SYNTHETIC STUDIES IN THE CARBOHYDRATE FIELD.

THESIS

presented to

THE UNIVERSITY OF GLASGOW

for the Degree of Doctor of Philosophy

by

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JULY 1961.

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SUMMARY OF Ph.D. THESIS

ARCHIBALD J. BAKER.

Part I - 2-Deoxy-DL-ribose.

Synthetic routes to 2-deoxy-DL-ribose from non-carbohydrate precursors have been investigated and an eight stage synthesis from propargyl alcohol is described. Kojic acid has been elaborated, via a known intermediate, to 2-deoxy-DL-ribose.

As an extension of this work a route to the 2,6-dideoxyhexoses from acetylenic precursors is described.

Appendix I.

The selective addition of hypobromous acid to hex-5-en-2-yn-1-ol is discussed.

Appendix II.

Some unsuccessful approaches to DL-ribulose from acetylenic precursors have been explored.

Part II - Apiose and Cordycepose.

A wide variety of synthetic approaches to the branched-chain sugars apiose and cordycepose, from non-carbohydrate precursors, has been studied. The synthesis of 2-phenyl-5-carboxy-1,3-dioxan, a derivative of the saccharinic acid, 4-hydroxy-3-hydroxymethyl propanoic acid which has not hitherto been synthesised, is described.

Part III - Rhodosamine.

Routes to the amino-sugar rhodosamine from acetylenic precursors are described. An approach from hept-1-en-4-yn-6-ol has given a compound with the gross structure of DL-aldehydo "rhodosamine" diacetate.

Anomalous oxidation of an intermediate amine is discussed in the light of recent investigations.

ACKNOWLEDGEMENT.

It is a pleasure to record my sincere thanks to Professor R.A.Raphael for his advice, guidance and friendship during the period of this research.

Grateful acknowledgement is made to Dr. R. Hodges for helpful discussions and to Mr.J. M. L. Cameron and his assistants for microanalyses.

CONTENTS.

INTRODUCTION.

Carbohydrate Chemistry as we know it today can be attributed in the beginning to the prodigous efforts of Emil Fischer whose work must rank for all times as one of the greatest contributions made by any single person to our understanding of Chemistry. The two papers by Fischer[1] in 1891 establishing the configuration of the individual monosaccharides laid the foundations on which this branch of chemistry stands firmly today. With the publication by Haworth[2] in 1926 of his proof of the pyranose ring structure for the common glucosides, carboyhdrate chemistry was truly established. The constitution of the better known oligosaccharides was unravelled within a few years followed by structural studies on polysaccharides which placed the chemistry of these compounds on a sound basis. Thanks to the vast effort by the many workers in the carbohydrate field there is now at our disposal a store of knowledge of the intricate reactions of the sugars and their derivatives which has helped considerably in the elucidation of the biochemistry of living matter.

From the synthetic viewpoint there are many examples of the transformation of one sugar into another and in this way stocks of rare sugars have been built up from commonly occurring ones. Ascorbic acid (Vitamin C) is made commercially from L - Sorbose which in turn is prepared from D - glucose via D - Sorbitol. The synthesis[3] of the disaccharide sucrose has been achieved by condensation of 1, 2 - anhydro - D - glucopyranose triacetate with 1, 3, 4, 6 - tetra - O - acetylfructose.

In contrast with the vast amount of inter-conversion work whereby sugars have been synthesised from naturally occurring starting materials it is remarkable that so little has been achieved by way of total synthesis from simple synthetic intermediates. This approach to the synthesis of carbohydrates is worthy of investigation in view of the increasing frequency with which sugars of new and altogether unconventional structure, such as branched-chain sugars, are being isolated from products of great biological importance e.g., streptomycin and other antibiotics. In a recent article Overend[4] has reviewed some new sugars and discussed their structures and some methods of synthesis. It is possible and not unreasonable to suggest that for at-least some of these/

these/

new sugars their synthesis will be best achieved by a total synthetic approach rather than by conventional transformation reactions.

As far back as 1890 Fischer[5] achieved, by a non-rational and non-stereoselective method, the total synthesis of glucose, fructose and mannose by the condensation of acrolein dibromide with glyceraldehyde.

The mixture of racemic hexosazones - acrosagone - were resolved at various stages by means of either fermentation procedures or by fractional crystallisations of strychnine salts and eventually D - glucose, D - and L - fructose and D - and L - mannose were isolated. This constituted the first total synthesis of a carbohydrate.

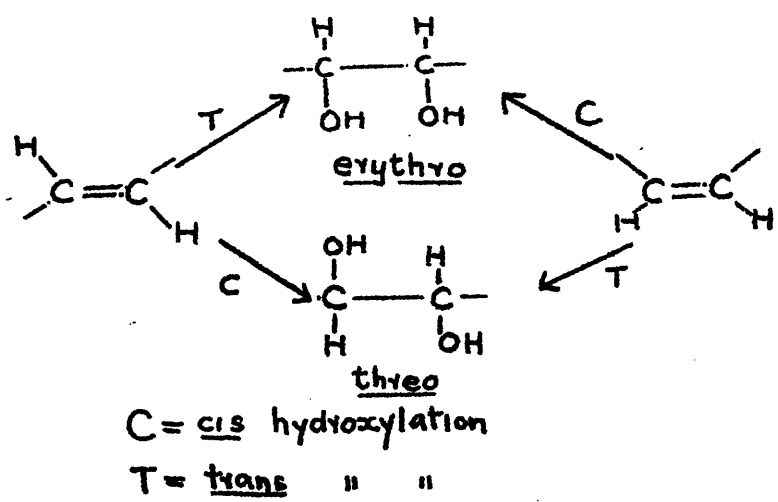
The total synthesis of any sugar can be rationally reduced to four individual problems:

1. The construction of the carbon skeleton of the sugar molecule including carbon - carbon branching if required.
2. The stereoselective incorporation of the hydroxyl groups into the carbon skeleton.
3. The introduction of the carbonyl functions at C (1) or C (2).

4. The resolution into optical enantiomorphs.

In the following paragraphs features (1), (2) and (3) are discussed in some detail. Feature (4) will not be discussed since at the present time very little work has been recorded on this aspect; on this point research will have to be done before the total synthetic method can compete effectively with the conventional transformation methods.

Owing to the polyhydroxy nature of carbohydrates the essence of a fruitful synthesis lies in the stereospecific introduction of hydroxyl groups. The general rule that <u>trans</u> addition to a <u>trans</u> double bond or <u>cis</u> addition to a <u>cis</u> double bond leads to the <u>erythro</u> arrangement of the added groups while <u>trans</u> addition to a <u>cis</u> double bond or <u>cis</u> addition to a <u>trans</u> double bond produces the <u>threo</u> configuration is the key consideration in the stereoselective introduction of pairs of hydroxyl groups.

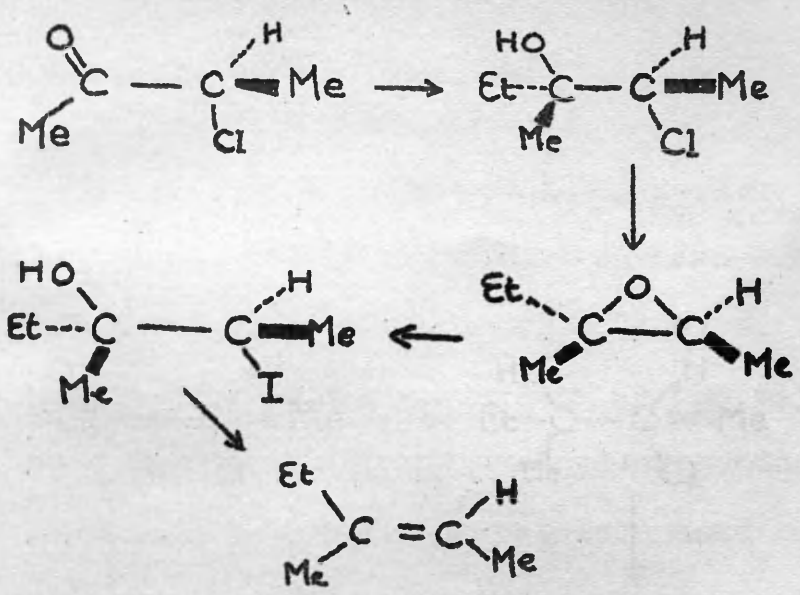


From this generalisation it follows that in building the carbon skeleton it is always desirable to have an unsaturated centre of known stereochemistry - or at least to have an arrangement whereby such a centre can be generated - at the site which will eventually bear the hydroxyl groups.

At this point it is pertinent to discuss the methods available for the preparation or introduction of ethylenic centres.

Cornforth[6] has described a general stereospecific synthesis of olefins from aliphatic α - chlorocarbonyl compounds. The addition of R.Mg Br or RLi to α - chlorocarbonyl compounds $R^1COC(Cl)R^2R^3$ is a stereospecific process, the chlorohydrin $RR^1C(OH)C(Cl)R^2R^3$ containing mostly the isomer in which R is anti to the larger of the groups R^2 and R^3 when OH and Cl are anti to each other. The chlorohydrins are converted to epoxides by alkali, the epoxides to iodohydrins by sodium iodide in a mixture of acetic and propionic acids at low temperature, and the iodohydrins to olefins by treatment with stannous chloride - phosphorus oxychloride in pyridine.

These three stages are stereospecific.

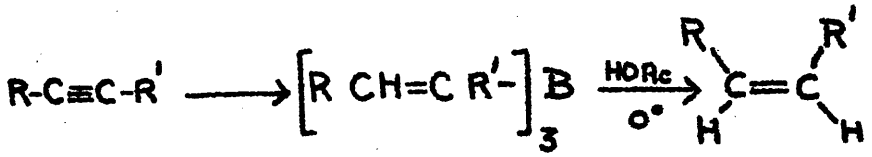


Partial reduction[7] of acetylenes offers a convenient route to ethylenes of known steric configuration. Catalytic semihydrogenation of a triple bond with palladium or with Raney nickel catalysts generally gives the cis - ethylene as the major product. The proportion of the trans - ethylene produced in the reaction varies with the catalyst used but with palladium is usually of the order of five per cent. Also there are reports that temperature[8], speed of hydrogenation[9] or pH of the medium[10] may influence the configuration of the product. However a catalyst has now been evolved which is specific for the partial catalytic hydrogenation of the triple bond in any molecular environment. It comprises a palladium - calcium carbonate catalyst which is partially inactivated by treatment with lead acetate; the

the/

specificity is further enhanced by the addition of quinoline[11]. The powers of this Lindlar catalyst have been strikingly demonstrated in the synthesis of vitamin A and the carotenoids.

Apart from catalytic hydrogenation, other methods for producing cis - ethylenes from acetylenes are available. Electrolytic reduction[12] of acetylenes at spongy nickel cathodes gives cis - ethylenes in good yields. Reduction with a copper zinc couple[13] in refluxing ethanol (containing a little water) is reported to give the cis - ethylene in high yield and purity. The hydroboration reaction[14] presents a new and convenient method for the conversion of disubstituted acetylenes to cis - olefins in high yield and complete stereochemical purity.



Diethyl aluminium hydride has also been used to reduce acetylenes to cis - olefins.[15].

The partial reduction of an acetylene to the corresponding trans - ethylene can be carried out by chemical reduction[16], e.g., sodium in liquid ammonia.

This procedure is highly specific for the partial reduction of an isolated triple bond (no saturated product is formed) and the ethylene produced always possesses the trans configuration. For an ethynyl group the presence of ammonium sulphate is necessary[17]. Metal - ammonia reductions have been successfully performed on acetylenic alcohols[18], amines[19] and urethanes[20]. In the case of α hydroxyacetylenes reductive fission of the propargylic hydroxyl group is a frequent side reaction but this can be overcome by reducing the preformed sodium salt of the alcohol[16]. This refinement is of obvious advantage in sugar synthesis. Further, trans - ethylenes may be obtained in excellent yield by reduction of acetylenes with lithium aluminium hydride provided the triple bond is flanked by a propargylic hydroxyl group[16].

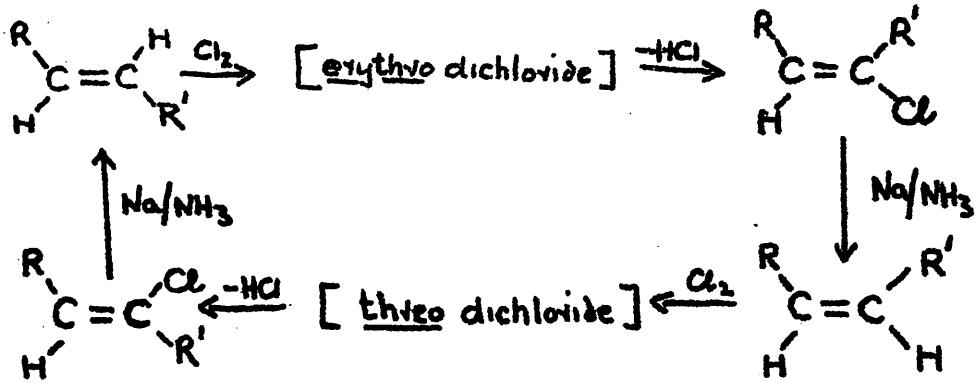
Dehydration offers a means of generating an ethylene but there is no general rule for the accurate prediction of the sterochemistry of the double bond produced. Many cases are known where dehydration of hydroxy compounds has given cis - trans mixtures[21]; β - hydroxy carbonyl compounds do, however, give trans αβ - unsaturated carbonyl compounds on dehydration.

Elimination of bromine[22], with metallic zinc or iodide ions, from a dibromide of known configuration proceeds by a trans stereospecific reaction, an E2-type,

type/

elimination mechanism being suggested. Dehydrohalogenation can give rise to ethylenes but generalisations as to the stereochemistry of ethylenes[23] produced by elimination reactions must be accepted with reserve.

Boord[24] has developed a method by which a pure trans - or cis - ethylene can be converted to its antipode in high purity. The method involves chlorination, dehydrochlorination and dechlorination, all of which are stereospecific. The procedure is outlined below:-



The stereospecific production of cis - and trans - ethylenes leads directly to the possibility of obtaining, with a similar degree of specificity, the corresponding erythro - and threo - dihydroxy - derivatives.

Among the reagents which result in *cis* - addition may be mentioned alkaline potassium permanganate[25], osmium tetroxide[26], osmium tetroxide - hydrogen peroxide[27], (Milas reagent), osmium tetroxide - catalysed metal chlorates (e.g., barium chlorate[28], sodium chlorate[29]), osmium tetroxide - vanadium pentoxide, and chromium trioxide - catalysed t - butyl hydroperoxide[30], and iodine - silver acetate in wet acetic acid[31].

The permanganate hydroxylation gives especially good results at low temperature if the reaction mixture is buffered, either by the addition of magnesium sulphate[32] or by the introduction of a current of carbon dioxide[33].

The reagents resulting in *trans* - hydroxylation or its equivalent include peracids followed by fission of the expoxide ring first produced[34], the iodine - silver benzoate complex (Prevost reagent)[35], and hypohalous acids[36]. A review on hydroxylation methods has appeared.[37]

For most purposes - and particularly in the case of synthesis of reducing sugars where the potential aldehyde is present as an acetal - the action on the double bond of ethereal perbenzoic acid gives the corresponding epoxide in good yield.

Similarly when the double bond is flanked by a hydroxyl group good yields of epoxide are obtained. The use of calcium hydroxide in working up facilitates the isolation of water soluble epoxides[38]. Epoxidation sometimes proves sluggish[39], especially when the ethylenic centre is in conjugation with a strong electron-attracting group. However αβ-unsaturated esters have been epoxidised in good yield by means of hydrogen peroxide and sodium tungstate at pH 4 - 5.5. Glycidaldehyde[41], has been obtained by treatment of acrolein with hydrogen peroxide at p.H 7.4:

$$CH_2=CH\,CHO \longrightarrow CH_2\!-\!\overset{O}{\overset{\diagup\diagdown}{}}\!-\!CH\,CHO$$

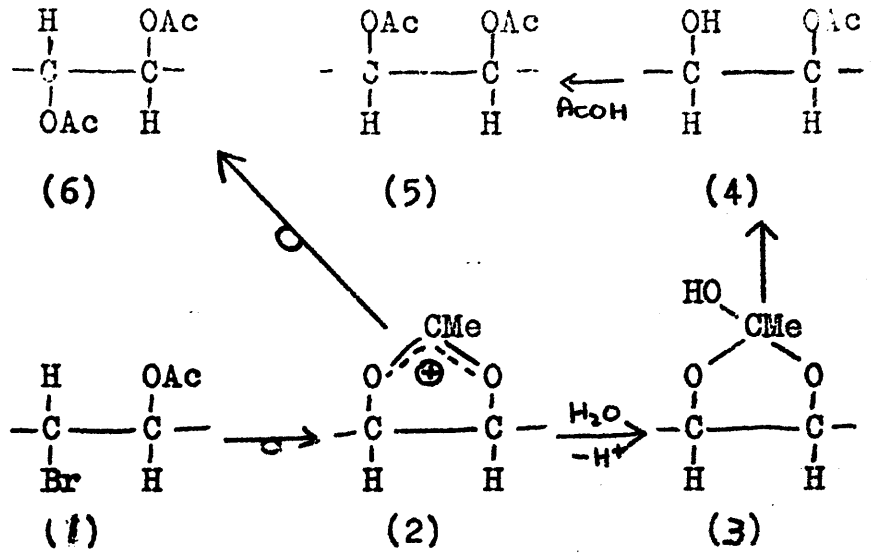
Recently αβ - unsaturated nitriles have been epoxidised with hydrogen peroxide under controlled pH. conditions. The major products are epoxyamides[42],

$$CH_2=CHCN \xrightarrow[pH\,7\text{-}7.5]{} CH_2\!-\!\overset{O}{\overset{\diagup\diagdown}{}}\!-\!CHCONH_2 \quad (70\%)$$

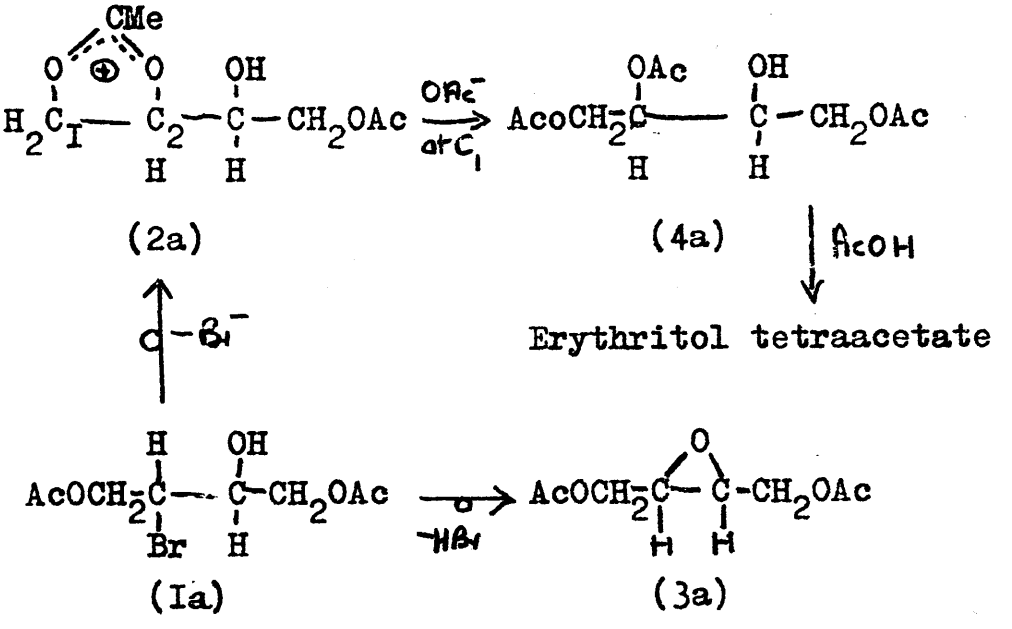
$$Tr\,CH_2=CHCN \xrightarrow[pH\,7\text{-}7.5]{} CH_2\!-\!\overset{O}{\overset{\diagup\diagdown}{}}\!-\!CHCONH_2 \quad (70\%)$$

room temper Treatment of αβ- unsaturated aldehydes at corresponding epoxides but in poor yield . αβ-unsaturated ketones can be epoxidised by means of t - butyl - hydroperoxide[44], in the presence of Triton B, but there are spatial requirements for the reaction to proceed.

The use of hypohalous acid is particularly useful in the case of terminal double bonds which are normally rather resistant to attack by peracids[45]. Subsequent replacement of the halogen (e.g. by acetoxyl) can be used to give diols. The replacement of halogen by acetoxyl can be achieved with retention or inversion of configuration depending on whether wet or dry solvent is used[46]. This is due to neighbouring group participation in the reaction of the halogen. Thus, the threo - bromoacetate (1) with silver or potassium acetate in dry acetic acid gave the threo - diacetate (6); with moist acetic acid or ethanol as solvent the erythro - diacetate (5) was obtained (See Flowsheet No.1., Scheme (a)). The initial step in each case involves the abstraction of bromide ion with simultaneous Walden inversion to give the acetoxonium ion (2). In dry acetic acid this is attacked by acetate ion at the rear of C_1 or C_2 with a second inversion producing the threo - diacetate(6) with overall retention of configuration. However, in moist acetic acid or ethanol, (2) is attacked by a water molecule with expulsion of a proton to furnish the unstable orthomonoacetate (3), the ring of which then opens to/



Scheme (a).



Scheme (b).

(→ signifies occurrence of a Walden inversion).

Flowsheet No. I

to/

give the monoacetate (4)esterification of which gives the erythro - diacetate (5).

A more complex case has been discussed by Raphael[47]. Addition of hypobromous acid to cis and trans - but - 2 - ene- 1, 4 - diol diacetates gave threo - (1a) and erythro - 2 - bromobutane - 1, 3, 4 - triol - 1, 4 - diacetates respectively. Treatment of the erythro - bromohydrin with potassium acetate in dry acetic acid gave exclusively threitol tetra-acetate; the same reagent in moist ethanol gave, after acetylation, erythritol tetra-acetate as the sole product. The threo - bromohydrin (1a) on similar treatment gave mainly erythritol tetra-acetate in dry acetic acid and threitol tetra-acetate in moist ethanol (see Scheme (b), Flow Sheet No.1.).

Abstraction of the bromide ion by potassium acetate in dry acetic acid results in the formation of the cyclic acetoxonium ion (2a) with inversion of configuration at $C_{(2)}$. Attack by acetate ion then takes place at the non- asymmetric $C_{(1)}$ which is sterically less hindered than $C_{(2)}$; overall inversion of configuration has occurred to give, after acetylation, erythritol tetra-acetate,. Reaction in moist alcohol, however, gives rise to the formation, with Walden inversion, of the epoxide/

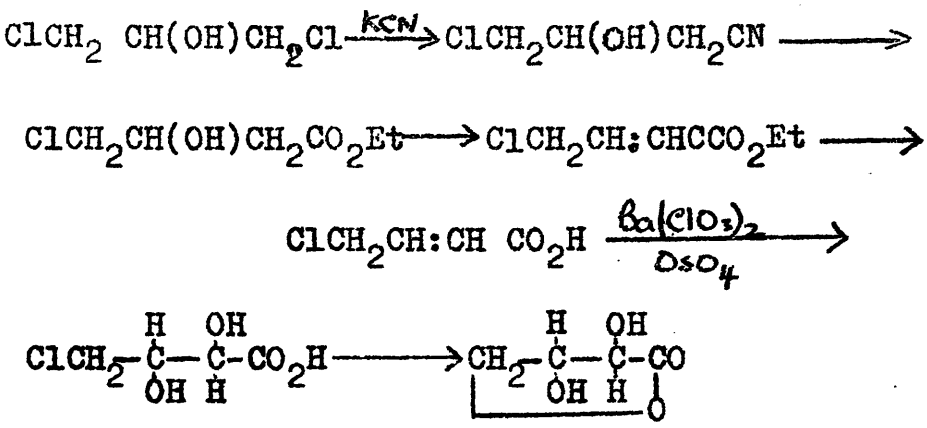
epoxide/

(3a) which on treatment with acetic anhydride, undergoes ring opening, again with Walden inversion, to give threitol tetra-acetate. The net result is retention of configuration.

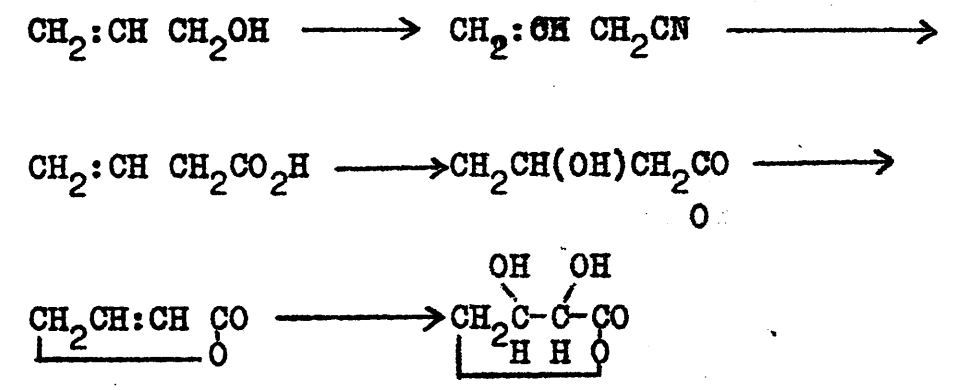
Before discussing the methods available for the production of an aldehyde group it seems pertinent at this point to review the total synthetic approach to carbohydrates from simple precursors.

Much of the early synthetic work in the carbohydrate field was carried out by the French chemist Lespieau.[48] In very early work Lespieau synthesised threonic acid as shown in flow sheet No.2. This synthesis employs dehydration as a means of generating a trans - ethylene. In a similar manner Glattfield[49] synthesised erythronic acid and threonic acid starting from allyl alcohol; by Rosenmund reduction of threonic acid chloride, (DL) threose was obtained, albeit in poor yield.

Lespieau[50] later turned his attention to the synthesis of hexitols and pentitols. Starting from divinyl glycol(7) which was prepared by the reductive coupling of acrolein (by means of a zinc-copper couple in acetic acid) a successful synthesis of allitol and mannitol was accomplished (see flowsheet No.3.).

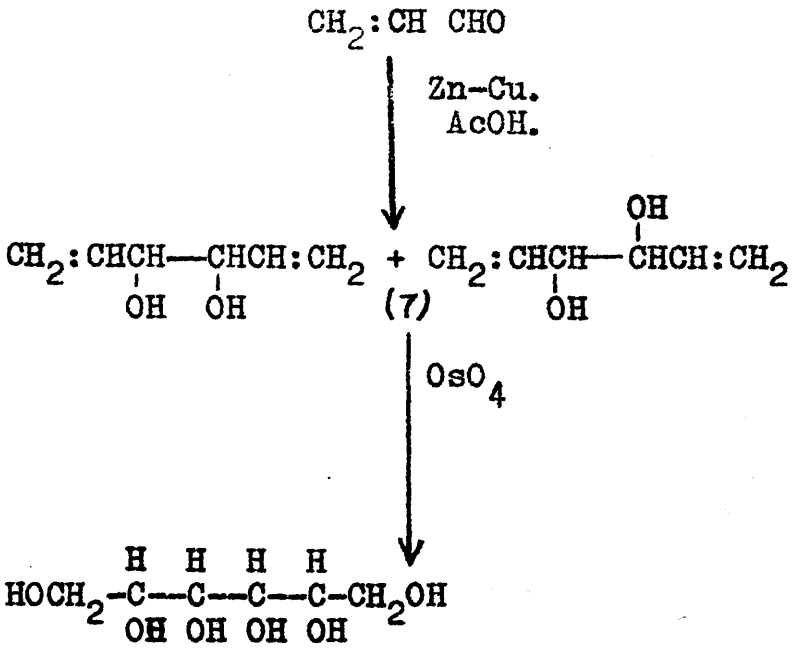


Synthesis of threonic acid. (Lespieau).



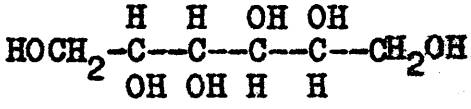
Synthesis of erythonic acid. (Glattfield).

Flowsheet No. 2.



Allitol.

+



Mannitol.

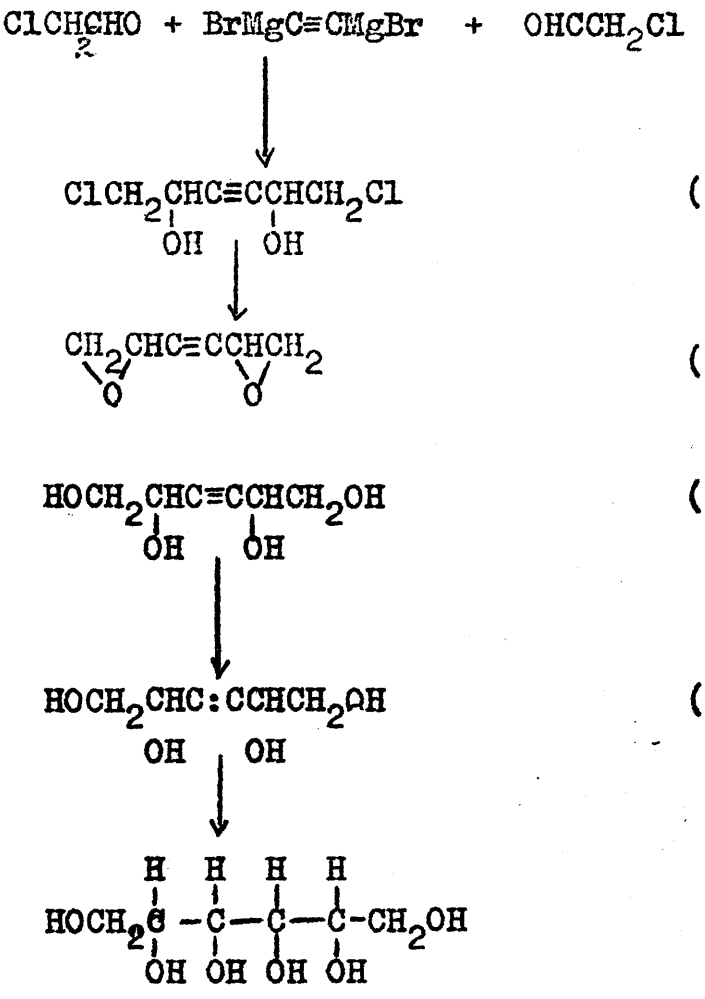
Synthesis of hexitols(Lespieau).

Flowsheet No. 3.

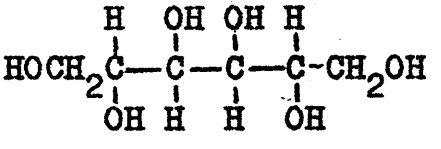
The use of acetylenic compounds for the synthesis of carbohydrates was first exploited by Lespieau[50]. This is illustrated by his synthesis of the hexitols allitol and dulcitol as shown in Flowsheet No.4.

The acetylenic glycol(8) obtained by condensation of chloroacetaldehyde with acetylene dimagnesium bromide was converted to the epoxide (9) on treatment with base. Hydrolysis of the epoxide to the acetylenic tetrol (10) followed by catalytic hydrogenation gave the cis - ethylenic tetrol (11). cis - Hydroxylation gave mainly allitol while cis - hydroxylation of the tetra acetate of (11) gave mainly dulcitol.

Using a similar approach Lespieau[50] extended his work to the synthesis of pentitols (see Flowsheet No.5). The acetylenic carbinol (12) from the condensation of dichloropropionaldehyde with sodium acetylide was converted via the epoxide (13) to the acetylenic triacetate (14) and then to the corresponding ethylenic triacetate (15). Hydroxylation and acetylation gave a product (16) separable into two penta acetates, hydrolysis ofwhich gave ribitol and arabitol.



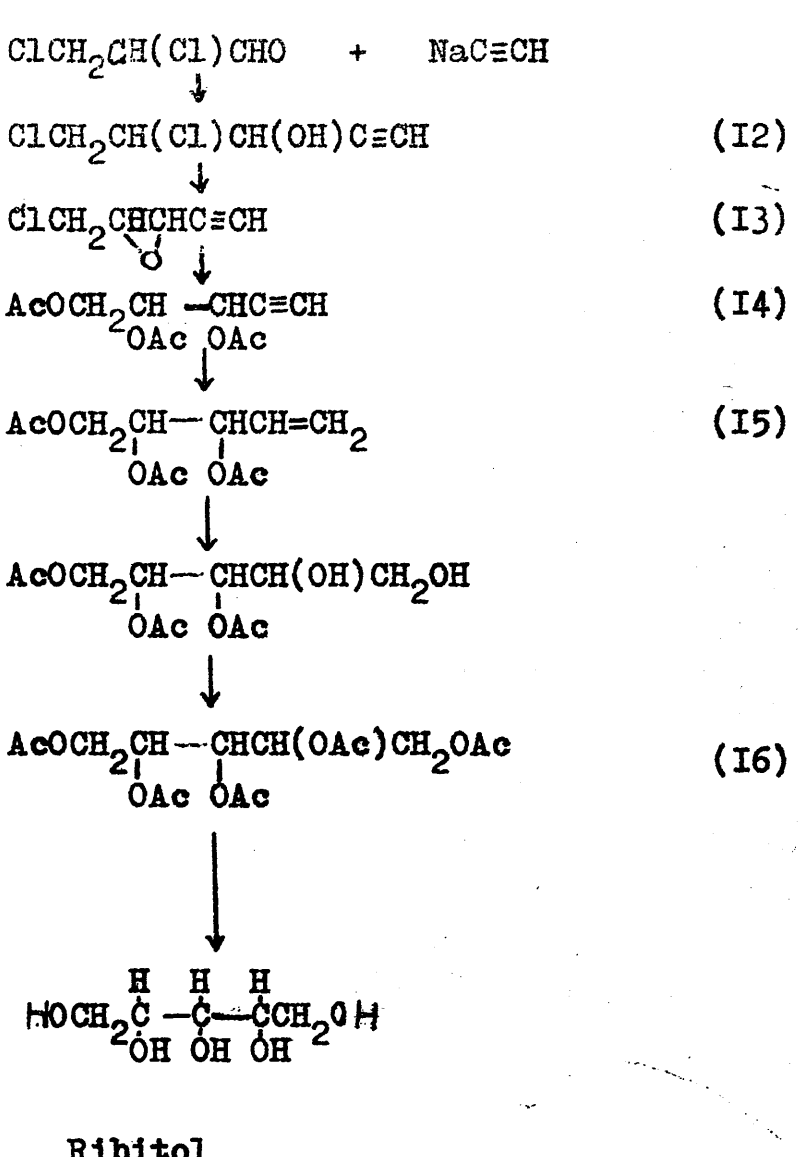
Allitol. +



Dulcitol.

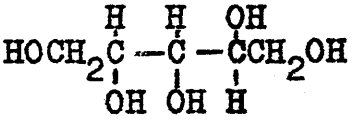
Synthesis of hexitols(Lespieau).

Flowsheet No. 4.



Ribitol

+



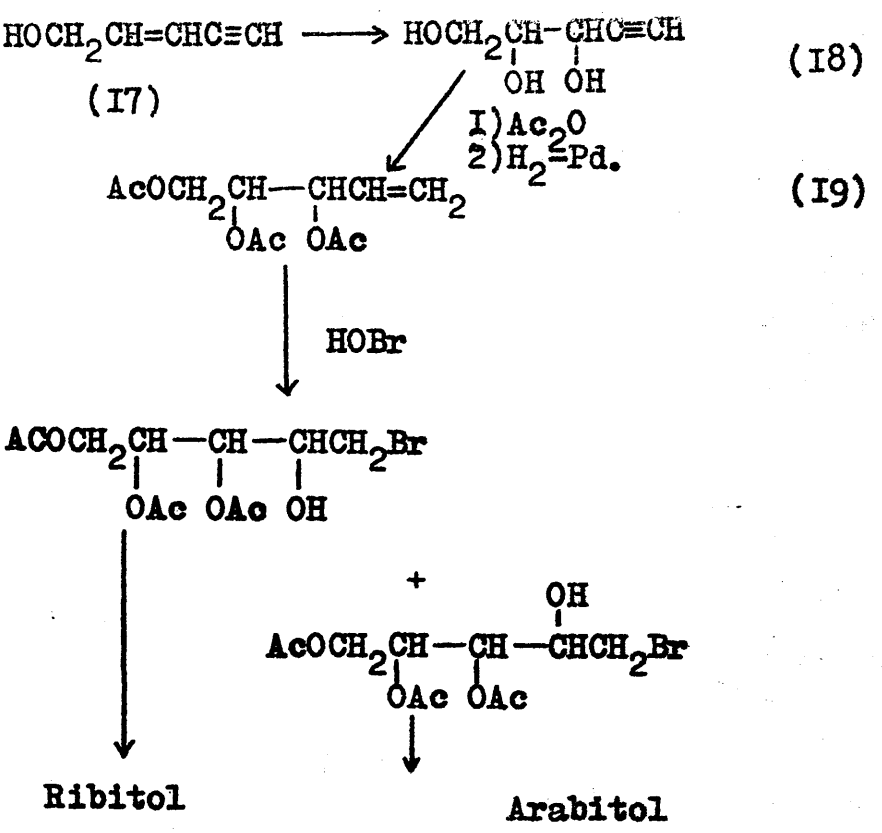
Arabitol

Acetylenic route to pentitols (Lespieau).

Flowsheet No. 5.

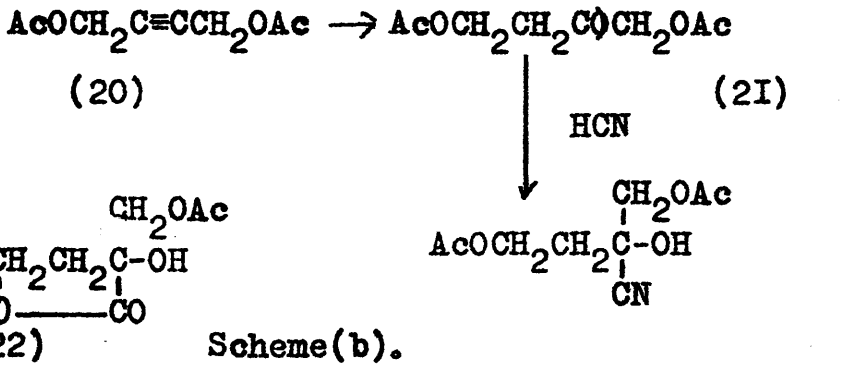
Since the time of Lespieau's pioneering work on sugar synthesis, acetylene chemistry has been extensively expanded with the result that simpler and more efficient methods of preparing acetylenic precursors are now available. Raphael[51] has elaborated pent-2-(trans) - en - 4 - yn - 1 - 01 (17) (made by condensation of epichlorohydrin with sodium acetylide) into arabitol and ribitol (see Flowsheet No.6. Scheme (a).). trans - hydroxylation of (17) with performic acid gave the acetylenic triol (18) with the erythro configuration. It is of interest and of considerable synthetic value that the triple bond was unattacked by this reagent. Acetylation and partial reduction gave the ethylenic triacetate (19). Treatment with hypobromous acid (from aqueous N - bromosuccinimide) gave a mixture of two separable diastereoisomeric bromohydrins, acetylation and hydrolysis of which gave ribitol and arabitol.

Aspinall[52], has used but-2-yn-1,4 - diol to prepare iso saccharinolactone (22), an alkali degradation product of xylan. Hydration of but-2-yn-1, 4-diol diacetate (20) gave 1, 4 - diacetoxybutanone (21). The carbon branching at C(2) was introduced by means/



Scheme(a).

Synthesis of ribitol and arabitol(Raphael).



Scheme(b).

Synthesis of isosaccharinolactone(Aspinal).

Flowsheet No.6.

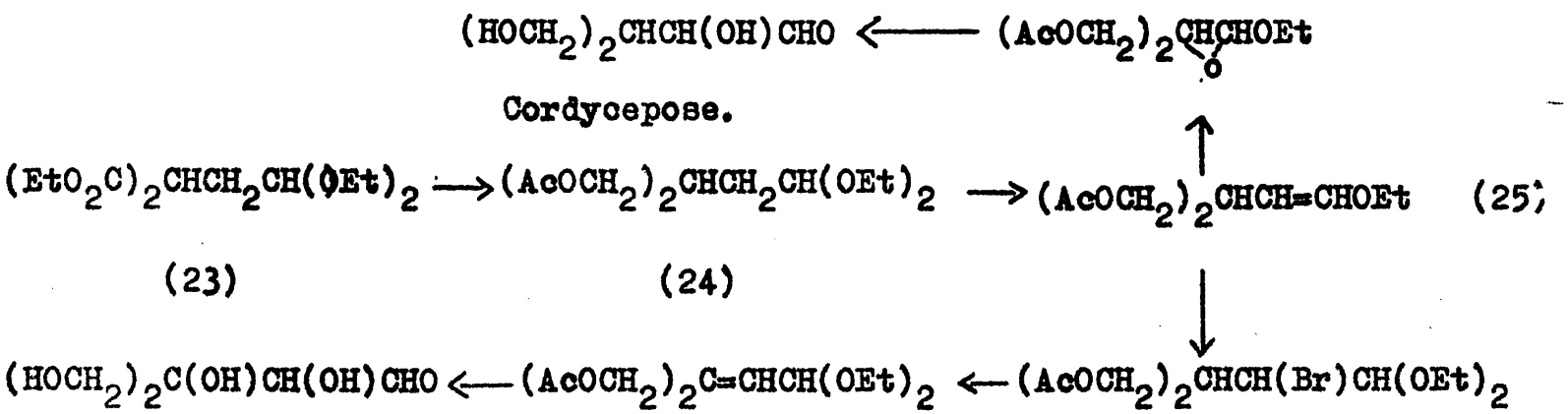
means/
of the cyanohydrin reaction. Hydrolysis gave the desired lactone as shown in Flowsheet No.6. (Scheme b).

The syntheses so far described have dealt with the sugar derivatives only.

The synthesis of the reducing sugars themselves poses a problem in regard to the timing of the introduction of the necessary carbonyl functions.

If introduced at an early stage in the synthesis, the aldehyde grouping must be protected throughout the subsequent reactions. For this purpose conversion into the acetal is a suitable means of protection but this introduces a limitation in that subsequent stages must avoid the use of acidic reagents. However almost all the published syntheses of reducing sugars use the early introduction of an acetal as the source of the eventual reducing group of the sugar.

Raphael and Roxburgh [53] in their synthesis of the branched -chain sugars apiose and cordycepose introduced the aldehyde function in the initial stage (see Flowsheet No.7). Condensation of bromoacetal with malonic ester gave ethyl - 2, 2 - diethoxyethylmalonate (23) which on reduction with lithium aluminium hydride followed by acetylation afforded the diacetoxyacetal (24). This on rapid distillation from sodium bisulphate gave the ether (25) which/



Synthesis of Apiose and Cordycepose (Raphael and Roxburgh).

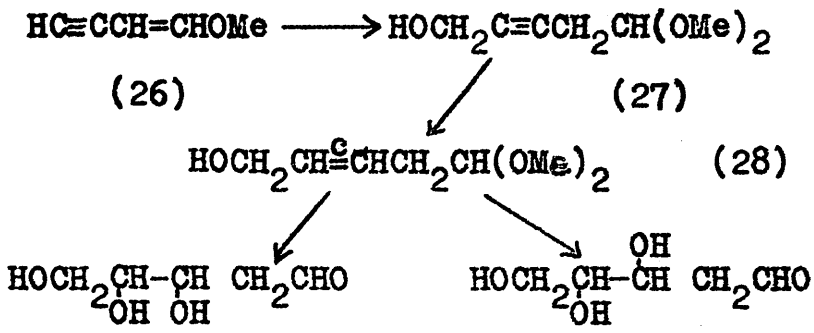
Flowsheet NO.7.

which/

provided the means of introducing a hydroxyl group at C(2). Elaboration of the enol ether as outlined gave apiose and cordycepose.

Weygand and Leube[54] also used the early introduction of an acetal as the source of the aldehyde group in their synthesis of 2-deoxyribose. Treatment of 1 - methoxybut-1-en-3-yne (26) with formaldehyde and methanol in the presence of potassium hydroxide gave the acetylenic hydroxyacetal (27), partial catalytic hydrogenation of which gave the *cis* - ethylenic acetal (29). Hydroxylation procedures and hydrolysis of the acetal grouping gave 2 - deoxyribose and 2 - deoxyxylose. The synthesis is outlined on Flowsheet No.8 Scheme (a).

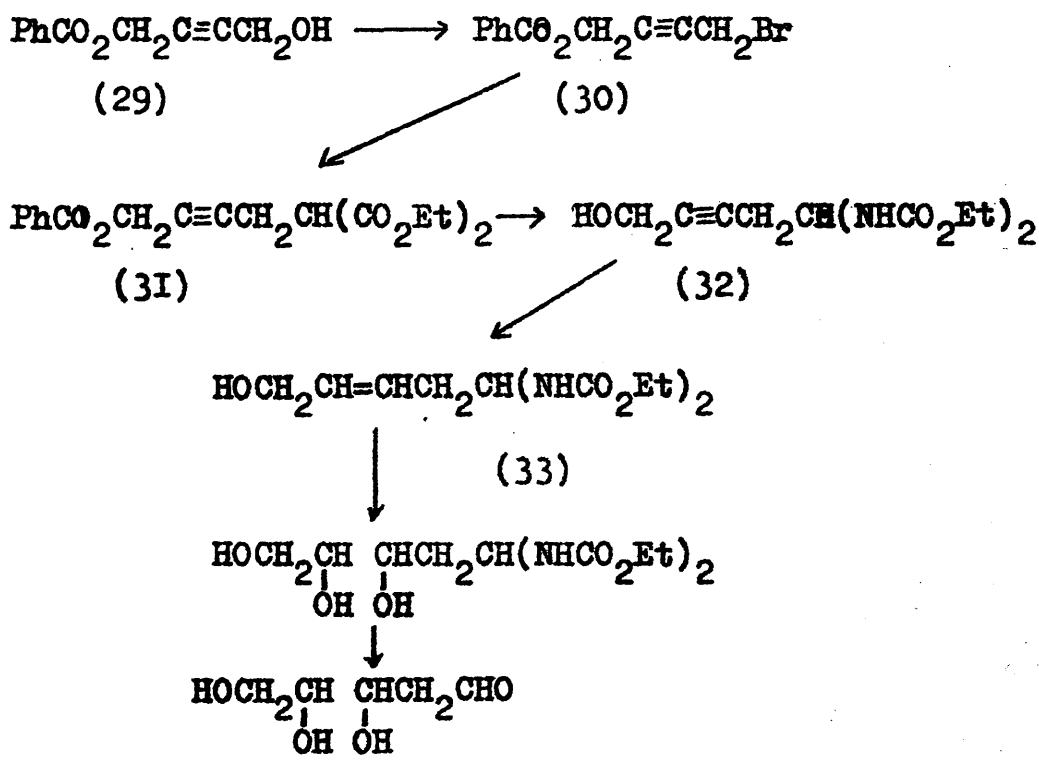
Raphael's[55] synthesis of 2 - deoxyribose used a double Curtius rearrangement to produce the aldehyde group (Flowsheet No.8. Scheme (b)). But-2-yn-1, 4-diol was mono-benzoylated, giving (29). This with phosphorus tribromide in pyridine afforded 1 - benzoyloxy-4-bromo-but-2-yne (30), which on condensation with malonic estergave the acetylenic diester (31). Treatment with hydrazine followed by nitrous acid and ethanol gave the acetylenic bisurethane(32) by the Curtius rearrangement. The usual procedure of partial catalytic hydrogenation to the *cis* - ethylenic bisurethane (33), followed by hydroxylation, etc., gave/



2-Deoxyribose. 2-Deoxyxylose.

Scheme(a).

Synthesis of 2-Deoxypentoses (Weygand).



2-Deoxyribose.

Scheme(b).

Synthesis of 2-Deoxyribose (Raphael).

Flowsheet No.8.

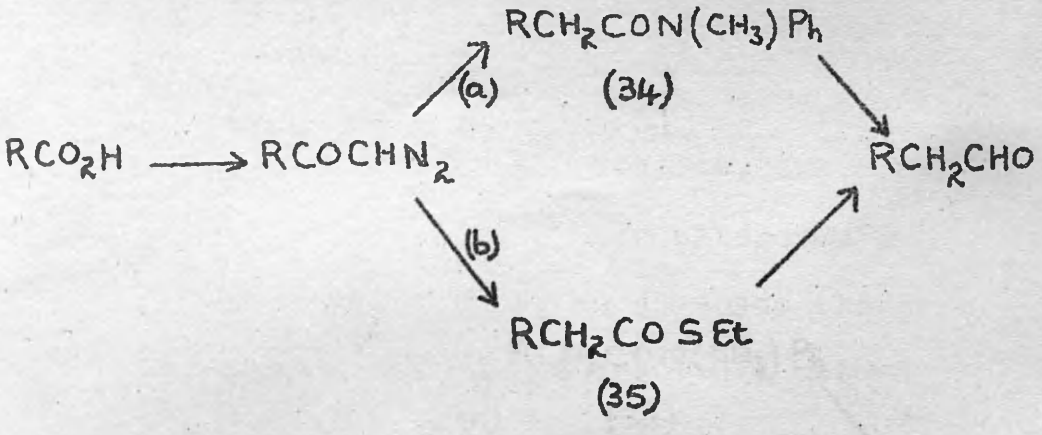
gave/

2 - deoxyribose in low yield.

Gattfield[49] in his synthesis of threose left the introduction of the reducing group until virtually the last stage. Synthetic threonic acid chloride was subjected to Rosenmund reduction whereby threose was obtained in very poor yield.

In view of the fact that new methods are available for the conversion of carboxylic acids to aldehydes it is probable that they will be used more and more in total carbohydrate synthesis. Furthermore from the point of view of optical resolution carboxylic acids are eminently suitable for this purpose. Acid chlorides may be reduced to aldehydes by treatment with lithium tri-t-butoxyaluminohydride[56] at - 78°. Reduction of γ-lactones with sodium borohydride,[57] or sodium amalgam[58] affords hydroxy - aldehydes directly.

Weygand[59] has described a method whereby the N- methylanilide of a carboxylic acid can be converted to the corresponding aldehyde by reduction with lithium aluminium hydride and this has been extended[60] to provide a means of preparation of the homologous aldehyde from the acid.



The acid is converted to the corresponding diazo-ketone which is then photolysed in the presence of N - methylaniline (route a) producing the homologous N - methylanilide (34) which on reduction gives the aldehyde. Alternatively the diazoketone may be converted to the homologous thio-ester (35), reduction of which affords the aldehyde (route b).

Weygand[61] has also described a method whereby the homologons α - hydroxyaldehyde can be prepared from an acid via the corresponding diazoketone as shown below.

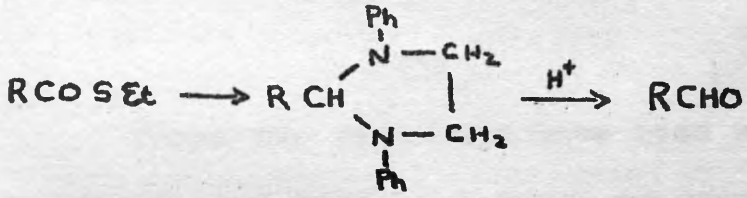
$$RCOCHN_2 \xrightarrow{R'SCl} RCOCH(Cl)SR' \longrightarrow RCOCH(SR')_2$$

$$\xrightarrow{LiBH_4} RCH(OH)CH(SR')_2 \xrightarrow{HgCl_2} RCH(OH)CHO.$$

Reduction of thio-esters with Raney nickel[62] in the presence of 1, 2 -dianilinoethane also gives the corresponding aldehyde via the intermediate/

intermediate/

di-anilide.



The above conversions of carboxylic acids to homologous aldehydes may find application in the synthesis of 2 - deoxy sugars since the reaction conditions are extremely mild. In this connection two other aldehyde syntheses seem promising. Both involve the abnormal hydration of a terminal acetylene.

Terminal acetylenes react with thiolacetic acid in the presence of a peroxide catalyst to produce an enol-thiolacetate (36) which can be transformed to an aldehyde by treatment with the usual carbonyl reagents (e.g., 2,4-dinitrophenyl-hydrazine) [63,64].

$$RC{\equiv}CH \longrightarrow RCH{=}CHSAc \longrightarrow RCH_2CHO$$
(36)

The second method involves the hydroboration reaction [14]. Treatment of a terminal acetylene with a dialkyl boron gives a dialkylborocethylene (37), oxidation of which with hydrogen peroxide gives an aldehyde.

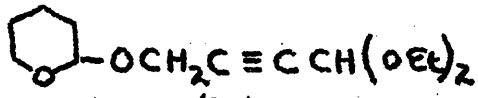
$$RC\equiv CH \longrightarrow \underset{(37)}{RCH=CHBR'_2} \longrightarrow RCH_2CHO$$

These two reactions have been applied to sugar synthesis (see Part 1) without success.

For the preparation of $\alpha\beta$ -unsaturated acetals of known double bond configuration the acetylenic route is probably the best method. Treatment of an acetylenic Grignard reagent with ethyl orthoformate gives the acetylenic acetal[65] (38).

$$RC\equiv CMgX \xrightarrow{CH(OEt)_3} \underset{(38)}{RC\equiv CCH(OEt)_2}$$

reduction of which can give rise to either the cis or trans ethylenic acetal. In this manner (39) has been prepared from propargyl alcohol.[66] Reduction,

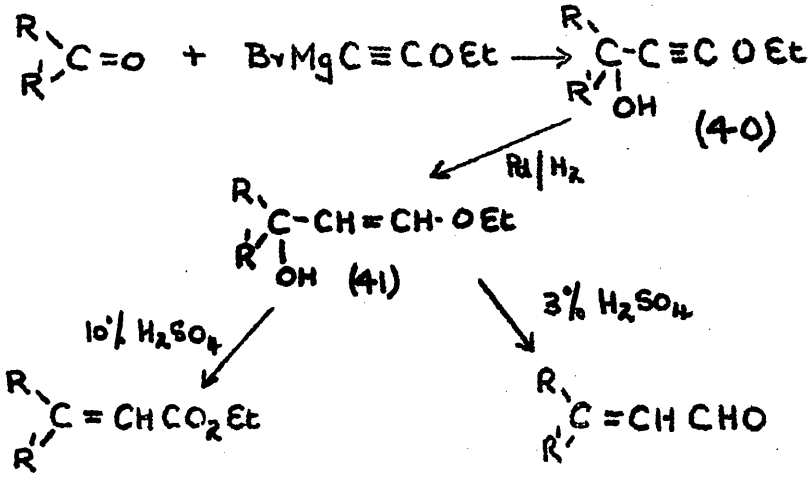


(39)

hydroxylation and hydrolysis should give threose or erythyrose.

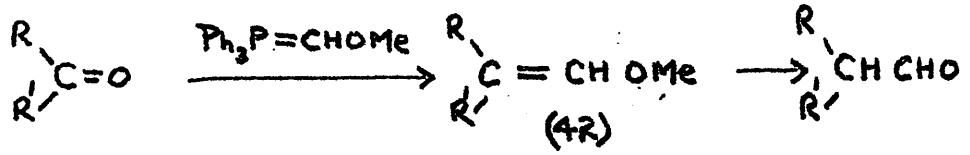
With regard to the synthesis of branched-chain sugars newer methods whereby a ketone may be converted to a branched-chain aldehyde may be mentioned. Treatment of a ketone with ethoxyacetylene magnesium bromide gives an/

ethoxyacetylenic carbinol(40) reduction of which gives the corresponding enol ether (41). This on treatment with dilute acid affords the αβ-unsaturated aldehyde.[67]

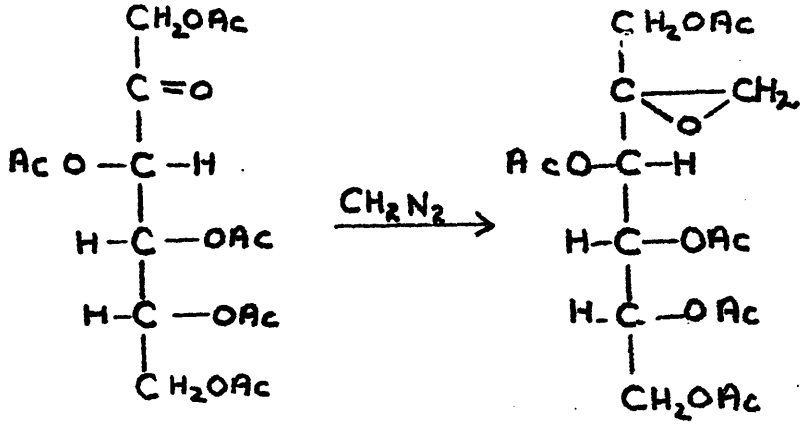


Treatment of (41) with stronger acid gives the αβ- unsaturated ester.

Another method for converting a ketone to a branched-chain aldehyde involves the Wittig condensation of methoxymethylene - triphenylphosphorane[68] with a ketone to give the enol ether (42) hydrolysis of which gives the aldehyde.

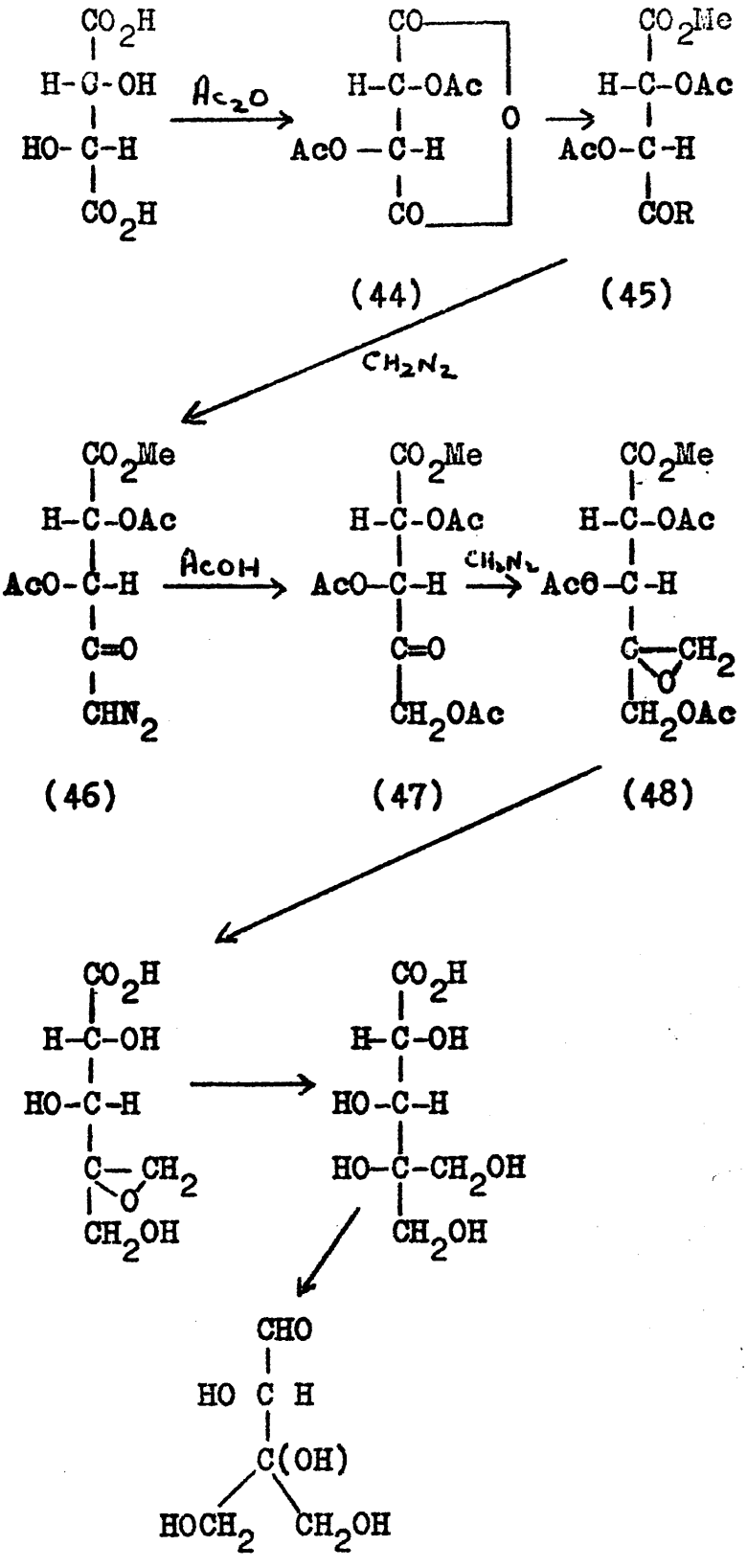


Branching of a carbon chain can be accomplished by the action of diazomethane on a suitably activated ketone. It has been shown[69] that fructose pentaacetate reacts with diazomethane to give the branched-chain epoxide (43) in high yields.



(43)

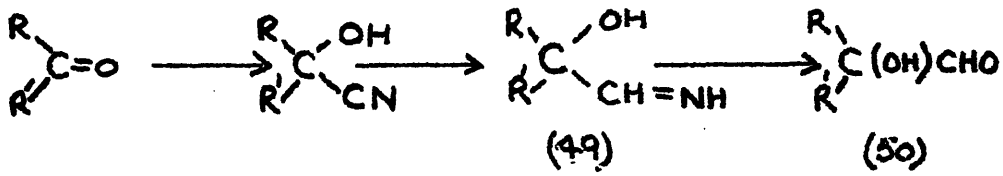
This reaction has been successfully applied, by Weygand[70], to the synthesis of L - apiose from (+) - tartaric acid (seeFlowsheet No.9.) (+) - Tartaric acid on treatment with acetic anhydride gave (+) - diacetoxy - tartaric anhydride (44) which with one mole of methanol gave the half ester (45, R=OH), This was converted to the corresponding acid chloride (45, R=ON) reaction of which with diazomethane gave the diazoketone (46). With acetic acid the triacetoxyketo-ester (47) was obtained which gave the branched chain epoxide (48) on treatment with diazomethane. The epoxide on hydrolysis and Ruff degradation gave L - apiose.



Synthesis of L-Apiose (Weygand).

Flowsheet No. 9.

The cyanohydrin reaction[71] can be used to produce α - hydroxy branched-chain aldehydes:



The cyanohydrin is partially reduced with a palladium oxide - barium sulphate catalyst in the presence of dilute acid to the imine (49), hydrolysis of which gives the α - hydroxy aldehyde (50) in good yield.

The aldol reaction of formaldehyde with a suitable active methylene compound provides a means of introducing a hydroxymethyl group with simultaneous carbon branching.[72]

$$CH_3CO\,CH_3 \longrightarrow CH_3CO\,C(CH_2OH)_3$$

A synthesis of L - apiose from a glucose derivative using this reaction has been recently announced[73].

With the great surge of development of newer chemical reagents and methods now in progress the stage would now seem to be set for a rational attack on carbohydrate synthesis by the total synthetic route. The contents of this thesis describe/

describe/

experiments towards this end in the field of the 2 - deoxy-, 2, 6 - dideoxy-, branched-chain- and amino-sugars.

PART 1.

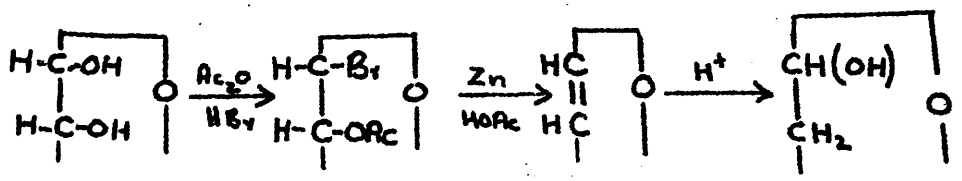
2 - DEOXY - DL - RIBOSE.

HISTORICAL.

2 - Deoxy-D-ribose was recognised as the sugar component of the biologically important substance, deoxribonucleic acid but for many years the nature of this sugar remained a mystery due mainly to its extreme instability. In 1929 Levene and London[74] succeeded in isolating the sugar from guanine nucleotide by careful hydrolysis and showed that it was a 2 - deoxy pentose. Levene[75] showed that the sugar was in fact 2 - deoxy - D - ribose by comparison with synthetic 2 - deoxy- L -ribose with which it was identical in all but optical rotation. With the isolation and identification of 2 - deoxyribose as a constituent of nucleic acids attention was directed towards methods of synthesising this biologically important carbohydrate. These will be described in the following paragraphs.

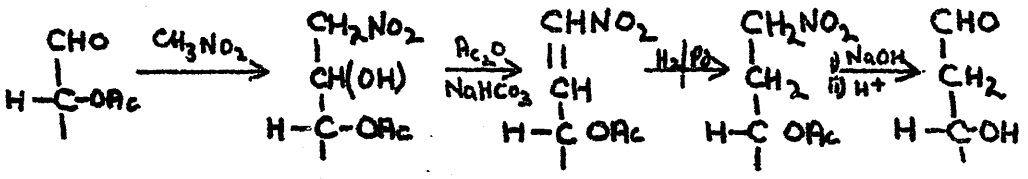
Two methods are available for the synthesis of 2 - deoxy sugars generally and of 2 - deoxy - D - ribose in particular. These are the Fischer glycal method,[76,77] and the nitro olefin method[78,79]. Other miscellaneous methods are available and these are discussed later.

The glycal method, the essential stages of which are shown below, has been thoroughly explored.



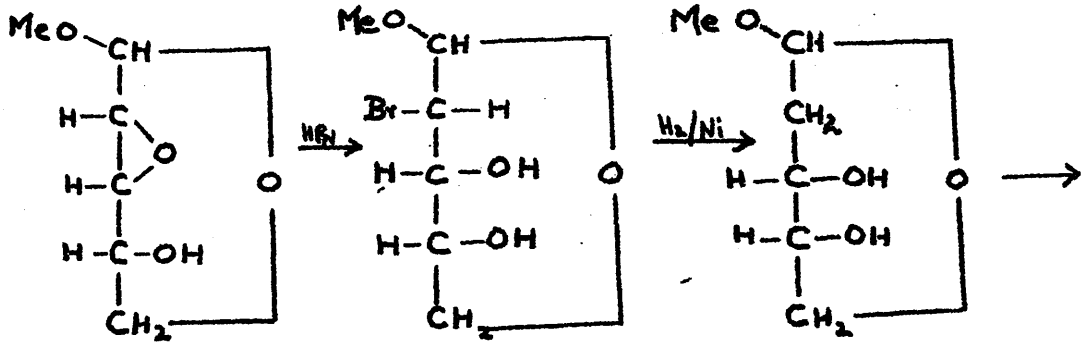
The method was first used by Meisenheimer and Jung[80] to prepare 2 - deoxy-L-ribose and was adapted by Levene and Mori in 1929 to prepare this sugar for comparison with the deoxy sugar obtained from thymus gland tissue. The overall yields were, however, very low (about 1%). In 1935 Felton & Freudenberg[81] modified the technique and increased the overall yield to 5%. More recently Stacey and coworkers[82] improved the yield to 10%.

The nitro-olefin route to 2-deoxy-D-ribose employed D-erythrose or derivatives thereof as the initial material[83,84]. This scheme is outlined diagrammatically below.

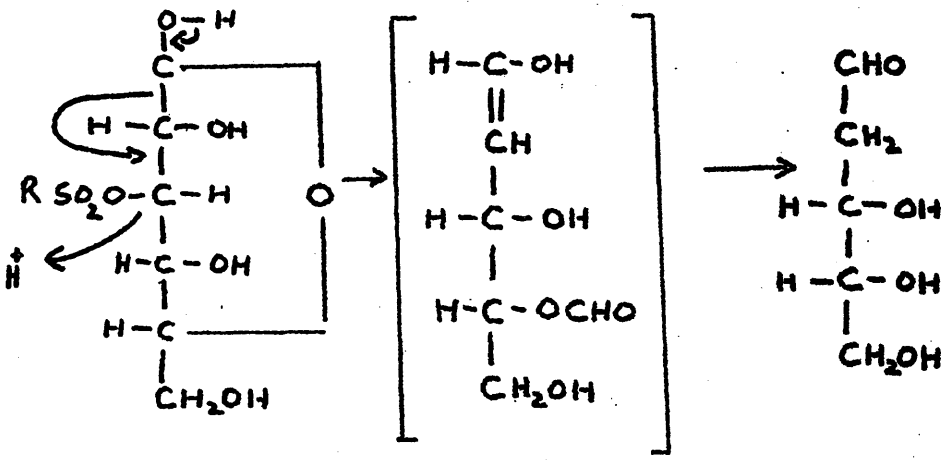


This method as applied by Stacey[84] gave crystalline 2 - deoxy-D-ribose in 0.5% yield. It was later improved by Sowden[83] who showed that overall yields of 20% could be obtained. This method has been adopted by Murray and Butler[85] for the preparation of 2 - deoxy-D-ribose - 1 - C^{14}.

The two methods just described, while giving pure 2-deoxy-D-ribose are not conducive to the large scale preparation of the sugar. To this end Stacey and his colleagues[86] investigated the action of hydrobromic acid on methyl 2,3-anhydro-β-D-riboside as shown below. This gave mainly methyl-β-3-bromo-3-deoxy-β-D-xyloside and only a small amount (10%) of methyl 2 -bromo-2-deoxy-β-D-arabinoside. This on hydrogenolysis afforded methyl-2-deoxy-β-D-riboside which on hydrolysis gave 2-deoxy-D-ribose in low overall yield.



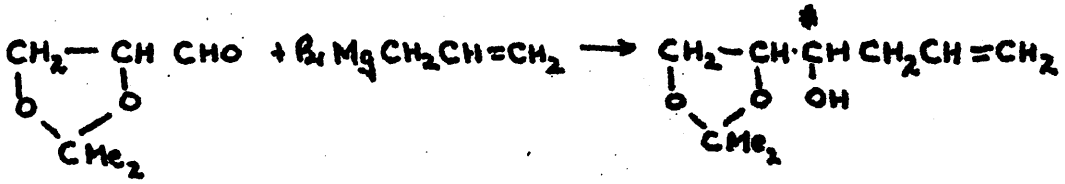
A convenient large scale synthesis of 2-deoxy-D-ribose is now available starting from D-glucose[87] which was converted to 3 - O - tosyl-, or 3 - O - mesyl - D - Glucose. This on treatment with aqueous base underwent facile elimination ofthe corresponding sulphonic acid to give 2 - deoxy - D - ribose as shown below. The variation on this theme described by Recondo & Rinderknecht[87c],



gave 2 - deoxy-D-ribose in 45% yield from 3 - O - mesyl - D - Glucose.

Hough[88] has outlined a lessproductive method for the synthesis of 2 - deoxy - D - ribose, An excess of allyl magnesium bromide was allowed to react with 2, 3 - isopropylidene - D - glyceraldehyde in ethereal solution and, syrupy 5, 6 - isopropylidene-hex-1 - ene - 4, 5, 6 - triol was obtained in excellent

yield. This reaction produced a



new asymmetric centre (*) at carbon atom 4. Hydroxylation by the Milas technique[89] afforded a fraction, separated on a column of cellulose, containing 5, 6 - isopropylidene - 3 - deoxyhexitols which on periodate oxidation gave, after acid hydrolysis, 2 - deoxy - D - ribose as the major component. From this it would appear that an asymmetric synthesis had occurred.

Another method for the preparation of 2 - deoxy - D - ribose using 2, 3 - isopropylidene - D - glyceraldehyde as an initial material has been outlined briefly by Overend & Stacey[90]. The glyceraldehyde derivative was condensed with acetaldehyde and afforded a mixture of 4, 5 - isopropylidene - 2 - deoxy -D - xylose and 4, 5 - isopropylidene - 2 - deoxy - D - ribose, the two sugars obtained on acid hydrolysis being separated by chromatographic means.

The two previous synthesis of 2 - deoxy - DL - ribose from non- carbohydrate precursors are

discussed in detail in the general introduction.

DISCUSSION.

The synthesis of 2 - deoxyribose is complicated by the fact that the deoxypentose is a very sensitive aldol and is readily destroyed by acid or alkali; even standing at room temperature will bring about a slow transformation to a green polymer. Any synthesis must, therefore, of necessity involve very mild reaction conditions as the goal is neared. The role of acetylenic compounds as precursors is particularly advantageous from this point of view.

The most obvious total synthetic route (see Flowsheet No.10) to 2 - deoxy - DL - ribose (A4) centred on the preparation of the hydroxyacetylenic acetal (A3). The corresponding dimethyl acetal has been prepared by Weygand and Leube[91], in low yield by interaction of 1 - methoxybut - 1 - en - 3 - yne with formaldehyde in methanolic potassium hydroxide solution and has been converted into 2 - deoxy - DL - ribose and 2 - deoxy - DL - xylose in good yield as described in the introduction. The most direct route to the acetylenic acetal (A3) and thus to 2 - deoxy - DL - ribose would involve the condensation of bromoacetal with a suitable

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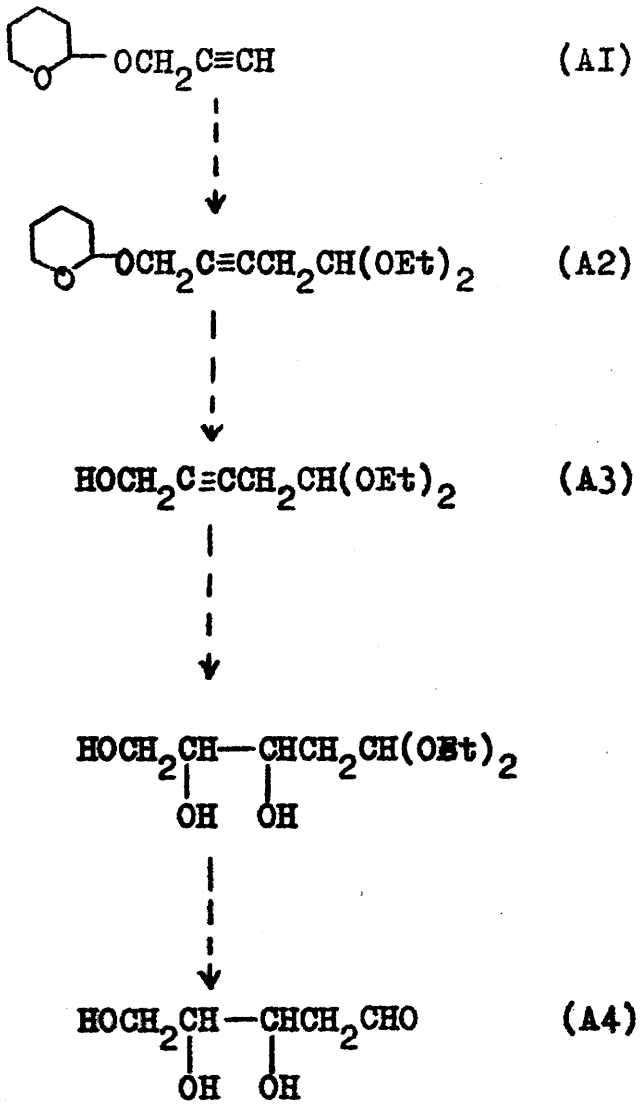

2-Deoxy-DL-ribose

Flowsheet No. IO.

suitable/ derivative of propargylalcohol. Smith[92], in his synthesis of DL - ricinoleic acid condensed bromoacetal with the lithium derivative of 1 - chloroctyne and obtained the corresponding $\alpha\beta\gamma$ - acetylenic acetal in 30% yield. Durand and Piaux[93] reported that lithium acetylides condense with bromoacetal in boiling dioxan containing a trace of copper powder to give $\alpha\beta\gamma$ - acetylenic acetals in fair yield.

In view of the above evidence for the previous success of this process, 3 - (2' - tetrahydropyranyloxy) - prop - 1 - yne (A1) was converted into its lithium derivative and treated with bromoacetal in boiling dioxan during thirty hours, the sole product of the reaction being unchanged 3 - (2' - tetrahydropyranyloxy) - prop - 1 - yne which was recovered in 70% yield. The failure of the reaction in this case might possibly be related to the presence of the oxygen function α to the acetylene group.

The second approach to 2 - deoxy - DL - ribose started from DL - erythro - pent - 4 - yn - 1, 2, 3 - triol (A6) as shown in Flowsheet No.11. Raphael[94] had shown that (A6) was the product from the/

the/

performic acid oxidation of <u>trans</u> - pent - 2 - en - 4 - yn - 1 01 (A5). This triol had the carbon skeleton required for the construction of a deoxypentose together with the stereospecific ally incorporated hydroxyl groups. All that remained to complete the synthesis was to effect the abnormal hydration of the triple bond.

Until 1949, hydration reactions of monosubstituted acetylenes had invariably resulted in the production of methyl ketones or their derivatives unless the triple bond was flanked by a carbonyl group. In view of analogous free radical additions of thiols to ethylenes[96], Heilbron[97], and his school investigated the addition reactions of thiolacetic acid with monosubstituted acetylenes. Mono - and di - adducts (A8) and (A9) were obtained in reasonable yields.

$RCH=CHSAc$ (A8) $RCH(SAc)CH_2SAc$ (A9)

The monoadducts were converted by the usual carbonyl reagents into the derivatives of the corresponding saturated aldehydes, while the diadducts under similar conditions, yielded 1, 2 - dithiols.

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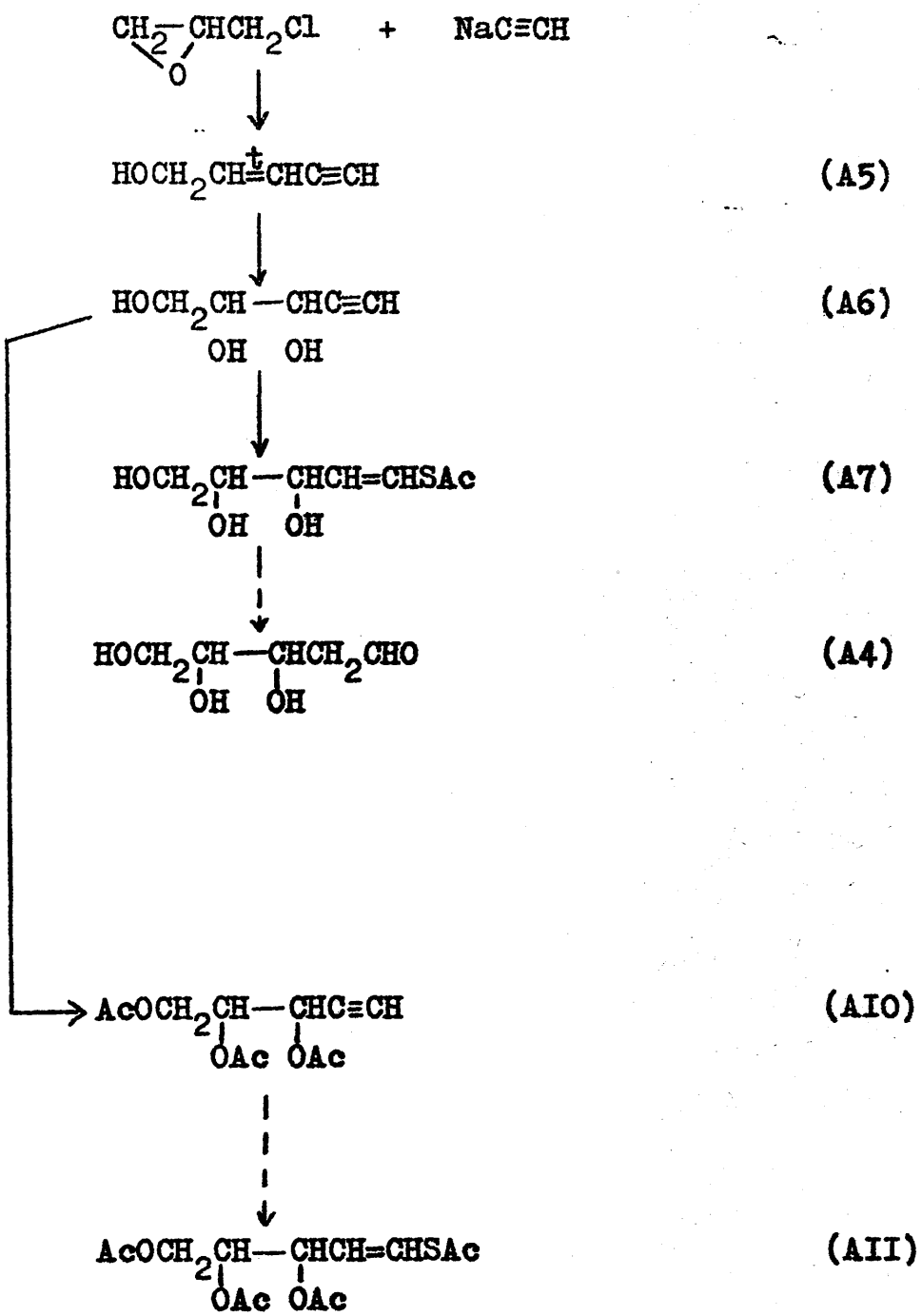


Flowsheet No. II.

Bader[98] extended the scope of this reaction to cover ethynyl carbinols and showed that the mono-adducts could be converted into aldols and αβ-unsaturated aldehydes. Although this reaction has been used successfully in a synthesis of linoleic acid[99], the method has not been as widely used as might be expected in view of the availability of acetylenic compounds.

The addition of thiolacetic acid to the acetylenic triol (A6) was studied under a variety of conditions but the yield of mono - adduct (A7) was very low. Furthermore the thiol and its mono-adduct had very similar high boiling points thus making the purification of the latter extremely difficult. A large amount of undistillable material was always obtained and this may have contained any di-adduct formed, although none was ever isolated.

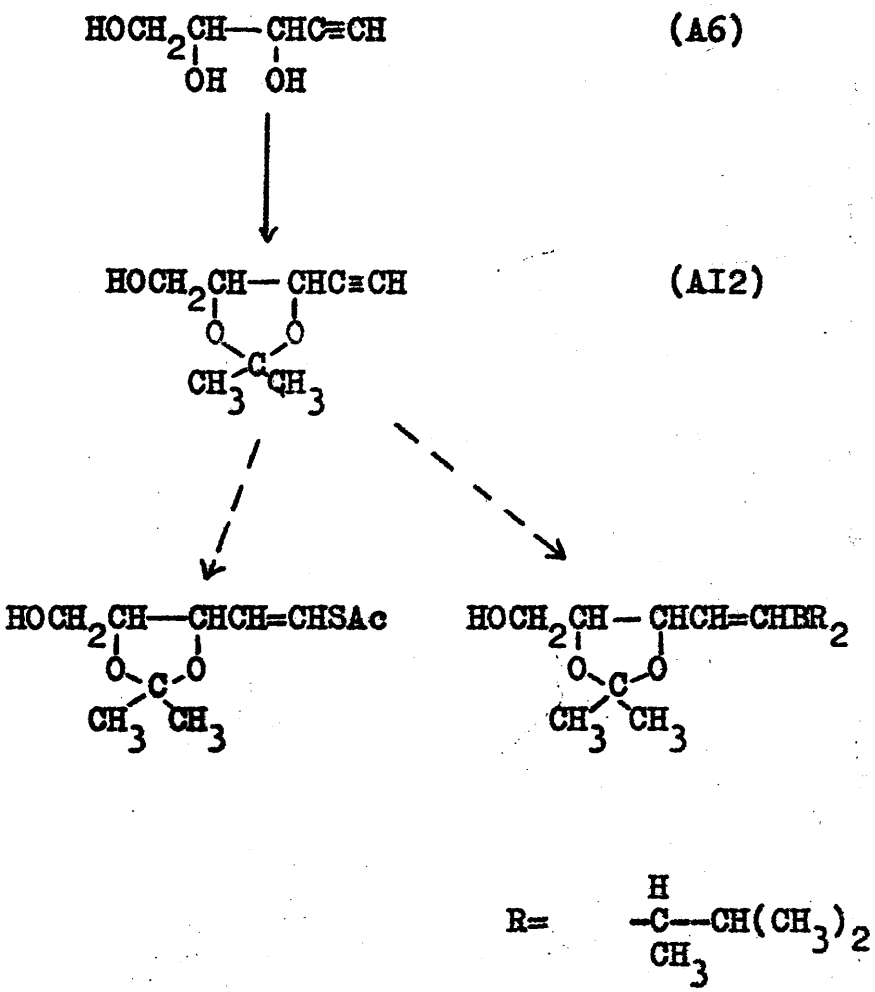
In an attempt to overcome the difficulty of separating the mono- adduct from the acetylenic triol, the addition ofthiolacetic acid to the acetylenic triol triacetate (A10) was studied under conditions similar to those employed for the parent triol. No addition product (A11) was obtained. (The di-adduct to be expected from this addition had already been prepared by Owen[100] by the reaction of erythro 4, 5 -

5 -/

dibromopentane - 1, 2, 3 - triol triacetate with potassium thiolacetate).

The monoadduct, DL - erythro pent - 5 - enylthiolacetate - 1, 2, 3 - triol (A7), was treated with 2, 4 - dinitro phenylhydrazine, α - benzylphenylhydrazine and aniline respectively, under the conditions described by Bader. However no derivative of 2 - deoxy - DL - ribose could be isolated although much hydrogen sulphide was evolved in each case. An attempt was made to convert the mono-adduct directly to 2 - deoxy - DL - ribose by hydrolysis with dilute barium hydroxide solution, conditions to which the deoxypentose is known to be stable[118]. The reaction was followed by titration of aliquots with hydrochloric acid and was virtually complete after forty-eight hours at room temperature. The deionised solution on evaporation gave a syrup which on paper chromatography showed no spot corresponding to a deoxypentose. With the Dische reagent a green colour was obtained instead of the intense blue colour expected from a 2 - deoxypentose.

Since the abnormal hydration of acetylenic carbinols had worked reasonably well, the addition reaction was next tried on the isopropylidene/



Flowsheet No. I2.

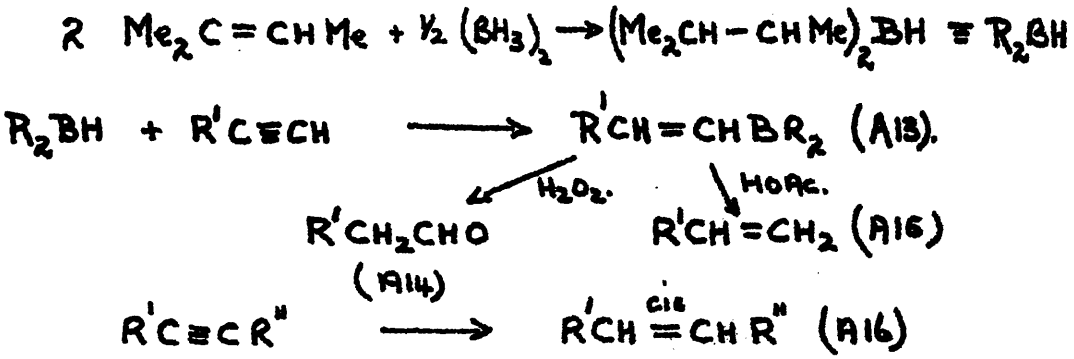
isopropylidene/
derivative (A12) of DL - erythro - pent - 4 - yne - 1, 2, 3 - triol, the structure of which is discussed later. When treated with thiolacetic acid in the presence of ascaridole as catalyst, at room temperature, the acetonide was recovered in high yield together with a small amount of a mixture of DL - erythro pent - 4 - yn - 1, 2, 3 - triol and its corresponding mono-adduct. These products had obviously been formed by acid hydrolysis of the acetonide followed by peroxide catalysed addition of thiolacetic acid to the resulting triol. Repetition at a higher temperature gave similar results.

In view of these unpromising results this appreach to the synthesis of 2 - deoxy - DL - ribose was abandoned.

A more recent method for effecting the abnormal hydration of monosubstituted acetylenes is the hydroboration technique which has been studied by Brown and his co-workers[101]. They have shown that a bulky dialkylborane such as bis - (1 - methyl isobutyl) borane will, for steric reasons, give only a mono-adduct with acetylenes. The resulting dialkylboroethylene (A13) on treatment with hydrogen peroxide/

peroxide/

in basic medium gave the saturated aldehyde (A14). When treated with acetic acid the product was the ethylene (A15). With a disubstituted acetylene the extremely pure corresponding cis - ethylene (A16) was obtained. So far the reaction has been applied only to acetylenic hydrocarbons.



The reaction was therefore extended to DL - erythro pent - 4 - yne - 1, 2, 3 - triol triacetate (A10) and to the acetonide (A12) of the acetylenic triol. In both cases starting material was recovered in high yield indicating that addition of the dialkyborane to the triple bond had not occurred. (When applied to hex - 1 - yne, the corresponding aldehyde was isolated in 72% yield). It would appear therefore that the presence of a propargylic substituent provides enough steric repulsion, even at this distance, to prevent the approach of the bulky dialkylborane to/

to/

the acetylenic centre.

To summarise the work already described, the first route to 2 - deoxy - DL - ribose envisaged the condensation of a two carbon unit containing an aldehyde function with a three carbon unit containing a hydroxyl group together with an unsaturated centre suitable for the stereochemically controlled introduction of a _cis_ diol grouping. The second attempt started from a five- carbon unit incorporating the required number of hydroxyl groups having the correct stereochemistry. The third and successful route to the deoxypentose (see Flowsheet No.13) involved initially the condensation of two - three-carbon units one of which contained an acetylenic centre for the introduction of the _erythro_ diol grouping, the other containing an ethylenic centre as the potential aldehyde function.

The six carbon unit employed hex - 5 - en - 2 - yn - 1 - ol (A17, R=H), the synthesis of which had been reported by Colonge and Falcotet[102] who obtained it in 12% yield by the condensation of the copper derivative of propargyl alcohol with allyl bromide. From a preparative viewpoint, this method was not very attractive and other methods of preparation were investigated. Nieuwland[103] had

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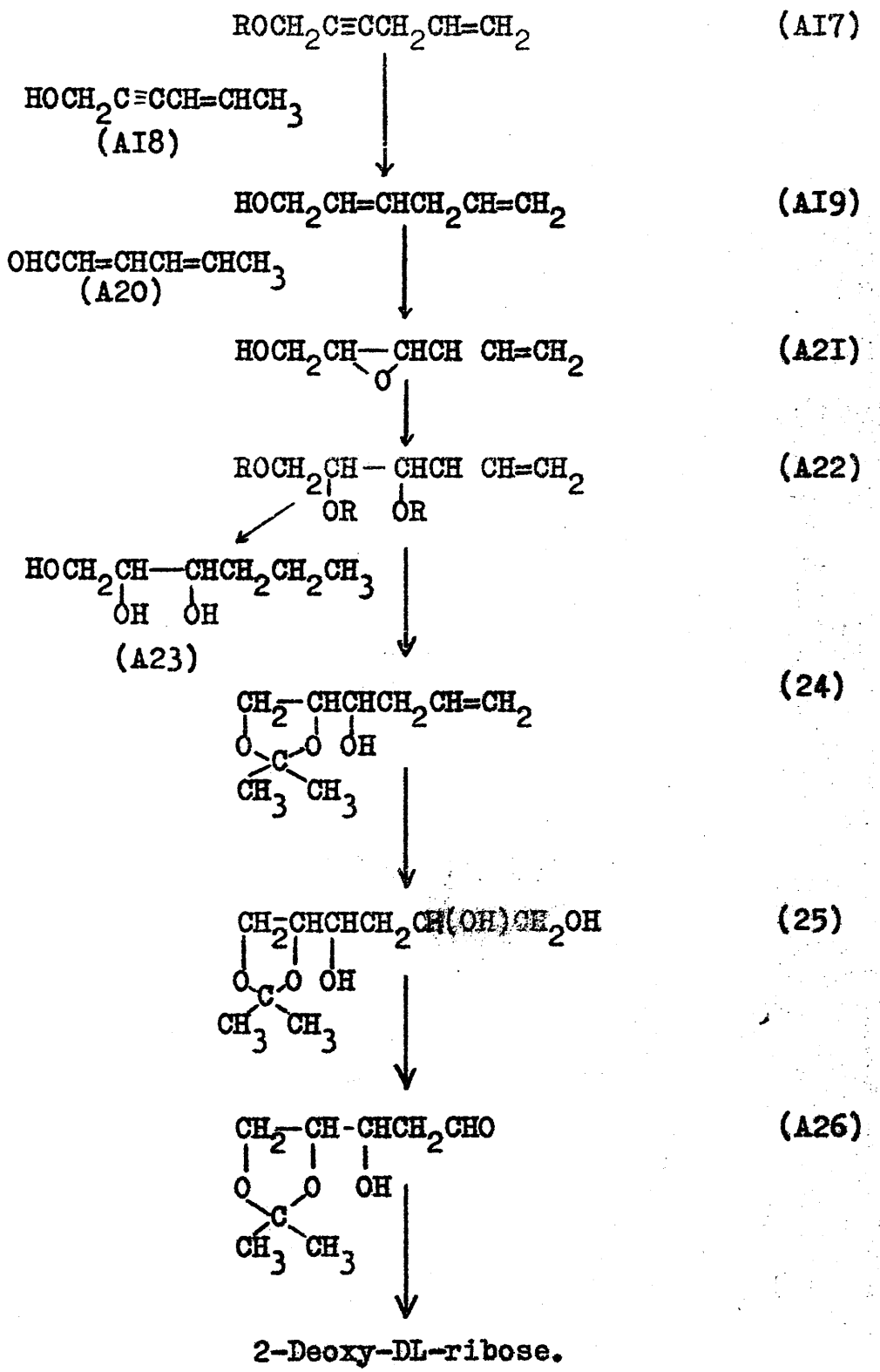


Flowsheet No. I3.

had/

shown that Grignard derivatives of acetylenes condensed with allyl halides in the presence of catalytic amounts of cuprous salts to give 1,4 - enynes in good yield. Accordingly the Grignard derivative of 3 - (2' - tetrahydropyranyloxy)-prop-1-yne (A1) was condensed with allyl bromide in the presence of cuprous chloride; 1 - (2' - tetrahydropyranyloxy) - hex - 5 - en - 2 - yne (A17, R = ) was obtained in 80% yield. When repeated on a molar scale, the tetrahydropyranyl ether was obtained in 45% yield, together with hex - 5 - en - 2 - yn - 1 - ol (A17, R=H) itself, formed by the acid catalysed hydrolysis of the tetrahydropyranyl group. Attempted removal of the protecting group by equilibration with methanol in the presence of sulphuric acid[104] resulted in the formation of polymeric material, while with dilute mineral acid a mixture of hex - 5 - en - 2 - yn - 1 - ol (A17, R=H) and the conjugated isomer hex - 4 - en - 2 - yn - 1 - ol (A18) was obtained. These two isomers could not be separated by distillation. When the tetrahydropyranyl derivative of (A17) was refluxed with dry acetic acid containing acetic anhydride hex - 5 - en - 2 - yn - 1 - ol acetate (A17, R=Ac) was obtained in good yield.

Hex - 5 - en - 2 - yn - 1 - ol (A17, R=H) was finally obtained directly in 67% yield by condensation of the di - Grignard derivative[105] of propargyl alcohol with allyl bromide in the presence of cuprous chloride as catalyst. The acetylenic alcohol was characterised as its crystalline α - naphthylurethane.

Reduction of hex - 5 - en - 2 - yn - 1 -ol with lithium aluminium hydride in ether solution afforded hexa - 2 (trans), 5 - dien - 1 - ol (A19), characterised as its α naphthylurethane, in 88% yield. Further proof of the structure of (A19) was obtained by oxidation with manganese dioxide, which specifically oxidises benzylic, allylic and propargylic alcohols to the corresponding carbonyl compounds. In the case of hexa - 2(trans), 5 - dien - 1 - ol the oxidation product was shown, by its infra-red absorptioncharacteristics, to be the all trans hex - 2, 4 - dien - 1 - al (A20) which was characterised as its 2, 4 - dinitrophenylhydrazone (λ max($CHCl_3$) 391 mμ., (ϵ = 38,000).

With perbenzoic acid in chloroform solution hexa - 2 (trans), 5 - dien - 1 -ol rapidly consumed one mole to give trans -2, 3 - epoxyhex - 5 - en - 1 -ol (A21) in high yield. The selective epoxidation of the disubstitiuted double bond was dependent on its greater nucleophilic character compared with that of the monosubstituted double bond.

It has been shown that the relative rates of addition of perbenzoic acid to monosubstituted and symmetrically disubstituted double bonds is about 1:2.[103] . With ethereal monoperphthalic acid no epoxidation occurred while with performic acid a complex mixture of hydroxy-compounds was obtained which was not further investigated. From this result it would appear that attack by performic acid is far less selective with regard to double bond type.

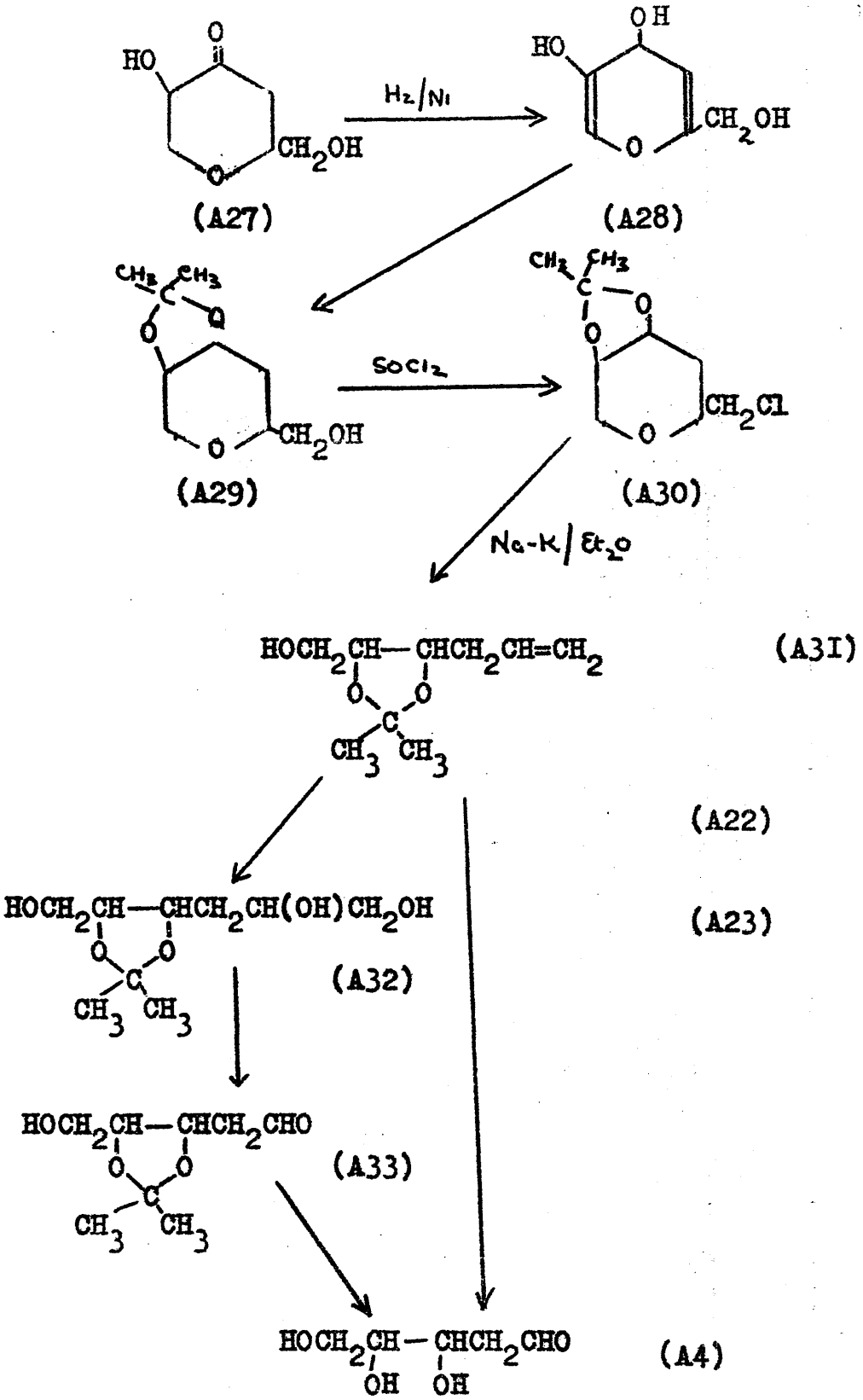
Hydrolysis of trans - 2, 3 - epoxyhex - 5 - en - 1 -ol with dilute sulphuric acid afforded DL - erythro - hex - 5 - en - 1, 2, 3 - triol (A22, R=H) in high yield as a colourless viscous liquid which solidified on storage at 0° for several weeks. The corresponding triacetate (A22, R=Ac) was obtained as a mobile liquid on treatment of the triol with acetic anhydride in pyridine. On catalytic hydrogenation, DL - erythro - hex - 5 - en - 1, 2, 3 - triol gave crystalline DL - erythro - hexane - 1, 2, 3 - triol (A23) which was identical with an authentic specimen.

On treatment with acetone in the presence of anhydrous copper sulphate, DL-erythro - hex - 5 - en - 1, 2, 3 - triol gave an isopropylidene derivate; this was shown to be 2, 2 - dimethyl - 4 -(1'-hydroxybut -

3' - eynl) - dioxolan (A24) by comparison with the isomeric 2, 2 - dimethyl - 4 - hydroxymethyl - 5 + allyl dioxolan (A31) which has been synthesised by Riobe and Herault[107] by an unambiguous route(See flowsheet No.14.).

On catalytic hydrogenation at 70° and 10b atmospheres pressure, kojic acid (A27) gave the hexahydro - derivative (A28) which with acetone was converted to the acetonide (A29). The remaining free hydroxyl group of this compound was replaced by chlorine on treatment with thionyl chloride in pyridine giving the chloro compound (A30). This β chloro-ether on treatment with a mixture of atomised sodium and potassium in ether gave 2, 2 - dimethyl - 4 - hydroxymethyl - 5 - allyldioxolan (A31). Acid hydrolysis of (A31) gave DL - erythro - hex - 5 - en - 1, 2, 3 - triol identical with that prepared from trans - 2, 3 - epoxyhex - 5 - en - 1 - ol.

Since the structure of the acetonide (A31) prepared from kojic acid was unambiguously proved by its mode of synthesis, the isomeric acetonide prepared from DL - erythro - hex - 5 - en - 1, 2, 3 - triol must have the structure /



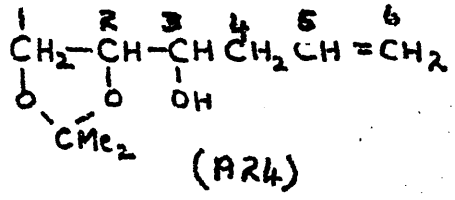
Flowsheet No. I4.

structure/

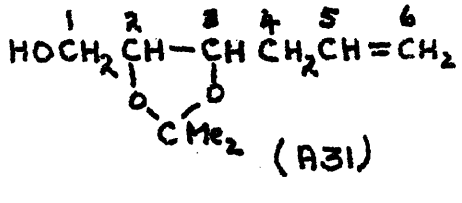
(A24) as shown. Furthermore the general rules governing the formation of cyclic acetals and ketals of polyols allowed the prediction to be made that the triol concerned would form an isopropylidene derivative in which the $C_{(1)}$ and $C_{(2)}$ hydroxyl groups were involved. That the two acetonides were not identical was shown by the fact that:

a) the two acetonides differed in refractive index values.

b) both acetonides formed a 3, 5 - dinitrobenzoate derivative, that from (A24) melted at 87 - 88°, while that from (A31) melted at 82.5 - 83°; the mixed melting point was 65 - 78°.



(A24)



(A31)

A mass spectrometric analysis of the two acetonides provided an indopendent proof of the structure assigned to (A24) since its breakdown on electron bombardment was radically different from that of (A31) derived from kojic acid. The first fragmentation of each acetonide resulted in the loss of a methyl group from the gem dimethyl group. This gave rise to a peak in the spectrum at 157 mass units/

units/

(i.e., 172 - 15) Both (A24) and (A31) gave fragments due to the breaking of the weak allylic bond between $C_{(3)}$ and $C_{(4)}$. (A24) gave riseto a fragment due to the cleavage of the $C_{(2)}$ - $C_{(3)}$ bond while (A31) gave a fragment due to cleavage of the $C_{(1)}$ - $C_{(2)}$ bond. Since A31 could not break between $C_{(2)}$ and $C_{(3)}$ and (A24) between $C_{(1)}$ and $C_{(2)}$ the structure of each acetonide was proved unambiguously.

The conversion of hex - 5 - en - 1, 2, 3 - triol or its derivatives to 2 - deoxy - DL - ribose necessitated the cleavage of the $C_{(5)}$ double bond. Several methods were investigated. Ozonolysis of DL - erythro - hex - 5 - en - 1, 2, 3 - triol, its triacetate or acetonide gave a complex mixture from which no derivative of the deoxypentose could be obtained (See Table No.2. in the experimental section for reaction conditions). 2, 2 - Dimethyl - 4 - hydroxymethyl - 5 - allyl dioxolan (A31) on ozonolysis in ethyl acetate - t- - butanol, (conditions used in the synthesis[109] of mevalonic acid from a β hydroxy ethylene) gave a minute yield of 2 - deoxy - DL - ribose isolated as its anilide, after removal of the/

the/

isopropylidene group. Attempts to cleave the double bond using the periodate - osmium tetroxide reagent developed by Lemieux[110] were, unfortunately, unsuccessful.

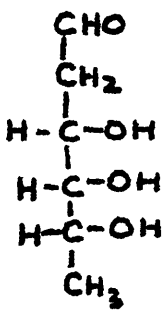
The conversion of DL - erythro - hex - 5 - en - 1, 2, 3 - triol to 2 - deoxy - DL - ribose was finally achieved indirectly by hydroxylation followed by cleavage of the resulting diol with sodium periodate. 2, 2 - Dimethyl - 4 - (1' hydroxybut - 3' - enyl) - dioxolan (A24) on hydroxylation with hydrogen peroxide and osmium tetroxide in t- butanol gave the deoxyisopropylidenehexitol (A25) in low yield. Oxidation of (A25) with sodium metaperiodate in a phosphate buffer yielded 4, 5 - O - isopropylidene - 2 - deoxy - DL - ribose (A26) from which 2 - deoxy - DL - ribose (A4) was obtained on mild acid hydrolysis. The deoxypentose was charactised as its crystalline anilide, m.p. 154 - 156°.

In a similar manner, the isomeric 2, 2 - dimethyl - 4 - hydroxymethyl - 5 - allyldioxolan (A31) was converted to 2 - deoxy - DL - ribose thus constituting a synthesis of the latter from kojic acid.

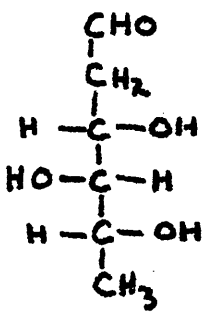
As an extension of this work a route to/

to/

the 2, 6 - dideoxyhexoses, constituents of the cardiac glycosides, has been explored (see flowsheet No.15) but not completed. D - Digitoxose [111,112] (2,6 - dideoxy - D - ribohexose) (A34) and D - boivinose [113] (2,6 - dideoxy - D - xylohexose) (A35) are examples of this class of sugars. [114]

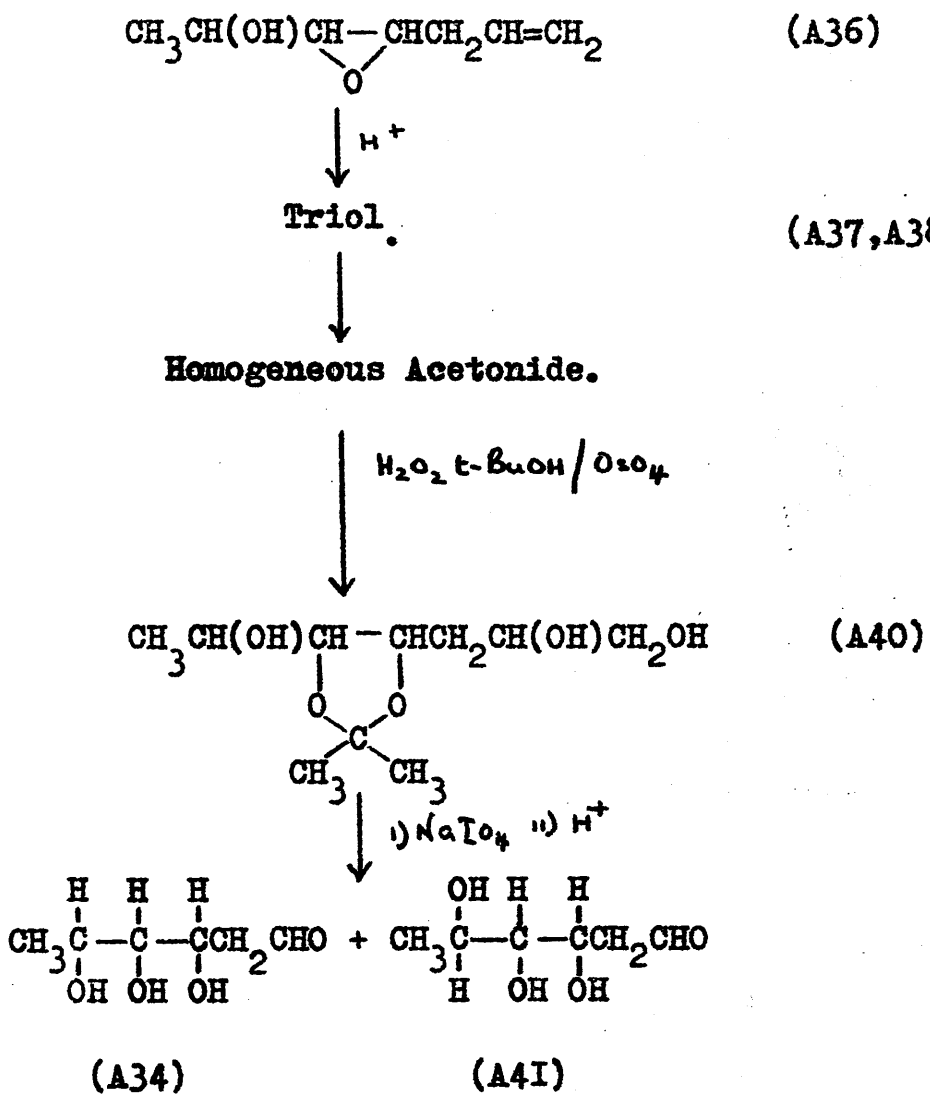


(A34)



(A35)

trans - 3, 4 - Epoxyhept - 6 - en - 2 - ol (A36), prepared in connection with the synthesis of rhodosamine (See Part 111), on hydrolysis with dilute acid gave a colourless viscous liquid which was probably a mixture of the two isomeric heptene triols (A37) and (A38). Although this would appear most likely, the fact that a sharp boiling acetonide (A39) was formed on treatment with acetone and the fact that this acetonide formed a sharp melting 3, 5 - dinitrobenzoate (m.p.112 - 115°) suggested that in fact a homogeneous triol had been obtained from the epoxide (A36). The acetonide (A39) was converted to a mixture of isomeric 3,7 - dideoxy - isopropylideneheptitols (A40) oxidation/



Flowsheet No. I5.

oxidation/

of which with sodium metaperiodate in a phosphate buffer followed by acid hydrolysis afforded a colourless syrup which was considered to be a mixture of DL - digitoxose (A34) and the isomeric DL - sugar (A41). Examination of this syrup by paper chromatography revealed only one spot with an R_F value similar to that of D - digitoxose. This fact strengthened the belief that only one heptene triol was obtained from trans - 3, 4 - epoxyhept - 6 - en - 2 - ol.

It is hoped that repetition of this work on a larger scale will enable the purification and identification of the product to be made.

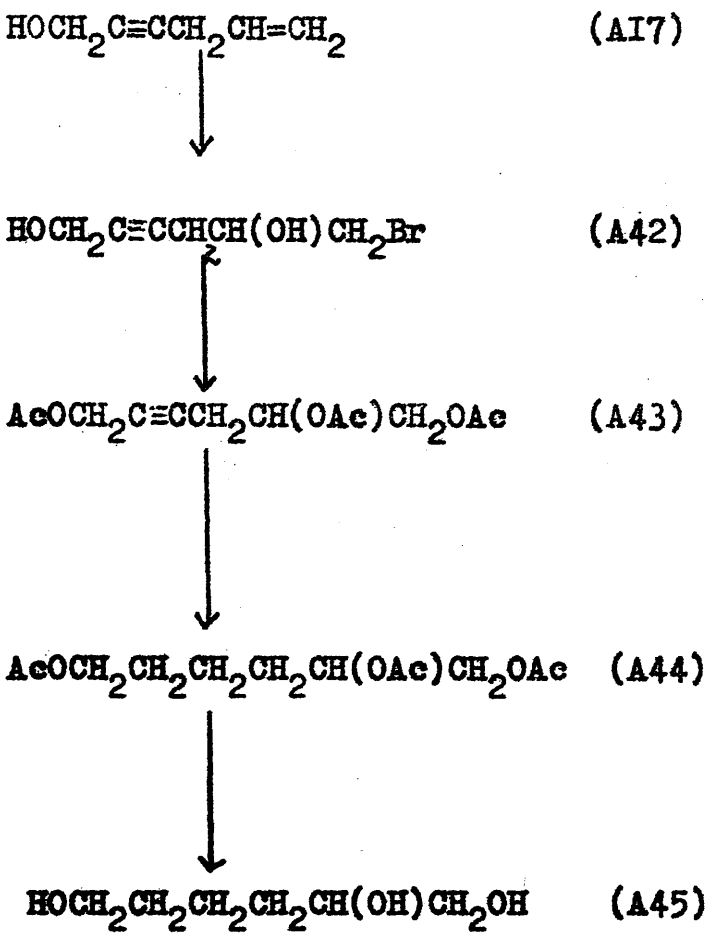
APPENDIX 1.

Selective addition of hypobromous acid to hex - 5 - en - 2 - yn-1 - ol.

The addition of hypobromous acid to double bonds constitutes a method for the introduction of a diol group. It has also been shown[115] that hypobromous acid adds readily to a triple bond with the formation of a dibromoketone.

$$RC \equiv C R' \longrightarrow R CO C(Br)_2 R'$$

It was of interest, in connection with carbohydrate synthesis, to study the possibility of selectivity in the addition of hypobromous acid to a molecule containing an unconjugated double and triple bond. Such a selectivity in fact occurred in the case of hex - 5 - en - 2 - yn - 1 - ol (A17, R=H) which by treatment with one mole of N - bromosuccinimide in water gave 6 - bromohex - 2 - yn - 1, 5 - diol (A42) as an unstable liquid. Treatment of this product with acetic acid - potassium acetate - acetic anhydride afforded hex - 2 - yn - 1, 5, 6 - triol triacetate (A43) which on catalytic hydrogenation produced hexane - 1, 2, 6 - triol triacetate (A44). Hydrolysis by the Zemplen technique furnished syrupy hexane - 1, 2, 6 - triol (A45) which was identified as its dicyclohexylamine adduct. These clathrate compounds have proved invaluable for the/



Flowsheet No. I6.

the/

characterisation and purification of diols and triols 116,117

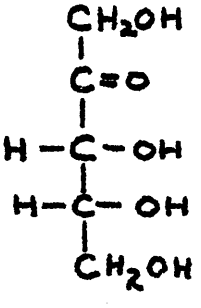
The fact that hypobromous acid has been found to add selectively to a double bond in a molecule also containing a triple bond is an observation which may findpossible application, in the future, to the synthesis of carbohydrate molecules.

APPENDIX 2.

Synthetic Approaches to DL - Ribulose

(DL - *erythro* Pentulose).

D - Ribulose (A50), a metabolic product of yeasts and many other organisms has been recognised, for many years, as an intermediate in photosynthesis and in the isomerisation, and interconversion of aldopentoses in biological systems[119].



(A50)

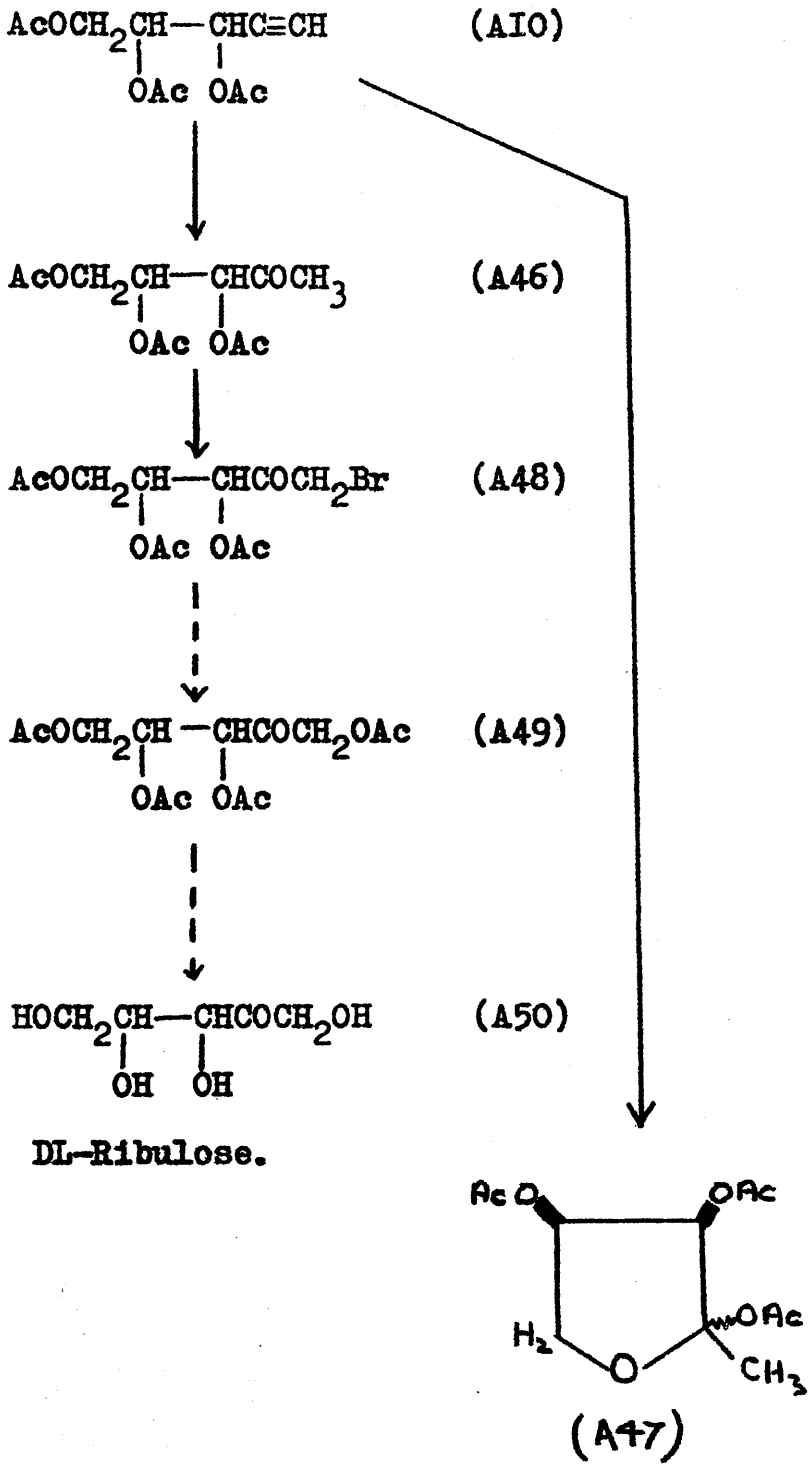
Cohen[120] showed that Escherichia coli contained an adaptive isomerase which catalysed the equilibrium D - arabinose $\rightleftharpoons$ D - ribulose and that the equilibrium, normally established at about 13 - 17% D - ribulose, could be shifted further towards D - ribulose.

Chemically D - ribulose has been synthesised in 23% yield by isomerisation of D - arabinose in pyridine[121]. L - ribulose has been prepared from L - ribitol by enzymic oxidation with Acetobacter Suboxydans[122].

In view of the importance of ribulose in biosynthesis, a synthesis of DL - ribulose was investigated.

The first approach envisaged the elaboration of DL - erythro - pent - 4 - yn - 1, 2, 3 - triol triacetate (A10) as shown in flow-sheet No.17. Hydration of the acetylenic triacetate (A10) by the standard method gave DL - erythro - pentan-4-one - 1, 2, 3 - triol triacetate (A46) as a pale yellow oil in poor yield. In an effort to improve the yield of ketone, the method employing a mercury impregnated resin was tried[123]; no improvement was obtained.

When boron trifluoride in acetic acid was used in the hydration reaction, a compound isomeric with the expected ketone was obtained. This compound showed no ketonic absorption in its infra-red spectrum but absorption at 1080 cm^{-1}, characteristic of a tetrahydrofuran, was observed. Accordingly, on this and analytical data the compound was formulated as 2 - methyl tetrahydrofuran - 2, - 3, 4 (erythro) triol triacetate (A47). Attempts to confirm this structure by pyrolysis to a known furan derivative proved unsuccessful as the pyrolysis product polymerised rapidly.

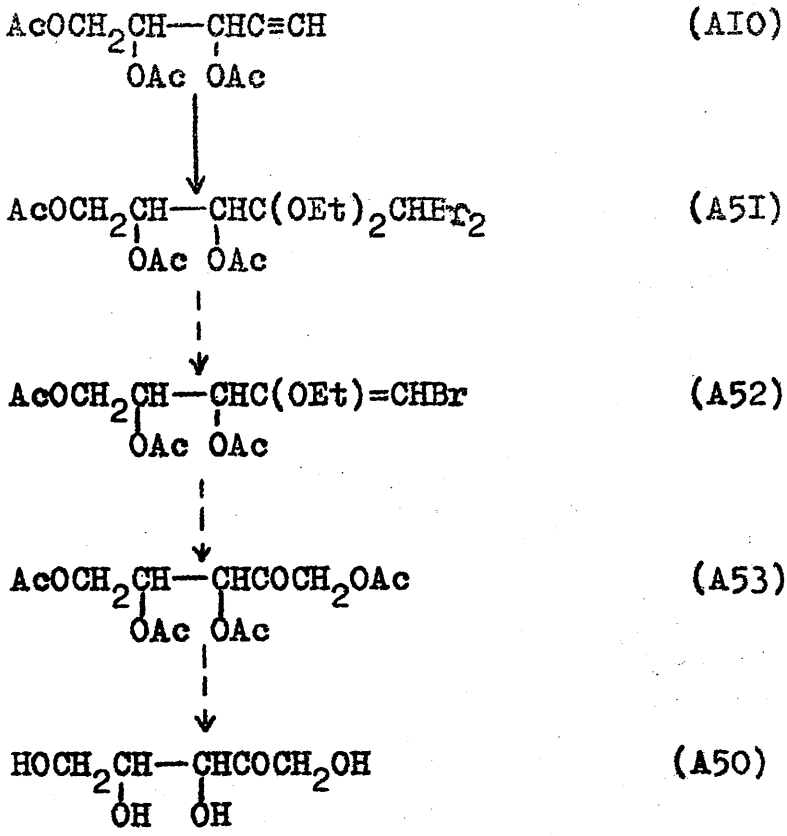


Flowsheet No. I7

Bromination of DL - erythro - pentan - 4 - one - 1, 2, 3 - triol triacetate (A10) in carbon tetrachloride gave a product which could not be purified because of its ready decomposition, and no derivative could be prepared. Although it was thought that this compound was in fact DL - erythro- 5 - bromopentan - 4 - one - 1, 2, 3 - triol triacetate (A48), treatment of it with potassium acetate in acetic acid failed to give DL - [redacted] - ribulose tetraacetate (A49).

In view of these unpromising results a second route to DL - ribulose from DL - erythro - pent 4 - yne - 1, 2, 3 - triol triacetate (A10) was investigated. It has been shown[124] that a triple bond reacts with two moles of ethyl hypobromite with the formation of the diethyl ketal of the corresponding $\alpha\alpha$ - dibromo ketone.

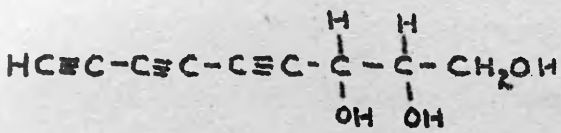
Accordingly DL - erythro - pent - 4 - yne - 1, 2, 3 - triol triacetate (A10) was treated with two moles of ethyl hypobromite (from N - bromosuccinimide in ethanol); the product which could not be purified because of its instability, showed no acetylenic absorption in its infra-red spectrum and was considered to be 1, 1 - dibromo - 2, 2 - diethoxypentane - 3, 4, 5 - triol triacate (51).



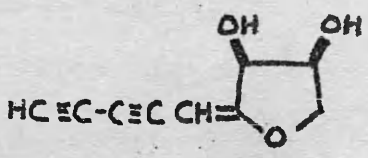
Flowsheet No. I8.

When treated with activated zinc in ethanol, conditions under which ethyl hypobromite is eliminated from an $\alpha\alpha$ - dibromodiethylketal[124], no pure product was isolated. Repetition of this reaction using zinc in dioxan gave similar results.

With the failure of this approach to DL - ribulose attention was directed towards a third possible synthetic route from DL - erythro - pent - 4 - yne - 1, 2, 3 - triol. Jones and Stephenson[125] showed that the acetylenic triol (A56), isolated from the Basidiomycete Coprinus quadrifidus, was transformed into the cyclic enol ether (A57) on treatment with base.

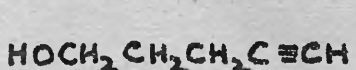


(A56)

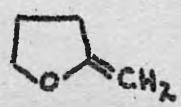


(A57)

It has been shown that[126] pent - 1 - yn - 5 - ol (A58) gave 2 - methylenetetrahydrofuran (A59) on treatment with base.



(A58)

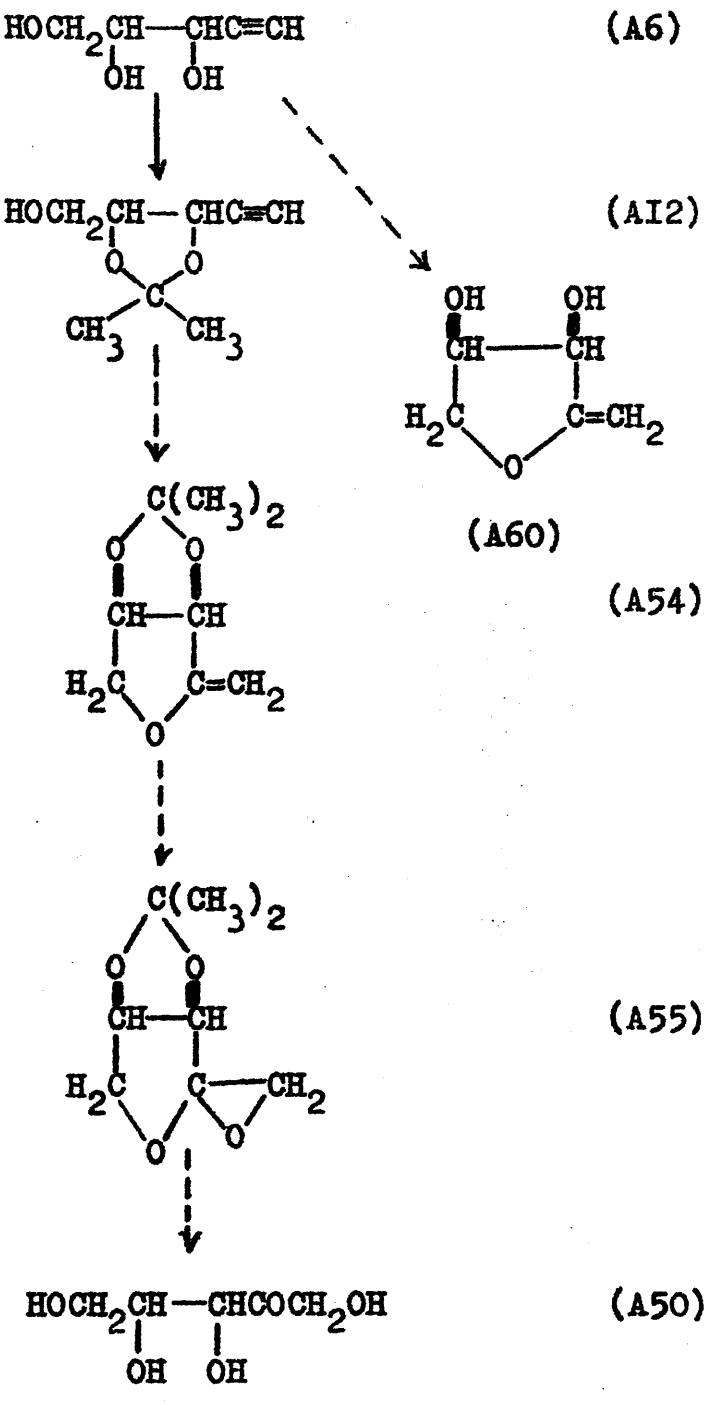


(A59)

The proposed route (see flowsheet No.19) envisaged the cyclisation of DL - erythro - pent - 4 - yne - 1, 2, 3 - triol (A6) or a derivative to the corresponding methylenetetrahydrofuran derivative followed by epoxidation and hydrolysis to DL - ribulose. Unfortunately DL - erythro - pent - 4 - yne - 1, 2, 3 - triol failed to undergo the cyclisation reaction.

Accordingly the acetonide (A12) was made by the reaction of DL - erythro - pent - 4 - yne - 1, 2, 3 - triol with acetone in the presence of anhydrous copper sulphate. Contrary to Barker's rules[127] for the formation of cyclic derivatives of polyols, the acetonide formed was conclusively shown to be 2, 2 - dimethyl - 4 - hydroxymethyl - 5 - ethymyl dioxolan (A12) and not the acetonide in which the hydroxyl groups on $C_{(1)}$ and $C_{(2)}$ were involved. The preferential formation of (A12) was probably governed by the fact that the propargylic hydroxyl group had a greater acidity than the other two.

The structure of the acetonide was proved by the fact that it did not give an ethynyl ketone on treatment with manganese dioxide or chromium trioxide. Further the corresponding methyl ether (A63) on removal of the isopropylidene group and oxidation with sodium periodate gave propargylaldehyde and methoxyacetaldehyde respectively/



Flowsheet No. I9.

respectively/
isolated and characterised as their 2, 4 - dinitro phenylhydrazones (This acetonide has been very recently reported by Bohlmann[128] who used it as an intermediate in his synthesis of (A57)).

When treated with base, under a variety of conditions, the acetonide (A12) was recovered unchanged. In view of these unpromising results, the synthesis of DL - ribulose was abandoned.

EXPERIMENTAL.

All infra-red spectra were measured as liquid films unless otherwise specified.

EXPERIMENTAL.

Attempted preparation of 5 - (2' - Tetrahydropyranyloxy) - 1, 1 - diethoxy - pent - 3 - yne.

a) A solution of 3 - (2' - tetrahydropyranyloxy) - prop - 1 - yne (70 g., 0.5 mole) in dry ether (150 ml) was added during 1 hr. to a stirred suspension of lithamide (from lithium, 3.65g) in liquid ammonia (1000 ml). Stirring was continued for a further four hours after which time the ammonia was removed by evaporation in a stream of nitrogen. Pure dry dioxan (1100 ml) was added and the mixture refluxed for 1 hr. while a slow stream of nitrogen swept out the remaining ammonia. Redistilled bromoacetal (118 g. 0.6 mole) in dry dioxan (50 ml) was added slowly with stirring and the mixture was refluxed for 30 hrs under nitrogen. After removal of most of the dioxan the remainder was poured into water (500 ml) and the precipitated oil extracted with ether. The combined ether extracts were washed with water and dried ($MgSO_4$) and evaporated. The residual dark brown oil on distillation gave unchanged 3 - (2'-tetrahydropyranyloxy) - prop - 1 - yne (60g) b.p. 74 - 75°/18 m.m., n_D^{25} 1.4565 as sole product.

b) Method of Durand & Piaux.

To a stirred refluxing solution of the lithium derivative of 3 - (2' - tetrahydropyranyloxy) - prop - 1 - yne (14 g. 0.1 mole) in dry dioxan (100 ml) under nitrogen was added copper powder (1.0g) followed by bromoacetal (19.67 g, 0.1 mole) in dry dioxan (20 ml). The mixture was refluxed for 23 hrs and worked up as described in the previous experiment. The sole product was 3 - (2' tetrahydropyranyloxy) - prop - 1 - yne (12.3 g.).

Pent - 2 - en - 4 - yn - 1 - ol.(A5).

To a solution of sodium acetylide in liquid ammonia (1750 ml) prepared from sodium (69 g.) epichlorohydrin (139g.) was run in during 2 hrs. with stirring and cooling (Methanol - Drikold). Nitrogen was passed in during the addition and the subsequent 16 hrs. stirring after which ammonium chloride (165 g.) was added during 2½ hrs. The ammonia was evaporated on the steam bath and ether (750 ml) added. The solid residue obtained on filtering was dissolved in water and a small quantity of tar removed by filtration. The aqueous filtrate was ether extracted and the combined ether extracts were washed with dilute

sulphuric acid and water. The dried solution on evaporation and distillation of the residual oil under nitrogen afforded pent - 2 - en - 4 - yn - 1 - ol (48 g) b.p. 71-73° / 19 m.m. η_D^{21} 1.4940.

94.
DL - erythro - Pent - 4 - yn - 1,2,3 - triol.(A6)

A solution of trans pent - 2 - en - 4 - yn - 1 - ol (22 g.) in 90% formic acid (116 ml.) was treated with hydrogen peroxide (35g. 100 vol.) added in one portion. The initially purple solution slowly decolourised and its temperature rose slowly to 50° at which point it was maintained by external cooling. After 16 hours the solution was evaporated under reduced pressure and the residual straw coloured liquid (triol monoformate) was steam - distilled until the distillate was no longer acid. The distilland was evaporated under reduced pressure and the residual syrup distilled to give DL - erythro - pent - 4 - yne - 1, 2, 3 - triol as a viscous pale yellow liquid b.p. 118 - 119° (9.69 x 10^{-2} m.m. η_D^{23} 1.4977. Lit. b.p. 120°/0.1 m.m. η_D^{4} 1.5000.

DL - erythro - Pent - 4 - yne - 1, 2, 3 - triol triacetate[94] .(A10)

Prepared by the action of acetic anhydride on the above triol had b.p. 98°/0.1 m.m. η_D^{22} 1.4487. Crystallisation from light petroleum (b.p. 60-80°) gave the triacetate as prisms m.p. 52 - 53°.

Lit. b.p. 108°/0.8.m.m.;m.p. 52 - 53°, η_D^{18} 1.4525.

DL - erythro - Pent - 5 - enylthiolacetate - 1, 2, 3 - triol (A7.)

a) Thiolacetic acid (2.25 g.) was added slowly to a mixture of DL - erythro - pent - 4 - yne - 1, 2, 3 - triol (3.43g.) and bisazoisobutyronitrile (0.1066 g.) at 0°C. The mixture was heated gently until reaction occurred after which it was heated at 100° for 1½ hours. After cooling and standing for 24 hrs at room temperature the mixture was distilled giving unchanged (1) thiol acetic acid (0.2 g.).

11) A yellow mobile liquid (0.82g.) which had an nauseating odour, b.p. 116 - 119°/0.15 - 0.175 m.m. and

111/ unchanged triol (10 g.) b.p. 120 -/

120 - 140°/0.15 m.m. Fractional distillation of fraction (11 gave DL -*erythro* - pent - 5 - enylthiol-acetate - 1, 2, 3 - triol (0.52 g.) b.p. 116 - 118°/ 0.15 m.m.,

Difficulty was encountered in obtaining a pure analytical sample owing to the similarity in boiling points of the adduct and the starting triol. Further experiments on the addition of thiolacetic acid to pent - 4 - yne - 1, 2, 3 - triol are described in the following table (Table No.1.).

Table No.1.

Triol g.	Thiolacetic acid g.	Catalyst.	Temp. °C.	Time. hrs.	Mono-adduct. g.
3.26	2.20	a	70-110	3	0.50
7.8	5.11	a	110	5	1.10
3.43	2.25	b	110	2	0.55
3.43	2225	b	0-17	30	0.72
3.83	2.25	c	17	20	-

a, *bis* azoisobutyronitrile b, ascaridole c, u.v.light.

Attempted addition of thiolacetic acid to pent - 4 - yne - 1, 2, 3 - triol triacetate to give(AII).

Thiolacetic acid (1.33 g.) was added to a mixture of pent - 4 - yne - 1, 2, 3 - triol triacetate (4.0g.) and ascaridole (0.10g.) at 20°. The temperature rose slowly to 25° and an exothermic reaction occurred. The temperature was maintained at 40° until the reaction subsided then raised to and maintained at 100° for three hours. Removal of unchanged thiolacetic acid and fractional distillation of the residual liquid gave the following fractions:

1.	0.21 g.	b.p. 98-100° / 0.1 m.m.	η_D^{21}	1.4557
2.	0.25 g.	100-104° / 0.1 m.m.	"	1.4493
3.	0.12 g.	104-118° / 0.1 m.m.	"	1.4533
4.	0.51 g.	136-140° / 0.1 m.m.	"	1.4669

Reaction of Thiolacetic acid with 2, 2 - dimethyl - 4 - hydroxy methyl - 5 - ethynyldioxolane.

To a mixture of 2, 2 - dimethyl - 4 - hydroxymethyl - 5 - ethynyl dioxolane (3.12 g.) and ascaridole (0.1g.) at 0°C, thiolacetic acid (1.52 g.) and ascaricole (0.1g.) were added during 10 mins. After 30 hrs at 17° the mixture was distilled giving unchanged dioxolane (2.41 g.) b.p. 86 - 90°/1 m.m. 1.4590 and a fraction (0.82 g.) b.p. 120 - 130°/ 0.2 m.m. η_D^{21} 1.4696 which appeared to consist/

consist/
of pent - 4 -- yne - 1, 2, 3, - triol (formed by acid hydrolysis of the O - isopropylidene group) containing pent - 5 - enylthiolacetate - 1, 2, 3 - triol to the extent of about 4%, by spectroscopic measurements (λ_{max} 251 mμ, ε = 323.).

The above reaction was repeated at 40°. for 30 hrs Distillation gave unchanged dioxolan (0.73 g.) and a fraction (1.71g.) b.p. 118-132°/ 0.2.m.m., η_D^{20} 1.4987. This was a mixture of pent - 4 - yne - 1, 2, 3, - triol and pent - 5 - enylthiolacetate - 1, 2, 3 - triol. Fractional distillation of this fraction gave almost pure enol thiolacetate (0.32g.) b.p. 116 - 118°/ 0.1 m.m. η_D^{20} 1.4923 and acetylenic triol (1.14 g.) b.p. 120 - 122°/ 0.1. m.m. η_D^{20} 1.4983. Fractions (1) and (2) solidified on standing and were identical with pent - 4 - yne - 1, 2, 3 - triol triacetate. Fraction (3) showed strong terminal acetylene absorption in the infra-red.
Fraction (4) on redistillation gave a yellow mobile liquid b.p. 136°/ 0.1 m.m., η_D^{24} 1.4662 and showed strong absorption in the infra-red spectrum for the presence of a terminal acetylene.
Found : C, 53.64; H, 6.29%
The analytical figures suggested that this material was impure pent - 4 - yne - 1, 2, 3, triol triacetate.

Attempted preparation of 2 - deoxy - DL - ribose - 2, 4 - dinitrophenylhydrazone.

A solution of DL - erythro - pent - 5 - enylthiolacetate - 1, 2, 3 - triol (145 mg.) and 2, 4 - dinitrophenylhydrazine (300 mg.) in absolute ethanol (10 ml.) was refluxed for 4 hours during which time hydrogen sulphide was evolved. The cooled solution was filtered through a column of bentonite - kieselguhr (4:1 W/W) and the eluant evaporated to a dark red oil (97 mg.) This, in chloroform, chromatographed on bentonite - kieselguhr (4:1 W/W) as one band. An oil (89 mg.) which could not be induced to crystallise was obtained. The oil was taken up in ethanol (2ml.) and stored at 0° for two months. No crystalline material was obtained.

Attempted preparation of 2 - deoxy - DL - ribose αα - benzyl phenylhydrazone.

A solution of DL - erythro - pent - 5 - enylthiolacetate - 1,2,3 - triol (436 mg.) αα - benzyl phenylhydrazine hydrochloride (800 mg.) and sodium acetate (300 mg.) in ethanol (20 ml.) was refluxed for 6 hours. On cooling brownish yellow crystals (14 mg.) m.p. 95 - 100° were obtained./

Three recrystallisations from ethanol raised the mp. to 107 - 108°. The mother liquor gave no crystalline material.
(Lit: 2 deoxy - DL - ribose - αα - benzylphenyl-hydrazone m.p. 115-116°).

Attempted preparation of 2 - deoxy - DL - ribose anilide.

A mixture of DL - erythro - pent - 5 - enylthiolacetate - 1, 2, 3 - triol (120 mg.) aniline (200 mg.) lead acetate (400 mg.) in ethanol (10 ml)., was refluxed for 4 hours. A black precipitate of lead sulphide was obtained. On filtration and removal of most of the solvent a white solid (10 mg.) m.p. 172 - 174° was obtained. On combustion this material left a residue which proved to be lead. The mother liquors afforded no crystalline material. (Lit: 2 - deoxy - DL - ribose anilide m.p. 154 - 156°).

Attempted preparation of 2 - deoxy - DL - ribose.

DL - erythro - Pent - 5 - enylthiolacetate - 1, 2, 3 triol (243.1 mg.) barium hydroxide solution (68.25 ml. of 0.05175N.) and ethanol (5 ml.) were shaken at room temperature for 100 hours and the reaction followed by titration with 0.050 N hydrochloric acid. After 48 hrs. hydrolysis was 97% complete. The solution was deionised on ion - exchange resins and concentrated to a pale yellow syrup (22 mg.) which/

which/
was shown by paper chromatography to contain no 2 - deoxy - DL - ribose. With the Dische reagent a faint green colour was obtained.

Attempted preparation of aldehydo - 2 - deoxy - DL - ribose triacetate by the hydroboration reaction.

To a mixture of 2 - methyl - but - 2 - ene (3.36 g. 0.048 mole) and sodium borohydride (0.68 g.) 0. 18 mole) in diglyme (15 ml.) at 0°C under nitrogen boron trifluoride - etherate (2.84 g. 0.02 mole) was added during 1 hour and the mixture stirred for a further half hour. DL - erythro - pent - 4 - yne - 1, 2, 3 - triol triacetate (4.84 g., 0.02 mole) in diglyme (5 ml.) was added during 30 minutes and the mixture was stirred for a further 1½ hrs. Ethylene glycol (2 ml.) was added to destroy any remaining sodium borohydride followed by hydrogen peroxide (20 ml. 100 vol), and sufficient sodium hydroxide solution to maintain the alkalinity of the solution between pH, 8 - 9. The oxidation was allowed to continue for 15 minutes at 0°C., after which/water was added and the solution was extracted with ether. The combined ether extracts were dried and evaporated to a pale yellow liquid (4.51g.). The infra-red spectrum showed strong acetylene absorption at /

at/

3300 cm. and 2100 $cm.^{-1}$ but no absorption due to the presence of an aldehyde group. Distillation gave DL - erythro - pent - 4 - yne - 1, 2, 3 - triol triacetate (4.31 g.) b.p. 98°/ 0.1 m.m, η_D^{22} 1.4482 as sole product.

Attempted preparation of 3, 4 - O - isopropylidene - 2 - deoxy - DL - ribose.

The method employed was that described in the preceding experiment. The acetylenic component was 2, 2 - dimethyl - 4 - hydroxymethyl - 5 - ethynyldioxolane (preparation p.95.).
The acetylene was recovered unchanged from the reaction.

1 - (2'-Tetrahydropyranyloxy) - hex - 5 - en - 2 - yne (A17. R= ).

a). To ethyl magnesium bromide (from magnesium (2.65g. 0.11 mole) and ethyl bromide 12.0g. 0.11 mole)) in ether (15 ml.) under nitrogen, a solution of 3 - (2'- tetrahydropyranyloxy) - prop - 1 - yne - (14.0 g. 0.10 mole) in dry tetrahydrofuran (20 ml) was added slowly with stirring. When the reaction was complete, the solution was refluxed for 1 hour while a stream of nitrogen removed any remaining ethane and/

and/

ethyl bromide. Freshly prepared anhydrous cuprous chloride (0.2g.) was added and the mixture allowed to cool to room temperature. Freshly distilled allyl bromide (13.3g. 0.11 mole) was added during 5 minutes, (by which time a flocculent greenish yellow precipitate had formed) and the mixture was then refluxed for 1 hour. The cooled mixture was poured into ice-cold dilute hydrochloric acid and rapidly ether extracted. The combined ether extracts were washed with sodium bicarbonate solution and water, dried ($MgSO_4$) and evaporated. The residual oil on distillation gave 1 - (2' - tetrahydropyranyloxy) - hex - 5 - en - 2 - yne (14.7 g. 80%) b.p. 125°/20 m.m., η_D^{23} 1.4758.

(Found: C, 72.81; H, 8.91. $C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95%). $\nu_{Max.}^{cm^{-1}}$ 3040(W), 2210 (W) 1640(M) 990(S) 910(S).

b) The above experiment, repeated on a molar scale gave:

1) Hex - 5 - en - 2 - yn - 1 - ol (21g. 22%) b.p. 80 - 82° / 18 m.m. η_D^{21} 1.4786.

2) 1 - (2' - tetrahydropyranyloxy) - hex - 5 - en - 2 - yne (81 g. 45%) b.p. 120°/18 m.m. η_D^{21} 1.4760.

Hex - 5 - en - 2 - yn - 1 - ol (A17, R=H).

a) Attempted preparation from 1 -(2' - tetrahydropyranyloxy) hex - 5 - en - 2 - yne.

The tetrahydropyranyl ether (5g.) was added to a solution of concentrated sulphuric acid (4ml) in methanol (90 ml.) and the mixture, which slowly darkened in colour, was allowed to stand at room temperature for forty-eight hours. The mixture was neutralised with methanolic sodium methoxide, the methanol removed and the black residue extracted with ethyl acetate. No material was obtained on evaporation.

b) The tetrahydropyranyl ether (5g.) in dilute sulphuric acid (50 ml. 0.1 N) was heated at 50° for 2 hours. The mixture was extracted with ethyl acetate and the combined extracts were washed with sodium bicarbonate solution and water then dried ($MgSO_4$). Evaporation and distillation gave a constant boiling mixture (2.7g.) b.p.79 - 81°/ 18 m.m., η_D^{21} 1.4838, which could not be separated by fractional distillation.

$\nu_{max.}^{cm^{-1}}$ 3400(S) 3040(W) 2200(M) 1645(M) 1050(S) 990(S) 970(S) 910(S)

$\lambda_{max.}$ 223 mμ(EtOH) (ε = 6,470).

The mixture contained hex - 5 - en - 2 - yn - 1 - ol and hex - 4 - en - 2 - yn - 1 - ol.

(c) Hex - 5 - en - 2 - yn - 1 - ol (A17, R=H).

To a solution of ethyl magnesium bromide (from magnesium (49.0 g., 2.01 mole) and ethyl bromide (218 g. 2.0 mole) in tetrahydrofuran (500 ml) under nitrogen, propargyl alcohol (56.0 g., 1.0 mole) was added at a rate such that the temperature did not exceed 30°. When the addition was complete the mixture was refluxed for 2 hrs. Cuprous chloride (2g.) was added and the mixture allowed to cool, to room temperature. Allyl bromide (121 g. 1.0 mole) was added during 10 minutes and the mixture was then heated under reflux for 12 hours. After cooling to - 5° water (150 ml.) followed by cold dilute hydrochloric acid (100 ml.) was added. The mixture was saturated with salt and extracted with ether. The combined dried ether extracts on evaporation and distillation of the residual liquid gave hex - 5 - en - 2 - yn - 1 - ol (65 g. 67%).

b.p. 91 - 92°/30 m.m. η_D^{19} 1.4786.

(Found: C, 71.17; H, 8.27. C_6H_8O requires C, 74.97; H, 8.39%)

$\upsilon_{max.}^{cm^{-1}}$ 3400(S), 3040(W), 2100(W), 1645(M,) 1050(S), 990(S), 910(S).

(Elemental analysis on compounds containing a terminal double bond gave consistenly low carbon value. Solid derivates analysed satisfactorily).

The α - naphthylurethane was obtained as colourless silkly needles, m.p. 67° from light petroleum (b.p. 40 - 60°).
(Found: C, 76.00, 76,79; H, 5.94, 6.35. $C_{17}H_{15}NO_2$ requires C, 76.96; H 5.70%).

Hex - 5 - en - 2 - yn - 1 - ol acetate (A17,R=Ac).

a) Hex - 5 - en - 2 - yn - 1 - ol (5.0g.) and acetic anhydride (8 ml) in pyridine (20 ml.) was allowed to stand for 24 hrs then worked up in the usual manner. Hex - 5 - en - 2 - yn - 1 - ol acetate (5.6 g.) b.p. 89°/ 28 m.m., η_D^{24} 1.4539 was obtained.
(Found: C, 68.36; H, 6.92. $C_8H_{10}O_2$ requires C,69.54; H,7.30%).

b) 1 - (2' - Tetrahydropyranyloxy) - hex - 5 - en - 2 - yne (5.0 g.) in dry acetic acid (25 ml.) containing acetic anhydride (5 ml.) was refluxed for 10 hrs. The cooled solution was poured into water and worked up in the usual way to give hex - 5 - en - 2 - yn - 1 - ol acetate (2.7 g. 64%).
b.p. 89°/ 28 m.m. η_D^{24} 1.4539 identical with that prepared by the first method.

$\upsilon_{max.}^{cm^{-1}}$ 3040 (M), 2210(M), 1735(S), 1640(M), 1240(S), 990(S) 910(S).

Hexa - 2 (trans), 5 - dien - 1 - ol (A19).

To a stirred suspension of lithium aluminium hydride (8.2 g.) in dry ether (100 ml) under nitrogen a solution of hex - 5 - en - 2 - yn - 1 - ol (28.3g.) in ether 50ml.) was added at a rate such as to maintain gentle reflux. After the addition was complete, the mixture was refluxed for 2 hrs then cooled to - 10° and ethyl acetate (10 ml) added to destroy excess hydride present. Water (20 ml) and 20% aqueous ammonium chloride solution (50 ml) was added and the mixture stirred for 1 hr. The ether layer was separated and the aqueous layer ether extracted. The combined ether extracts were dried and evaporated. Distillation of the residual liquid gave hexa - 2(trans), 5 - dien - 1 - ol (25.9g.) 88. p.b. 78-80°/30 m.m. η_D^{19} 1.4571.

$\upsilon_{max.}^{cm^{-1}}$ 3400 (s), 3040(W), 1645(M), 990(S), 970(S), 910(S).

The α-naphthylurethane was obtained as colourless Silky needles, m.p. 73.5 - 74°, from light petroleum (b.p. 40 - 60°)

(Found: C, 76.60; H, 6.26. $C_{17}H_{17}NO_2$ requires C, 76.38; H, 6.41%).

Trans - Hexa - 2, 4 - dien - 1 -ol. (A20).

Hexa 2, 5 - dien - 1 - ol (10g.) was shaken with active manganese dioxide (10g.) in methylene chloride (30 ml.) at room temperature for 48 hrs. The filtered solution on evaporation gave an oil (0.85g.) whose infra-red spectrum proved it to be the all trans hexa - 2: 4 - dien 1 - ol. The 2:4 - dinitrophenylhydrazone, small dark red needles from ethyl acetate had m.p. 192-193° λ_{max} 391 mμ (ε= 38,000). (Found: C, 52.05; H,4.64. $C_{12}H_{12}N_4O_4$ requires C, 52.17; H,4.38%).

Trans - 2, 3, Epoxyhex - 5 - en - 1 - ol (A21).

a) Hexa - 2(trans)- 5 - dien - 1 - ol (5.0g.) was added to a solution of perbenzoic acid (7.04g.) in chloroform (220 ml.) at 0°C and the consumption of peracid followed iodometrically. After 64 hrs the reaction was virtually complete. Solid calcium hydroxide (20g.) was added and the solution was stirred until neutral. After filtering and evaporating the solution, distillation of the residual liquid gave trans - 2, 3 - epoxy - hex - 5 - en - 1 - ol (4.1g.) b.p. 96 - 98°/30 m.m., η_D^{22} 1.4590.

(Found: C,57.48; H,8.31. $C_6H_{10}O_2$ requires C, 63.13; H,8.82%).

$\nu_{max.}^{cm^{-1}}$ 3400(S), 3040(W), 1645(M), 990(S), 910(S), 860(M).

Reaction of Hexa - 2 (trans) - 5 - dien - 1 - ol with performic acid.

Hexa - 2(trans) - 5 - dien - 1 - ol (16.2g) was added to a solution of hydrogen peroxide (5.6g 18.6 gm. of 100 vol) in formic acid (100ml). The temperature rose slowly to 50° at which it was maintained by cooling. After 3 hours the solution was evaporated under reduced pressure to a syrup (18.9g.) which was steam distilled until the distillate was neutral. Evaporation of the distilland gave a viscous liquid (17.2g.). On distillation the main fraction (12.8g.) distilled at 120 - 134°/ 0.2.m.m. η_D^{20} 1.4918. The infra-red spectrum showed that this material was a mixture of polyhydroxy compounds. Vinyl and trans double bond absorption was present.

DL - erythro - Hex - 5 - en - 1, 2, 3 - triol (A22, R=H).

trans - 2, 3 - Epoxy-hex - 5 - en - 1 -ol (3.5g) in 2.5N sulphuric acid (50ml) was shaken for 24 hrs. then ether extracted to remove any unreacted epoxide. The aqueous phase was neutralised with solid barium carbonate, filtered and evaporated to a pale/

pale/

yellow syrup (3.25g). Distillation gave DL - erythro - hex - 5 - en - 1, 2, 3 - triol as a colourless syrup b.p. 125 - 130°/0.2 m.m. η_D^{20} 1.4883.

$\upsilon_{max.}^{cm^{-1}}$ 3500 - 3100 cm (S), 1645(M) 990(S) 910(S)

Lit.[49] b.p. 172 - 173°/ 25 m.m. η_D^{24} 1.4870, m.p. 40 - 41°.

A portion (1.0g) was taken up in ethanol (0.3ml) and stored at 0°. This deposited crystals (0.7g.) m.p. 39-41° after two weeks.

Triacetate b.p. 110°/0.1 m.m., η_D^{21} 1.4420.

(Found: C, 55.50H, 7.26. $C_{12}H_{18}O_6$ requires C, 55.80; H, 7.03%).

DL - erythro - Hexane - 1, 2, 3 - triol (A23)

DL - erythro - Hex - 5 - en - 1, 2, 3 - triol (1.0g) in ethyl acetate(10 ml) was hydrogenated over a 10% palladium - charcoal catalyst until absorption of hydrogen ceased. The solution after filtration and evaporation afforded an oil (0.95g) which solidified. Crystallisation from ethyl acetate gave DL - erythro - hexane - 1, 2, 3, - triol as colourless micro-prisms m.p. and mixed in p. 66°.

(Found: C 53.51; H. 10.52. $C_6H_{14}O_3$ requires C,53.71; H,10.54%)

$\upsilon_{max.}^{cm^{-1}}$ 3500 - 3100(S), 1100 - 1000(S).

2,2 - Dimethyl - 4 - (1' - hydroxybut - 3' - enyl) - dioxolan (A24).

A mixture of DL - erythro - hex - 5 - en - 1, 2, 3 - triol (2.0g.) and anhydrous copper sulphate (15g.) in dry acetone (40 ml) was shaken at room temperature for 24 hrs. The solution was filtered, excess acetone removed by filtration and the residual oil distilled to give 2,2 - dimethyl - 4 (1' hydroxybut - 3' - enyl) - dioxolan (2.2g.) b.p. 107 - 108° /20 m.m. η_D^{21} 1.4509.

(Found: C, 61.01, H, 9.34. $C_9H_{16}O_3$ requires C, 62.76; H, 9.36%).

Molecular Weight (by mass spectrometry) 172 Calc. 172.

The 3:5 dinitrobenzoate prepared in 86% yield was obtained as prisms m.p. 87 - 88° from ethanol. (Found: C, 52.28; H, 4.66. $C_{16}H_{18}N_2O_8$ requires C, 52.46; H.4.95%).

DL - erythro - 2 - Hydroxymethyl tetrahydropyran - 4,5 diol (Hexahydrokojic acid).(A28).

Kojic acid (96.4 g.) in ethanol (650 ml) was hydrogenated over a Raney nickel (W7) Catalyst at 70° and 100 ats for 4 hours. The solution was filtered and the ethanol removed by evaporation. The residual liquid on distillation gave hexahydrokojic acid (98.8 g. 98%) b.p. 175-177°/0.65 m.m $n_D^{22.5}$

1.5084.

(Lit. b.p. 212 - 215/ 13 m.m. $\eta_D^{13.5}$ 1.5073.)

DL - 2 - Hydroxymethyl - 4, 5 - isopropylidenedioxy tetrahydropyran.[107] (A29).

Hexahydrokojic acid (100g), acetone (300 ml) petroleum ether (300 ml. 40 - 60° fraction) and p - toluenesulphonic acid (3g.) were heated under reflux for 43 hours and the water formed in the reaction removed as its azeotrope with petroleum ether. After cooling, potassium carbonate (10g.) was added and the mixture stirred for 10 hrs. The solution was filtered, and evaporated to an oil which on distillation afforded the acetonide (80.4g) b.p. 116 - 118° /0.8 m.m.

η_D^{23} 1.4695.

(Lit. b.p. 149 - 151°/17 m.m. $\eta_D^{19.5}$ 1.4695).

DL - 2 - Chloromethyl - 4, 5 - isopropylidenedioxy tetrahydropyran.[107] (A30).

To a solution of DL - 2 - hydroxymethyl -4, 5 - isopropylidenedioxytetrahydropyran (60g, 0.32. mole) in pyridine (31.6g.) freshly distilled thionyl chloride (40.12g., 0.34 mole) was added at a rate such that the temperature remained below 60°. After the addition was complete the mixture was stirred for a further 4 hours then poured into water and/

and/

the chloro - compound extracted with ether. The combined extracts were dried and evaporated to a brown viscous liquid. Distillation gave the chloro-compound (34g., 34%) b.p. 134 - 136°/20 m.m. η_D^{19} 1.4705. (Lit. n.p. 134 - 135° / 20 m.m. η_D^{26} 1.4705).

2, 2 - Dimethyl - 4 - hydroxymethyl - 5 - allyldioxolan. (A31.)

To a stirred mixture of atomised sodium (4.29g.) and potassium (2.15 g.) in ether, DL - 2 - chloromethyl - 4, 5 - ispropylidenedioxytetrahydropyran (33.4g. 0.143 mole) was added dropwise. The mixture was stirred for a further 8 hours after the addition then decanted from residual alkali metal into ice water. The precipitated oil was isolated by ether extraction. The dried extracts on evaporation and distillation of the residual liquid gave 2, 2 - dimethyl - 4 - hydroxymethyl - 5 - allyldioxolan (21.3g.) b.p. 115 - 116° /20 m.m. η_D^{23} 1.4563.

(Lit. b.p. 115 - 116° /20 m.m., $\eta_D^{21.5}$ 1.4550)

(Found: C, 61.93; H.9.18. Calc. for $C_9H_{16}O_3$; C, 62.76; H, 9.36%).

Molecular wt. Found (by mass spectrometry) 172. Calc.172.

The 3, 5 - dinitrobenzoate was obtained as colourless needles, m.p. 82.5 - 83° from ethanol.

(Found: C, 52.71; H.4.65. $C_{16}H_{18}N_2O_8$ requires C, 52.46; H. 4.95%).

Mixedm.p. with the 3, 5 - dinitrobenzoate of 2, 2 - dimethyl 4 - (1' - hydroxybut - 3' - enyl) - dioxolan, 65 - 78°.

DL - erythro - Hex - 5 - en - 1, 2, 3, - triol (A22).

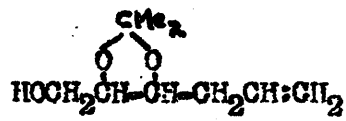
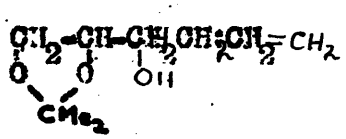
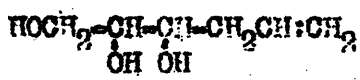
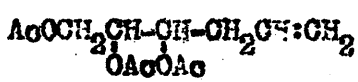
2, 2 - dimethyl - 4 - hydroxymethyl - 5 - allyldioxolan (2.0g.) in 0.1N sulphuric acid (2.0 ml) was heated at 50° for 30 minutes by which time the solution was homogeneous. The solution was neutralised with barium carbonate, filtered, and evaporated to a viscous liquid (1.82g.) the infra-red spectrum of which was identical with that of hex - 5 - en - 1, 2, 3, - triol prepared as described earlier. Catalytic hydrogenation gave DL - erythro - hexane - 1, 2, 3 - triol m.p. 66° undepressed on admixture with (A22) from hex - 5 - en - 2 - yn - 1 - ol.

Ozonolysis of 2, 2 - dimethyl - 4 - hydroxymethyl - 5 - allyldioxolan.

(A typical ozonolysis experiment is described below. Other attempted ozonolysis experiments are summarised in Table No.2.).

A solution of 2,2 - dimethyl - 4 - hydroxymethyl - 5 - allyldioxolan (1.0g.) in ethyl acetate (25 ml) containing t - butanol (5 ml) at - 40° was ozonised for 40 minutes. The solution was hydrogenated over 10% palladium - charcoal at -20°, filtered and evaporated to a colourless liquid (0.82g.) (The infra-red spectrum of this liquid showed complex absorption in the carbonyl region). This liquid was teated with 0·01N sulphuric acid at 50° for 1 hour, neutralised with barium carbonate, filtered and evaporated to a yellow syrup (0.71g). The syrup (0.71g.) in dry ethanol (10 ml.) containing aniline (1.2g) was refluxed 5 hours, then evaporated to a thick brown syrup. This was taken up in ethanol (2ml) and stored at 0° for 4 days. The 2 - deoxy - DL - ribose anilide (14 mg.) which crystallised out was removed by filtration and recrystallised from ethanol. Pure 2 - deoxy - DL - ribose anilide (12 mg.) m.p. 154 - 156° was obtained.

TABLE NO.2.

Compound	Solvent	Temp.	Time (min)	Anilide
	CH_2Cl_2	-70°	20	---
(1.0 g. samples	CH_2Cl_2-pyridine	-70°	20	---
in each case)	EtAc-t-BuOH	-70°	20	---
	(25 ml.:5 ml. 20 ml.:15 ml.)	-40°	40	12 mg
	CH_2Cl_2-t-BuOH	-50°	30	5.7 mg.
	pyridine	-20°	25	---
	CH_2Cl_2	-70°	20	---
	EtAc-t-BuOH			
	25ml. 5ml.	-40°	40	---
	20ml. 15ml.	-40°	40	---
	CH_2Cl_2-pyridine	-30°	15	---
	EtAc	-40°	20	---
	EtAc-t-BuOH			
	25ml. 5ml.	-70°	30	---
	20ml. 5ml.	-60°	30	---
	10ml. 10ml.	-20°	40	---
	EtAc-t-BuOH	-70°	20	---
	CH_2Cl_2	-40°	40	---

Attempted preparation of 3, 4 - O - isopropylidene - 2 - deoxy - DL - ribose.

To a mixture of 2,2 - dimethyl - 4 - hydroxymethyl - 5 - allyldioxolan (0.86g.0.005 mole) and osmium tetroxide (0.01271 g., 5 x 10^{-5} mole) in a mixture of ether (15 ml) and water (15 ml), sodium metaperiodate (2.24 g., 0.0105 mole) was added during 2 hours with stirring. After an additional 4 hours stirring the mixture was extracted with ethyl acetate, the combined extracts dried and evaporated to a pale brown oil (0.79g.). Distillation gave 2,2 - dimethyl - 4 - hydroxymethyl - 5 - allyl dioxolan (0.72g) b,p. 115 - 116° /20 m.m. η_D^{23} 1.4563. as sole product.

DL - 4 , 5 - O - Isopropylidene - 3 - deoxyhexitol(A32).

A mixture of 2,2 - dimethyl - 4 - hydroxymethyl - 5 - allyl dioxolan (2.8g.), osmium tetroxide (12 ml. of a 0.5% solution in t- butanol) and hydrogen peroxide (12 ml. of a 6.4% solution in t- butanol) was allowed to stand at room temperature for 24 hours. Potassium carbonate (1g.) was added and the mixture was evaporated to dryness. The residue was extracted with acetone, filtered and evaporated to dryness. Evaporative distillation at 100° and 0.1. m.m. gave unreacted acetonide (1.2g.) The residual syrup on chromatography on a cellulose column using n- butanol - light petroleum/

petroleum/

(b.p. 80-100°)(40:60 V/V) gave the deoxyisopropylidene hexitol (0.71g.)as a pale yellow syrup.

$\nu_{max.}^{cm^{-1}}$ 3400 - 3200(S), 1378(S), 1100-1000(S).

DL - 5, 6 - O - Isopropylidene - 3 - deoxyhexitol(A25).

When treated as in the preceding experiment 2, 2 - dimethyl - 4 - (1' - hydroxybut - 3' - enyl)-dioxolan (2.8g.) gave the corresponding deoxyisopropylidenehexitol (0.74g.) as a pale yellow syrup.

3, 4 - O - Isopropylidene - 2 - deoxy - DL - ribose(A33).

The stereoisomeric 4, 5 - O - isopropylidene - 3 - deoxy hexitols (0.71g.) were oxidised with sodium metaperiodate (27 ml. 0.17 M.) in a phosphate buffer (pH 7.4, 35 ml) at room temperature in darkness. After 2 hrs. the solution was extracted with chloroform (3 x 75 ml). The combined extracts were dried (K_2CO_3) and evaporated to give 3, 4 - O - isopropylidene - 2 - deoxy - DL - ribose (0.33 g.) as a pale yellow syrup.

4, 5 - O - Isopropylidene - 2 - deoxy - DL - ribose (A26).

This was obtained from the 5, 6 - O - isopropylidene 3 - deoxyhexitols by the procedure described in the previous experiment.

2 - deoxy - DL - ribose (A4).

3, 4 - Or 4, 5 - O - isopropylidene - 2 - deoxy - DL - ribose (0.38g) was hydrolysed in 0.01N sulphuric acid (25 ml) for 1 hour at 100°. The cooled solution was neutralised with barium carbonate, filtered and evaporated to give 2-deoxy-DL - ribose (0.29g) as a pale yellow syrup.

2 - deoxy - DL - ribose anilide.

2 - deoxy - DL - ribose (0.29g) in ethanol (4 ml) containing aniline (1.0g) was heated under reflux for 4 hours. The anilide (142 mg) which precipitated on cooling was recrystallised from ethanol as prisms m.p. 154 - 156°. (Found: C, 63.13; H, 7.00; N, 6.77. Calc. for $C_{11}H_{15}NO_3$: C, 63.14, H.7.23; N.6.69%)

Acetonide of hept - 6 - en - 4,5-(erythro) - triol(A39.)

Hept - 6 - ene - 4, 5 - erythro - 6, - triol (1.4g) and anhdrous copper sulphate (20g.) in acetone (150ml) was shaken at room temperature during 24 hrs. Filtration evaporation and distillation gave the triol as a colourless liquid (1.1g) b.p. 102°/ 20 m.m. η_D^{22} 1.4485.

$\nu_{max.}^{cm^{-1}}$ 3400(S), 3040(W), 1635(M) 1378(S) 990(S) 910(S)

The 3,5 - dinitrobenzoate formed in 81% yield crystallised as prisms m.p. 112 - 115° from ethyl acetate - pet - ether (40-60).
(Found: C, 53.50; H.5.16. $C_{17}H_{20}N_2O_8$ requires C, 53.68; H, 5.30%).

The Conversion of the acetonide (A39) to a mixture of deoxyhexomethyloses.

A mixture of the acetonide (A39) (0.9g), osmium tetroide (0.5 ml. of a 0.5% 50/n int - butanol) and hydrogen peroxide (8ml. of a 6.4% 50/n in t - butanol) was allowed to stand at room temperature for 24 hours. The solution was worked up as described earlier to give the O - isopropylidene - 3, 7 - dideoxyhepitols (XXXI). (0.18g.) as a colourless syrup. This/

This/
was oxidised with sodium metaperiodate (10 ml. 0.17 M) in a phosphate buffer (pH 7.4 12 ml) at room temperature in darkness. The solution, on work up in the usual manner, gave the crude O - isopropylidene - 2, 6 - dideoxyhexomethyloses (85 mg.) This on hydrolysis with 0.01N sulphuric acid (5ml) at 100° for 1 hour followed by neutralisation (solid barium carbonate) and evaporation gave a colourless syrup (53 mg.) Examination by paper chromatography on Whatman No.1. paper using the solvent system n-butanol - pyridine - water (3:1:3) revealed only one spot R_f 0.68 D - Glucose run under similar conditions had R_f 0.22 (Aniline phthalate was used as developer.)

Addition of HoBr to hex - 5 - en - 2 - yn - 1 - ol 6 - Bromohex - 2 - yn - 1, 5 - diol (A42).

A mixture of hex 5 - en - 2 - yn - 1 - ol (2.0g.) and N - bromosuccinimide (3.70g.) in water (20 ml) containing three drops of glacial acetic acid was shaken for 16 hours at room temperature. The solution was extracted with ether and the combined ether extract washed with sodium bicarbonate solution and dried./

dried/

($MgSO_4$). Evaporation left a pale brown oil (2.15g.) Decomposition occurred on attempted distillation.

$\nu_{max.}^{cm^{-1}}$ 3400(S) , 2210(W) No. C≡C. absorption.

Hex - 4 - yne - 1, 2, 6 triol triacetate (A43.)

6 Bromohex - 2 - yn - 1, 5 - diol (2.0g) and potassium acetate (2.0g.) in a mixture of acetic acid (10 ml.) and acetic anhydride (20 ml) were heated under reflux for 16 hours then evaporated to dryness at 20 m.m. Water(20 ml.) and ether (50 ml.) were added. The ether layer was separated, dried and evaporated to a brown oil which on distillation gave hex - 4 - yne - 1, 2, 6 - triol triacetate (2.8g.) b.p. 128-130°/0.35 m.m. η_D^{19} 1.4605.

(Found: C, 55.50: H. 6.43. $C_{12}H_{16}O_6$ requires C, 56.24, H, 6.29%).

Hexane - 1, 2, 6 - triol (A45).

Hydrolysis of hexane - 1, 2, 6 - triol & triacetate (0.95 g.) by the Zemplen method afforded hexane - 1, 2, 6 triol (0.47g.) b.p. 156 - 158°/ 5×10^{-3} m.m. η_D^{17} 1.4772.

The dicyclohexylamine adduct, colourless silky needles m.p. 52 - 53° from acetone was shown by analysis to be a 1: 1 - adduct and not a 1:3 adduct as described in the literature[116].

(Found: C, 68.86, H,12.08; N, 4.93. Calc. for $C_{18}H_{37}NO_3$. C, 68.57; H,11.74; N,4.44%)

Attempted hydration of DL - erythro - pent - 4- yn - 1, 2, 3 - triol.

a) To a solution of DL - erythro - pent - 4 - yn - 1, 2, 3 - triol (2.0g.) in 90% acetic acid (100 ml.) mercuric acetate (1.0g) and concentrated sulphuric acid (0.5 ml) were added, and the mixture was refluxed for 5 hours. The solution was evaporated to small bulk at 0.1 m.m. Water was added and the solution after neutralisation with sodium bicarbonate was deionised on Amberlite ion exchange resins and concentrated to a pale yellow syrup which showed acetylenic but no carbonyl absorption in the infra-red spectrum. Distillation gave pent - 4 - yn - 1, 2, 3 - triol (1.21 g.) b.p. 120°/ 0.1 m.m. as sole product.

b) A solution of the acetylenic triol (2.0g.) in ethanol (10 ml) was added to a mixture of mercuric oxide (0.6 g.) trichloroacetic acid (5 mg.) and borontrifluoride - etherate (0.3 ml) in ethanol (50 ml.). The mixture was refluxed for 5 hours, then evaporated to a pale brown oil (2.1g.) This was dissolved in water and neutralised on ion exchange resins. Evaporation and distillation gave unchanged pent - 4 - yn - 1,2,3, - triol (1.42 g.) b.p. 120°/ 0.1 m.m. as sole product.

DL - erythro - Pentan - 4 - one - 1, 2, 3 - triol triacetate (A46).

a) To a solution of DL - erythro - pent - 4 - yn - 1, 2, 3 - triol triacetate (2.0g.) in 90% acetic acid (100 ml.) mercuric acetate (0.9g.) and concentrated sulphuric acid (0.4 ml.) were added and the mixture was refluxed for five hours. The cooled solution was poured into water and extracted with ether. The combined ether extracts were washed with sodium bicarbonate solution and dried ($MgSO_4$). Evaporation and distillation of the residual oil gave DL - erythro - pentan - 4 - one - 1, 2, 3 - triol triacetate (0.4g.) as a pale yellow oil. b.p. 104 - 106 /0.1 m.m. η_D^{21} 1.4439.

(Found: C, 50.92; H. 6.20. $C_{11}H_{16}O_7$ requires, C, 50.77, H.6.14%),

$\nu_{max.}^{cm^{-1}}$ 1735(S) 1710(S) 1240(S).

A 2, 4 - dinitrophenylhydrazone or semi carbazone could not be obtained.

b). Mercury impregnated resin method.

A solution of the acetylenic triacetate (2g.) in acetic acid (100 ml.) containing mercury impregnated Amberlite IR120(H) resin (10g.) was heated under reflux for two hours. The solution was filtered and the resin washed with ether. The combined filtrates were poured into water and the mixture extracted with ether. The combined extracts were washed with sodium bicarbonate solution, dried and evaporated. The residual liquid after acetylation gave on distillation DL - erythro - pentan - 4 - one - 1, 2, 3 - triol triacetate (0.7g.) b.p. 104-106°/0.1 m.m.

η_D^{21} 1.4439.

c) A solution of the acetylenic triacetate (2g.) in ethanol (10 ml) was added to a mixture of mercuric oxide (0.5g.) , trichloroacetic acid (5 mg.) and borontrifluoride etherate (0.3 ml. of 45% solution) in ethanol (50ml) at 40°. The mixture was shaken at room temperature for 24 hours and refluxed for a further 2 hours. The mixture was poured into sulphuric acid (100 ml. 2N) and the ketone isolated with ether.

The crude material which had suffered partial deacetylation was reacetylated (Ac_2O - pyridine) acid distilled to give DL - erythro - pentan - 4 - one - 1, 2, 3 - triol triacetate (0.4g.) b.p. 104-106°/ 0.1 m.m.

2 - Methyltetrahydrofuran - 2, 3, 4 -(erythro)- triol Triacetate (A47.).

A solution of DL - erythro - pent - 4 - yn - 1, 2, 3 - triol triacetate (2g.) in acetic acid (10 ml) was added to a mixture of mercuric oxide (1.0g), trichloroacetic acid (5 m.g.) and boron trifluoxide - acetic acid complex (0.4 ml). in acetic acid (15 ml). After the initial exothermic reaction had subsided, the mixture was poured into water and extracted with ether. The combined ether extracts were washed with sodium bicarbonate solution and dried. Evaporation of the solvent and distillation of the residual liquid gave - 2 - methyl - tetrahydrofuran - 1, 2, 3 - erythro - triol triacetate (1.74g.) b.p. 125 - 128°/0.35 m.m.

η_D^{25} 1.4391.

(Found: C, 50.58: H, 6.10. $C_{11}H_{16}O_7$ requires, C, 50.77 H, 6.20%)

$\nu_{max}^{cm^{-1}}$ 1735(S) 1240(S) 1058(S).

Attempted Pyrolysis of 2 - methyl tetrahydrofuran - 1, 2, 3 -(erythro)triol triacetate.

The tetrahydrofuran (2g.) in diethyl phthalate (20 ml) was heated slowly under nitrogen at 0.1 m.m. to 150°. A colourless liquid was obtained on distillation. By the time this material reached the receiver it was dark brown in colour. No pure compound was obtained from this reaction.

5 - Bromopentan - 4 - one - 1, 2, 3 - triol triacetate(A48.)

A solution of the triacetoxyketone (2.5g.) in dry carbon tetrachloride (10 ml) was treated dropwise with a solution of bromine (0.8g.) in carbon tetrachloride (5 m.l.) Removal of solvent gave the bromoketone as a pale brown oil (2.6g.) which decomposed on distillation at 0.1 m.m.

This compound failed to give a thiouronium picrate.

Attempted preparation of DL - ribulose tetracetate (A49).

Crude 5 - bromopentan - 4 - one - 1, 2, 3 - triol triacetate (2.5g) in acetic acid (20 ml.) and acetic anhydride (10 ml) containing fused potassium acetate (3g.) was refluxed for 16 hours. The solution was evaporated to dryness and ether and water were added. The dark brown ether layer was washed with sodium bicarbonate solution, dried and evaporated to a dark brown viscous oil (2.1g.) No pure compound was isolted/

from this material.

DL - 1, 1 - Dibromo - 2, 2 - diethoxyerythro -pentane - 3, 4, 5 triol triacetate (A51.)

A solution of DL - erythro - pent - 4 - yne - 1, 2, 3 - triol triacetate (7.1g) in dry ethanol (50 ml) at - 10° was treated with N - bromosuccinimide (11.0g.) during 10 hours and stirred for a further 10 hours. The solution was filtered, diluted with water and extracted with ether. The dried extracts oneveporation gave a colourless oil (7.6 g.) which decomposed slowly on standing and rapidly on attempted distillation.

$\nu_{max.}^{cm^{-1}}$ 1735(S), 1240(S) 1200 - 1000(S).

Attempted preparation of 1 - bromo - 2 - ethoxypent - 1 - en - 3, 4, 5 - triol triacetate (A52).

A solution of crude 1, 1 - dibromo - 2, 2 - diethoxypentane - 3, 4, 5 - triol triacetate (1.0g.) in ethanol (50 ml) containing activated zinc (5.0g) was refluxed for 4 hours. The cooled solution was filtered and evaporated to a pale yellow syrup (0.87g.) from which no pure compound could be isolated.

2, 2 - Dimethyl - 4 - hydroxymethyl - 5 - ethynyldioxolan (A12.)

A mixture of DL - erythro - pent - 4 - yn - 1, 2, 3 - triol (4.7g.) and anhydrous copper sulphate(80g.) in dry acetone (1000 ml) was shaken at room temperature for four days after which time the solution was filtered and the excess acetone removed by distillation. The residual liquid on distillation gave 2, 2 - dimethyl - 4 - hydroxymethyl - 5 - ethynyl dioxolan (5.29g, 85%) b.p. 93 - 94° /2 m.m. η_D^{22} 1.4595.

(Found: C, 59.71, 59.32; H. 7.22, 7.84. $C_8H_{12}O_3$ requires C, 61.52 H, 7.75%)

$\upsilon_{max.}^{cm^{-1}}$ 3400(S) 3250(S) 2100(M).

This acetonide was unaffected by treatment with (a) active manganese dioxide in light petroleum, (b) chromium trioxide in pyridine or (c) oxygen in the presence of a platinium catalyst.

The phenylurethane, formed in 93% yield was obtained as colourless needles m.p. 133 - 134° from light petroleum (60-80°).

(Found: C, 65.39; H, 6.34. $C_{15}H_{17}NO_4$ requires C, 65.44; H.6.22%.)

The 3, 5 - dinitrobenzoate formed in 88% yield was OBTAINed as white plates m.p. 115.5 - 116° from/

aqueous ethanol.

(Found: C, 51.10: H, 4.37. $C_{15}H_{14}O_8$ requires C, 51.43; H, 4.00%).

The same acetonide was formed using sulphuric hydrochloric, or p - toluenesulphonic acid as catalyst. The yields were considerably lower.

Cyclohexylidene ketal formed by pent - 4 - yn - 1, 2, 3 - triol.

A mixture of DL - erythro - pent - 4 - yn, 1, 2, 3 - triol (2.5g) cyclohexanone (3.0g.) and p - toluene sulphonic acid (0.5g) in benzone (50 ml) was refluxed for ten hours and the water liberated was removed as its benzene azeotrope. The cooled solution was washed with sodium bicarbonate solution and dried. Removal of the solvent and distillation of the residual oil gave the cyclohexylidene ketal (2.8g.) b.p. 109 - 110o/ 0.6 m.m. n_D^{20} 1.4961.

(Found: C, 70.76 ; H, 8.41 $C_{11}H_{16}O_3$ requires C, 67.32; H, 8.22%).

This compound was not oxidised by active manganese dioxide.

2, 2 - Dimethyl - 4 - benzoyloxymethyl - 5 - ethynyl. dioxolan (A61).

Prepared by the action of benzoylchloride on 2,2 - dimethyl - 4 - hydroxymethyl - 5 - ethynyldioxolan in pyridine this compound was obtained as a colourless oil b.p. 114-116° /0.15 m.m. η_D^{18} 1.5231. (Found: C, 69.52; H, 6.56. $C_{15}H_{16}O_4$ requires C, 6921; H, 6.20%)

$\upsilon_{max}^{cm^{-1}}$ 3250(S) 2100(M) 1725(S(1250(S).

DL - erythro - Pent - 4 - yn - 1, 2, 3 - triol - 1 - benzoate (A62.

2, 2 - dimethyl - 4 - benzoyloxymethyl - 5 - ethynyldioxolan (2.0g) in 2N sulphuric acid (25 ml) was heated at 90° for thirty minutes. The cooled solution was extracted with chloroform,, the combined extracts washed with sodium bicarbonate solution, dried, and evaporated to a colourless viscous oil (1.75g.) The infra-red spectrum of this material was consistent with the above formulation.

$\upsilon_{max.}^{cm^{-1}}$ 3500(S), 3250(S.sh), 2100(M) 1725(S) 1250(S).

The triol monobenzoate on complete benzoylation with benzoyl chloride in pyridine afforded pent - 4 - yn - 1, 2, 3, - triol tribenzoate m.p. and mixed m.p. 110-111° resolidifying and remelting at 118-119°.

Periodate oxidation of DL - erythro - pent - 4 - yn - 1, 2, 3 - triol - 1 - benzoate.

A mixture of DL - erythro - pent - 4 - yn - 1, 2, 3 - triol - 1 - benzoate (0.50g.) and sodium metaperiodate (0.68g) in 50% aqueous dioxan (50ml) was allowed to stand at room temperature for eighteen hours, by which time 0.96 mole of periodate had been consumed (iodometric titration). The solution was steam distilled into an aqueous solution of 2, 4 - dinitrophenylhydrazine sulphate. The reddish-yellow precipitate was collected and dried. Chromatography on bentonite-kieselguhr (4:1 W/W) using chloroform as eluant afforded propargylaldehyde - 2, 4 - dinitrophenylhydrazone (0.36g) (Theory 0.46g.) orange-yellow starlets, m.p. and mixed m.p. 121 - 122° from aqueous ethanol.

2, 2 - Dimethyl - 4 - methoxymethyl - 5 - ethynyldioxolan (A63).

a) Dimethyl sulphate (9.0g) was added slowly to a mixture of 2, 2 - dimethyl - 4 - hydroxymethyl - 5 - ethynyl - dioxolan (4.9g) and potassium carbonate (20g) in acetone (150ml). The mixture was refluxed for eighteen hours. Most of the solvent

solvent/

was removed by distillation, water(100 ml) was added and the mixture was extracted with ether. The dried extracts on evaporation and distillation gave unchanged acetonide (4.51g).

b) To a solution of 2, 2 - dimethyl - 4 - hydroxymethyl - 5 - ethynyldioxolan (5.0g) in methyl iodide (20 ml) silver oxide (20g) was added and the mixture was shaken at room temperature for 24 hours. More silver oxide (15g.) was added/and the mixture was shaken for a further 24 hours. Ether (100 ml) was added and the mixture was filtered. The filtrate was evaporated and the residual oil distilled to give 2, 2 - dimethyl - 4 - methoxymethyl - 5 - ethynyldioxolan (1.7g.) b.p.130° (bath temp) (0.3 m.m. η_D^{21} 1.4654.

$\nu_{max.}^{cm^{-1}}$ 3250 (S) 2100 (M) 1378(S) 1200 - 1000 (S).

DL - erythro - Pent - 4 - yn - 1, 2, 3 - triol - 1 - methylether (A64).

2, 2 - dimethyl - 4 - methoxymethyl - 5 - ethynyldioxolan (1.6g) in 2N sulphuric acid (20 ml) was heated at 90° for thirty minutes and cooled. The solution was extracted with chloroform and the combined extracts after washing with sodium/

sodium/

bicarbonate solution were dried and evaporated to a viscous liquid (0.72g.)

$\nu_{max.}^{cm^{-1}}$ 3500(S) 3250(S.sh) 2100(M(.

<u>Periodate oxidation of DL - erythro pent - 4 - yn - 1, 2, 3 - triol - 1 - methyl ether.</u>

Crude DL - <u>erythro</u> - pent - 4 - yn - 1, 2, 3 - triol - 1 - methyl ether (0.71g; 0.00546 mole) in 50% aqueous dioxan (50 ml) was treated with a solution of sodium meta-periodate (0.1176g; 0.0055 mole) in water (10 ml) and the mixture allowed to stand at room temperature for 16 hours, then steam distilled into an aqueous solution of 2, 4 - dinitrophenylhydrazine sulphate. The reddish-orange precipitate was collected and dried (2.42g.) the mixture of 2, 4 - dinitrophenylhydrazones (0.5g)was chromatographed on a column of bentonite-kieselguhr using chloroform as eluant to give methoxyacetaldehyde - 2, 4 - dinitrophenylhydrazone (0.22g) orange plates m.p. and mixed m.p. 125 - 126° from ethanol and propargyl aldehyde - 2, 4 - dinitrophenylhydrazone (0.20g) orange yellow starlets m.p. and mixed m.p. 121 - 122° from aqueous ethanol.

Attempted preparation of 2 - methylene - 3, 4 - isopropylidene dioxytetrahydrofuran (A54).

a) To freshly prepared sodamide (from sodium (0.3g)) 2, 2 - dimethyl - 4 - hydroxymethyl - 5 - ethynyldioxolan (1.0g.) was added and the mixture kept at room temperature under nitrogen for 24 hours. The mixture was extracted with benzene and the combined extracts evaporated to a pale yellow oil (0.95g.) which gave unchanged acetonide on distillation.

When heated with sodamide at 50° the mixture decomposed violently.

b) A mixture of the acetonide (1.0g) and sodamide(0.1g.) in benzene (80 ml) was refluxed under nitrogen for eight hours. Work up as above gave unchanged acetonide as sole product.

c) A mixture of the acetonide (1.0g.) in 0.1N sodium hydroxide solution (100 ml) was refluxed under nitrogen for 24 hours. The straw-coloured solution was extracted with ether, the combined extracts dried and evaporated to give unreacted acetonide (0.92g) as sole product.

d) The above reaction was repeated using 1N and 3 N sodium hydroxide solution. No cyclisation product was obtained.

Reaction (b) was repeated using potassium t - butoxide or sodium hydride as catalyst. No cyclisation occurred.

Attempted preparation of 2 - methylene - tetrahydrofuran-3, 4 (erythro) - diol (A60).

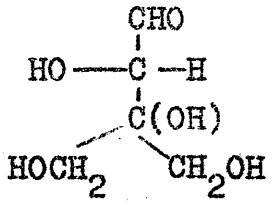
DL - erythro - pent - 4 - yn - 1, 2, 3 - triol (1.0g.) in 4N sodium hydroxide solution (50Ml) was refluxed under nitrogen for 10 hours. The cooled solution was deionised on Amberlite ion-exchange resins and concentrated to a yellow syrup (0.93g) distillation of which gave DL - erythro-pent - 4 - yn -1, 2, 3 - triol (0.91g.) b.p. 120° /0.1 m.m. as sole product.

PART II.

APIOSE and CORDYCEPOSE.

Branched-chain sugars have been isolated from varied sources of natural origin. Until about 1950 the only natural products which were known to contain a branched-chain sugar were the flavone glycoside of the parsley plant (apiose)(B.1) and the hamameli-tannin obtainable from the bark of witch-hazel (hamamelose). The search, during the last decade, for new antibiotics has led to the isolation of new branched-chain sugars, e.g. Streptose[131](B.2), 5-hydroxystreptose[132](B.3), cordycepose[133](B.4), noviose[134](B.5), mycarose[135](B.6) and cladinose[136](B.7).

The identification of these new branched-chain sugars as components of natural products has stimulated interest in methods for their synthesis. Hough and Jones[137] have suggested that the biosynthesis of apiose, hamamelose and streptose might result from the condensations respectively of dihydroxyacetone with glycollic aldehyde, glyceraldehyde with itself and/



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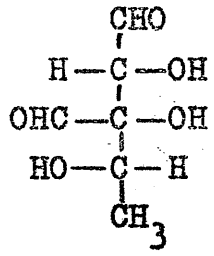

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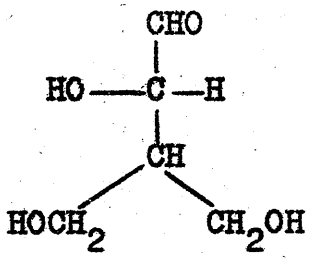

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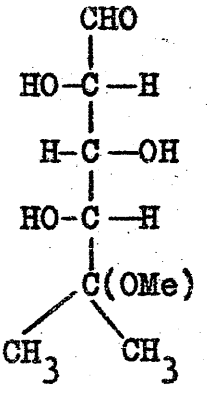
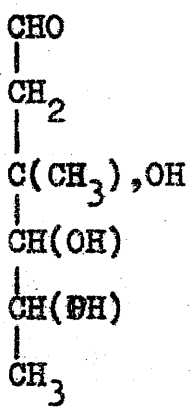
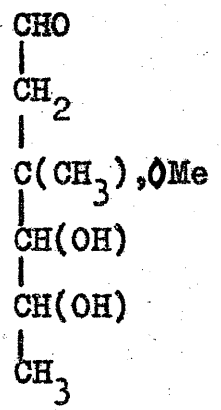


(B5)

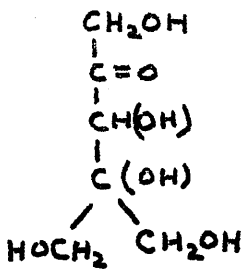


(B6)



(B7)

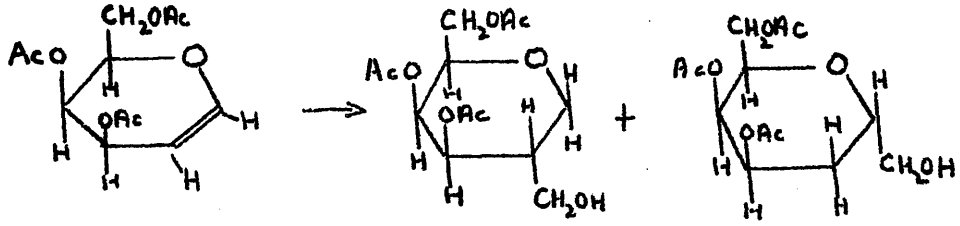
and tartaric dialdehyde with acetaldehyde. There are some chemical analogies for the formation of branched-chain sugars by aldol condensations. For example Utkin[138] has reported the chemical synthesis of a branched-chain ketose, dendroketose(B.8) by the self condensation of dihydroxyacetone in alkali.



(B8)

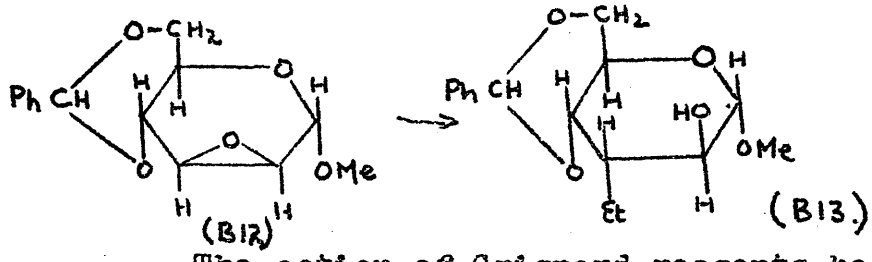
The cyanohydrin reaction has been applied to fructose to furnish branched-chain sugars containing seven carbonatoms which have been used as intermediates in the preparation of other branched-chain derivatives. Using this method Perlin and Gorin [139] converted 3-O-benzyl-D-fructose into D-apiose. Attempts have been made to apply the Oxo reaction to unsaturated sugars[140]. A new seven carbon branched-chain carbohydrate has been obtained by treating 3,4,6-tri-O-acetyl-D-galactal (B.9) with carbon monoxide and hydrogen in the presence of preformed dicobalt-octacarbonyl and ethyl orthoformate at an elevated temperature/

temperature. Two products (B.10) and (B.11) are possible and it has been demonstrated that in fact (B.10) is formed.



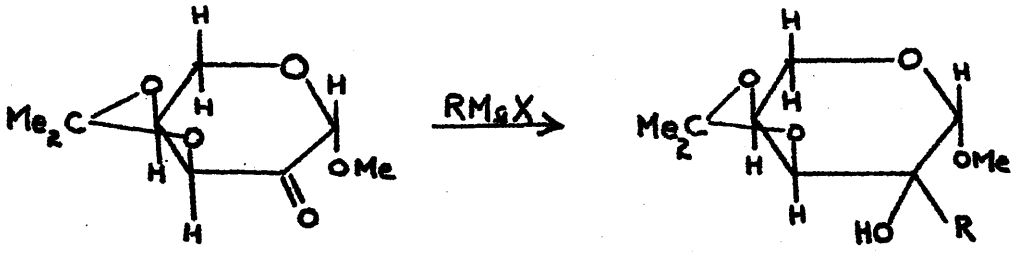
(B9.) (B10) (B11.)

The opening of anhydro sugars by Grignard reagents provides a method of preparing branched-chain sugars. Thus methyl-4,6-O-benzylidene-3-deoxy-3-C-ethyl-α-D-altroside.(B.13) has been prepared from methyl-2,3-anhydro-4,6-O-benzylidene-α-D-mannoside (B.12)[141].



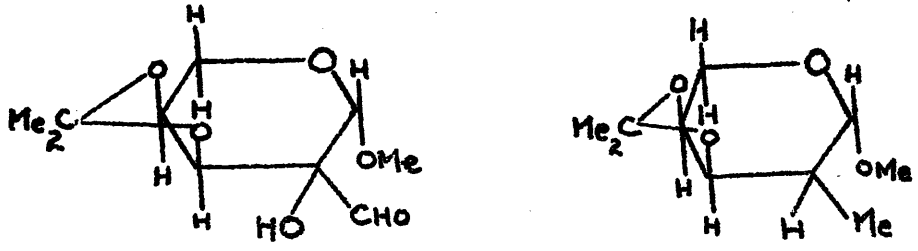
(B12) (B13.)

The action of Grignard reagents has also been used to produce branched-chain sugars. Overend[142] has prepared methyl 3,4-O-isopropylidene-2-oxo-β-L-arabinoside, and from it a series of branched-chain sugars (B.14) by reaction with suitable Grignard reagents.



(B14)

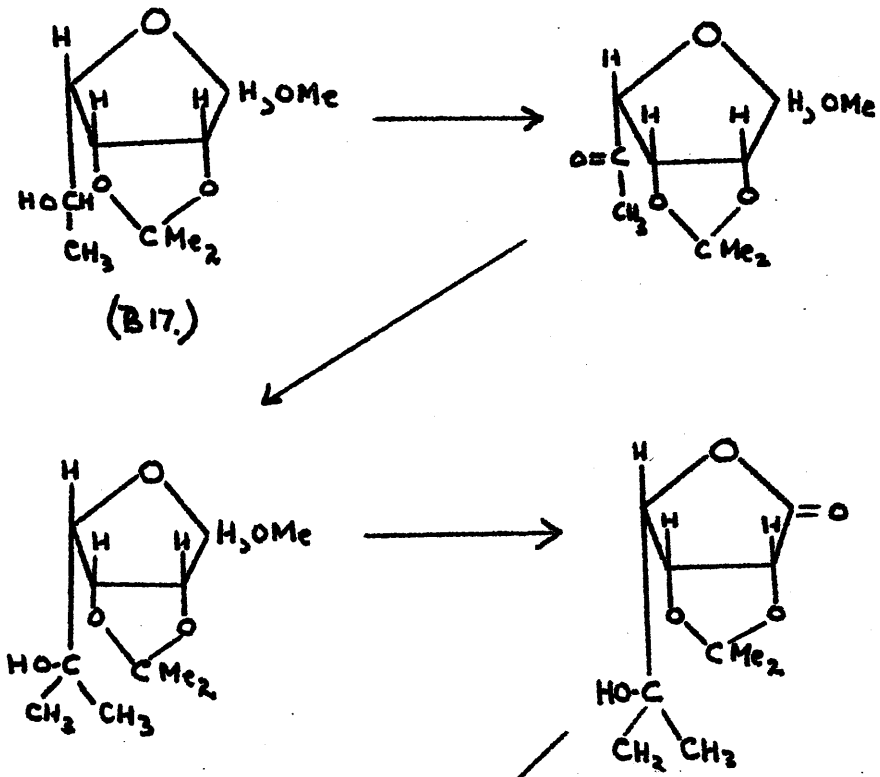
(B.14 R = $-CH=CH_2$) on ozonolysis afforded the 2-C-formyl-3,4-O-isopropylidene-β-L-pentoside (B.15).



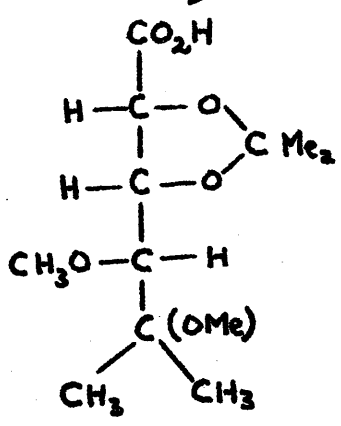
(B15) (B16.)

(B.14 , R = Me) formed a monotosylate which on reduction with lithium aluminium hydride afforded the 2-deoxy-3,4-O-isopropylidene-2-C-methyl-β-L-pentoside (B.16).

In a similar way 2,3-O-isopropylidene-5-O-methyl novionic acid (B.18) has been synthesised[143] from methyl-2,3-O-isopropylidene-L-rhamnofuranoside (B.17) as shown below. This was identical with the corresponding derivative of novionic acid obtained from noviose.



(B17.)



(B18.)

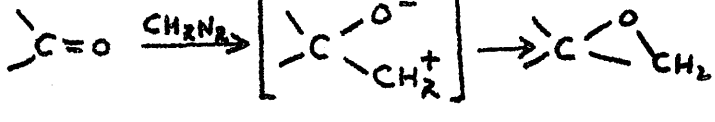
DISCUSSION.

Although the synthesis of apiose and cordycepose described in the introduction rigidly proved the constitutions of these two sugars, the method of synthesis was long and the yield low and thus was not applicable to the relatively large scale production of the racemic sugars which were required for resolution studies.

Accordingly new and more direct synthetic routes were investigated with this object in view. This section is concerned with these investigations.

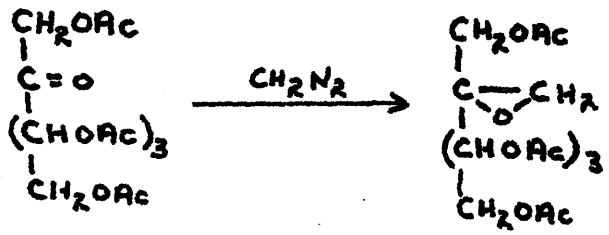
In the first approach to apiose (see flowsheet No.20), the essence of the synthesis centred on the preparation of 1,1-diethoxy-2,3-epoxy-4-acetoxymethylbutan-4-ol acetate (B.24) from which apiose should be obtained on acid hydrolysis.

With aldehydes and ketones, which have electrophilic groups attached to the α-carbon atom or atoms diazomethane is known to give the epoxide rather than the homologous aldehyde or ketone.



Thus/

Thus keto-D-fructose pentaacetate gives the corresponding epoxide in high yield:

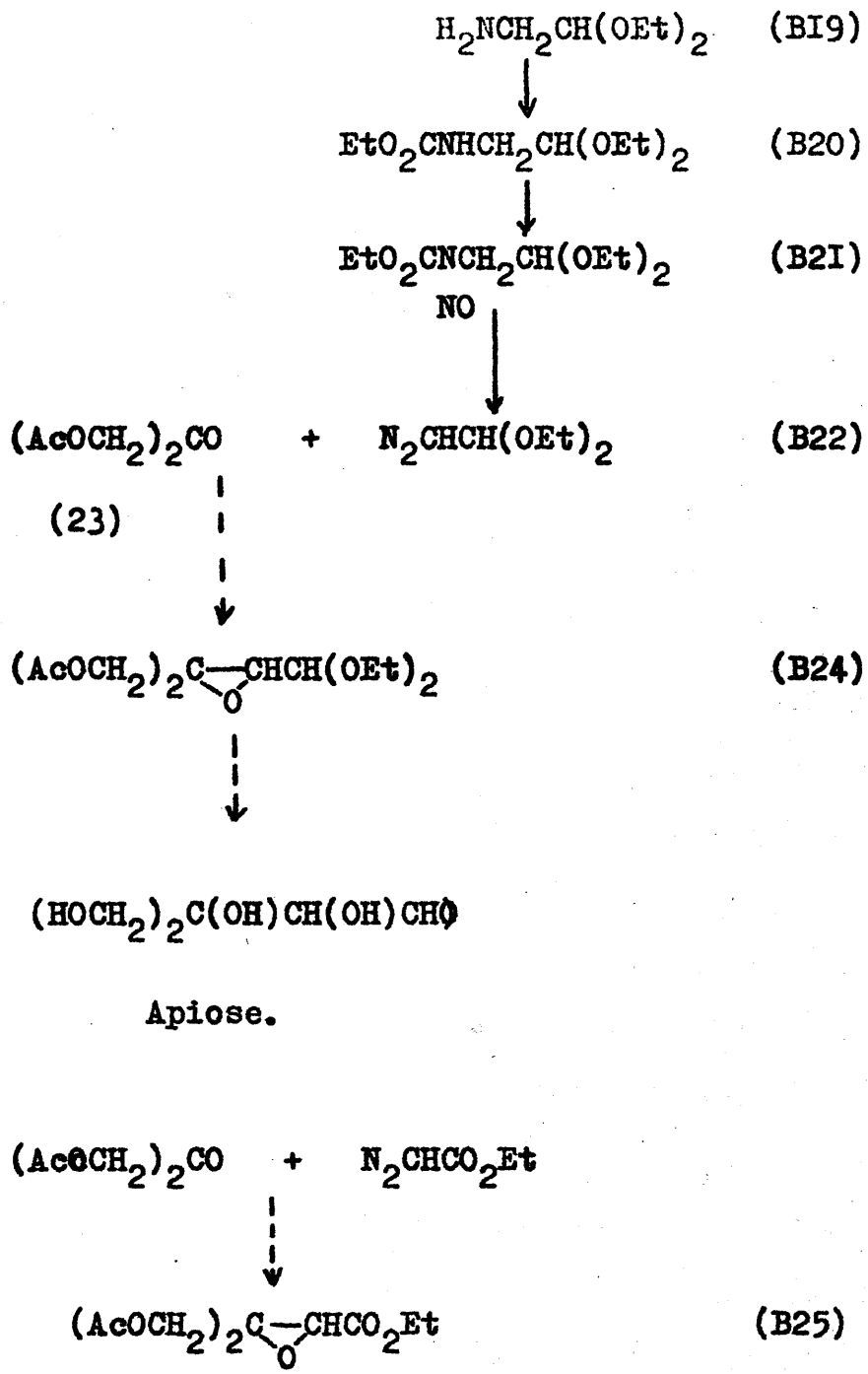


By analogy with this reaction it was considered possible that diacetoxyacetone (B.23) would react with diazoacetaldehyde diethyl acetal (B.22) to produce (B.24) directly. As diazoacetal had not hitherto been reported, a synthesis of this compound had first to be established.

Aminoacetal (B.19) on treatment with methyl chloroformate gave an almost quantitative yield of 1,1-diethoxy-2-methoxycarbonylaminoethane (B.20) which was characterised as its corresponding 2,4-dinitrophenylhydrazone. The preparation of the N-nitrosourethane (B.21) from (B.20) by the action of nitrous acid proved unsuccessful even when the reaction was carried out at low temperature.

N-Nitroso-1,1-diethoxy-2-methoxycarbonylaminoethane (B.21) was finally prepared by the action of the powerful nitrosating agent, nitrosyl chloride on the urethane (B.20). Attempts

to/



Flowsheet No. 20.

to purify the N-nitroso compound were unsuccessful, as decomposition occurred on distillation. The crude N-nitroso compound on treatment with base, afforded diazoacetaldehyde diethyl acetal (B.22) as a yellow mobile liquid, the infra-red absorption of which was consistent with the above formulation.

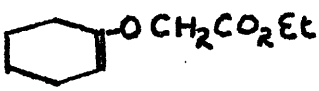
Attempts were made to condense the diazoacetal (B.22) with diacetoxyacetone (B.23) which was prepared from 1,3-dichloroacetone by the method of Weygand[144]. At room temperature in chloroform solution no reaction occurred and the ketone was recovered. In carbon tetrachloride at 90° in the presence of copper powder, no pure compound was obtained. This attractive route to apiose had therefore to be abandoned.

However, the reaction of diacetoxyacetone with ethyl diazoacetate was studied in the hope that ethyl-$\alpha\beta$-epoxy-β-acetoxymethyl-γ-acetoxybutyrate (B.25) might be obtained. This on hydrolysis would furnish apionic acid and thence apiose (see Flowsheet No.20).

Kharasch[145] studied the reaction of cyclohexanone and acetone with ethyl diazoacetate

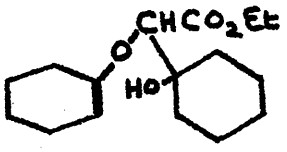
and/

and succeeded in isolating four compounds from the reaction. These were (B.26) - (B.29); yields are shown in brackets.



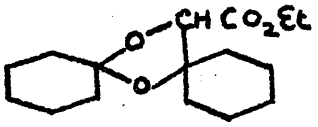
(43%)

(B 26)



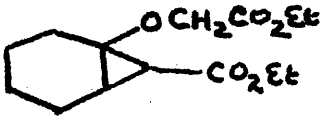
(16%)

(B 27)



(4%)

(B 28)



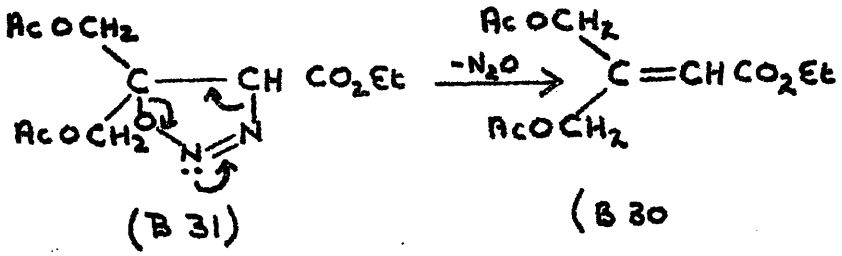
(1%)

(B 29)

With diacetoxyacetone under similar reaction conditions, only one compound was isolated in poor yield. This compound analysed for $C_{11}H_{16}O_6$, showed infra-red absorption at 1735 and 1625 cm^{-1}, and had an absorption maximum in the ultra-violet at

210/

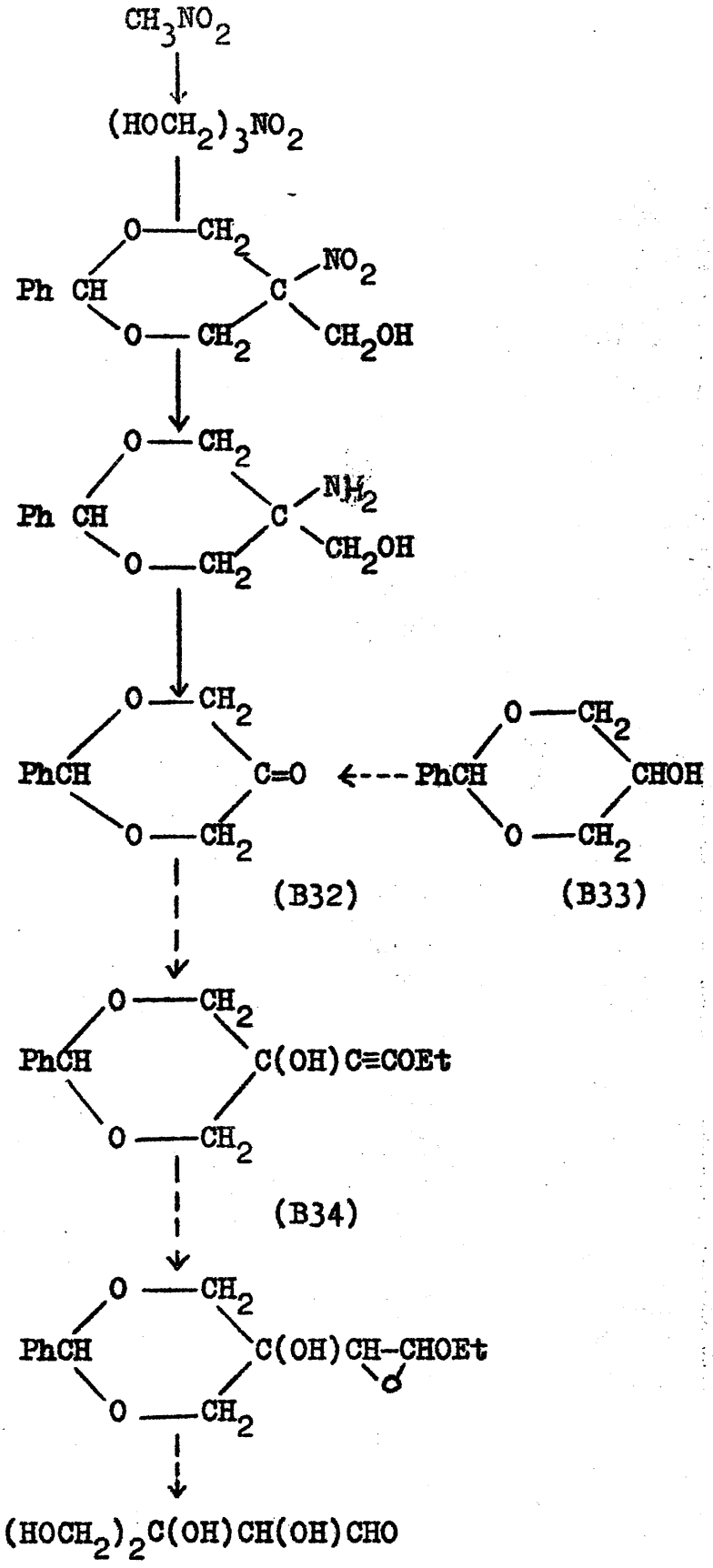
210 mμ. (ε = 11,000) characteristic of an αβ-unsaturated ester. On microhydrogenation one mole of hydrogen was absorbed. On the basis of this information this compound was formulated as ethyl 3-acetoxymethyl-4-acetoxybut-2-enoate (B.30) formed



(B 31) (B 30

presumably by elimination of nitrous oxide from the postulated oxazoline intermediate (B.31). This unsaturated ester (B.30) if it could have been prepared in sufficient quantity, would have provided a useful intermediate from which a synthesis of apiose might have been achieved. However, an attempt to prepare it more conviently by a Reformatsky reaction between diacetoxyacetone and ethyl bromoacetate was unsuccessful.

The next approach to apiose (see Flowsheet No.21) utilised benzylidene dihydroxyacetone (B.32) as starting material. This was prepared, according to the method of Raphael and Marei[146], from nitromethane as shown in Flowsheet No.21. Unfortunately this/



Flowsheet No. 2I,

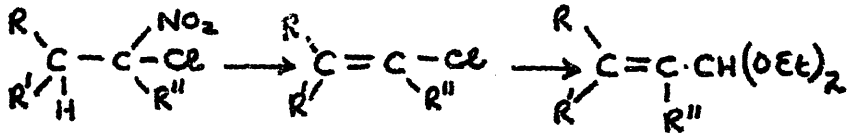
this compound was very unstable and could not be prepared in quantity by this method. As an alternative method of preparation was desirable, 2-phenyl-5-hydroxy-1,3-dioxan (1,3-O-benzylidene glycerol) (B.33) was prepared by the method of Stacey[147], but unfortunately it was resistant to oxidation by the chromium trioxide-pyridine complex or by manganese dioxide and so the initial method of preparation was used.

It has been shown [148] that benzylidene dihydroxyacetone condensed normally with ethynylmagnesium bromide to give 2-phenyl-5-hydroxy-5-ethynyl-1,3-dioxan. With ethoxyethynylmagnesium bromide, however, a complex mixture was obtained from which the desired compound, 2-phenyl-5-hydroxy-5-ethoxyethynyl-1,3-dioxan (B.34) could not be isolated. This approach had therefore to be abandoned.

In a recent paper Dornow and Muller[149] have shown that vic chloro-nitro compounds, in which the nitro group is tertiary, lost nitrous acid on treatment with sodium methoxide; the product formed in good yield was the chloro-olefin.

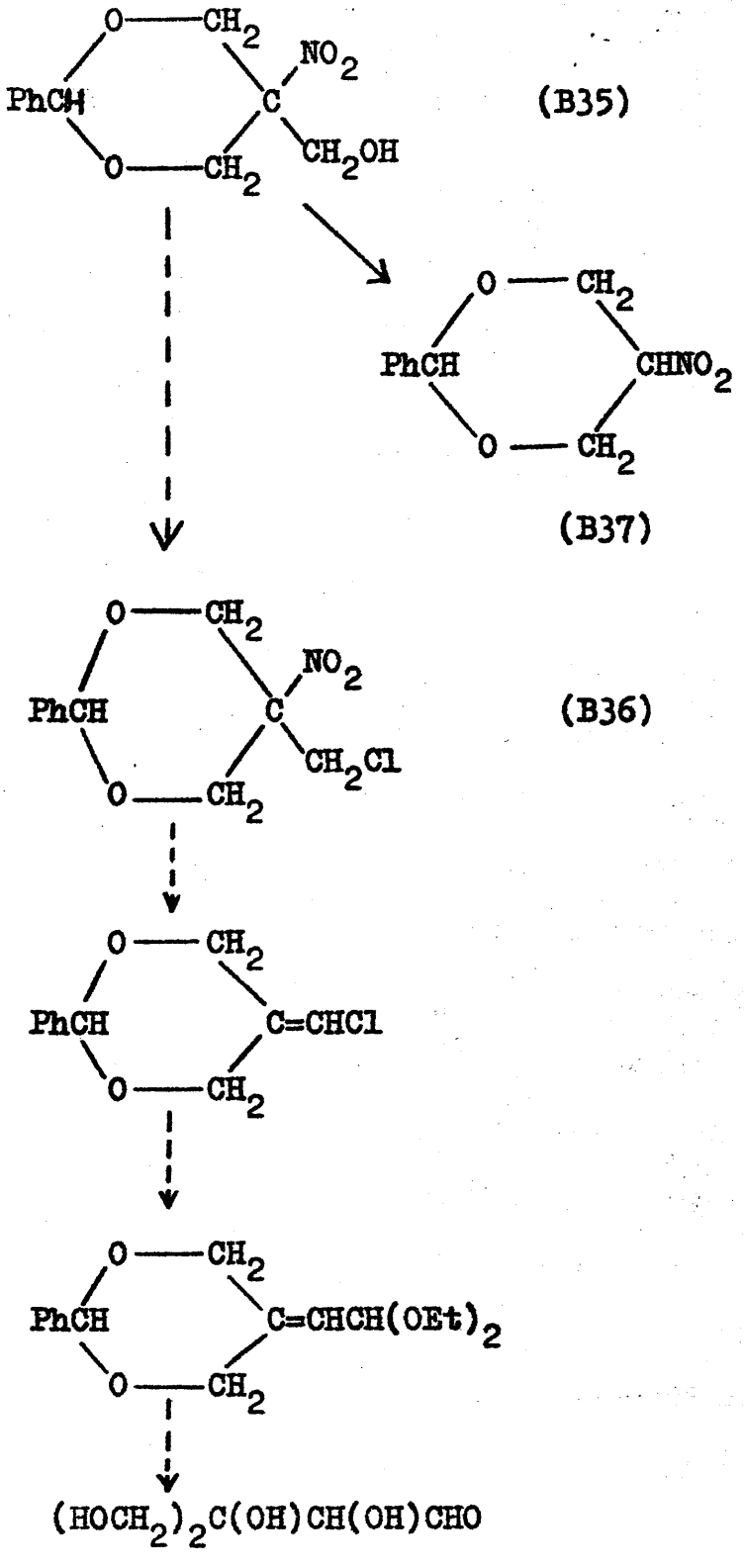
By this reaction 1-nitro-1-chloromethyl cyclohexane was converted to chloromethylene cyclohexane in 74% yield.

The applicability of this reaction to the synthesis of branched-chain sugars was considered since the chloro-olefin could be converted to an $\alpha\beta$ - unsaturated acetal by reaction of its lithium derivative with ethyl orthoformate. Hydroxylation



followed by hydrolysis of the protecting groups should then produce a branched-chain sugar.

The compound chosen for this approach to apiose (see Flowsheet No.22) was 2-phenyl-5-nitro-5-hydroxymethyl-1,3-dioxan (B.35), an intermediate in the synthesis of benzylidene dihydroxyacetone. However attempts to prepare 2-phenyl-5-nitro-5-chloromethyl-1,3-dioxan (B.36) from (B.35) by reaction with thionyl chloride in pyridine resulted in the formation of 2-phenyl-5-nitro-1,3-dioxan (B.37) by a retro-aldol reaction. Since chlorination could not be effected directly, attempts were made to prepare the chloro-nitro compound (B.36) by halide exchange reactions/



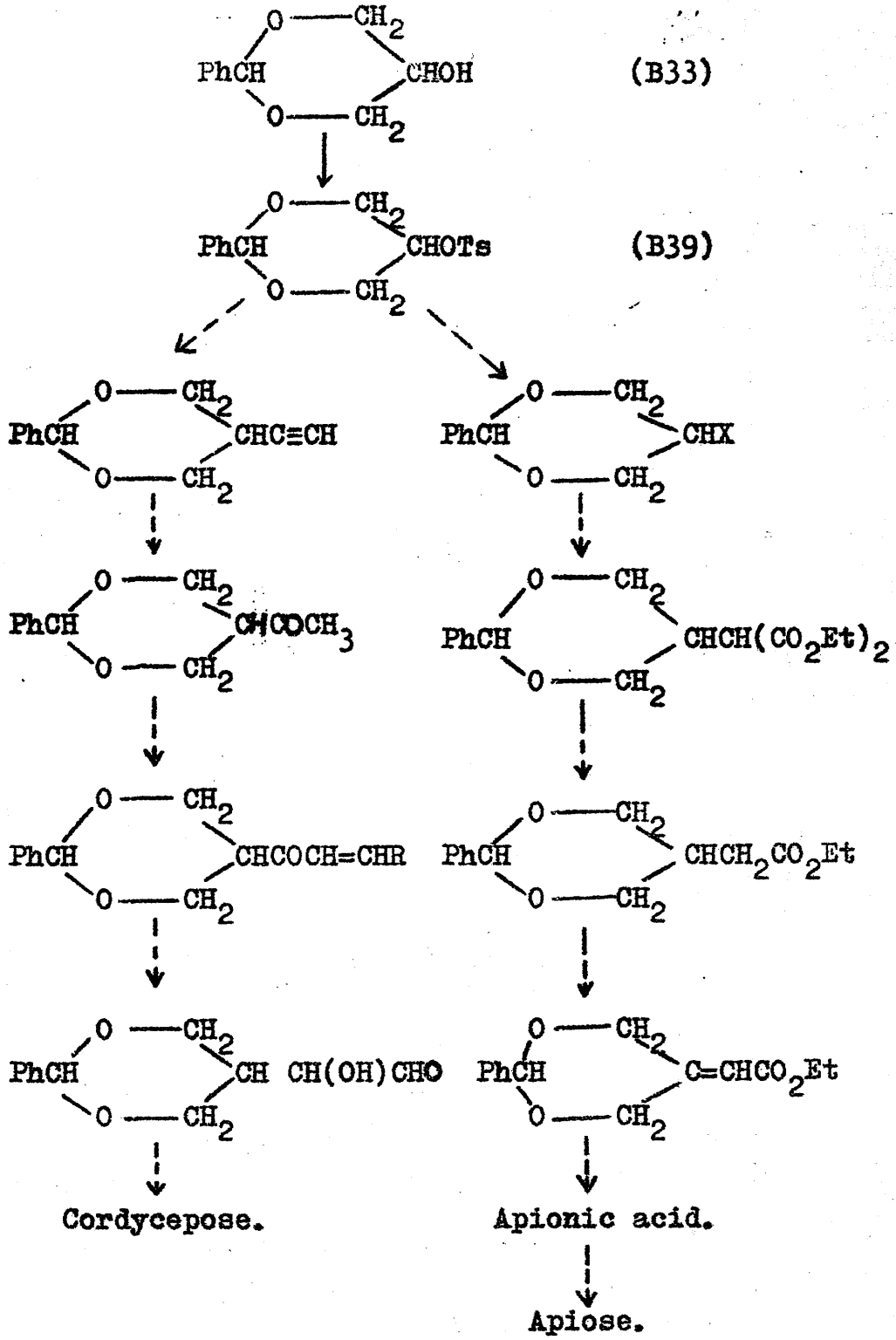
Flowsheet No.22.

reactions with the tosylate (B.38) of 2-phenyl -5-nitro-5-hydroxymethyl-1,3-dioxan. No exchange occurred when lithium chloride in ethanol or sodium iodide in acetone were used.

Since the synthesis of apiose or cordycepose could not be achieved by this attractive route attention was directed to the possibility of utilising 2-phenyl-5-tosyloxy-1,3-dioxan (B.39) as a synthetic intermediate as outlined in Flowsheet No.23. The tosylate, prepared from either cis or trans-1,3-O-benzylideneglycerol (B.33) appeared to consist of only one isomer because of its sharp melting point.

However attempts to condense the tosylate (B.39) with sodium acetylide, or diethyl malonate proved unsuccessful. Attempts to prepare a halide from 2-phenyl-5-tosyloxy-1,3-dioxan by exchange reactions were also abortive, although in one experiment using sodium iodide in acetone at 100° in a sealed tube, the quantitative amount of sodium-ρ-tolnenesulphenate was precipitated but benzaldehyde was the sole organic product isolated.

With the failure of these attempts to synthesise apiose and cordycepose an entirely different approach (see Flowsheet No.24) was made in which/



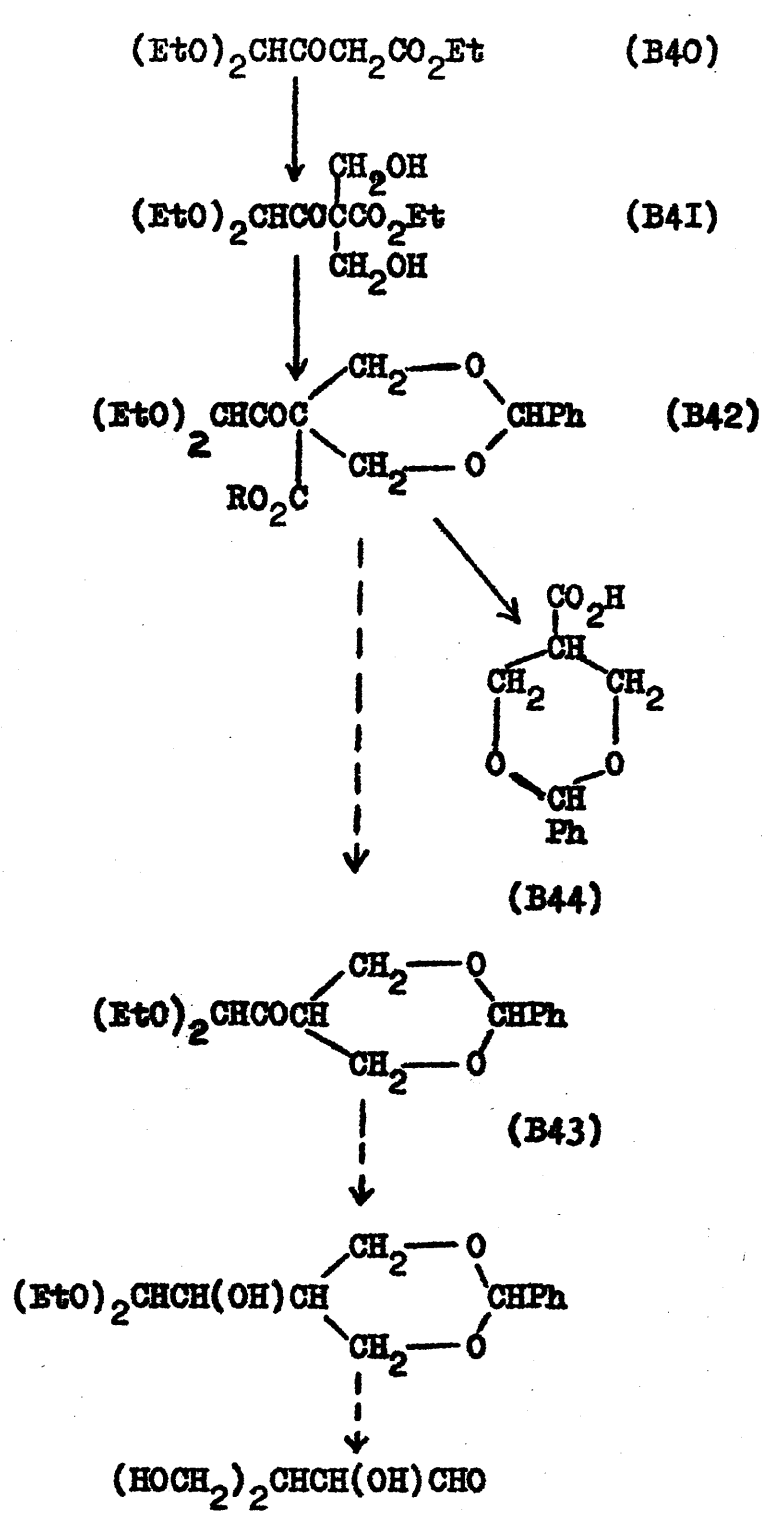
Flowsheet No. 23.

which the aldol reaction was used to introduce branching on a selected compound. The chosen compound was ethyl-γγ-diethoxyacetoacetate (B.40) prepared by the condensation of ethyl diethoxyacetate with ethyl acetate.

With formaldehyde in aqueous solution ethyl-γγ-diethoxyacetoacetate gave ethyl-αα-bishydroxymethyl-γγ-diethoxyacetoacetate (B.41) as a colourless viscous oil. No attempt was made to purify this compound because of the known ready rearrangement of the corresponding derivative of ethyl acetoacetate on distillation.

The diol, therefore, was converted to its benzylidene acetal, 2-phenyl-5-diethoxyacetyl-5-carbethoxy-1,3-dioxan (B.42 R = Et.). On treatment with weak base it was hoped that this compound would undergo "ketonic hydrolysis" with removal of the carbethoxy group to furnish (B.43). However, since it was known that ethyl-αα-diethyl acetoacetate gave α-ethylbutyric acid under these conditions it was not surprising to find that the product obtained from (B.42, R = Et.) was 2-phenyl-5-carboxy-1,3-dioxan (B.44) instead of 2-phenyl-5-diethoxyacetyl-1,3-dioxan (B.43).

In/



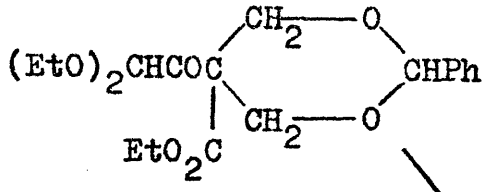
Flowsheet No. 24.

In an effort to overcome this difficulty attempts were made to prepare the corresponding benzyl ester (B.42, R = Ph CH_2) by transesterification of (B.42, R = Et), since Bowman[150] has shown that hydrogenolysis of substituted benzyl acetoacetates gave the corresponding ketones in good yield. Unfortunately, however, transesterification could not be effected in this case.

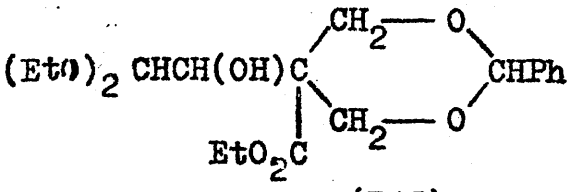
In the light of these investigations it would appear that a synthesis of cordycepose might best be achieved from benzyl-$\gamma\gamma$-diethoxy acetoacetate, which could be converted to (B.42, R = Ph CH_2) and thence to cordycepose by hydrogenolysis, reduction and hydrolysis.

It was of interest to note that 2-phenyl-5-carboxy-1,3-Dioxan was the benzylidene acetal of the saccharinic acid, 3-hydroxy-2-hydroxymethylpropanic acid the synthesis of which has never been achieved[151]. The only other known derivative of this acid is the ethyl ester, the preparation of which has been reported recently by Arens[152].

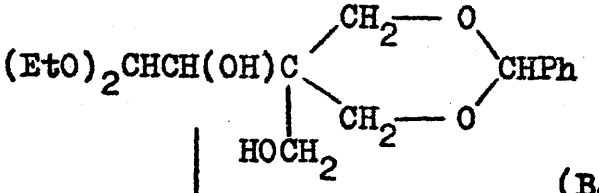
At this point the reduction of 2-phenyl-5-diethoxyacetyl-5-carbethoxy-1,3-dioxan (B.42) with metal hydrides was investigated. With sodium borohydride/



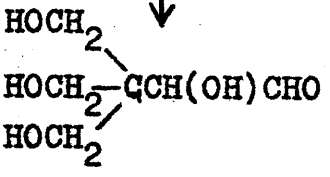
(B42)



(B45)



(B46)



(B47)

Flowsheet No. 25.

borohydride in aqueous methanol or dioxan 2-phenyl-5-(1′-hydroxy-2′,2′-diethoxyethyl)-5-carbethoxy-1,3-dioxan (B.45) was obtained.

When treated with lithium aluminium hydride in ether solution, (B.42) afforded the diol, 2-phenyl-5-(1′-hydroxy-2′,2′-diethoxyethyl)-5-hydroxymethyl-1,3-dioxan (B.46) as a viscous syrup, the infra-red spectrum of which was consistent with this formulation.

Hydrolysis of (B.46) with dilute mineral acid gave a reducing sugar which was considered to be 3-deoxy-3-C-hydroxymethyl-DL-apiose (B.47).

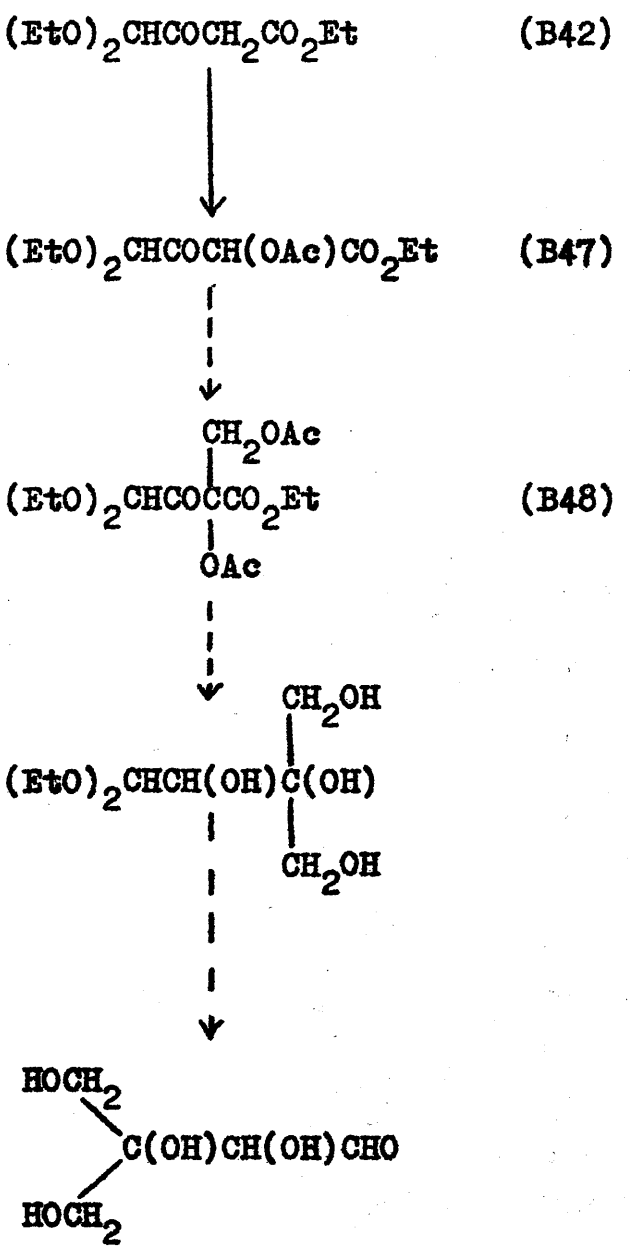
Since removal of the carbethoxy group from (B.42) could not be effected a scheme was devised (see Flowsheet No.26) whereby it might be utilised in a synthesis of apiose.

It was known that lead tetraacetate reacted with active methylene groups with the introduction of an acetoxyl group. Ethyl acetoacetate gave ethyl-$\underline{\alpha}$-acetoxyacetoacetate (B.49) in 30% yield.

$$CH_3CO\,CH(OAc)\,CO_2Et$$

(B.49)

Accordingly ethyl-$\underline{\gamma\gamma}$-diethoxyacetoacetate (B.42) was treated with lead tetraacetate under various conditions/



Flowsheet No. 26.

conditions. Ethyl-α-acetoxy-γγ-diethoxyacetate (B.47) was obtained, but in low yield. It was hoped that reaction of (B.47) with formaldehyde would produce, after acetylation, ethyl-α-acetoxy-α-acetoxymethyl-γγ-diethoxyacetoacetate (B.48) which on hydride reduction followed by hydrolysis would furnish DL-apiose. However reaction of (B.47) with formaldehyde gave, after acetylation, a mixture of unidentifiable compounds.

With the failure of this approach to the branched-chain sugars apiose and cordycepose a third and final approach, in this case to cordycepose, using the aldol reaction was investigated. This is shown in Flowsheet No.27.

The aim of this approach was to prepare a bis hydroxymethyl derivative of acetone, condensation of which with an aldehyde would produce an αβ-unsaturated ketone which could be elaborated to an α-hydroxyaldehyde by reduction and ozonolysis.

Acetone itself could not be used as the starting material for this scheme since it was known that reaction of acetone with formaldehyde could not be stopped after the introduction of two hydroxymethyl/

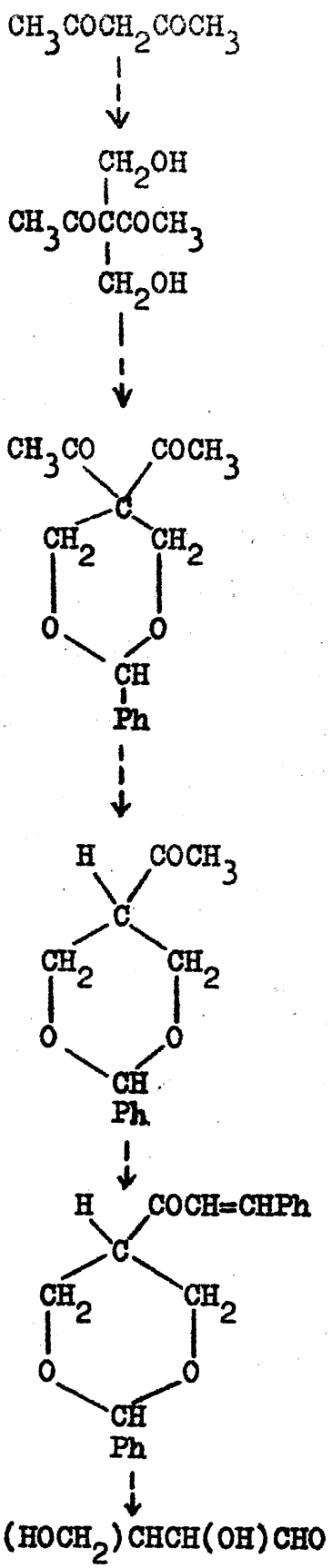
methyl groups[72], the product being the trighydroxy-methyl derivative (B.50). Likewise acetaldehyde gave

$(HOCH_2)_3COCH_3$ (B50.) $(HOCH_2)_3CCHO$ (B51)

pentaerythrose (B.51)[153].

Accordingly acetylacetone (B.52) was chosen as starting material. This was reacted with two moles of formaldehyde in very dilute aqueous base. The product, a viscous syrup, was converted directly into its benzylidene acetal, but the structure of this compound could not be established. The infra-red spectrum showed that the compound was a non-enolic ketone and the presence of benzenoid absorption indicated that a benzylidene acetal had been formed. These conclusions were confirmed chemically by the non-formation of a copper enolate and by the fact that benzaldehyde was liberated on treatment with dilute acid.

The analytical data indicated an empirical formula $(C_8H_{10}O_3)_n$; the analytical data on the semicarbazone derivative indicated that the compound was a diketone since the derivative analysed for a bis semicarbazone of $(C_8H_{10}O_3)_n$: The structures of these/



Flowsheet No.27.

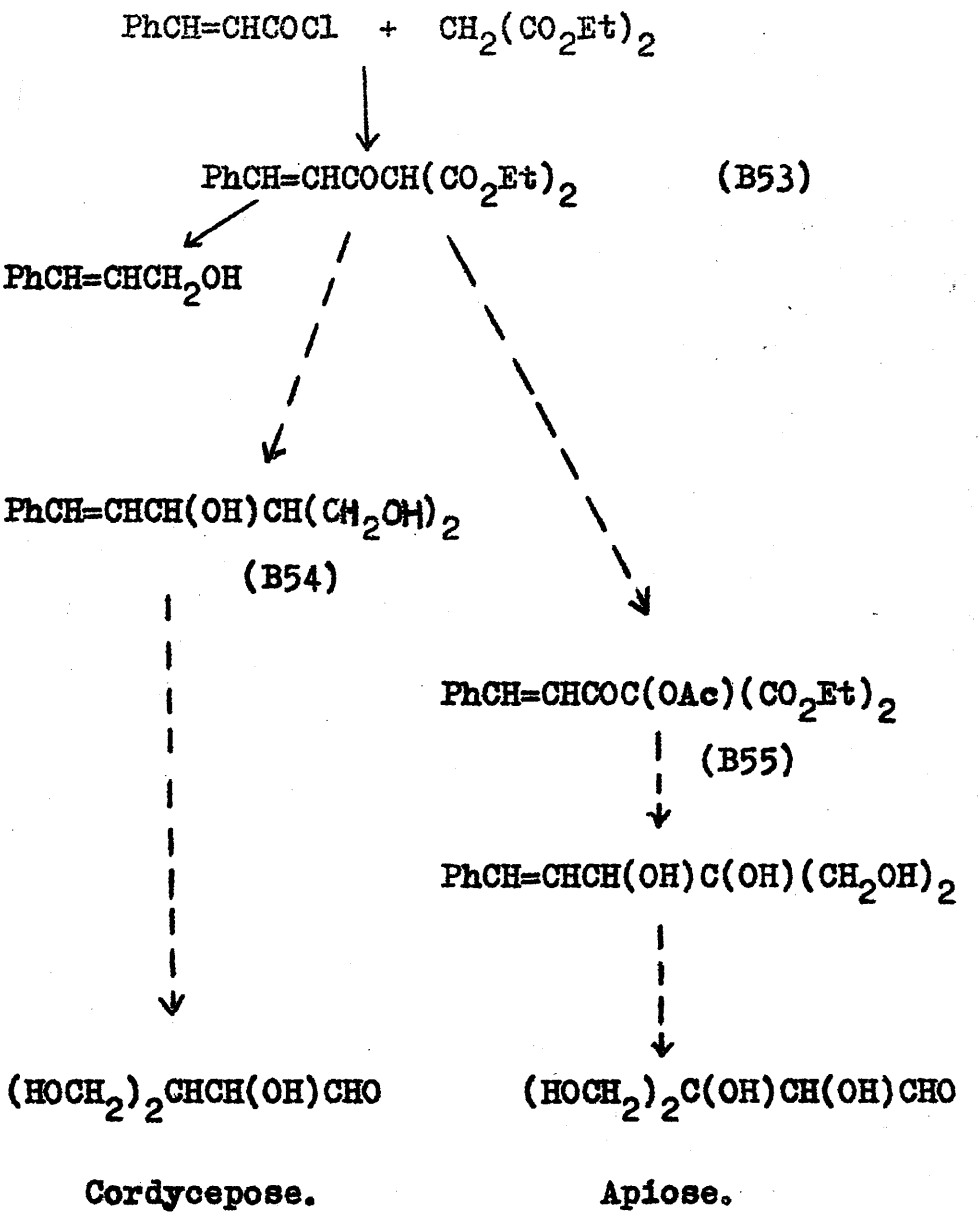
these compounds are under investigation.

Finally, an approach was made to the synthesis of cordycepose using a keto-diester of the type R CO CH $(CO_2Et)_2$. If R is a grouping readily convertible to an aldehyde but resistant to reduction by lithium aluminium hydride, it would appear that complete reduction of this keto-diester with the latter reagent should give a simple derivative of cordycepose.

Accordingly cinnamoyl malonic ester (B.53) the double bond of which would provide the aldehyde function of the sugar, was reduced with lithium aluminium hydride. The product was an intractable gum.

The complexity found in the hydride reduction of β -keto esters has been observed in simpler cases. Thus Dreiding and Hartman[154] reported that 2-carbethoxy cyclohexanone, on hydride reduction, gave a mixture of 2-methylenecyclohexanol, 1-hydroxymethyl cyclohexene and 2-hydroxymethylcyclo hexanol.

With sodium borohydride, even in buffered solution, it was found that cleavage of the molecule occurred/



Flowsheet No.28.

occurred; the products isolated were cimmamoyl alcohol and diethyl malonate.

An attempt was also made to utilise cinnamoylmalonic ester in a synthesis of apiose. Since non-enolic β-keto esters are reduced normally by lithium aluminium hydride it was the intention, as shown in Flowsheet No.28, to replace the active hydrogen atom of cinnamoyl malonic ester by acetoxyl by reaction with lead tetraacetate. The product (B.55) which would have been non-enolic might possibly have afforded DL-apiose by the outlined route. However, reaction of cinnamoyl malonic ester with lead tetraacetate gave us identifiable product.

EXPERIMENTAL.

All infra-red spectra were measured as liquid films unless otherwise specified.

1,1-Diethoxy-2-methoxycarbonylaminoethane (B.20).

To a vigorously stirred solution of aminoacetal (13·0 g.) in ether (150 ml.) at 0°, methyl chloroformate (10 g.) and a solution of sodium hydroxide (4 g.) in water (40 ml.) were added dropwise simultaneously. The ether phase was separated and the aqueous phase was ether extracted. The combined extracts were dried (K_2CO_3) and evaporated. Distillation of the residual oil gave 1,1-diethoxy-2-methoxycarbonylaminoethane (11·9 g.) b.p. 131-132°/20 m.m. n_d^{25} 1·4320.

(Found: C, 48·76; H, 8·13. $C_8H_{17}NO_4$ requires C, 50·25; H, 8·96%)

$\upsilon_{max.}^{cm^{-1}}$ 3410(s) 1730(s) 1550(s) 1200-1000(br.s)

The corresponding 2,4-dinitrophenylhydrazone, golden-yellow needles from ethanol had m.p. 172-173°.

(Found: C, 40·36; H, 3·39 : $C_{10}H_{11}N_5O_6$ requires C, 40·41; H, 3·73%).

N-Nitroso-1,1-diethoxy-2-methoxycarbonylaminoethane(B.21)

(a) Attempted preparation using nitrous acid.

To a mixture of 1,1-diethoxy-2-methoxycarbonylamino ethane (10 g.), sodium nitrite (60 g.), crushed ice (10 g.) and water (80 ml.) covered with ether/

ether (30 ml.) at 0°, a cold solution of conc. nitric acid (20 ml.) in water (30 ml.) was added slowly from a dropping funnel, the end of which was immersed in the aqueous phase. After the addition was complete, the mixture was stirred for a further 20 minutes, after which the ether layer was separated and the aqueous phase extracted with ether. The combined ether extracts were washed with cold sodium bicarbonate solution, dried (Na_2SO_4) and evaporated to a pink coloured liquid.

The infra-red spectrum of the crude material showed that no N-nitrosation had occurred.

Distillation gave unchanged urethane (8·5 g.) as the sole product.

(b) The above reaction, repeated at 14° gave unchanged urethane as sole product.

(c) Preparation using nitrosyl chloride as nitrosating agent:

Nitrosyl chloride (4·3 g.) in acetic anhydride (5.0 ml.) was added to a solution of 1,1-diethoxy-2-methoxycarbonylaminoethane (1 g.) in pyridine (5 ml.) at 0° and the mixture allowed to stand/

stand for 45 minutes. The mixture was poured into ice (20 g.) and extracted with ether. The combined extracts on drying (K_2CO_3) and evaporation afforded a brown oil (0·8 g.) which decomposed on distillation.

$\upsilon_{max.}^{cm^{-1}}$ 1730(s) 1490(s) 1200-1000 (br.s.).

Absence of absorption at 3410 and 1550 cm^{-1}.

Diazoacetaldehyde diethyl acetal. (B.22)

N-Nitroso-1,1-diethoxy-2-methoxycarbonyl-aminoethane (0·65 g.) was added to a mixture of potassium hydroxide (4 g.) water (10 ml.) and ether (20 ml.) and the mixture allowed to stand at room temperature for 30 minutes with occasional shaking. The yellow ether layer was removed and dried (KOH). Evaporation at 20° gave the diazoacetal (0·32 g.) as a yellow oil.

$\upsilon_{max.}^{cm^{-1}}$ 2150(s), 1200-1000 (br.s.).

Propan-2-one1,3-diol diacetate[144] (B.23) (Diacetoxy acetone).

This was prepared (as described by Weygand) by the action of potassium acetate in acetic acid on 1,3-dichloropropan-2-one. The compound obtained in 20% yield had m.p. 47-48° (Lit. m.p. 47°).

Attempted/

Attempted preparation of 1,1-diethoxy-2,3-epoxy-4-acetoxymethyl butan-4-ol acetate (B.24)

a) Propan-2-on-1,3-diol diacetate (0·75 g.) in dry ethanol (20 ml.) containing dry potassium carbonate (1 g.) was treated dropwise with the nitrosourethane (B.21) (1·1 g.). There was no apparent evolution of nitrogen and after 24 hours the solution was dark brown in colour. The solution was poured into water and ether extracted. The combined, dried extracts on evaporation gave a dark brown resinous material from which no pure compound was isolated.

b) To a solution of propan-2-onc-1,3-diol diacetate (0·46 g.) in absolute chloroform (20 ml.) containing dry methanol (2 ml.) a solution of diazoacetaldehyde diethyl acetal (from 4·5 g. (B.21)) in chloroform (7 ml.) was added. The mixture was allowed to stand at room temperature for 24 days. Removal of most of the chloroform and addition of petroleum ether (40-60°) gave diacetoxyacetone (0·38 g.) m.p. and mixed m.p. 46-47°. No other product was isolated.

c) Propan-2-one-1,3-diol diacetate (2 g.), diazoacetaldehyde diethyl acetal (4.3 g.) and copper powder (0·3)/

(0.3 g.) in carbon tetrachloride (20 ml.) were heated under reflux in an atmosphere of nitrogen for 8 hours. The solution was filtered and evaporated to a dark brown resinous material from which no pure compound was isolated.

Condensation of propan-2-one-1,3-diol diacetate with ethyl diazoacetate. Ethyl-3-acetoxymethyl-4-acetoxybut-2-enoate (B.30).

Propan-2-one-1,3-diol diacetate (2 g.), ethyl diazoacetate (1·40 g.) and copper powder (0·3 g.) in carbon tetrachloride (20 ml.) were heated under reflux in an atmosphere of hitrogen for 8 hours. Filtration, evaporation of solvent and distillation of the residual liquid gave a colourless liquid (0·6 g.) b.p. 126-127°/18 m.m. n_d^{20} 1.4476. (Found: C, 54·24; H, 6·36. $C_{11}H_{16}O_6$ requires C, 54·09 : H, 6·60%).

$\upsilon_{max.}^{cm^{-1}}$ 1735(s), 1625(s), 1240(s).

λ max. 210 mμ., (ε, 11,000)

Microhydrogenation revealed the presence of one double bond.

Attempted/

Attempted preparation of ethyl-3-acetoxymethyl-4-acetoxy but-2-enoate (B.30).

To a mixture of propan-2-one-1,3-diol diacetate (3·5 g.) and freshly activated zinc wool (1·32 g.) in benzene (10 ml.) under nitrogen, a solution of ethylbromoacetate (3·4 g.) in benzene (5 ml.) was added with stirring. The mixture was heated under reflux for 48 hours, cooled and poured on to a mixture of ice and dilute acetic acid. The solution was extracted with ether and the combined extracts after being washed with cold dilute sodium bicarbonate solution and water were dried and evaporated to a brown oil. Distillation gave unchanged ethyl bromoacetate (1.4 g.) and propan-2-one-1,3-diol diacetate (0·85 g.) b.p. 110-130/0·1 m.m. which solidified on standing.

2-Nitro-2-hydroxymethyl-propane-1,3-diol[155].

Prepared by the condensation of formaldehyde with nitromethane according to the method of Schmidt and Wilkendorf, this compound had m.p. 157-158°.

2-Phenyl/

2-Phenyl-5-nitro-5-hydroxymethyl-1,3-dioxan[156](B.35)

Prepared according to the method of Scattergood and Maclean, this compound had m.p. 126-127°.

2-Phenyl-5-amino-5-hydroxymethyl-1,3-dioxan[146].

Prepared according to the method of Marei and Raphael, this compound was obtained as colourless needles, m.p. 114-115° from ethyl acetate.

2-Phenyl-5-keto-1,3-dioxan[146] (B.32).

Prepared according to the method of Marei and Raphael, this compound was obtained as an unstable solid, m.p. 69-71° υ max 1751 cm^{-1} ($CHCl_3$ soln)

2,4-Dinitrophenylhydrazone m.p. 174-175°

Semicarbazone m.p. 214-215°.

Attempted preparation of 2-phenyl-5-hydroxy-5-ethoxy ethynyl-1,3-dioxan (B.34).

A) To a solution of ethoxyethynyl magnesium bromide[67] (from magnesium (0.187 g.), ethyl bromide (2.4 g.) and ethoxyacetylene (0.54 g.)) in tetrahydrofuran (10 ml.) under nitrogen at 0°, a solution of 2-phenyl/

phenyl-5-keto-1,3-dioxan (1·37 g.) in tetrahydrofuran (10 ml.) was added during 30 minutes. After addition was complete the mixture was heated under reflux for 4 hours. To the ice-cold solution saturated ammonium chloride solution was added and after stirring for one hour the mixture was extracted with ether. The combined extracts were dried and evaporated to a brown oil (0·82 g.) from which no pure compound was obtained either by distillation or chromatography.

B) The above experiment was repeated using a five-fold excess of ethoxyethynyl magnesium bromide and a reaction time of seven hours. No pure compound was isolated.

1,3-O-Benzylidene glycerol[147] (B.33).

Benzaldehyde (200 g.), glycerol (220 g.) and concentrated sulphuric acid (0·5 ml.) was heated at 95° while a current of air was blown through the mixture. Benzene (275 ml.) was added and the water of condensation removed as its azeotrope with benzene. The benzene solution was washed with aqueous ammonia/

ammonia solution, dried and evaporated to a thick yellow oil which slowly crystallised.

Chromatography on alumina gave the cis isomer m.p. 83-84° followed by the trans isomer m.p. 64·5-65·5°. ¥

Attempted preparation of 2-phenyl-5-keto-1,3-dioxan (B.34)

a) To a solution of cis-1,3-O-benzylidene glycerol (1·8 g.) in pyridine (5 ml.), a solution of the chromium trioxide-pyridine complex (from chromium trioxide 1·4 g.)), in pyridine (5 ml.) was added and the mixture set aside for sixty hours. The mixture was diluted with water and extracted with ether. The combined extracts were dried and evaporated to give unchanged benzylidene glycerol (1·3 g.) m.p. 83-84° from methanol.

Footnote:

¥ This "trans" isomer has been shown to be a cis-trans mixture[181].

b) /

b) 1,3-O-benzylidene glycerol (2·0 g.) in methylene chloride (100 ml.) was treated with active manganese dioxide (40 g.) and the mixture shaken at room temperature for 48 hours. Filtration and evaporation of solvent gave unchanged benzylidene glycerol (2·0 g.) m.p. 83-84°.

1,3-O-Benzylidene-2-O-tosyl glycerol (B.39)

Prepared by the reaction of p-toluene sulphonyl chloride with either cis or trans 1,3-O-benzylidene glycerol, the tosylate was obtained as prisms m.p. 124-125° from methanol.
(Found: C, 61·24; H, 5·53. Calc. for $C_{17}H_{18}SO_5$, C, 61·07: H, 5·43%).

Attempted condensation of 1,3-O-benzylidene-2-O-tosyl-glycerol with diethyl malonate.

a) To a solution of sodio diethyl malonate (from diethyl malonate (1·6 g.)) in ethanol (50 ml.), 1,3-O-benzylidene-2-O-tosyl glycerol (3·33 g.) was added and the mixture refluxed for five hours. The cooled solution was poured into water and extracted with ether. The combined dry extracts on evaporation gave/

gave a solid mass which on trituration with methanol afforded unchanged 1,3-O-benzylidene-2-O-tosyl-glycerol (2·9 g.) m.p. 124-125°.

Attempted preparation of 2-phenyl-5-iodo-1,3-dioxan

a) A mixture of 1,3-O-benzylidene-2-O-tosyl glycerol (1·0 g.) and sodium iodide (3·0 g.) in acetone (75 ml.) was refluxed for twentyfour hours.

The solution on filtration and evaporation gave unchanged tosylate (0·95 g.) m.p. 124-125°.

b) A mixture of tosylate (1·0 g.) and sodium iodide (0·6 g.) in acetone (20 ml.) was heated in a sealed tube at 100° for two hours. The cooled, dark solution was filtered ~~and~~ from the precipitated sodium-p-toluene sulphonate (0·503 g. theoretical for complete replacement 0·545 g.).

The filtrate was washed with sodium thiosulphate solution and sodium bicarbonate solution and dried. The residual brown oil obtained on evaporation gave only benzaldehyde on distillation. Much polymeric material remained.

c) Diethyl malonate (1·60 g.) was added to a suspension of sodium hydride (0·24 g.) in dry tetrahydrofuran (20 ml.)/

(20 ml.) under nitrogen. The mixture was refluxed for one hour, cooled and 1,3-O-benzylidene-2-O-tosyl glycerol (3·34 g.) in tetrahydrofuran (10 ml.) added. The mixture was refluxed for twentyseven hours then worked up as in (a). The tosylate (3.2g.) was recovered unchanged.

d) As in (c) but mixture heated in an autoclave at 100° for twentyfour hours. The tosylate (3.14 g.) was recovered.

Attempted preparation of 2-phenyl-5-ethynyl-1,3-dioxan.

To a solution of lithium acetylide (from lithium 1·5 g.) in dry dioxan (20 ml.) under nitrogen, 1,3-O-benzylidene-2-O-tosyl glycerol (3·34 g.) in dioxan (10 ml.) was added and the solution refluxed for fortyeight hours and cooled. The solution was poured into water and extracted with ether. The dried extracts on evaporation gave unchanged tosylate (3·25 g.) m.p. 124-125°.

2-Phenyl-5-nitro-5-tosyloxymethyl-1,3-dioxan (B.38).

Obtained as colourless needles, m.p. 143-144° (from/

(from methanol-ethylacetate) by reaction of p-toluene sulphonyl chloride with 2-phenyl-5-nitro-5-hydroxymethyl-1,3-dioxan in pyridine.
(Found: C, 55·24; H, 4·57, $C_{18}H_{19}NSO_7$ requires C, 54·96; H, 4·87%).

Attempted preparation of 2-phenyl-5-nitro-5-chloromethyl-1,3-dioxan (B.36)

a) Thionyl chloride (13·0 g.) in carbon tetrachloride (20 ml.) was added slowly to a stirred solution of 2-phenyl-5-nitro-5-hydroxymethyl-1,3-dioxan (23·9 g.) and pyridine (7·9 g.) in carbon tetrachloride (50 ml.). at 5%. After addition was complete, the mixture was stirred for a further hour after which the solvent was removed under reduced pressure. The residual oil was heated at 95° under 30 m.m. pressure for one hour, then taken up in chloroform (100 ml.) and washed with water and dried. On removal of the solvent a brown solid was obtained. Crystallisation from benzene-petroleum ether (60-80 fraction) gave colourless needles m.p. 126-127° underpressed on admixture with 2-phenyl-5-nitro-1,3-dioxan (prepared by demethylolation of 2-phenyl-5-nitro-5-hydroxy-methyl-1,3-dioxan with sodium methoxide in benzene).

b) /

b) Using the above procedure but with reverse addition also resulted in dealdolisation

c) A solution of 2-phenyl-5-nitro-5-tosyloxymethyl-1,3-dioxan (0·5 g.) in ethanol (20 ml.) containing lithium chloride (1·0 g.) was refluxed for four hours, the ethanol removed by distillation and the residue extracted with ether. Removal of the solvent gave unchanged nitrotosylate (0·47 g.).

d) With sodium iodide in acetone and a ten hour reflux period, no exchange took place.

Ethyl-γγ-diethoxyacetoacetate (B.40).

This was prepared as described by Royals and Robinson[157] by the condensation of ethyl diethoxyacetate and ethyl acetate. The product had b.p. 74-75° / 0·4 m.m. n_D^{25} 1·4259.

Ethyl-2,2-bishydroxymethyl-4,4-diethoxy acetoacetate (B.41)

To a solution of ethyl-γγ-diethoxy acetoacetate (10 g.) in distilled water (70 ml.) containing potassium carbonate (2 g.) at 0°, formaldehyde (2·9 g. ; 1 g. 40% Soln.) was added dropwise/

dropwise with occasional shaking until the solution became homogeneous. (20 min). The solution was extracted with ether and the combined dry extracts were evaporated at 30° to a colourless viscous liquid (10·2 g.).

Distillation was not attempted because of the known rearrangement of the corresponding derivative of ethyl acetoacetate.

$\upsilon_{max.}^{cm^{-1}}$ 3300(s) 1735(s) 1705(s) 1050(s)

2-Phenyl-5-carbethoxy-5-diethoxyacetyl-1,3-dioxan (A.42)

A Mixture of ethyl-2,2-bishydroxymethyl-4,4-diethoxy acetoacetate (2·5 g.), redistilled benzaldehyde (1·5 ml.) and p-toluenesulphonic acid (20 mg.) in dry benzene (50 ml.) was heated under reflux for 12 hours, the water liberated being removed as its benzene azeotrope. The cooled solution was washed with sodium bicarbonate solution and water, dried and evaporated to an orange coloured viscous liquid.

Distillation gave 2-phenyl-5-carbethoxy-5-diethoxyacetyl-1,3-dioxan (2·41 g.) b.p. 168/170°/0·02 mm. n_d^{22} 1·4909. On standing, the oil gradually solidified. The solid isomer was removed by filtration/

filtration. Crystallisation from light petroleum (40-60°) gave the above compound a prisms m.p.75-77°.

(Found; C, 62·00; H, 7·13. $C_{19}H_{26}O_7$ requires C, 62·28; H, 7·15%)

$\nu_{max.}^{cm^{-1}}$ (NUJOL) 1735(s) 1705(s) 1240(s) 760(s) 710(s).

The remainder of the oil solidified gradually giving the same compound (2·15 g.) m.p. 75-77°.

Action of 5% NaOH on ethyl-2,2-bishydroxymethyl-4,4-diethoxyacetoacetate.

The dihydroxyketo ester (3 g.) in aqueous sodium hydroxide solution (100 ml. of 5% soln) was agitated at room temperature for 30 minutes. The solution was neutralised with cold sulphuric acid and extracted with ether. The combined extracts were dried and evaporated to a dark brown oil (1·1 g.), which decomposed on distillation at 0·001 m.m.

Attempted/

Attempted preparation of 2-phenyl-5-diethoxyacetyl-1,3-dioxan (B.43).

a) **2-Phenyl-5-carboxy-1,3-dioxan (B.44).**

2-Phenyl-5-carbethoxy-5-diethoxyacetyl-1,3-dioxan (2 g.) in sodium hydroxide solution (100 ml. of 5% soln.) was stirred at room temperature for 8 hours by which time the solution was homogeneous. The solution was neutralised with dilute sulphuric acid and extracted with ether. The dried extracts on evaporation gave 2-phenyl-5-carboxy-1,3-dioxan (1·21 g.). Crystallisation from benzene gave the acid a colourless plates m.p. 161-163°.

(Found; C, 63·98; H, 5·70. $C_{11}H_{12}O_4$ requires C, 63·54; H, 5·81%)

$\nu_{max.}^{cm^{-1}}$ (NUJOL) 170(s) 750(s) 700(s)

b) Using 1% sodium hydroxide solution for the hydrolysis 2-phenyl-5-carboxy-1,3-dioxan was obtained as the sole product.

c) 2-Phenyl-5-carbethoxy-5-diethoxyacetyl-1,3-dioxan (1·0 g.) and water (5 ml.) were heated at 170° in a sealed tube for 4 hours. The cooled solution/

solution was extracted with ether and the combined dry extracts were evaporated. Distillation of the residual liquid gave the starting material (0.74 g.) as the sole product.

d) 2-Phenyl-5-carbethoxy-5-diethoxyacetyl-1,3-dioxan (3·66 g., 0·01 mole) and lithium iodide (9·38 g., 0·07 mole) in 2,4,6-collidine (50 ml.) were heated under reflux for 6 hours. The cooled solution was poured into water and the mixture was extracted with ether. The combined ether extracts were washed with sodium bicarbonate solution and dried. Evaporation of the solvent gave a dark brown oil (1·15 g.) which on distillation gave the starting material (0·87 g.).

The sodium bicarbonate washings on acidification with hydrochloric acid and extraction with ether gave 2-phenyl-5-carboxy-1,3-dioxan (0.63 g.) m.p. 161-163°.

Attempted preparation of 2-phenyl-5-diethoxy acetyl-5-benzyloxycarbonyl-1,3-dioxan (B.42, R = $PhCH_2$) by trans esterification.

2-Phenyl-5-diethoxyacetyl-5-carbethoxy-1,3-dioxan/

dioxan (9.6 g.) and benzyl alcohol (4.7 g.) in benzene (100 ml.) containing sodium ethoxide (0.13 g.) was heated under reflux for 10 hours with occasional removal of benzene by distillation to remove any ethanol formed. The cooled solution was washed with water and dried ($MgSO_4$). Evaporation of the solvent followed by distillation of the residual oil gave 2-phenyl-5-diethoxyacetyl-5-carbethoxy-1,3-dioxan (8.9 g.) b.p. 172-174°/0.05 m.m.

2-Phenyl-5-(1'-hydroxy-2',2',-diethoxyethyl)-5-carbethoxy-1,3-dioxan (B.45).

To a solution of 2-phenyl-5-diethoxy acetyl-5-carbethoxy-1,3-dioxan (1.5 g.) in methanol (10 ml.) at 0° a solution of sodium borohydride (3.2 g.) in water (7 ml.) was added slowly with stirring. After 24 hours at room temperature the mixture was extracted with ether. The dried extracts on evaporation gave a colourless liquid (1.41 g.) b.p. 165-168°/0.09 m.m.

n_d^{21} 1-4523 (short path distillation).

(Found; C, 60.85; H, 7.28. $C_{19}H_{28}O_7$ requires C, 61.94; H, 7.66%)

$\upsilon_{max.}^{cm^{-1}}$ /

$\nu_{max.}^{cm^{-1}}$ 3400(s) 1735(s) 1240(s) 1190-980(s)
760(s) 700(s)

2-phenyl-5-(1' -hydroxy-2',2' -diethoxyethyl)-5-hydroxy methyl-1,3-dioxan (B.46)

To a stirred suspension of lithium aluminium hydride (1.1 g.) in ether (20 ml.) at 0° under nitrogen, a solution of 2-phenyl-5-diethoxy acetyl-5-carbethoxy-1,3-dioxan (0.75 g.) in ether (5 ml.) was added dropwise. After addition was complete the mixture was heated under reflux for 4 hours then cooled to -10°. Ethyl acetate (5 ml.) was added followed by cold aqueous ammonium chloride solution. The organic layer was separated and the aqueous phase was extracted with ether. The combined extracts were dried and evaporated to a colourless viscous syrup (0.54 g.). Distillation at 0.001 m.m. resulted in decomposition.

The infra-red spectrum was consistent with the above formulation.

$\nu_{max.}^{cm^{-1}}$ 3400(s), 1200-1000(s) 760(s) 700(s).

3-Deoxy/

3-Deoxy-3-C-hydroxymethyl-DL-apiose (B.47).

2-Phenyl-5-(1'-hydroxy-2',2'-diethoxy ethyl)-5-hydroxymethyl-1,3-dioxan (0.22 g.) in dilute hydrochloric acid (5 ml. 2N) was heated at 100° for one hour. The cooled solution was extracted with ether to remove the benzaldehyde liberated in the hydrolysis. The aqueous solution was neutralised with silver carbonate filtered through charcoal and evaporated to a colourless syrup (0.14 g.) which was considered to be 3-deoxy-3-C-bydroxymethyl-DL-apiose. The substance reduced Fehlings solution and gave a positive silver mirror test.

Ethyl-α-acetoxy-$\gamma\gamma$-diethoxyacetoacetate (B.47).

To a solution of ethyl-$\gamma\gamma$-diethoxy acetoacetate (10 g.) in dry benzene (100 ml.) at 10°, lead tetraacetate (20 g.) was added with stirring over a thirty minute period. After each addition the solution developed a dark yellow colour which gradually faded and lead acetate precipitated. After stirring for one hour the solution was filtered. The combined filtrate and washings were washed with aqueous sodium bicarbonate solution, dried and evaporated to a pale yellow liquid (9.8 g.). Distillation gave starting/

starting material (3.4 g.) and a fraction (4.4 g.) b.p. 88-92°/0.2 m.m. n_d^{20} 1.4378 which was ethyl-α-acetoxy-γγ-diethoxyacetoacetate.

(Found; C, 52.71; H, 7.66. $C_{12}H_{20}O_7$ requires C, 52.16; H, 7.30%)

$\nu_{max.}^{cm^{-1}}$ 1735(s) 1705(s) 1240(s).

Attempted preparation of ethyl-α-acetoxy-α-acetoxy methyl-γγ-diethoxyacetoacetate (B.48).

To a suspension of ethyl-α-acetoxy-γγ-diethoxy acetoacetate (5.0 g.) in water (75 ml.) containing potassium carbonate (0.5 g.) at 5°, formaldehyde (0.6 g., 2 ml. 40° solution) was added and the mixture allowed to stand for 2 hours with occasional shaking. The solution was extracted with ether; the combined extracts were dried and evaporated at 20°. The residual pale yellow oil (4.7 g.) was acetylated (acetic aubydride-pyridine). Distillation of the acetylated material gave the following fractions:-

(1)	b.p. 75-82 / 0.06 m.m.		n_d^{19}	1.4305	0.9 g.
(2)	" 82-86	"	"	1.4341	1.3 g.
(3)	" 86-90	"	"	1.4386	1.1 g.
(4)	" 90-92	"	"	1.4421	0.7 g.

All/

All fractions gave a positive ferric chloride test. Fractions 2 and 3 were combined and fractionally distilled. Fraction 2^1 had b.p. 84-86°/0.06 m.m. n_d^{33} 1.4372 and gave a positive ferric chloride test.

(Found; C, 55.33; H, 8.07. $C_{15}H_{24}O_9$ requires C, 53.25; H, 7.10%)

The composition of this material was unknown but was not the desired compound since it was enolic.

Reaction of acetyl acetone with formaldehyde.

To a suspension of acetyl acetone (100 g.) in water (500 ml.) containing potassium carbonate (3.0 g.) formaldehyde (60 g. ; 180 g. of 40% solution) was added slowly, the temperature of the mixture being kept between 0-5°. After two hours the solution was extracted with ether. The combined dried extracts on evaporation at 30° gave a colourless syrup (114.5 g.) which could not be distilled.

$\nu_{max.}^{cm^{-1}}$ 3400(s) 1700(s) 1050(s).

Benzylidene acetal.

The above oil (104.5 g.) and benzaldehyde (200 g.) in benzene (500 ml.) containing p-toluene sulphonic/

sulphonic acid (1.0 g.) was refluxed for 15 hours, the water of condensation being removed azeotropically. The cooled solution was washed with sodium bicarbonate solution and water, dried, and evaporated to a dark brown oil (297.4 g.). Distillation of a portion (32 g.) of this material gave, after a small foretun of benzaldehyde, a pale yellow oil (6.3 g.) b.p. 132-134°/0.3 m.m. n_D^{24} 1.5400.
A large polymeric residue was left.

(Found; C, 62.41; H, 6.75. $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94%).
The structure of this compound is as yet unknown.

$\upsilon_{max.}^{cm^{-1}}$ 1700(s) 1600(s) 740(s) 690(s).
(The analysis fits an empirical formula $(C_8H_{10}O_3)_n$ which requires C, 62.32; H, 6.54%).

That this compound was a benzylidene acetal was shown by the fact that benzaldehyde-2,4-dinitrophenyl hydrazone m.p. 237° was formed on warming with methanolic 2,4-dinitrophenylhydrazine hydrochloride.

On treatment with semicarbazide acetate in methanol a compound (prisms) m.p. 239-240° from aqueous alcohol was obtained which analysed for a

bis- /

bis-semicarbazone of $(C_8H_{10}O_3)_n$.

(Found; C, 45.26; H, 6.06; N, 31.22. $C_{10}H_{16}N_6O_3$ requires C, 44.77; H, 6.01; N, 31.33%).

Cinnamoyl malonic ester (B.53).

Cinnamoyl malonic ester, b.p. 152-154°/ 5.39×10^{-7} n_D^{21} 1.5910, was prepared in 89% yield by the condensation of cinnamoyl chloride with magnesiomalonic ester.

$\nu_{max.}^{cm^{-1}}$ 1718(s) 1640(s), 756(m), 694(s).

Reaction of cinnamoyl malonic ester with sodium borohydride.

a) Cinnamoyl malonic ester (1.0 g.) in methanol (10 ml.) was treated with a solution of sodium borohydride (0.8 g.) in water (2 ml.), the reaction temperature being kept below 5°. After the initially vigorous reaction had subsided the mixture was allowed to stand at room temperature for twenty four hours. The solution was diluted with water (100 ml.) and extracted with ether. The combined dried extracts on evaporation gave a pale brown oil (0.56 g.). Distillation gave malonic ester (0.15 g.) b.p./

b.p. 90-92°/20 m.m. and a colourless oil (0.38 g.)
b.p. 80°/0.2 m.m. n_d^{22} 1.5771.

$\nu_{max.}^{cm^{-1}}$ 3300(s) 1620(m) 1600(m) 978(s), 740(m) 690(m)

$\lambda_{max.}^{(Etoh)}$ 255 mμ

This compound was shown to be cinnamyl alcohol by the following reactions:-

1) Reaction with bromine in carbon tetrachloride gave a solid which crystallised as colourless needles m.p. 73-74° from benzene. (Dibromocinnamyl alcohol. lit. m.p. 73-74°).

2) Oxidation with manganese dioxide in methylene chloride gave cinnamic aldehyde. The 2,4-dinitrophenyl hydrazone, red plates m.p. 247-248° from acetic acid was identical with an authentic sample.

b) The reaction of cinnamoyl malonic ester with sodium borohydride in methanol was repeated, this time in the presence of glycerol to act as a buffer. On working up in the usual manner diethyl malonate, cinnamyl alcohol and a small amount of cinnamic aldehyde were isolated.

Reaction/

Reaction of cinnamoyl malonic ester with lithium aluminium hydride.

A solution of cinnamoyl malonic ester (12 g.) in tetrahydrofuran (10 ml.) was added to a suspension of lithium aluminium hydride (1.1 g.) in tetrahydrofuran (20 ml.) and the mixture refluxed for ten hours. After cooling to 0^{o}, ethyl acetate (20 ml.) was added dropwise followed by water and ammonium chloride solution. The solution was extracted with ether and the combined extracts were dried and evaporated to a viscous syrup (10.3 g.) from which no identifiable material was isolated.

Reaction of cinnamoyl molonic ester with leadtetra-acetate.

To a solution of cinnamoyl malonic ester (11.6 g.) in benzene (100 ml.) at 40°, lead tetraacetate (17.32 g.) was added in small portions during one hour. After stirring for a further hour a test for residual lead tetraacetate was negative. The mixture was filtered to remove lead acetate and concentrated at 30° to a pale yellow viscous oil (11.7 g.) from which no pure compound could be isolated either by distillation at 10^{-4} m.m. or by chromatography.

PART III

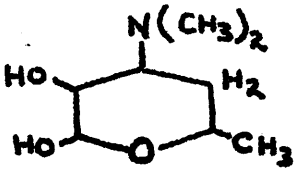
Rhodosamine

HISTORICAL.

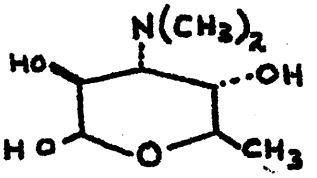
Amino-sugars are not commonly encountered in plant materials although the well known D-glucosamine is found as chitin in some fungal polysaccharides and N-methyl-L-glucosamine[158] has been isolated from streptomycin and hydroxy-streptomycin.

During the past decade, as a result of the search for new antibiotics, amino-sugars of novel structure have been isolated. 3-Amino-3-deoxy-D-ribose has been shown[159] to be part of the molecule of puromycin. D-Gulosamine, identified by synthesis[160] is a component of streptothricin and streptolin B[161]. The antibiotic, kanamycin is composed of residues of 2-deoxystreptamine, 3-amino-3-deoxy-D-glucose and 6-amino-6-deoxy-D-Glucose[162].

From antibiotics elaborated by Streptomycetes a new type of amino-sugar has been recognised which contains a dimethylamino group at $C_{(3)}$. Desosamine (pikrocin) (Cl) has been identified as a constituent of the macrolide antibiotics pikromycin[163], erythromycin[164], narbomycin[165], methymycin[166], neomethymycin[167] and oleandomycin[168].



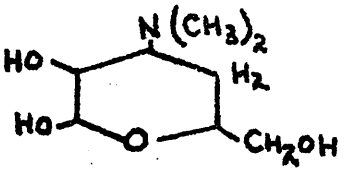
(C1.)



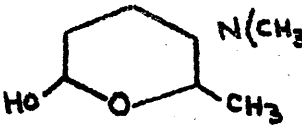
(C2)

From magnamycin, the amino-sugar, mycosamine (C2) has been isolated together with the branched-chain sugar mycarose[169] (B.6).

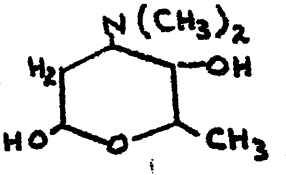
Amosamine (C.3) has been identified as a constituent of the antibiotic, amicetin[170] and the unusual amino-sugar (C.4) has been isolated from the spiramycins A, B and C[171].



(C3)



(C4)



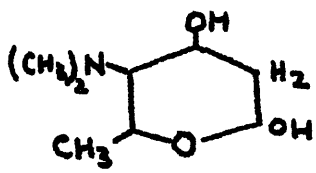
(C5)

Rhodosamine, the constitution of which is considered to be (C.5)[172] is the sugar component of the antibiotic glycosides pyrromycin[173], rutilantin[174], rhodomycin[175] and the cinerubins A and B[176] all of which have been isolated from strains of Streptomycetes and Actinomycetes.

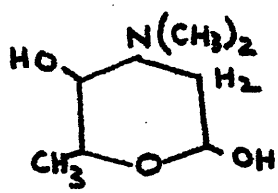
A closely related antibiotic, aklavin, which has very recently been isolated[177] contains a basic sugar which is thought to be isomeric with amosamine and mycaminose.

DISCUSSION.

Since the structure of rhodosamine was not known for certain, a total synthesis of the amino-sugar was undertaken. By analogy, two possible gross structures (neglecting stereochemistry) (C.5) and (C.6) are plausible and the synthetic approach was based on these considerations.



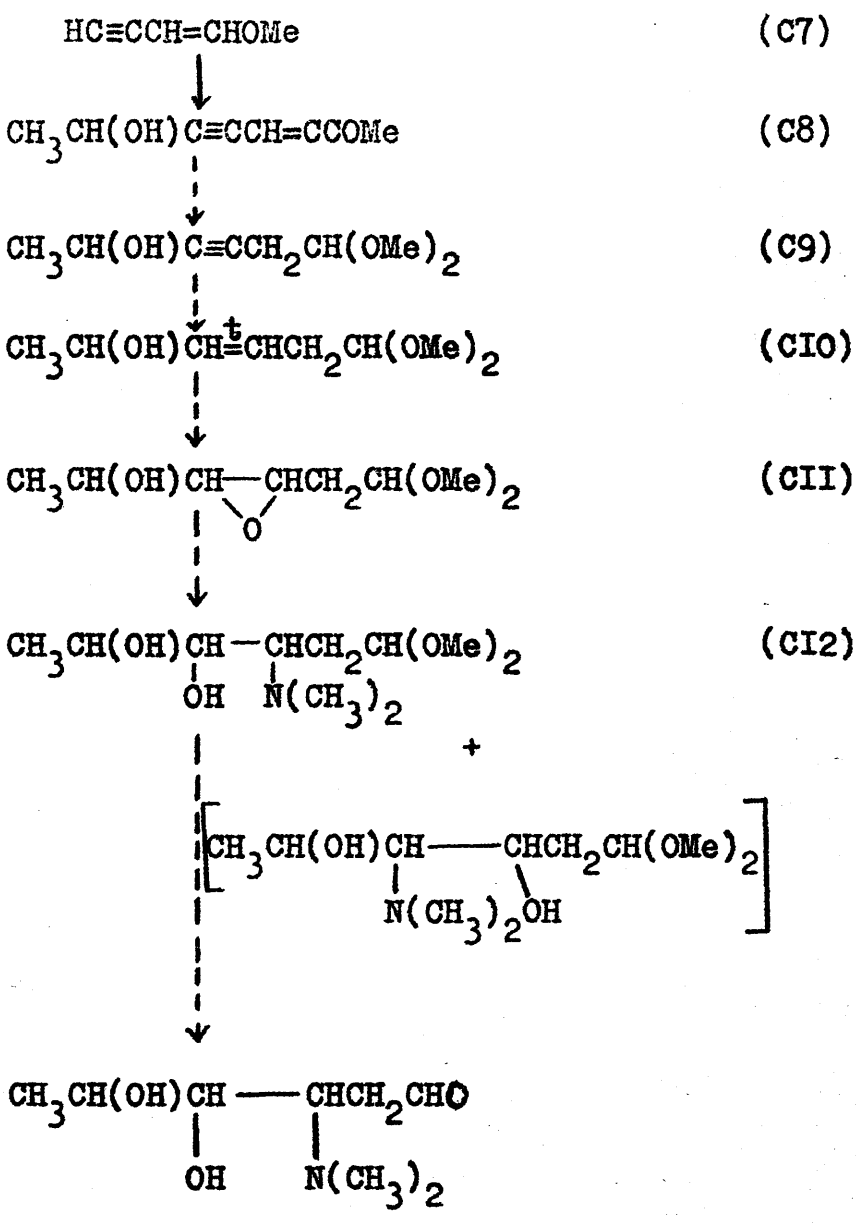
(C6)



(C5)

The first route to rhodosamine (see Flowsheet No.29) had as its goal the synthesis of 1,1-dimethoxy hex-3-en-5-ol, epoxidation of which would give 1,1-dimethoxy-3,4-epoxyhexan-5-ol (C.11). Treatment of (C.11) with dimethylamine would be expected to give the dimethyl acetal of rhodosamine or its isomer.

1-Methoxy-but-1-en-3-yne (C.7) on condensation with acetaldehyde (Grignard reaction) gave 1-methoxyhex-1-en-3-yn-5-ol (C.8) in reasonable yield but attempts to prepare 1,1-dimethoxyhex/



"Rhodosamine"

Flowsheet NO.29.

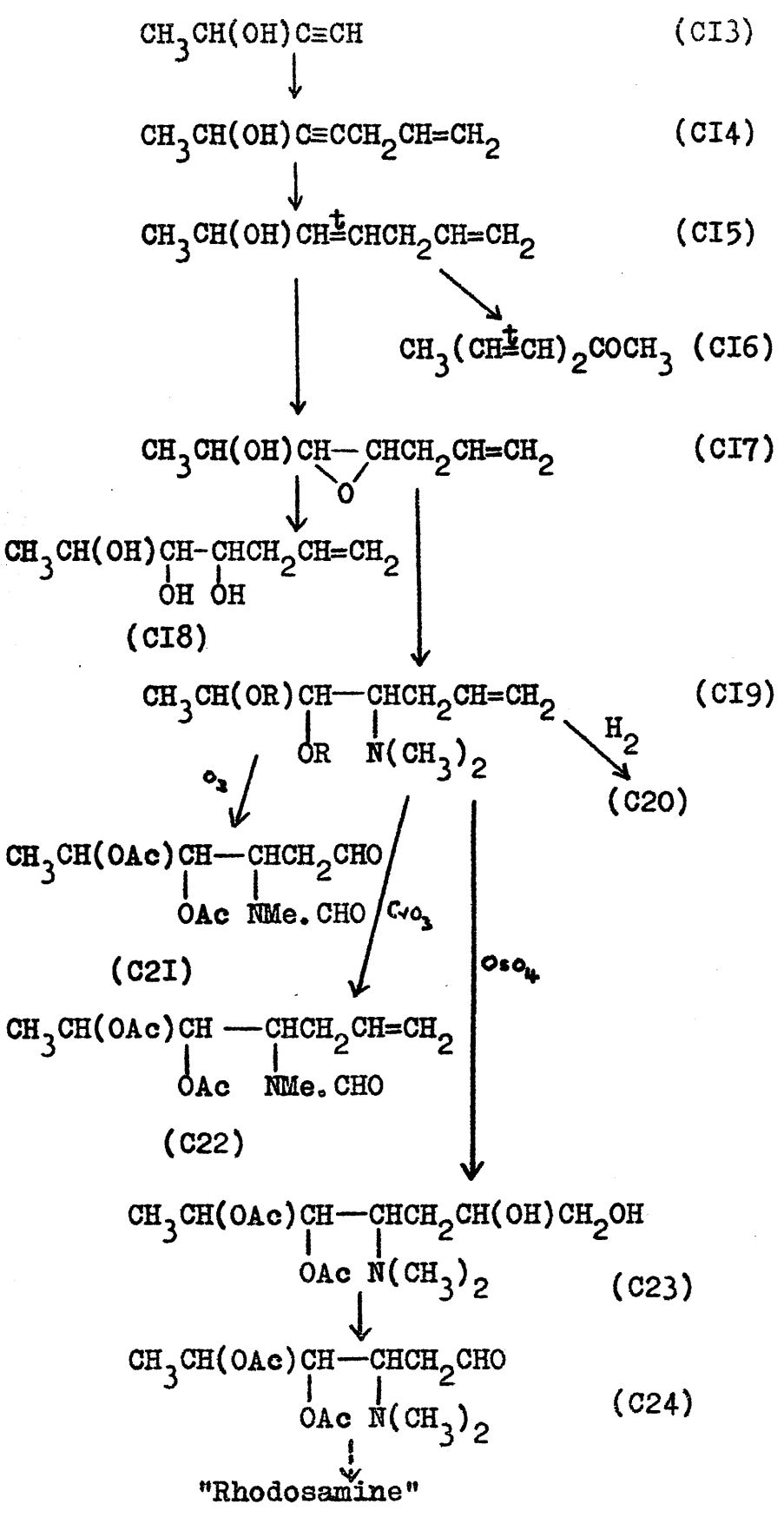
dimethoxyhex-3-yn-5-ol (C.9) from it by addition of methanol across the double bond proved fruitless.

Weygand[91] in his synthesis of 2-deoxy-DL-ribose employed 1,1-dimethoxypent-3-yn-5-ol as starting material and prepared it (see introduction), albeit in low yield, by the reaction of 1-methoxy but-1-en-3-yne with formaldehyde in methanolic potassium hydroxide solution.

The reaction of 1-methoxybut-1-en-3-yne with acetaldehyde, under similar conditions, was not considered since under the strong alkaline conditions of the reaction it seemed most likely that acetaldehyde would undergo self-condensation faster than it would react with the acetylene.

In view of the inability to prepare 1,1-dimethoxyhex-3-yn-5-ol from 1-methoxyhex-1-en-3-yn-5-ol or by the direct condensation of 1-methoxy but-1-en-3-yne with acetaldehyde, attention was focussed on a second route to rhodosamine (see Flowsheet No.30) based on the successful synthesis of 2-deoxy-DL-ribose described in Part I of this Thesis.

The Grignard derivative of but-1-yn-3-ol (C.13) was condensed with allyl bromide in the presence/



Flowsheet NO. 30.

presence of a catalytic amount of cuprous chloride; hept-1-en-4-yn-6-ol (C.14), characterised as its 3,5-dinitrobenzoate, was obtained in high yield.

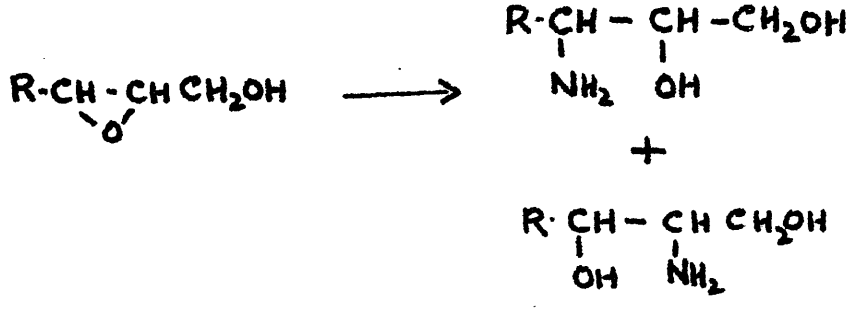
Reduction of hept-1-en-4-yn-6-ol with lithium aluminium hydride in ether solution gave hepta-1,4 (trans)-dien-6-ol (C.15), the structure of which was proved by the fact that it gave a positive iodoform test. Further, oxidation with manganese dioxide gave cratonylidene acetone (C.16). (It was interesting to note that the terminal double bond of (C.15) had moved into conjugation during the oxidation.)

With perbenzoic acid in chloroform solution hepta-1,4(trans)-dien-6-ol was smoothly converted into 4,5-epoxyhept-1-en-6-ol (C.17). That the selective epoxidation had proceeded in this manner was shown by the following degradation. Hydrolysis of the epoxide with dilute acid gave DL-hept-1-en-4,5 (erythro),6-triol (C.18) which on oxidation with sodium metaperiodate gave acetaldehyde and crotonaldehyde (again by bond shift) identified as their 2,4-dinitrophenylhydrazones.

4,5-Epoxyhept-1-en-6-ol (C.17) on

reaction/

reaction with anhydrous dimethylamine in methanol (containing a catalytic amount of perchloric acid) at 80° in an autoclave produced DL-4-N-dimethy laminohept-1-en-5,6-diol (C.19, R = H) in high yield. It was expected that the two possible isomeric dimethylamino diols would be produced in the aminolysis by anology with the reaction of ammonia with α-epoxyalcohols.



However, the product from 4,5-epoxy-hept-1-en-6-ol formed a single picrate in 78% yield and was oxidised rapidly by periodate, liberating acetaldehyde, the dimedone derivative of which was isolated in 89% yield. From these facts it would appear that the reaction had produced only one dimethylamino diol (C.19, R = H).

Further stereoselectivity in the formation and reactions of epoxides have been described/

described by Henbest[178]. It was found that perbenzoic acid oxidised cyclohex-2-enol and its derivatives to cis epoxides whereas the corresponding acetate in which hydrogen bonding in the cis transition state was impossible gave mainly the trans epoxide at a much slower rate. Henbest further showed that violation of the rule of diaxial opening of epoxides occurred in special circumstances, steric and electronic.

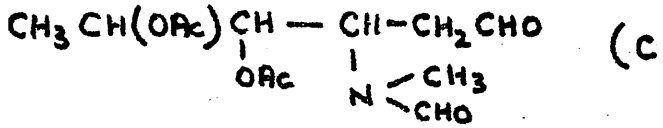
The selective formation of the dimethylamino diol (C.19, R = H) from the epoxide (C.17) could only be explained, in the light of present knowledge, as attack by the bulky dimethylamino reagent from the least hindered side (since ammonia was known to give a mixture of two amino diols).

The transformation of DL-4-N-dimethylaminohept-1-en-5,6-diol to rhodosamine or its isomer necessitated the cleavage of the double bond to produce the aldehyde function. For this purpose the diacetate (C.19, R =Ac), which did not form a picrate, was prepared. Hydrogenation gave DL-4-N-dimethyl aminoheptane-5,6-diol diacetate (C.20) as a pale yellow oil.

The/

The methods available for the conversion of the dimethylaminoheptene (C19) to the amino-sugar were limited because of the presence of the dimethyl amino group which was susceptible to oxidation.

Ozonolysis in methylene chloride at - 60° gave an unstable compound, the infra-red spectrum of which suggested that it had the structure (C21); the absorption at 990 and 910 $c.m.^{-1}$.

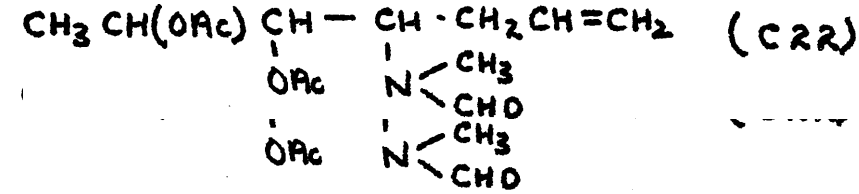


(C 21)

present in DL - 4 - N - dimethylaminohept - 1 - en - 5, 6 - diol diacetate were absent but there now was strong absorption at 1680 cm^{-1} indicative of an amide. When Dl - 4 - N - dimethylaminohept-1-en 5, 6 - diol diacetate was treated with one equivalent of ozone a substance was obtained which showed strong amide absorption at 1680 cm^{-1} and double bond absorption at 3040, 1635, 990 and 910 cm^{-1}. Although purification of this substance could not be achieved because of its instability, it appeared that ozone oxidised the N - methyl group faster that it oxidised the double bond. With the chromium trioxide - pyridine reagent a compound was obtained, the infrared spectrum of/

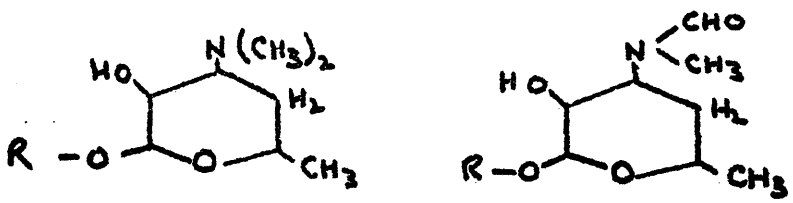
of/

which was identical with that of the pompound obtained from the controlled ozonolysis experiment. The structure was considered to be (C22).



(C22)

The ready formation of an amide from a tertiary amine has been known for some time. Djerassi,[179] in his studies on methymycin, found that ozonolysis or oxidation of the marcrolide with chromium trioxide-pyridine gave rise to an amide in good yield and since the nitrogen function in methymycin was contained in the desosamine moiety, oxidation had produced an N - formyl derivative of desosamine:-



Henbest[180], in a series of papers, studied amine oxidation in detail, and showed that alkyl and dialkyl anilines were oxidised readily by manganese dioxide at room temperature. Three general reactions were discerned:

a) $>N\text{-}CH_3 \longrightarrow >N\text{-}CHO$

b) $>N\cdot CH_2R \longrightarrow >NH + R\cdot CHO$

c) $>N\cdot CH_2CH_2R \longrightarrow [>N\cdot CH=CH\cdot R] \longrightarrow >N\cdot CHO + R\cdot CHO$

Conversion (a) was exemplified by the oxidation of dimethylaniline to N - methyl formanilide in 80% yield. Monomethylaniline was oxidised analogously to formanilide in over 80% yield.

With the Milas reagent, DL - 4 - N - dimethylaminohept - 1 - en - 5, 6 - diol diacetate gave an intractable gum. Since hydrogen peroxide in alcohol solution is just the reagent used for the preparation of N - oxides, it was possible that the failure of this hydroxylation procedure was due to polymerisation of the N - oxide of DL - 4 - N - dimethyl aminohept - 1 - en - 5, 6 - diol diacetate.

However, with osmium tetroxide in ether solution the DL - 4 - N - dimethylaminohept - 1 - en - 5, 6 - diol diacetate (C19, R=Ac) afforded DL - 4 - N - dimethylaminoheptane - 1, 2, 5, 6 - tetrol - 5, 6 - diacetate (C23,) cleavage of which with sodium metaperiodate gave a compound with the gross structure of DL - aldehyde "rhodosamine" diacetate (C24). That this/

this/

compound was in fact a β - dimethylaminoaldehyde was shown by the ready elimination of dimethylamine on treatment with base. The hydrolysis of the diacetate (C24) to the free amino-sugar is at present under investigation.

EXPERIMENTAL.

All infra-red spectra were measured as liquid films unless otherwise specified.

1 - Methoxyhex - 1 - en - 3 - yn - 5 - 01(C8).

1 - Methoxybut - 1 - en - 3 - yne(117g) in dry tetrahydrofuran (200 ml) was added dropwise with stirring to a solution of ethylmagnesium bromide (from magnesium (26g)) in dry tetrahydrofuran (500ml) under nitrogen. After an additional hour of stirring at room temperature, the reaction mixture was cooled(0°) and acetaldehyde (50g) in tetrahydrofuran (100ml) was slowly added. After the addition was complete the mixture was stirred at room temperature for ten hours. Most of the tetrahydrofuran was removed by distillation and replaced by ether. Saturated ammonium chloride solution (300 ml) was added, and the mixture was stirred for a further 3 hours at 0°C. The ether phase was separated and the aqueous phase was extracted with ether. The combined extracts were washed with sodium bicarbonate solution and dried. Evaporation of the solvent and distillation of the residual oil gave - 1 - methoxyhex - 1 - en - 3 - yn - 5 - 01(62g) b.p. 118-119°/ 24 mm. η_D^{20} 1.4991.

$\upsilon_{max}^{cm^{-1}}$ 3400 (s), 3020(ω), 2100 (ω), 1620 (m), 970(s).

Attempted preparation of 1,1-dimethoxyhex - 3 - yn - 5 - ol(C9).

a) 1 - Methoxyhex - 1 - en - 3 - yn - 5 - ol(10g) in dry methanol (100ml) containing sodium methoxide (1.0g) was allowed to stand at room temperature for 24 hours. The solution was neutralised with acetic acid and evaporated. The residual oil on distillation gave unchanged 1 - methoxyhex - 1 - en - 3 - yn - 5 - ol (9.7g.)

b) As in (a) but solution was refluxed for 24 hours. Starting material was recovered unchanged.

c) 1 - MethoxyHex - 1 - en - 3 - yn - 5 - ol (10g) in methanol (100 ml) containing potassium hydroxide (10g) was refluxed for 24 hours. Neutralisation with acetic acid followed by evaporation gave a pale brown oil which on distillation afforded starting material (9.2g).

d) 1 - Methoxyhex - 1 - en - 3 - yn - 5 - ol(7.2g) in dry methanol (100 ml) containing concentrated sulphuric acid (1 ml) was allowed to stand for 24 hours at room temperature. The solution darkened rapidly within one hour. The mixture was neutralised with methanolic sodium methoxide solution and evaporated to a black viscous oil. Distillation gave starting material (1.4g) . Much polymeric/

material remained.

Hept - 1 - en - 4 - yn - 6 - 01 (C14).

To a solution of ethyl magnesium bromide (from magnesium (46g) and ethyl bromide (218g)) in tetrahydrofuran (200 ml) under nitrogen, but - 1 - yn - 3 -01 (65g) was added slowly with vigorous stirring. When addition was complete the mixture was refluxed for 3 hours; cuprous chloride (3g) was added and the mixture allowed to cool to room temperature. Allyl bromide (122g) was added and the mixture was stirred at room temperature for 12 hours followed by a 12 hour period under reflux. Most of the tetrahydrofuran was replaced by ether and the cooled mixture was poured into ice-water containing dilute hydrochloric acid. The mixture was extracted with ether (5 x 200 ml) and the combined extracts after washing with aqueous sodium bicarbonate solution and water, were dried ($MgSO_4$) and evaporated. Distillation of the residual oil gave hept - 1 - en - 4 - yn - 6 - ol (83.6g; 82%), b.p. 74°/ 30 m.m. η_D^{20} 1.4662. (Found: C,71.97; H,8.93. $C_7H_{10}O$ requires C,76.32 H,9.15%) $\upsilon_{max}^{cm^{-1}}$ 3400(S) 3040(M), 2210(W), 1640(M), 990(S) 910(S).

The 3,5 - dinitrobenzoate, colourless needles from benzene - light - petroleum (40-60o) had m.p. 82 - 83°.

(Found: C, 55.30; H, 4.19; N, 9.02, $C_{14}H_{12}N_2O_6$ requires C, 55.26; H.3.98; N, 9.21%)

Hepta - 1, 4 -(trans) - dien - 6 - 01 (C15).

To a stirred suspension of lithuium aluminium hydride (10g) in dry ether (200 ml) under nitrogen, hept 1 - en - 4 - yn - 6 - 01(40g) in dry ether (50 ml) was added at a rate such that gentle reflux was maintained. After addition was complete the mixture was heated under reflux for three hours then cooled to - 10°. Ethyl acetate (5ml) in ether (5ml) was added followed by a 20% solution of aqueous ammonium chloride (150 ml). The mixture was extracted with ether, the combined extracts washed with sodium bicarbonate solution and water and dried ($MgSO_4$). Evaporation of the solvent and distillation of the residual oil gave hepta -1, 4 (trans) - dien - 6 - 01 (39.3g; 97%) b.p. 65 - 66°/50 m.m. η_D^{21} 1.4521.

(Found: C, 74.23; H.10.60. $C_7H_{12}O$ requires C,74.95; H,10.78%)

$\upsilon_{max.}^{cm^{-1}}$ 3400(S) 3040(W), 1640(M), 990(S), 980(S) 910(S).

The product gave a positive iodoform test. Oxidation of hepta - 1, 4 (trans) dien - 6 - 01 with manganese dioxide gave crotonylidene acetone identified as its 2, 4 - dinitrophenylhydrazone m.p. 202 - 203°.

(Found: C, 53.64; H, 4.64; N, 19.36. Calc. for $C_{13}H_{14}N_4O_4$; C, 53.79; H.4.86; N.19.30%)

4, 5 - Epoxyhept - 1 - en - 6 - 01(C17).

Hepta - 1, 4 (trans) - dien - 6 - 01 (14.34g) in chloroform (20 ml) was treated with a solution of perbenzoic acid (17.68g) in chloroform (800 ml) at 0°C. Reaction was complete in 48 hours. Solid calcium hydroxide (50g) was added and the mixture was stirred vigorously until neutral to litmus. The chloroform solution was filtered through anhydrous magnesium sulphate and evaporated. Distillation of the residual oil gave 4, 5 - epoxyhept-1 - en - 6 -01 (13.72g) b.p. 90°/ 20 m.m. η_D^{21} 1.4509.

(Found; C, 62.99; H.8.99; $C_7H_{12}O_2$ requires C, 65.59 H,9.44%) $\upsilon_{max.}^{cm^{-1}}$ 3400(S), 3040(W), 1635(M), 990(S) 910(S), 870(S).

DL - Hept - 1 - en - 4, 5 (erythro) 6 - triol(C18.)

4, 5 - Epoxyhept - 1 - en - 6 - ol (1.50g) in dilute sulphuric acid (20 ml 0.5N) was shaken at room temperature for 24 hrs. The solution was neutralised with solid barium carbonate, filtered and evaporated to a colourless syrup (L.52g).

$\upsilon_{max}^{cm^{-1}}$ 3500 - 3200(S), 1655(M), 990(S), 910(S).

This syrup consumed two moles of periodate giving acetaldehyde and crotonaldehyde identified as their 2, 4 - dinitrophenylhydrazones m.p. 168° and 189° respectively. The formic acid liberated was not estimated.

The 3, 5 - dinitrobenzoate of the O - isoproylidene derivative of hept - 1 - en - 4, 5 (erythro) 6 - triol analysed correctly (See experimental to Part 1.).

DL - 4 - N - Dimethylaminohept - 1 - en - 5, 6 - diol, (4, 5 erythro) (C.19, R=H).

4, 5 - Epoxyhept - 1 - en - 6 - ol (10g). and anhydrous dimethylamine (90g) in anhydrous methanol (800ml) containing perchloric acid (0.25 ml. of 70% solution). were heated at 80° in an autoclave for four days.

The resulting brown solution was evaporated to a dark brown oil which on distillation gave DL - 4 - N - dimethylaminohept - 1 - en - 5, 6 - diol (9.43g) b.p. 80 - 82° / 2.15×10^{-3} m.m. η_D^{21} 1.4742. (Found C, 60.89, H.10.51; N, 8.34. $C_9H_{19}NO_2$ requires: C,62.39; H.11.05; N, 8.09%)

(M.W. Found (Mass Spec.)173. Calc for $C_9H_{19}NO_2$: 173)

$\upsilon_{max.}^{cm^{-1}}$ 3500 - 3200(S) 2800(S) 1635(M) 1050(S) 990(S) 910(S).

The <u>picrate</u>, formed in 78% yield, was obtained as bright yellow plates m.p. 147 - 148° from ethanol. (Found: C,44.47; H, 5.38; N.13.94. $C_{15}H_{22}N_4O_9$ requires: C, 44.77; H, 5.51; N.13.93%)

<u>Periodate oxidation of 4 - N - dimethylaminohept - 1 - en - 5, 6 - diol.</u>

The dimethylaminodiol (0.5g) in water (5 ml) was treated with a solution of sodium metaperiodate (0.65g) in water (5ml). Acetaldehyde was immediately liberated. After 15 minutes the solution was steam distilled into an aqueous solution of 2, 4 - dinitrophenylhydrazine sulphate. The precipate - formed was extracted with chloroform and chromatographed on a column of bentonite - kieselguhr (4:1 W/W). Acetaldehyde - 2, 4 - dinitrophenylhydrazone (0.38g 59%)

m.p. and mixed m.p. 167 - 168° was obtained.

Isolation of the acetaldehyde produced, as its dimedone derivative gave the derivative (0.781g 89%) m.p. and mixed m.p. 140 - 141°.

DL - 4 - N - Dimethylaminohept - 1 - en - 5, 6 - diol diacetate (C19, R=Ac).

To 4 - N - Dimethylaminohept - 1 - en - 5, 6 - diol (5.1g) in dry pyridine (50 ml) acetic anhydride (15ml) was added and the solution kept at room temperature, for 36 hrs. The pyridine and excess acetic anhydride was removed at steam-bath temperature and 20 m.m. Water and ether were added to the residual oil, the ether layer removed, and the aqueous phase ether extracted. The combined extracts were washed with sodium bicarbonate solution and water, dried and evaporated to a pale yellow oil (5.0g). Distillation gave 4 - N - dimethylaminohept - 1 - en - 5, 6 - diol diacetate (4.8g) b.p. 132 - 134°/ 40 m.m. η_D^{17} 1.4510.

(Found: C, 60.45; H, 8.73; N, 5.40. $C_{13}H_{23}NO_4$ requires, C, 60-68; H.9.01; N, 5.44%)

$\upsilon_{max.}^{cm^{-1}}$ 3040(W), 2800(M), 1735(S), 1635(M), 1240(S), 990(S) 910(S).

DL - 4 - N - Dimethylaminoheptane - 2, 3 - diol diacetate (C20.).

Hydrogenation of 4 - N - dimethylaminohept - 1 - en - 5, 6 - diol diacetate in ethyl acetate using 10% palladium - charcoal as catalyst gave 4 - N - dimethylaminoheptane - 2, 3 - diol diacetate, b.p. 130 - 132°/ 25 m.m. η_D^{16} 1.4398.

(Found: C, 60.49; H.9.51; N, 5.54. $C_{13}H_{25}NO_4$ requires, C, 60.20; H, 9.72: N, 5.40%).

$\upsilon_{max.}^{cm^{-1}}$ 2800(S) 1735(S) 1240(S).

Ozonolysis of DL - 4 - N - dimethylaminohept - 1 - en - 5, 6 - diol diacetate.

a) DL - 4 - N - dimethylaminohept - 1 - en - 5, 6 diol diacetate (0.5g) in methylene chloride (20 ml) at - 60° was ozonised until the characteristic blue colour developed. The ozonide was decomposed by hydrogenation over ten per cent palladium on charcoal at - 20°. The solution was filtered and evaporated to a pale yellow liquid (0.32g). This on chromatography on silicagel gave a pale yellow oil (0.31g) from benzene - ether (1:1 V/V). Distillation resulted in decomposition.

$\upsilon_{max.}^{cm^{-1}}$ 2700(W) 1735(S), 1705(S) 1680(S).

b) DL - 4 - N - dimethylaminohept - 1 - en - 5, 6-diol diacetate (0.5g) in methylene chloride (20ml) was treated with one molar equivalent of ozone at - 40° and the mixture worked up as described above. A pale yellow oil (0.41g) was obtained.

$\upsilon_{max.}^{cm^{-1}}$ 3040(W), 1735(S), 1680(S), 1635(M), 990(S) 910(S).

Chromic acid oxidation of DL - 4 - N - dimethylaminohept - 1 - en - 5, 6 - diol diacetate.

A solution of the dimethylamino olefin (1.0g) in dry pyridine (10 ml) was treated at 0°C with a solution of the chromium trioxide - pyridine complex (from 0.8g chromium trioxide) in pyridine (10ml). The mixture was allowed to stand at room temperature for 12 hours then poured into water and extracted with ether. The combined extracts were washed with water, dried, and evaporated to a pale yellow oil (0.81g). Distillation gave unchanged starting material (0.69g) b.p. 76 - 78°/0.1 m.m. η_D^{18} 1.4507, and a residual high boiling material (0.26g) which from its infra-red spectrum was considered to be DL - 4 - N - methyl - N - formylaminohept - 1 - en - 5, 6 - diol diacetate.

$\upsilon_{max}^{cm^{-1}}$ 3040(W), 1735(S), 1680(S) 1635(M) 990(S), 910(S).

DL - 4 - N - Dimethylaminoheptane - 1, 2, 5, 6 - tetrol - 5, 6 - diacetate. (C.23).

a) A solution of DL - 4 - N - dimethylamino-hept - 1 - en - 5, 6 - diol diacetate (1.1g) in t - butanol (5 ml) containing hydrogen peroxide/

peroxide/

(5 ml of 6.1% sol^{n} in t - butanol) and osmium tetroxide (0.1 ml of a 1% sol^{n}. in t - butanol) was stored at room temperature for twentyfour hours. The dark brown solution was evaporated under reduced pressure to a dark brown syrup (0.8g) from which no pure material could be isolated either by short path distillation or by chromatography on silicagel.

b) A mixture of DL - 4 - N-dimethylaminohept - 1 - en - 5, 6 diol diacetate (1.52g) and osmium tetroxide (1.5g) in ether (50 ml) was set aside in darkness for seven days. The osmate ester was decomposed with hydrogen suphide in the presence of sodium bicarbonate (4g). The solution was filtered through celite to remove osmium sulphide and concentrated to a syrup (1.24g). Chromatography on silicagel using benzene - ether (1:1 V/V) as eluant gave the tetrol diacetate as a pale yellow oil (1.21g).

$\upsilon_{max}^{cm^{-1}}$ 3400(S) 2780(M) 1735(S) 1240(S) 1050(S).

DL - aldehyde "Rhodosamine" diacetate (C24).

The above tetrol diacetate (1.21g) in water (15 ml) was treated with a solution of sodium meta-periodate (1.15g) in water (15 ml) and the mixture set aside in darkness for 2 hrs. The solution was extracted with ether (3 x 50 ml) and the combined dry extracts were evaporated to a pale yellow oil (0.71g).

$\upsilon_{max}^{cm^{-1}}$ 2780(M) 2720(W) 1735(S) 1705(S) 1240(S).

Reaction of DL - aldehydo"rhodosamine" diacetate with base.

DL - aldehydo Rhodosamine diacetate (0.41g) was heated at 90° in 3N sodium hydroxide solution (20Ml) for ten hours. The solution was then evaporatively distilled into a dry-ice trap until 5 ml of distillate had been collected. The distillate was treated with picric acid and set aside for twenty four hours after which time the precipate was removed. This recrystallised from aqueous ethanol as yellow plates m.p. 157 - 158° (Literature m.p. for dimethylamine picrate, 158°).

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