STUDIES RELATED TO DAUCIC ACID

A thesis presented by

BARRY DAVID BROWN

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Hofmann Laboratory,

Imperial College,

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Finally, I wish to thank my parents for their support during my further education.

To my parents -

Muchas gracias

para todo.

ABSTRACT.

This thesis is concerned with the isolation of daucic acid and the degradation of one of its derivatives, dimethyl daucate, to 2,5 furoic dimethyl ester and to chelidonic acid dimethyl ester. Detailed studies of dimethyl daucate, dimethyl daucate diacetate and dibenzoate are included. Dihydropyrans and dihydrofurans derived from sugars are extensively reviewed.

An account of the step-wise degradation of dimethyl daucate to 2,5 furoic acid dimethyl ester is given. The degradation products were confirmed by synthesis. Attempts to determine the stereochemistry of dimethyl daucate are discussed.

Borohydride reduction of chelidonic acid dimethyl ester is described and the products substantiated.

Dimethyl and diethyl meconate derivatives were prepared and borohydride reductions attempted.

CONTENTS

Contents (continued)

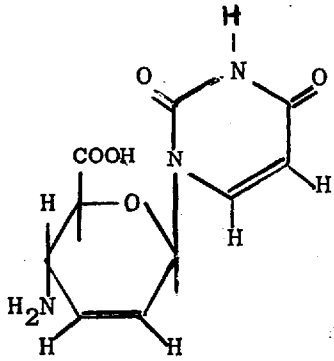
Contents (continued)

REVIEW.

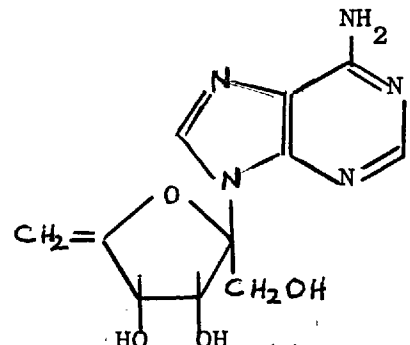
Dihydropyrans and Dihydrofurans derived from Sugars.

Introduction.

Unsaturated sugars are important synthetic and biological intermediates. Interest in these compounds has grown since the detection of unsaturated derivatives in the naturally occurring antibiotic nucleosides cystosinine [1,2] (1) and angustomycin [3,4] (2).

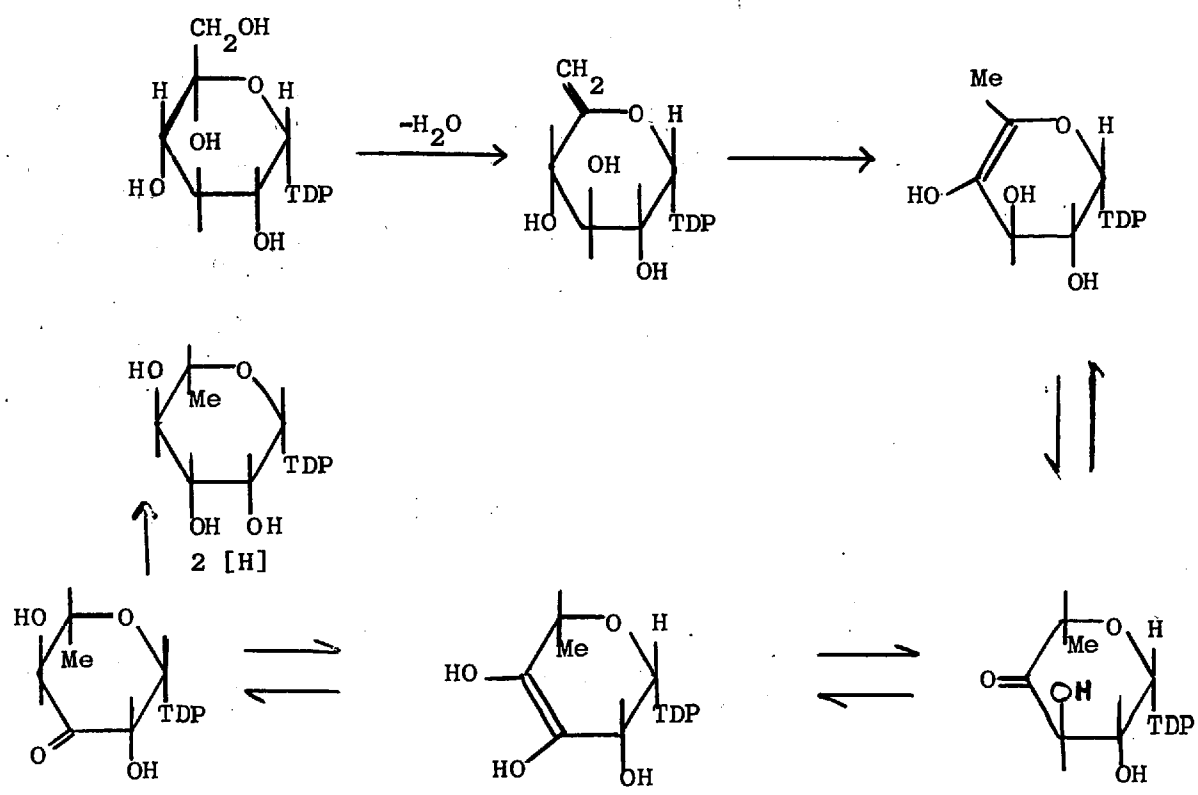


(1)



(2)

Nucleotide derivatives of 6-deoxy-α-D-xylohex-5-enopyranose are possible intermediates in the biosynthetic pathways of sugars, e.g. L-rhamnose[5] (Scheme I).



T.D.P. ≡ Thymidine diphosphate.

SCHEME I

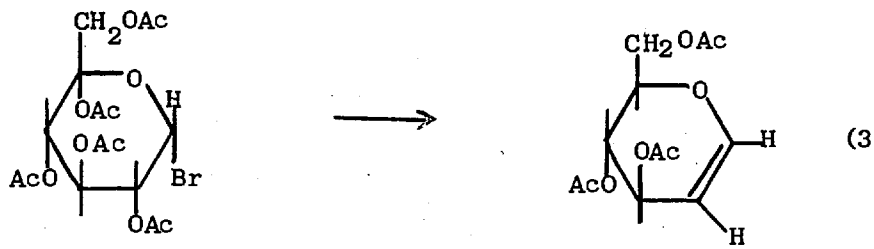
Other biosynthetic pathways such as those to streptose[6] and 6-deoxy-6-sulpho-D-glucose are thought to proceed in a similar manner.

As isolation procedures become more refined the known naturally occurring unsaturated sugars (and derivatives) will of necessity increase in number, and pose some interesting problems structurally, biosynthetically and synthetically.

1,2 Dehydropyranose and 1,2 Dehydrofuranose derivatives.

Synthesis.

The pyranoid glycals are usually prepared by reduction of the appropriate acetylated glycosyl halide with zinc in acetic acid, first described by E. Fischer and K. Zach in 1913. More recent methods[7,8] have employed low temperature[9] and activated zinc[10] reduction (Scheme II).



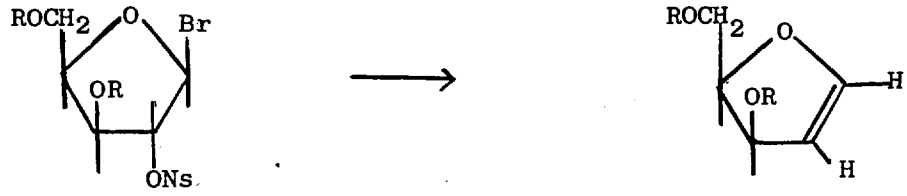
(3)

SCHEME II

Furan glycals cannot be prepared by this method due to their high reactivity which leads to re-arranged products.

3,5-Di-O-benzoyl-1,2-dideoxy-D-erythropent-1-enofuranose has been prepared from 2O-(p-nitrobenzene sulphonyl)-β-D-ribofuranosyl bromide by an elimination reaction using sodium iodide and acetone at -5°[11] (Scheme III).

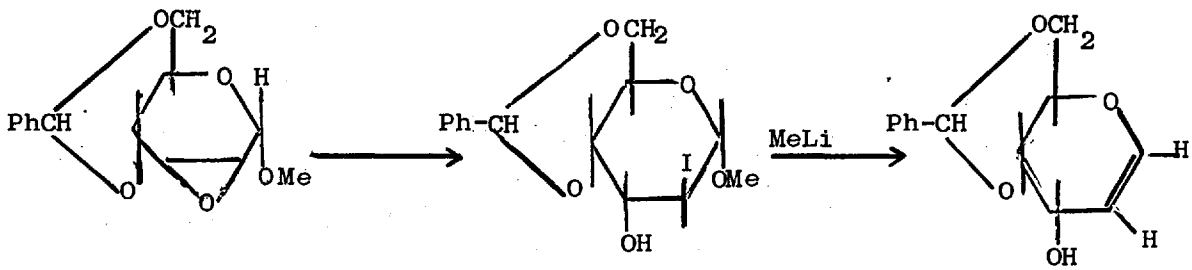
/See over for Scheme III/



R ≡ C_6H_5CO

SCHEME III

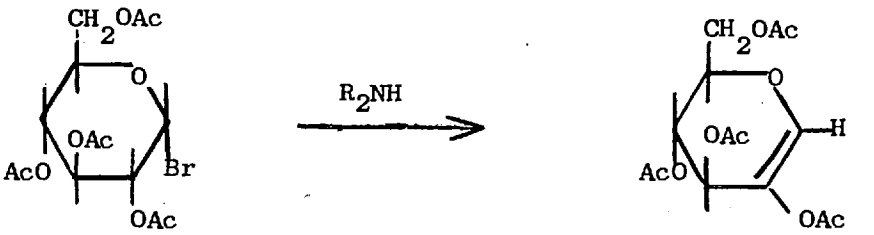
1,2-Dehydropyranose derivatives can be prepared via elimination reactions [12, 13, 14] using fresh methyl lithium (Scheme IV).



SCHEME IV

A new method for making tri-O-acetyl-D-glucal (3), involved the treatment of 3,4,6-tri-O-acetyl-1,2-anhydro-D-glycopyranose with sodium cobalt tetracarbonyl and carbon dioxide in ether [15].

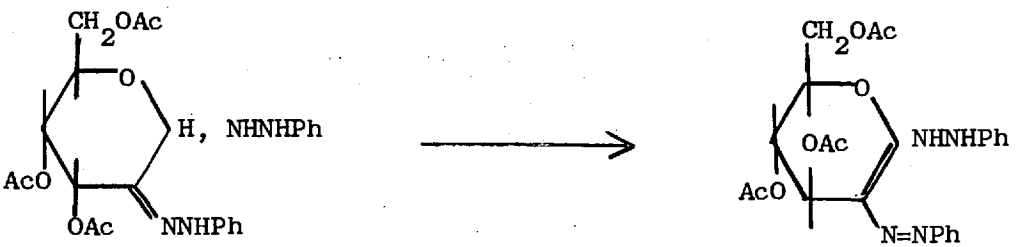
2-Acetoxy tri-O-acetyl-D-glucal was obtained in high yield from tetra-O-acetyl α-D-glucopyranosyl bromide [16] (Scheme V).



SCHEME V

The use of the iodide (via bromide exchange with acetone and sodium iodide) resulted in better yields for the reaction [17].

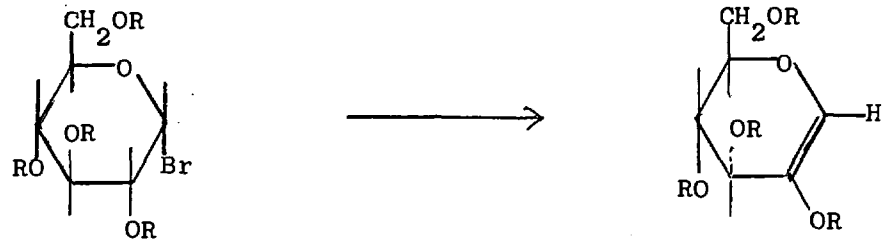
D-ribohexulosephenylozazone triacetate and its D-arabino isomer, were oxidized in alkaline solution to give 3,4,6-tri-O-acetyl-2-benzeneazo-1-(2-phenyl hydrazino)-D-allal [18] (Scheme VI).



SCHEME VI

During attempts to condense tetra-O-benzyl-α-D-glucopyranosyl bromide with indole in liquid ammonia 3,4,6-tri-O-benzyl-2-benzyloxy-D-glucal was obtained [19] (Scheme VII).

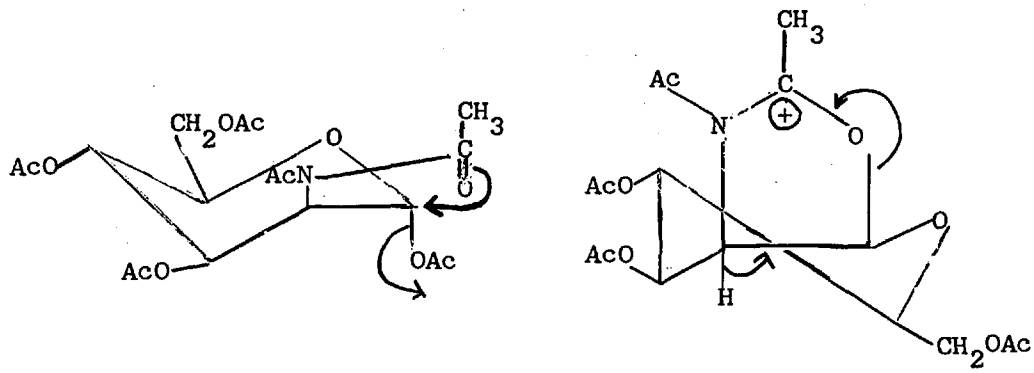
/See over for Scheme VII/



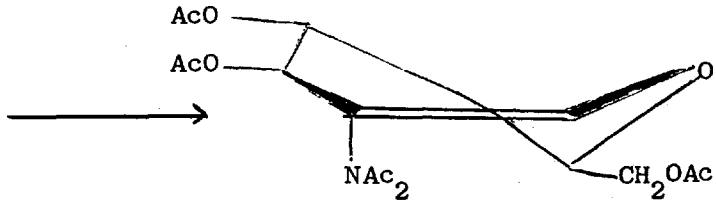
R ≡ $C_6H_5CH_2$

SCHEME VII

Acetylation of 2-acetamido-2-deoxy-D-mannose with isopropenyl acetate and catalytic amounts of p-toluenesulphonic acid gave a mixture of products [20] one of which 3,4,6-tri-O-acetyl-2-(N-acetylacetamido)-D-glucal was isolated in poor yield (Scheme VIII).

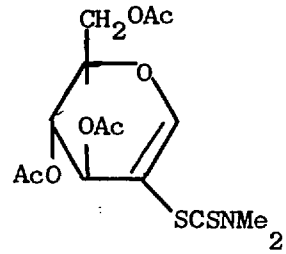


α-D isomer



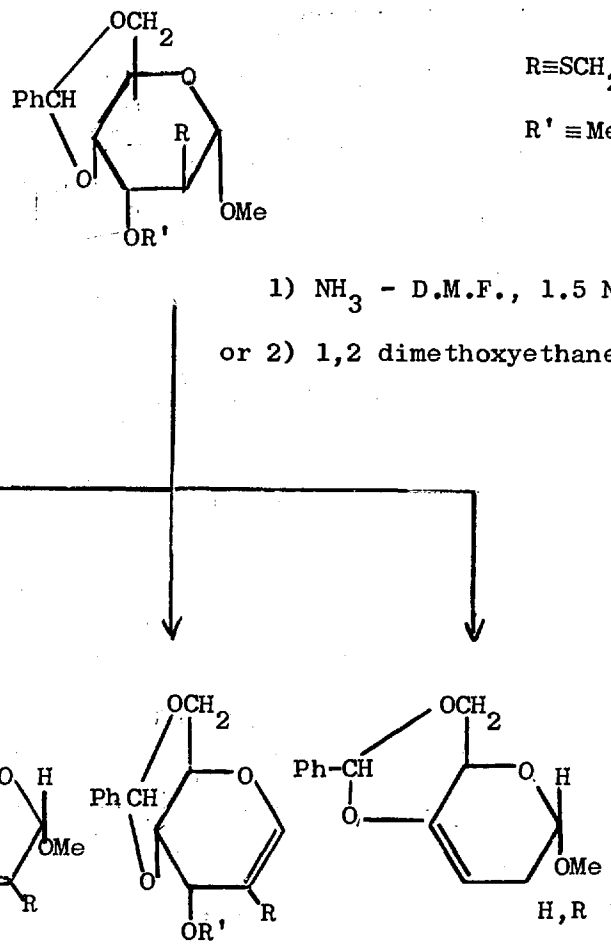
SCHEME VIII

3,4,6-Tri-O-acetyl-2-O-(methylsulphonyl)-β-D-glucopyranosyl N,N-dimethyldithiocarbamate reacted with potassium acetate in ethanolic acetone [21] to give (4).



(4)

A recent reaction led to a mixture of 1,2,2,3 and 3,4 unsaturated dehydropyranose derivatives [22] (Scheme IX).

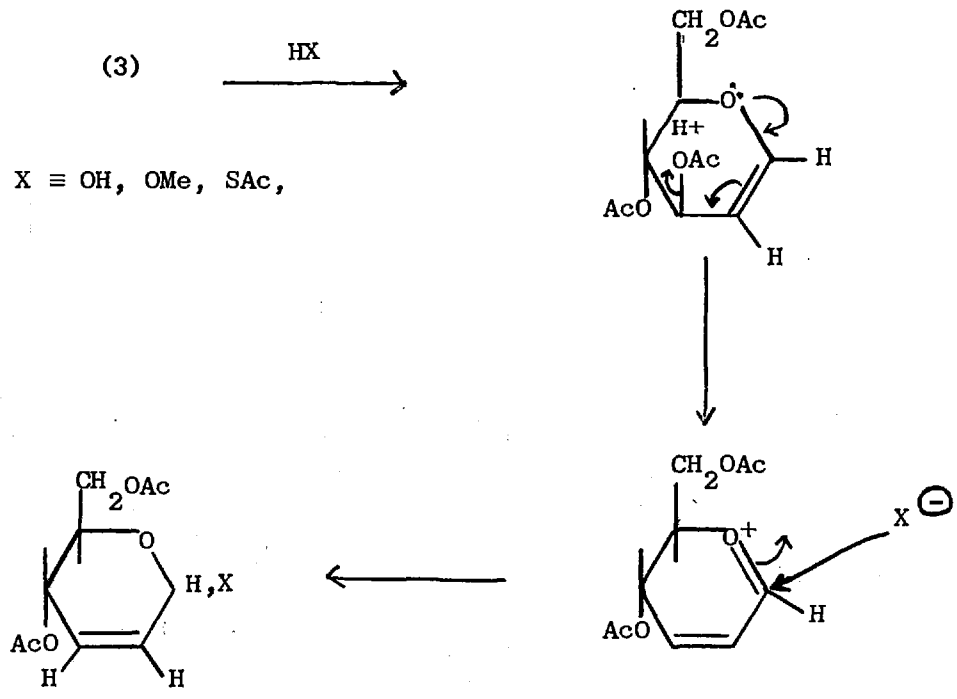


SCHEME IX

Similar results were obtained with analogous 4,6-O-ethylidene derivatives [23].

Rearrangement reactions.

Acetylated glycals are vinyl ethers, and readily undergo rearrangement reactions in the presence of an electrophile to give 2,3 unsaturated products, bearing the nucleophilic counterion at C1. They react readily with water, alcohols, phenols, carboxylic acids etc. (Scheme X).



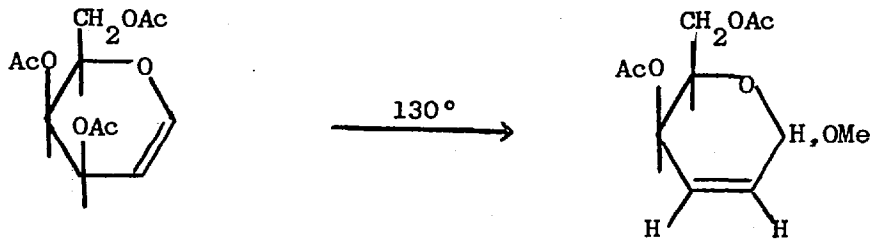
SCHEME X

The above reaction when properly controlled provides a useful synthesis of 2,3 unsaturated glycosides.

Tri-O-acetyl-D-glucal (3) reacts with alcohols and phenols in the absence of catalysts to give unsaturated glycoside derivatives [24] (Scheme XI).

SCHEME XI

Tri-O-acetyl-D-galactal also undergoes these reactions, but markedly less readily, presumably because the ester group on C-4 cannot assist the departure of the 3-acetoxyl group. Nevertheless, 4,6-di-O-acetyl-2,3 dideoxy-α-D-threo-hex-2-enopyranosides have been obtained in poor yield [25] (Scheme XII).

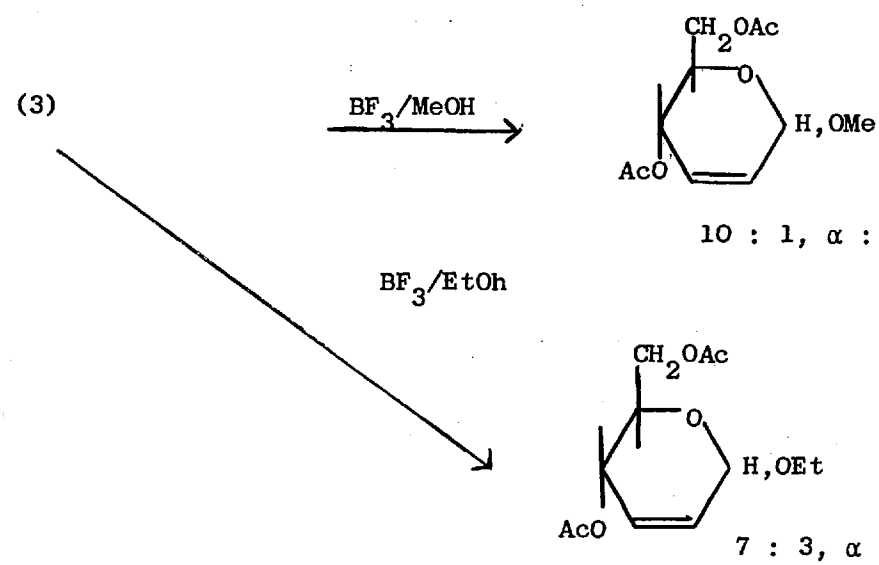


1.5 : 1; α : B

SCHEME XII

Products from these reactions are invariably anomeric mixtures, and usually only the thermodynamically favoured α-isomer is able to be isolated.

Recently, the stereoselectivity and ease of these reactions have been improved by the use of inert solvents and boron trifluoride etherate as catalyst [26,27]. (Scheme XIII).

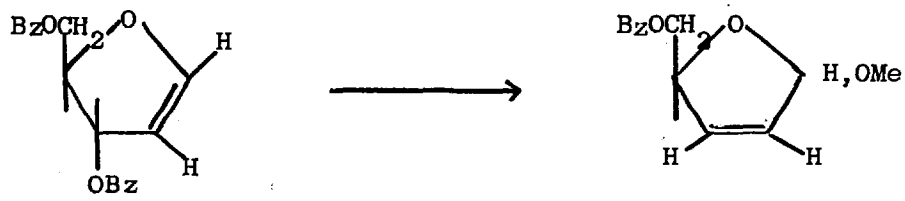


10 : 1, α : β

7 : 3, α : β

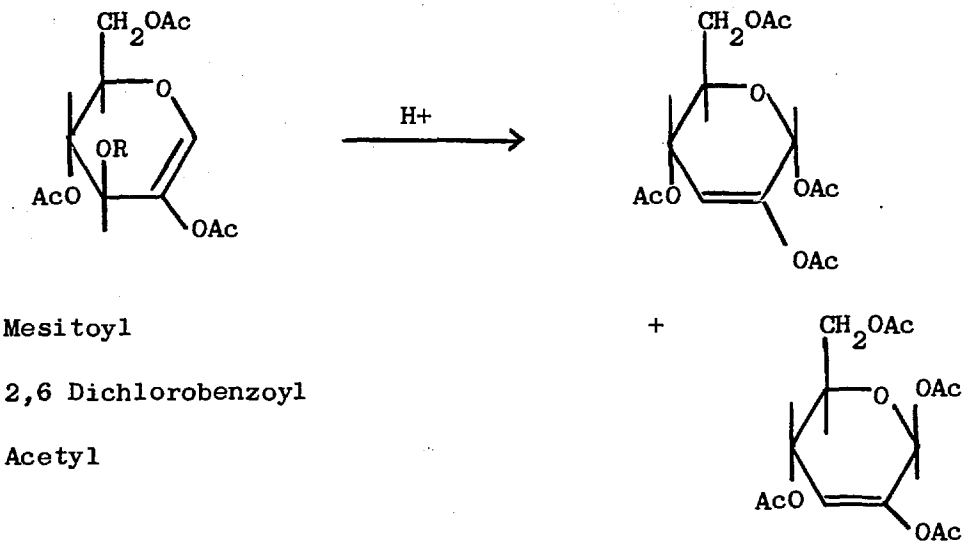
SCHEME XIII

The furanoid glycals rearrange with even greater facility than the pyranoid glycals. 1,2-Dideoxy-D-erythropent-1-enofuranose 3,5-dibenzoate in methanol yields the 2,3 unsaturated glycoside with the liberation of benzoic acid [11] (Scheme XIV).



SCHEME XIV

The introduction of different substituents at C-3 on the rate of these reactions has been studied[28] (Scheme XV).



1,R ≡ Mesitoyl

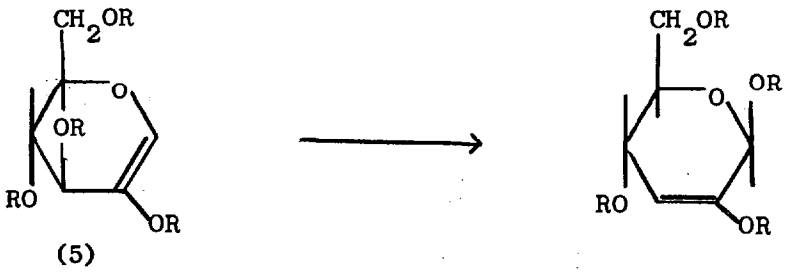
2,R ≡ 2,6 Dichlorobenzoyl

3,R ≡ Acetyl

SCHEME XV

It was found that reaction (XV/1) proceeded at 6.7 times the rate of reaction (XV/2) and 0.34 times the rate of reaction (XV/3).

2-Hydroxyglycal esters have been thermally isomerized using refluxing nitrobenzene as solvent, to yield 2,3 stereospecific unsaturated derivatives [29] (Scheme XVI).



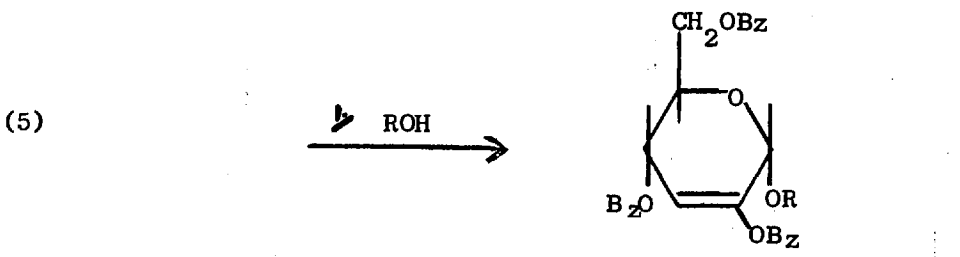
(5)

R ≡ Acetyl
R ≡ Benzoyl

β-anomer

SCHEME XVI

Alternatively, these types of reaction can be carried out at room temperature using trace amounts of boron trifluoride [30]. The α—anomer is formed in good yield (Scheme XVII).



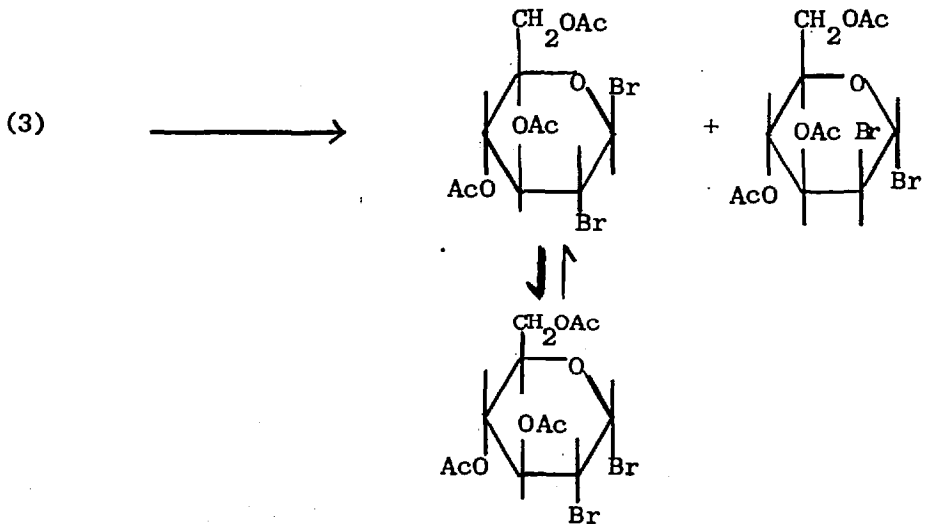
R ≡ Benzoyl

R ≡ Me, Et, C_6H_{11} etc.

SCHEME XVII

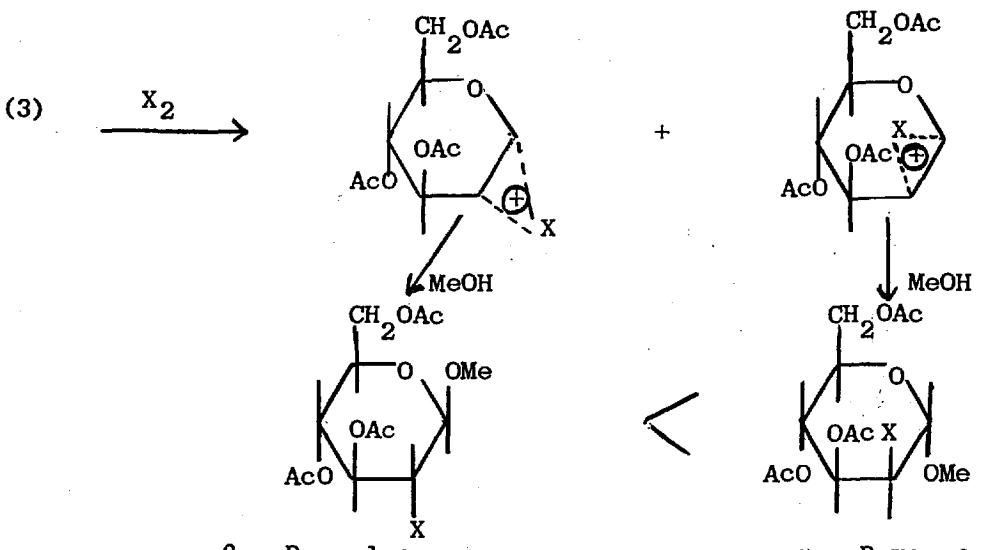
Halogen reactions.

Bromination of tri-O-acetyl-D glucal [31] yields a mixture of isomeric 1,2 dibromo derivatives. The α-D gluco isomer is in preponderance over the α-D manno isomer (Scheme XVIII).



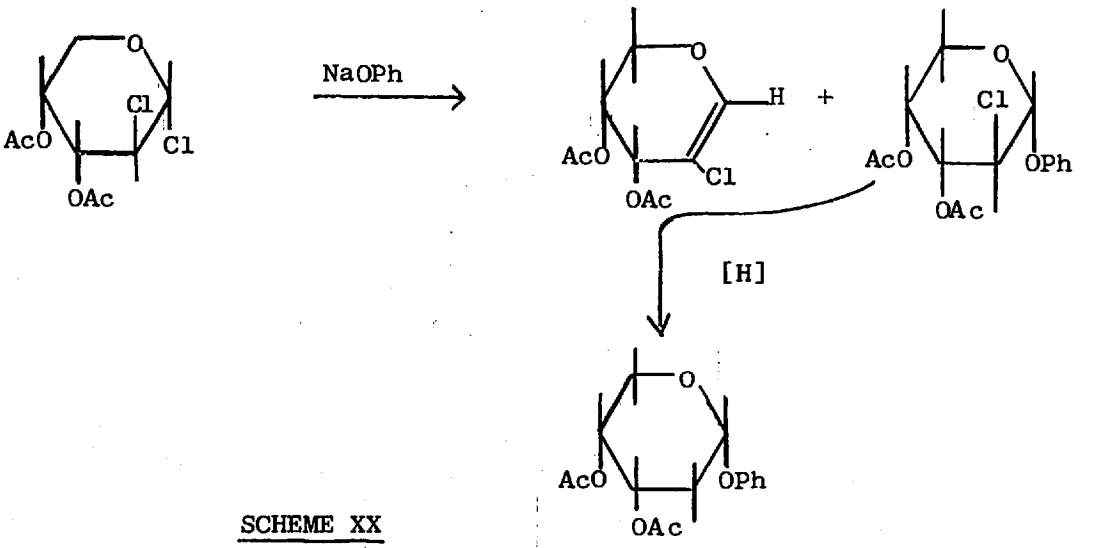
SCHEME XVIII

Chlorination follows a similar route [32]. Alkyl 3,4,6-tri-O-acetyl-2-deoxy-2-halogenopyranoside derivatives are formed when tri-O-acetyl-D-glucal reacts with a halogen in the presence of an alcohol containing silver carbonate. The products arise via 1,2-epi-halonium ions and the proportions of the α-D manno isomer usually exceeds that of the β-D-gluco isomer [31] (Scheme XIX).



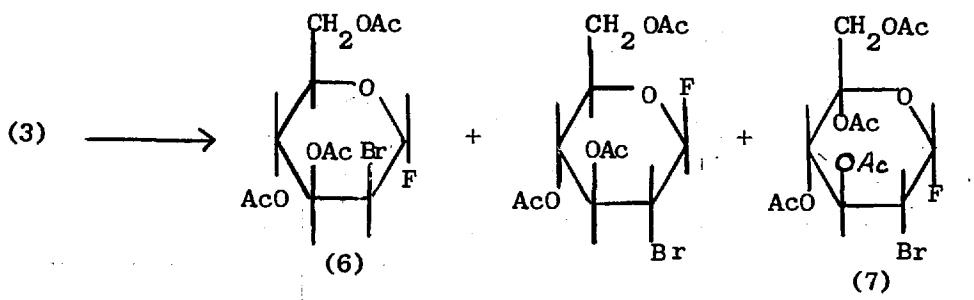
SCHEME XIX

The 1,2 dihalogeno adducts of glycals are important precursors of 2-deoxy derivatives of aldoses [33] (Scheme XX).



SCHEME XX

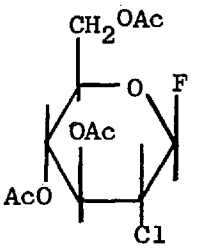
Triacetyl D-glucal reacts with bromine in the presence of finely divided silver monofluoride to give a mixture of three products, each of which was a 2-bromo-2-deoxyglycosyl fluoride [34] (Scheme XXI).



SCHEME XXI

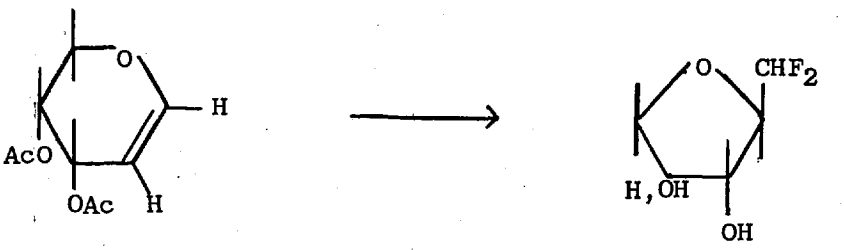
Similarly, BrF generated from N-bromoacetamide and hydrogen fluoride in ether at -80° gave the same three products. When iodine replaced bromine, analogous adducts were obtained. It was found that ClF (generated in the same way as BrF) reacted in a similar way, but here the major product of reaction was found to

be the β-D-gluco adduct [35], (8).



(8)

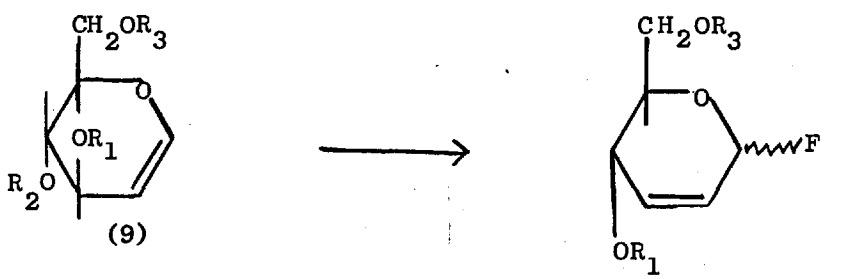
2,5 Anhydro-1,1 difluoroalditols are formed when acetylated glycals are treated with hydrogen fluoride in dichloromethane, in the presence of lead tetra-acetate [36,37] (Scheme XXII).



SCHEME XXII

Tri-O-acetyl-D-glucal reacts with N-bromosuccinimide and hydrogen fluoride in ether at -60° to give two products [38,39], (6) and (7).

Tri-O-benzoyl-D-glucal reacts with anhydrous hydrogen fluoride at -70° during thirty minutes to give the 2,3 unsaturated fluoride [40] (Scheme XXIII).

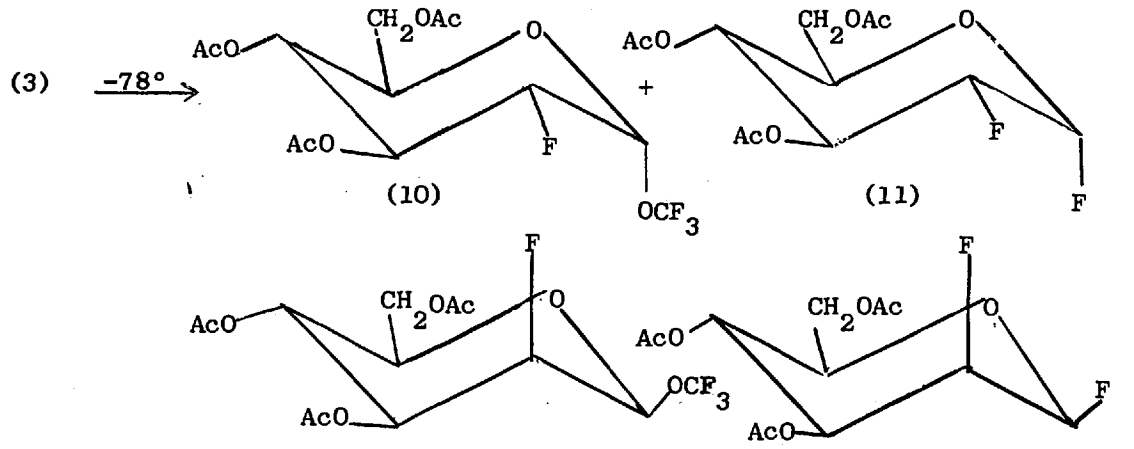


(9)

$R_1 \equiv R_2 \equiv R_3 \equiv C_6H_5CO$

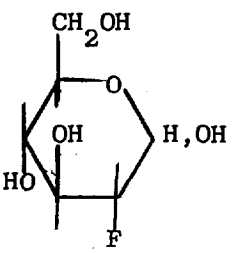
SCHEME XXIII

Tri-O-acetyl-D-glucal in trichlorofluoromethane as solvent reacts with trifluoro (fluoro-oxy)-methane ($FOCF_3$) at low temperatures to give four products [41] (Scheme XXIV).



SCHEME XXIV

Hydrolysis of the α-D gluco adducts (10) and (11) affords a means of obtaining 2-deoxy-2-fluoro-D-glucose (12).



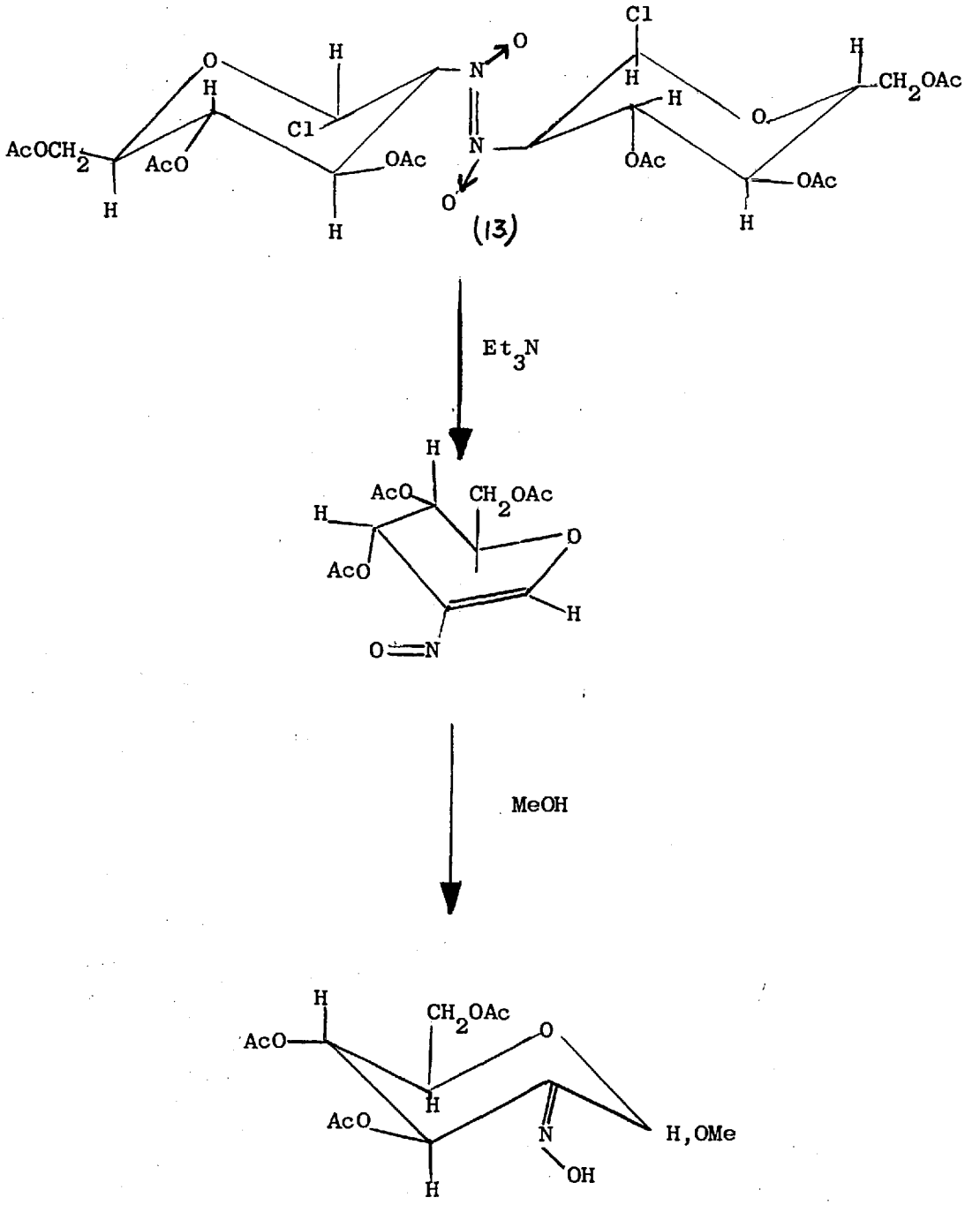
(12)

The same reaction has recently been applied to tri-O-acetyl-D-galactal [42].

Reactions with nitrosyl chloride and dinitrogen tetroxide - synthetic use.

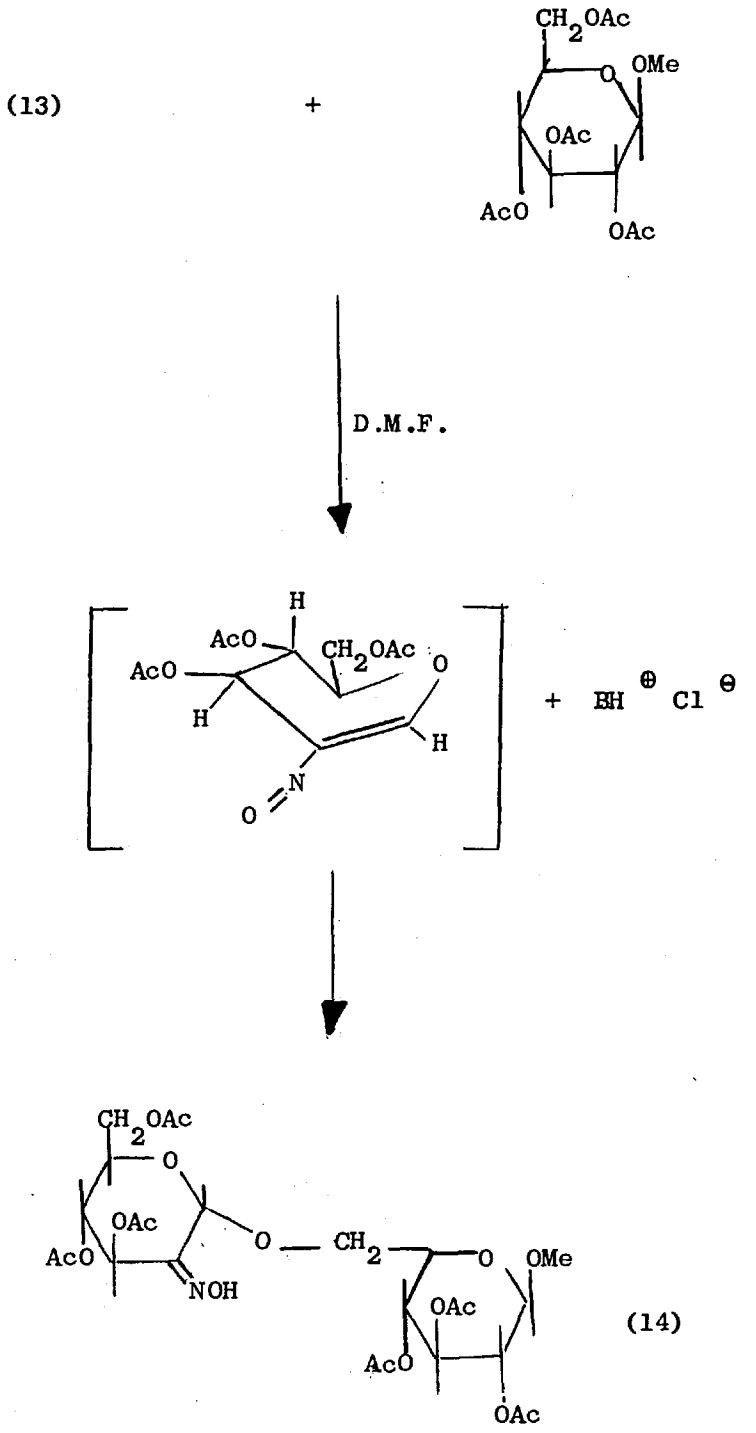
Tri-O-acetyl-D-glucal undergoes cis-addition of nitrosyl chloride in ether or dichloromethane at low temperatures.

A dimer (13) is formed, which is reducible to the 2-amino-derivative and susceptible to dehydrochlorination to produce 2-nitroso-D-glucal triacetate. The latter readily adds alcohols to form 2-oximino-glycosides [43, 44] (Scheme XXV).



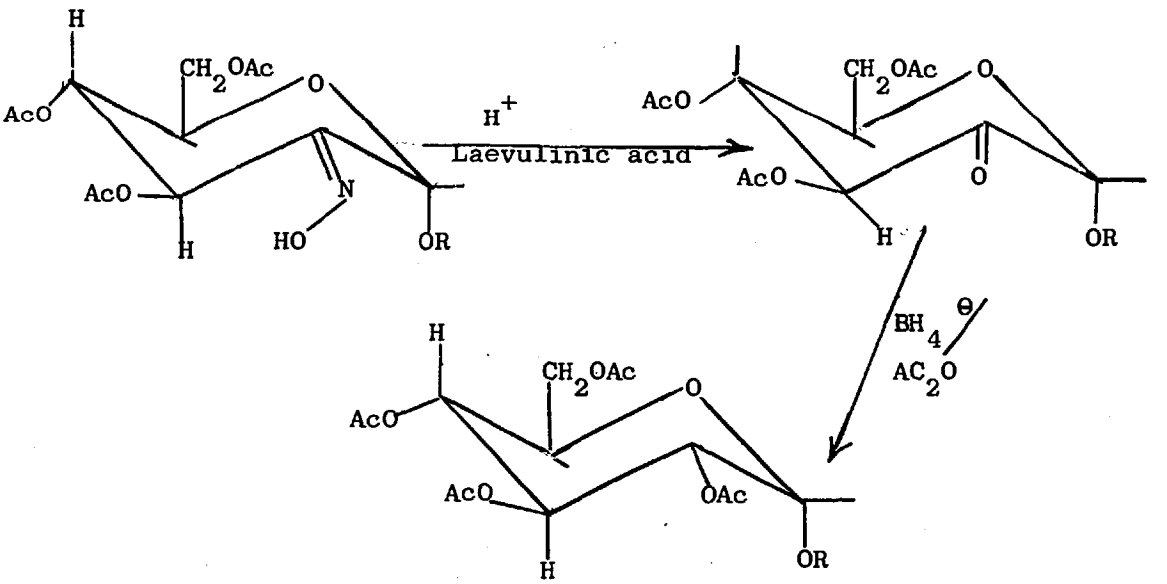
SCHEME XXV

The reaction of nitrosyl chloride with certain glucals to yield dimers, has been put to synthetic use [45] (Scheme XXVI).



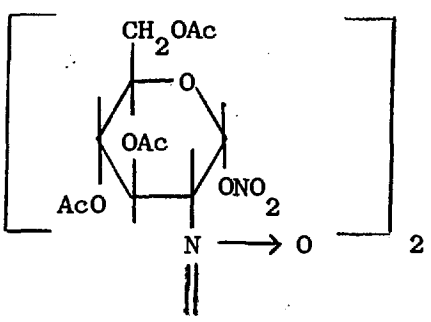
SCHEME XXVI

Compounds such as (14) can be reduced with palladium and hydrochloric acid to give -2-amino-2-deoxy-α-D hexopyranosides [46]. Similarly, deoximation and borohydride reduction of the resulting glycosiduloses opened a route for the synthesis of α-D glycosides. Reduction with borodeuteride provided a means of labelling H-2 specifically [47] (Scheme XXVII).



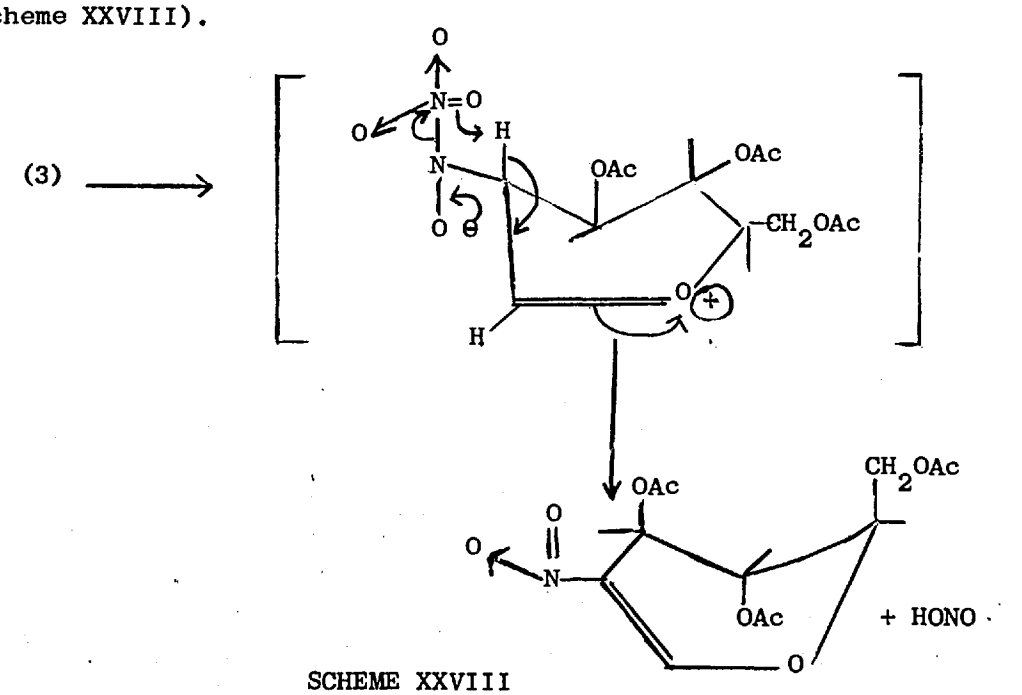
SCHEME XXVII

Acetylated glycals react with dinitrogen tetroxide in ether at 0°, to give dimeric acetylated 2-deoxy-2-nitroso, α-D-glycosyl nitrates (15).



(15)

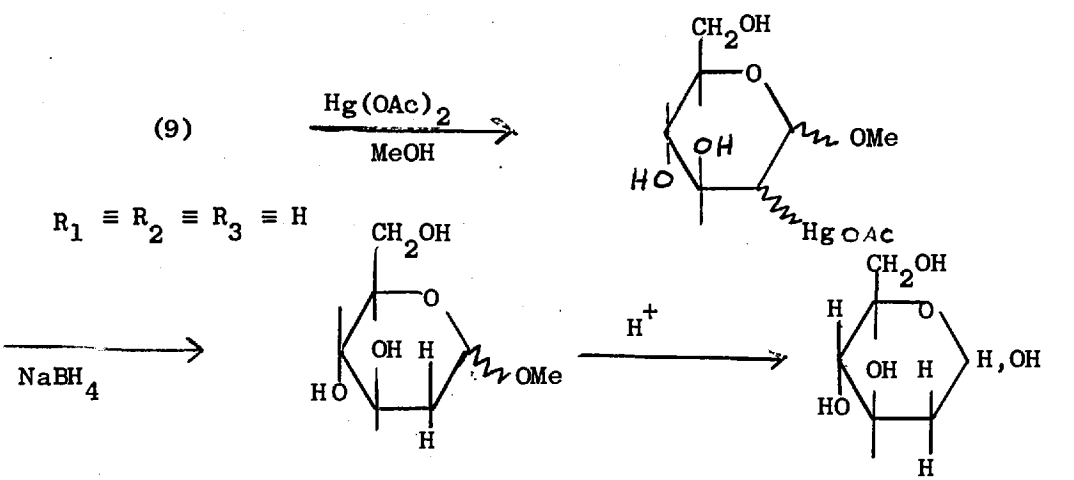
However, when dichloromethane at -70° was used as solvent, no such compounds were obtained. Instead acetylated 2-nitroglycals (not formed by way of the 2-nitroglycosyl nitrates) were the products [48] (Scheme XXVIII).



SCHEME XXVIII

Methoxymercuration.

Reaction of glycals or substituted glycals in the presence of mercuric acetate yield 2-deoxy glycosides having mercury attached directly at C-2 [49] (Scheme XXIX).

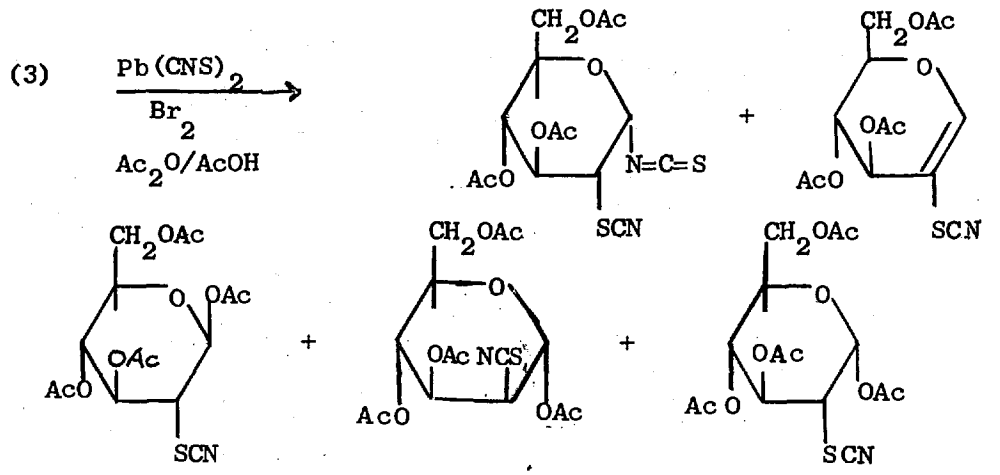


SCHEME XXIX

A new series of compounds has been made having the β-D-gluco configuration, and the following groups bonded to the mercury atom :- Cl, I, CN, NO_3, PhCOO, S-isoPr, SPh, S-p-tolyl, SCH_2Ph. In addition the reaction has been applied to the synthesis of other unsaturated carbohydrates [50], and in the first stage of the synthesis of L-daunosamine [51].

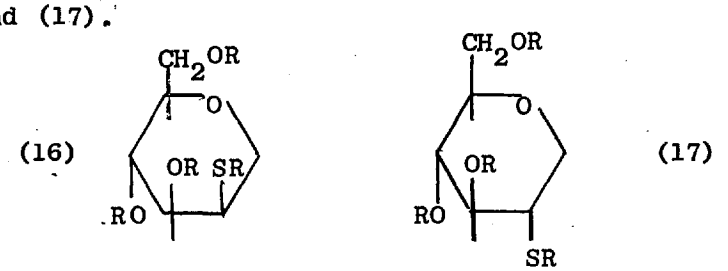
Addition of sulphur containing reagents.

It has been found that tri-O-acetyl-D-glucal reacts in acetic acid with pseudo-halogen thiocyanogen to give a complex mixture of products [52] (Scheme XXX).



SCHEME XXX

Tri-O-acetyl-D-glucal and D-glucal undergo reaction with thiolacetic and α-toluenethiol respectively [53,54], to give the products (16) and (17).

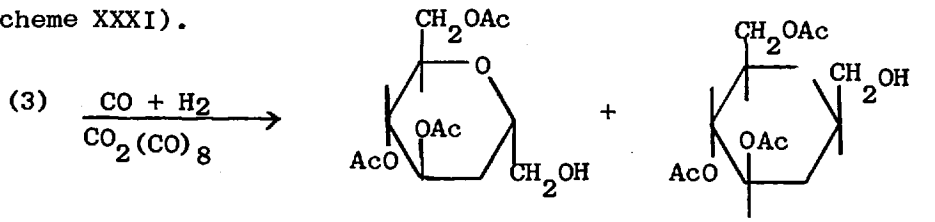


1) (16), R ≡ Ac; (17), R ≡ Ac, 7 : 3.

2) (16), R ≡ CH_2Ph; (17), R ≡ CH_2Ph, 1 : 1.

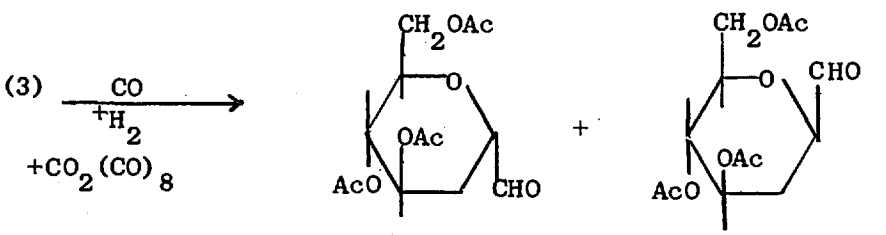
Hydroformylation, hydrogenation and oxidation reactions.

The oxo-reaction has been applied successfully to glycals [55], (Scheme XXXI).



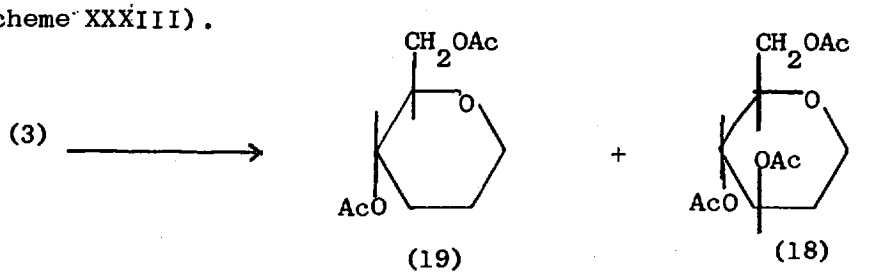
SCHEME XXXI

Under carefully monitored conditions the products of direct hydroformylation can be obtained (Scheme XXXII).



SCHEME XXXII

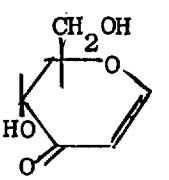
Platinum catalysts with ethyl acetate as solvent give direct additions (18), to the double bond. The incorporation of small proportions of dimethylamine promote hydrogenolysis [56] (19), Scheme XXXIII).



(19) (18)

SCHEME XXXIII

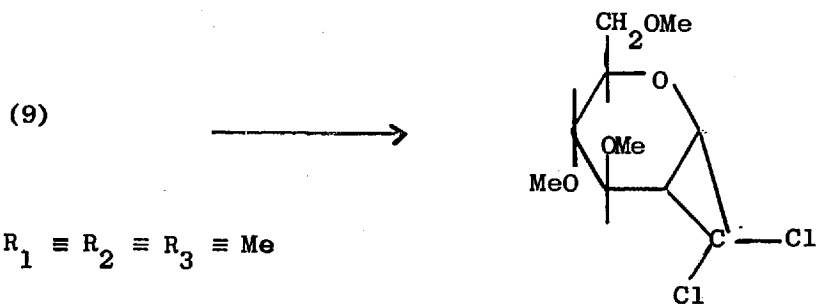
D-glucal can be selectively oxidized to the corresponding enone (20) in good yield using silver carbonate and celite [57].



(20)

Carbene addition.

Addition of dichloro-carbene (ethyl trichloroacetate and sodium methoxide) to 3,4,6-tri-O-methyl-D-glucal was shown to occur in good yield [58], (Scheme XXXIV).

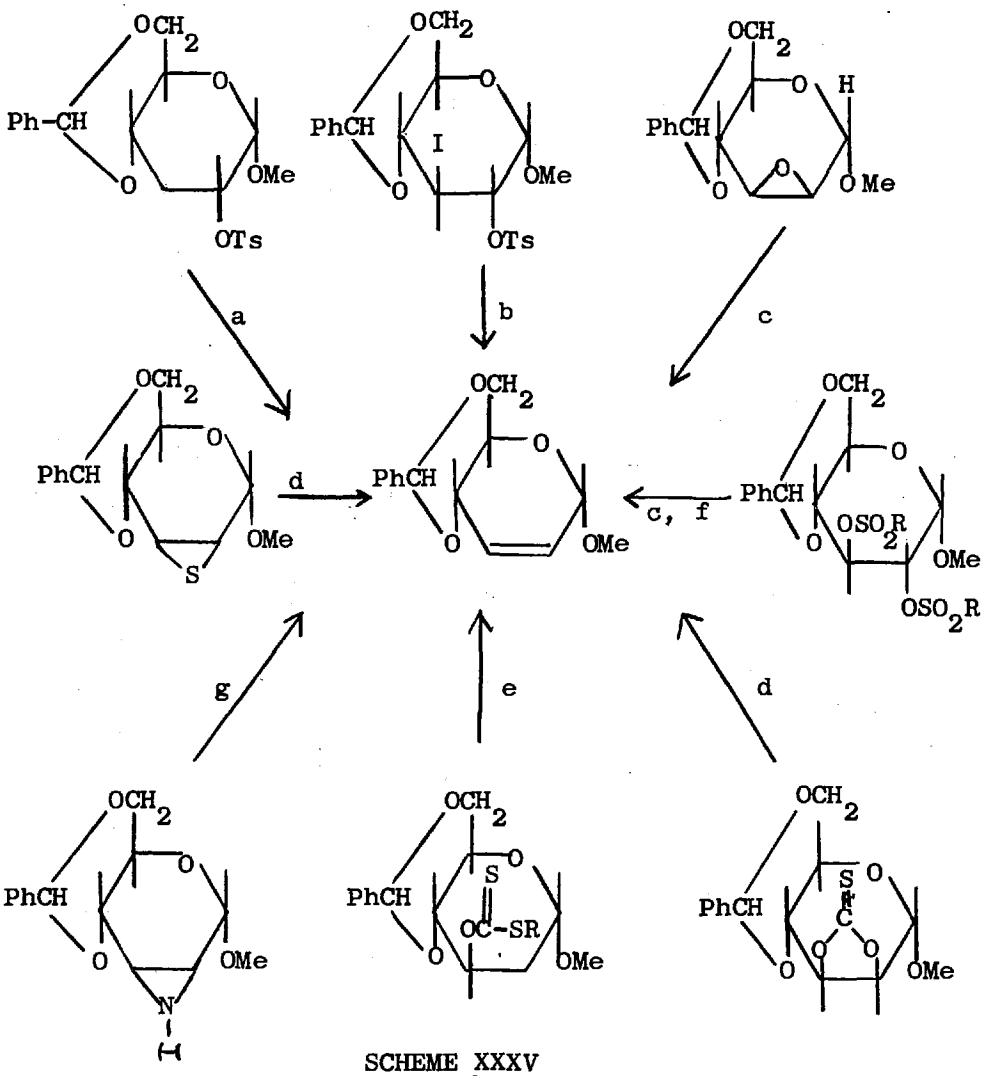


SCHEME XXXIV

2,3 Dehydropyranoses.

Synthesis.

As seen earlier, these compounds can be prepared by rearrangement of 1,2 unsaturated compounds. They can also be prepared by direct elimination from C-2 and C-3 of glycosyl derivatives. The best known member of this group, namely, 4,6-O-benzylidene-2,3 dideoxy-α-D-erythro-hex-2 enoside has been obtained by several routes (Scheme XXXV).



SCHEME XXXV

The methods include:-

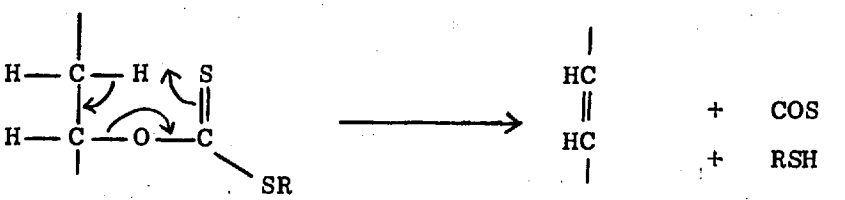
(a). Reaction of soda lime on 3-deoxy-2-O-tosyl-ribohexo-pyranoside [59].

(b). The reaction of 3-iodo-2-O-tosylglucopyranoside with sodium iodide in acetone [60].

(c). Treatment of various 2,3 disulphonate esters and epoxides with potassium ethyl xanthate [61].

(d). Elimination of sulphur from 2,3 episulphide or 2,3 thiocarbonate by reaction with triethyl phosphite to form an unstable carbene which gives the -2 enoside [62,63].

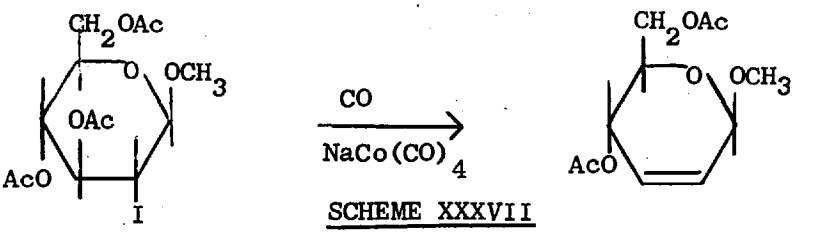
(e). Pyrolytic decomposition (Chugaev reaction) of the 3-O-[(methythio)-thiocarbonyl] derivative of methyl 2-deoxy-D-arabinohexpyranoside in diphenyl ether [24] (Scheme XXXVI).



SCHEME XXXVI

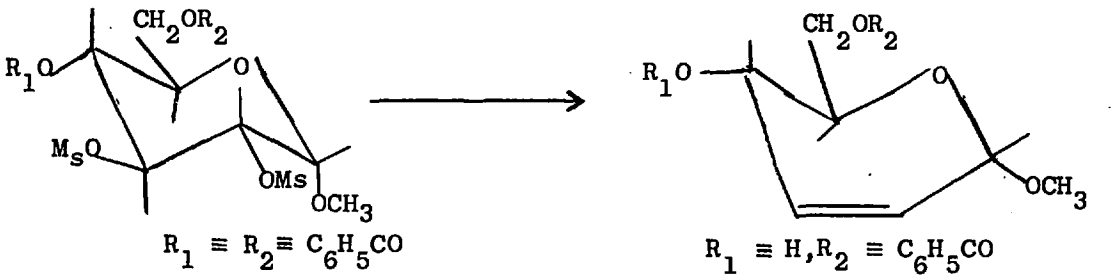
(f). The action of sodium iodide-zinc dust in N,N-dimethyl-formamide upon the 2,3 disulphonate ester [63].

(g). The reaction of nitrous acid on the 2,3-epimo derivative, via the unstable N-nitroso epimine [64]. Iodo compounds have been used to synthesis unsaturated glycosides of this series [15] (Scheme XXXVII).



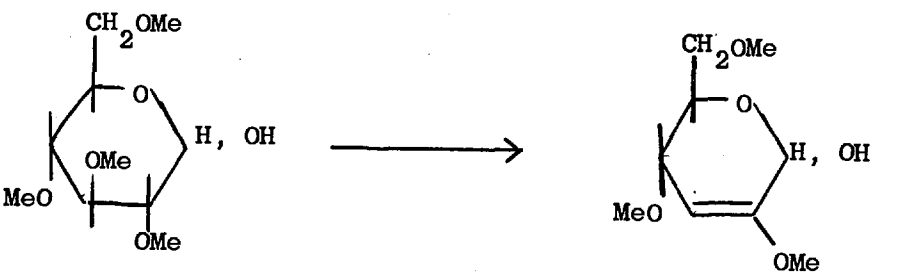
SCHEME XXXVII

Recent workers have employed potassium iodide and a zinc-copper couple in refluxing D.M.F.[65] (Scheme XXXVIII).



SCHEME XXXVIII

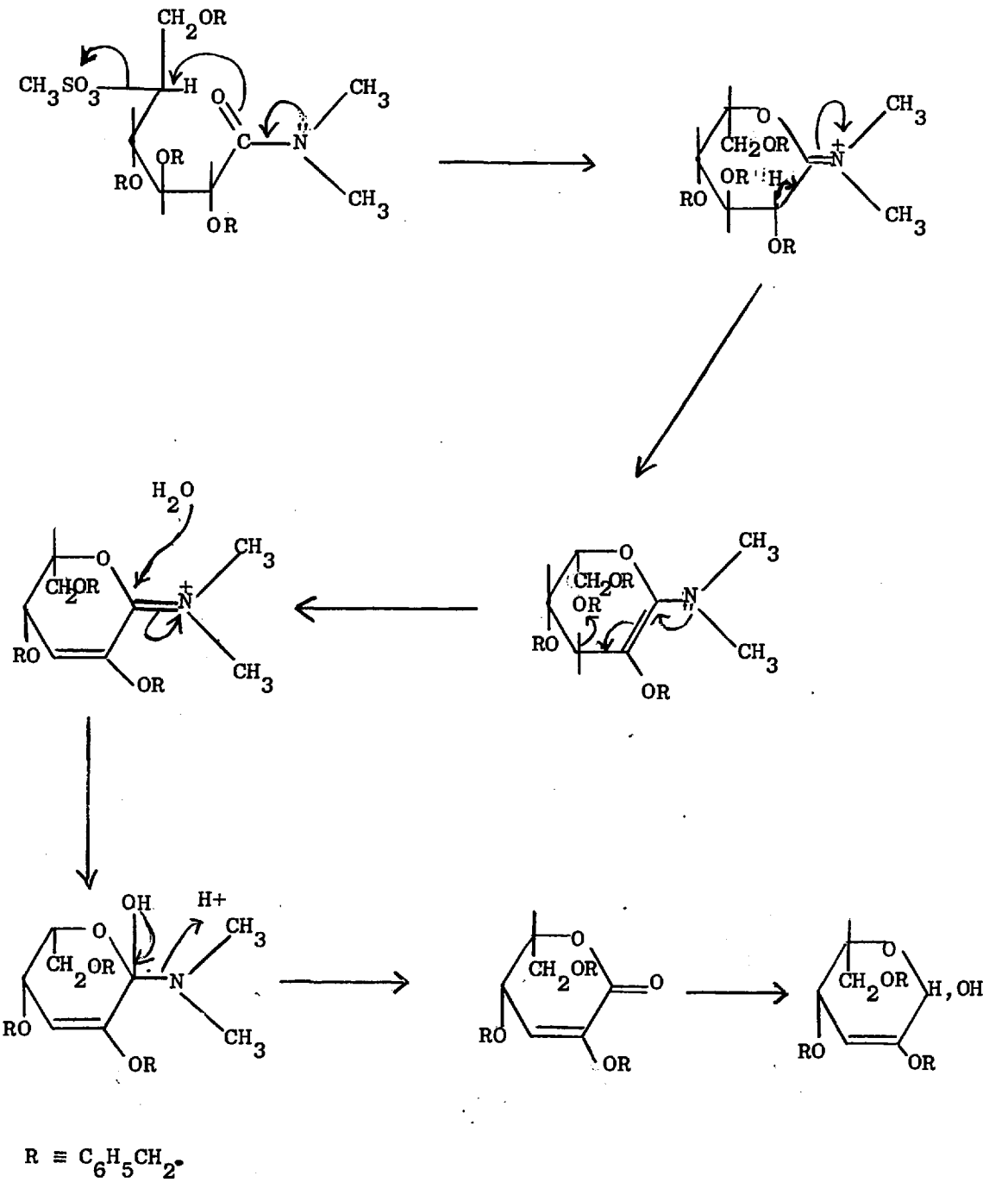
Alkaline degradation of 2,3-di-O-methyl sugars leads to these derivatives[66, 67] (Scheme XXXIX).



SCHEME XXXIX

2,3,4,6-Tetra-O-benzyl-N, N-dimethyl-5-O-(methylsulphonyl)-D-gluconamide reacts with potassium acetate in refluxing D.M.F. to give an α-β unsaturated ketone. This can be reduced with lithium aluminium hydride in ether[68] (Scheme XL).

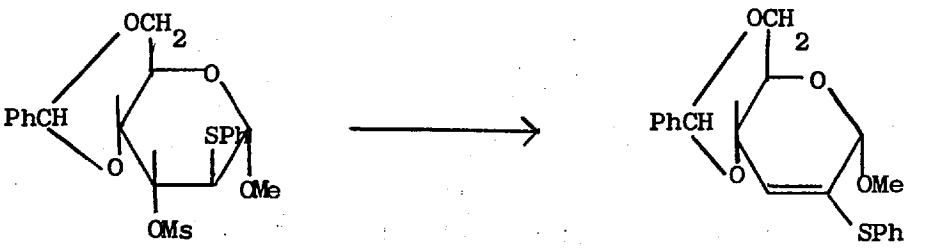
/See over for Scheme XL/



R ≡ $C_6H_5CH_2$•

SCHEME XL

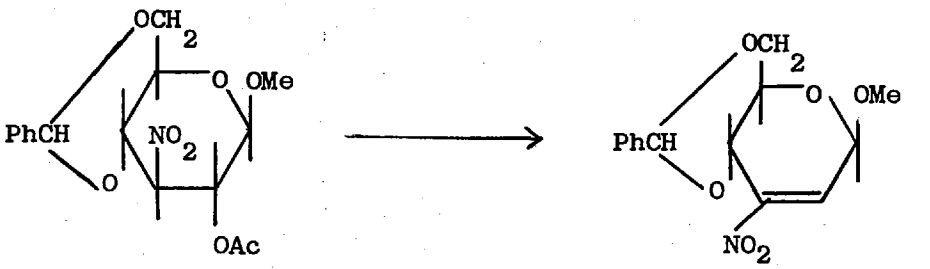
2-Thiophenyl compounds have been prepared by elimination of C-4 sulphonic ester derivatives, using 1,5 diazabicyclo [4,3,0]-5-nonene in D.M.S.O. [69] (Scheme XLI).



MS ≡ CH_3SO_2.

SCHEME XLI

H. H. Baer and co-workers prepared these types of compound by base catalysed elimination of acetic acid from appropriate 2-O-acetyl-3-deoxy 3-C-nitroglycopyranosides [70,71] (Scheme XLII).

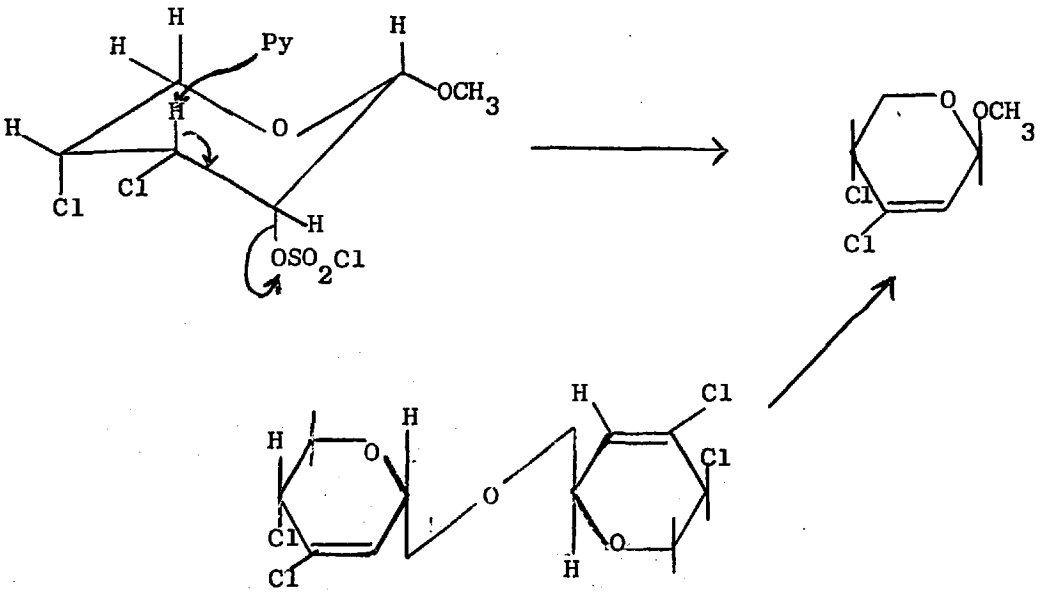


SCHEME XLII

The α-D anomer has been prepared in a similar manner [72].

Methyl α-L-arabinopyranoside on treatment with sulphuryl chloride and pyridine gave crystalline methyl 3,4-dichloro-3,4-dideoxy-β-D ribopyranoside 2-chlorosulphate, which in turn on standing in pyridine underwent the loss of chlorosulphuric acid to give crystalline methyl 3,4-dichloro-2,3,4-trideoxy-β-D-glycero-pent-2-enopyranoside. [73] Similarly, amongst the reaction

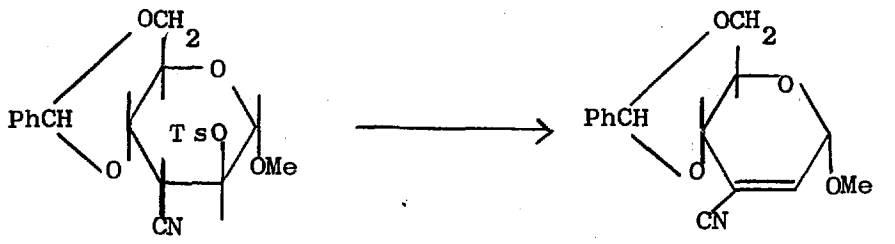
products of L-arabinose with sulphuryl chloride and pyridine was a dimer,3,4-dichloro-2,3,4-trideoxy-α-D-glycero-pent-2-enopyranosyl 3,4 dichloro-2,3,4-trideoxy-α-D-glycero-pent-2-enopyranoside. Methanolysis of this dimer gave the same final product (Scheme XLIII).



SCHEME XLIII

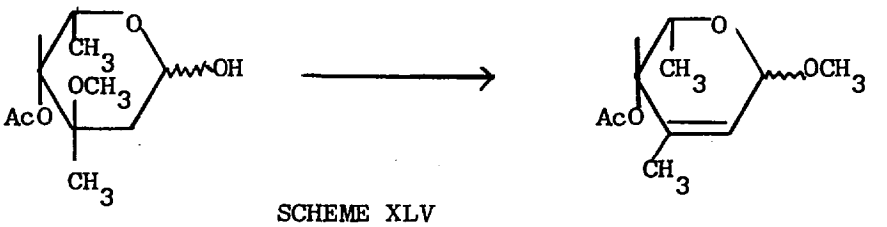
The α-D isomer has been synthesized in a similar manner and shown to be less stable than the β-D anomer [74].

Methyl 4,6-O-benzylidene-3-cyano 2,3 dideoxy-α-D-erythro-hex-2-enopyranoside can be tosylated. The tosylate, when react with diethylamine in T.H.F., gave the cyano-olefin in good yield[75]. (Scheme XLIV).



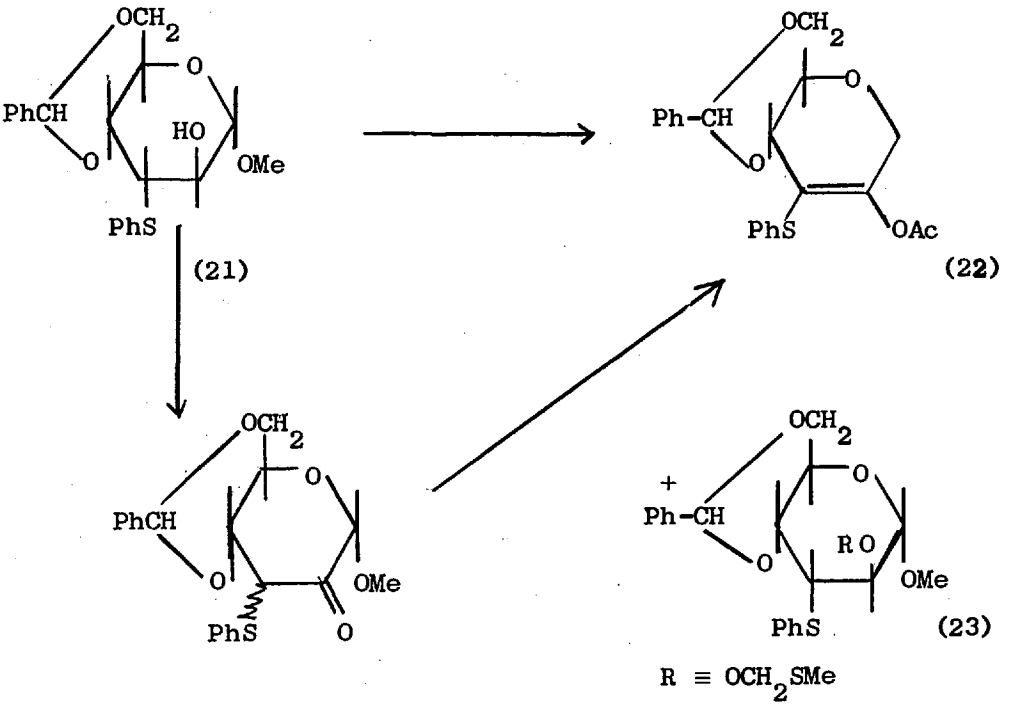
SCHEME XLIV

Methyl 4-O-acetyl-2,3,6-trideoxy-3-C-methyl-L-threo-hex-2-enopyranoside is formed on treatment of methyl 4-O-acetyl-2,6 dideoxy-3-C,O-dimethyl-L-xylo-hexopyranoside with hydrogen chloride in dichloromethane [76] (Scheme XLV).



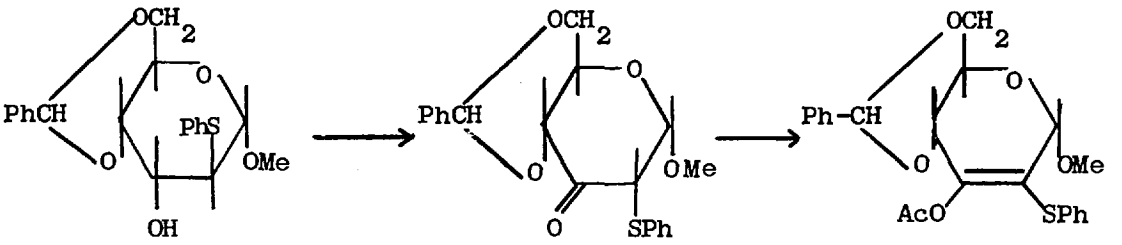
SCHEME XLV

Oxidation [77] of methyl 4,6-O-benzylidene -3-S-phenylthio-α-D-altropyranoside (21) with acetic anhydride and D.M.S.O. gave a mixture of two products (22) and (23). Oxidation of (21) using D.M.S.O. - D.C.C. in the presence of pyridineum trifluoroacetate, afforded the expected 2-ulose derivative which could be transformed into the enol acetate (22) (Scheme XLVI).



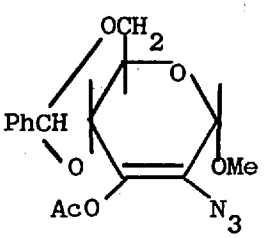
SCHEME XLVI

Similarly, oxidation of methyl 4,6-O-benzylidine-2-S-phenyl-2-thio-α-D altropyranoside with D.M.S.O and acetic anhydride, gave the 3-ulose derivative. Treatment of the 3-ulose with acetic anhydride and pyridine gave the enol acetate (Scheme XLVII).



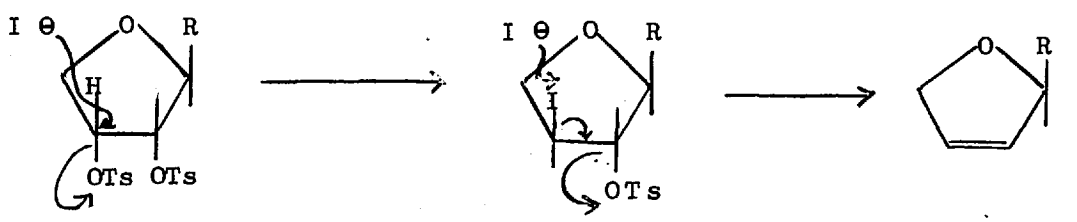
SCHEME XLVII

The C-2, azo, C-3, acetoxy derivative (24) has been similarly prepared [78].



(24)

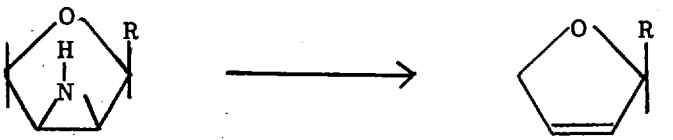
In the furanose analogues 2,3 double bonds have been introduced by treatment of appropriate 2,3-cis (or trans)-di-p-toluenesulphonic esters with the Tipson-Cohen reagent[79,80,81,82,83], namely, sodium iodide in hot D.M.F in the presence of zinc (Scheme XLVIII).



R ≡ CH (S isobutyl)$_2$

SCHEME XLVIII

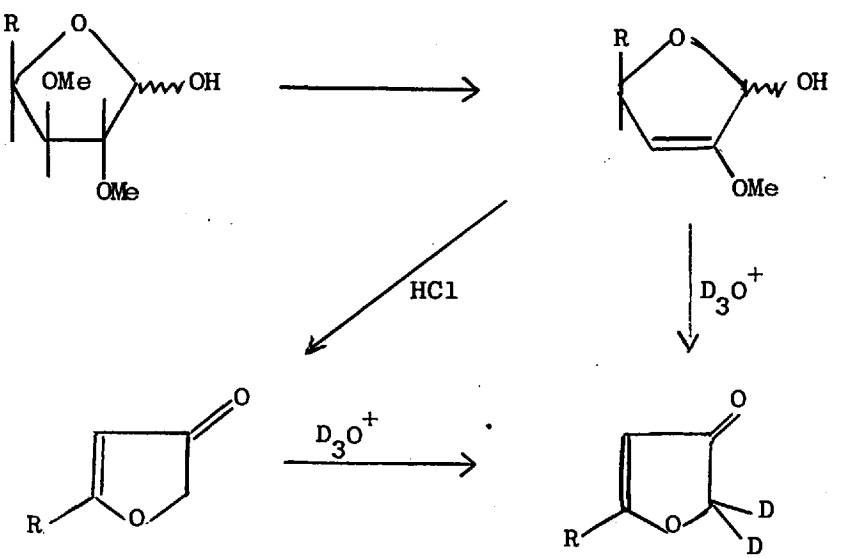
In the pyranoid series, the Tipson-Cohen reaction is not generally applicable. A method which is applicable both to the pyranoid and furanoid series, is the treatment of appropriate aziridines with sodium nitrite in acetic acid [84] (Scheme XLIX).



R ≡ H.

SCHEME XLIX

3-Deoxy-2-O-methyl-β-D-erythro-hex-2-enofuranose can be obtained by mild alkali treatment of 2,3-di-O-methyl-D-glucose. Similarly, 3-deoxy-2,5,6-tri-O-methyl-D-erythro-hex-2-enofuranose has been prepared by the action of calcium hydroxide on 2,3,5,6 tetra-O-methyl-D-glucofuranose. Studies revealed the compound to be very acid sensitive [85] (Scheme L)

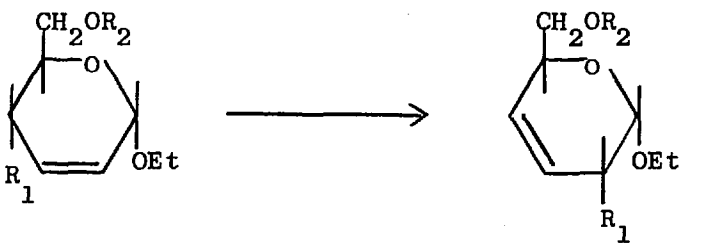


R ≡ $MeOCH_2CHOMe$.

SCHEME L

Rearrangement reactions.

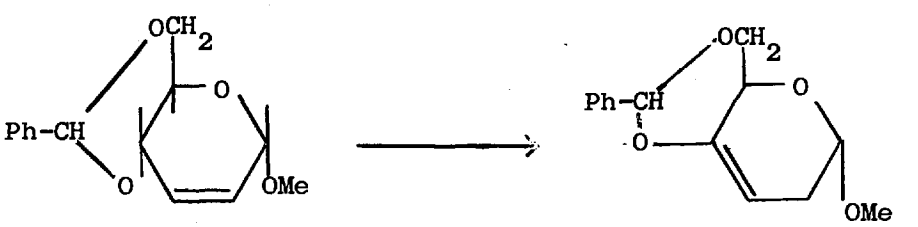
2,3 Unsaturated hexopyranoside derivatives with azido thiocyanato, vinyloxy, and (methylthio)-thiocarbonyloxy- groups at C-4, rearrange thermally to give 3,4-unsaturated isomers with azido, isothiocyanato, acetaldehydo, and (methylthio) carbonylthio- groups attached to C-2. The asymmetry of C-4 in the initial compounds is transmitted to C-2 during the isomerizations [86] (Scheme LI).



R_1	R_2	R_1	R_2
N_3	$MeSO_2$	N_3	$MeSO_2$
SCN	$MeSO_2$	NCS	$MeSO_2$
$OCH=CH_2$	$COC_6H_4NO_2$	CH_2CHO	$COC_6H_4NO_2$
O.CS.SMe	O.CS.SMe	SC.OSMe	OCS.SMe

SCHEME LI

Under basic conditions, (D.M.S.O and potassium tertiary butoxide) at room temperature, isomerization of the double bond can occur [69] (Scheme LII).



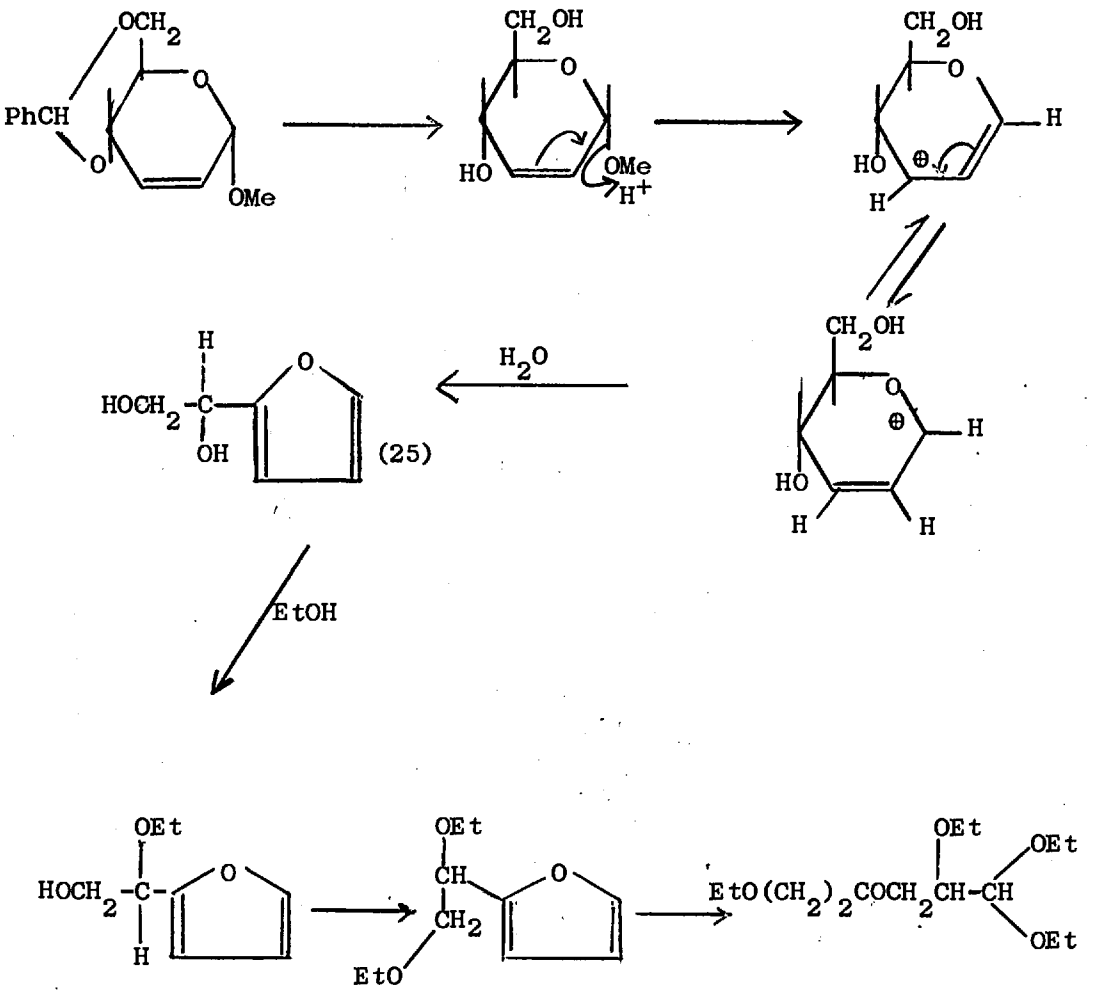
SCHEME LII

Methyl 4,6-O-benzylidene-2,3-dideoxy α-D-erythro-hex-2-enopyranoside is extremely sensitive to acids and acidic conditions:-

(a). Prolonged contact with silica gel leads to its decomposition

(b). In aqueous acetic acid at 70°, it is rapidly hydrolysed to give 2-(D-glycero-1,2-dihydroxyethyl) furan [63] (25).

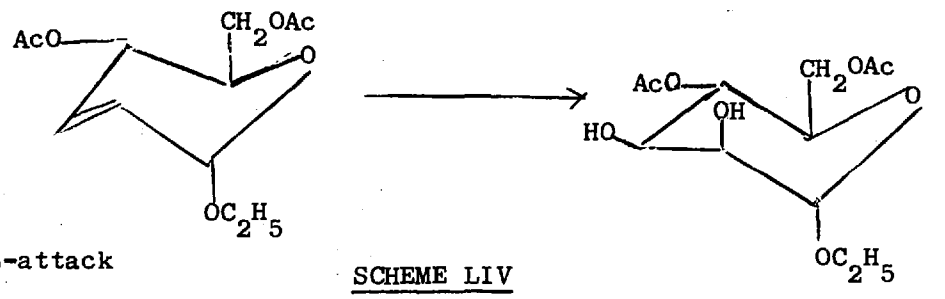
(c). In ethanol containing sulphuric acid, the same product is initially formed, but it then reacts with ethanol to give successively 2-(1-ethoxy-2-hydroxyethyl)furan, 2-(1,2 diethoxyethyl)furan and finally, 2,6 diethoxy-4-oxohexanal diethyl acetal (all racemic) [87] (Scheme LIII).



SCHEME LIII

Oxidation reactions.

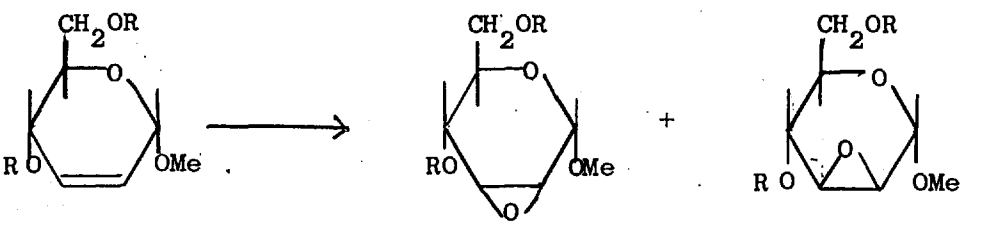
These types of compound undergo cis hydroxylation with hydrogen peroxide and osmium tetroxide. 2,3 Dideoxy-α-D-erythro-hex-2-enopyranoside and its diacetate gave D-manno products almost exclusively, the acetate being crystalline and obtained in good yield [88] (Scheme LIV).



SCHEME LIV

Similarly, methyl-5-O-trityl-β-D ribofuranoside was obtained by oxidizing methyl 2,3-dideoxy-5-O-trityl-β-D glycero-pent-2-enoside with osmium tetroxide.[89]. There are many more examples [90,91].

Epoxidation of methyl 4,6 di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside gave methyl 4,6-di-O-acetyl-2,3-anhydro-α-D allopyranoside and -mannopyranoside in the ratio of 2:3. However, consistent with expectations the 2,3-anhydro-D-alloside was the major product (allo:manno, 3:1) when the oxidation was carried out on the unacetylated analogue (Scheme LV).

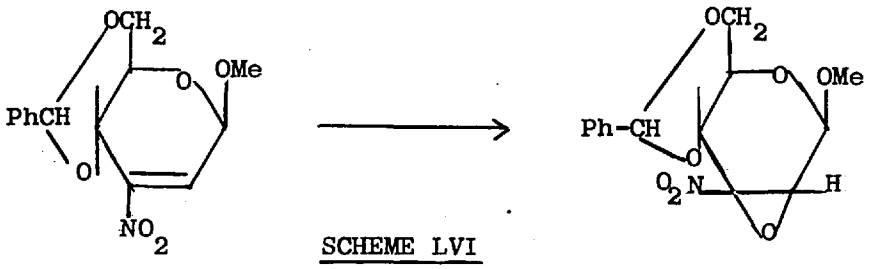


a) R ≡ CH_3CO

b) R ≡ H

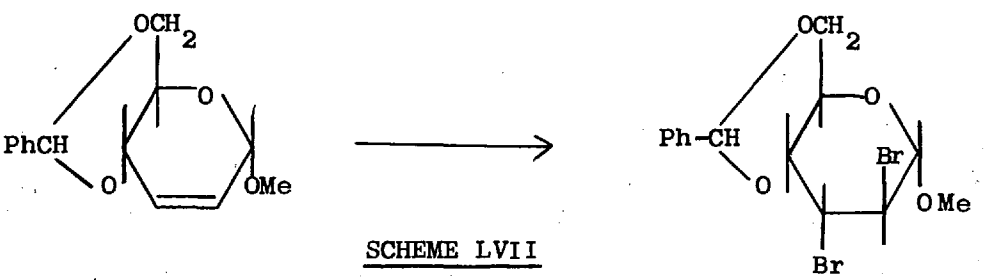
SCHEME LV

Methyl 4,6-O-benzylidene-2,3 dideoxy-3-C-nitro-β-D-erythro-hex-2-enopyranoside reacts with sodium hypochlorite in T.H.F. to give a nitroepoxide, the first member in the field of sugar chemistry [92] (Scheme LVI).



SCHEME LVI

Recently, bromination of methyl 4,6-O-benzylidene-2,3 dideoxy-α-D-erythro-hex-2-enoside has been achieved with good results [93] (Scheme LVII).

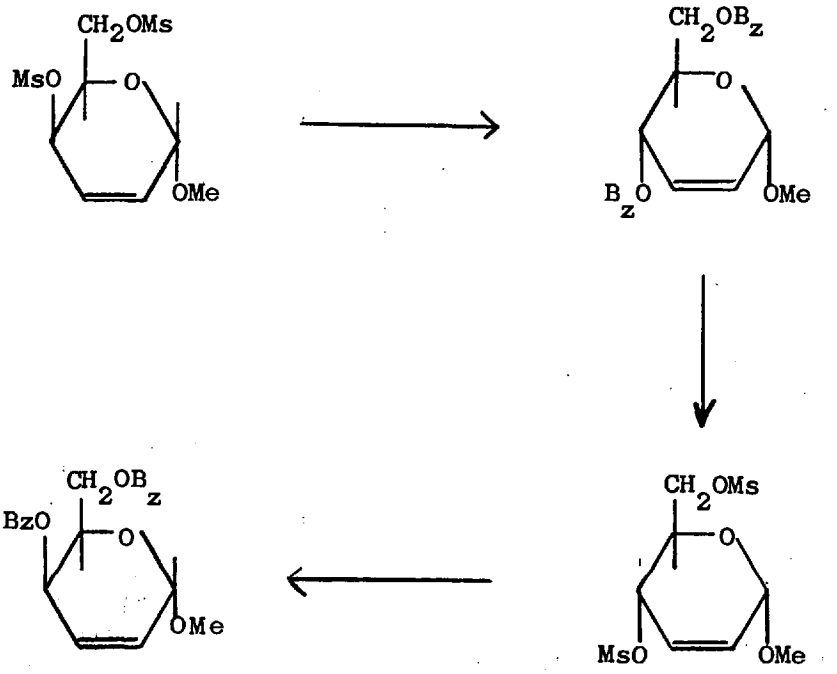


SCHEME LVII

Nucleophilic displacement and addition reactions.

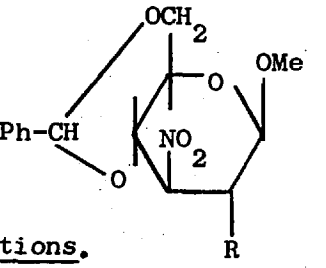
Methyl 2,3 didehydro-2,3-dideoxy-4,6-di-O methanesulphonyl-α-D-erythro-and-threo hexoside, react with sodium benzoate in D.M.F. solution, undergoing direct displacement of the 4-sulphonyl oxy-group with inversion of configuration followed by reaction at the primary site. No evidence was obtained for the formation of compounds having a 3,4 double bond [94] (Scheme LVIII).

/See over for Scheme LVIII/



SCHEME LVIII

From methyl 4,6-O-benzylidene-2,3 dideoxy-3C-nitro-β-D erythro-hex-2-enopyranoside, adducts having the structure (26) where R ≡ H [96], NH_2 [97], OMe, OEt, OCH_2Ph, SCH_2Ph, NEt_2, NC_5H_{10}, $NHCH_2COOEt$ [98], $OCCH(Me)CI_2$-iso Pr [99], $CHR'NO_2$, $CH(COOEt)_2$ [100] have been prepared by Michael type additions

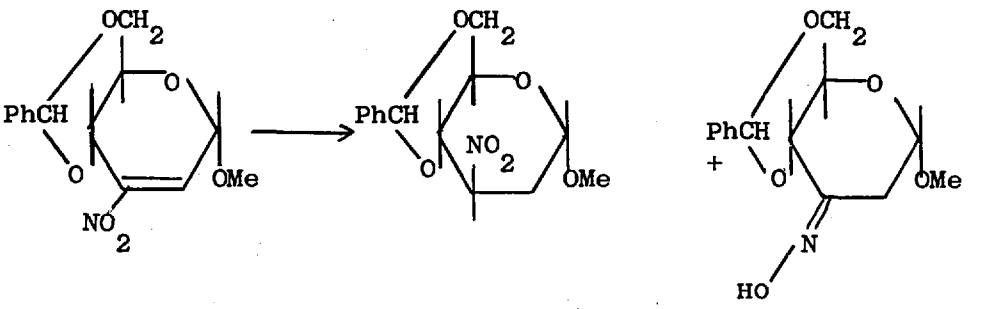


(26)

Hydroformylation and hydrogenation reactions.

Hydroformylation of 1,2,4,6-tetra-O-acetyl-3-deoxy-α-D-erythro-hex-2 enopyranose has been carried out [95].

α-D anomeric compounds gave unexpected hydrogenation products. β-D anomers, however, gave expected products using palladium on charcoal and ethyl acetate as solvent [72] (Scheme LIX).

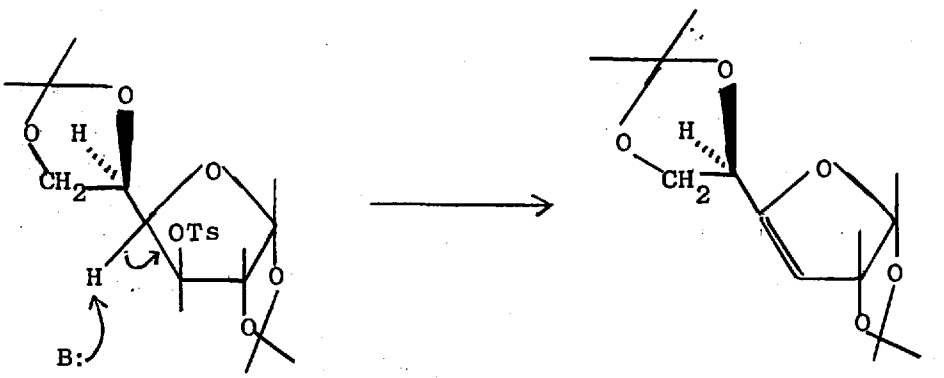


SCHEME LIX

3,4 Dehydrofuranose derivatives.

Synthesis.

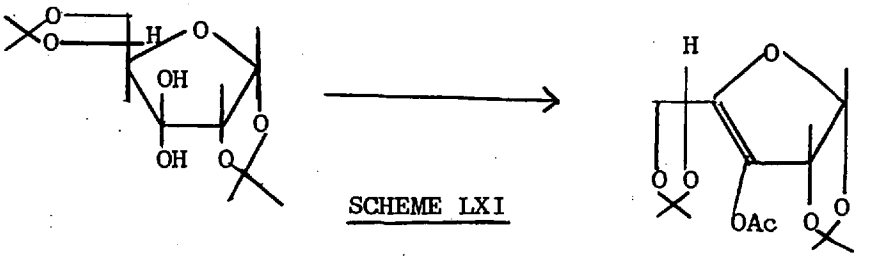
3-Deoxy-1,2:5,6-di-O-isopropylidene α-D-erythro-hex-3-enose was isolated as a by-product (20%) yield from the reaction between 1,2:5,6-di-O-isopropylidene-3-O-p-tolylsulphonyl-α-D glucofuranose and hydrazine [101]. The yield has now been improved by heating the tosyl precursor with soda-lime under vacuum [102], or by heating it with tetrabutyl ammonium fluoride in acetonitrile [103] (Scheme LX).



B: ≡ Base

SCHEME LX

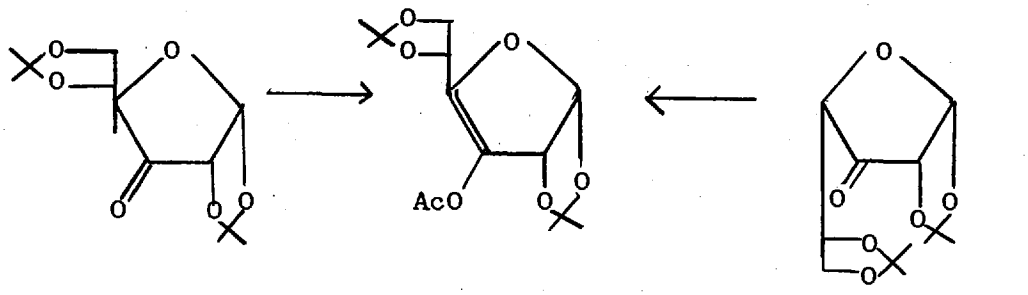
Similarly, 3-O-acetyl-1,2:5,6-di-O-isopropylidene-α-D-erythro-hex-3-enose has been prepared in good yield by reaction of 1,2:5,6-di-O-isopropylidene-α-D-ribo-3-hexulose hydrate with acetic anhydride and pyridine [104], (Scheme LXI).



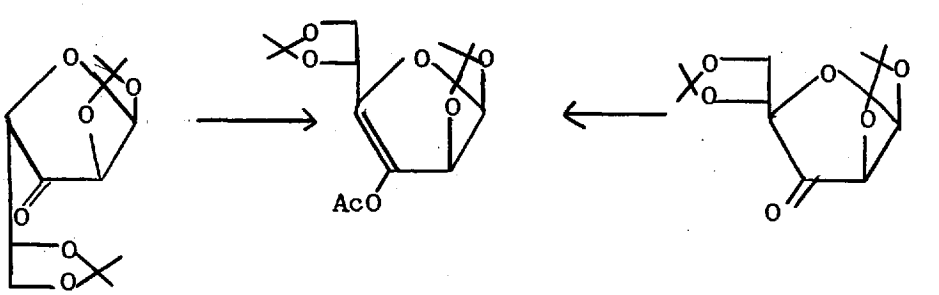
SCHEME LXI

Other analogues have been synthesized and their reactions studied [105].

Treatment of the four ketones (27), (28), (29) and (30) as 1% solutions of the sugar in 30% acetic anhydride and pyridine at room temperature, yielded the enolic sugars (31) and (32) [106].

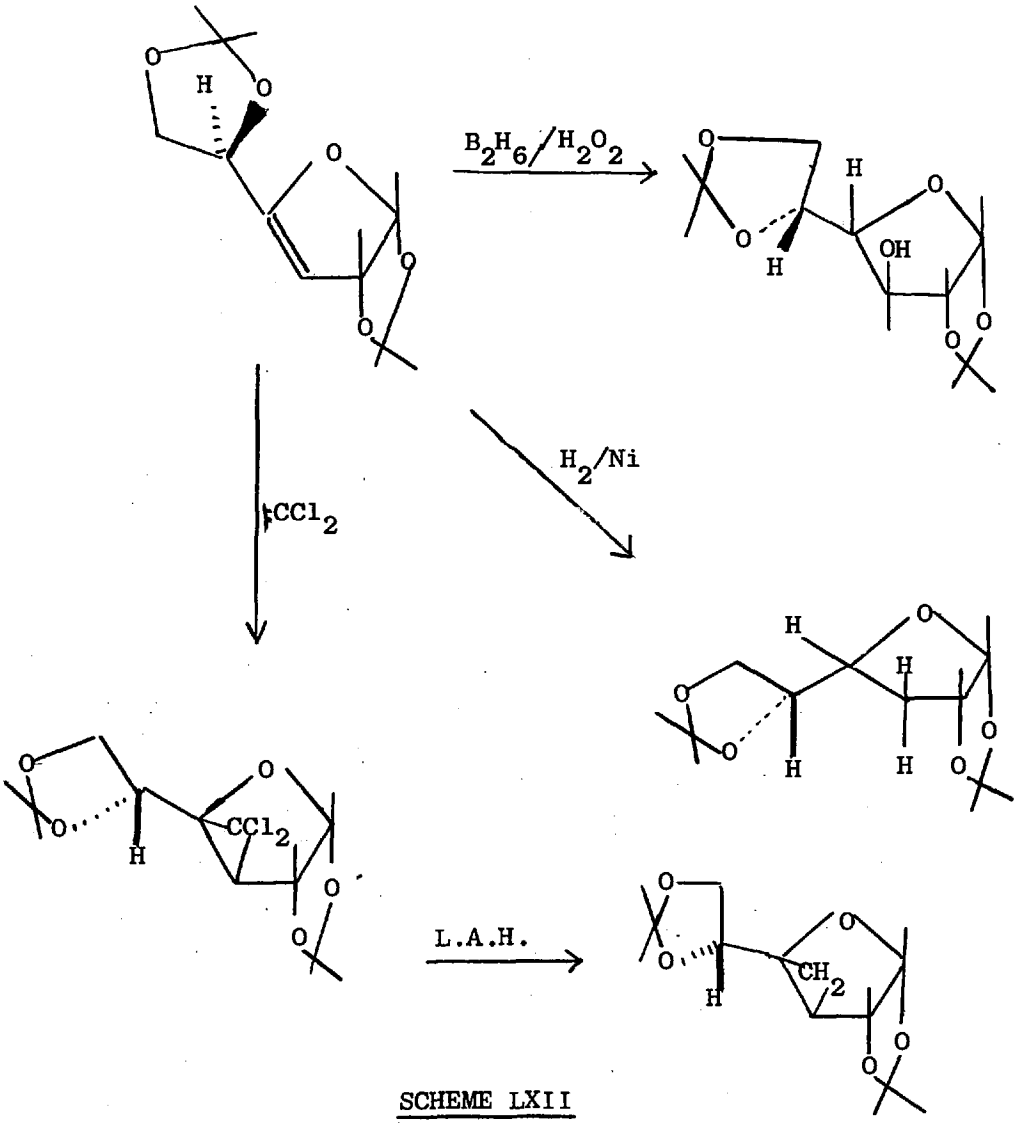


(27) (31) (28)



(29) (32) (30)

The reactions of 3-deoxy-1,2:5,6-di-O-isopropylidene α-D-erythro-hex-3-enofuranose have been studied [107,108] (Scheme LXII).



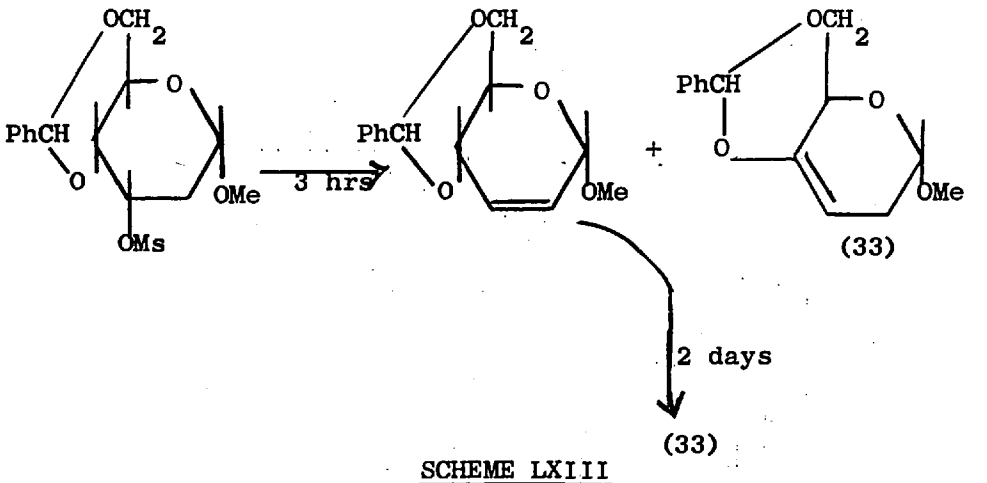
SCHEME LXII

3,4 Dehydropyranose derivatives.

Synthesis.

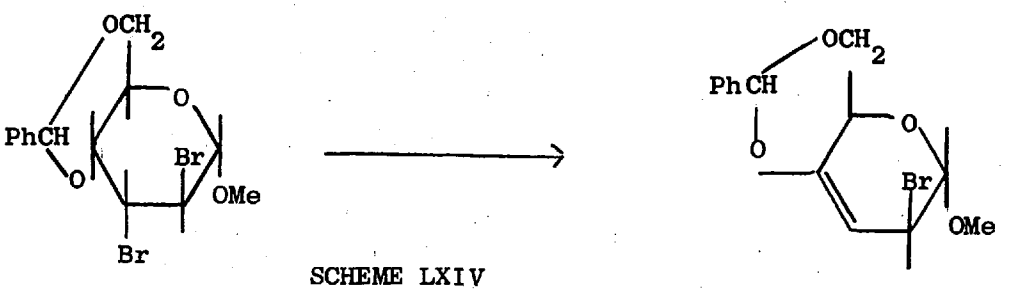
These types of compound are usually prepared by direct elimination reactions. Base catalysed elimination of methyl 4,6-O-benzylidene-2-deoxy-3-O-(methylsulphonyl)-α-D-arabino-hexopyranoside, using potassium tertiary butoxide in D.M.S.O., gave as the main product 4,6-O-benzylidene-2,3-dideoxy-α-D-glycero-hex-3-enopyranoside [69] (33) (Scheme LXIII).

/See over for Scheme LXIII)



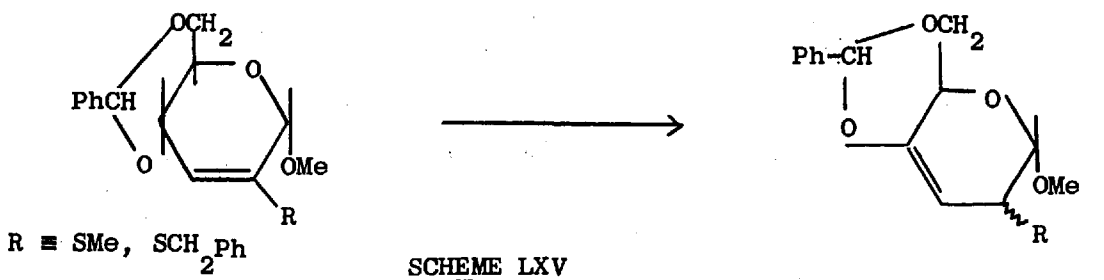
SCHEME LXIII

Similarly, methyl 4,6-O-benzylidene-2,3 dibromo-2,3 dideoxy-α-D altropyranoside reacts with potassium tertiary butoxide in refluxing xylene to give methyl 4,6-O-benzylidene-2-bromo-2,3 dideoxy-α-D-threo-hex-3-enopyranoside in high yield [93] (Scheme LXIV)



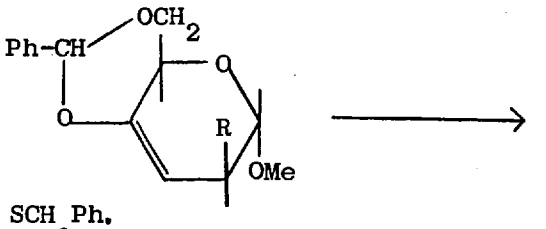
SCHEME LXIV

It has been found that 2,3 unsaturated compounds bearing an alkylthio group on C-2, are isomerized using potassium hydroxide in D.M.E. to give products having C-3-C-4 double bonds with stereochemistry undefined at C-2 [22, 23] (Scheme LXV).



SCHEME LXV

The 2-alkythio derivatives undergo reductive desulphurization using deactivated nickel in refluxing acetone [22, 23] (Scheme LXVI).

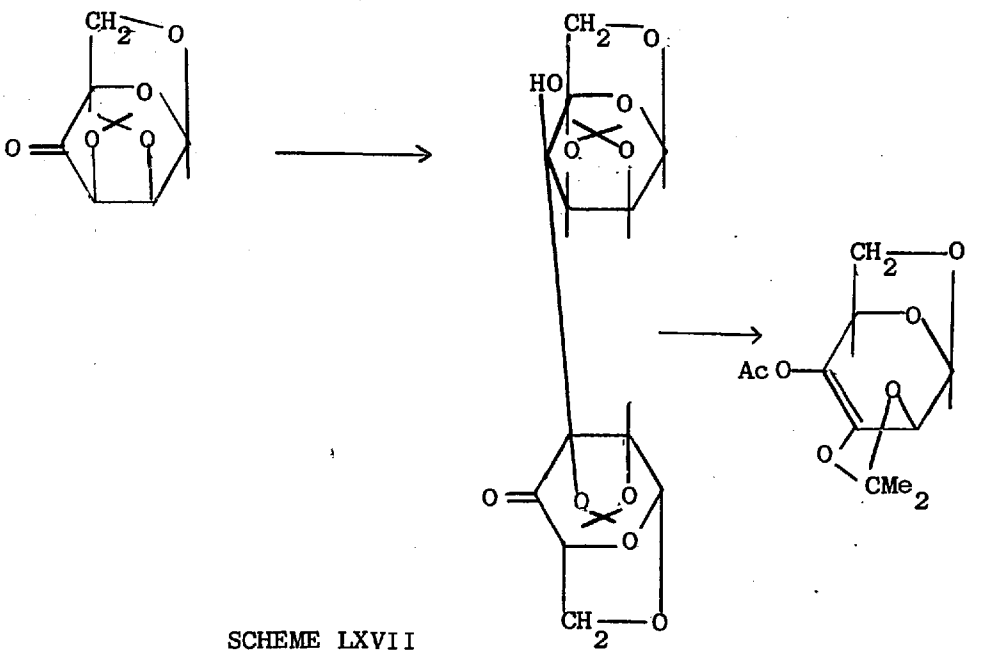


(33)

R ≡ SMe, SCH_2Ph.

SCHEME LXVI

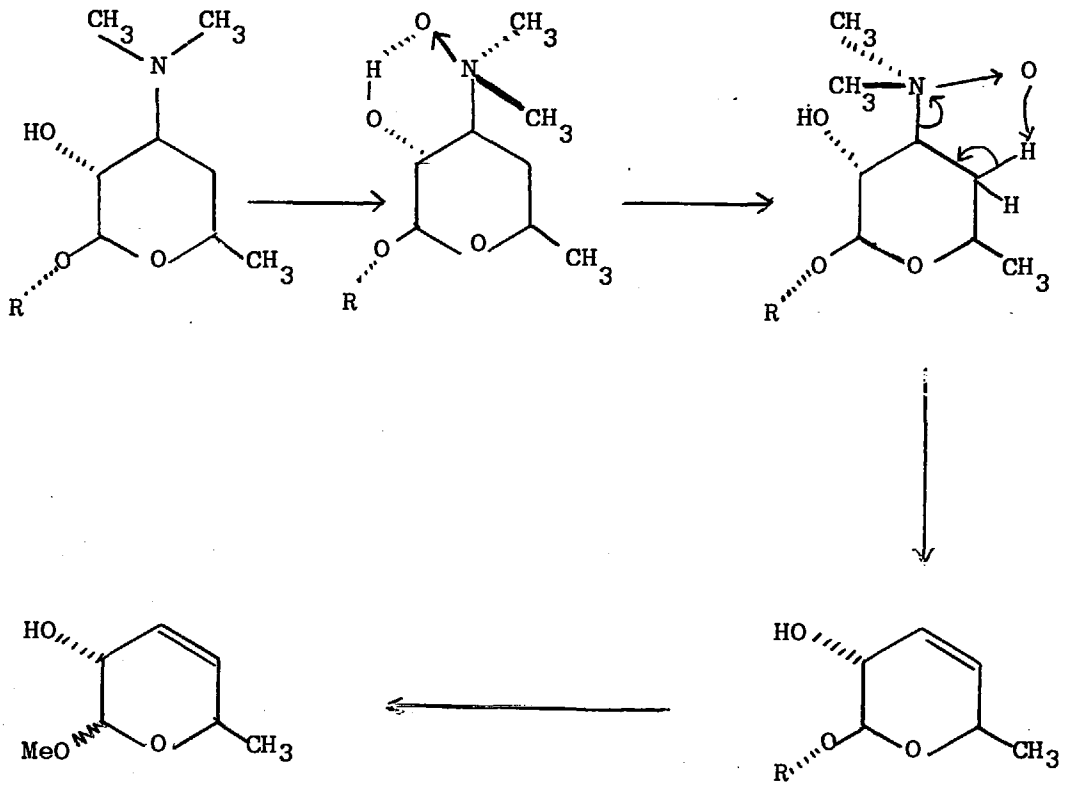
1,6 Anhydro-2,3-O-isopropylidene-β-D-lyxo-hexopyranos-4-ulose, is converted by acetic anhydride and triethylamine at room temperature into a dimer. Under more vigorous conditions, the same reagent converts the dimer into the crystalline 3,4-enediol acetate [109] (Scheme LXVII).



SCHEME LXVII

Pyrolysis of the N-oxides of erythromycin A and B gave products with dihydropyranyl residues (Cope elimination), from which methyl 3,4,6-trideoxy-hex-3-enopyranosides were obtained by sodium borohydride reduction and subsequent methanolysis [110] (Scheme LXVIII).

/See over for Scheme LXVIII/



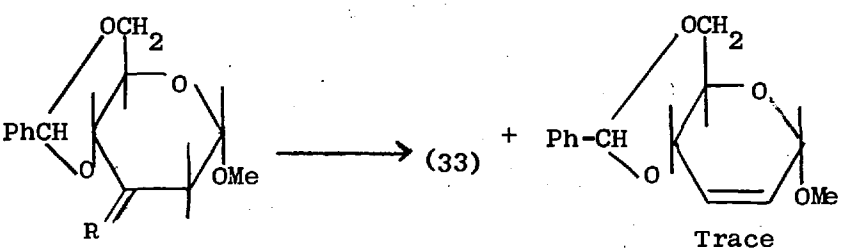
SCHEME LXVIII

The 3,4 thiocarbonate of benzyl 2-O-benzyl-β-L-arabino-pyranoside is converted to 3,4-dideoxy-3-enoside on heating in trimethyl phosphite under nitrogen [111] (Scheme LXIX).

R ≡ CH_2Ph.

SCHEME LXIX

The toluene-p-sulphonylhydrazone of methyl 4,6-O-benzylidene-2-deoxy-α-D-erythrohexoside-3-ulose undergoes elimination in N-methyl-2-pyrrolidone containing sodium methoxide to give enolic 2,3 dideoxy-α-D- glycerohex-3-enoside [24] (Scheme LXX).



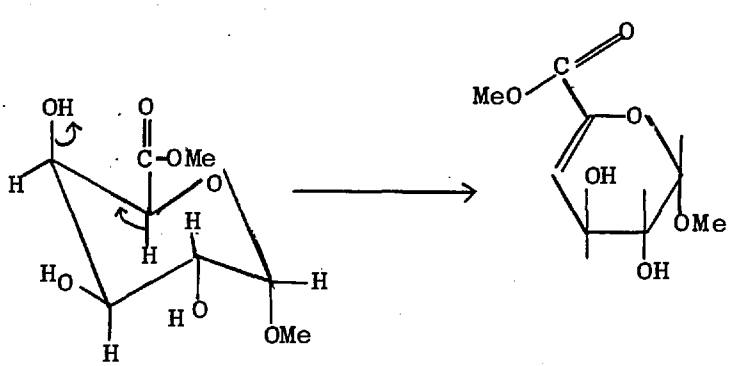
R ≡ N $NHSO_2C_6H_4Me$

SCHEME LXX

4,5 Dehydropyranose derivatives.

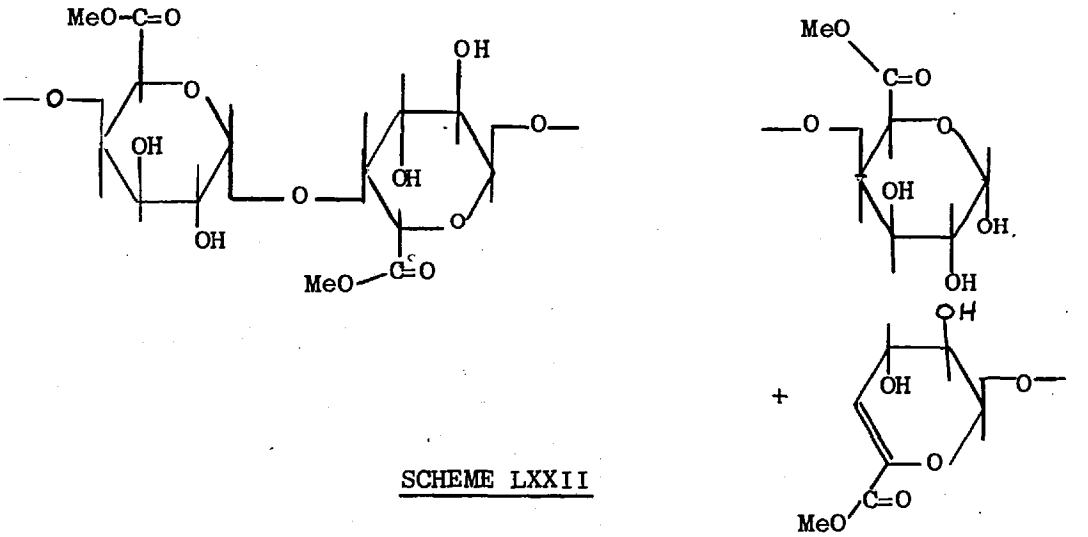
Synthesis.

Early work in the synthesis of these compounds was by base or enzyme catalysed elimination reactions of hexuronic acid derivatives. For example, methyl (methyl α-D-galactopyranoside) uronate undergoes elimination with sodium methoxide in refluxing methanol to give the corresponding 4-deoxy-4-enoside [112] (Scheme LXXI).



SCHEME LXXI

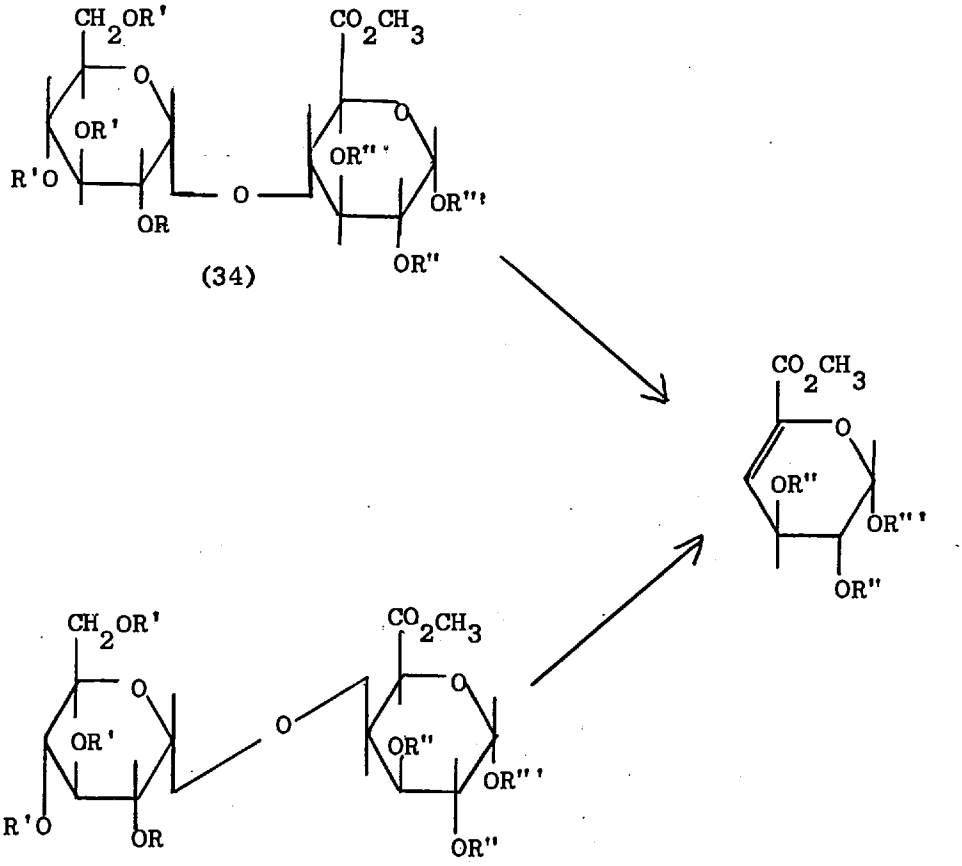
In nature, enzymatic hydrolysis of polysaccharides containing uronic acids can involve elimination reactions that result in the formation of 4,5 unsaturated uronic acid derivatives [113] (Scheme LXXII).



SCHEME LXXII

Recently, workers have studied these types of elimination in detail [114]. For studying the cis (e, a)-elimination, they synthesized the α-D-glucopyranosyl-(1-4)-α-D-glucopyranosiduronate derivative (34) and for proving of the trans (a, a) elimination, they chose the corresponding α-D glucopyranosyl-(1-4)-α-D-galactopyranosiduronate derivative (35). Eliminations were effected by using sodium methoxide in methanol and benzene at room temperature (Scheme LXXIII).

/see over for Scheme LXXIII/



(34)

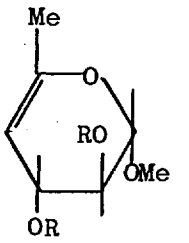
(35)

R ≡ H, SO_2CH_3; R' ≡ H, $COCH_3$.

R'' ≡ $CH_2C_6H_5$; R''' ≡ CH_3, $CH_2C_6H_5$.

SCHEME LXXIII

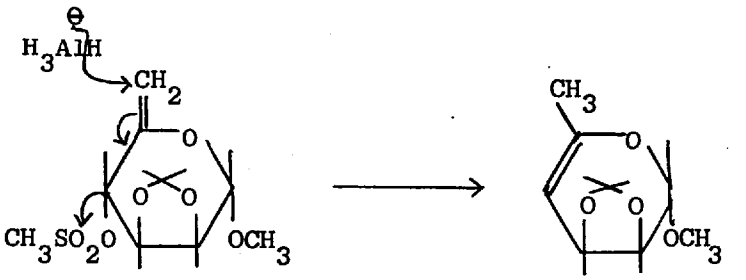
Eliminations of this type have been successfully applied to other appropriately saturated derivatives [115]. Methyl 2,3-di-O-benzyl-4,6-dideoxy-α-D-threo-hex-4-enopyranoside (36) has been recently synthesized from 2,3-di-O-benzyl-4,6-dideoxy-4-(dimethylamino)-α-D-idopyranoside (methiodide) and -α-D-altropyranoside (N-oxide) by application of the Hofmann and Cope reactions [116].



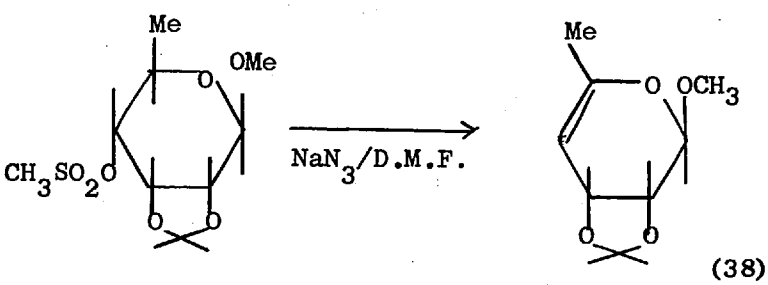
(36)

R ≡ CH_2Ph

The enantiomeric compounds (37) and (38) have been synthesized [117, 118] (Scheme LXXIV)



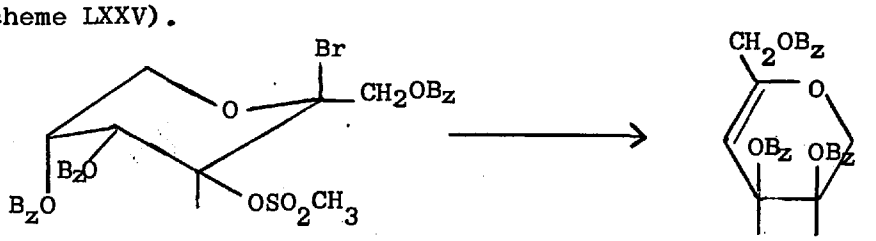
(37)



(38)

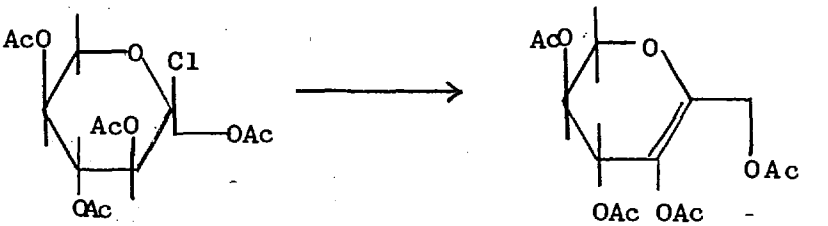
SCHEME LXXIV

Treatment of 1,4,5-tri-O-benzoyl-3-O-(methylsulphonyl)-β-D fructopyranosyl bromide with sodium iodide in acetone gave 1,5-anhydro-2,3,6-tri-O-benzoyl-4-deoxy-L-erythro-hex-4-enitol [119]. (Scheme LXXV).



SCHEME LXXV

2,3,6-Tri-O-acetyl-1,5-anhydro-4-deoxy L-threo-hex-4-enitol has been prepared [120] from (39) by treatment with mercuric cyanide in refluxing benzene, and some addition and acid degradation reactions studied (Scheme LXXVI).

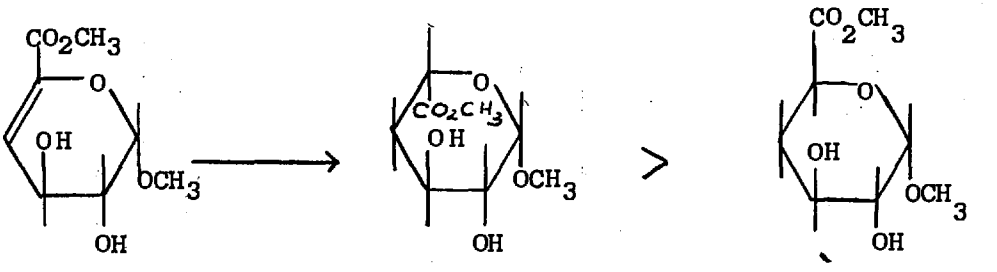


(39)

SCHEME LXXVI

The rates of elimination and formation of 4,5 dehydropyranose derivatives have been studied [121].

4-deoxy sugars and derivatives can be obtained by hydrogenation using palladium of 4-deoxy-4-enoses [122, 123] (Scheme LXXVII).



SCHEME LXXVII

The work described is comparatively recent. The chemistry of 3,4 and 4,5 dehydropyrans has not yet been fully explored. Interest in these unsaturated compounds is continually growing, and their application in the synthesis of nucleosides may prove to be of great significance. The isolation of the known naturally occurring derivatives should act as an impetus to further study in the field of unsaturated sugars.

RESULTS AND DISCUSSION.

Introduction.- The interest in this problem began with the detection by U.V. analysis of an unknown acidic contaminant in the nucleotides of plants [124]. The contaminant was found to be fairly widespread. It occurred in substantial quantities in carrots (Daucus carota), wheat (Triticum sativum), sugar beet (Beta vulgaris), sunflower (Helianthus annuus) and tobacco (Nicotiana tabacum). The contaminant was shown to be a hydroxy acid and was conveniently named daucic acid (40). Attempts were made to isolate the compound in a pure state, free from nucleotide and polysaccharide material. An extraction procedure was developed by Dr. A. J. Keys and his co-workers [125], but the material could only be isolated in crystalline form as the hydrated sodium and barium salts. It was at this stage that the problem was taken up by the Chemistry Dept.

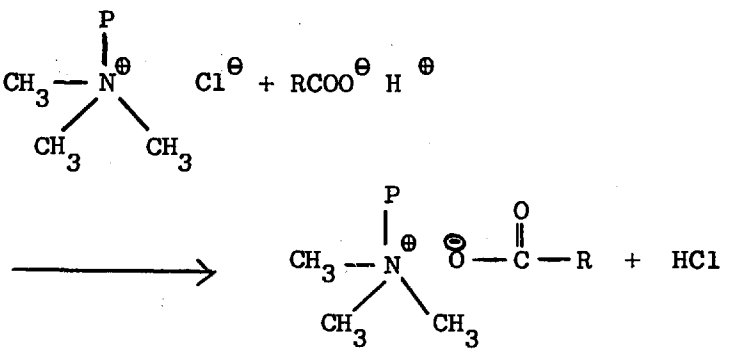
Initial work involved attempts to shorten the extraction procedure by direct extraction of acidified carrot juice with ether and ethyl acetate. Neither this nor chromatographic separation on silica plates or paper of ammoniacal carrot juice was successful. It was found, however, that gel filtration, first on sephadex G.50 and then on G.10 gave enriched fractions of daucic acid ammonium salt.

Concurrently, attempts were made to convert daucic acid sodium salt into its p-bromophenacyl ester. Many methods were employed, but none was successful. It was found that daucic acid could be methylated in methanol with dry diazomethane in ether to give two crystalline derivatives of daucic acid. An isolation procedure was thus available.

[128]

Isolation of daucic acid (40). - Clear aqueous carrot juice was acidified (dil. HCl, pH 1.5-2) and treated with activated charcoal to adsorb all the polar material from solution. After washing the charcoal with distilled water the material was desorbed with dilute ammonia solution (0.02N). The ammoniacal extract was concentrated in vacuo and subjected to gel filtration on columns of sephadex G.50 and G.10 successively using water as eluent. The effluent was examined by U.V. and partial fractionation between high M.W. compounds (nucleosides, nucleotides) and low M.W. compounds (amino acids, sugars) was achieved. The low M.W. fraction was shown by U.V. (240 n.m. absorption) to contain substantial quantities of daucic acid ammonium salt.

The ammoniacal enriched daucic acid solution was introduced on to a tertiary ammonium chloride cross-linked ion exchange column (Dowex 1x4, 200-400 mesh) [126], that had been equilibrated with formate buffer [127]. Only the very polar acidic material was retained on the column. Other less polar material (sugars and polysaccharides) were removed by washing the column with distilled water (Scheme LXXVIII).

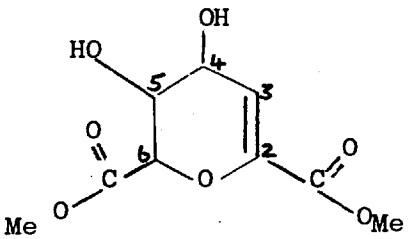


P ≡ Polystyrene.

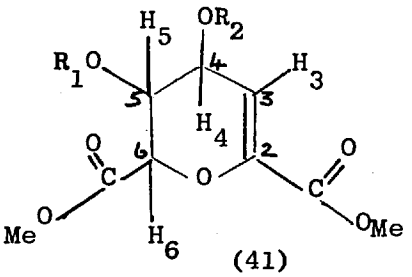
SCHEME LXXVIII

Acidic compounds were eluted with a formate buffer concentration gradient [127]. Fractions rich in daucic acid determined by U.V. ($E^{1\%}_{1\ cm}$ values) were combined. Desalting of the combined enriched daucic acid fractions was achieved by adding activated charcoal to the solution. The charcoal was washed (distilled water) to remove adhering inorganic salts. Desorption of daucic acid was achieved by extracting the charcoal with dilute ammonia (0.02N). Evaporation to dryness in vacuo gave daucic acid ammonium salt. Liberation of free daucic acid was achieved by cation H^+ exchange. Daucic acid (40) was crystallized m.p. 85-87° but gave incorrect microanalysis.

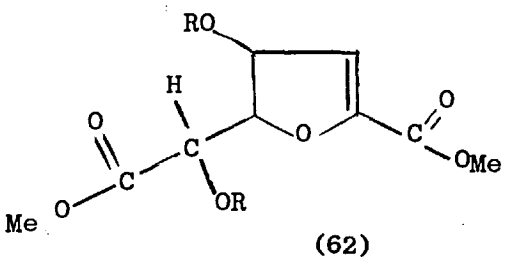
Derivatives of daucic acid. - Rapid methylation of daucic acid in methanol at room temperature with dry diazomethane in ether [128] gave optically active dimethyl daucate (41, $R_1 \equiv R_2 \equiv H$) and dimethyl daucate monomethyl ethers (41, $R_1 \equiv H$, $R_2 \equiv Me$; $R_1 \equiv Me$, $R_2 \equiv H$) as a 3:1 mixture (determined by n.m.r.). Dimethyl daucate m.p. 130-131° showed a parent mass ion M^+232, with significant peaks at $\frac{m}{e}$ 169, 155 (100%), 145 (100%), 139 and 127. Microanalysis confirmed the formula $C_9H_{12}O_7$. The i.r. spectrum had bands at 3, 500, 1740, 1720 and 1650 $cm.^{-1}$ indicating hydroxy, ester and double band absorptions. The u.v. spectrum showed $\lambda_{max.}$ (EtOH) 242 n.m. (ϵ 5,600) indicating an α,β unsaturated carbonyl chromophore. The n.m.r. spectrum exhibited two methyl ester group singlets (6.20, 6.23 τ) one vinylic multiplet hydrogen (3.96 τ) and three other multiplet hydrogens attached to carbon atoms bearing oxygen (5.34, 5.49, 5.70 τ). INDOR [129] decoupling experiments gave $J_{3,4} \equiv 3H_z$, $J_{4,5}$ indeterminate, $J_{4,6} \equiv 1H_z$, $J_{3,5} \equiv 1H_z$, $J_{3,6} \equiv 0$ and $J_{5,6} \equiv 2H_z$. These values favoured the structure of dimethyl daucate as (41, $R_1 \equiv R_2 \equiv H$) rather than the 2,3 dihydrofuran isomer (62, $R \equiv H$).



(40)



(41)



(62)

Acetylation of dimethyl daucate gave dimethyl daucate diacetate (41, $R_1 \equiv R_2 \equiv Ac$). The mass spectrum showed a parent ion M^+ of 316. The n.m.r. spectrum showed a six proton singlet at 8.21τ confirming a diacetate. INDOR [129] decoupling experiments gave $J_{3,4} \equiv 2.6$ H_z, $J_{4,5} \equiv 4.4$. H_z, $J_{4,6} \equiv 0.8$, $J_{3,5} \equiv 1.5$ H_z, $J_{3,6} \equiv 0$ and $J_{5,6} \equiv 1.8$ H_z again confirming the pyranoid structure rather than the furanoid. Benzoylation of dimethyl daucate afforded dimethyl daucate dibenzoate m.p. 112° (41, $R_1 \equiv R_2 \equiv OCC_6H_5$). The n.m.r. displayed a four proton multiplet at 2.07τ and a six proton multiplet at 2.64τ indicating a dibenzoate. Microanalysis confirmed the dibenzoate structure.

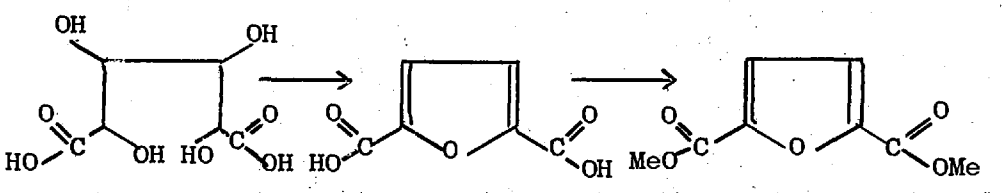
Degradation of daucic acid. Methanolysis [130] of dimethyl daucate using refluxing dry hydrogen chloride - saturated methanol gave

optically active α-hydroxy-5-methoxycarbonyl-2-furanacetic acid methyl ester. (42, R ≡ H) m.p. 134 - 135° in 40% yield.. The mass spectrum showed a parent peak M^+ at 214 and microanalysis confirmed the formula $C_9H_{10}O_6$. The i.r. spectrum displayed ester bands at 1740 and 1720 $cm.^{-1}$, a hydroxy band at 3550 $cm.^{-1}$ and double bond absorption at 1600 $cm.^{-1}$. The u.v.spectrum showed λ_{max}. (EtOH) 256 nm (ε 16,600) characteristic of an aromatic system. The n.m.r. displayed two, one proton doublets at 2.93τ (J ≡ 4 H_z) and 3.58 τ (J ≡ 4 H_z) characteristic of a 2,5 disubstituted furanoid rather than a 2,3 disubstituted furanoid derivative. A one proton singlet at 4.80τ indicated a proton attached to a carbon atom, bearing oxygen. The presence of a hydroxy group was confirmed by acetylation to give α-acetoxy-5-methoxycarbonyl-2-furanacetic acid methyl ester (42, R ≡ Ac) the n.m.r. of which gave a three proton singlet at 7.86τ confirming an acetate. Finally, racemic α-hydroxy-5-methoxycarbonyl-2-furanacetic acid methyl ester (42, R ≡ H) was synthesised (Scheme LXXX) and shown to be identical in all respects except for m.p. and optical rotation with the natural form.

Chromic acid [131] oxidation of the diester (42, R ≡ H) in acetone gave poor yields of the optically inactive 5-methoxycarbonyl-2-furanglyoxylic acid methyl ester (43).

Selenium dioxide [132] oxidation in refluxing dry xylene, however, afforded better yields of the ketodiester (43) m.p. 115 - 116°. Mass spectrum showed a parent ion M^+ at 212 with significant peaks at $\frac{m}{e}$ 181, 153(100%) and 140. Microanalysis served to confirm the formula $C_9H_8O_6$. The u.v. spectrum absorption was shifted to 293 n.m. (ε 13,000) consistent with increased conjugation. Once again the n.m.r. spectrum showed two, one proton doublets at 2.2τ and

2.63τ characteristic of a 2,5 disubstituted furanoid derivative. Comparison with synthetic ketodiester (43) confirmed the structure beyond doubt. (Scheme LXXX). Alkaline peroxide [133] oxidation of the ketodiester (43) yielded 2,5-furan dicarboxylic acid which on subsequent methylation gave the dimethyl ester (44) m.p. 109-110°. The mass spectrum showed a parent ion M^+ 184 and n.m.r. displayed an expected two proton singlet at 2.90τ and a six proton singlet at 6.18τ. Synthetic diacid was prepared by concentrated sulphuric acid dehydration [134] of muconic acid (45). Methylation of the diacid in methanol with dry diazomethane in ether [128] furnished the synthetic material (Scheme LXXIX).



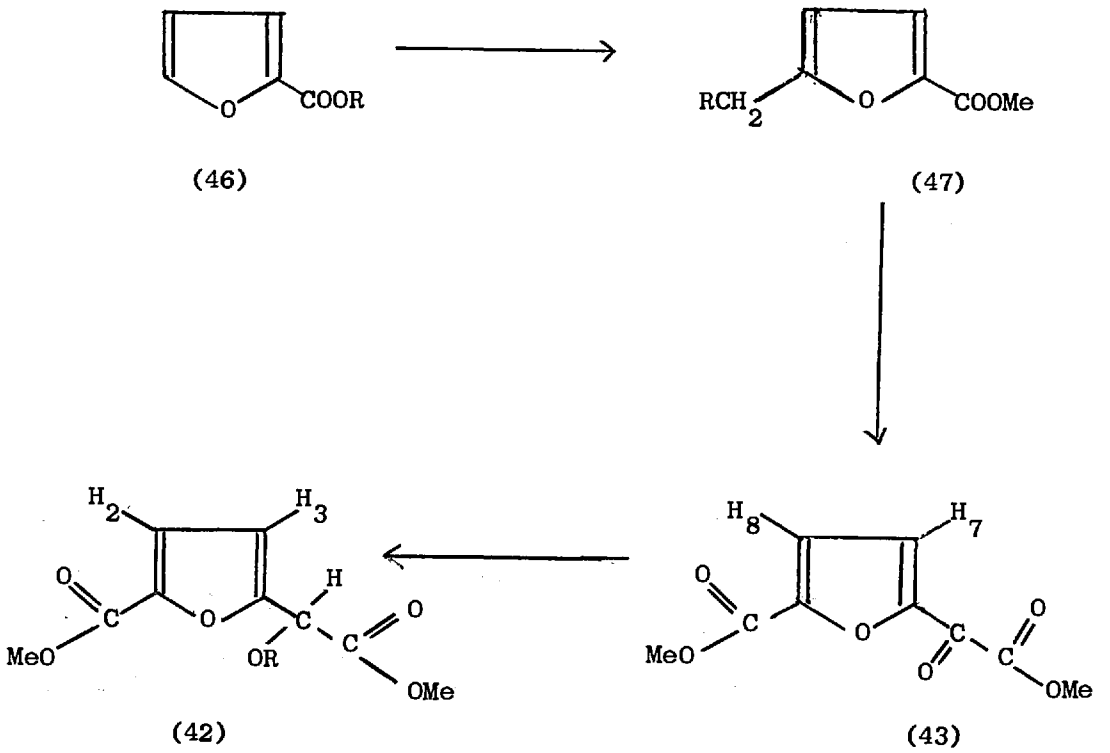
(45) (44)

SCHEME LXXIX

The natural material was in all respects identical to the synthetic. The 2,5 disubstitution pattern was thus established.

Synthesis of the degradation products.- Synthesis of the two degradation products α-hydroxy-5-methoxycarbonyl-2-furanacetic acid methyl ester (42, R ≡ H) and 5-methoxycarbonyl-2-furanglyoxylic acid methyl ester (43) was achieved via (Scheme LXXX).

/See over for Scheme LXXX/



SCHEME LXXX

2-Furoic acid (46, R ≡ H) was methylated in methanol with dry ethereal diazomethane [128], to give 2-furoic methyl ester (46, R ≡ Me) λ_{max} 250.5 n.m. (lit.[135] λ_{max} 250.5 n.m.).

Room temperature Blanc-chloromethylation [136] in chloroform employing zinc chloride and paraformaldehyde, afforded 5-chloromethylene-2-furoic acid methyl ester (47, R ≡ Cl) in good yield. The mass spectrum showed parent peaks M^+ at 174 (s), and 176 (s) attributable to the isotopes of chlorine. The n.m.r. spectrum displayed two, one proton doublets at 2.81τ and 3.42τ, a two proton doublet at 5.33τ and a three proton singlet at 6.07τ;

consistent with the expected structure.

The conversion to the 5-cyanomethylene-2-furoic acid methyl ester (47, R ≡ CN) proved difficult. Favourable conversion was obtained using a large cyanide concentration, high dilution and high polarity solvents. The 5-chloromethylene-2-furoic acid methyl ester was converted using sodium cyanide (molar ratio 0.5:11) in dry D.M.S.O. [137] at 30° to the 5-cyanomethylene-2-furoic acid methyl ester (47, R ≡ CN) m.p. 47-48° (from T.L.C. plates). The mass spectrum gave the parent peak M^+ 165 and the n.m.r. had two, one proton doublets at 2.86τ and 3.48τ, a two proton doublet at 6.05τ and a three proton singlet at 6.15τ; serving to confirm the structure. The compound like its chloro-analogue [136] was a powerful vesicant. Micro analysis proved unsatisfactory as the compound was unstable in solution and light sensitive.

The 5-cyanomethylene-2-furoic acid methyl ester (47, R ≡ CN) was hydrolysed to the diacid with refluxing 10% potassium hydroxide/ methanol [138]. Methylation in methanol with excess dry diazomethane in ether [128] yielded 5-carbomethoxymethylene-2-furoic acid methyl ester (47, R ≡ COOMe). Alternatively, iminolysis of the cyano compound (47, R ≡ CN) with dry hydrogen chloride-methanol [139] at 0° followed by <u>in situ</u> hydrolysis [140] of the imino ether at 40°, afforded 5-carbomethoxymethylene-2-furoic acid methyl ester (47, R ≡ COOMe). Evidence in support of the structure was furnished by n.m.r. which displayed two, one proton doublets at 2.77τ and 3.50τ, a two proton singlet at 6.13τ and two, three proton singlets at 6.03τ and 6.17τ. Final confirmation was by microanalysis.

Selenium dioxide [132] oxidation of the diester in refluxing xylene gave 5-methoxycarbonyl-2-furanglyoxylic acid methyl ester (43). This compound, as previously noted, was in all respects

identical to its naturally derived analogue.

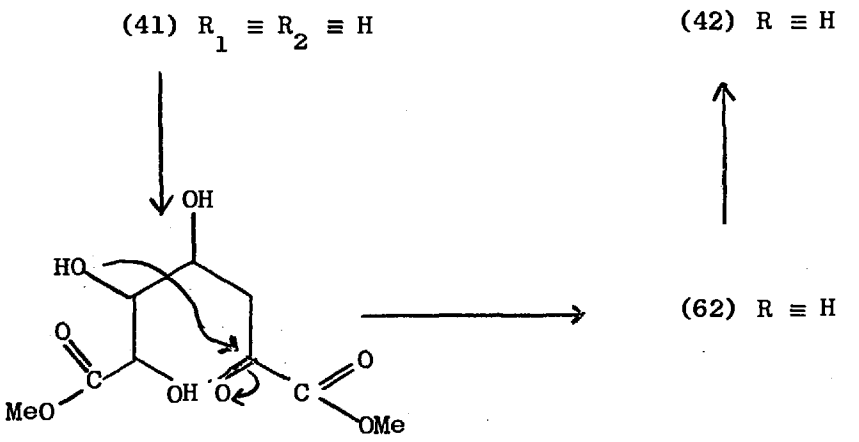
Room temperature sodium borohydride [141] reduction of the α-ketodiester (43) in dry methanol afforded racemic α-hydroxy-5-methoxycarbonyl-2-furanacetic acid methyl ester m.p. 102-103° (42, R ≡ H). The sample was in all respects identical except for m.p. and optical rotation with the natural optically active compound.

Oxidative degradation of dimethyl daucate (41, $R_1 \equiv R_2 \equiv H$). - At this point in the work the alternative structure (62, R ≡ H) for dimethyl daucate was still under consideration. Chemical proof in support of the structure (41, $R_1 \equiv R_2 \equiv H$) was required.

Selenium dioxide-xylene [132] and manganese dioxide-chloroform [152] oxidations of dimethyl daucate proved surprisingly ineffective (no reaction). It was found, however, that room temperature chromium trioxide-pyridine complex oxidation [142] of dimethyl daucate in pyridine (mole ratio 1:2.5) gave chelidonic acid dimethyl ester m.p. 115-116° (48). The mass spectrum exhibited a parent peak M^+ 212. The n.m.r. spectrum showing a two proton singlet at 2.92τ and a six proton singlet at 6.08τ fit the assigned structure. Conclusive proof was provided by direct comparison with an authentic prepared sample of the diester. The alternative structure (62, R ≡ H) had thus been eliminated.

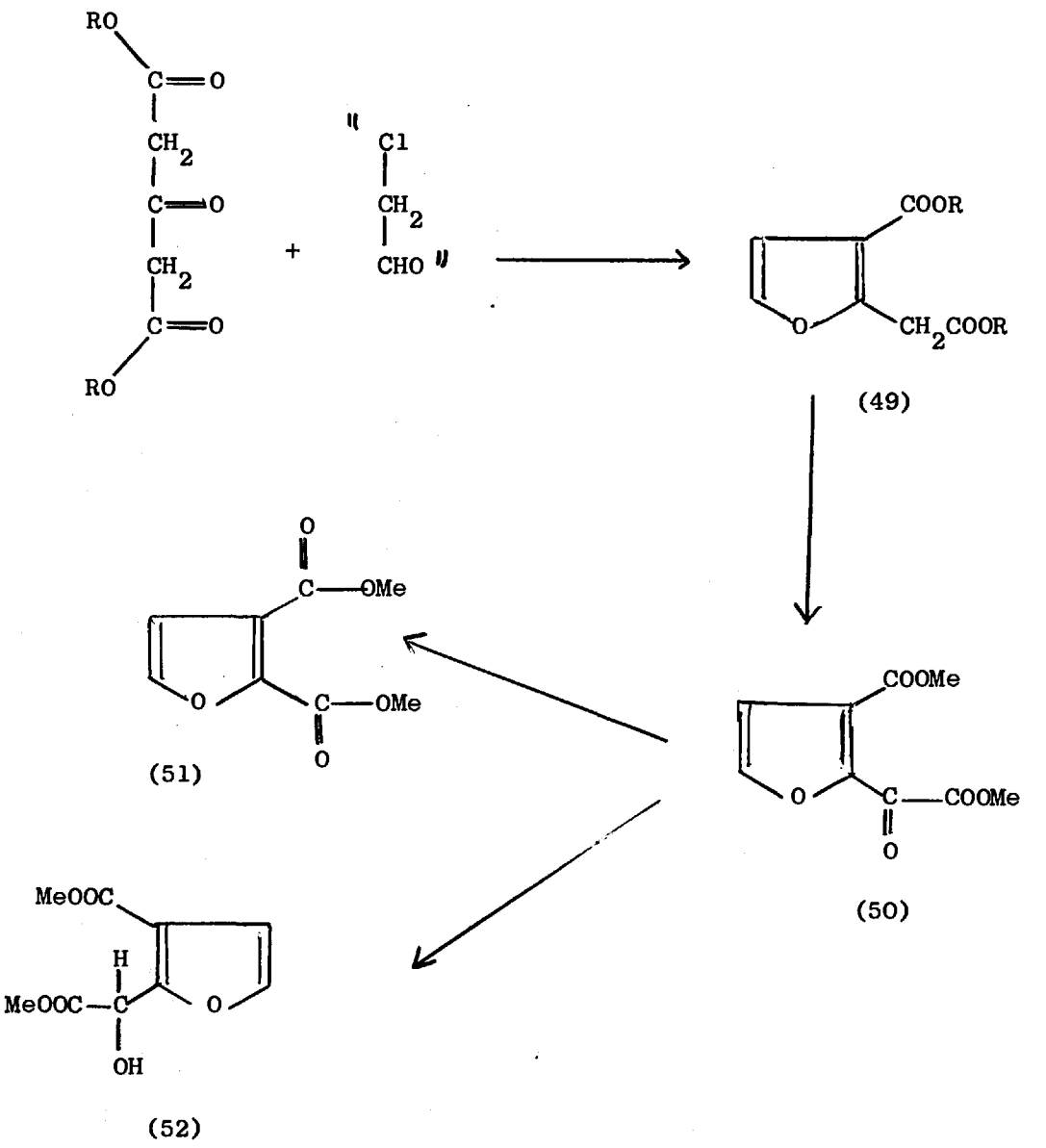
Methanolysis of dimethyl daucate to yield optically active α-hydroxy-5-methoxycarbonyl-2-furanacetic acid methyl ester (42, R ≡ H) was attributed to acid rearrangement (Scheme LXXXI).

/See over for Scheme LXXXI/



SCHEME LXXXI

Synthesis of 3-Carbomethoxy-2-furanglyoxylic acid methyl ester (50) and α-hydroxy-3-carbomethoxy-2-furanacetic acid methyl ester (52). The above two compounds were synthesized during early degradation studies. This was in order to disprove the possibility that the natural degradation products (42, R ≡ H; 43) were 2,3 disubstituted furanoid derivatives rather than the 2,5 analogues.



SCHEME LXXXII

Attempts to condense chloroacetaldehyde with acetone dicarboxylic acid dimethyl ester (Scheme LXXXII) using sodium hydride in benzene and sodium methoxide in methanol, failed. Condensation in benzene using the thallium [143] salt of acetone dicarboxylic acid dimethyl ester also failed.

Condensation of chloroacetaldehyde and acetone dicarboxylic acid dimethyl ester in pyridine [144] at room temperature, however, gave 3-carbomethoxy-2-furanacetic acid methyl ester (49, R ≡ Me). The mass spectrum showed a parent peak at M^+ 198. The i.r. spectrum showed ester bands at 1740 $cm.^{-1}$ and 1720 $cm.^{-1}$ and unsaturation bands at 1640 $cm.^{-1}$ and 1620 $cm.^{-1}$, consistent with the structure. The n.m.r. spectrum exhibited two, one proton doublets at 2.55τ and 3.25τ characteristic of 2,3 disubstituted furanoid derivatives, as well as a singlet methylene absorption at 5.89τ. Hydrolysis with base of the diester afforded the parent diacid (49, R ≡ H) m.p. 215°. All data including microanalysis were in accordance with the proposed structure.

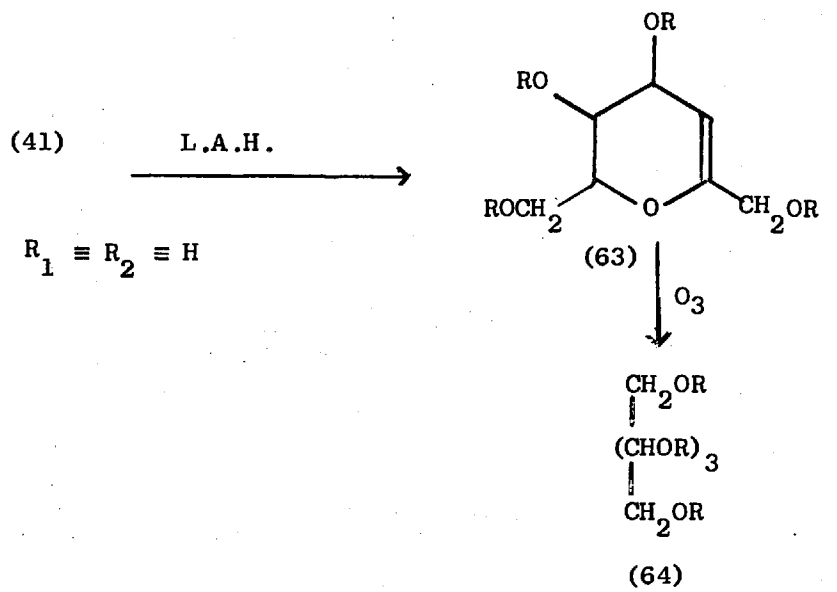
Oxidation of the diester (49, R ≡ Me) with selenium dioxide in refluxing xylene [132], furnished the α-keto derivative (50) m.p. 49-50°. The n.m.r. spectrum was as expected. It showed two, one proton doublets at 2.20τ and 3.03τ, and two methoxy singlet resonances at 6.02τ and 6.08τ. Microanalysis served to confirm the structure.

Sodium borohydride [141] reduction of the keto-diester (50) in methanol afforded the racemic α-hydroxy diester (52) m.p. 64-65°. The n.m.r. spectrum displayed the expected features, and microanalysis served to confirm the structure. It was found that the

hydroxy diester (52) could be reconverted into the keto-diester (50) in high yield, by oxidation with selenium dioxide (1 equiv.) in refluxing xylene [132].

Finally, alkaline peroxide oxidation [133] of the ketodiester (50) gave 2,3-furan dicarboxylic acid dimethyl ester (51) m.p. 35-36° (lit. [145] m.p. 39°, 36°, 37°).

Attempts to determine the stereochemistry of dimethyl daucate (41, $R_1 \equiv R_2 \equiv H$). - It was proposed to reduce dimethyl daucate with L.A.H. [146] in dry T.H.F. Subsequent ozonolysis and reduction of the ozonide with L.A.H. in T.H.F. might be expected to give a pentol (64, R ≡ H) of known stereochemistry (Scheme LXXXIII). The relative stereochemistry at C_4, C_5 and C_6 in dimethyl daucate (41, $R_1 \equiv R_2 \equiv H$) would hence be known.

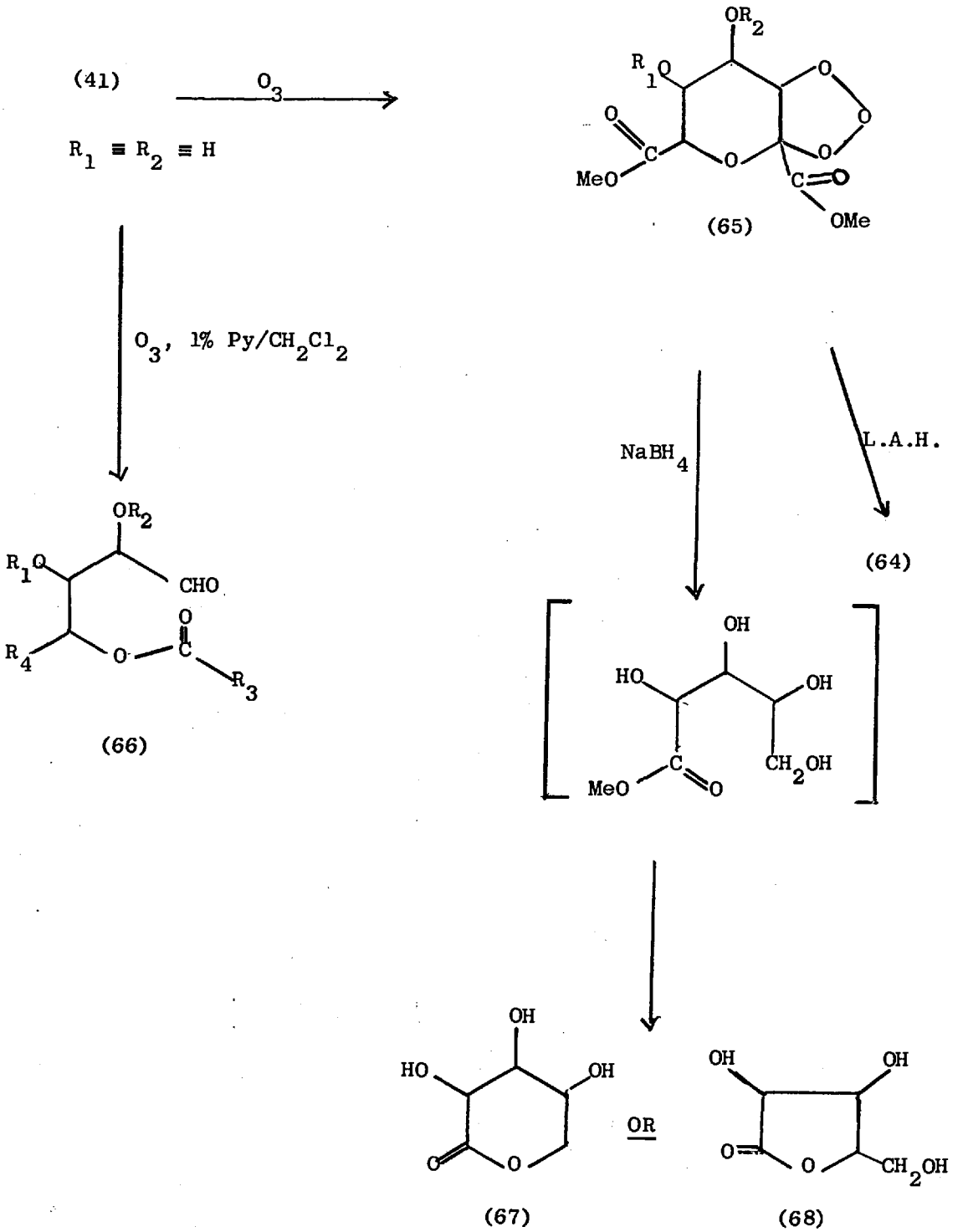


SCHEME LXXXIII

Many unsuccessful attempts were made to prepare the 2,3 dihydropyran tetra-ol (63, R ≡ H). Attempts too, were made to isolate the tetra-acetate (63, R ≡ Ac) and the tetra benzoate (63, R ≡ C_6H_5CO) by acetylation and benzoylation during work-up. These experiments were unsuccessful.

A second scheme was envisated (Scheme LXXXIV). It was hoped that low temperature (-70°) ozonolysis of dimethyl daucate (41, $R_1 \equiv R_2 \equiv$ H) in chloroform or methylene dichloride [147] might give the ozonide (65, $R_1 \equiv R_2 \equiv$ H). Reduction of the ozonide with L.A.H. (excess) in T.H.F., followed by acetylation might give the pentol acetate (64, R ≡ Ac). Alternatively, sodium borohydride (excess)-methanol reduction of the ozonide (65, $R_1 \equiv R_2 \equiv$ H), could give either the δ-lactone (67) or the γ-lactone (68). Finally, ozonolysis of dimethyl daucate in 1% pyridine-methylene dichloride, it was considered, could give the aldo-pentose (66, $R_1 \equiv R_2 \equiv$H, $R_3 \equiv R_4 \equiv$ COOMe). Many experiments were carried out, and the scheme proved to be unsatisfactory.

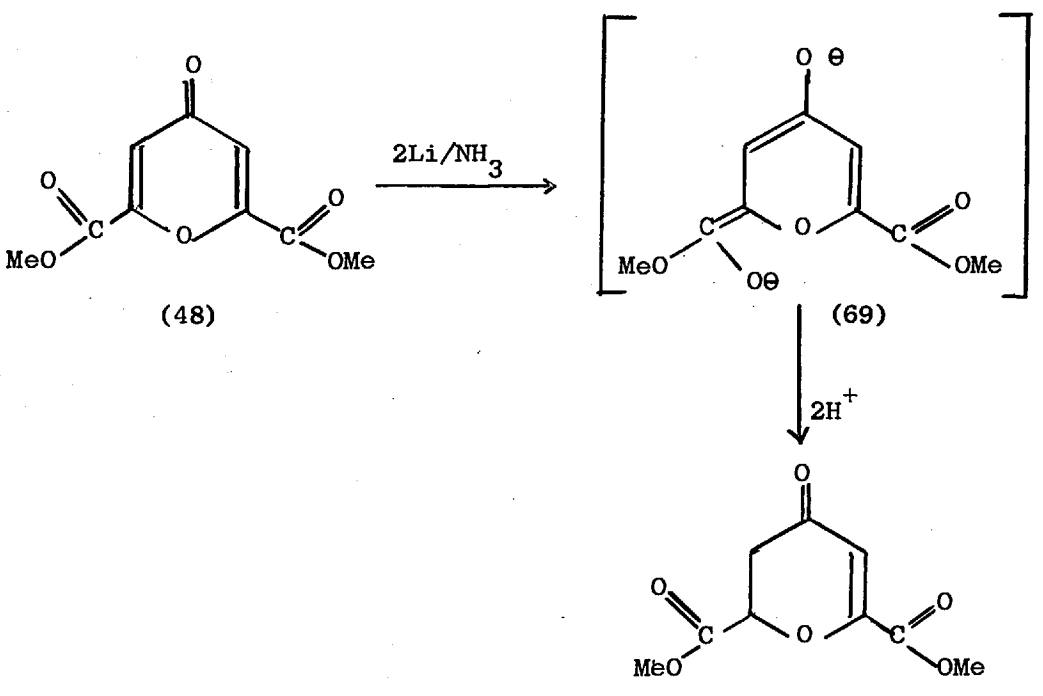
/See over for Scheme LXXXIV/



SCHEME LXXXIV

Triacetal glucal [148] (3) was chosen as a suitable model for ozonolysis. Many ozonolyses (-70°) in different solvents (methanol, methanol-methylene dichloride) followed by borohydride (excess) reduction and acetylation were carried out. The penta-acetate (64, R ≡ Ac) was not isolated. Attempts to isolate the dialdehyde (66, $R_1 \equiv R_2 \equiv$ Ac., $R_3 \equiv$ H, $R_4 \equiv CH_2OAc$) by ozonolysis in 1% pyridine-methanol also failed.

Direct attempts to synthesize dimethyl daucate (41, $R_1 \equiv R_2 \equiv$ H). - Lithium [149] - liquid ammonia reductions of chelidonic acid dimethyl ester (48) in ether were attempted (Scheme LXXXV). Acidification of the intermediate (69) with either ethanol or ammonium chloride it was postulated might give the 2,3 dihydro-γ-pyrone (57).

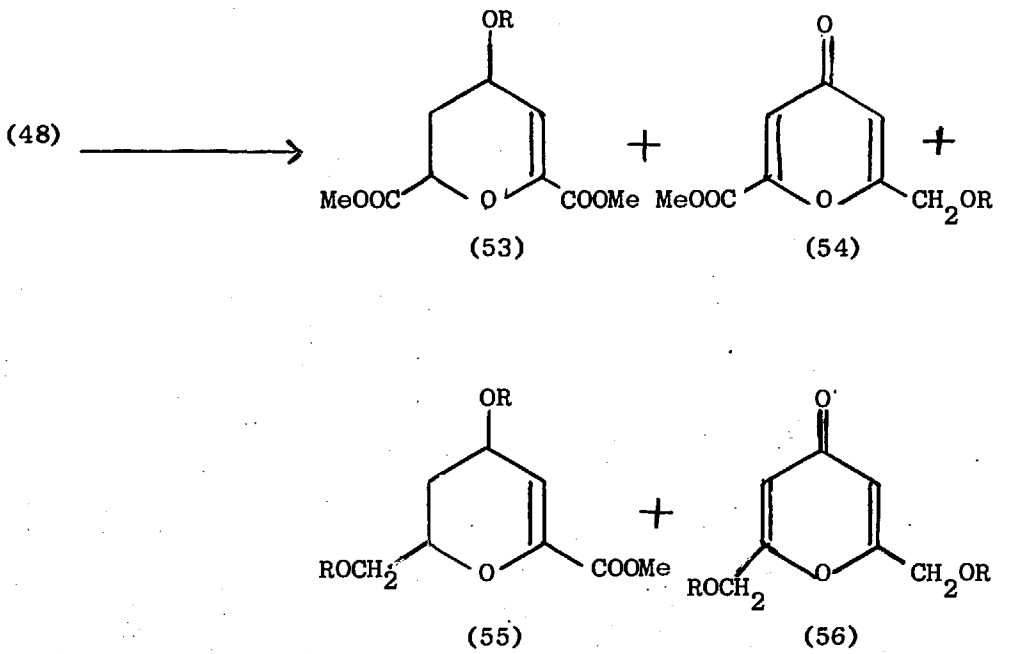


(48) (69) (57)

SCHEME LXXXV

In practice, the 2,3 dihydro-γ-pyrone (57) was not obtained, the reaction conditions being too severe.

Sodium borohydride reduction of chelidonic acid dimethyl ester in dry methanol. - Chelidonic acid dimethyl ester in dry methanol was reduced at room temperature with sodium borohydride [150] (mole ratio 1:1.25) to give four products (Scheme LXXXVI).



SCHEME LXXXVI

They were in order of decreasing R.F. values the 2,3 dihydropyran (53, R ≡ H), the γ-pyrone (54, R ≡ H) m.p. 138-139°, the 2,3 dihydropyran (55, R ≡ H) and the γ-pyrone (56, R ≡ H) m.p. 111-112°.

The γ-pyrones (54, R ≡ H; 56, R ≡ H) showed mass spectrum parent ions at M^+ 184 and M^+156 respectively, and gave correct microanalyses. Other spectral data was in accordance with the structures assigned. They formed crystalline mono and dibenzoates

respectively which exhibited mass spectrum parent peaks at M^+ 288 and M^+364, and gave correct microanalyses. Oxidation with lead tetraacetate [151] of the γ-pyrone (54, R ≡ H) in pyridine followed by methylation with dry diazomethane in ether [128] gave the γ-pyrone acetate (54, R ≡ Ac) and chelidonic acid dimethyl ester (48) both identical with authentic samples.

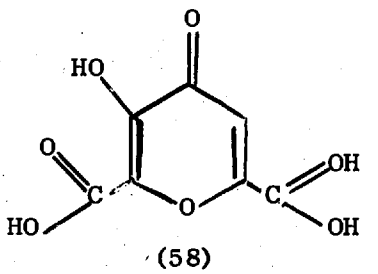
The 2,3 dihydropyrans (53, R ≡ H; 55, R ≡ H) gave parent mass spectrum peaks at M^+216 and M^+188 respectively. Once again other chemical data served to confirm their proposed structures. They formed crystalline mono and dibenzoates which showed parent mass spectrum peaks at M^+320 and M^+396 respectively, and exhibited correct microanalyses. Oxidation of the 2,3 dihydropyran (53, R ≡ H) with manganese dioxide [152] in chloroform gave the 2,3 dihydro-γ-pyrone m.p. 76-77° (57). The n.m.r. spectrum was as expected showing a vinylic one proton singlet at 3.70τ, a one proton triplet at 4.83τ and a methylene doublet at 7.07τ. Finally, microanalysis confirmed the empirical formula. Oxidation, however, of the 2,3 dihydropyran (53, R ≡ H) in dry refluxing xylene with selenium dioxide [132] (mole ratio 1:3) gave chelidonic acid dimethyl ester, identical in all respects with an authentic sample.

Attempts to make the reduction more selective. - Room temperature sodium borohydride reduction of chelidonic acid dimethyl ester (48) in oxygen saturated dry methanol gave more of the 2,3 dihydropyran (53, R ≡ H) than the γ-pyrone (54, R ≡ H) product. Reduction in an oxygenator gave all four products, characteristic of a normal reduction with no significant change in yield.

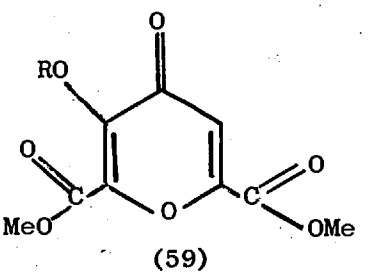
Zinc-acetic [153] acid reduction of chelidonic acid dimethyl ester (mole ratio 1 :10) was found to be too severe. Chromous acetate [154] reduction of chelidonic acid dimethyl ester was tried in various solvents (dry D.M.S.O., D.M.F., methanol, T.H.F and acetonitrile) at various temperatures (Reflux, room temperature, 0°, -20°, -40° and -70°). Once again the reagent proved too severe.

Preparation of meconic acid (58) derivatives. - Various derivatives of dimethyl and diethyl meconate [155] (59, R ≡ H; 60, R ≡ H) were prepared by standard procedures, for use in trial sodium borohydride-methanol reductions. They were in the dimethyl series trimethyl meconate m.p. 142-143° (59, R ≡ Me), dimethyl meconate acetate m.p. 114-115° (59, R ≡ Ac), dimethyl meconate benzoate m.p. 129-131° (59, R ≡ C_6H_5CO), dimethyl meconate 3,5 dinitrobenzoate (59, R ≡ $COC_6H_3(NO_2)_2$, unstable), dimethyl meconate mesitoate m.p. 106-107° (59, R ≡ mesitoyl) and dimethyl meconate tosylate m.p. 125-127° (59, R ≡ $O_2SC_6H_4pCH_3$).

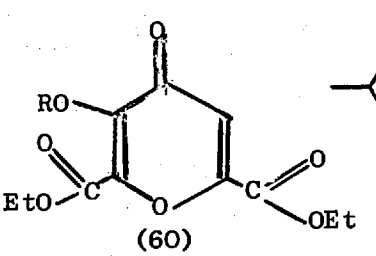
In the diethyl series diethyl meconate tosylate (60, R ≡ $O_2SC_6H_4pCH_3$) and diethyl meconate mesitoate [160] (60, R ≡ mesitoyl) were prepared.



(58)



(59)



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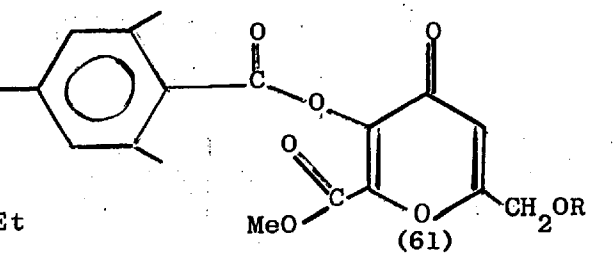


(61)

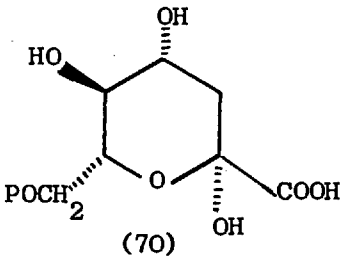
All the derivatives were characterised by n.m.r., and their structures finally confirmed where possible by microanalysis. Yields in general were low.

Sodium borohydride reductions of the dimethyl meconate derivatives. - Attempts were made to reduce each of the dimethyl mecaonate derivatives in dry methanol directly to dimethyl daucate (41, $R_1 \equiv R_2 \equiv H$) or, alternatively, to a suitable derivative thereof (41, $R_1 \equiv R_2 \equiv Ac$; $R_1 \equiv R_2 \equiv OCC_6H_5$). In general, the reactions led to a multitude of products bearing no relationship to dimethyl daucate, its acetate or its benzoate.

Room temperature borohydride reduction of dimethyl meconate mesitoate (59, R ≡ mesitoyl) in methanol gave as major product the γ-pyrone mesitoate (61, R≡H). The acetate (61, R ≡ Ac) gave a mass spectrum parent peak at M^+388 (ω) with significant peaks at $\frac{m}{e}$ 146(s) and 147(s). The benzoate (61, $R \equiv OCC_6H_5$) m.p. 150-151° showed a parent mass spectrum peak at M^+450 and gave correct microanalysis. Other chemical data seemed to confirm the structure. This work [156] is being continued.

Summary. - A certain amount of information can be derived from the n.m.r. spectra of dimethyl daucate (41, $R_1 \equiv R_2 \equiv H$) and dimethyl daucate diacetate (41, $R_1 \equiv R_2 \equiv Ac$). The coupling constants of the above two compounds were determined and none found to exceed 4.5 H_z. Conformations for the two compounds involving trans diaxial protons were hence eliminated. The derivation of daucic acid (40) from an intermediate of the shikimic acid pathway [161], namely,

heptulosonic acid (70) was precluded too.



(70)

Although the gross structure of daucic acid (40) and its derivatives is known with some certainty, the detailed stereochemistry cannot be determined without further work.

EXPERIMENTAL.

All melting points were determined on a Kofler block and are uncorrected.

Infra-red spectra were taken on either a Perkin-Elmer 257 or a Unicam S.P.200 Spectrophotometer.

Ultra violet spectra were recorded on a S.P. 800 Spectrophotometer.

N.m.r. spectra were recorded on a Varian A.60, Varian H.A. 100 or Varian T.60 Spectrometer.

Mass spectra were run on an A.E.I. M.S.9 Spectrometer.

Thin layer T.L.C. (0.025 mm thickness) and preparative layer chromatography P.L.C. (1 mm thickness) were performed on Kieselgel $G.F_{254}$, activated at 110° for 1 hr.

Acetylations and benzoylations were carried out, overnight at room temperature, with acetic anhydride and benzoyl chloride in pyridine respectively. Solvents were removed in vacuo at as low a temperature as possible.

Solvents were purified and dried according to standard procedures [157]. The activated charcoal used was prepared by soaking ordinary activated charcoal in hydrochloric acid (2N) for 30 minutes. The charcoal was washed with distilled water, first by decantation and then on the filter. Finally, it was dried in the oven at 100°.

Preliminary extractions.

a). Fresh carrots.

Carrots (9 lbs) were ground to a fine pulp. The pulp was added to 1% sodium bicarbonate solution (5 l.) at 50°. The mixture was stirred and heated for 2 hrs at 50-100°. The solution

was then allowed to stand for 3 hr. at room temperature. It was filtered (woolly asbestos) and divided into two equal portions (a) and (b).

Solution (a) was extracted with ether (1 l. portions, a hundred times). The aqueous solution was acidified (pH3, conc. HCl), and evaporated to small bulk. The solution was continuously extracted with ether and ethyl acetate. Each extract was examined by U.V. for 240 n.m. absorption but none was evident.

Activated charcoal (2 x 10g) was added to the solution. The charcoal was collected and washed with distilled water (1 l.), and treated with dilute ammonia solution (0.02N; 3 x 200 ml). The U.V. spectrum of the ammonia extract showed a 240 n.m. shoulder, indicating that the unknown carrot acid had not been extracted from the solution by the ether or ethyl acetate.

The solution (b) was acidified to pH3 (conc. HCl) and extracted with ether and ethyl acetate to give succinic acid (2 g) m.p. 186 - 187° (acetone), (lit.[158] m.p. 185°); ν_{max} (Nujol), 1700, 3000 cm.$^{-1}$; τ($CDCl_3$), 7.55 (4H,s,); 2 H's low field (D_2O exchanged).

b) Mature carrots.

The carrots (9 lbs) were washed and pulped, after removal of the tops. The pulp was added to boiling water (3 l.) with vigorous stirring). The solution was left to cool (overnight) and filtered (woolly asbestos). The clear filtrate was acidified to pH 1.5 - 2 (N. HCl). The acidified carrot juice solution was treated with activated charcoal (2 x 30 g). The charcoal was collected and washed with distilled water (1 l.).

The charcoal filter cakes were suspended in dilute ammonia solution(0.02N, 600 mls) and 2N ammonia solution added dropwise to pH 7.5-8. After ½ hr. with occasional stirring, the charcoal was collected and subjected to two more extractions with dilute ammonia solution. The ammoniacal filtrate (1800 mls) was concentrated (to 3 mls) by distillation at 30° under nitrogen at approximately 1 cm.Hg. pressure. The solution was introduced on to a column of sephadex G.50. (15 g, 20 x 1.8 cm). The acids were eluted with water. Fractions (1 ml.) of the effluent were collected and examined by U.V. The high M.W. fraction (1-40) showed very little 240 n.m. absorption. The low M.W. fraction (40 - 100) showed a strong 240 n.m. absorption.

This solution was concentrated (to 3 mls) by vacuum distillation (as above) and introduced on to a column of sephadex G.10. (25 g, 20 x 1.8 cm). The acids were eluted with water, and fractions collected (1 ml.) and examined by U.V. The 240 n.m. compound appeared in the fractions 20-35. Partial purification could be improved by successive re-introductions of the combined 240 n.m. fractions on to the column. Seven runs, however, still resulted in impure 240 n.m. compound.

The impure 240 n.m. combined fractions were introduced on to a Dowex 1 x 4, 200-400 mesh ion-exchange column [126] (2.8 c.m. diameter, 15 cm. long) which had been equilibrated with a solution (450 mls) containing formic acid (63 mls of Analar, 90%) ammonium formate (13.5 g) and sodium chloride (29.5 g) per litre. The column was washed with distilled water until the U.V. absorption had fallen to a low level. The acidic material was eluted with a gradient [127] of the above buffered salt solution (1050 mls) against distilled

water (6,050 mls). Fractions (25 mls) were collected at a flow rate of 5 mls/min. and the column effluent was continuously monitored for compounds absorbing U.V. light at 251 n.m.

The fractions containing the required compound (Nos. 177-200; $E^{1\%}_{1\ cm} \equiv 150$ for the purest fractions) were bulked. Charcoal (1.5 g) was added and the solution stirred occasionally during 15 mins. The charcoal was collected, and washed thoroughly with distilled water (500 mls). The procedure was repeated four times, until the filtrate and washings showed no 240 n.m. absorption.

The combined portions of charcoal (4 x 1.5 g) were suspended in dilute ammonia solution (60 mls, 0.02N). 2N Ammonia was added dropwise to pH > 7.5. The solution was left to stand with occasional stirring for 15 min.

The charcoal was collected and the extraction procedure repeated twice more. The combined charcoal extracts (180 mls) were concentrated under vacuum (to 3 mls) and introduced on to a cation exchange resin column in the hydrogen form (Zeo Karb 225 or Dowex). The extract was eluted with distilled water and the fractions (1 ml) analysed by U.V. until no more 240 n.m. acid compound was eluted. The combined 240 n.m. fractions were evaporated to dryness under vacuum. An oil (190-295 mgs) was obtained, which could be crystallized from ethyl acetate to give impure daucic acid (40) m.p. 85 - 87°; [Found C, 41.9; H, 4.5; $C_7H_8O_7$ requires C,41.2; H,4.0%].

Dimethyl daucate and dimethyl daucate monomethyl ether.

The oil (40, 30 mgs) was dissolved in methanol (10 mls). Dry diazomethane [128] in ether was added in excess. The solution

was left to stand at room temperature for 5 mins. Evaporation of the solvent and excess diazomethane gave an oil which was purified by T.L.C. (30% acetone/petrol, plates developed three times; or 40% acetone petrol, plates developed twice) to give;—

a). dimethyl daucate (41, $R_1 \equiv R_2 \equiv H$), (77 mgs) m.p. 130-131° (ethyl acetate - petrol) $[\alpha]_D^{24.5}$ - 202° (C, 0.9, acetone); M^+ 232 with significant peaks at $\underline{m}/\underline{e}$ 169, 155, 145 (100%), 139 and 127; λ_{max} (EtOH) 242 n.m. (ε 5,600) ν_{max} (Nujol) 3,500, 1740, 1720, 1650 cm^{-1}; τ ($CDCl_3$) 3.96 (1H, m, H-3), 5.34 (1H, m, H-6), 5.49 (1H, m, H-4), 5.70 (1H, m, H-5), 6.20 (3H, s, OMe), 6.23 (3H,s,OMe), 6.72 (2H, m, OH). INDOR ^{129} decoupling experiments gave $J_{3,4} \equiv 3H_z$, $J_{4,5}$ indeterminate, $J_{4,6} \equiv 1H_z$, $J_{3,5} \equiv 1\ H_z$, $J_{3,6} \equiv 0$, $J_{5,6} \equiv 2\ H_z$ [Found: C, 46.4; H, 5.0; $C_9H_{12}O_7$ requires C, 46.6; H, 5.2%].

b). dimethyl daucate monomethyl ether mixture (inseparable, 38 mgs). m.p. 114-115° (ethyl acetate - petrol); $[\alpha]_D^{23.0}$ - 86 (C, 0.2, chloroform); M^+246 (ω); ν_{max} (Nujol) 3500, 1740, 1720, 1650 cm^{-1}; λ_{max} (EtOH) 242 n.m. (ε 5,490); [Found: C, 48.8; H, 5.7; $C_{10}H_{14}O_7$ requires C, 48.8; H, 5.7%].

Dimethyl daucate diacetate (41, $R_1 \equiv R_2 \equiv Ac$). - Dimethyl daucate (19 mgs) was acetylated. T.L.C. purification (40% acetone/petrol) gave dimethyl daucate diacetate (29 mgs, oil). M^+316 (ω), with significant peaks at $\underline{m}/\underline{e}$ 285(s), 197 (v.s.); λ_{max} (EtOH), 237 n.m.; ν_{max} ($CHCl_3$) 1755, 1745 (sh.), 1665 cm^{-1}; τ (C_6D_6) 3.98 (1H, m, H-3), 4.15 (1H, m, H-5), 4.37 (1H, m, H-4), 5.65 (1H, m, H-6) 6.56 (6H, s, OMe), 8.21 (6H, s, $COCH_3$); INDOR ^{129}

decoupling experiments gave, $J_{3;4} \equiv 2.6$ H_z, $J_{4;5} \equiv 4.4$ H_z, $J_{4;6} \equiv 0.8$ H_z, $J_{3,5} \equiv 1.5$ H_z, $J_{3;6} \equiv 0$, $J_{5;6} \equiv 1.8$ H_z; τ ($CDCl_3$) 4.04 (1H, m, H-3), 4.27 (1H, m, H-5), 4.27 (1H, m, H-4), 5.18 (1H, m, H-6), $J_{4;3} \equiv J_{3;4} \equiv 2.3$ H_z, $J_{4;6} \equiv J_{5,6} \equiv 1.2$ H_z, $J_{3;6} \equiv 0$, $J_{4;5}$ - not observable.

Dimethyl daucate dibenzoate (41, $R_1 \equiv R_2 \equiv C_6H_5CO$). - Dimethyl daucate (26 mgs) was benzoylated with benzoyl chloride in pyridine. T.L.C. purification (40% acetone/petrol) gave the crystalline dimethyl daucate dibenzoate (46 mgs) m.p. 112° (methanol); λ_{max} (EtOH) 231 n.m.; ν_{max} ($CHCl_3$) 1763, 1757, 1743, 1737, 1723, 1684 cm^{-1}; $\frac{m}{e}$ 218 (ω), 259 (s), 197 (s); τ ($CDCl_3$) 2.07 (4H, m,), 2.64 (6H, m,), 3.90 (3H, m,), 4.93 (1H, m,), 6.10 (3H, s,), 6.27 (3H, s,); [Found: C, 62.7; H, 4.7; $C_{23}H_{20}O_9$ requires C, 62.7; H, 4.6%].

α-Hydroxy-5-methoxycarbonyl-2-furanacetic acid methyl ester (42, R ≡ H). - Dimethyl daucate (200 mgs) in anhydrous methanol was treated with an excess of a saturated solution of dry hydrogen chloride gas in anhydrous methanol [130]. The solution was refluxed until complete reaction (4 hrs). The solvent and excess reagent were removed under vacuum. The oily residue was dissolved in anhydrous methanol, and dry diazomethane in ether [128] was added. Evaporation gave a crystalline compound, which could be purified by T.L.C (40% acetone /petrol) to give α-hydroxy-5-methoxycarbonyl-2-furanacetic acid methyl ester (102 mgs) m.p. 134 - 135° (ethyl acetate-petrol); $[\alpha]_D^{25}$ + 79.3 (C, 0.2, acetone); M^+214, with significant peaks at $\frac{m}{e}$ 183, 155 (100%) and 122; $\lambda_{max.}$ (EtOH) 256 n.m. (ε 16,600);

ν_{max} ($CHCl_3$) 3550, 1740, 1720, 1600 cm^{-1}; τ ($CDCl_3$) 2.93 (1H, d, J ≡ 4 Hz, H-3), 3.58 (1H, d, J ≡ 4 Hz, H-2), 4.80 (1H, s, α-H), 6.16 (3H, s, OMe), 6.23 (3H, s, OMe), 6.74 (1H, broad exchangeable with D_2O, OH); [Found: C, 50.3; H, 4.6; $C_9H_{10}O_6$ requires C, 50.5; H, 4.7%].

The compound was identical in all respects except for m.p. and optical rotation with a racemic synthetic sample.

α-Acetoxy-5-methoxycarbonyl-2-furanacetic acid methyl ester (42, R ≡ Ac). - The α-hydroxy-5-methoxycarbonyl-2-furanacetic acid methyl ester (42, R ≡ H; 10 mgs) was acetylated. T.L.C. (40% acetone/petrol) purification gave the α-acetoxy-5-methoxycarbonyl-2-furanacetic acid methyl ester (13.8 mgs., oil). $\lambda_{max.}$ (EtOH) 253 n.m. (ε 15,820); M^+256; τ ($CDCl_3$) 2.91 (1H, d, H-3), 3.50 (1H, d, H-2), 3.92 (1H, s, α-H), 6.20 (6H, d, OMe), 7.86 (3H,s, COMe).

5-Methoxycarbonyl-2-furanglyoxylic acid methyl ester (43). - α-Hydroxy-5-methoxycarbonyl-2-furanacetic acid methyl ester (90 mgs) was dissolved in dry xylene (3 mls). Selenium dioxide [132] was added to the solution. The reaction was refluxed until complete (1 hr., T.L.C. 40% acetone/petrol).

The selenium and excess selenium dioxide was filtered off and washed with small portions of hot xylene. The combined filtrate and washings were concentrated in vacuo, to yield a yellow crystalline solid which was purified by T.L.C. (40% acetone/petrol). Further purification (removal of the last traces of selenium) was achieved by a further running on plates (as above).

White crystalline 5-methoxycarbonyl-2-furanglyoxylic acid methyl ester (44 mgs) was obtained, m.p. 115 - 116° (ethyl acetate - petrol or ethyl acetate), M^+212 with significant peaks at $\frac{m}{e}$ 181, 153 (100%) and 140; $\nu_{max.}$ ($CHCl_3$) 3050, 1735, 1685 $cm.^{-1}$; $\lambda_{max.}$ (EtOH) 293 n.m. (ε13,000), 257 n.m. (sh.); τ ($CDCl_3$) 2.2 (1H, d, H-7), 2.63 (1H, d, H-8), 6.00 (6H, d, OMe); [Found: C, 51.1; H, 3.6; $C_9H_8O_6$ requires C, 51.0; H, 3.8%].

α-Hydroxy-5-methoxycarbonyl-2-furanacetic acid methyl ester (12.1 mgs) was dissolved in acetone (3 mls.). Chromic acid [131] (1 ml. ≡ 20.16 mgs, [O], by standardization) was added to the solution dropwise. Twice the theoretical amount of chromic acid solution was consumed, to obtain complete reaction. Work up gave 5-methoxycarbonyl-2-furanglyoxylic acid methyl ester in poor yield (1.4 mgs), identical in all respects with an authentic synthetic sample.

2,5-Furan dicarboxylic acid dimethyl ester (44). -

The 5-methoxycarbonyl-2-furanglyoxylic acid methyl ester (25 mgs) was dissolved in methanol (2 mls). A mixture of 10% potassium hydroxide (2 mls) and methanol (2 mls) was added to the stirred solution in ice. The hydrolysis reaction was quick (< 5 mins). Hydrogen peroxide [133] (30% w/v solution) was added in excess. The oxidative decarbonylation could be followed by U.V.(2 hrs), shift in U.V. (EtOH) from $\lambda_{max.}$ 293 n.m. to $\lambda_{max.}$ 261 n.m.)

The methanol was removed in vacuo and distilled water (4 mls) was added to the solution. The solution was acidified (dil. H.Cl.),

saturated with ammonium sulphate and continuously extracted with ether (8 hrs). The ether was evaporated to yield an oil ($\lambda_{max.}$ (EtOH) 262 n.m., 273 n.m. (sh.) and 255 n.m. (sh.))

The oil was dissolved in methanol (3 mls), and dry diazomethane [128] in ether added in excess. Purification by T.L.C. (30% acetone/petrol) gave 2,5-furan dicarboxylic acid dimethyl ester (6 mgs), m.p. 109-110° (petrol); M^+184; $\lambda_{max.}$ (EtOH) 263 n.m. (ε 23, 460), 273 n.m. (sh.), 255 n.m. (sh.); $\nu_{max.}$ ($CHCl_3$) 1720, 1590 cm^{-1}; τ ($CDCl_3$) 2.90 (2H, s,), 6.18 (6H, s, OMe). Mixed m.p. 109 - 110° with an authentic sample of 2,5-furan dicarboxylic acid dimethyl ester showed no depression. Physical data including T.L.C. behaviour was the same in all respects too.

Preparation of an authentic sample of 2,5-furan dicarboxylic acid dimethyl ester (44). -

A stirred solution of mucic acid (45, 2 g.) in conc. sulphuric acid (4 g) was heated in a bath (132 - 134°) for forty minutes [134]. The charred product was cooled to room temperature and thrown into an ice-water mixture (8 g). The mixture was heated (steam bath, 10 mins.) and allowed to cool overnight (refrigerator). The solution was filtered, and the charred mass washed with ice-cold water (3 x 5 mls). The filtrate was examined by U.V. and shown to contain little of the 2,5-furan dicarboxylic acid dimethyl ester. The charred mass was extracted with boiling methanol (half an hour; 200, 100, 100 and 100 mls portions respectively). The combined extracts were concentrated in vacuo [128]. Dry diazomethane in ether was added in excess. Evaporation of the solvent and excess diazomethane gave an oil which was purified

first on grade 3 alumina (column, 25 x 2 cm; 30% acetone/petrol eluent) and then by P.L.C. (15% acetone/petrol, three times developed). 2,5-Furan dicarboxylic acid dimethyl ester (266 mgs) was obtained, m.p. 109-110° (petrol); $\lambda_{max.}$ (EtOH) 263 n.m. (ε 21,660), 273 n.m. (sh.) and 255 n.m. (sh.); (lit.[159] $\lambda_{max.}$ (EtOH) 263 n.m. (ε 15,500); $\nu_{max.}$ ($CHCl_3$) 1720, 1590 $cm.^{-1}$; τ($CDCl_3$) 2.90 (2H, s,), 6.18 (6H,s,OMe).

Synthesis of 2-furoic acid methyl ester (46, R ≡ Me). — Technical 2-furoic acid (46, R ≡ H, 10 g), was dissolved in methanol (150 mls). Dry diazomethane in ether[128] was added in excess. Evaporation of the solvent and excess diazomethane gave an oil. The oil was purified on grade 3 alumina (elute with 30% acetone/petrol). 2-Furoic acid methyl ester was obtained (oil, 9.3 g). M^+ 126, $\lambda_{max.}$(EtOH) 250.5 n.m.; (lit.[135] $\lambda_{max.}$ 250.5.n.m.); $\nu_{max.}$(film) 1725, 1710 (sh.), 1590, 1580 (sh.) $cm.^{-1}$; $\nu_{max.}$ ($CHCl_3$) 1723, 1706, 1590 $cm.^{-1}$; τ($CDCl_3$) 2.26 (1H, m,); 2.72 (1H, m,), 3.36 (1H, m,), 6.10 (3H, s,).

Synthesis of 5-chloromethylene-2-furoic acid methyl ester (47, R ≡ Cl). - 2-Furoic acid methyl ester (46, R ≡ Me, 8g), paraformaldehyde (2.7 g) and anhydrous zinc chloride (2.3 g) were suspended in dry chloroform (15.9 g). Dry hydrogen chloride gas was passed through the stirred suspension at room temperature for four hours[136].

The reaction mixture was poured into water (100 mls) and chloroform added (150 mls). After separation of the two layers, the aqueous layer was re-extracted with chloroform (2 x 150 mls).

The combined chloroform extracts were washed with water (100 mls) and dried (sodium sulphate). Filtration and removal of the solvent in vacuo gave 5-chloromethylene-2-furoic acid methyl ester (10.3 g). M^+ 174 (s), 175 (ω), 176 (s); $\lambda_{max.}$ (EtOH) 258 n.m.; $\nu_{max.}$ (film) 1740, 1723, 1710, 1600 $cm.^{-1}$; $\nu_{max.}$ ($CHCl_3$) 1720, 1710 (sh.), 1600 $cm.^{-1}$; τ($CDCl_3$) 2.81 (1H, d,), 3.42 (1H, d,), 5.33 (2H, d,), 6.07 (3H, s,).

Synthesis of 5-cyanomethylene-2-furoic acid methyl ester (47, R ≡ CN). - To a stirred solution of sodium cyanide (15.43 g) in dry D.M.S.O.[137] (288 mls) in a thermostatically controlled bath (30°) was added dropwise 5-chloromethylene-2-furoic acid methyl ester (2.5 g) dissolved in dry D.M.S.O. (20 mls) over a period of five minutes. The reaction mixture was allowed to stir for a further ten minutes, and then poured into water. The aqueous solution was extracted with chloroform, and the combined chloroform extracts washed with saturated sodium chloride solution and dried (calcium chloride).

Work up of two batches (2 x 2.5 g), followed by removal of the solvent in vacuo gave an oil (6.1 g). The oil was purified by P.L.C. (30% acetone/petrol, twice developed), to give 5-cyanomethylene-2-furoic acid methyl ester (1.142 g) m.p. 47 - 48°, M^+165; $\lambda_{max.}$ (EtOH) 253 n.m.; $\nu_{max.}$ ($CHCl_3$) 2310, 1728, 1615 $cm.^{-1}$ τ ($CDCl_3$) 2.86 (1H, d,), 3.48 (1H, d,), 6.05 (2H, d,), 6.12 (3H, s,).

Synthesis of 5-carbomethoxymethylene-2-furoic acid methyl ester (47, R ≡ CO_2Me). —

Two methods were tried and proved successful:-

a). 5-Cyanomethylene-2-furoic acid methyl ester (50 mgs) was refluxed with alcoholic methanol [138] (10% KOH/MeOH, 8 hrs). The methanol was removed in vacuo, and water added. The aqueous solution was acidified (dil. HCl.), saturated with ammonium sulphate and continuously extracted with ether (8 hrs). Evaporation of the ether gave an oil which was dissolved in methanol and methylated with dry diazomethane in ether [128]. Removal of the solvents and excess diazomethane in vacuo, and T.L.C. purification gave 5-carbomethoxymethylene-2-furoic acid methyl ester as an oil (36.5 mgs).

b). 5-Cyanomethylene-2-furoic acid methyl ester (1.142 g) was dissolved in anhydrous methanol (6 mls) and dry ether (20 mls). Dry hydrogen chloride gas was passed through the ice-cooled [139] stirred mixture until saturation was achieved (1 hr.). The flask was then stoppered and left to stand overnight at 0°. The reaction mixture was poured into warm water [140] (100 mls, 40°). The stirred solution was allowed to reach room temperature. The aqueous solution was extracted with ether, warmed once again to 40°, and re-extracted with ether. The ether extracts were dried (calcium chloride) and removal of the ether in vacuo gave 5-carbomethoxymethylene-2-furoic acid methyl ester as an oil, (1.242 g). M^+ 198; $\lambda_{max.}$ (EtOH) 258 n.m. (ε 16,930); $\nu_{max.}$ ($CHCl_3$) 1740 (b), 1610 (ω) $cm.^{-1}$; τ ($CDCl_3$) 2.77 (1H, d,),

3.50 (1H, d,), 6.03 (3H, s,), 6.13 (2H, s,), 6.17 (3H, s,); [Found: C, 54.3; H, 5.2; $C_9H_{10}O_5$ requires C, 54.5; H, 5.1%].

Synthesis of 5-methoxycarbonyl-2-furanglyoxylic acid methyl ester (43). - 5-Carbomethoxymethylene-2-furoic acid methyl ester (1.077 g) was dissolved in the minimum volume of dry xylene. Selenium dioxide [132] (10.77 g) was added to the solution. The mixture was refluxed until complete reaction (5.25 hr; T.L.C., 30% acetone/petrol).

The reaction mixture was cooled to room temperature and filtered, and the reaction flask and selenium residues were rinsed with portions of hot xylene. Evaporation of the solvent gave a yellow crystalline residue, which was purified by P.L.C. (20% acetone/petrol, twice developed), to give 5-methoxycarbonyl-2-furanglyoxylic acid methyl ester (265 mgs) m.p. 114-115° (ethyl acetate - petrol); M^+212, $\lambda_{max.}$ (EtOH) 293 n.m. (ε 12,850), 257 n.m. (sh.); $\nu_{max.}$ ($CHCl_3$), 3050, 1735, 1685 $cm.^{-1}$; τ ($CDCl_3$) 2.24 (1H,d,), 2.69 (1H, d,), 6.00 (6H, d,).

Synthesis of racemic α-hydroxy-5-methoxycarbonyl-2-furnacetic acid methyl ester (42, R ≡ H). - 5-Methoxycarbonyl-2-furanglyoxylic acid methyl ester (43; 160.1 mgs) was dissolved in anhydrous methanol (4 mls). Sodium borohydride (7.15 mgs, 1 eqv.) was added to the stirred solution at room temperature [141]. The solution was stirred for ten minutes. Removal of the solvent in vacuo and T.L.C. (30% acetone/petrol) gave α-hydroxy-5-methoxycarbonyl -2-furanacetic acid methyl ester (racemic, 98 mgs), m.p. 102-103° (ethyl acetate-petrol); M^+214; $\lambda_{max.}$ (EtOH) 256 n.m. (ε 16,500); $\nu_{max.}$ ($CHCl_3$) 3550, 1740, 1720, 1600 $cm.^{-1}$; τ ($CDCl_3$) 2.88 (1H, d,), 3.52 (1H, d,), 4.75 (1H, s,), 6.15 (6H, d,),

~ 6.15 (1H, OH).

Degradation to chelidonic acid dimethyl ester (48). - Oxidation of dimethyl daucate was done in two batches (15.4 mgs and 18.6 mgs respectively). The two batches were combined during work-up.

Chromium trioxide-pyridine complex [142] (43.12 mgs) was stirred with dry pyridine (2 mls). Dimethyl daucate (15.4 mgs, mole ratio 1:2.5) in dry pyridine (1 ml) was added to the solution. The mixture was stirred at room temperature overnight. The reaction mixture was poured into water, saturated with ammonium sulphate and extracted continuously with ether (8 hrs). Removal of the solvent in vacuo gave an oil.

Purification by T.L.C. (30% acetone/petrol, twice developed) of the combined product from both batches gave chelidonic acid dimethyl ester (6 mgs) m.p. 115 - 116°C (ethyl acetate-petrol); M^+212; $\lambda_{max.}$ (EtOH) 270 n.m. (ε 10,660), 280 n.m. (sh.); $\nu_{max.}$ ($CHCl_3$) 1750, 1665, 1637, 1605 $cm.^{-1}$; τ ($CDCl_3$) 2.92 (2H, s,), 6.08 (6H, s,). The sample was in all respects identical with an authentic sample of chelidonic acid dimethyl ester.

Preparation of an authentic sample of chelidonic acid dimethyl ester (48). - Chelidonic acid monosodium salt dihydrate (tech., 2 g) was dissolved in water (50 mls). The solution was filtered. The filtrate was passed down a Dowex exchange resin in the H^+ form (column, 1 x 10 cm.). The experiment was performed in two batches, (25 mls). Evaporation of the effluent gave an amorphous powder (1 g, $\lambda_{max.}$ (EtOH) 269 n.m.).

The amorphous powder was dissolved in methanol and dry diazomethane [128] in ether added in excess. Evaporation of the solvent and excess diazomethane gave a yellow crystalline solid. Purification of the solid by P.L.C. (30% acetone/petrol, twice developed) gave chelidonic acid dimethyl ester (267.2 mgs) m.p. 114 - 116° (ethyl acetate-petrol), M^+212; $\lambda_{max.}$ (EtOH) 270 n.m. (ε 10,220), 280 n.m. (sh.); $\nu_{max.}$ ($CHCl_3$) 1750, 1665, 1637, 1605 $cm.^{-1}$; τ ($CDCl_3$) 2.90 (2H, s,), 6.09 (6H, s,).

Synthesis of 3-carbomethoxy-2-furanacetic acid methyl ester (49, R ≡ Me). - Chloroacetal (4.5 g) was distilled from dilute 6N. sulphuric acid. N.m.r. of the distillate (88 - 90°) showed it to be a mixture of chloroacetal, ethanol, chloroacetaldehyde and hydrate. The distillate was treated with acetone dicarboxylic acid dimethyl ester (1 g) and an equal volume of distilled water. Pyridine [144] was added to the stirred solution at room temperature to keep the pH > 7. The reaction was followed by T.L.C. (30% acetone/petrol) and was complete in 45 minutes.

The reaction mixture was thrown into water and the solution acidified (dil. HCl). The aqueous solution was extracted with ether (2 x 150 mls) and the combined ether extracts were washed with water (2 x 100 mls), and dried (calcium chloride). Filtration and evaporation of the ether yielded a two component mixture (2.153 g). The mixture was purified by column chromatography (100 g silica, 30% acetone/petrol as eluent). Fairly pure 3-carbomethoxy-2-furanacetic acid methyl ester was obtained (0.51 g, oil, 45%). M^+198; $\nu_{max.}$ (film) 1740, 1720, 1640,

1620 cm.$^{-1}$; $\lambda_{max.}$ (EtOH) 239 n.m. (ε 5,315); τ ($CDCl_3$) 2.55 (1H, d,), 3.25 (1H, d,), 5.89 (2H, s,), 6.17 (3H, s,), 6.29 (3H, s,).

Synthesis of 3-carboxyl-2-furanacetic acid (49, R ≡ H). - Pure 3-carbomethoxy-2-furanacetic acid methyl ester was converted into the free acid (49, R ≡ H) by refluxing with 10% potassium hydroxide - methanol (1:1 volume). m.p. 215° (dec.) (ethyl acetate); M^+170; $\lambda_{max.}$ (EtOH) 242 n.m. (ε 4,780); $\nu_{max.}$ (Nujol) 1700, 1690, 1610 cm.$^{-1}$; τ (D.M.S.O. - D_6) - 2.23 (2H, s, D_2O exchange), 5.90 (1H, s,), 6.67 (1H, s,), 9.23 (2H, s,); [Found: C, 49.2; H, 3.5; $C_7H_6O_5$ requires C, 49.4; H, 3.5%].

Synthesis of 3-carbomethoxy-2-furanglyoxylic acid methyl ester (50). - 3-Carbomethoxy-2-furanacetic acid methyl ester (396 mgs) was dissolved in the minimum volume of dry xylene. Selenium dioxide (4 g) was added to the solution [132]. The mixture was refluxed until the reaction was complete (3 days). The reaction mixture was filtered and the excess selenium washed with hot xylene. The combined filtrate and washings were evaporated to yield an oil (96 mgs). Purification by P.L.C. (30% acetone/petrol, three times developed) gave 3-carbomethoxy-2-furanglyoxylic acid methyl ester (67.5 mgs). m.p. 49-50° (petrol); M^+212; $\lambda_{max.}$ (EtOH) 295 n.m. (ε 7,218), 239 n.m. (ε 3,512); $\nu_{max.}$ ($CHCl_3$) 1740, 1680 cm.$^{-1}$; τ ($CDCl_3$)

2.20 (1H, d,), 3.03 (1H, d,), 6.02 (3H, s,), 6.08 (3H, s,); [Found: C, 51.0; H, 3.9; $C_9H_8O_6$ requires C, 51.0; H, 3.8%].

Synthesis of 2,3-furan dicarboxylic acid dimethyl ester (51). - 3-Carbomethoxy-2-furanglyoxylic acid methyl ester (100 mgs) was dissolved in methanol (6 mls). A mixture of 10% potassium hydroxide (2 mls) in methanol (2 mls) was added to the stirred solution at room temperature. The solution was stirred until complete reaction (5 mins).

Hydrogen peroxide [133] (30% w/v, excess) was added to the solution, and the whole stirred overnight at room temperature. The methanol was removed in vacuo, and the solution acidified (dil. HCl.) and saturated with ammonium sulphate. The solution was continuously extracted with ether (8 hrs). Evaporation of the ether gave a white crystalline compound. The white crystalline compound was dissolved in methanol and dry diazomethane in ether [128] added in excess. Evaporation of the solvents and excess diazomethane gave 2,3-furan dicarboxylic acid dimethyl ester (31.1 mgs). m.p. 35 - 36°; (lit. [145] m.p. 39°, 36°, 37°); $\lambda_{max.}$ (EtOH), 261 n.m. (ε 7,943), M^+184; $\nu_{max.}$ ($CHCl_3$) 1730, 1720, 1590 $cm.^{-1}$; τ($CDCl_3$) 2.37 (1H, d,), 3.05 (1H, d,), 6.05 (6H, d,).

Synthesis of α-hydroxy-3-carbomethoxy-2-furanacetic acid methyl ester (52). - 3-Carbomethoxy-2-furanglyoxylic acid methyl ester (67.5 mgs) was dissolved in anhydrous methanol (3 mls) and sodium borohydride [141] added (3.03 mgs., 1 equiv.) to the stirred solution at room temperature. The reaction was allowed to proceed to completion (< 5 mins.). Purification by T.L.C. (40% acetone/petrol)

gave α-hydroxy-3-carbomethoxy-2-furanacetic acid methyl ester (51 mgs.) m.p. 64-65° (ethyl acetate-petrol); M^+214; $\lambda_{max.}$ (EtOH) 246 n.m. (ε 5,403); $\nu_{max.}$ ($CHCl_3$) 3550, 1740, 1720, 1610 $cm.^{-1}$; τ ($CDCl_3$) 2.56 (1H, d,), 3.19 (1H, d,), 4.23 (1H, s,), 5.3 (1H, OH), 6.06 (3H, s,), 6.15 (3H, s,); [Found: C, 50.4; H, 4.9; $C_9H_{10}O_6$ requires C, 50.5; H, 4.7%].

Conversion of α-hydroxy-3-carbomethoxy-2-furanacetic acid methyl ester (52) into 3-carbomethoxy-2-furanglyoxylic acid methyl ester (50). - α-Hydroxy-3-carbomethoxy-2-furanacetic acid methyl ester (19.1 mgs) was dissolved in the minimum volume of dry xylene. Selenium dioxide [132] (10 mgs., 1 equiv.) was added to the solution. The mixture was refluxed until complete reaction (30 mins.). Usual work-up gave 3-carbomethoxy-2-furanglyoxylic acid methyl ester (19 mgs) in all respects identical with an authentic sample.

Lithium aluminium hydride reductions of dimethyl daucate (41, $R_1 \equiv R_2 \equiv H$). - Dimethyl daucate (19.68 mgs) was dissolved in dry T.H.F. (2 mls.). The solution was added to a refluxing, stirred solution of L.A.H. [146] (4.72 mgs) in dry T.H.F. (5 mls). No reaction was observed by T.L.C. (40% acetone/petrol). More L.A.H. was added (total, 6.5 mgs) until complete reaction. Distilled water (few drops) was added, and the reaction mixture filtered. The solvent was removed in vacuo, and the residue acetylated. Purification by T.L.C. (40% acetone/petrol) gave a dark brown oil (~ 1 mg.) $\frac{m}{e}$ 284 (ω), 242 (s).

Ozonolysis of dimethyl daucate (41, $R_1 \equiv R_2 \equiv H$). -

a). Dimethyl daucate (10 mgs) was dissolved in dry 1% pyridine - methylene dichloride (4 mls), and ozonized at -70°. The reaction was followed by T.L.C. (40% acetone/petrol) and U.V., until complete. T.L.C. (40% acetone/petrol) separation gave three products, the one of highest R.F. showed a positive test with Brady's reagent. All three products were in small amount and were not characterised.

b). Dimethyl daucate (6 mgs) was dissolved in dry methylene dichloride (3 mls) and ozonized at -70°. The methylene dichloride was removed *in vacuo* at -70°, and L.A.H. (excess) in dry T.H.F. added, and the resulting mixture allowed to warm up to room temperature. The solvent was removed *in vacuo*, and the residue extracted several times with n-butanol. Removal of the solvent *in vacuo* and acetylation of the residue gave two products, (negligible amounts) which were not characterised.

Reduction of chelidonic acid dimethyl ester (48). - Chelidonic acid dimethyl ester (88 mgs) was dissolved in dry ether (10 mls). Liquid ammonia (5 mls). was added to the stirred solution. Lithium (5 mgs., 2 equiv.) was added to the solution over a period of ten minutes[149]. The solution was observed to change colour from yellow to light brown and finally to dark brown. The solution was stirred for a further ten minutes.

Absolute ethanol was then added dropwise to the solution until the dark brown colour of the solution was discharged back to the initial yellow colour. The solvents and excess liquid ammonia were

removed in vacuo, and ether and water were added to the reaction mixture product. The ether layer was separated, dried (calcium chloride) and examined by T.L.C. No product was apparent.

Sodium borohydride - methanol reduction of chelidonic acid dimethyl ester (48). - Chelidonic acid dimethyl ester (179 mgs) was dissolved in the minimum volume of dry methanol. Sodium borohydride (40 mgs., mole ratio 1:1.25) was added to the stirred solution at room temperature ^{15O}. The reduction was followed by T.L.C. (40% acetone/petrol) until completion (20 mins.). The solvent was removed in vacuo. Separation by T.L.C. (30% acetone/petrol) gave four products. They were in order of decreasing R.F values:-

the 2,3 dihydropyran (53, R ≡ H, 25 mgs),
the γ-pyrone (54, R ≡ H, 38 mgs),
the 2,3 dihydropyran (55, R ≡ H, 7 mgs),
and the γ-pyrone (56, R ≡ H, 7 mgs).

A larger scale reaction of chelidonic acid dimethyl ester (48,287 mgs) in dry methanol with sodium borohydride (64.05 mgs) at room temperature gave (48, 15 mgs; 53, R ≡ H, 47 mgs; 54, R ≡ H, 76 mgs; 55, R ≡ H, 15 mgs and 56, R ≡ H, 15 mgs.).

Characterisation of the γ-pyrone (54, R ≡ H). - The γ-pyrone showed m.p. 138-139° (ethyl acetate - petrol); M^+184; $\lambda_{max.}$ (EtOH) 261 n.m. (ε 7,570); $\nu_{max.}$ (Nujol) 3200, 1755, 1740, 1670, 1650, 1615, 1593 $cm.^{-1}$; τ ($CDCl_3$) 3.00 (1H, d,), 3.50 (1H, m,), 5.45 (2H, d,),

6.05 (3H, s,), 6.4 (1H, OH); $\tau(C_2D_6CO)$ 3.58 (1H, d,), 4.00(1H, s,), 5.93 (2H, s,), 6.50 (3H, s,) - could not locate OH; [Found: C, 52.4; H, 4.6; $C_8H_8O_5$ requires C, 52.2; H, 4.4%]

The γ-pyrone (54, R ≡ H) was acetylated to give the γ-pyrone mono-acetate (54, R ≡ Ac) M^+226; $\tau(CDCl_3)$ 2.90 (1H, d,), 3.55 (1H, d,), 5.00 (2H, s,), 6.00 (3H, s,), 7.80 (3H, s,).

The γ-pyrone (54, R ≡ H) was benzoylated to give the γ-pyrone mono-benzoate (54, R ≡ C_6H_5CO). - m.p. 121-122° (dry methanol); M^+288, $\lambda_{max.}$ (EtOH) 225 n.m. (ε 21,190), 261 n.m. (ε 10,070); $\nu_{max.}$ ($CHCl_3$) 1740, 1670, 1664, 1630, 1605 $cm.^{-1}$; $\tau(CDCl_3)$ 1.90 (2H, m,), 2.40 (3H, m,), 2.94 (1H, d,), 3.43 (1H, d,), 4.75 (2H, s,), 6.00 (3H,s,); [Found: C, 62.4; H, 4.1; $C_{15}H_{12}O_6$ requires C, 62.5; H, 4.2%].

Oxidation of the γ-pyrone (54, R ≡ H). - Lead tetraacetate (54.34 mgs) was dissolved in dry pyridine (1 ml). γ-Pyrone (54, R ≡ H, 14.1 mgs) dissolved in dry pyridine (1 ml) was added to the stirred solution at room temperature [151]. After 1 hr. the reaction was worked up.

The solvent was removed in vacuo, and the residue dissolved in distilled water (10 mls). The solution was acidified (dil. HCl), saturated with ammonium sulphate and continuously extracted with ether (8 hrs). The ether was evaporated off, and the residual oil dissolved in methanol and dry diazomethane in ether [128] added in excess. Evaporation of the solvents and excess diazomethane

gave an oil composed of three products by T.L.C. (40% acetone/ petrol). The three products were isolated by T.L.C. (40% acetone/ petrol) and shown by comparison of chemical data with authentic samples to be the γ-pyrone (54, R ≡ H, unreacted), the γ-pyrone acetate (54, R ≡ Ac) and chelidonic acid dimethyl ester (48) respectively.

Characterisation of the γ-pyrone (56, R ≡ H). - This showed m.p. 111-112° (ethyl acetate-petrol); M^+156; $\lambda_{max.}$ (EtOH) 247 n.m. (ε 13,550); $\nu_{max.}$ (mull) 3160-3340, 1665, 1610 cm.$^{-1}$; [Found: C, 53.6; H, 5.1; $C_7H_8O_4$ requires C, 53.8; H, 5.2%].

The γ-pyrone (56, R ≡ H) was benzoylated to give the γ-pyrone dibenzoate (56, R ≡ C_6H_5CO), m.p. 145-146° (dry methanol); M^+364; $\lambda_{max.}$ (EtOH) 232 n.m. (ε 34,620), 256 n.m. (sh.); $\nu_{max.}$ ($CHCl_3$) 1730, 1675, 1630, 1604 cm.$^{-1}$; τ ($CDCl_3$) 2.00 (4H, m,), 2.50 (6H, m,), 3.50 (2H, s,), 4.80 (4H,s,); [Found: C, 69.0; H, 4.6; $C_{21}H_{16}O_6$ requires C, 69.2; H, 4.4%].

Characterisation of the 2,3 dihydropyran (53, R ≡ H). - This showed M^+216; $\lambda_{max.}$ (EtOH) 236 n.m.; $\nu_{max.}$ (film) 3440, 1730, 1647 cm.$^{-1}$; τ ($CDCl_3$) 3.80 (1H, d,), 5.10 (1H, m,), 5.65 (1H, m,), 6.15 (3H, s,), 6.23 (3H, s,), 7.80 (2H, m,), 7.8 (1H, OH); [Found: C, 51.1; H, 6.0; $C_9H_{12}O_6$ requires C, 50.0; H, 5.6%]

The 2,3 dihydropyran (53, R ≡ H) was acetylated to give the 2,3 dihydropyran mono-acetate (53, R ≡ Ac). M^+258, τ($CDCl_3$) 3.83 (1H, d,), 4.65 (1H, m,), 5.05 (1H, m,), 6.13 (3H, s,), 6.20 (3H, s,), 7.55 (2H, m,), 7.98 (3H, s,).

The 2,3 dihydropyran (53 R ≡ H) was benzoylated to give the 2,3 dihydropyran mono-benzoate (53, R ≡ C_6H_5CO) m.p. 115-116° (dry methanol); M^+320; $\lambda_{max.}$ (EtOH) 234 n.m. (ε 19,410),240 n.m.(sh). $\nu_{max.}$ ($CHCl_3$), 1762, 1740, 1723, 1655, 1605 $cm.^{-1}$; [Found: C, 59.8; H, 4.8; $C_{16}H_{16}O_7$ requires C, 60; H, 5.0%].

Characterisation of the 2,3 dihydropyran (55, R ≡ H). - This showed M^+188. 2,3 Dihydropyran (55, R ≡ H) was benzoylated to give the 2,3 dihydropyran dibenzoate (55, R ≡ C_6H_5CO) m.p. 120-122° (dry methanol); M^+396; $\lambda_{max.}$ (EtOH) 232 n.m. (ε 29,750); $\nu_{max.}$ ($CHCl_3$) 1725, 1655, 1605 $cm.^{-1}$; τ($CDCl_3$) 1.90 (4H, m,), 2.45 (6H, m,), 3.75 (1H, m,), 4.27 (1H, m,), 5.35 (2H, s,), 5.52 (1H, m,), 6.15 (3H, s,), 7.80 (2H, m,); [Found: C, 66.7; H,5.1; $C_{22}H_{20}O_7$ requires C, 66.7; H, 5.1%].

Synthesis of the 2,3 dihydro-γ-pyrone (57). - The 2,3 dihydropyran (53, R ≡ H, 33.6 mgs) was dissolved in dry chloroform. Activated manganese dioxide (270 mgs, mole ratio 1:20), was added to the stirred solution at room temperature [152]. The reaction was followed by T.L.C. (30% acetone/petrol) to completion (1 hr). The manganese dioxide was filtered off and washed with chloroform. Evaporation of the solvent, of the combined filtrate and washings, yielded a brown oil, which could be crystallized (ethyl acetate-petrol) to give the 2,3 dihydro-γ-pyrone (57; 34.2 mgs), m.p. 76-77° (ethyl acetate-petrol); M^+214; $\lambda_{max.}$(EtOH) 276 n.m. (ε 10, 240); $\nu_{max.}$ ($CHCl_3$) 1749, 1690, 1613 $cm.^{-1}$; τ($CDCl_3$) 3.70 (1H, s,), 4.83 (1H, t,), 6.10 (3H, s,), 6.19 (3H, s,),

7.07 (2H, d,); [Found: C, 50.7; H, 4.7; $C_9H_{10}O_6$ requires C, 50.5; H, 4.7%].

Synthesis of chelidonic acid dimethyl ester (48). - The 2,3 dihydropyran (53, R ≡ H, 61.2 mgs) was refluxed in dry xylene (2 mls) with selenium dioxide [132] (124,4 mgs, mole ratio 1:3) until the reaction was complete by T.L.C. (40% acetone/petrol). Usual work up gave chelidonic acid dimethyl ester (48; 13 mgs) identical in all respects with an authentic sample.

Sodium borohydride-methanol reduction of chelidonic acid dimethyl ester (48) in the presence of oxygen. - Chelidonic acid dimethyl ester (48, 102.1 mgs) was dissolved in dry methanol, and the solution saturated with dry oxygen (15 mins., sodium hydroxide/calcium chloride drying tubes). Sodium borohydride was added one equivalent at a time, until the reaction was complete by T.L.C. (40% acetone/petrol). Ten minutes elapsed between each successive addition of borohydride. Seven equivalents of borohydride (31.9 mgs, 1.75 m.moles) were consumed. All four products corresponding to a normal reduction were obtained (53, 54, 55 and 56; R ≡ H). A reversal in yield, however, was found amongst the major products (53, R ≡ H, 16.1 mgs; 54, R ≡ H, 9.9 mgs).

Synthesis of trimethyl meconate (59, R ≡ Me). - Meconic acid hydrate (58, 157 mgs) was dissolved in methanol. Dry diazomethane in ether [128] was added in excess. Evaporation of the solvents and excess diazomethane, followed by T.L.C. purification (40% acetone/petrol)

gave trimethyl meconate (59, R ≡ Me, 116 mgs) m.p. 142-143° (ethyl acetate-petrol); M^+ 242; $\lambda_{max.}$ (EtOH) 283 n.m. (ε 6,184); $\nu_{max.}$ ($CHCl_3$), 1747, 1660, 1627 (sh.) $cm.^{-1}$; τ($CDCl_3$) 2.80 (1H,s,), 5.98 (3H, s,), 6.03 (6H, s,); [Found: C, 49.7; H, 4.2; $C_{10}H_{10}O_7$ requires C, 49.6; H, 4.2%].

Preparation of dimethyl meconate (59, R ≡ H). - Meconic acid (58) was dried in the oven (100°) for two hours. It was then dried under vacuum at room temperature before weighing.

Anhydrous meconic acid (89.7 mgs) was dissolved in the minimum volume of anhydrous methanol. Dry hydrogen chloride gas (conc. sulphuric acid dried) was passed through the stirred refluxing solution for 2/3 days [155]. The reaction can be followed by n.m.r. Evaporation of the solvent and hydrogen chloride gas gave dimethyl meconate (93 mgs). τ($CDCl_3$) 2.75 (2H, s,; 1H after D_2O exchange), 5.93 (3H, s,), 6.00 (3H, s,). Scaling up of the reaction led to poorer yields. Meconic acid (522 mgs) gave dimethyl meconate (435 mgs).

Preparation of diethyl meconate (60, R ≡ H). - Anhydrous meconic acid (313 mgs) was dissolved in the minimum volume of anhydrous ethanol [155]. A few drops of conc. sulphuric acid were added to the solution. The solution was refluxed for one week, the ethanol being removed daily and replaced by fresh anhydrous ethanol. Diethyl meconate (225 mgs) was obtained. τ($CDCl_3$) 2.80 (2H, s, ; 1H after D_2O exchange), 5.52 (4H, m,), 8.60 (6H, m,).

Preparation of dimethyl meconate acetate (59 R ≡ Ac). - Dimethyl meconate (59, R ≡ H; 33.2 mgs) was acetylated with acetic anhydride-pyridine. Removal of the solvents in vacuo and T.L.C. (30% acetone/petrol) gave dimethyl meconate acetate (36 mgs) m.p. 114-115° (ether-petrol or ether); M^+ 270; $\lambda_{max.}$ (EtOH) 210 n.m. (ε 15,050); 274 n.m. (ε 8,668); $\nu_{max.}$ ($CHCl_3$) 1785, 1750, 1670 $cm.^{-1}$; τ ($CDCl_3/CCl_4$) 2.80 (1H, s,), 6.00 (6H, s,), 7.68 (3H, s,); [Found: C,48.9; H, 3.8; $C_{11}H_{10}O_8$ requires C, 48.9; H, 3.7%].

Scaling up of the reaction and P.L.C. purification on large silica plates gave poor yields. Dimethyl meconate (503 mgs) gave dimethyl meconate acetate (156 mgs).

Preparation of dimethyl meconate benzoate (59, R ≡ C_6H_5CO). - Dimethyl meconate (414 mgs) was benzoylated as above. Removal of the solvents in vacuo and P.L.C. purification (40% acetone/petrol) gave dimethyl meconate benzoate (360 mgs), m.p. 129-131° (dry methanol); M^+ 332; $\lambda_{max.}$ (EtOH) 232 n.m. (ε 27,450), 274 n.m. (ε 10, 880); $\nu_{max.}$ ($CHCl_3$) 1755, 1670, 1608 $cm.^{-1}$; τ ($CDCl_3$) 1.83 (3H, m,), 2.49 (2H, m,), 2.69 (1H, s,), 5.98 (3H, s,), 6.09 (3H, s,); [Found: C, 57.7; H, 3.6; $C_{16}H_{12}O_8$ requires C, 57.8; H, 3.6%].

Preparation of dimethyl meconate 3,5 dinitrobenzoate (59, R ≡ $OCC_6H_3(NO_2)_2$). - Dimethyl meconate (346 mgs) was dissolved in dry pyridine. 3,5 Dinitrobenzoyl chloride (420 mgs) was added to the stirred solution. The solution was stirred at room temperature

overnight. Removal of the solvents in vacuo and P.L.C. purification (40% acetone/petrol) gave dimethyl meconate 3,5 dinitro-benzoate (62.2 mgs).

The 3,5 dinitro-benzoate can be crystallized (acetone-petrol or ethyl acetate-petrol) but is extremely unstable. The compound was used directly in borohydride-methanol reduction reactions, and was not fully characterised. M^{+} 422, $\lambda_{max.}$ (EtOH) 213 n.m., $\nu_{max.}$ ($CHCl_3$) 1750, 1710, 1670, 1630, 1610 $cm.^{-1}$; τ($CDCl_3$) (2H, s, offset), 2.73 (1-2H, m,), 5.95 (3H, s,), 6.03 (3H, s,).

Preparation of dimethyl meconate mesitoate (59, R ≡ mesitoyl). - Dimethyl meconate (30.6 mgs) was dissolved in dry pyridine. Mesitoyl chloride (36 mgs) was added to the stirred solution at room temperature. The solution was observed to turn green on initial addition of mesitoyl chloride, but soon turned brown (further 10 mins.). Stirring was continued overnight. Removal of the solvents under vacuum and T.L.C. purification (40% acetone/petrol) gave dimethyl meconate mesitoate (17 mgs), m.p. 106-107° (ethyl acetate-petrol); $\frac{m}{e}$ 174; $\lambda_{max.}$ (EtOH) 230 n.m. (ε 37,410); $\nu_{max.}$ ($CHCl_3$) 1750, 1670, 1615 $cm.^{-1}$; τ (CCl_4) 2.76 (1H, s,), 3.12 (2H, s,), 6.03 (6H, s,), 7.51 (6H, s,), 7.70 (3H, s,); [Found C, 60.7; H, 4.7; $C_{19}H_{18}O_8$ requires C,61.0; H, 4.8%].

Preparation of dimethyl meconate tosylate (59, R ≡ $O_2SC_6H_4p.CH_3$). - Dimethyl meconate (140 mgs) was dissolved in dry pyridine. Tosyl chloride (129 mgs) was added to the stirred solution at room temperature. Stirring was continued overnight. Removal of the solvents

in vacuo and T.L.C. purification (15% acetone/petrol) gave dimethyl meconate tosylate (35 mgs) m.p. 125-127° (carbon tetrachloride); $\frac{m}{e}$ 350 (ω) 318 (s), 260 (s) and 155 (s); $\lambda_{max.}$ (EtOH) 226 n.m. (ε 25,070), 267 n.m. (ε 8,762); $\nu_{max.}$ ($CHCl_3$) 1755, 1680, 1600 $cm.^{-1}$;

τ($CDCl_3$) 2.14 (2H, d,), 2.67 (2H, d,), 2.90 (1H, s,), 6.02 (6H, s,), 7.53 (3H, s,); [Found: C,50.2; H, 3.8; $C_{16}H_{14}O_9S$ requires C, 50.3; H, 3.7%].

Preparation of diethyl meconate tosylate (60, R ≡ $O_2SC_6H_4p.CH_3$). - Diethyl meconate (60, R ≡ H, 55 mgs) was dissolved in dry pyridine. Tosyl chloride (44 mgs) was added to the stirred solution at room temperature. The solution was stirred overnight. Removal of the solvent in vacuo and T.L.C. (15% acetone/petrol) purification gave diethyl meconate tosylate (35 mgs, oil) τ($CDCl_3$) 2.16 (2H, d,), 2.70 (2H, d,), 2.92 (1H, s,), 5.58 (4H, m,), 7.57 (3H, s,), 8.60 (6H, m,).

Preparation of diethyl meconate mesitoate (60, R ≡ mesitoyl). — Imidazole [160] (9 mgs) was dissolved in dry T.H.F. Lithium hydride (1.04 mgs, ground in a glove box) was added to the stirred solution. The solution was refluxed to effect partial dissolution. The solution was cooled, and diethyl meconate (33.2 mgs) in dry T.H.F. was then added. Mesitoyl chloride (23.7 mgs) in dry T.H.F. was added to the stirred mixture at room temperature. The solution was stirred overnight. Filtration, evaporation of the solvent and T.L.C. (40% acetone/petrol) purification gave diethyl meconate mesitoate

(23 mgs, oil) $\tau(CDCl_3)$ 2.80 (1H, s,), 3.15 (2H, s,), 5.65 (4H, m,), 7.55 (6H, s,), 7.72 (3H, s,), 8.67 (6H, m,).

Reductions of diethyl and dimethyl meconates (59, R ≡ H; 60, R ≡ H).

a). Diethyl meconate (60, R ≡ H, 31.3 mgs) was dissolved in dry ethanol. Sodium borohydride (5.8 mgs mole ratio 1:1.25) was added to the stirred solution at room temperature. The U.V. of the solution was checked $\lambda_{max.}$ (EtOH) 252 n.m., 261 n.m. (sh.), 293 n.m., 385 n.m. The ethanol was removed in vacuo and the residue acetylated. T.L.C. (40% acetone/petrol) gave seven products; three in major proportions which were isolated. Diethyl meconate acetate (60, R ≡ Ac; 7.8 mgs) was isolated. m.p. 117-121° (from plates); M^+ 298; $\tau(CDCl_3)$ 2.69 (1H, s,), 5.53 (4H, m,), 7.60 (3H, s,), 8.56 (6H, m,). The other two compounds were in small amount and were not fully characterised.

b). Dimethyl meconate (59, R ≡ H; 48 mgs) was dissolved in dry methanol (2 mls). Sodium borohydride (40 mgs. mole ration 1:5) was added to the stirred solution at room temperature. The methanol was removed in vacuo and the residue acetylated. T.L.C. (40% acetone/ petrol) gave six products. The products were isolated and their U.V.'s (EtOH) checked. None agreed with that of dimethyl daucate diacetate (41, $R_1 \equiv R_2 \equiv Ac$).

Reduction of trimethyl meconate (59, R ≡ Me). - Trimethyl meconate (38.3 mgs) was dissolved in dry methanol (2 mls). Sodium borohydride was added to the stirred solution at room temperature, one equivalent at a time (1.54 mgs). Four equivalents were added for complete reaction by T.L.C. (40% acetone/petrol). Removal of the methanol in vacuo and T.L.C. (40% acetone/petrol) gave two products.

(a). (16 mgs); m.p. 119-120° (ethyl acetate-petrol); M^+246; $\lambda_{max.}$ (EtOH) 223 n.m., 268 n.m. The n.m.r. showed the product to be a mixture.

(b). (4 mgs); M^+218; $\lambda_{max.}$ (EtOH) 258 n.m., 215 n.m.

Reduction of dimethyl meconate acetate (59, R ≡ Ac). - Dimethyl meconate acetate (156 mgs) was dissolved in anhydrous methanol (10 mls). Sodium borohydride was added two equivalents at a time (11 mgs) until the reaction was complete by T.L.C. (30% acetone/petrol). Sodium borohydride (44 mgs. mole ratio 1:2) was required. U.V. of the solution gave $\lambda_{max.}$ (EtOH) 242 n.m., 248 (sh.) and absorption also between 260 to 300 n.m. The methanol was removed in vacuo, and the residue acetylated. T.L.C. (40% acetone/petrol) work up gave seven products, three in major proportions:

(a). (8.3 mgs); M^+318 with peaks at $\frac{m}{e}$, 316 (s), 243(s), 228 (s), 199 (s) and 197 (ω); $\lambda_{max.}$ (EtOH) 271 n.m.

(b), (15.5 mgs); $\lambda_{max.}$ (EtOH) 226 n.m.; M^+ 318 (ω) with peaks at $\frac{m}{e}$, 316 (s), 241 (s) and 200 (s); $\lambda_{max.}$ (EtOH) 226 n.m.

(c). (4 mgs); M^+ 330 (ω) with peaks at $\frac{m}{e}$ 257 (ω), 243 (ω), 228 (ω) and 198 (s); $\lambda_{max.}$ (EtOH) 256 n.m.

Reductions of dimethyl meconate benzoate (59, R ≡ C_6H_5CO). -

a), Dimethyl meconate benzoate (46.6 mgs) was dissolved in anhydrous methanol (5 mls). Sodium borohydride was added to the stirred solution at room temperature one equivalent at a time (5.3 mgs) until complete reaction by T.L.C. (40% acetone/petrol). Sodium borohydride (25.2 mgs mole ratio 1:4.75) was required. The methanol was removed in vacuo and the residue benzoylated. T.L.C. (40% acetone/petrol) work-up gave five products:

(a). $\frac{m}{e}$ 370 (ω), 352 (ω); $\lambda_{max.}$ (EtOH) 228 n.m., 268 n.m.

(b). $\frac{m}{e}$ 150 (ω),122 (s); $\lambda_{max.}$ (EtOH) 238 n.m.

(c). $\frac{m}{e}$ 378(ω), 364 (ω), 228 (ω); $\lambda_{max.}$ (EtOH) 231 n.m.

(d). $\frac{m}{e}$ 304 (s); $\lambda_{max.}$ (EtOH) 228 n.m.

(e). $\frac{m}{e}$ 264 (ω), 260 (s); $\lambda_{max.}$ (EtOH) 229 n.m.

None of the five products was identical with dimethyl daucate dibenzoate (41, $R_1 \equiv R_2 \equiv C_6H_5CO$.)

b), Dimethyl meconate benzoate (100 mgs) was dissolved in dry methanol (3 mls). Sodium borohydride (57 mgs mole ratio 1:5) was added to the stirred solution at room temperature. Removal of the methanol in vacuo and acetylation of the residue gave on T.L.C. (40% acetone/petrol) work-up one major product. $\frac{m}{e}$ 330 (ω), 198 (s); $\lambda_{max.}$ (EtOH) 252 n.m.; $\tau(CDCl_3)$ 2.72 (1H, s,), 7.85 (3H,s,), 7.67 (3H, s,).

Reduction of dimethyl meconate mesitoate (59, R ≡ mesitoyl). - Dimethyl meconate mesitoate (68 mgs) was dissolved in dry methanol (15 mls). Sodium borohydride (19 mgs. mole ratio 1:2.75) was added to the stirred solution at room temperature. The methanol was removed in vacuo and T.L.C. (40% acetone/petrol) work-up gave two products the γ-pyrone mesitoate (61, R ≡ H, 115 mgs) and an unstable compound (9.8 mgs). The γ-pyrone mesitoate (61, R ≡ H) had the following physical data: $\frac{m}{e}$ 281 (ω), 262 (ω), 205 (ω), 207 (ω), 181 (s), 147 (s); $\nu_{max.}$ ($CHCl_3$) 1750, 1670, 1615 $cm.^{-1}$; $\tau(CCl_4)$ 3.15 (2H, s,), 3.40 (1H, s,), 5.58 (2H, s,), 6.15 (3H, s,), 7.55 (6H, s,), 7.70 (3H, s,), 7.70-7.55 (OH). The γ-pyrone mesitoate was acetylated to give the γ-pyrone mesitoate mono-acetate (61, R ≡ Ac). M^+388 (ω) with peaks at $\frac{m}{e}$ 146 (s), 147 (s); $\nu_{max.}$ ($CHCl_3$) 1750, 1670, 1613 $cm.^{-1}$; $\lambda_{max.}$ (EtOH) 213 n.m., 252 n.m. The γ-pyrone mesitoate was benzoylated to give the γ-pyrone mesitoate mono-benzoate (61, R ≡ $.OCC_6H_5$). m.p. 150-151° (ethyl acetate-petrol); M^+450; $\lambda_{max.}$ (EtOH) 210 n.m. (ε 35,990), 228 n.m. (ε 23,750); $\nu_{max.}$ ($CHCl_3$) 1750, 1670, 1615 $cm.^{-1}$;

τ ($CHCl_3$ - poor spectrum) 1.85 (3H, m,), 2.38 (2H, m,), 3.00 (2H, s,), 3.25 (1H, s,), 4.67 (2H, s,), 6.05 (3H, s,), 7.40 (6H, s,), 7.65 (3H, s,); [Found: C, 67.0; H, 4.9; $C_{25}H_{22}O_8$ requires C,66.7; H, 4.9%].

The unstable oil had the following physical data: $\frac{m}{e}$ 164 (ω), 147 (s); $\lambda_{max.}$ (EtOH) 212 n.m., 243 n.m. It formed a crystalline benzoate m.p. 145-146° (ethyl acetate-petrol).

Reduction of dimethyl meconate 3,5 dinitrobenzoate (59, R ≡ $.OCC_6H_3(NO_2)_2$). - Dimethyl meconate 3,5 dinitrobenzoate (29 mgs) was dissolved in dry methanol (1 ml). Sodium borohydride (5.2 mgs. mole ratio 1:2) was added to the stirred solution at room temperature. The solution was observed to turn a royal blue colour. The reaction solution was divided into two (a), and (b):—

(a), The methanol was removed in vacuo and the residue acetylated. T.L.C. (40% acetone/petrol) work-up, gave four products, none of which had the same U.V. (EtOH) as dimethyl daucate diacetate (41, $R_1 \equiv R_2 \equiv Ac$).

(b), More sodium borohydride was added (large excess). The reaction solution was observed to turn a light brown colour. The methanol was removed in vacuo. Work-up, as in (a), gave five products, none of which had the same U.V. (EtOH) as dimethyl daucate diacetate (41, $R_1 \equiv R_2 \equiv Ac$).

Reduction of dimethyl meconate tosylate (59, R ≡ $O_2SC_6H_4pCH_3$). - Dimethyl meconate tosylate (18.5 mgs) was suspended in dry methanol (2 mls). Sodium borohydride was added to the stirred solution at room temperature, two equivalents at a time (0.9 mg.) until the reaction was complete by T.L.C. (40% acetone/petrol). A total of sodium borohydride (4 mgs. mole ratio 1:2) was added. Removal of the methanol in vacuo, and T.L.C. (40% acetone/petrol) gave two products:-

(a). (3.3 mgs); crystalline from ethyl acetate-petrol; $\frac{m}{e}$ 464* (ω), 433* (ω), 392* (ω), 284 (s), 271 (s), 155 (s); $\lambda_{max.}$ (EtOH) 226 n.m.

(b). (3.6 mgs); $\frac{m}{e}$ 298* (ω), 290 (ω), 232 (s), 201 (s), 172 (s), 155 (s); $\lambda_{max.}$ (EtOH) 226 n.m.

* May be spurious.

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