid(I) and shikimic acid(II), which occupy an intermediate position in the biochemical conversion of carbohydrates and cyclitols to aromatic compounds. Both acids are widely distributed in the plant world and have been found in microbes and other living organisms[33,34].

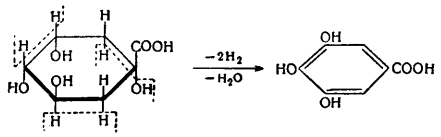


Like *meso*-inositol, quinic and shikimic acids have spatial configurations related to that of D-glucose.

Over 30 years ago Butkevich[48] and Kizel'[49,50] showed that quinic acid is genetically related to glucose in natural materials. In plants quinic acid is readily formed by the biochemical conversion of inositol, which, as shown above, is obtained from carbohydrates[31].

Quinic acid has recently been prepared by a multi-stage chemical synthesis from 4-chlorocyclohexanone[51]. A complete synthesis of shikimic acid was not achieved until in 1960, when it was prepared from 2-acetylfuran and maleic anhydride *via* a number of intermediate reactions[52]. Quinic and shikimic acids are readily interconvertible (by the action of chemical agents) both *in vivo* and *in vitro*.[53,55]

In 1935 Blagoveshchenskii put forward the hypothesis that quinic acid is a precursor of gallic acid, one of the most widely distributed constituents of tea tannins[56]. It is not difficult to suppose that the conversion of quinic acid to gallic acid occurs by dehydration and oxidative dehydrogenation in the following way:

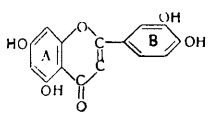


Kursanov showed[31] that, when quinic acid is introduced into the tea leaf, it is readily converted to polyphenols with vicinal hydroxyl groups.

Recently the attention of many workers has been drawn to shikimic acid as the probable precursor of aromatic compounds in living tissue. Thanks to the studies of Davis and his coworkers[57,58], it has been established that radioactive shikimic acid can be produced by a culture of *Escherichia coli* growing in glucose labelled with ^{14}C. Similarly, shikimic acid is obtained in 90% yield from sedoheptulose 1,7-diphosphate or mixtures containing erythrose 4-phosphate and phosphoenolpyruvate[59,60]. The mechanism of these interesting conversions, which was elucidated by Davis's school, comprises a preliminary cleavage of sedoheptulose 1,7-diphosphate into erythrose phosphate and dihydroxyacetone phosphate. The latter is oxidised to phosphoenolpyruvate, which condenses with erythrose 4-phosphate to form shikimic acid. Shikimic acid plays an important part in the formation of aromatic lignin components in various plants.

Brown and Neish[61,62] introduced [^{14}C]shikimic acid into wheat stems and maple twigs, and they isolated radioactive vanillin and syringic aldehyde from the lignin of these plants. Eberhardt and Schubert[63] introduced [^{14}C]shikimic acid into sugar-cane leaves over a period of six days. After oxidative degradation of lignin isolated from the plant, radioactive vanillin containing ^{14}C in the same positions as the initial shikimic acid was obtained. It has been shown by the tracer method that shikimic acid is converted in the metabolic process by specific enzymes to aromatic acids[64] and other cyclic compounds.

Neish and coworkers[65], who studied the mechanism of the biosynthesis of the flavonol quercitin in buckwheat, suggested that shikimic acid is probably the precursor of the aromatic B-ring in the quercitin molecule.

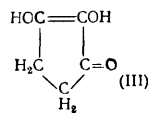


In recent years new and convincing evidence has been obtained, showing that the enzyme systems of microorganisms (lower fungi, bacteria) can synthesise from carbohydrates aromatic and heterocyclic amino-acids[34,66] necessary for their biological activity. Gilvarg and Bloch[67], who grew the yeast *Saccharomyces* on a culture medium containing [1-^{14}C]glucose, isolated from the solution phenylalanine and tyrosine labelled in positions 2 and 6. In the same way, microorganisms supported on a carbohydrate nutrient produce *p*-aminobenzoic acid, tryptophan[68], and other cyclic amino-acids[34,66,69].

3. CHEMICAL METHODS OF CONVERTING CARBOHYDRATES TO CARBOCYCLIC COMPOUNDS

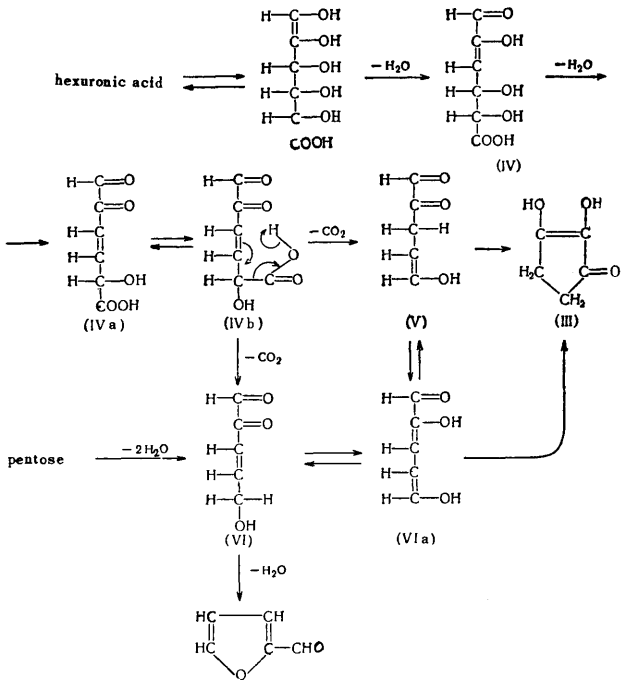
The possibility of converting carbohydrates and their derivatives into alicyclic and aromatic compounds by the usual methods of organic chemistry has long attracted the attention of many workers.

The conversion of carbohydrates to compounds of the cyclopentane series, which was first achieved by Reichstein and Oppenauer in 1933,[70,71] is of great interest. By heating hexuronic acids or pentoses with dilute sulphuric acid to 150° in an autoclave, they consistently obtained a yellow crystalline compound with m.p. 213°–213.5°. Because of the presence of an enediol grouping adjacent to a carbonyl group, the chemical properties of this compound are very similar to those of ascorbic acid, but, unlike ascorbic acid, it was found to be a cyclopentane derivative and was named reductic acid (III):



It was found that lactones and esters of hexuronic acid, polyuronides, methyl-3-oxo-β-D-glucopyranoside[72], 2,5-diethoxytetrahydrofurfural diethylacetal[73], and several other compounds are easily converted to reductic acid when heated with water or a weakly acid solution at high pressure (100°–150°). Furfural, succinic, fumaric, pyruvic, α-ketoglutaric acids, and several compounds of unknown structure were obtained as by-products of this reaction. In the acid cleavage of galacturonic acid the yield of furfural and reductic acid depends largely on the nature of the mineral acid: orthophosphoric acid promotes the formation of reductic acid (yield up to 41%)[74,75] and hydrochloric acid promotes the formation of furfural.

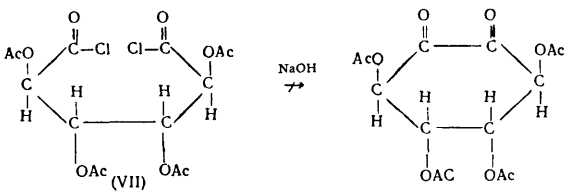
Stutz and Deuel[74] suggest that the mechanism by which reductic acid is formed comprises the stepwise dehydration of tautomeric enol forms of hexuronic acids to β,γ-unsaturated acids (IV, IVa, IVb) which are then decarboxylated to α-ketoglutaric dialdehyde (V);[73,76] this cyclises in the tautomeric form to give reductic acid (III) or furfural. The synthesis of reductic acid from pentoses is similar, the same intermediate (V) being formed in the dehydration:



However, the decarboxylation of the unsaturated acid (IVb) as presented in the scheme, with the transfer of a proton to the third carbon atom, is unrealistic. It is most probable that (IVb) is decarboxylated in the usual way to the unsaturated pentosone (VI), an intermediate in the dehydration of pentoses, the enol form of which (VIa) cyclises to reductic acid.

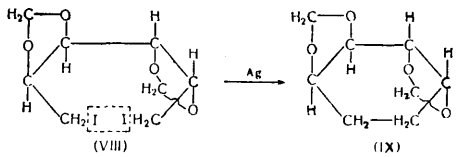
The ease with which pentoses are converted to cyclopentane derivatives (reductic acid) suggests the possibility of a similar process occurring in nature. In fact, cyclopentane compounds are important constituents of petroleum, a product of geological changes in the remains of carbohydrate-containing plants; these might be formed by the cyclisation of pentoses at high temperatures and pressures.

In plants and living organisms carbohydrates are readily converted to inositol, and many unsuccessful attempts have been made to effect this conversion by chemical means. The first experiments on those lines were undertaken by Diels and Lôflund in 1914.[77] These workers hoped that by splitting off a molecule of chlorine from tetraacetylmucyl chloride (VII) the cyclohexane ring would be closed by the reaction



However, neither this method nor the thermal decomposition of tetraacetylmucyl azide led to the desired result[77].

A successful cyclisation was first achieved in Micheel's laboratory[78] by heating a toluene solution of 1,6-dideoxy--1,6-diiodo-*O*-dimethylenemannitol (VIII) to 165°–170° for 8 h with molecular silver. *O*-Dimethylenetetrahydroxycyclohexane (IX) was obtained from (VIII) in this way:

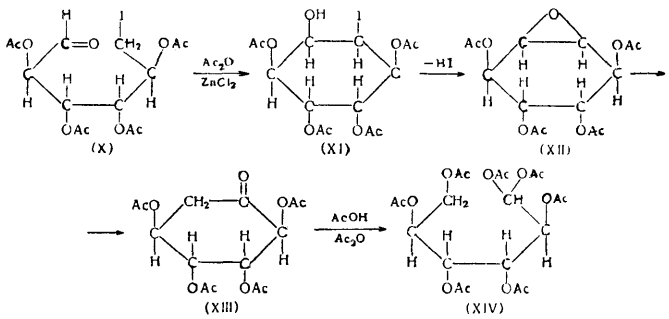


Wolfrom and Usdin[79] examined the possibility of cyclising 1,6-dibromogalactitol hexaacetate to inositol derivatives by heating it with active metals (Ag, Zn, Mg, Ca, Na), but their results were negative. They showed, however, that the tendency of carbohydrates to cyclise depends on their spatial configuration.

Cyclisation of aldoses by intramolecular aldol condensation, which has not yet been effected in one stage *in vitro*, is of particular interest. Attempts to carry out an aldol condensation of glucose in an alkaline medium[80] led only to isomerisation of the carbon chain and the formation of saccharinic acids. Reducing sugars are known to undergo a variety of conversions in an alkaline medium, forming numerous carbohydrate and non-carbohydrate products, but no carbocyclic compounds whatever[81,82] have been found. Negative results were obtained in attempts to cyclise 1,2,3,4-tetraacetyl-6-chloroglucose and 6-cyano-6-deoxyglucose in alkaline solution[16]. However, intramolecular aldol condensation of hexoses was successful when the hydrogen atom at C_6 was activated by substituting iodine, carboxyl, or the nitro-group for the hydroxyl.

Micheel and Ruhkopf[83] made a detailed examination of the possibility of cyclising 2,3,4,5-tetraacetyl-6-deoxy--6-iodo-aldehydo-D-galactose (X) by heating it with acetic anhydride in the presence of anhydrous zinc chloride. Under these conditions, the compound cyclises smoothly to form an unstable inositol derivative (XI); this is then converted to the epoxy-compound (XII), which isomerises to deoxyinosose tetraacetate (XIII). The isomerisation of compound (XII) is a special case of intramolecular oxidation-reduction disproportionation fairly frequently encountered in carbohydrate chemistry.

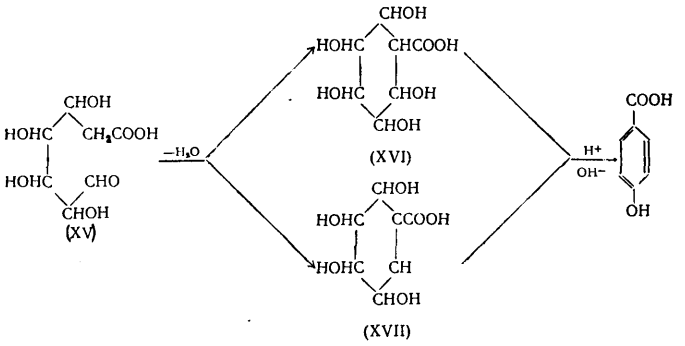
Compound (XIII) is unstable in acetic acid and, according to the authors, it is easily decyclised to form aldehydo-D--galactose heptaacetate (XIV) with an open carbon chain:



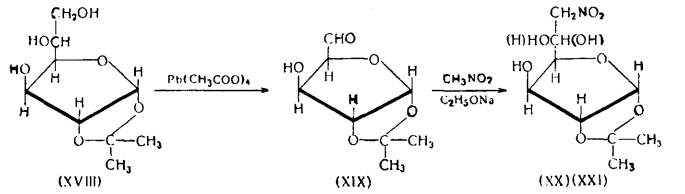
In our opinion, the results of this work are not entirely convincing and need to be confirmed.

Prey and Szabolcs[84], studying possible routes for the conversion of carbohydrates into carbocyclic compounds in living matter, carried out the intramolecular condensation of 6-deoxyhepturonic acid (XV). This conversion was achieved by prolonged heating of an aqueous solution of the

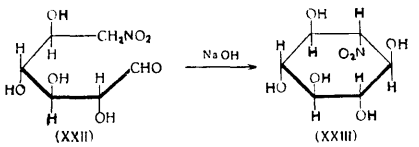
6-deoxyhepturonic acid (90°, 24 h) with an excess of the ion-exchange resin Amberlite IRA-400. Chromatography of the reaction mixture on the same resin yielded a small quantity of pentahydroxycyclohexanecarboxylic acid (XVI) and tetrahydroxycyclohexenecarboxylic acid (XVII), which were dehydrated by mineral acids or alkalis to form *p*-hydroxybenzoic acid:



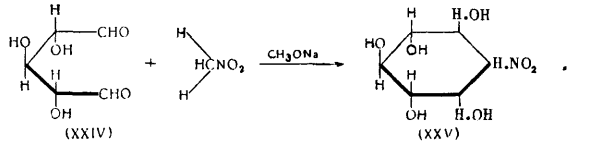
The nitromethane method proposed by Grosheintz and Fischer[85,86] was shown to be the most promising for converting aldoses to inositol. In this method D-glucose is treated with acetone in the presence of sulphuric acid and 1,2-monoacetone-D-glucose (XVIII) is obtained; this is oxidised by lead tetraacetate in benzene solution to 1,2--monoacetone-D-*xylo*-trihydroxyglutaric dialdehyde (XIX), which is then condensed with nitromethane in the presence of an alcoholic solution of sodium ethoxide[85]. When the aldehyde group of the acetonated dialdehyde (XIX) is condensed with nitromethane, a new asymmetric centre arises, and a mixture of the isomers 1,2-monoacetone-6-deoxy--6-nitro-D-glucofuranose (XX) and 1,2-monoacetone-6--deoxy-6-nitro-L-idofuranose (XXI) is formed:



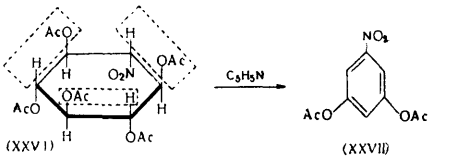
The mixture of acetonated deoxysugars cannot be separated by fractional crystallisation; however, repeated acetonation of the mixture yields the diacetone derivative of deoxynitro-L-idose, which can easily be separated from the unchanged 1,2-monoacetone-6-deoxy-6-nitro-D-glucofuranose (XX). When (XX) is hydrolysed, 6-deoxy-6-nitro--D-glucose (XXII) is formed, and in the presence of a solution of sodium or barium hydroxide, this cyclises to give, from the mixture of isomers, crystalline-2-deoxy-2-nitroinositol (XXIII) in 40% yield, corresponding in spatial configuration to 2-deoxy-2-nitroscyllitol[86]



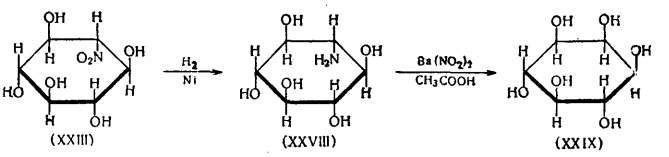
Brocca and Dansi[87] described the cyclisation of D-*xylo*--trihydroxyglutaric dialdehyde (XXIV) to a mixture of isomers of 2-deoxy-2-nitroinositol (XXV), which occurs in one step when the dialdehyde is treated with nitromethane in the presence of sodium methoxide:



The cyclic character of the deoxynitroinositols was demonstrated by the quantitative conversion of their pentaacetates (XXVI) to diacetyl-5-nitroresorcinol (XXVII), which is readily formed when (XXVI) is treated with hot pyridine:

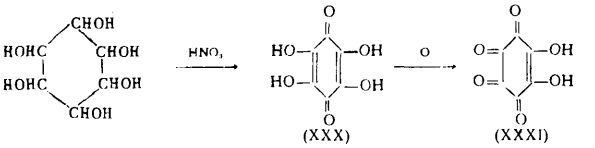


2-Deoxy-2-nitroscyllitol (XXIII) can be converted to *meso*--inositol without difficulty: it is hydrogenated catalytically in the presence of Raney nickel to give 2-amino-2-deoxyscyllitol (XXVIII)[86] in 69% yield; on treatment with barium nitrite solution in acetic acid, the amino-group of (XXVIII) is replaced by hydroxyl, and *meso*-inositol (XXIX)[88] is formed by a Walden inversion:



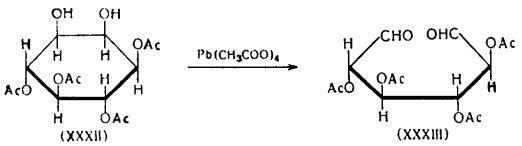
Posternak and coworkers used this method[89] to synthesise *meso*-inositol labelled with ^{14}C in position 2, starting from 1,2-monoacetone-D-*xylo*-trihydroxyglutaric dialdehyde (XIX) and labelled nitromethane, $^{14}CH_3NO_2$.

It has been pointed out above that *meso*-inositol is an intermediate in plant metabolism, being readily converted to polyhydric phenols. A similar conversion of *meso*--inositol and its derivatives to di- and tri-hydric phenols has been successfully carried out under laboratory conditions[15,87,90]. In general, the exceptionally easy aromatisation of the ring is characteristic of inositol and other cyclitols. Quercitol, for example, when heated under reduced pressure decomposes to form quinone, hydroquinone, and pyrogallol; when it is reduced with hydriodic acid, benzene, phenol, hydroquinone, and quinone[91] are obtained. On heating with nitric acid, inositol is oxidised to tetrahydroxyquinone (XXX), and then to rhodizonic acid (XXXI), which also has an aromatic structure:

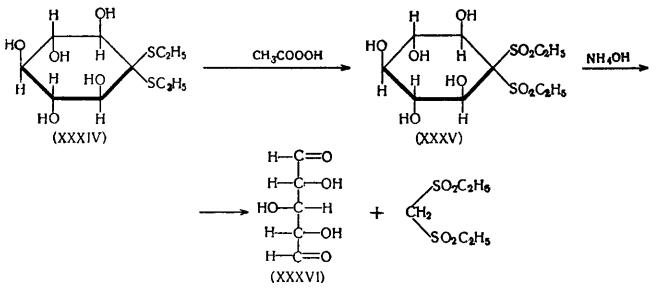


The reverse conversion of inositol to the dialdehyde is achieved fairly easily under laboratory conditions by various methods based on oxidative ring cleavage. Oxidation of tetraacetyl-*meso*-inositol (XXXII) to the acetylated

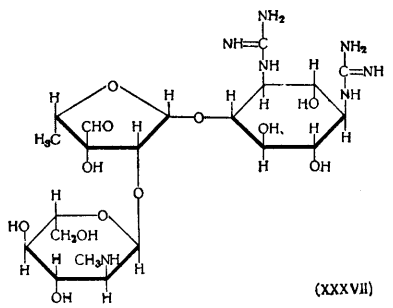
dialdose (XXXIII) proceeds smoothly when (XXXII) reacts with lead tetraacetate[92]:



MacDonald and Fischer developed a simple method of opening the inositol ring[93] by cleaving the disulphone (XXXV) with ammonia, the disulphone being obtained by oxidising *meso*-inosose diethylmercaptal (XXXIV). The dialdehyde (XXXVI) obtained in this way contains one carbon atom less than the initial cyclitol:



The nitromethane method of closing six-membered rings has been successfully used to establish conclusively the structure and synthesis of the streptidine part of the streptomycin molecule. Detailed structural studies showed this antibiotic to be *N*-methyl-α-L-glucosaminido-β-L-streptosidostreptidine (XXXVII)[94]

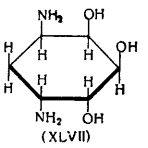


When heated with dilute acids, streptomycin hydrolyses to streptidine and streptobiosamine[95].

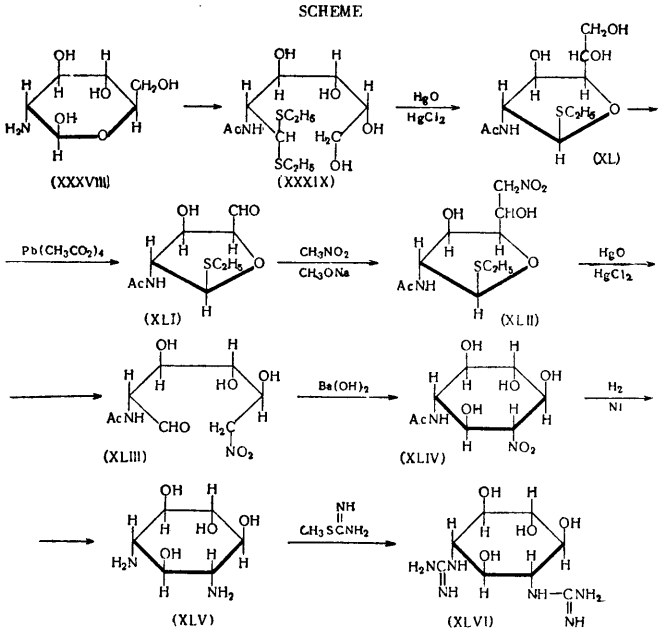
Wolfrom[96,97] synthesised the streptidine part of the streptomycin molecule in 1950 by cyclising D-glucosamine by the nitromethane method. Natural D-glucosamine (XXXVIII) (which has a known configuration), with its amino-group protected by acetylation, is converted to the diethylmercaptal (XXXIX) by treatment with ethylmercaptan; mercuric chloride and mercuric oxide in aqueous solution converted the mercaptal into *S*-ethyl 2-amino-α-D-glucothiofuranoside (XL), and then the amino-derivative of the dialdehyde (XLI) was obtained after glycol cleavage with lead tetraacetate. This was condensed with nitromethane in the presence of sodium methoxide by the method described above[67], and the nitrosaccharide (XLII), formed after the ethylthio-group had been hydrolysed (to yield XLIII), was cyclised by aldol condensation in the presence of barium hydroxide.

When the nitro-derivative of inositol (XLIV) is reduced catalytically, a mixture of isomeric diamino-compounds is formed, from one of which the diamine (XLV), identical with streptamine obtained by saponification of streptidine in an alkaline medium, is isolated. Condensation of streptamine with *S*-methylthioisourea yields streptidine (XLVI) (see scheme below). The streptidine synthesised in this way was identical with the compound obtained by hydrolysing streptomycin.

An optically inactive analogue of streptidine, 1,3-diamino-4,5,6-trihydroxycyclohexane [deoxystreptamine (XLVII)] is obtained by acid hydrolysis of the new antibiotics neomycin, kanamycin, and paromomycin, of which it is a constituent, linked by a glucoside bond[98,99].

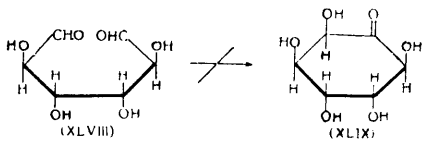


SCHEME

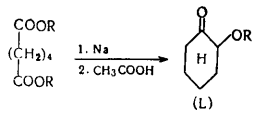


Besides the work cited above on the cyclisation of the carbon chain of carbohydrates by splitting out halogen in a reaction of the aldol-condensation type, attempts at ring closure by an acyloin-condensation reaction should be mentioned.

Wolfrom and Usdin[79], who used galactodialdohexose (XLVIII), obtained by reducing tetraacetylmucyl chloride (VII), showed that the acyloin condensation with the formation of the expected inosose (XLIX) does not occur:



In 1950, Sheehan and coworkers [100] showed that it was possible to cyclise dimethyl adipate to adipoin (L) by the acyloin method.

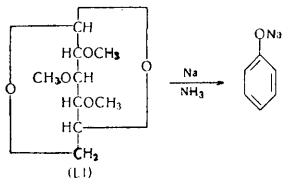


where R=H, CH_3.

(L)

However, the attempt by Brocca and Dansi [101] to carry out a similar cyclisation by boiling dimethyl 2,4,3,5-*O*--dimethylene-D-glucarate in toluene solution with potassium was unsuccessful.

In 1939, Shorygin and Shorygina [27] made the first successful attempt to convert carbohydrates directly to aromatic compounds. By treating 2,3,4-trimethyllaevoglucosan (LI) with sodium in liquid ammonia, they obtained phenol in 34% yield. They put forward a reaction scheme for this conversion, based on the cleavage of the ether bonds of 2,3,4-trimethyllaevoglucosan with sodium:



(LI)

Bright yellow transient intermediate products (probably organosodium compounds) are formed in the reaction. Shorygina and Perfil'eva [102] improved the reaction procedure and increased the yield of phenol from 50 to 56%; the yield of phenol is directly proportional to the quantity of sodium used in the reaction, the optimum quantity of sodium required for the cleavage of the three groups of trimethyllaevoglucosan corresponding exactly to 6 g-atoms per gramme-molecule of (LI). In experiments with amounts of sodium less than the amount required by the equation, unreacted trimethyllaevoglucosan was obtained, and an excess of sodium did not increase the yield of phenol. These facts are of great importance as regards confirmation of the authors' reaction scheme. By-products of the aromatisation of (LI) include the dihydric phenols resorcinol and catechol, which were isolated from the reaction mixture by paper chromatography [102].

It appears that the group of carbohydrate compounds capable of being aromatised under the conditions of the Shorygin reaction is somewhat limited, since when sodium, alone or in liquid ammonia, reacts with methylglucoside or methyl-2,3,4,6-tetramethyl-D-glucoside, no phenol or phenolic compound is formed [103].

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ADVANCES IN THE SYNTHESIS OF POLYSACCHARIDES

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