THE DECOMPOSITION OF 1,4;3,6-DIANHYDROHEXITOL DINITRATES

by

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ABSTRACT

The dinitrate esters of the three known isohexides (1,4;3,6-dianhydrohexitols) were prepared and characterised and the rates and products of their reaction with pyridine were investigated. It was shown that none of the parent isohexides were formed in the reaction and the yield of mononitrates did not exceed 8%. These results differed from the rapid and selective removal of one nitrate group and its replacement by a hydroxyl group which occurs when hexitol hexanitrates react with the same reagent. Comparative rates of reaction for the three isohexide dinitrates and activation energies were determined.

Addition of water to the pyridine caused a retardation of rate. The rate of thermal decomposition of these nitrate esters in other organic solvents was found to be slow at the temperatures used for the pyridine reaction and independent of the solvent and isomer used.

The rates of the reactions of isohexide ditosylates with sodium iodide in acetic anhydride were investigated and used to prove the position of monotosylation of isosorbide. The reaction of iodo derivatives of the isohexides with silver nitrate in acetonitrile gave a low yield of a mixture of the isohexide nitrate products. The rates of these reactions together with those of alkali on the isohexide ditosylates and acetic anhydride/sulphuric acid on the dinitrates were compared to those of the dinitrates with pyridine.

Appropriate chromatographic and analytical procedures were developed for the separation and identification of the isohexides and their derivatives.
PROGRAMME OF THE

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M. Sc., University of Manchester, 1956

IN ROOM 213, CHEMISTRY BUILDING

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THE DECOMPOSITION OF 1,4;3,6-DIANHYDROHEXITOL DINITRATES

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**PUBLICATION**

The action of sodium iodide on O-p-toluenesulfonyl-1,4;3,6-dianhydrides of D-mannitol, D-glucitol and L-iditol.

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Department of Chemistry

The University of British Columbia, Vancouver 8, Canada.

Date April 13, 1959.
# TABLE OF CONTENTS

## INTRODUCTION

Page

## HISTORICAL INTRODUCTION

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>The Formation and Structure of the 1,4;3,6-Dianhydrohexitols</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>Stereochemistry</td>
<td>11</td>
</tr>
<tr>
<td>III</td>
<td>Chemical Properties of the Isohexides</td>
<td>27</td>
</tr>
<tr>
<td>IV</td>
<td>Reactions of Nitrate Esters</td>
<td>42</td>
</tr>
</tbody>
</table>

## RESULTS AND DISCUSSION

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>The Reaction of the Isohexide Dinitrates with Pyridine</td>
<td>57</td>
</tr>
<tr>
<td>VI</td>
<td>Rate Studies on the Decomposition of Isohexide Dinitrates</td>
<td>81</td>
</tr>
<tr>
<td>VII</td>
<td>Comparison of the Nitrate-Pyridine Reaction with Other Reactions</td>
<td>95</td>
</tr>
</tbody>
</table>

## EXPERIMENTAL

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Materials</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>Analytical Methods — Estimation Procedures</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>Analytical Methods — Chromatographic Procedures</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>Isohexide Dinitrate-Pyridine Reaction</td>
<td>127</td>
</tr>
<tr>
<td></td>
<td>Other Reactions</td>
<td>135</td>
</tr>
</tbody>
</table>

## APPENDIX I

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The Colorimetric Determination of Nitrate Esters</td>
<td>143</td>
</tr>
</tbody>
</table>

## APPENDIX II

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paper Chromatography</td>
<td>147</td>
</tr>
</tbody>
</table>

## REFERENCES

Page 154
<table>
<thead>
<tr>
<th>TABLES</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Derivatives of the Isohexides</td>
<td>40</td>
</tr>
<tr>
<td>II Physical Constants of the Isohexide Dinitrates</td>
<td>59</td>
</tr>
<tr>
<td>III Chromatography of Fractions in Preliminary Separations</td>
<td>62</td>
</tr>
<tr>
<td>IV Recoveries Obtained from Alumina Columns</td>
<td>70</td>
</tr>
<tr>
<td>V Pyridinium Nitrate Formed in Nitrate-Pyridine Reaction</td>
<td>74</td>
</tr>
<tr>
<td>VI Ether Extraction of Nitrate Ester from the Aqueous Pyridine Solutions</td>
<td>82</td>
</tr>
<tr>
<td>VII Results of Kinetic Investigation of Nitrate-Pyridine Reaction</td>
<td>84</td>
</tr>
<tr>
<td>VIII Analysis of Nitrate Ester Products of Nitrate-Pyridine Reaction with Water Added</td>
<td>88</td>
</tr>
<tr>
<td>IX The Effect of Water on the Rate of the Nitrate-Pyridine Reaction</td>
<td>90</td>
</tr>
<tr>
<td>X Reaction of Silver Nitrate with Iodo Derivatives in Acetonitrile</td>
<td>103</td>
</tr>
<tr>
<td>XI Products of Silver Nitrate-Iodo Derivative Reaction</td>
<td>103</td>
</tr>
<tr>
<td>XII Compounds Prepared by Reported Procedures</td>
<td>110</td>
</tr>
<tr>
<td>XIII Analyses of Derivatives</td>
<td>117</td>
</tr>
<tr>
<td>XIV Position of Elution of Various Compounds from Alumina Columns</td>
<td>122</td>
</tr>
<tr>
<td>XV Summary of Separations</td>
<td>128</td>
</tr>
<tr>
<td>XVI The Effect of Sulphuric Acid Concentration on the Formation of Nitroxylenol</td>
<td>145</td>
</tr>
<tr>
<td>XVII The Deterioration of Nitroxylenol Solution</td>
<td>145</td>
</tr>
<tr>
<td>XVIII The Effectiveness of the Distillation in the Colorimetric Determination</td>
<td>146</td>
</tr>
<tr>
<td>XIX Rf Values in Petroleum Ether/Methanol Solvent Systems</td>
<td>152</td>
</tr>
<tr>
<td>XX Rf Values in Petroleum Ether/Methanol/Water Solvent Systems</td>
<td>153</td>
</tr>
<tr>
<td>XXI Rf Values in Petroleum Ether/Benzene/Methanol/Water Solvent Systems</td>
<td>153</td>
</tr>
</tbody>
</table>
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INTRODUCTION

Certain of the hexitol hexanitrites have been shown to react vigorously with pyridine at 25–50°C. From the reaction products the corresponding pentanitrites were isolated in the cases of sorbitol, D-mannitol and dulcitol. The reaction is highly selective in that it is the nitrate group on the 3-position which is removed and the pentanitrites are stable to further attack under the same conditions. The configuration of the hexitol appears to have an effect on the ease of this denitration. To assist in elucidation of the mechanism of this reaction and in particular its stereochemical nature, nitrates with well-known and fixed conformations were sought.

One such group of compounds with these requirements is the 1,4; 3,6-dianhydrides of the hexitols. The three known isomers in this group have a fused ring structure which imparts rigidity to the molecule. The nitrate esters of two of these have been prepared and were crystalline. A considerable amount of work has been done on the isohexides and their acetate and sulphonate esters which forms a background for the present investigation.

It was therefore proposed to prepare all three of the isohexide dinitrates and to study their reaction with pyridine. It was hoped that some indication of the mechanism of the nitrate-pyridine reaction might be gained from a comparison of their relative rates of this reaction with those of other nitrate esters and with those of other reactions in the isohexide series.

The chemistry and stereochemistry of the isohexides and certain
pertinent reactions of nitrate esters will be reviewed before entering into a discussion of the results.
HISTORICAL INTRODUCTION

CHAPTER I

THE FORMATION AND STRUCTURE OF THE 1,4;3,6-DIANHYDROHEXITOLS

The acid catalysed removal of two moles of water from a hexitol results, in the case of D-mannitol, sorbitol (D-glucitol) and L-iditol, in the formation of the corresponding 1,4;3,6-dianhydrides. These compounds have been given the trivial names isomannide (I), isosorbide (II) and isoidide (III) respectively, and the class as a whole is known as the isohexides.¹

¹ These short names will be used for convenience throughout this work. The terms tosyl, mesyl, etc. will be used for the p-toluene-sulphonyl, methanesulphonyl, etc. acyl groups substituted on oxygen in the isohexides. The terms nitroxy, tosylvoy (O-tosyl), etc. refer to the ester (or ether) groups substituted on carbon. In general the formal numbering (2,5-) will be omitted in the names of symmetrically disubstituted derivatives of the isohexides where the structure is obvious.
The corresponding compounds from the other three hexitols — dulcitol (galactitol), D-talitol (D-altritol) and allitol — have not been prepared. The chemistry of the isohexides up to 1947 has been reviewed by Wiggins (1). This review will be summarised and extended to the Spring of 1959 here.

Isomannide was first prepared in 1884, but it is only recently that its structure has been proved conclusively. Fauconnier (2) reacted D-mannitol with hydrochloric acid and isolated a \( C_{6}H_{10}O_{4} \) compound which he named isomannide to distinguish it from another dianhydride of mannitol separated previously. A year earlier he had obtained a compound with the same molecular formula from the dry distillation of mannitol (3); it is probable that this too was isomannide. Fauconnier found that isomannide had two free hydroxyl groups which he thought were primary and thus proposed formula (IV) for the structure of the compound.

\[
\begin{align*}
\text{HO} & \cdot \text{CH} \cdot \text{CH} \cdot \text{CH} \cdot \text{CH} \cdot \text{CH}_{2}\text{OH} \\
// & \quad // \\
0 & \quad 0
\end{align*}
\]

(IV)

On the basis of rates of esterification with phosphoric acid Carre (4) concluded that the hydroxyl groups were secondary. This was later supported by Van Romburgh and Van Der Burg (5) who also showed that the hydroxyl groups were not on adjacent carbons, by boric acid conductivity measurements and by the fact that acetone would not react to give a \( \alpha \)-isopropylidene derivative. They degraded mannitan to \( \alpha \)-vinyl-tetrahydrofuran and \( \alpha \)-ethyl-tetrahydrofuran
and on the basis of this and the easy formation of isomannide from mannitan proposed a 1,4;3,6-dianhydride structure for isomannide. This seems to have been accepted without question until 1945. In the intervening years the compound was used several times, but no further work was done on the proof of its structure.

It is of interest to note the work of Brigl and Grunner who, in 1934-5, unknown to themselves, prepared several derivatives of isomannide. They found that 1,6-di-0-benzoyl-D-mannitol on heating or on refluxing in tetrachloroethane gave a di-0-benzoyldianhydromannitol (6). They assumed that the benzoyl groups had not migrated and this appeared to be supported by the fact that debenzoylation gave a syrup which upon tosylation gave a ditosyl derivative. The tosyloxy groups of this compound were easily replaced by iodine under the action of sodium iodide in acetone at 110°C. (7). This seemed to indicate that the tosyl groups were primary (Oldham and Rutherford Rule (8)).

Hockett and co-workers (9) have prepared the dibenzoate of isomannide and shown it to be identical with that formed by Brigl and Grunner. The tosylate and iodo compounds also have physical constants identical to those of the isomannide derivatives. Thus, benzoyl migration must have occurred but was overlooked due to the fact that tosyloxy groups on five-membered rings are quite reactive in replacement reactions (10).

The only other major work on the isohexides before 1945, apart from some patents on the use of these compounds and their esters as plasticisers, blending and wetting agents, was carried out by Krantz and Carr. They investigated the effect of isomannide and isosorbide on the conductivity of boric acid solutions and found they caused very
little variation. On the basis of this and the similarity of the two compounds they proposed the 1,4;3,6-dianhydride structure for isosorbide (11). This was the first time isosorbide had been reported as being crystalline. Krantz also studied the physiological effects of the two anhydrides and their dinitrates, the former were found to be non-toxic and diuretic (12), while the latter had a vaso-dilatory effect (13), characteristic of many nitrate esters.

In 1945 Wiggins (14) gave proof of the structure of isomannide based on the following facts:

1. The molecular formula is $C_{10}H_{16}O_{4}$, representing the loss of two moles of water from D-mannitol.

2. It has two free hydroxyl groups; dichloro, dibenzoyl and ditosyl derivatives were formed.

3. The rings were stable to the action of hot sodium ethoxide and methanolic ammonia and therefore are not ethylene oxide rings.

4. The free hydroxyl groups are not on adjacent carbon atoms as the compound was not attacked by lead tetraacetate.

5. Heating with fuming hydrochloric acid gave 1,6-dichloro-1,6-dideoxy-D-mannitol, showing that the positions 1 and 6 are involved in the ring.

6. Dichloroisomannide, on treatment with fuming hydrochloric acid, gave a tetrachloro compound. This was identical with the synthetic product 1,2,5,6-tetrachloro-1,2,5,6-tetradideoxy-mannitol, and complete chlorination gave hexachloromannitol. The configuration, therefore, is not altered during the dehydration.
7. 1,6-dichloro-1,6-dideoxy-2,5-dimethyl-D-mannitol was prepared and shown to be identical with the product formed when dimethylisomannide was treated with fuming hydrochloric acid. This shows that the 2- and 5-positions are not involved in the ring system.

These results leave only two possibilities for the compound - 1,4;3,6-dianhydro-D-mannitol or 1,3;4,6-dianhydro-D-mannitol. Wiggins thought that only the former structure was correct due to the difficulty in making models of the latter and the fact that four-membered rings are uncommon, especially in carbohydrate chemistry.

The work of Hockett and Goepp (9) gave further confirmation to this structure. They showed that the hydroxyl groups are secondary on the basis of tritylation rate studies. The formation of isomannide from 1,4-anhydro-D-mannitol by the action of concentrated sulphuric acid showed the origin of one anhydride ring, although it was recognized that rearrangement might have occurred under the conditions of this reaction.

The presence of the 3,6-anhydro ring was demonstrated (14) by the formation of isomannide by the following series of reactions -

\[
\begin{align*}
3,6\text{-anhydro-D-mannitol} & \xrightarrow{\text{tosylation}} 1\text{-O-tosyl-3,6\text{-anhydro-D-mannitol}} \\
& \text{1 mole tosyl chloride} \\
& \text{complete acetylation} \\
\text{sodium} & \xrightarrow{\text{isomannide}} 1\text{-O-tosyl-2,4,5\text{-tri-O-acetyl-methoxide}} \\
& \text{3,6\text{-anhydro-D-mannitol}}
\end{align*}
\]

This series of reactions involves relatively mild conditions which are not expected to cause rearrangements.
Isomannide is best prepared by refluxing D-mannitol with fuming hydrochloric acid for three days (14). This reaction was investigated thoroughly by Montgomery and Wiggins (15) and it was found that an equilibrium was set up; 1,6-dichloro-1,6-dideoxymannitol is formed initially and comes into equilibrium with isomannide and hydrochloric acid as the reaction proceeds. Isomannide is formed as the hydrochloric acid is driven off. Isomannide is also obtained by heating mannitol with catalytic amounts of sulphuric acid under vacuum (9), and from 1,6-di-O-benzoyl-D-mannitol by heating with p-toluenesulphonic acid in tetrachloroethylene (6).

Isosorbide is formed from sorbitol by the action of fuming hydrochloric acid. The yield is considerably higher than that of isomannide from mannitol (16). The dehydration of sorbitol with sulphuric acid as catalyst also gives higher yields than the corresponding reaction with mannitol (17) and is the more convenient preparation for isosorbide. This isohexide has very similar properties to those of isomannide. Hockett, Fletcher, Sheffield and Goepp (17) have given evidence towards the proof of the 1,4-3,6-dianhydride structure in the following observations:

1. Analysis and formation of a dibenzoate indicate two anhydro rings and two free hydroxyl groups.

2. Mild hydrolytic agents did not bring about ring opening. The rings are therefore not of the ethylene oxide type.

3. The compound was not attacked by lead tetraacetate, showing that the free hydroxyl groups are not on adjacent carbon atoms.

4. Tritylation studies indicate that the hydroxyl groups are
secondary.

5. 1,4-anhydrosorbitol and 3,6-anhydrosorbitol both yielded isosorbide in 67-79\% yield when heated in vacuo with sulphuric acid whereas 1,5-anhydrosorbitol did not.

Further proof of the anhydro ring structure was given by Wiggins and co-workers who synthesised isosorbide from 3,6-anhydrosorbitol (16), and from 1,4-anhydrosorbitol (18), by the same series of reactions as were used for the synthesis of isomannide from 3,6-dianhydro-D-mannitol. They were also able to synthesise dimethylisosorbide from 2,5-di-O-methyl-3,6-anhydro-\(\alpha\)-methyl-D-glucofuranoside previously prepared by Haworth et al. (19), thus giving final proof of the ring structure.

Isoidide was the last of the known isohexides to be prepared, probably due to the rarity of its parent hexitol - L-iditol. It can be formed by similar methods to the other isohexides but the yields are usually higher (20). There is evidence that the isoidide configuration is more stable than that of isomannide (21), accounting for the higher yields.

Proof of the structure of isoidide was obtained by comparison with isosorbide and isomannide which it resembles closely and by the following syntheses of the compound -

1. The action of sodium methoxide on 3,4-di-O-tosyl-D-mannitol or 3,4-di-O-tosyl-1,2,5,6-tetra-O-acetyl-D-mannitol gave isoidide directly in both cases (20). This reaction involves inversions at both the C\(_3\) and C\(_4\) positions of D-mannitol to give the L-iditol configuration.

2. Treatment of either isomannide or isosorbide with Raney
nickel followed by hydrogenation gave isoidide which was
classified by its dibenzoyl derivative (21). This inter-
conversion is thought to proceed through dehydrogenation to
a keto derivative followed by rehydrogenation to the hydroxyl
form in the isoidide configuration, this being formed more
readily.

There have been no reports of the formation of 1,4;3,6-dianhydrides
from the other three hexitols. Models indicate that their ring struc-
ture would be more strained than that of the three isohexides described.
In the present work tests indicated that dulcitol dehydrated in a
similar manner to D-mannitol as far as the rate of removal of water
was concerned but no well-defined product was obtained on distillation
of the residue from the dehydration.

Direct dehydration methods are liable to lead to a variety of
products and it is possible that the remaining isohexides could be
prepared by more specific methods especially if the 2 and 5 positions
were protected. A possible route is from 2,5-di-O-methyl-3,6-anhydro-
sorbitol (15). If this compound were tritylated to protect the primary
position then tosylated at the remaining free hydroxyl group, the 4-
position, treatment with acid to remove the trityl group and finally
alkaline hydrolysis would be expected to cause anhydro ring formation
with inversion at C₄, thus giving the dulcitol derivative. A second
method could be through 1,3;4,6-di-O-benzylidenedulcitol (23). The
2- and 5-positions in this compound could be protected by methylation
after which removal of the benzylidene groups would afford 2,5-di-O-
methyldulcitol which could be dehydrated by a number of routes.
The field of stereochemistry today may be divided into two sections, the study of configuration and the study of molecular conformation. The former is concerned with the arrangement of the groups or atoms around an asymmetric atom or molecule. The latter has been defined by Klyne (24) as the different arrangements in space of the atoms in a molecule, which are produced by rotating or twisting (but not breaking) the bonds. It is this field which has received much attention in recent years.

The representation of three-dimensional structures on paper is a necessary part of stereochemical work and presents a problem which has not yet been completely satisfactorily solved. Two types of notation are in use—perspective and projectional (Figure I).

Perspective drawings show all the bonds in their correct relationships but are difficult to draw and interpret. The Fischer projection formulae (25) are excellent for configurational analysis but not for
conformation work. The newer Newman formulae (26) in which the molecule is viewed along one carbon-carbon bond show the relative positions of the groups attached to these carbon atoms plainly. With the perspective drawings the convention is to draw the forward atoms to the left and lower while the backward ones are drawn to the right and higher.

The direction of bonds may be indicated in several ways –

a) bonds drawn with normal lines, thus \( \text{C} \rightarrow \text{C} \) are in the plane of the paper.

b) bonds drawn with dotted lines, thus \( \text{C} \cdots \text{C} \) are directed backwards into the paper.

c) bonds drawn in a wedge-shaped manner, either \( \text{C} \angle \text{C} \) or \( \text{C} \leftrightarrow \text{C} \) are directed in front of the paper – outwards.

The study of configuration has been the subject of many papers and reviews and is sufficiently well-known to be omitted here. It is highlighted by the early work of Fischer on the configuration of the sugars, and the recent correlation of the conventional representation of the space arrangement of atoms in D-glyceraldehyde to that actually present in this compound by the X-ray work of Bijuoet and co-workers (27).

The term "conformation" was first introduced by Haworth in 1929 (28) in connection with the study of the ring form of the sugars.

Most of the work in conformational analysis has been in the investigation of cyclic structures, in particular cyclohexane and its derivatives.

An example of conformational analysis is best presented in the acyclic systems, ethane and butane being the simplest of these.

Calculations of thermodynamic properties using statistical mechanics gave good agreement with molecules possessing a rigid structure but when applied to hydrocarbons, assuming free rotation about a
bond, the results were poor. Kemp and Pitzer (29) postulated a sinusoidal barrier for the internal rotation in ethane (Figure II).

In position A the hydrogen atoms are furthest apart, rotating about the carbon-carbon bond the position B has to be passed. Here the hydrogen atoms are closer together and therefore the molecule is assumed to have a higher energy. Further rotation brings the molecule to A' so that there is a minimum in the energy curve every 120° of rotation. As every position throughout the complete revolution can be regarded as a conformation we have to restrict the definition in order to simplify the situation. Thus only those conformations which are capable of finite existence, i.e. lie at a minimum in the potential curve, are considered. We must remember that the energies involved are quite small and therefore any position may be taken up during the course of a reaction. The height of the barrier in ethane has been
estimated as being about 3000 cal./mole. This is intermediate between thermal energies (ca. 600 cal./mole) and a barrier which would prevent rotation at room temperature (ca. 20,000–30,000 cal./mole). So neither free rotation nor completely fixed conformation exist (30).

There are three possible conformations for ethane but as the hydrogen atoms are indistinguishable the conformations are also, and from hereon these conformations produced by rotating methyl groups will be disregarded.

In the case of butane, considering only the rotation about the C₂–C₃ bond, the rotation of methyl groups being ignored, we find the possible conformations are as shown in Figure III.

![Figure III: The Conformations of Butane](image)

The conformations of butane may be regarded as being A, C and E as these lie at the minima of the potential energy curve. The position A will be slightly more favoured than C or E as the methyl groups, which have the greater interaction, are furthest apart.
Baeyer (31) explained the stability of ring compounds on the basis of planar structures, but Sachse (32) and Mohr (33) recognized that strain free (bond angles not altered from the tetrahedral angle) rings could be formed in six- or more membered cases if a non-planar form was adopted. Two conformations for cyclohexane were seen to be possible theoretically. These are most commonly called the chair and boat forms, although several alternative names exist (Figure IV).

![boat and chair conformations](image)

**Figure IV: The Conformations of Cyclohexane**

This theory has since been supported by experimental observations and the chair form found to be the most stable (34).

Kohlrausch (35) was first to recognize that the carbon-hydrogen bonds in the chair conformation of cyclohexane are of two different types.

![axial and equitorial bonds](image)

**Figure V: Axial and Equitorial Bonds of Cyclohexane**
The bonds shown as •••••• in Figure V are now generally called the axial bonds, being directed parallel to the general axis of the molecule. There are three axial bonds on each side of the molecule in the chair form. The six other carbon-hydrogen bonds are directed in the general plane of the molecule, actually being directed alternately slightly above and slightly below this plane. These are called equatorial bonds, shown as —— in Figure V. By inverting the molecule the bonds originally axial become equatorial and vice versa. This transformation can occur with ease in cyclohexane.

The conformational analysis of cyclohexane has been extended to the tetrahydropyran rings of the sugars by Reeves (36). In this case there are two chair and six boat forms possible, depending upon the position of the oxygen atom.

Five-membered rings were for a long time thought to be planar. However it was found that spectroscopic measurements (37), electron diffraction studies (38) and entropy considerations (39) indicated a non-planar structure, although the deviation was not very great — calculated to be 0.2 Å out of plane by Pitzer (39).

The situation was summed up by Barker and Stephens (40) —

"In a regular pentagon the interior angles are very close to the tetrahedral value (108°, cf. 109° 28') so a planar structure is stabilized by forces tending to maintain tetrahedral bond angles. Conversely, the repulsions between the hydrogen atoms of neighbouring methylene groups are at a maximum in a planar structure and tend to produce torsional forces around the carbon-carbon bonds which would pucker the ring."

Two possible conformations have been considered for cyclopentane (41). The C₅ conformation (Figure VI) has four atoms in a plane and one either above or below this plane.
Figure VI: $C_S^4$ Conformation of Cyclopentane

The other (Figure VII), called the $C_2$ conformation, has three atoms in a plane $C_2$, $C_4$ and $C_5$ with $C_1$ above and $C_3$ below this.

Figure VII: $C_1^3$ Conformation of Cyclopentane

The latter seems to be the more symmetrical and would probably be taken up by cyclopentane. This is indicated by molecular polarisability measurements of Le Fevre and Le Fevre (41) whose results fit only the $C_2$ conformation. This was also confirmed with the mono-halide derivatives of cyclopentane. It should be noted that the conformation of cyclopentane is not fixed but probably changes continually.

The same workers have studied tetrahydrofuran and propose a similar conformation for this molecule. The furanose rings of sugars can be regarded as being derivatives of tetrahydrofuran as can the rings in the isohexides.
Fused Ring Systems

Various saturated fused ring systems are known, the most common are those found in the steroid and alkaloid fields. Considering the simpler fused ring systems as are present in the bicyclo[4,4,0] decanes (the decalins), the bicyclo[4,3,0] nonones (the hydrindanes) and the bicyclo[3,3,0] octanes, it is found that two isomers are formed in each system. These isomers arise from the configurations at the ring junctions. If the two hydrogen atoms at the ring junctions are on the same side of the rings then the compound is designated "cis", if they are on opposite sides the compound is called "trans" (Figure VIII).

![cis and trans isomers of decalin](image)

**Figure VIII: The Isomers of Decalin**

The two isomers of decalin were isolated by Hückel (42). At first it was assumed that the trans isomer would take up the double chair form as its most stable conformation while the cis would be in the double boat form (Figure IX). Later it was found that a double chair form was possible in the cis isomer. This latter conformation was supported by electron diffraction studies of Bastianson and Hassel (43) which showed that this was the actual conformation taken up by cis-decalin. Calculations of energy differences between the cis and trans forms agree quite well with experimental values for the
heat of isomerisation which is 2.12 kcal. – the trans isomer being the more stable (44).

Figure IX: Conformations of the Decalin Isomers

In the bicyclo[3,3,0] octane series we have two five-membered rings. It has been seen that cyclopentane rings are very close to planar and in these compounds the cis isomer is the more stable. This was shown in the combustion data of Barrett and Linstead (45), the energy difference being 6.0 kcal./mole. In the case of the related carbonyl compound (IV) it was found that only the cis compound could be prepared. The trans, when formed, presumably reverts immediately to the cis via an enolisation (46).

The hydrindanes have only a small energy difference between the two isomers. This is due to an increase in the energy of the trans
compared to the cis caused by the five-membered ring forcing the bonds at the bridge heads on the hexane ring into a plane; this operation causes strain in the case of the trans isomer (47) but not in the cis isomer.

The 1,4;3,6-Dianhydrohexitols

The compounds in this series are related to the bicyclo[3,3,0] octanes in that they possess two fused five-membered rings (compare formulae B and D in Figure X). These rings are of the tetrahydrofuran type which it has been seen have a very similar steric form to the cyclopentane ring. In actual fact the bond angle of the oxygen is found to be 111° ± 2° and the carbon-oxygen bond length 1.43 ± 0.03 Å (48) compared to a C-C-C angle of 108° and a carbon-carbon bond length of 1.53 ± 0.03 Å for cyclopentane (49). Thus the tetrahydrofuran ring is somewhat deformed compared to the cyclopentane ring but not to a great extent. The shortening of the carbon-oxygen bond compared to the carbon-carbon and the widening of the C-O-C angle compared to the C-C-C angle will probably tend to make the ring more planar; there will also be fewer non-bonded hydrogen-hydrogen interactions tending to increase this effect.

As there are two isomers of bicyclooctane so it would be expected that the fused tetrahydrofuran ring system could exist in two forms depending upon the arrangement of the hydrogens at the ring junction. If we relate the bicyclooctane system to the isohexide rings and then convert this to the Fischer projection formulae showing it as a derivative of the hexitols we have the relationship as shown in Figure X.
Figure X: The Ring Structure of the Isohexides
This shows that a trans arrangement at the ring junction would arise from an erythro configuration of hydroxyl groups at carbon atoms 3 and 4 (formulae A, C and E, Figure X). The cis form would stem from a threo configuration (formulae B, D and F, Figure X).

The group of hexitols – D- or L-mannitol, sorbitol and D- or L-iditol – possess the threo configuration at C₃ and C₄ and would be expected to give a cis arrangement at the junction of the rings, while the other hexitols – dulcitol, allitol and D- or L-altritol – would give a trans form. Isohexides have been formed from the first three hexitols while the second group have not been reported to give isohexide derivatives. This is probably due to the greater stability of the cis isomers of fused five-membered ring systems. Although the energy difference is not very great, it seems to be sufficient to preclude the formation of isohexides from the dulcitol group by direct dehydration. It is probable that some other product is formed preferentially; perhaps by intra-molecular dehydration.

The above assignment of the cis ring junction to the known isohexides rests upon the assumption that the configuration of the parent hexitol is retained in the dianhydride. Proof of this is given by the work of Wiggins (14) who degraded dichloroisomannide to hexachloromannitol which was identical with the product obtained by direct chlorination of mannitol. Also, in the case of isosorbide, if this compound had a trans ring junction it would have to be a meso structure, but as it has a specific rotation of +45° it must therefore be cis (compare with reference (50)).

It is fairly well established, therefore, that the known isohexides possess the cis ring form. We can now go further into the
conformation of the molecules. If we assume that the rings themselves are planar then their planes will be inclined to one another at an angle of about 120°, forming a V-shaped molecule when viewed from the side (Figure XI). This ring structure should be fairly rigid; it is impossible for it to invert as is found in the cyclohexane ring system.

The final point to be considered in the molecule is the positions of the substituents on positions 2 and 5. The carbon atoms in these positions each have two bonds not involved in the rings. One pair of these bonds (one on each carbon) is directed approximately at right angles to the general plane of the molecule on the inside of the V of the rings. These are called the endo bonds. The other pair are directed more in the general plane of the molecule on the outside of the V and are called exo bonds. The relative positions of these bonds are best seen when the molecule is viewed along the bond of the ring junction - the C₃-C₄ bond. The rings are seen as lines being the arms of a shallow V (Figure XI).

In the isohexides themselves each of two carbon atoms, C₂ and C₅, are bonded to a hydrogen atom and a hydroxyl group. By having the hydroxyl group in the exo or endo position three isomers are possible.

The positions of the hydroxyl groups or other substituents become important in two types of reaction. The direction of the bond and ease of attack at its back is important in SN2 type reactions and the proximity of the groups on C₂ and C₅ is important when interaction or bridge formation can occur, i.e. in the formation of imido- and anhydro-bridges.
Figure XI: Conformation of the Isohexide Molecule
In an SN2 reaction the nucleophile attacks the molecule in a direction along the bond to be broken and from the opposite side of the carbon atom from the group being displaced. For this type of attack to occur in the isohexides, if the leaving group is in the exo position, the nucleophile must pass close to the face of the second ring (Figure XI). From measurements of models it appears that there is less than 1Å between the van der Waals radii of the carbon atoms in the second ring and the line along which attack must be made to be directly along the bond holding the leaving group. It is obvious that only a very small nucleophile could approach in this ideal direction. In the case of displacement of an endo group the attack is on the side of the ring away from the second ring and thus there is no hindrance. The selectivity observed in SN2 reactions in the isohexides is readily explained on the basis of this steric hindrance.

Several bridge compounds have been formed in the isohexide series between positions 2 and 5 – anhydro, imide and methylene. It has been assumed in the first two cases that these derivatives must possess the endo-endo configuration as the distance between the positions in the other configurations is too great to be bridged. The anhydro and imide bridges have only one atom between the two carbons C2 and C5. In these cases it is necessary to compress the ring, i.e. make the angle of the V smaller, in order to form the bridge. Measurements, from models, show that the distances between the centres of the oxygen atoms in hydroxyl groups at C2 and C5 are approximately 4.5Å for an endo-endo and 5.5Å for an exo-exo configuration. Although there is not much difference between these distances it seems likely
that it will be easier to distort the molecule by closing the V rather
than by bending it in the other direction as would be required for an
exo-exo bridge.

In the methylene bridge system the CH₂ group joins the two oxygen
atoms. Thus the bridge is composed of three atoms and can span a
larger distance. These derivatives have been prepared for both iso­
mannide and isoidide (51). The isosorbide configuration has one
substituent on each side of the ring system and it seems unlikely
that these small bridges would join these two positions.
CHAPTER III

CHEMICAL PROPERTIES OF THE ISOHEXIDES

Chemical Reactivity

The tetrahydrofuran rings of the isohexide system are particularly stable towards chemical attack. Only a few instances of ring opening have been recorded. These cases have involved the use of acidic reagents; alkali appears to have no effect on the rings.

The action of fuming hydrochloric acid on isomannide in a sealed tube was shown to give 1,6-dichloro-D-mannitol (14). This compound was found to be an intermediate in the formation of isomannide from D-mannitol by the action of fuming hydrochloric acid (15). The same reagent with isosorbide gave 6-chloro-1,4-anhydrosorbitol (22). It was inferred from this that the 1,4-ring (the isoidide type) was the more stable and this is supported by evidence from comparison of yields in the formation of isohexides from the hexitols. Hydrobromic acid does not affect the rings, however phosphorous tribromide reacts with isomannide and isosorbide to give the corresponding 1,6-dibromo-hexitols (21).

As the ring system is very stable the chemistry of the isohexides normally involves the two carbon atoms bearing the free hydroxyl groups - carbons 2 and 5 - and substituents at these positions. During the past fifteen years a considerable number of reactions have been investigated in the isohexide series. The nature and configuration of the products shows that in some cases the reactions are extremely stereospecific but in others there is no such selectivity.
We may conveniently divide the reactions into two groups depending on the centre involved in the reaction and into sub-groups depending on the mechanism:

(A) When the carbon atom is the reaction site
   (1) SN2 type reaction
   (2) SN1 type reaction

(B) When the carbon atom is not attacked and the reaction site is in the substituent group. (Mechanisms are difficult to distinguish in this group.)

The group (A) reactions can be recognised by the property that they normally involve a configurational change. The sub-group (1) will involve inversion of configuration while the sub-group (2) will normally be accompanied by racemisation (there is no indication that neighbouring group effect, accompanied by retention of configuration, occurs in the isohexides, although it may be possible in some isosorbide derivatives). In the group (B) reactions, on the other hand, retention of configuration would be expected.

The group (A1) reactions are found to occur only when the substituent is in the endo and not when it is in the exo position. In the formation of most of the common derivatives retention of configuration is observed and both positions react with equal ease, although there are indications of small variations in rates; thus these reactions are classified into group (B).
The SN2 reaction in its simplest form as defined by Ingold (52) involves the attack of a nucleophile, A, on an atom, C, causing the displacement of a substituent, B. The reaction is visualised as proceeding through the attack of A in the direction of the C-B bond from the side of C opposite to B. This is followed by the formation of a bond between A and C and the simultaneous breaking of the C-B bond and the loss of B. It may be represented by the following scheme -

$$\text{A}^- + \text{C}--\text{B} \rightarrow \text{A}--\text{C} + \text{B}^-$$

(1) (2) (3)

Various experimental observations have been used to characterise this mode of reaction (53) -

1. Second order kinetics (rate dependant upon concentration of A and C-B).
2. No retardation by addition of B.
3. When C is an asymmetric atom inversion of configuration is observed.
4. Small solvent effect (compared to SN1 reaction).

The reactions in the isohexide series which show specificity in reacting only when the substituent is in the endo position are thought to have the SN2 mechanism. The first reaction of this type to be noted was the replacement of tosylxy groups by iodine which occurs when the isohexide ditosylates are treated with sodium iodide in various solvents. Both groups of isomannide ditosylate were replaced.
and only one of isosorbide ditosylate while isoidide ditosylate is not affected. Matheson and Angyal first proposed an SN2 mechanism for this reaction (53, 54) and recently all the reactions of this type in the isohexides have been reviewed by Cope and Shen (55).

The SN2 reaction requires the nucleophile to attack from the back of the carbon atom and it is this requirement which causes the specificity in the isohexides. From the conformation of these compounds it is seen that to attack the back of a carbon atom with its substituent in the exo position it is necessary for the incoming group to approach from the inside of the V of the rings. This mode of attack is therefore hindered by the second ring. In the case of an endo group the attack is from the outside of the V and is not hindered.

The following reactions are stereospecific in the same sense and are assigned the SN2 mechanism (Group A1):

1. Reaction of Thionyl Chloride with the Isohexides

The action of thionyl chloride in pyridine solution readily gave a dichloro derivative from isomannide and a monochloro derivative from isosorbide but fails to react with isoidide (56). Under more rigorous conditions - thionyl chloride in benzene followed by phosphorous pentachloride at 140°C. - isosorbide gave a dichloro derivative (56). The halogenation of alcohols by thionyl chloride proceeds through a chlorosulphite derivative which then decomposes to the halogen compound in one of two ways. Attack of the chlorosulphite by chloride ion causes displacement and a chloro compound with inverted configuration. However in some cases an internal displacement reaction occurs, an SNi mechanism,
and a chloro compound with the same configuration as the hydroxyl compound is formed (58).

\[
\begin{align*}
&\text{^-C-OH + SOCl}_2 \\
&\downarrow \\
&\text{^-C-O-SO-Cl}_a \\
&\downarrow \\
&\text{^-C-Cl + SO}_2
\end{align*}
\]

\(\text{ retention }\)  \(\text{ inversion }\)

Using pyridine as solvent for the reaction, Coudrey and co-workers (58) have shown that in all cases tested inversion occurs and similar intermediate complexes are thought to occur with other chlorinating agents and their decomposition follows the same pattern. The reaction with thionyl chloride in pyridine with the isohexides appears to follow the inversion mechanism.

(2) Reaction of Sulphonate Esters with Alkali Halides

Hockett and co-workers reacted the ditosylates of isomannide and isosorbide with sodium iodide in various solvents and obtained a diiodo derivative from isomannide (9) and a monoiodo compound from isosorbide (17). Matheson and Angyal (54) have compared these reactions with those of other secondary tosylxy groups by isolating the sodium toluenesulphonate which was precipitated. The following yields of this salt were obtained –

- Isomannide ditosylate – 2 moles sodium tosylate
- Isosorbide ditosylate – 1 mole sodium tosylate
- Isoidide ditosylate – zero

These workers proposed the SN2 mechanism for the reaction and
explained the differences in reactivity by steric hindrance. About the same time Wiggins and Wood carried out reactions with sodium iodide on the ditosylates and the dimesylates of the isohexides (59). They also reacted lithium chloride with these sulphonates. This latter reaction proceeds in a similar way to that with sodium iodide but slightly higher temperatures are required. The chloro compound prepared in this way from isomannide dimesylate was identified with that from the direct chlorination of isomannide with thionyl chloride. The chloromesyl derivative from isosorbide was treated with sodium hydroxide which removed the mesyl group and gave a chloro compound identical to that formed by direct chlorination of isosorbide under mild conditions. Thus a link is formed between the two reactions and their mechanisms.

The reaction of alkali halide with primary sulphonates is rapid and was originally used as a test for primary alcohol groups in carbohydrate (8). However in certain cases a secondary group will react readily as seen with isomannide. Tipson has reviewed all the examples of this reaction in carbohydrate chemistry to 1951 (60). No kinetic data are available for this reaction, however it is most certainly an SN2 reaction in the case of a primary group and probably is the same for secondary groups when these react.

(3) Reaction of Tosylates with Tetraethylammonium Acetate

Isoidide diacetate was found to be the product of the reaction of isomannide ditosylate with tetraethylammonium acetate (55).
The configuration of the final product is known by comparison with the acetate prepared by direct acetylation of isoidide, and thus the inversion is clearly demonstrated. Similarly ditosyl isosorbide when reacted with this reagent gave an acetyl tosyl derivative. This compound after deacetylation and tosylation gave isoidide ditosylate showing that the configuration at $C_5$ had been inverted (55). There was no reaction with isoidide ditosylate.

In this reaction the inversion of configuration can be shown directly while in the halide reactions this cannot be done. Thus in this case the evidence is strongly in favour of the SN2 mechanism.

(4) Introduction of Amino Groups and Other Amino Derivatives

By treating the tosylate esters of the isohexides with ammonia in methanol in sealed tubes at $180^\circ$C. the tosyloxy groups are replaced by amino groups (61). Diamine derivatives are formed from isomannide and isosorbide ditosylates, however isoidide ditosylate gives a good yield of a compound containing only one nitrogen which is secondary (62). The evidence points to this compound having an imido-bridge between positions 2 and 5. From measurement of models this could only occur with the endo-endo configuration and therefore the compound is a derivative of isomannide. Cope and Shen (55) have reacted dimethylamine with the tosylates. At $120^\circ$C. replacement occurs only in the two groups of isomannide and one of isosorbide. However at a higher temperature, $165^\circ$C., two groups are introduced into isosorbide.
These two bisdimethylamino compounds are identical with those formed by exhaustive methylation followed by lithium aluminum hydride reduction of the diamino derivatives formed by direct amination. The diamino derivative from isomannide ditosylate was also formed from the tosylate by treatment with potassium phthalimide followed by reduction (55).

It seems quite certain that these reactions involve inversion and an SN2 mechanism. The variation in reactivity of endo and exo groups is masked in the amination reaction with ammonia due to the use of a high temperature at which both types undergo replacement readily. A second factor may also be important in this group of reactions. The nucleophile in these reactions is not changed whereas all other examples have negatively charged nucleophiles. Thus attack will be facilitated by the absence of electrostatic interactions, making attack on the inside of the V of the molecule more probable.

Tipson (60) has reviewed the reactions of tosylate esters with ammonia and amines. Primary groups usually undergo replacement readily but isolated secondary groups are more difficult to replace. When there are free or potential hydroxyl groups present anhydro ring formation may result. No kinetic work has been carried out on this reaction.

(5) The Formation of Sulphur Derivatives

Only one example in this group has been reported (63). Isomannide ditosylate reacts with potassium thioacetate to give the dithiol-acetate derivative which can be readily hydrolysed to the dithiol.
As stated in Tipton's review (60), it is most likely that this reaction also proceeds via an SN2 mechanism involving inversion.

The above reactions, with the exception of that of the tetraethylammonium acetate, involve the replacement of a carbon-oxygen bond, of which the configuration is known, with a carbon to nitrogen, sulphur or halogen bond whose configuration is uncertain. It is only by comparison with other reactions that it can be said that inversion occurs; no definite proof has yet been presented. However it is fairly certain that in all these reactions inversion occurs. Cope and Shen (55) have presented a table revising the nomenclature of these compounds as many of them were incorrectly named from their parent compounds.

**SN1 Reactions at the Carbon Atoms (Group A2)**

The second type of reaction which involves the breaking of the carbon to substituent bond is that with an SN1 mechanism. The only example of this kind of reaction in the literature of the isohexides is in the diamination of amino derivatives with nitrous acid (62). The mechanism of this reaction has been reviewed and the following mechanism proposed

$$\text{HNO}_2 \quad \text{OH}^-$$

$$\text{R} \cdot \text{NH}_2 \rightarrow \text{R} \cdot \text{NH} \cdot \text{NO} \rightarrow \text{RN}_2^+ \rightarrow \text{R}^+ \rightarrow \text{ROH}$$

This reaction involves a carbonium ion as intermediate and racemisation would be expected to occur. In working with optically active substances Ingold and co-workers found that the products contained
both racemised and inverted material in the products of this reaction (64).

In the isohexides the amino derivatives from isomannide and isosorbide ditosylates – diamino dideoxy isoidide and diamino dideoxy isosorbide – were treated with nitrous acid (62). Isolation followed by distillation gave a syrup with near to theoretical yield for formation of isohexide. Methanesulphonylation of this syrup gave a low yield of isoidide dimesylate in both cases. It is quite probable that the syrup consisted of a mixture of the three isohexides formed from the carbonium ion intermediate but that only the dimesylate of isoidide crystallised out.

The only other example of the formation of a carbonium ion is in the present work when the iodo derivatives of the isohexides were reacted with silver nitrate in acetonitrile. In this case a low yield of a mixture of the three isohexide dinitrates was obtained; analysis of this mixture showed that the isoidide derivative was present in the highest concentration.

In the same connection it is interesting to note the dehydrogenation-hydrogenation reaction carried out on isomannide and isosorbide using Raney nickel catalyst (21). Here a mixture of the isohexides was obtained – as shown by chromatography – but only isoidide dibenzoate could be isolated and characterised. The reaction is thought to proceed via a keto derivative followed by hydrogenation, so the asymmetry of the carbon is lost during the reaction as when a carbonium ion is formed.

In both the latter reactions and probably in the former the isoidide derivative is formed in the highest yield. This shows that
this configuration is formed more readily. This is probably due to
the exo side of the molecule being more readily attacked than the
endo rather than the fact that a group in the exo position is more
stable than when in the endo.

Reactions Characterised by Retention of
Configuration (Group B)

In this group of reactions the bond between the carbon and the
substituent group is not broken, the reaction occurring only in the
substituent group. This is the case in the formation of ester and
ether derivatives of the isohexides. In these reactions the hydrogen
atom of the hydroxyl group is replaced by some other group. Similar
situations occur in the methylation of amino derivatives and of thiol
derivatives but there are only a few examples of these and this dis­
cussion will be restricted to those compounds with oxygen directly
attached to the carbon atom.

In the preparation of most of the common derivatives of the iso­
hexides the reaction proceeds readily for each of the isomers, i.e.
in methylation, tosylation, acetylation, benzylation. No variation
in reaction rate, as seen with the SN2 reactions at the carbon atom,
is noted. This may be due to a masking effect by the use of conditions
which will bring about reaction of both types of groups whereas
milder conditions may only attack one type.

Retention of configuration is the main criterion for the identi­
fication of this type of reaction. Proof of this is sometimes diffi­
cult but in several cases reconversion to the parent isohexide in
good yield is good indication of this. In other cases comparison to
other compounds has to be used. The isohexide diacetates were readily converted to the parent alcohols in high yield by the action of dilute alkali (0.1 Normal barium methoxide at room temperature) (55). The ditosylates have also been hydrolysed by stronger alkali at reflux and fair yields of the isohexides were obtained (66). Dibenzoxyli isomannide has been hydrolysed to isomannide by the action of ammonia in methanol (7). In the present work the three isohexide dinitrates were reduced to their parent isohexides by the action of palladium on charcoal.

It is possible to gain some information as to the relative ease of reaction of the endo and exo groups in the case of isosorbide when attempts are made to prepare partially substituted derivatives. The only example of this type of reaction was found in the partial tosylation of isosorbide carried out by Cope and Shen (66). These workers, using dilute solutions in pyridine and mole to mole ratios of tosyl chloride and isosorbide, obtained a crystalline acetylosyl derivative of isosorbide after acetylation of the syrup from the tosylation. The tosyl group on this compound will be shown later to be in the endo position, i.e. on the 5-position. Thus the endo positions are more readily attacked in this case.

Turning from the formation of derivatives to their reactions, usually those involved in the removal of these groups to form the original isohexide, we find only a little information is available. The action of alkali on the tosylates (66) gave fair yields of the isohexides with retained configuration in the cases of isomannide and isoidide - isomannide ditosylate with sodium methoxide (1 Normal).
for four hours at reflux gave a 64% yield, isoidide ditosylate with barium methoxide (0.3 Normal) for eight hours reflux gave a 52% yield (as the dibenzoate). In the case of isosorbide ditosylate only a very low yield of isosorbide was obtained, the main product being trianhydro-mannitol. There seems to be little variation in the rates of hydrolysis in these cases, however the formation of the trianhydride via a normal anhydro ring formation would require the endo group to be removed primarily. There is not sufficient evidence in reported work for a comparison to be made but the endo group has been shown to be the more readily attacked in the present work.

The reported derivatives of the isohexide are listed in Table I, together with their physical constants. The numerous uncharacterised ethers and esters described in patent literature have been omitted.
TABLE I

Derivatives of the Isohexides

2,5-Disubstituted Derivatives with Configuration Retained

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Isomannide</th>
<th>Isosorbide</th>
<th>Isoidide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diacetyl</td>
<td>b.p. 118°C./0.5 mm.</td>
<td>m.p. 60-61°C.</td>
<td>m.p. 57-57.6°C.</td>
</tr>
<tr>
<td></td>
<td>$[\alpha]_D +194.5^\circ$</td>
<td>$[\alpha]_D +133.6^\circ$</td>
<td>$[\alpha]_D +89.6^\circ$</td>
</tr>
<tr>
<td></td>
<td>(2)</td>
<td>(21)</td>
<td>(55)</td>
</tr>
<tr>
<td>Dibenzoyle</td>
<td>m.p. 133°C.</td>
<td>m.p. 102-103°C.</td>
<td>m.p. 111-111.3°C.</td>
</tr>
<tr>
<td></td>
<td>$[\alpha]_D +225.7^\circ$</td>
<td>$[\alpha]_D +24.0^\circ$</td>
<td>$[\alpha]_D +141.9^\circ$</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(17, 61)</td>
<td>(67, 20)</td>
</tr>
<tr>
<td>Diethyl</td>
<td>b.p. 135°C./10 mm.</td>
<td>b.p. 132°C./12 mm.</td>
<td>m.p. 65-65.6°C.</td>
</tr>
<tr>
<td></td>
<td>$[\alpha]_D +128.8^\circ$</td>
<td>$[\alpha]_D +66.4^\circ$</td>
<td>(59)</td>
</tr>
<tr>
<td></td>
<td>(1)</td>
<td>(1)</td>
<td>(68)</td>
</tr>
<tr>
<td>Dimesyl</td>
<td>m.p. 104°C.</td>
<td>m.p. 122-123°C.</td>
<td>m.p. 155-156°C.</td>
</tr>
<tr>
<td></td>
<td>$[\alpha]_D +138.7^\circ$</td>
<td>$[\alpha]_D +77.7^\circ$</td>
<td>$[\alpha]_D +41.9^\circ$</td>
</tr>
<tr>
<td></td>
<td>(59)</td>
<td>(18)</td>
<td>(20)</td>
</tr>
<tr>
<td>Dimethyl</td>
<td>m.p. 75-76°C.</td>
<td>b.p. 93°C./0.1 mm.</td>
<td>m.p. 52°C.</td>
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<tr>
<td></td>
<td>$[\alpha]_D +175^\circ$</td>
<td>$[\alpha]_D +92.9^\circ$</td>
<td>(68)</td>
</tr>
<tr>
<td></td>
<td>(14)</td>
<td>(61)</td>
<td>(68)</td>
</tr>
<tr>
<td>Dinitrate</td>
<td>m.p. 85.5°C.</td>
<td>m.p. 52°C.</td>
<td>m.p. 105-106°C.</td>
</tr>
<tr>
<td></td>
<td>(68)</td>
<td>(68)</td>
<td>(54)</td>
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<tr>
<td>Ditosyl</td>
<td>m.p. 93-94°C.</td>
<td>m.p. 101-102°C.</td>
<td>m.p. 105-106°C.</td>
</tr>
<tr>
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<td>$[\alpha]_D +92.2^\circ$</td>
<td>$[\alpha]_D +57.8^\circ$</td>
<td>$[\alpha]_D +33^\circ$</td>
</tr>
<tr>
<td></td>
<td>(61)</td>
<td>(61)</td>
<td>(54)</td>
</tr>
<tr>
<td>Ditrityl</td>
<td>m.p. 92-94°C.</td>
<td>m.p. 92-94°C.</td>
<td>m.p. 92-94°C.</td>
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<td></td>
<td>$[\alpha]_D +44.3^\circ$</td>
<td>$[\alpha]_D +44.3^\circ$</td>
<td>(9)</td>
</tr>
<tr>
<td></td>
<td>(9)</td>
<td>(17)</td>
<td></td>
</tr>
</tbody>
</table>

2-0-Acetyl-5-0-tosylisosorbide

<table>
<thead>
<tr>
<th></th>
<th>m.p. 64-65°C.</th>
<th>$[\alpha]_D +50.5^\circ$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(68)</td>
<td></td>
</tr>
</tbody>
</table>
TABLE I (cont'd.)

Derivatives Formed by Reaction Involving Inversion

<table>
<thead>
<tr>
<th>Derivative</th>
<th>m.p.</th>
<th>[α]₀</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaminoisoidide</td>
<td>59-62°C</td>
<td>+33.6°</td>
<td>(61)</td>
</tr>
<tr>
<td>Diaminoisosorbide</td>
<td>105-110°C/0.1 mm.</td>
<td>+43.6°</td>
<td>(61)</td>
</tr>
<tr>
<td>Dichloroisoidide</td>
<td>67°C</td>
<td>+93.5°</td>
<td>(14,59)</td>
</tr>
<tr>
<td>Monochloroisoidide</td>
<td>105°C/15 mm.</td>
<td>+55.8°</td>
<td>(56)</td>
</tr>
<tr>
<td>Diiodoisoidide</td>
<td>61-63°C</td>
<td>+107.9°</td>
<td>(59)</td>
</tr>
<tr>
<td>Iodotosylisoidide</td>
<td>90.8-91.3°C</td>
<td>+52.7°</td>
<td>(17)</td>
</tr>
<tr>
<td>Iodomesylisoidide</td>
<td>104-105°C</td>
<td>+74.2°</td>
<td>(59)</td>
</tr>
<tr>
<td>Chloromesylisoidide</td>
<td>115-116°C</td>
<td>+71.6°</td>
<td>(59)</td>
</tr>
<tr>
<td>Acetyltosylisoidide</td>
<td>95.5-96.3°C</td>
<td>+50.5°</td>
<td>(55)</td>
</tr>
</tbody>
</table>

Derivatives Involving Bridges Between the 2- and 5-position

<table>
<thead>
<tr>
<th>Derivative</th>
<th>m.p.</th>
<th>[α]₀</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,5-methylene-isomannide</td>
<td>84-85°C</td>
<td>+133.2°</td>
<td>(51)</td>
</tr>
<tr>
<td>2,5-methylene-isosorbose</td>
<td>83-84°C</td>
<td>-152.1°</td>
<td>(51)</td>
</tr>
<tr>
<td>1,4;2,5;3,6-tri-anhydro-D-mannitol</td>
<td>66.5-67.2°C</td>
<td>+128.4°</td>
<td>(66)</td>
</tr>
<tr>
<td>2,5-imido-2,5-deoxyisomannide</td>
<td>99-100°C</td>
<td>+90.5°</td>
<td>(61)</td>
</tr>
</tbody>
</table>
CHAPTER IV

REACTIONS OF NITRATE ESTERS

Hydrolytic Decomposition

The products of alkaline hydrolysis of nitrate esters are found to be the parent alcohol and nitrate ion together with aldehyde and olefinic compounds and nitrite ion. The formation of the latter products was explained by Farmer (69) as being due to oxidation-reduction reactions of the initial products. In a series of papers Baker and Easty (70-72) have made a kinetic study of the alkaline hydrolysis of simple nitrate esters. They put forward three modes of reaction for nitrate esters with alkali -

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Nucleophilic substitution</td>
<td>alcohol</td>
</tr>
<tr>
<td>(2) $\beta$-Hydrogen elimination</td>
<td>olefin</td>
</tr>
<tr>
<td>(3) $\alpha$-Hydrogen elimination</td>
<td>carbonyl compound</td>
</tr>
</tbody>
</table>

These reactions may be either bimolecular or unimolecular depending upon conditions. The kinetic work supports these three modes of reaction and the earlier mechanisms are generally discounted.

Nitrate esters may be compared to the corresponding alkyl halides in many reactions. However structurally they have more in common with the carboxylic esters. In these compounds there are two modes of bond fission and the nitrate esters have two similar modes -
Baker's work shows that hydrolysis of primary and secondary alkyl nitrate occurs much more slowly than in the corresponding halide. In the series methyl, ethyl, isopropyl and t-butyl nitrate the change-over from SN2 to SN1 mechanism was at isopropyl nitrate, as shown by comparative rates. In this series of nitrates the decomposition occurred nearly entirely by the nucleophilic substitution mechanism, only 5% of the isopropyl and 10% of the t-butyl nitrate reactions being of the \( \beta \)-hydrogen elimination type.

\( \beta \)-Hydrogen elimination is impossible in benzyl nitrate and Baker used this compound to show the effect of decreasing the nucleophilic power of the reagent (72). As the nucleophilicity was decreased the rate decreased to reach a constant value. It is at this point that a unimolecular reaction is taking place. However the \( \alpha \)-hydrogen elimination reaction did reach a constant rate indicating that this reaction always proceeds via a bimolecular reaction. Baker used this decrease in rate with weaker nucleophiles to explain the suppression of "oxidised" products which is observed when substances such as thiophenol are added. The hydroxyl ion exchanges with the thiophenol, the thiophenyl ion is then too weak a nucleophile to affect the \( \alpha \)-elimination reaction.

Baker states that there was no indication in their kinetic work
that the nucleophilic attack occurs anywhere but on the carbon atom. However Anbar et al. (73) have obtained evidence that in primary alkyl nitrates the attack is on the nitrogen atom. Cristol and co-workers (74) have carried out kinetic and other work on optically active 2-octyl nitrate. With this compound they have shown that about 70% of the alcohol formed in the alkaline hydrolysis had the configuration retained. Their kinetic data was comparable to that of Baker for isopropyl alcohol but separation of the optically active products indicated that the reaction was breaking the oxygen-nitrogen bond rather than the oxygen-carbon one which would be the case in attack of the carbon atom.

Cristol and co-workers also investigated the neutral hydrolysis and in this case inversion of products predominated. They proposed that this was due to the attack of the neutral water molecule on the carbon atom. It is worth noting their statement that 2-octyl nitrate behaves as an ester in alkaline hydrolysis but as a halide or sulphonate in neutral conditions.

In the hydrolysis of nitrate esters with alkoxyl ions the formation of ethers has been observed (75). The action of alkali on carbohydrate nitrates containing a free hydroxyl group is to form an anhydro ring (76). On the other hand a single isolated nitrate group will give the alcohol as shown by the reaction of 1,2;3,4-di-O-isopropylidene-D-galactose 6-nitrate to the corresponding alcohol by Honeyman and Stering (77). The action of alkali on D-glucopyranoside tetranitrates has been studied and was found to be rapid in 0.1 Normal methanolic sodium hydroxide, 3 mole equivalent of nitrite and 0.8–0.9
mole equivalent of nitrate being formed (78). The reaction products were not isolated but it was suggested that the reaction proceeded mainly by the α-hydrogen elimination reaction to yield carbonyl products which then decomposed further.

Nitrate esters are reasonably stable to acid hydrolysis. Baker (72) found that there was no acid catalysis of the hydrolysis reactions. Concentrated sulphuric acid does however cause ionisation which will be discussed later.

**Reductive Cleavage**

Many reagents have been described for the reduction of nitrate esters: electrolysis, Grignard reagents, hydrazine, hydrogen, lithium aluminum hydride, acid plus metal and alkaline sulphides (79). The majority of these reductions yield the parent alcohol and nitrite ion - or its reduction products. The alcohol in most cases shows retention of configuration and thus the reaction is thought to proceed via oxygen-nitrogen bond fission. The reductions with sulphides and hydrazine have been reviewed (79) but will be described here as well the work on catalytic hydrogenation which proves to be a useful tool in confirming the configuration of nitrate esters.

Kuhn (80) used platinum or palladium as catalyst for the denitration of nitrate esters with hydrazine. The reaction was quantitative and rapid. One mole of hydrazine was consumed for each mole of nitrate group to yield the parent alcohol and 1.5 moles of gas, of which one mole was nitrogen and 0.5 moles nitrous oxide. Merrow and Dolah (81) found that with large excess of hydrazine the reaction proceeded
without a catalyst. The products in this case were not as simple as in the presence of a catalyst. In alcoholic solvents primary aliphatic nitrates gave appreciable amounts of alkylated hydrazine but in the absence of solvent there was a higher percentage of reduction to the parent alcohol. The gas evolved was at a maximum of 1.35 moles in large excess of hydrazine, of this about one mole was nitrogen, the remainder being nitrous oxide and ammonia.

Merrow and co-workers (82) have studied the action of alkaline hydrosulphides on nitrate esters which was similar in many ways to that of hydrazine and they proposed a general mechanism for the initial step in both these reactions:

\[ \text{B:} + \text{R.O.NO}_2 \rightarrow \text{RO}^- + \text{B: NO}_2^+ \]

Thus, in the case of hydrazine the nitrated hydrazine \( \text{H}_2\text{N.NH}_2\cdot\text{NO}_2 \) decomposes after a loss of proton to the alkoxy ion. Using optically active 2-octyl nitrate high retention of configuration was obtained in the conversion to the parent alcohol (83). 1,2-Cyclohexane diol dinitrates were also reduced with retention of configuration.

Merrow's work does not distinguish between the two modes of nucleophilic attack (i.e. at the alkoxy oxygen or at the nitrogen). However the formal positive change on the nitrogen atom is thought to make it the more likely site for the nucleophilic attack than the oxygen. Rate studies were made on benzyl nitrate which give predominantly benzyl hydrazine and on simple aliphatic nitrates which give mainly reduction (84). The \( \text{N}_2\text{H}_3^- \) ion is thought to be the active species in the reduction reaction and \( \text{NH}_2\cdot\text{NH}_2 \) in the alkylation. The
former attacking the nitrogen atom and the latter the carbon (c.f.
basic and neutral hydrolysis, page 42).

Sugar nitrates are reduced to the corresponding alcohols only by
boiling with hydrazine (85). This reaction does not affect tosyl
groups.

Hydrogenation using various catalysts has been applied to several
nitrate esters (86). In all cases the parent alcohols are obtained
with retention of configuration. Raney nickel as catalyst converts
the nitrogen to ammonia which may be undesirable in the case of
carbohydrates. Palladium on either charcoal or calcium carbonate
however gives the nitrogen as N₂ and has been used successfully in
the denitration of several sugar nitrates to their parent alcohols
with retention of configuration (87). This reaction is very useful
in confirmation of the structure of nitrate derivatives.

Trans-nitration

Several types of this reaction have been recorded and are reviewed
by Boschan et al. (79). The trans-nitration reactions carried out in
sulphuric acid solution will be dealt with later. Lewis acids have
been used to induce ethyl nitrate to nitrate benzene and toluene (88).
Nitration under alkaline conditions was noted with ethyl nitrate and
the sodium salt of pyrrole β-nitropyrrrole was formed (89). In the
presence of ethoxy ions alkyl nitrates can be used to nitrate active
methylene groups as in phenylacetonitrile and cyclohexanone the latter
gave a di- and mononitro derivative (90).

N-Nitration occurs in some cases, as in the formation of phenyl-
nitramine from aniline (91) and of nitrated ethylurea (92). N-Nitration is also proposed as the first step in the reduction of nitrate esters with hydrazine (82) and in the decomposition of hydroxylamine with ethyl nitrate in the presence of sodium ethoxide (93).

**Ionisation in Sulphuric Acid**

Solutions of nitrate esters in sulphuric acid are known to be good nitrating agents. The van't Hoff i factors have been determined for several nitrates and found to be approximately five. Kuhn (94) has studied this ionisation with ethyl nitrate. The ultra-violet spectra of ethyl nitrate in sulphuric acid corresponds exactly to that of nitric acid in sulphuric acid and is different from that of ethyl nitrate in chloroform. The ionisation process was proposed to proceed via the following scheme -

\[
\begin{align*}
R.0\text{NO}_2 + H_2S\text{O}_4 & \rightarrow [R-0-\text{NO}_2]^+ + H\text{SO}_4^- \\
\text{H} & \quad \frac{\cancel{\text{H}}}{[R-0-\text{NO}_2]^+} \quad \rightarrow \quad \text{ROH} + \text{NO}_2^+ \\
R.\text{OH} + 2H_2\text{SO}_4 & \rightarrow R.0\text{SO}_3\text{H} + H_3\text{O}^+ + H\text{SO}_4^-
\end{align*}
\]

This scheme explains the observations that the nitrates were not re-generated when the sulphuric acid solution was poured into water and that the solutions act as nitrating agents. The latter property is due to the presence of the nitronium ion.

The ionisation, giving a nitrating solution, is utilised in the
colorimetric determination of nitrate esters (95). In this case an easily nitrated substance (usually a phenol) is placed in the solution and its nitration product isolated and estimated. There are no reports of the action of sulphuric acid alone on carbohydrate nitrates but a solution of sulphuric acid in acetic anhydride was shown to result in the denitration and acetylation of several aldoses and sugar alcohols (96). The acetates formed in this reaction have the same configuration as the nitrates.

**Thermal Decomposition**

This problem has been approached from two directions. Due to the interest in nitrates as explosives a considerable amount of work has been carried out on the thermal decomposition of solid and liquid explosives including those of the nitrate ester type. On the other hand the simple alkyl nitrates, i.e. methyl, ethyl and propyl nitrates, have been used for thermal decomposition studies in the gaseous state.

Ethyl nitrate has been used in most investigations in the gaseous state (97-100). Its decomposition curve is nearly linear in first order rate plot but there is a slight autocatalytic effect present. This has caused some variation in the value of the activation energy obtained from these plots. One group of workers (97) used the latter parts of the curves which approximate to straight lines, while most workers have used the initial near-linear part (98,100). The latter results are thought to be the more accurate and to represent the truer values. The kinetic results are put further in doubt due to the demonstration that nitrogen dioxide retards the reaction (98, 100).
Thus it was necessary to propose that the initial and rate determining step is reversible. Levy (100) attempts to avoid this complication by the introduction of nitric acid or acetaldehyde to combine with the nitrogen dioxide formed.

The initial rate determining step in the decomposition of simple nitrate esters is well established and is the homolytic breaking of the oxygen-nitrogen bond -

\[ R.O.NO_2 \rightarrow R.O^* + NO_2 \]

As both these products are very reactive the secondary reactions are very complicated and no complete scheme explaining all experimental results has been elucidated. The products of these secondary reactions include ethyl nitrite, nitromethane, methyl nitrite, nitric oxide, nitrogen dioxide, carbon dioxide and carbon monoxide (100).

The activation energies determined for decomposition of ethyl nitrate, together with those of other alkyl nitrates, have been summarised by Gray (101) and by Luft (102). They fall in the general range of 35-40 kcals. per mole, the higher values being thought to be the more accurate.

In the study of solid and liquid nitrate explosives, two methods are available for the determination of the rate of isothermal decomposition; the measurement of the pressure of the gaseous products and of the loss in weight of the sample, determined on a quartz spring balance.

In these rate determinations on condensed samples experimental difficulties are encountered due to the lag in heating at the beginning
of the experiment. This is appreciable in the studies involving the measurement of the gaseous products since these usually employ fairly large samples and temperatures which give reaction times of from seconds to a few minutes. Methods involving insertion of the sample between two heated copper plates (103) or dropping the sample into a preheated glass tube (104) have been used to overcome this difficulty. Another problem is the self-heating effect due to the high heat of reaction, this necessitates the use of small samples.

Cook (105), using the quartz spring method, has studied the decomposition of several explosives, among these was pentaerythritol-tetranitrate. This method can only be used for materials which have low vapour pressures as evaporation of the sample will lead to errors in the rates. Ammonium nitrate was found to obey a first order rate law for decomposition to 100% completion, however pentaerythritol-tetranitrate, nitroglycerol and nitroglycerine showed a strongly autocatalytic rate plot. This autocatalytic effect is due to the formation of non-volatile reaction products which react with the compound. Cook used the initial rates, determined from the tangent to the autocatalytic curve at the origin, to determine activation constants. These values fall fairly well into a line with the results from the decomposition of alkyl nitrates.

The uncertainty in the values obtained for the activation energies make it difficult to draw any definite conclusions in relating the activation energies to explosive properties.
Reaction with Amines

Primary and some secondary alkyl nitrates react with amines causing N-alkylation of the amine. However with most secondary and tertiary nitrates the reaction is complicated by the decomposition of the nitrate esters and by a change in the mechanism of the reaction. Nitrate groups adjacent to electron attracting groups are highly reactive towards secondary amines and yield the carbonyl derivative by a $\alpha$-hydrogen elimination reaction of the type found in alkaline hydrolysis of nitrate (106). Certain polynitrates on the other hand have been shown to undergo a rapid and selective reaction with pyridine removing the nitrate group and leaving a hydroxyl derivative (107, 108).

The general reaction of an amine with a nitrate ester in the case of simple alkyl nitrates is:

$$\text{B}: + \overset{\text{\sigma}}{\text{C}} \rightarrow \text{B} + \overset{\text{\sigma}}{\text{C}} + \text{NO}_3^-$$

Ryan and Cassey (109) have studied the reactions of several alkyl nitrates with various aromatic amines. The primary amines - aniline, toluidine and m-xylidine - gave alkylated amines together with the amine nitrate when heated with primary nitrates for periods of eight to twenty four hours at 100°C. Secondary and tertiary amines were found to give products of red or violet colour which were viscous syrups and were not identified. Comparison of the colour developed in these reactions showed that the comparative rates for the nitrates
investigated were - ethyl nitrate 1, mannitol hexanitrate 22.9, gun cotton 9.4.

More recently Lane (110) prepared several quaternary ammonium nitrates by the action of alkyl nitrates on tertiary amines. This reaction was satisfactory when primary nitrate esters were reacted with trimethylamine or pyridine, and was complete after six to twenty four hours at 100°C. or reflux. Higher tertiary amines failed to react. Secondary nitrate esters usually gave olefinic compounds but butyl nitrate reacted normally to give quaternary salts. Cyclohexyl nitrate and t-butyl nitrate were shown to give cyclohexene and butylene respectively on treatment with pyridine; neopentyl type nitrates also failed to give quaternary salts.

These experimental results suggest that the mechanism of the reaction in the case of primary nitrates is of the SN2 type, with the amine as the nucleophile. The changeover to SN1 mechanism appears to occur at the secondary nitrates as some of these react by the SN2 mechanism while others yield olefins - presumably by a mechanism involving \( \beta \)-hydrogen elimination by the base -

\[
\begin{align*}
\text{B:} & \quad \cdots \quad \text{H} - \text{C} - \\
& \quad \text{\text{\text{\text{\text{\text{-C} \quad \cdots \quad \text{ON}}}}} \\
& \quad \text{\text{\text{\text{\text{\text{- ON}}}}}} \\
& \quad \text{\text{\text{\text{\text{- ON}}}}}
\end{align*}
\]

The SN2 reaction is not possible in the neopentyls due to the steric hindrance of backside attack.

Emmons and Freeman (106) have shown that nitrate ester groups which are activated by electron-attracting groups - chloride or carbonyl - are very reactive. At 0°C. they reacted vigorously and
exothermically with secondary amines to yield the carbonyl derivative —

\[
\begin{align*}
\text{CCl}_3 & \quad \text{CCl}_3 \\
\text{B:} + \text{H-C-H} & \quad \text{CH} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{B:} + \text{H-C-H} & \quad \text{CH} \\
\end{align*}
\]

Tichanowitsch (111) degraded mannitol hexanitrate to a penta-
nitrate derivative by the action of ammonia in ether. Wigner (112) found that the yields were improved by the use of pyridine as reagent. The mannitol pentanitrate formed by this reaction was characterised (107) as D-mannitol 1,2,3,5,6-pentanitrate by methylation followed by dehydrogenation and characterisation of the monomethyl-D-mannitol. Dulcitol (108) and sorbitol (113) hexanitrates have been shown to react similarly with pyridine. Mannitol hexanitrate reacts vigorously and exothermically when dissolved in pyridine at room temperature, but the dulcitol derivative requires warming to 50°C before the exothermic reaction commences.

Cellulose trinitrate is degraded to an amorphous powder by the action of pyridine; when free hydroxylamime is added the reaction is more rapid and the product is a fibrous material containing approximately two nitrate groups per glucose unit (114). The hydroxylamine was added in an attempt to react with carbonyl groups thought to be formed in the reactions and so prevent further degradation. However the number of oxine groups in the final product was low and it was found that the nitrate groups removed had been replaced by hydroxyl groups. The point of denitration was shown to be the 2-position by
methylation, denitration and hydrolysis to 2-methyl-D-glucose. α- and β-Methyl-D-glucopyranoside tetranitrates have been reacted with hydroxylamine in pyridine (115). The products contained several tri- and dinitrates but the main point of denitration was found to be at the 4-position; the 2-nitrate group was also removed to some extent.

The reaction of polynitrate esters with pyridine or hydroxylamine in pyridine is seen to be highly selective in nature. In the hexitol hexanitrates there are considerable differences in the reactivity between the various members and between the individual nitrate groups. The pentanitrate derivative once formed is stable to further denitration under the same conditions. A similar situation exists in the physiological action of nitrate esters which has been shown to vary considerably from nitrate to nitrate (116). It is thought that the conformation of the various nitrate groups in these compounds is concerned with their varying reactivities.

The gaseous products formed in these denitration reactions have been investigated. When hydroxylamine is present nitrogen gas is formed in mole to mole ratio with the nitrate group removed (114). When the reagent is simply pyridine the gaseous products are more complexed, consisting of nitric oxide, nitrous oxide and nitrogen (117). Falconer and Purves (118) have proposed a trans-nitration mechanism for the reaction with hydroxylamine -

\[
\text{NH}_2\cdot\text{OH} + R\cdot\text{ONO}_2 \rightarrow \text{NO}_2 - \text{NH}_2\cdot\text{OH} + R\text{O}^-
\]

It has been seen that a similar reaction has been proposed for the
action of hydrazine with nitrate esters and several N-nitrations of this type have been noted with alkyl nitrates under basic conditions.

The nitrated hydroxylamine is thought to be decomposed to nitrogen by the action of further hydroxylamine. It is quite possible that a similar situation occurs in the case of pyridine alone. The decomposition of the N-nitrated product in this case would be more complicated. Pyridine seems to be less reactive than hydroxylamine in these reactions, but hydroxylamine alone is much less reactive than in the presence of pyridine.
RESULTS AND DISCUSSION

CHAPTER V

THE REACTION OF THE ISOHEXIDE DINITRATES WITH PYRIDINE

Materials

Isomannide and isosorbide were prepared by the dehydration of D-mannitol using fuming hydrochloric acid (14) and of sorbitol using concentrated sulphuric acid (17). L-Iditol was not readily available and the most convenient method reported for the preparation of isoidide was from isomannide ditosylate (55). This compound was treated with tetraethylammonium acetate in acetone solution and gave isoidide diacetate by an SN2 reaction which has been previously described. Isoidide was obtained by hydrolysis of the diacetate with barium methoxide. This method proved to be unsatisfactory in that it was difficult to obtain complete reaction in the formation of the diacetate although a yield of 85% had been reported (55). An alternative synthesis was investigated and found to be more satisfactory. L-Sorbose was hydrogenated at 80°C. and 50 p.s.i. with Raney nickel as catalyst and the syrupy product from this reaction was dehydrated directly by the action of hydrochloric acid. The resulting mixture of isoidide and isosorbide was separated by fractional distillation under reduced pressure to give a good yield of crystalline isoidide.

Each of the isohexides were recrystallised after which their melting points and specific rotations and those of their acetate and
tosylate esters were found to correspond closely to previously reported values. In the preparation of the dinitrates two nitration methods were used – the sulphuric acid/nitric acid (68) and the acetic acid/ acetic anhydride/nitric acid (119). The former method was that used by Krantz (68) to prepare isomannide and isosorbide dinitrates. The latter method was found to give higher yields and was used in all subsequent preparations. Sutherland (120), in the nitration of isomannide, obtained a comparatively low yield of the crystalline dinitrate on dilution of the nitration mixture with water. Similar results were obtained here in the nitration of isosorbide and isoidide. The yields were improved, however, by the isolation of a further quantity of the dinitrates by extracting the diluted nitration mixture with chloroform or ether. The total yields were then generally about 90% of theoretical.

The three isohexide dinitrates were recrystallised to constant melting point and their specific rotations, nitrogen content and infrared spectra were determined. Isomannide and isosorbide dinitrates were previously prepared by Krantz (68) for physiological studies and their melting points only were reported. Isosorbide dinitrate was also prepared by Goldberg (121) who reported melting point and specific rotation. Isoidide dinitrate has not previously been prepared. The physical constants reported and found are recorded in Table II.

The two reports of a melting point about 70°C. for isosorbide dinitrate could not be duplicated in the present work and no second crystalline form was encountered, although diiodoisoidide does have two crystalline forms which melt at different temperatures in some
TABLE II

Physical Constants of the Isohexide Dinitrates

<table>
<thead>
<tr>
<th></th>
<th>Melting point</th>
<th>[α]D</th>
<th>Nitrogen Content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Found</td>
<td>Reported</td>
<td>[α]D</td>
</tr>
<tr>
<td>Isomannide</td>
<td>64.5–65°C</td>
<td>65°C.</td>
<td>+335°</td>
</tr>
<tr>
<td>dinitrate</td>
<td>65.5°C.</td>
<td>(120)</td>
<td>+319.2°</td>
</tr>
<tr>
<td></td>
<td>65.5°C.</td>
<td>(68)</td>
<td></td>
</tr>
<tr>
<td>Isosorbide</td>
<td>50.5–70°C</td>
<td>70°C.</td>
<td>+141°</td>
</tr>
<tr>
<td>dinitrate</td>
<td>51.5°C.</td>
<td>(121)</td>
<td>+134°</td>
</tr>
<tr>
<td></td>
<td>71°C.</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>52°C.</td>
<td>(68)</td>
<td></td>
</tr>
<tr>
<td>Isoidide</td>
<td>68–69°C.</td>
<td></td>
<td>+72.9°</td>
</tr>
<tr>
<td>dinitrate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Determined by the Micro-Kjeldahl method.
2 Determined by Dr. Bernhardt (combustion method).
Kaiser Wilhelm Platz 1, Mulheim, Germany.

cases (9). The slightly low nitrogen content of isoidide dinitrate may be due to difficulty in the determination caused by the higher reactivity of the nitrate groups or by solvent of crystallisation. Isoidide itself has been reported to crystallise with one half mole of water.

The configuration of the nitrate esters was established by hydrogenation to their parent isohexides in high yield with palladium-charcoal catalyst. This method of denitration has been shown to result in retention of configuration in all cases tested (87).
The infrared spectra of the dinitrates confirmed the presence of the nitrate groups, showed no hydroxyl peak, and had bands which could be attributed to the tetrahydrofuran ring. The structures of the three dinitrates were therefore well substantiated.

The pyridine used in these reactions was reagent grade and was redistilled one or two times before use. Preliminary experiments indicated that pyridine dried by refluxing over barium oxide still contained a little moisture. The later reactions were run with pyridine which had been dried over calcium hydride before distillation and this treatment proved to be very effective and consistent.

Investigation of Reaction Products in the Nitrate-Pyridine Reaction

Preliminary Investigation

Initial tests, carried out on small samples of the three iso-hexide dinitrates in pyridine dried over barium oxide, showed that there was no reaction at 25°C. The iso-hexide dinitrates were very soluble in pyridine and gave colourless solutions. The optical rotation of the solutions did not change over a period of several weeks. However when the solutions were heated to about 50°C, colour developed very slowly, at 100°C this was more rapid, a pale brown colour appearing in about one hour. Comparison of the colour produced in this reaction showed an order of reactivity of isomannide dinitrate < isosorbide dinitrate < isoidide dinitrate. It was not possible to follow the reaction by measurement of optical rotation due to darkening of the solutions.
The reaction mixtures from these initial tests were poured into water \((10 \times \text{volume of pyridine solution})\) and from the resulting mixture unreacted dinitrate was isolated either by filtration or, more efficiently, by extraction of the aqueous pyridine mixture with ether. It appeared that much of the starting material remained after a few hours at \(100^\circ\text{C}\). As the reaction was slow at these temperatures, the solutions of nitrate in pyridine were refluxed for various times and the products of the reaction separated in a preliminary manner as in Figure XII -

![Figure XII: Preliminary Separation of Reaction Products](image)

Using this separation procedure it was possible to separate the reaction products into three distinct groups. The ether solution contained all the unreacted dinitrate, the aqueous solution contained all the inorganic nitrate (present as pyridinium nitrate), and the insoluble portion consisted of a brown or black amorphous substance. The separation of the nitrate into organic and inorganic fractions was demonstrated by paper chromatography in methylethylketone/water solvent.
system using diphenylamine in sulphuric acid as detecting agent (Table II). It was later shown that any parent diol formed in the reaction would be present in the aqueous solution.

TABLE III

Chromatography of Fractions in Preliminary Separations

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Rf (methylethylketone/water solvent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Reaction mixture</td>
<td>+</td>
</tr>
<tr>
<td>Ether solution</td>
<td>zero</td>
</tr>
<tr>
<td>Aqueous solution</td>
<td>+</td>
</tr>
<tr>
<td>Pyridinium nitrate</td>
<td>+</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>zero</td>
</tr>
</tbody>
</table>

The unreacted isohexide dinitrates were isolated from the reaction products in various reactions involving 10 to 90% decomposition at reflux temperature (114-115°C.). These products were recrystallised and melting points and mixed melting points taken for identification. One sample from each of the dinitrates at about 50% decomposition at both 100°C. and 87°C. was checked in the same way. Infrared spectra were run on several of these samples and found to be identical with those of the starting materials. Thus no change had occurred in the unreacted portion of the nitrate ester. In all separations carried out the ether fractions were investigated by paper chromatography using hexane/methanol solvent system and the isohexide dinitrate characterised by running known samples in parallel lanes.
Attempt to Isolate Parent Diols in the Reaction Products

In the reactions of hexitol hexanitrates with pyridine, the nitrate group was removed and replaced by a hydroxyl group with retention of configuration (107, 108). In the isohexides two products are possible from this type of denitration, either the mononitrate ester or the parent isohexide, depending upon whether the denitration was partial or complete. Paper chromatographs of the ether extracts showed a weak nitrate-containing spot in a position expected for a mononitrate. This represented only a small portion of the nitrate decomposed and the possibility of the completely denitrated material being present was investigated.

The tosylate ester derivatives of the isohexides are well defined and easily crystallised (59). Attempts were made to tosylate the reaction products and to separate the isohexide ditosylates. The reaction mixture was treated with tosyl chloride after cooling, but only a small amount of what was probably p-toluenesulphonic acid was separated. In other experiments the reaction mixture was evaporated, pyridine added, and re-evaporated to remove any water present, and the residue was then tosylated. No isohexide tosylate was obtained with this procedure.

From the solubilities of the isohexides it would be expected that they would be present in the aqueous solution of the extraction procedure. Evaporation of this solution gave a dark brown glass which was extracted with hot ethanol. The ethanol solution, on evaporation, gave a red syrup. A brown amorphous solid was left unextracted by the ethanol. The isohexides are readily soluble in
alcohol and therefore the alcohol extract from one separation was
tosylated but again no isohexide ditosylate was isolated.

To test the validity of the assumption that the isohexides
would be separated into this alcohol extract, reactions were run with
the isohexide added to the initial reaction mixture: 200 mg. of the
dinitrate and 500 mg. of the isohexide were refluxed in pyridine for
sixty hours in the case of both isomannide and isosorbide. After
this time the reaction mixtures were worked up and the alcohol
extract separated. The material in this fraction weighed 550 mg. It
was characterised as the unchanged isohexide by recrystallisation of
one half to constant melting point when melting points and mixed
melting points corresponded to those of the isohexide initially added.
The second half was tosylated to give an almost quantitative yield
of the ditosylate which was also characterised by melting points and
mixed melting points. In these experiments, therefore, isohexide
added to the reaction initially was recovered quantitatively.

Paper chromatography was also employed in the hope that small
quantities of the isohexides might be more readily detected. However
it was found that very few of the available developing agents could
be used to detect the isohexides on paper chromatographs. The iso-
hexides contain few functional groups. The ring systems are very
stable and there does not appear to be a reaction of the tetrahydro-
furan ring which could be applied to detection of these materials.
The only other active groups in the molecule are the two non-vicinal
secondary hydroxyl groups and the problem of detecting these amongst
similar groups in the cellulose of the paper seemed insoluble. Hexitols
under similar conditions are readily detectable by oxidising reagents which selectively oxidise vicinal hydroxyl groups.

When present on the paper in high concentration the isohexides could be detected by exposure to iodine vapour. Also when the papers had been run in methylethylketone/water solvent system the isohexides showed as white spots against a brown background when treated with p-anisidine/hydrochloric acid reagent (122). This test also was not very sensitive or reliable. With the iodine detection method it was shown that methylethylketone/water and n-butanol/water were suitable solvent systems for the separation of the isohexides but the means of detection required high concentrations of isohexide. The alcohol extracts from the nitrate-pyridine reactions were run in both these solvent systems. Several brown and fluorescent spots were visible before treatment with iodine and after this treatment the brown spots were enhanced but no material could be detected which could be identified with the isohexides.

The use of column chromatography and the detection of the isohexides by the optical activity of the fractions was investigated. A note on the chromatography of the isohexides using adsorptive clays has been published but very few details were given (123). A favourable report (124) on the use of Celite columns for partition chromatography prompted an investigation of their use in the isohexide series. This material has the advantages over cellulose that it is easily packed into the column and that the prepared columns have a rapid flow rate. Using n-butanol saturated with water as solvent system the isohexides were separated completely from each other when run
either in pairs or as a mixture of all three. Chromatography of the alcohol extracts on the Celite columns, the fractions being estimated by measurement of their optical rotation, showed a peak of optical activity immediately following the solvent front but none in a position expected for the isohexides (Figure XIII).

Figure XIII: Elution Patterns from Celite Column Chromatography
The optically active material flowing with the front was not isohexide as was shown by carrying out reactions with isohexide added initially and chromatographing the products. In these cases 200 mg. of isohexide was added to 500 ml. of dinitrate initially. Chromatography of the alcohol extracts showed two peaks of activity, one immediately after the solvent front and the other in the correct position for the isohexide, showing that the first peak was not isohexide.

The sensitivity of this method was estimated from the polarimeter reading produced when known amounts of isohexide were eluted from the columns. The smallest amount of isosorbide detectable would have been about 10 mg., this represents a 5% yield from the decomposed dinitrate. The yield of isohexide was therefore below this value.

**Partially Denitrated Products**

Paper chromatographs of various fractions of the reaction products of the pyridine reaction showed a nitrate-containing spot in a position expected for a mononitrate derivative of the isohexides—in the hexane/methanol system the spot moved off the starting line (indicating it was not inorganic nitrate) but was well behind the isohexide dinitrate (therefore more hydrophilic). To test this assumption attempts were made to prepare partially nitrated isohexides. There are few reported cases in which partially O-nitrated compounds have been prepared by direct nitration (125). These preparations have usually used one to one mole ratios of nitric acid to hydroxyl group to be nitrated. In the aromatic compounds nitration is usually controlled by using nitrating mixtures of varying "powers", i.e. nitric acid in
acetic acid, concentrated nitric acid alone, nitric acid/sulphuric acid mixtures, but this method has not been used in the nitration of hydroxyl compounds.

Nitrations were carried out with mole to mole ratios of nitric acid and the isohexide but only low yields of product, consisting mainly of dinitrate, were obtained even when low temperatures and efficient mixing were used. The failure of these syntheses was thought to be due to the rapid rate of the nitration reaction. An investigation to determine whether the "power" of the nitrating mixture could be varied was carried out by using varying proportions of acetic anhydride to acetic acid in the nitration mixture. It was hoped that the nitration reaction could be slowed down sufficiently to prepare the partially nitrated derivatives.

The nitrations using 1:1 (v/v) ratios of acetic acid to acetic anhydride were found to be complete in less than one hour and when the nitration was carried out in acetic acid alone no nitrate ester was obtained. Using acetic acid containing a small amount of acetic anhydride a low yield of a syrup was obtained and this was shown to be a mononitrate derivative by paper chromatography.

In this way small amounts of the mononitrate derivative of each of the isohexides were obtained. The yields would probably be improved by a more thorough investigation of the reaction conditions. Only isomannide mononitrate crystallised and isosorbide mononitrate showed two spots on paper chromatographs (run in hexane/methanol solvent). Isomannide and isoidide can only have one monosubstituted derivative, whereas in isosorbide the 2- and 5-positions can be distinguished and therefore two products are to be expected.
A monotosyl derivative of isosorbide has been prepared and isolated as its crystalline acetyl derivative (66). The monotosylate of isosorbide was nitrated and a crystalline tosylnitrate was obtained after separation of the products on an alumina column using paper chromatography (hexane/methanol) to identify fractions. Similarly by partial tosylation followed by nitration and alumina chromatography crystalline tosylnitrate derivatives were prepared from isomannide and isoidide. These three monotosylatemononitrates were recrystallised to constant melting point. Their infrared spectra showed peaks corresponding to both tosyl and nitrate groups. Reaction with diphenylamine, in the presence of sulphuric acid or on exposure to ultraviolet light, confirmed the presence of nitrate while the latter condition also showed the presence of tosyl groups. These crystalline derivatives provided a further means for characterising partially nitrated products.

The synthetic isohexide mononitrates were run on paper chromatographs and were detected in the expected position running parallel to those from the ether solution of the pyridine reactions. As the paper chromatography system separated the mono and dinitrate very readily a liquid-liquid extraction procedure using the same solvents was attempted in order to separate larger quantities. This method proved to be unsatisfactory, after ten extraction processes no appreciable separation was obtained. Zane used cellulose columns with the methanol/hexane solvent to separate the mono and dinitrate esters of cyclohexane 1,2-diols (126). The separation was good but the columns were difficult to handle due to the methanol separating out of the
hexane when the temperature dropped slightly. The use of alumina columns was investigated and proved to be very successful in the separation of the dinitrates from the mononitrate and even in the resolution of a mixture of all three isohexide dinitrates into its components. Three grades of alumina were tested and the recoveries obtained in passing the various nitrate esters through columns of them were determined (Table IV). It can be seen that the acid washing of the alumina improved the recovery; this is probably due to the removal of basic sites in the alumina. Recently Honeyman has reported the use of alumina columns for the separation of sugar mononitrates from their dinitrate derivatives (127).

**TABLE IV**

<table>
<thead>
<tr>
<th></th>
<th>Alcoa &quot;Grade F-20&quot;</th>
<th>Merck &quot;Acid washed&quot;</th>
<th>Alcoa after acid washing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isomannide dinitrate</td>
<td>97.2%</td>
<td>97.2%</td>
<td>-</td>
</tr>
<tr>
<td>Isomannide mononitrate</td>
<td>90.0%</td>
<td>99.3%</td>
<td>100.7%</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>95.8%</td>
<td>98.3%</td>
<td>-</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>76.4%</td>
<td>100.1%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Isoidide dinitrate</td>
<td>101.0%</td>
<td>97.3%</td>
<td>-</td>
</tr>
</tbody>
</table>

The ether solutions of several nitrate-pyridine reactions were investigated using the alumina columns. The unreacted dinitrate was eluted in a pure state by ether/ethyl acetate mixtures and usually crystallised immediately on evaporation of solvent. The mononitrate
material was eluted later by acetone/methanol mixtures. It was found that the mononitrate represented only a very small yield from the decomposed dinitrate and this seemed to be appreciably lower than was estimated in earlier experiments using paper chromatography. The only change in conditions was the method of drying the pyridine. The first trials were run with pyridine dried over barium oxide while in the later reactions calcium hydride was used as drying agent. The latter reagent proved to be a more reliable and efficient drying agent. The effect of the presence of water on the products and the rate of the reaction was studied and is described in detail in a later section.

The partially nitrated material isolated by alumina chromatography was characterised in the following manner. Nitrogen determinations were carried out on the syrup obtained from evaporation of the fractions from the column. Nitrogen content was 5.4% whereas an isohexide mononitrate required 7.32%. The low result indicated that some impurity was present, and this was probably residual solvent since the high vapour pressure of the mononitrate prohibited vacuum drying even at low temperatures. A sample of the partially nitrated material from a reaction of isosorbide dinitrate and pyridine (Rf 0.035 in hexane/methanol) was nitrated in the usual way and the nitrate ester thus prepared was found to have Rf 0.22 (in hexane/methanol) and to run parallel to isosorbide dinitrate. This nitrination was carried out on a very small scale and no crystalline product was isolated.

**Pyridinium Nitrate**

Pyridinium nitrate has been shown to be formed in the denitration
of mannitol hexanitrate (117). It was found on the walls of the reaction vessel above the pyridine solution when the reaction mixture was exposed to the air. In the present experiments crystals were noted inside the condenser when no drying tube was used to seal the reaction mixture. Samples of these crystals were taken and had the same melting point as pyridinium nitrate. This pyridinium nitrate was probably formed by the air oxidation of nitric oxide followed by the formation of nitric acid in the presence of water vapour and pyridinium nitrate by reaction with the pyridine.

As far as could be determined this crystalline deposit was formed from the oxides of nitrogen given off from the reaction. A solution of pyridinium nitrate in pyridine when refluxed failed to give any deposit in the condenser so that the nitric acid must have been formed in the gaseous condenser phase. It is to be noted that this pyridinium nitrate solution remained colourless even after refluxing for three days and therefore there was no decomposition to coloured products similar to those formed in the nitrate-pyridine reaction.

Pyridinium nitrate was also found to be present in the reaction solution. Paper chromatography showed that all the inorganic nitrate formed in the reaction was present in the aqueous solution after the preliminary extraction process. This nitrate had Rf corresponding to that of pyridinium nitrate when run in methylethylketone/water or n-butanol/water solvent system. Using alumina columns it was possible to isolate pyridinium nitrate from the aqueous extract and identify it by its melting point, mixed melting point, nitrogen content and production of pyridine when treated with alkali.
The amounts of inorganic nitrate formed during the reaction were estimated during analysis of products in the rate studies. This nitrate was determined by measurement of the nitrate content of the aqueous solutions which had been extracted with ether to remove nitrate ester material. Paper chromatography had showed that these solutions contained nitrate as pyridinium nitrate only. Table V shows the amount of inorganic nitrate as a percentage of the nitrate ester decomposed. The results are for reactions at reflux temperature in dry pyridine with varying amounts of water added.

A test of the effect of other decomposition products on the nitrate determination was made by adding a known amount of nitrate ion to some of the solutions being analysed. The increase in nitrate content corresponded exactly to that which had been added.

**Coloured Polymeric Material**

During the course of the reaction the pyridine solution became red-brown in colour, finally turning to dark brown with a black precipitate forming. From visual comparisons there did not appear to be any appreciable difference in the depth of the colour produced at a given percentage decomposition of the nitrate ester for reactions at different temperatures. The colour and precipitate were also formed when water was present in the reaction mixtures.

In the separation procedure this coloured material was found in two places. That portion which is insoluble in ether and aqueous pyridine was a black solid ("Insoluble Material A") and was recovered by filtration. The ether extract was usually only yellow in colour.
#### TABLE V

**Pyridinium Nitrate Formed in Nitrate-Pyridine Reaction**

- **A** - Time (hours)
- **B** - Concentration (moles/litre)
- **C** - Percentage of nitrate decomposed

<table>
<thead>
<tr>
<th></th>
<th>Dry</th>
<th>1 mole water per mole nitrate group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoidide dinitrate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>4.5</td>
<td>9.0</td>
</tr>
<tr>
<td>B</td>
<td>0.033</td>
<td>0.044</td>
</tr>
<tr>
<td>C</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>7</td>
<td>22.2</td>
</tr>
<tr>
<td>B</td>
<td>0.089</td>
<td>0.064</td>
</tr>
<tr>
<td>C</td>
<td>57</td>
<td>19</td>
</tr>
</tbody>
</table>

| **Isosorbide dinitrate** |                                    |                                     |
| A   | 2     | 5.5   | 8.1   | 13   | 34   | 3     | 8.7 | 21   |
| B   | 0.017 | 0.048 | 0.074 | 0.086 | 0.078 | 0.017 | 0.05 | 0.11 |
| C   | 39    | 43    | 48    | 40   | 24   | 40    | 34   | 27   |
|     |       |       |       |   | 2 moles water per mole nitrate group | 4 moles water per mole nitrate group |
| A   | 3     | 12    | 26    |     |     | 3     | 11   | 33   |
| B   | 0.018 | 0.11  | 0.125 |     |     | 0.014 | 0.075 | 0.13 |
| C   | 33    | 64    | 40    |     |     | 36    | 50   | 44   |

<table>
<thead>
<tr>
<th><strong>Isomannide dinitrate</strong></th>
<th>Dry</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5.5</td>
</tr>
<tr>
<td>B</td>
<td>0.0009</td>
</tr>
<tr>
<td>C</td>
<td>1.5</td>
</tr>
</tbody>
</table>
but the aqueous solution was dark brown. Evaporation of the latter followed by extraction of the residue with ethanol left a brown amorphous power ("Insoluble Material B").

Various tests were conducted on these materials but no conclusive results were obtained. The material "A" burned only very slowly in a Bunsen flame while "B" was combusted rather more quickly. Both fractions were insoluble in organic solvents and in water, however "B" dissolved in mixtures of pyridine and water. This was probably due to the basic character of this mixture as "B" was readily soluble in sodium hydroxide solutions. Material "A" was soluble, but not completely, in 3 Normal sodium hydroxide whereas "B" dissolved completely in 0.1 Normal sodium hydroxide. The brown-black material was reprecipitated on acidification or on treatment with excess ethanol. The material from the latter process was readily soluble in water. These results indicated that the material was probably polymeric in nature and contained acidic groups.

Infrared and ultraviolet spectra were taken of the various fractions obtained. The infrared spectra showed that very little change was brought about by the base-acid dissolution and precipitation procedure. The spectra (Figure XIV) consisted of very few peaks which could not be positively attributed to any groups.
Investigation of Other Reaction Products and Material Balances

The materials described above, except for the insoluble materials "A" and "B", did not represent major products of the reaction. The preliminary separation procedure gave three fractions, two of these were solutions which were evaporated before investigation of their contents. It was possible that some volatile products were lost in this procedure and to test for such products two experiments were carried out. Firstly the pyridine reaction mixture was distilled carefully and the distillate collected in several fractions. The optical rotation and refractive index of these fractions were checked. The former was zero and the latter correct for pyridine in all cases. The final traces of pyridine were removed under high vacuum with a trap cooled in solid carbon dioxide/methanol as receiver. A small amount of liquid was collected, its refractive index was correct for pyridine and the fraction was colourless. However on standing several weeks the liquid became brown in colour. In the second experiment the reaction mixture was poured into chloroform instead of water. Distil-
lation of the solution after filtration gave fractions which possessed no optical activity.

Thus, although the results are not completely conclusive, it appears that no volatile products were formed apart from the oxides of nitrogen. The three fractions represent the total of the products. The constitution of the insoluble material is not known. Isohexide mono and dinitrate accounted for 80-95% of the material in the ether fraction. The remaining material represented only a small proportion of the products (maximum of 60 mg. from decomposition of 4 g. dinitrate) and was not eluted from the alumina columns in a definite peak and was not investigated further.

The aqueous solution was investigated and divided into two fractions, as described, by extraction with ethanol. This gave a brown amorphous material which was thought to be related to the black insoluble precipitate—possibly a lower molecular weight polymer. The alcohol extract has been shown to contain pyridinium nitrate by alumina chromatography. However this accounted for only about 50% of this fraction. Various attempts were made to separate the pyridinium nitrate from the other material and from these experiments it was concluded that the material was optically active and of an acidic nature. The alcohol extract was red-brown in colour but it was possible to remove this coloured material from the fraction by passing the solution through a short column of charcoal. This procedure caused little or no loss in weight or optical activity. The solution obtained in this way was passed through ion-exchange resins. Pyridine was removed by an anionic column (Amberlite IR 120 in H⁺ form).
The solution after this treatment was acidic, had its optical activity retained, and contained nitrate. Passing a portion of this solution through a cationic column (Dowex 1 in OH⁻ form) gave a neutral solution with no optical activity, giving a negative nitrate test and, on evaporation, a negligible amount of residue. A second portion was evaporated to dryness and several portions of water added and evaporated off in an attempt to remove free nitric acid present. However even after repeating this process several times the residue still contained nitrate.

Titration of an aliquot of the eluate from the Amberlite IR 120 column gave two different end points when phenol phthalein and methyl red were used as indicators. This indicates the presence of a strong acid (nitric acid) and a weak acid. No method was found to isolate the latter component.

Nitrogen Balance

No overall nitrogen balance was attempted due to the evolution of gaseous products, difficulties associated with their analysis and the large amount of nitrogen present in the pyridine.

Other Possible Reaction Products

By comparison with the alkaline hydrolysis of nitrate esters (see page 42) α- or β-hydrogen elimination mechanisms might be expected to occur in the pyridine reaction. The products from these types of reaction would be carbonyl and olefinic derivatives respectively. The transitory formation of a carbonyl compound from isomannide and isosorbide had been reported in their conversion to isoidide using Raney nickel to cause dehydrogenation followed by hydrogenation back
to the hydroxyl derivatives (22). The carbonyl derivative was not isolated but it was assumed that the reaction proceeded through a compound of this type. The dehydrogenation reactions were repeated but failed to give any reaction. Under the conditions reported the isohexide sublimed to some extent but failed to form any carbonyl compound; trans-hydrogenation in the presence of cyclohexane also failed. As an alternative method oxidation under various conditions was used. Acidic dichromate and acidic and alkaline permanganate were tried but only very low yields of an acidic substance were obtained even though several techniques were used.

The related compound, \( \beta \)-hydroxyl-tetrahydrofuran, was prepared and investigated by Pariselle (128). The corresponding keto derivative was formed from the isomerisation of acetylenic glycols. The keto compound exists to a large extent in the enol form and forms salts with alkalis. The compound is readily oxidised by permanganate to a dicarboxylic acid. It is probable that over-oxidation occurred in the direct oxidation of the isohexides.

\( \alpha \)-Hydrogen elimination yields olefinic compounds. This type of elimination is common with halogen compounds under the action of alkali. Diiodoisosorbide was reacted with methanolic potassium hydroxide solution. A colourless material was isolated by extraction with ether, evaporation of this solution gave a colourless syrup which decomposed on removal of all the ether to a black amorphous powder containing free iodine. The decomposition was found to be initiated by heat but not light; samples allowed to evaporate at \(-5^\circ C\) remained colourless and the ether solutions were stable indefinitely. Washing
of the ether solutions with acid and alkali failed to make the syrup more stable. The black product of the decomposition was insoluble in organic solvents and acid or base. Its infrared spectrum was somewhat similar to that of the insoluble material from the nitrate-pyridine reaction.

Conclusion

The results of the investigation of the reaction products were rather inconclusive. It appeared that the main products in the reaction were the insoluble materials, "A" and "B", which appeared to be polymeric in nature. The reaction was much slower than that of the hexitol hexanitrates but comparable to that of the cyclohexane diol dinitrates. The unreacted portion of the original dinitrate could be recovered unchanged. The nitrate group decomposed became in part inorganic nitrate; the remainder was probably lost as oxide of nitrogen.

In contrast to the reaction with the hexitol hexanitrates none of the parent diol was formed in the reaction and only a very small part was isolated as the mononitrate derivative. The low yields of the partially nitratated isohexide and the absence of any other partially nitratated material indicated that when one nitrate group was removed the molecule was activated to cause a rapid loss of the second group.
CHAPTER VI

RATE STUDIES ON THE DECOMPOSITION
OF ISOHEXIDE DINITRATES

Rate Studies on the Nitrate-Pyridine Reaction

It was of interest to study the rate of the nitrate-pyridine reaction to compare the relative rates for the three isomeric dinitrates, in order to be able to carry the reactions to the same stage before isolation of products. It was also desirable to determine the effect of temperature on the reaction and hence to obtain activation energies.

Kinetic studies were made by estimating the unreacted isohexide dinitrate. The reactions were carried out at three temperatures in bulbs fitted with reflux condensers and drying tubes or in sealed tubes. The latter were used when the reactions had half lives of longer than about twenty four hours; in these cases the open system failed to give reproducible results, probably due to the slow evaporation of solvent. Samples of the reaction solution were taken at various times and diluted with water. The aqueous solution was extracted with ether and the nitrate in the ether extract was determined by a colorimetric method.

Tests, described previously, showed that by extraction of the diluted reaction mixture with ether, the nitrate present as isohexide dinitrate was removed completely from the pyridinium nitrate which remained in the aqueous pyridine solution. Tests to determine the completeness of the extraction process are shown in Table VI.
TABLE VI

Ether Extraction of Nitrate Ester from the Aqueous Pyridine Solutions

<table>
<thead>
<tr>
<th>Percent Recovery of Isohexide Dinitrate</th>
<th>Isomannide dinitrate</th>
<th>Isosorbide dinitrate</th>
<th>Isoidide dinitrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st extraction</td>
<td>90</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>2nd extraction</td>
<td>9</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>3rd extraction</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>101</td>
<td>100</td>
<td>98</td>
</tr>
</tbody>
</table>

It is seen from these results that 90% of the nitrate ester was extracted with the first portion of ether. As three extractions were used in each case the extraction procedure was quantitative. The ether extracts were pooled and made up to 10 ml. and three 1 ml. samples were taken for the colorimetric estimation. Details and a discussion of this estimation procedure are given in Appendix I.

The method was not highly accurate but was more rapid than precise ones.

Straight lines were obtained for plots of log(concentration of nitrate ester) against time for each of the isoheoxide dinitrates at the three temperatures studied - 115°C, 100°C. and 87°C. It is most likely that the reaction is a second order process but as pyridine, one of the reactants, was used as a solvent it was present in excess. The plots were confirmed by large scale reactions in which the un-reacted isoheoxide dinitrate was isolated as crystalline material, weighed and characterised. Several points were obtained in this way.
Figure XV: Rate Plots of Isohexide Dinitrate-Pyridine Reaction at 115°C.

Figure XVI: Arrhenius Plots of Rate Constants
in the cases of isomannide and isosorbide dinitrate at 115°C. and each of the other plots were confirmed by two macro-reactions (Figure XV).

The half lives for the reactions at the three temperatures are shown in Table VII. Arrhenius plots (log \( k \) against \( \frac{1}{T} \)) of the rate constants for the reactions are shown in Figure XVI. From the straight lines drawn through the points apparent activation energies and frequency factors were determined for the reaction of each of the isohexide dinitrates.

**TABLE VII**

<table>
<thead>
<tr>
<th></th>
<th>Temp.</th>
<th>( k ) (sec.(^{-1} \times 10^{-6} ))</th>
<th>( H ) (kcal.s.)</th>
<th>Frequency factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoidide dinitrate</td>
<td>115</td>
<td>25.4</td>
<td>21</td>
<td>( 10^{7.6} )</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>8.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>87</td>
<td>3.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>115</td>
<td>15.2</td>
<td>24</td>
<td>( 10^{8.9} )</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>2.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>87</td>
<td>1.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isomannide</td>
<td>115</td>
<td>8.07</td>
<td>41</td>
<td>( 10^{18.3} )</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>87</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The reaction of the nitrate esters of the isohexides with pyridine required a higher temperature than did that of the hexitol hexanitrate. In order to determine what part thermal decomposition played at these temperatures the dinitrates were heated at 115°C. in various solvents.

It was necessary to have an inert solvent with a boiling point above 115°C. for these experiments. Zane found that the cyclohexane-1,2-diol dinitrates when refluxed in 3-methylheptane (boiling point 115°C.) were decomposed fairly rapidly (126). The isohexides were only slightly soluble in this solvent and in other hydrocarbons. The chlorinated hydrocarbons, however, are better solvents for nitrate esters and should be quite inert. One of these, tetrachloroethane, and three other solvents of different types, nitrobenzene, diethylcarbinol and m-xylene, were used. This group of solvents represented a wide range of polar characteristics.

The dinitrate was dissolved in the solvent and heated at 115°C. or 100°C. for a given period. The solution was then cooled, diluted with ether and loaded directly onto an alumina column from which the unreacted dinitrate was isolated by elution with ether/ethyl acetate mixtures. The recovered dinitrates were crystallised by seeding and their melting points determined to check purity and identity.

The results are summarised in Figure XVII. At 100°C. for the solvents tetrachloroethane, nitrobenzene and m-xylene there was very little loss of nitrate ester even after fifty hours. At 115°C. the decomposition was more rapid but proceeded at the same rate in each
of the three solvents and for each of the isohexide dinitrates, within
the experimental error. In the case of diethyldiethylcarbinol the more
rapid reaction at 115°C. and particularly 100°C. can be explained on
the basis of trans-nitration reaction of the type

\[ \text{R.OH} + \text{R'O.NO}_2 \rightarrow \text{R.O.NO}_2 + \text{R'O.H} \]

It would appear from these results that the thermal decomposition
in solution represented only a small proportion of the loss of nitrate
in the pyridine reaction, except in the case of isomannide where a
larger part of the reaction could be accounted for by thermal decom-
position.
In the cases of tetrachloroethane and nitrobenzene the colour of the solution remained unchanged during heating. The solution using the other two solvents became yellow to orange in colour during the course of the decomposition and in the case of \( m \)-xylene two yellow substances appeared as bands following the nitrate ester on the alumina columns. There was no formation of a deep brown colour and precipitate as in the case with pyridine.

The amount of decomposition was independent of solvent in the three solvents other than diethylcarbinol. These solvents had a wide range of dielectric constants and these results, therefore, indicated that the decomposition was probably occurring by a radical mechanism as found in the gaseous state (101).

**Effect of water on the Product of the Reaction**

Preliminary investigations into the pyridine reaction indicated that a partially nitrated compound was being formed during the reaction. However when the reactions were run on larger scales this product could not be detected. The only variation in reaction conditions was the method of drying the pyridine and it was thought that in the later reactions the pyridine was drier than in the earlier ones.

Simultaneous reactions were carried out with the calcium hydride-dried pyridine to which small portions of water had been added. The products of the reaction were separated and the material in the ether solution was run on paper chromatographs in hexane/methanol solvent to detect partially nitrated materials. The results for isosorbide dinitrate are shown in Table VIII.
TABLE VIII

Analysis of Nitrate Ester Products of Nitrate-Pyridine Reaction with Water Added

Isosorbide dinitrate (0.1 g. in 1 ml. pyridine at 115°C.)

<table>
<thead>
<tr>
<th>% water in pyridine</th>
<th>Estimated ratio of mono- to dinitrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reaction time</td>
</tr>
<tr>
<td></td>
<td>18 hours 24 hours 30 hours</td>
</tr>
<tr>
<td>dry</td>
<td>no mono-nitrate no mono-nitrate</td>
</tr>
<tr>
<td>1</td>
<td>- 1:2</td>
</tr>
<tr>
<td>2</td>
<td>- 1:2</td>
</tr>
<tr>
<td>4</td>
<td>mono very faint 1:2 1:1.5</td>
</tr>
<tr>
<td>10</td>
<td>no mono-nitrate 1:2 1:2</td>
</tr>
</tbody>
</table>

Rate studies were run to test the effect of the presence of water on the rates of the reaction. These rate determinations were carried out in the same way as for the studies in dry pyridine. Three different amounts of water were added equivalent to one, two and four moles of water per nitrate group in the original solution and a temperature of 114°C. was used.

The results were plotted as log (concentration nitrate ester) against time and were found to be slightly curved in a direction indicating that the rate of the reaction increased with time (Figure XVIII). This could be interpreted as being due to the removal of the water by reaction or by the formation of some material which catalysed the reaction or which reacted with nitrate esters in some way.
The initial rates of these reactions were calculated from the rate plots (Table IX). The variation in rates corresponds to a rate expression of the form:

\[
\text{Rate} = \frac{k [\text{Nitrate Ester}]}{k' + k'' [H_2O]}
\]

in the cases of isosorbide and isoidide dinitrate.

![Figure XVIII: Rate Plots for Nitrate-Pyridine Reaction with Water Added](image)

Although the presence of water had a retarding effect on the reaction there was no visible change in the reaction products. The brown colour developed at the same rate and an insoluble black material
was deposited during the latter stages of the reaction. In the course of the rate studies the aqueous solutions obtained after extraction of the nitrate esters were analysed for nitrate (see page 74).

TABLE IX

The Effect of Water on the Rate of the Nitrate-Pyridine Reaction

Rate constants expressed in sec.\(^{-1}\) \(\times 10^{-5}\)

<table>
<thead>
<tr>
<th>Moles (H_2O) per mole isohexide dinitrate</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoidide dinitrate</td>
<td>2.55</td>
<td>1.88</td>
<td>1.35</td>
<td>1.03</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>1.52</td>
<td>1.27</td>
<td>1.00</td>
<td>0.79</td>
</tr>
<tr>
<td>Isomannide dinitrate</td>
<td>0.35</td>
<td>0.33</td>
<td>0.36</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Nitrate-Pyridine Reaction in the Presence of Xylenol

A possible mechanism for the denitration reaction in pyridine is one of trans-nitration (see page 47). It has been seen that nitrate esters can act as nitrating agents under various conditions. In the presence of concentrated sulphuric acid the reaction is believed to proceed via the nitronium ion, \(NO_2^+\), formed in the ionisation of the nitrate ester. No mechanism has been put forward for the trans-nitration under alkaline conditions.

Various reactions were carried out with isohexide dinitrate in pyridine to which 3,4-dimethylphenol was added. Dimethylphenol was used in the colorimetric determination of nitrate and is an easily nitrated compound which can be isolated readily. The reaction mixtures
were heated at reflux or 100°C. for some time and then diluted with water and excess sulphuric acid added. The resulting solutions were subjected to steam distillation in the same manner as in the colorimetric determination and the distillate was estimated colorimetrically.

The results indicate that a small portion (2-5%) of the nitrate decomposed was converted to the nitroxylenol. The amount of nitroxylenol formed was independent of the xylenol concentration over a wide range but varied with nitrate ester concentration or amount of nitrate ester decomposed. Tests showed that nitroxylenol was stable in pyridine solution under reflux for periods of up to twenty four hours. A single experiment showed that pyridinium nitrate and xylenol in pyridine also produced a small amount of the nitroxylenol on heating at 100°C. for eighteen hours.

The results of these experiments were not conclusive but indicate that trans-nitration reactions may occur under the conditions used in the reaction of nitrate with pyridine.

Activation energies have been determined for the thermal decomposition of several alkyl nitrates (see page 50) and fall in the range 35-40 kcal. with frequency factors about $10^{16}$. Solid nitrates were found to have an activation of about 39 kcal. and frequency factor $10^{12}$ for their decomposition (105). Whether it is possible to draw any conclusions from a comparison of these values with those obtained for the nitrate-pyridine reaction is doubtful due to the wide range of conditions used in the various experimental procedures. The low values for the activation energies of isoidide and isosorbide di-nitrate were well outside the experimental error and indicated that some reaction occurred with these compounds which was different from
the thermal decomposition of nitrate esters and the reaction which occurred with isomannide dinitrate in pyridine.

The rate of thermal decomposition of the isohexide dinitrate in solution was slow compared to their reaction with pyridine by factors of -

<table>
<thead>
<tr>
<th>Nitrate</th>
<th>Ratio nitrate-pyridine to thermal decomposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isomannide dinitrate</td>
<td>3</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>6</td>
</tr>
<tr>
<td>Isoidide dinitrate</td>
<td>10</td>
</tr>
</tbody>
</table>

The rate of thermal decomposition may be more rapid in pyridine. This was not, however, indicated by the thermal decomposition studies in various solvents in which the solvent has little effect on the rate. The mechanism by which isomannide dinitrate is decomposed in pyridine may well be that of simple thermal decomposition.

The studies on the effect of water on the nitrate-pyridine reaction and the activation energies of the reaction point to a different mechanism for the decomposition of isomannide dinitrate compared to the other two nitrates. This could be due to two factors. Firstly the nitrate groups on isomannide are very close together compared to the other two nitrates and may interact to deactivate the reaction with the pyridine. Secondly the reaction with pyridine may only occur readily with groups in the exo position and slowly with endo groups. In this case isoidide dinitrate would react readily as would one group in isosorbide. Thus isoidide and isosorbide dinitrates would have similar activation energies and similar water effects due to the
reaction of the exo group masking that of the endo group. It was seen in the investigation of reaction products that very little partially nitrated material was isolated, from this it was assumed that when one nitrate group was removed the second one was lost very rapidly. This would also account for the fact that isoidide and isosorbide react similarly but their reaction is different from that of isomannide.

Thus it can be said that the reactions of the isohexides in pyridine are not simply thermal decomposition reactions although this may play the major part in the reaction of isomannide dinitrate. The main reaction product of the pyridine reaction, the insoluble material, appeared to be very similar with each of the three dinitrates and quite different from the thermal decomposition reaction. This would contradict the findings of the activation energies and effect of water on the reaction which indicated that isomannide dinitrate reacted differently to the other isohexides. The observation that the rates of the nitrate-pyridine reaction at 115°C are quite similar for the three dinitrates also indicates similarity of their behaviour with pyridine.

More extensive kinetic studies on both the reaction with pyridine, the thermal decomposition reactions in inert solvents and the action of pyridine in the presence of inert solvents would help to clarify the situation. The method of estimation of nitrate used in the present rate studies was rather laborious and a more rapid method would aid the work. It was hoped at first that it might be possible to follow the reaction by measurement of optical rotation making use of the high
specific rotation of the nitrate esters. However this was impossible due to the coloured products formed in the reaction. This method could probably be applied in one of two ways. The ether extracts which were estimated for nitrate by the colorimetric method could probably be estimated more rapidly by polarimetric measurement. The ether fractions have been investigated quite thoroughly and shown to contain mainly unreacted isohexide dinitrate together with a little of the mononitrate derivatives, thus they are comparatively pure; in fact the syrup obtained on evaporation of these fractions could usually be induced to crystallise on seeding. The second alternative would be to estimate the optical rotation of the pyridine solution directly after passing through a charcoal column. Charcoal columns were shown to remove the coloured material from the alcohol fractions and would probably remove the colour from the pyridine solution. The results obtained here using the direct estimation of the nitrate ester could be used as a basis to test any indirect method investigated.
CHAPTER VII
Comparison of the Nitrate-Pyridine Reaction
with Other Reactions

As was seen in Chapter III, when a reaction in the isohexide series had an SN2 mechanism there was a high degree of selectivity depending upon the configurational position of the group being attacked. In this type of reaction the endo and exo groups were quite different in their reactivity, no other types of reaction in the isohexides have been shown to have a similar stereochemical selectivity. The following reactions were studied to determine the relative rates for reaction at the endo and exo positions. It was hoped that in this way further information as to the mechanism of the denitration reaction might be obtained. The reaction of sodium iodide with the tosyl derivatives was also investigated to show the position of tosylation in acetyl-tosylisosorbide. The results of this study are included here as a typical example of an SN2 reaction in the isohexides.

Reaction of Nitrates with Sulphuric Acid

The colorimetric determination of nitrate, utilising the transnitration reaction between nitrate esters and 2,4-xylenol in concentrated sulphuric acid (95) was investigated as an analytical method in the rate studies of the nitrate-pyridine reaction. As the determination procedure was relatively simple, experiments were made to determine the rate of formation of the nitroxylenol with each of the three isohexide dinitrates. The reaction was quite rapid but with efficient stirring and instantaneous quenching by addition of water reasonable rate plots were obtained (Figure XIX). The method used
was to prepare a sulphuric acid solution of the xylenol and then add the dinitrate in a small volume of ether. The reaction was quenched and the nitroxylenol removed by distillation and estimated colorimetrically. Plots of \( \log (O.D._{\infty} - O.D._t) \) against time were straight lines. The half lives obtained from these plots, however, proved to be the same for each of the isohexide dinitrates within the estimated experimental error. It would appear from these results that the rate determining step in this reaction was not the ionisation of the nitrate but rather the rate of nitration of the xylenol.

A second approach to this reaction, or a similar one, was in the reaction which occurs between nitrate esters and acetic anhydride in the presence of sulphuric acid. Wolfrom and co-workers have treated several sugar nitrates with acetic anhydride containing about 10%
sulphuric acid and obtained the corresponding acetates in good yield (96). These acetates have the same configuration as the nitrate esters. The reaction therefore involves only the substituent group and not the carbon atom it is joined to. The benzyl ether of isomannide has been reacted with sulphuric acid in acetic anhydride and the reaction followed by measurement of the optical rotation (129). This reaction was found to be slow and complex in nature.

Each of the isohexide dinitrates were dissolved in acetic anhydride containing 10\% sulphuric acid and the change in optical rotation with time was measured. The plots of $\log (\alpha_\infty - \alpha_t)$ are shown in Figure XX. There was very little change in rotation in the case of isoidide as the specific rotation of the dinitrate and the diacetate are very similar (isoidide dinitrate $[\alpha]_D +72.9$, isoidide diacetate $[\alpha]_D +89.6$).

![Figure XX: Reaction of Isohexide Dinitrates with Sulphuric Acid in Acetic Anhydride](image-url)
When the observed rotation had become constant the reaction mixtures were poured into water and extracted with chloroform. The chloroform solutions were dried and evaporated and the resulting syrups distilled in a short-path distillation apparatus. The products would not crystallise. The isoidide dinitrate reaction mixture showed only a small quantity of nitrate to be present at twelve hours, however in the isomannide dinitrate when stopped at this time 50% of the dinitrate was recovered.

This reaction appeared to have an order of reactivity of exo group > endo group. However a more thorough investigation is required, including isolation of the reaction products, before definite conclusions can be drawn.

Alkaline Hydrolysis of Tosylates

Various reactions can occur with tosyl esters and basic reagents (60). In the isohexides the tosyl groups are secondary and isolated (except in the special case of isosorbide). Cope and Shen (66) have converted both isomannide and isoidide ditosylates to the parent isohexides in fair yields (~60%). Isosorbide ditosylate however forms the trianhydromannitol by an internal displacement mechanism.

Cope and Shen (66) have stated that the tosyl groups in isomannide were less susceptible to alkali than those in isoidide. This was based on the several alkali hydrolysis reactions carried out on isomannide ditosylate and one on isoidide. However in none of these cases were the conditions identical.

When isomannide and isoidide ditosylates were reacted under the
same conditions (0.3 Normal barium methoxide in methanol at reflux — the conditions used by Cope and Shen for the reaction of isoidide ditosylate) it was found that barium sulphonate was precipitated much more rapidly in the case of isomannide. The reactions were stopped after three hours and the excess alkali titrated; isoidide ditosylate had used 50% of the theoretical and the isomannide derivative 100% of the theoretical. Investigation of the products showed that 50% of the ditosylisoidide was recoverable as a crystalline material but only 8% of the isomannide derivative.

These results showed that the group in the endo position was removed more readily. This was consistent with the high yield of tri-anhydromannitol from isosorbide ditosylate. In this case the endo group was hydrolysed first to form an alkoxy ion which then caused internal displacement of the second tosyl group. If the exo group had been hydrolysed first this reaction could not have taken place.

Action of Sodium Iodide on Isohexide Ditosylates

Previous work on this reaction has been reviewed earlier. A study of the reaction was carried out when it was found that the acetyltosylisosorbide of Cope and Shen (66) reacted readily with sodium iodide. A comparison was made of the rate of this reaction with that of several other isohezide tosylates with sodium iodide.

The tosylate esters were reacted with sodium iodide in acetic anhydride solution at reflux. The reaction was stopped at two, four and eight hours and, after cooling, the precipitated sodium p-toluene-sulphonate was filtered off and weighed. The yields of this salt obtained are shown in Figure XXI.
Figure XXI: Reaction of Sodium Iodide with Isosorbide Tosylates

The curve for the replacement of the tosyloxy group in acetyl-
tosylisosorbide closely followed those for the reaction of an endo

group (two in isomannide ditosylate and one in isosorbide ditosylate)
whereas it was vastly different from those of the exo tosyloxy groups
(isoidide ditosylate and iodotosylisoidide). Thus the tosyloxy group
in this compound must be in an endo position. In isosorbide this is
found at the 5-position, the compound is therefore 2-O-acetyl-5-O-p-
toluenesulphonylisosorbide.

The ease of replacement was confirmed by the isolation in high
yield (87%) of an iodo compound from the reaction products. This compound was obtained crystalline and analysed for iodoacetylisoidide. Its infrared spectrum confirmed the presence of the acetyl group and of the tetranhydrofuran rings. The isoidide configuration was assigned by comparison with the other reactions in this series. This compound is 2-0-acetyl-5-iodo-5-deoxy-L-isoidide.

**Silver Nitrate-Halide Reaction**

The reaction of silver nitrate with alkyl halides has been used for the preparation of a large variety of alkyl nitrates. Most of this preparative work has used heterogeneous conditions, with the alkyl halide alone or with some solvent. Better yields are obtained by using a homogeneous reaction mixture, utilising the high solubility of silver nitrate in acetonitrile. This method was only employed widely after the report of Ferris *et al.* (130) although it had been used some years previously (131).

The kinetics of the reaction has been investigated several times (132, 133, 134, 135). It has second order kinetics—first order in alkyl halides and silver ion and even third order for the reaction of methyl iodide with silver nitrate (133). Constitutional changes of the halide gave changes in rate consistent with an SN1 type mechanism (134, 135). This mechanism was supported by the work involving the reaction with neopentyl iodide in which rearrangement of the carbon skeleton occurs (136). Stereochemical data (135) shows a large proportion of inversion to occur, characteristic of an SN2 mechanism. Recently (137) complete inversion has been observed in 2-bromo-3-butanol nitrate.
In the related reaction of alkyl halides with silver nitrite complete inversion of configuration has also been observed. The slow reaction of substances which are sterically hindered towards backside attack, i.e. neopentyl halides, also indicates that the SN2 mechanism is important. This evidence led Kornblum (138) to propose a "push-pull" mechanism. That is, a mechanism in which both the nucleophilic attack of the incoming group and the removal of the halogen by the silver ion are involved. One part without the other would cause a very much reduced rate. There seems to be sufficient evidence for a "push-pull" mechanism in the silver nitrate reaction and this has been proposed by Vona and Steigman (132).

Three halogen compounds were available in the isohexide series – diiodoisoidide, iodotosylisoidide and iodoacetylisisoidide. These compounds were all assumed to have the iodo group in the exo position for reasons considered previously. Chloro derivatives of isomannide and isosorbide are also known, these too are expected to have the exo configuration.

Preliminary tests with the iodo derivatives failed to give any reaction, as indicated by the precipitation of silver iodide and the working up of the reaction mixture to isolate the organic nitrate compound. The acetonitrile used in these experiments was redistilled and dried over phosphorous pentoxide. When calcium hydride was used to dry the acetonitrile the reaction was found to proceed fairly quickly (Table X).
TABLE X

Reaction of Silver Nitrate with Iodo Derivatives in Acetonitrile

<table>
<thead>
<tr>
<th>Run</th>
<th>Compound</th>
<th>Temp.</th>
<th>Time</th>
<th>Yield silver iodide by wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>diiodoisoidide</td>
<td>reflux</td>
<td>6 hours</td>
<td>70%</td>
</tr>
<tr>
<td>2</td>
<td>diiodoisoidide</td>
<td>50°C.</td>
<td>36 hours</td>
<td>66% *</td>
</tr>
<tr>
<td>3</td>
<td>diiodoisoidide</td>
<td>reflux</td>
<td>6 hours</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td>iodotosylisoidide</td>
<td>reflux</td>
<td>6 hours</td>
<td>81%</td>
</tr>
<tr>
<td>5</td>
<td>iodoacetylisoidide</td>
<td>reflux</td>
<td>6 hours</td>
<td>94%</td>
</tr>
</tbody>
</table>

* 17% of the starting material recovered unreacted

TABLE XI

Products of Silver Nitrate-Iodo Derivative Reaction

<table>
<thead>
<tr>
<th>Run</th>
<th>Compound</th>
<th>Yield (isoidide dinitrate, isosorbide dinitrate, isomannide dinitrate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diiodoisoidide</td>
<td>4.4% 2.9% 1.3%</td>
</tr>
<tr>
<td>2</td>
<td>Diiodoisoidide</td>
<td>14.5% 6.8% 3.7%</td>
</tr>
<tr>
<td>4</td>
<td>Iodotosylisoidide</td>
<td>Rf 0.40 and 0.33 17.5% 37.5% 1.7%</td>
</tr>
<tr>
<td>5</td>
<td>Iodoacetylisoidide</td>
<td>Rf 0.34 Rf 0.19 15.0% 1.3%</td>
</tr>
</tbody>
</table>
The organic products of the reaction were isolated and analysed by alumina and paper (hexane/methanol solvent) chromatography. Table XI shows the nitrate ester products isolated. It is seen that the reaction with diiodoisoidide gave a mixture of the three isohexide dinitrates as products with that of isoidide in the highest yield. These nitrates were characterised by melting points and mixed melting points.

This reaction serves to show the effect of an SN 1 mechanism in the isohexide series. The normal "push-pull" mechanism of the silver nitrate reaction is not possible for the reaction of an exo halide group in the isohexides as the backside attack is hindered. This accounts for the slowness, compared to alkyl halides, of the reaction and the racemisation which was observed. The stereoisomers were not formed in equal proportions due to the different ease of attack on the two faces of the ring system. Thus in this particular case the reaction involved the removal of the iodine atom to form a carbonium ion which then reacted with the nitrate ion.

It would be extremely interesting to be able to carry the reaction out on the corresponding iodo derivative having the endo configuration. If the "push" part of the mechanism was at all important we would expect very much increased rates of reaction and a single product having an inverted configuration. Unfortunately no method of obtaining this compound has been found.
Conclusions

The sodium iodide-tosylate and silver nitrate-iodo derivative reactions described above serve to illustrate typical SN2 and SN1 reactions involving the carbon atoms at positions 2 and 5 in the isohexide ring, i.e. groups A1 and A2 in the classification described in Chapter III. These reactions are typified in the isohexides by the large variation in reactivity of the endo and exo configurations in the former reaction and by the isolation of racemised products in the latter. The alkaline hydrolysis of the tosylate esters has been shown to yield the hydroxyl groups with retention of configuration and is thus class in group B. In this reaction it is again the endo group which is the more reactive but the variation in reactivity is not large, the exo group reacting quite readily. The reaction catalysed by sulphuric acid appears to have the reverse order for the rates but its mechanism is not known. A fifth reaction can also be included since it was shown that the monotosylation of isosorbide occurred on the endo position. Thus for this reaction, also in group B, the endo position is the more reactive.

The rate studies on the nitrate-pyridine reaction gave an order of isoidide dinitrate > isosorbide dinitrate > isomannide dinitrate. This order of reactivity and the comparatively small variation in rates as a whole rules out the SN2 mechanism at the carbon atom for this reaction and indicates a group B type of reaction. The SN2 mechanism would seem to be quite a probable one for the reaction of pyridine with the nitrates. Pyridine, although it is a weak nucleophile, has
been shown to yield quaternary nitrate salts on reaction with primary and some secondary alkyl nitrates (110). It is most probable that the mechanism of this reaction is a nucleophilic, $\text{SN}_2$, attack by the pyridine on the carbon atom of the nitrate (see page 52). In the isohexides this could only occur with isomannide or with the 5-position of isosorbide dinitrate. There was no indication in the investigation of any reaction of this type. Similar mechanisms have been found in the neutral hydrolysis of nitrate esters where the nucleophile, water, attacks the carbon atom, and in the reaction of hydrazine with nitrate to yield alkylated hydrazines (see Chapter IV).

Nucleophilic agents have also been shown to attack at a centre in the nitrate group, most probably the nitrogen atom. This occurs in alkaline hydrolysis and the reaction of nitrate esters with hydrazine to cause denitration. This mechanism seems to be a very favourable one for the denitration of hexitol hexanitrate with pyridine (107, 108) and of cellulose trinitrate with hydroxylamine in the presence of pyridine (114). A trans-nitration reaction was proposed for the latter reaction. The general reaction would therefore be -

\[
\begin{align*}
\text{B} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \QUALITY="3">
not known – its decomposition would be complicated by the nitrogen being attached to carbon atoms in the ring. This could account for the variety of nitrogenous products observed when pyridine reacts with mannitol hexanitrate.

One objection to this mechanism is possible in comparison with the hydrolysis and hydrazine reactions of nitrate esters. In both these reactions two nucleophiles exist, one being neutral – the water and hydrazine molecule, and the other being negatively charged – the hydroxyl and the hydrazide ion. The neutral species attack at the carbon atom and the charged species at the nitrogen. The above mechanism requires a neutral species to attack at the nitrogen. Whether this is possible is not known.

The mechanism proposed above, although it relates the reactions with pyridine and with hydroxylamine and fits in with those of alkaline hydrolysis and the action of hydrazine, does not explain the high selectivity of the former reactions.

This mechanism would be placed in group B of the reactions of the isohexides. The action of pyridine on hexitol hexanitrates and of hydroxylamine on cellulose trinitrate has been shown to result in denitrination, giving the hydroxyl group with the configuration retained so that if the same reaction was occurring in the isohexides it would necessarily be in group B.

While this mechanism is possible for the polynitrates, the isohexide dinitrates reacted much less readily and gave a polymeric material as product. This may be taken to indicate that an SN1 reaction at carbon occurred to yield a carbonium ion which decomposed to the
polymeric material. This mechanism would require the formation of nitrate ion. It has been seen that relatively little inorganic nitrate was produced in the reaction, thus this mechanism could not account for all of the decomposition. The most probable process is therefore one of oxygen-nitrogen fission paralleling that found in various reactions of nitrate esters.

The thermal decomposition of nitrate esters has been shown to have a radical mechanism (100). A reaction of a similar type may well occur in the nitrate-pyridine reaction of the isohexides, however the steric requirements of this type of reaction are not known. The formation of the polymeric material may point to this type of reaction.

Thus the course of the decomposition of the isohexide dinitrates is not known, neither the reaction products nor the rate studies gave any definite conclusions towards this aim. The isohexides, however, prove to be a useful set of compounds for the observation of the steric nature of various reactions. It would be of interest to determine more fully the relative reactivities of groups in the endo and exo positions towards reactions classified in group B.

The isohexides yield no explanation for the high selectivity of the nitrate-pyridine reaction in the polynitrates. The nitrate groups are widely separated in the cases of isoidide and isosorbide dinitrates but are quite close in isomannide dinitrate. The only interactions which could occur in these compounds would be a field effect in the case of isomannide dinitrate and a backside-neighbouring-group effect in the case of isosorbide. The field effect in isomannide dinitrate does not seem to be great as isomannide dinitrate is the least reactive
of the isohexides whereas an activation was observed in the polynitrates. The nitrate group has recently been shown to be ineffective in the neighbouring-group effect (139, 140), ruling out interaction in the case of isosorbide dinitrate. Thus the variation in reactivity is probably steric in nature.
**EXPERIMENTAL**

**Materials**

**TABLE XII**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Starting Material</th>
<th>Method</th>
<th>Yield</th>
<th>Found Physical Constants</th>
<th>m.p.</th>
<th>$[\alpha]_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isomannide</td>
<td>D-mannitol</td>
<td>(1)</td>
<td>40%</td>
<td></td>
<td>86-88°C</td>
<td>+89.8°</td>
</tr>
<tr>
<td>Isosorbide</td>
<td>sorbitol</td>
<td>(17)</td>
<td>50%</td>
<td></td>
<td>62-63°C</td>
<td>+45.2°</td>
</tr>
<tr>
<td>Isoidide</td>
<td>diacetyl-isoidide</td>
<td>(55)</td>
<td>95%</td>
<td></td>
<td>42-45°C</td>
<td>+21.0°</td>
</tr>
<tr>
<td>Isomannide, 2,5-dinitrate</td>
<td>isomannide</td>
<td>(13)</td>
<td>46%</td>
<td></td>
<td>65-85.5°C</td>
<td>+319°</td>
</tr>
<tr>
<td>Isosorbide, 2,5-dinitrate</td>
<td>isosorbide</td>
<td>(13)</td>
<td>53%</td>
<td></td>
<td>50-51°C</td>
<td>+141°</td>
</tr>
<tr>
<td>2,5-di-O-tosyl-isomannide</td>
<td>isomannide</td>
<td>(61)</td>
<td>85%</td>
<td></td>
<td>90-91°C</td>
<td>+98.5°</td>
</tr>
<tr>
<td>2,5-di-O-tosyl-isosorbide</td>
<td>isosorbide</td>
<td>(17)</td>
<td>-</td>
<td></td>
<td>100-101°C</td>
<td>+57.8°</td>
</tr>
<tr>
<td>2,5-di-O-tosyl-isoidide</td>
<td>isoidide</td>
<td>(62)</td>
<td>95%</td>
<td></td>
<td>105-105.5°C</td>
<td>+40.5°</td>
</tr>
<tr>
<td>2,5-di-O-acetyl-isomannide</td>
<td>isomannide</td>
<td>(22)</td>
<td>89%</td>
<td></td>
<td>16°C</td>
<td>-</td>
</tr>
<tr>
<td>2,5-di-O-acetyl-isosorbide</td>
<td>isosorbide</td>
<td>(22)</td>
<td>94%</td>
<td></td>
<td>60-61.5°C</td>
<td>+145.5°C</td>
</tr>
<tr>
<td>2,5-di-O-acetyl-isoidide</td>
<td>isoidide</td>
<td>(22)</td>
<td>90%</td>
<td></td>
<td>56-57°C</td>
<td>+85.3°</td>
</tr>
<tr>
<td>2,5-di-O-acetyl-ditosyl</td>
<td>isomannide</td>
<td>(55)</td>
<td>60%</td>
<td></td>
<td>51-53°C</td>
<td>+87.0°</td>
</tr>
<tr>
<td>2-O-acetyl-5-O-tosyl-isosorbide</td>
<td>isosorbide</td>
<td>(66)</td>
<td>18%</td>
<td></td>
<td>64-65°C</td>
<td>+77.9°</td>
</tr>
<tr>
<td>2,5-diodo-2,5-ditosyl-dideoxy-isoidide isomannide</td>
<td>(9)</td>
<td>98%</td>
<td>61-62°C</td>
<td>+110°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-O-tosyl-5-ido-ditosyl-5-deoxy-isoidide isosorbide</td>
<td>(17)</td>
<td>95%</td>
<td>82-83°C</td>
<td>+56.5°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,4;2,5;3,6-tri-acetyltosyl</td>
<td>anhydro-D-mannitol</td>
<td>(66)</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Procedures and Compounds not Previously Reported

**Isoidide.** L-Sorbose (50 g.) in water (200 ml.) was hydrogenated at 55 p.s.i. and 80°C. for four hours using Raney nickel catalyst (from 10 ml. alcoholic sludge) (141). The catalyst was removed by filtration and the solution evaporated to dryness – portions of ethanol were added and then evaporated to remove final traces of water. Yield – 50 g. syrup (mixture of sorbitol and iditol).

The syrup was dissolved in concentrated hydrochloric acid (300 ml.) and the solution saturated with dry hydrogen chloride gas. The resulting solution was refluxed for twenty hours and the excess hydrochloric acid removed by repeated evaporation under reduced pressure with several additions of water. The residual syrup was fractionally distilled under reduced pressure.

- **Fraction 1** – b.p. 135-140°C., pressure 0.18-0.20 mm., Hg 8 g. – isosorbide
- **Fraction 2** – b.p. 140-143°C., pressure 0.20-0.22 mm., Hg 5 g. – mixture
- **Fraction 3** – b.p. 143-155°C., pressure 0.22-0.25 mm., Hg 12 g. – isoidide

Fraction 3 was recrystallised (ethyl acetate) – m.p. 44-46°C.

**Isomannide 2,5-dinitrate.** To isomannide (2 g.) in acetic acid/acetic anhydride (2:1, 15 ml.) at 0°C. was added, dropwise and with stirring, a mixture of acetic acid/acetic anhydride (1:1, 15 ml.) and fuming nitric acid (sp. gr. 1.45, 5 ml.), prepared by adding the nitric acid to the acetic mixture slowly, keeping the temperature below 5°C. The reaction mixture was kept below 5°C. during the addition and then allowed to stand at 5°C. for two hours. After this time
the mixture was poured into ice-water (400 ml.). Part of the nitrate ester crystallised out on standing at room temperature for eighteen hours, this was filtered off and washed well with water. Yield - 2.2 g. (68%), m.p. 63-65°C.

The filtrate was extracted with ether (3 x 100 ml.) and the ether extracts washed with water and saturated sodium bicarbonate solution then dried over sodium sulphate. After evaporation a syrup was obtained which crystallised on seeding with the first portion of the product. Yield syrup - 0.6 g., total yield - 2.8 g. (86%). Recrystallised (methanol) - m.p. 65-65.5°C. (constant).

Isosorbide 2,5-dinitrate. Preparation as for isomannide dinitrate.

Yield - 88%. Recrystallised (methanol) - m.p. 50.5-51.5°C.

Isoidide 2,5-dinitrate. Preparation as for isomannide dinitrate.

Yield - 88%. Recrystallised (methanol) - m.p. 68-69°C. (constant).

\[\alpha\]_D^{22} +72.9º (c. 1.09, CHCl_3).

Analysis - C Found 30.9% Required 30.5%
N Found 11.1% Required 11.86%
H Found 3.95% Required 3.41%

2-O-Acetyl-5-iodo-5-deoxyisoidide. Acetyltosylisosorbide (2 g.) in acetic anhydride (dry, 25 ml.) was refluxed with sodium iodide (3 g.) for eight hours. Excess acetic anhydride was removed by distillation after filtering off the precipitate of sodium toluenesulphonate. The residue was treated with water (50 ml.), allowed to stand for four hours then extracted with chloroform (3 x 20 ml.). The
combined extracts were washed with water, saturated sodium bicarbonate solution and 2% sodium thiosulphate solution, dried over sodium sulphate then evaporated.

The residual oil crystallised on standing at 0°C. Yield = 1.5 g. (87%), m.p. 42-44°C. Recrystallised (methanol) - m.p. 44-45°C. (constant). \([\alpha]_D^{22} +100.5 \text{ (c. 0.83, CHCl}_3\).

Analysis - C Found 32.46% Required 32.23%
H Found 3.57% Required 3.72%
I Found 42.37% Required 42.59%

5-0-Tosylisosorbide-2-nitrate

Isosorbide (15 g.) was partially tosylated by the method of Cope and Shen (66). The excess isosorbide ditosylate was removed by crystallisation from ethanol (95%) - 4.0 g. isosorbide ditosylate, m.p. 98-100°C.

The mother liquors were concentrated to a syrup (18.5 g.). After trial runs on one gram samples the bulk (16.5 g.) was dissolved in benzene subjected to alumina chromatography, (22 mm. x 30 cm. column). Isosorbide ditosylate (3 g., m.p. 98-99°C.) was eluted with chloroform/acetone (1:1) and the monotosylate (12.5 g. syrup) with methanol. This syrup could not be crystallised.

Part (2.55 g.) was acetylated by the method of Cope and Shen (66) to give 2.95 g. of 2-0-acetyl-5-0-tosylisosorbide, m.p. 64-65°C.

A further quantity (0.98 g.) was dissolved in acetic acid/acetic anhydride (1:1, 5 ml.) at 0°C. and nitric acid (4 ml.) in acetic acid/acetic anhydride (1:1, 6 ml.) at 0°C. was added slowly. After standing
at 0°C. for two hours the mixture was poured into water (100 ml.) and left for twelve hours. The solution was extracted with chloroform (3 x 30 ml.) and the chloroform extracts washed with saturate sodium bicarbonate solution and water then dried over sodium sulphate and evaporated. Yield - 1.10 g. colourless syrup.

0.20 g. of this syrup were dissolved in benzene (5 ml.), loaded onto an alumina column (7.5 mm. x 20 cm.) and eluted with chloroform. The fractions were evaporated and left to stand at 0°C. One crystallised on scratching. Seed crystals from this caused the bulk of the original syrup to crystallise. Recrystallised methanol - m.p. 75.0-75.5°C. (constant after four recrystallisations).

This material ran as one spot on paper chromatographs in hexane/methanol solvent (Rf 0.21) and gave reaction with diphenylamine/ultraviolet light characteristic of both nitrate and tosylate.

**Tosylisoidide nitrate.** Isoidide (1 g.) was partially tosylated in a similar manner to yield ditosylisoidide (0.53 g.) and a syrup (1.42 g.) after fractional crystallisation from ethanol.

The syrup was nitrated directly by dissolving in acetic anhydride/acetic acid (1:1, 5 ml.) and adding nitric acid (3 ml.) in acetic anhydride/acetic acid (1:1, 5 ml.) at 0°C. The reaction mixture was worked up as before to yield 1.35 g. of a colourless syrup. This syrup was dissolved in benzene (5 ml.), loaded onto an alumina column (5 mm. x 30 cm.) eluted with benzene (5 ml.) and ether (50 ml.). Fractions were collected and samples from them subjected to paper chromatography (hexane/methanol solvent) followed by treatment with diphenylamine/ultraviolet developer. The fractions containing a spot
with Rf 0.35 and showing both nitrate and tosylate colour tests were pooled and evaporated. Yield - 0.285 g. colourless syrup. Crystallised on scratching at 0°C. Recrystallised to constant melting point (methanol) - m.p. 73-74°C.

This material ran as a single spot on paper chromatographs in hexane/methanol solvent (Rf 0.35) and gave the tosylate and nitrate reactions.

**Tosylisomannide nitrate.** Isomannide (5 g.) was treated in a similar manner to isoidide above and gave ditosylisomannide (5.8 g.) and a syrup (2.15 g.). Nitration of this syrup followed by alumina chromatography gave 0.421 g. of a crystalline compound flowing as one spot on paper chromatographs in hexane/methanol solvent (Rf 0.12) and gave the tosylate and nitrate reactions. Recrystallised (methanol) - m.p. 120-121°C. (constant).

**Tetraethylammonium acetate.** Triethylamine (25 g.) was refluxed with ethyl iodide (45 g.) in ethanol (25 ml.) for four hours. The mixture was allowed to cool and the resulting crystals were collected and washed with ethanol. This product, tetraethylammonium iodide, was dissolved in water and a saturated solution of barium acetate in water was added until further addition caused no more precipitation. The barium iodide was removed by filtration and the filtrate was evaporated to dryness. Yield - 34 g., m.p. 45-46°C.

This material was also prepared from tetraethylammonium bromide by passing a solution of this compound through a column of Dowex I ion exchange resin in the hydroxyl form and neutralising the eluate with acetic acid.
Partial Nitration of the Isohexides

Isomannide (4.6 g.) was dissolved in acetic acid (20 ml.) and nitric acid (20 ml.) in acetic acid/acetic anhydride (2:1, 30 ml.) was added slowly at 0°C. After standing at 0°C. for three hours the mixture was poured into water and extracted with ether after twenty four hours. The ether solution was washed with water and sodium bicarbonate solution then dried and evaporated. The resulting syrup (1.6 g.) showed two spots on paper chromatographs and was subjected to alumina chromatography. Isomannide dinitrate (0.85 g.) was eluted by ethylacetate and the mononitrate derivative (0.75 g.) was eluted by methanol.

The mononitrate became partially crystalline on standing at 0°C. but no solvent suitable for recrystallisation was found.

By similar procedures isosorbide (2.1 g.) gave syrupy mononitrate (0.17 g.) and isoidide (0.9 g.) gave syrupy mononitrate (0.17 g.).

Elementary analyses of various derivatives of the isohexides are shown in Table XIII.

Infrared spectra of each of the isohexide derivatives were recorded using the potassium bromide disc technique. These confirmed the presence of the substituent groups in all cases.
### TABLE XIII

**Analyses of Derivatives**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Element</th>
<th>Method</th>
<th>Found</th>
<th>Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ditosylisomannide</td>
<td>S</td>
<td>1</td>
<td>14.0, 13.6</td>
<td>14.1</td>
</tr>
<tr>
<td>Ditosylisosorbide</td>
<td>S</td>
<td>1</td>
<td>13.7, 13.5</td>
<td>14.1</td>
</tr>
<tr>
<td>Ditosylisoidide</td>
<td>S</td>
<td>1</td>
<td>13.9, 13.9</td>
<td>14.1</td>
</tr>
<tr>
<td>Acetyltosylisosorbide</td>
<td>S</td>
<td>1</td>
<td>9.2, 9.2</td>
<td>9.35</td>
</tr>
<tr>
<td>Iodotosylisoidide</td>
<td>S</td>
<td>1</td>
<td>7.8, 7.4</td>
<td>7.5</td>
</tr>
<tr>
<td>Isomannide dinitrate</td>
<td>N</td>
<td>2</td>
<td>11.7, 11.8</td>
<td>11.85</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>N</td>
<td>2</td>
<td>11.7, 11.8</td>
<td>11.85</td>
</tr>
<tr>
<td>Isoidide dinitrate</td>
<td>N</td>
<td>2</td>
<td>10.8, 11.3</td>
<td>11.85</td>
</tr>
<tr>
<td>Isomannide mononitrate</td>
<td>N</td>
<td>3</td>
<td>4.1</td>
<td>7.33</td>
</tr>
</tbody>
</table>

1. Oxygen flask method, see page 120
2. Micro-Kjeldahl method, see page 118
3. Colorimetric method, see page 118
Analytical Methods - Estimation Procedures

Colorimetric Determination of Nitrate Nitrogen (95, 142)

The nitrate sample (10-80 μg. nitrogen), most conveniently dissolved in ether, was added to 10-15 ml. 70% (v/v) sulphuric acid and 1 ml. of a 1% solution of 3,4-dimethylphenol in ether added. After swirling to mix, the mixture was left to stand for thirty to sixty minutes at 30°C. It was then transferred to a 250 ml. round-bottomed standard taper flask, washing in with 150 ml. water. Boiling chips were added and the flask was fitted with an inverted U-shaped take-off tube which led into a 25 ml. volumetric flask, containing 2% sodium hydroxide solution (2.5 ml.), standing in a bath of cold water. The steam distillation was carried out until about 20 ml. of distillate had collected. The resulting alkali solution, after making up to 25 ml. and bringing to 24°C. in a constant temperature bath, was estimated colorimetrically at 435 μm with a Bausch and Lomb colorimeter.

A calibration curve was made using samples of potassium nitrate, isosorbide dinitrate and isomannide dinitrate (Figure XXII). A discussion of this method of analysis is given in Appendix I.

Micro-Kjeldahl Nitrogen Determination (143)

Digestion. To the sample, containing 0.2-1.0 mg. nitrogen, in a digestion flask was added 2 ml. concentrated sulphuric acid and 0.1 g. salicylic acid. The mixture was shaken until all had dissolved, left to stand for thirty minutes then sodium thiosulphate (0.3 g.) was added and heated for five minutes. Powdered potassium sulphate (0.6 g.)
and a trace of selenium catalyst was added and the mixture gently heated until the foaming had stopped, then refluxed until colourless.

**Distillation.** This was carried out in the apparatus described by Ma and Zjazaga (144). The digestion mixture was diluted with 2 ml. of water and transferred to the flask, rinsing in with 2 x 2 ml. water. Then 8 ml. 30% sodium hydroxide solution was added and the steam distillation begun. The ammonia was collected in 10 ml. of a 2% boric acid solution and titrated against 0.01 Normal hydrochloric acid, using bromocresol green/methyl red mixed indicator.
Sulphur Determination (145)

25 ml. of a 6% solution of hydrogen peroxide were placed in a 250 ml. Iodine flask. A drop of methyl red indicator was added and the solution brought to the end point by addition of 0.200 Normal sodium hydroxide solution — the end point was compared in colour to a similar volume of solution previously brought to neutrality. The sample (~5 mg.) was weighed onto a 2 cm. square of ashless filter paper (Whatman No. 41) having a 3 mm. x 2 cm. wick projecting from one corner. The filter paper was then folded twice lengthways and rolled into a tight cylinder which was inserted into the centre of a spiral of platinum wire so that the wick protruded from the spiral. The sample, in the platinum holder, was hung below the stopper of the Iodine flask. Holding the stopper with sample in one hand the flask was flushed out with a steady stream of oxygen for thirty seconds, then the wick was lighted and the stopper quickly introduced into the flask and held firmly down until the combustion was completed. The flask was shaken to absorb all gases formed in the combustion then opened. The stopper and walls were washed down with 100 ml. of distilled water and the flask was placed on a hot plate. Evaporation by boiling was continued until the volume had reached about 25 ml. when a further 100 ml. of water were added and the volume again reduced to 25 ml.

The solution was titrated, after cooling and addition of further indicator. The end point was again compared to the colour of the standard prepared previously. Iodine in the sample was found not to interfere with the determination.
Alumina Column Chromatography

Three grades of alumina were used -

(1) Alcoa "Grade F-20" 80-200 mesh.
(2) As above, but treated with 50% hydrochloric acid for eighteen hours, brought to neutrality by repeatedly washing with distilled water, then dried at 200°C. before use.
(3) Merck "Acid washed grade" 100-200 mesh.

The alumina was poured into glass columns dry, with light tapping, until the alumina would not pack down any further. No pre-wash was given, the mixture was loaded directly onto the dry column in a small volume of a solvent which would not cause elution of the substances. A column height of 20-30 cm. was used and about 0.5 g. of material was loaded for each square centimeter of cross-sectional area of the column. The solvents used for elution were in order of increasing eluting power: petroleum ether (b.p. 65-70°C.), benzene, diethyl ether, chloroform, ethyl acetate, acetone, methanol, water, water-pyridine mixtures.

All the organic solvents used were "Reagent Grade" and were dried and redistilled before use. Table XIV shows the elution positions of the various compounds chromatographed. The elution of the isohexide dinitrates was controlled more readily when mixtures of diethyl ether and ethyl acetate were used rather than chloroform alone.

Method Used to Determine the Recovery of Nitrate Esters on Passing Through Alumina Columns

A sample of the isohexide dinitrate (∼200 mg.) was dissolved in
TABLE XIV

Position of Elution of Various Compounds from Alumina Columns

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petroleum ether</td>
<td></td>
</tr>
<tr>
<td>Ether</td>
<td></td>
</tr>
<tr>
<td>Ether 50, E.A. 1</td>
<td>isoidide dinitrate</td>
</tr>
<tr>
<td>Ether 20, E.A. 1</td>
<td>isosorbide dinitrate</td>
</tr>
<tr>
<td>Ether 10, E.A. 1</td>
<td>isomannide dinitrate</td>
</tr>
<tr>
<td>Ether 5, E.A. 1</td>
<td></td>
</tr>
<tr>
<td>Ether 1, E.A.10</td>
<td>trianhydromannitol</td>
</tr>
<tr>
<td>Ethylacetate</td>
<td></td>
</tr>
<tr>
<td>Acetone</td>
<td></td>
</tr>
<tr>
<td>Acetone 1, methanol 1</td>
<td>isohexide mononitrates</td>
</tr>
<tr>
<td>Methanol</td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td></td>
</tr>
<tr>
<td>Water 1, pyridine 1</td>
<td>pyridinium nitrate</td>
</tr>
</tbody>
</table>

E.A. = ethyl acetate

The numbers indicate the proportions used in mixed solvents.

acetone in a 25 ml. volumetric flask and made up to the mark. The optical rotation was measured then the whole solution was evaporated to dryness. The residue was dissolved in a small amount of ether, loaded onto a column (5.5 mm. diameter, 25 cm. high), and washed on with more ether. After standing for three hours the column was eluted
with acetone until the eluent gave a negative nitrate test with diphenylamine/sulphuric acid reagent. The acetone eluent was evaporated to about 15 ml. then transferred to the 25 ml. volumetric flask, made up, and the optical rotation measured.

For the mononitrates a similar procedure was used except that methanol was used in place of acetone. Percent recoveries were calculated from the loss in optical rotation.

Celite Column Chromatography (124)

Celite No. 535 (Johns-Manville) was acid washed (147) then dried at 110°C. This Celite was mixed thoroughly with an equal weight of water then slurried with the developing solvent (n-butanol saturated with water) and poured into the column. The Celite was compressed by suction at the bottom of the column and by tamping down at the top. (About 45 g. of Celite (dry) when packed into a 28 mm. diameter tube formed a column 25 cm. high.) It was helpful to place about 1 mm. of dry Celite at the bottom of the tube before adding the wet Celite, this absorbed any water which separated out of the butanol with a fall in the temperature.

Three methods were used for loading the column -

1) A layer of dry Celite was placed at the top of the column, the material was dissolved in a weight of water equal to that of the dry Celite and was then introduced onto the top of the column.

2) The material was dissolved in a small amount of water then mixed well with dry Celite (weight equal to the water present). This mixture was added to the top of the column in a slurry with the
developing agent.

(3) The material was dissolved in the smallest possible amount of developing agent and loaded onto a normal column. The latter method was used in most cases. A rate of about 1 ml. per minute was used; greater rates were possible if the resolution required was not great.

**Paper Chromatography**

Whatman No. 1 filter paper was used in all cases with the solvent flow in the machine direction of the paper. Glass tanks with glass or stainless steel fittings were used to contain the solvents. Descending flow was used in all cases.

**Solvent Systems**

**Methylethylketone/water azeotrope.** Prepared by the distillation of methylethylketone (Reagent Grade) and distilled water, both being maintained in the distillation flask in sufficient quantity to give two layers. The Rf values were: isomannide 0.26, isosorbide 0.33, isoidide 0.45, pyridinium nitrate 0.05, nitrate esters 0.96.

**n-Butanol/water.** Redistilled n-butanol (Reagent Grade) was saturated with distilled water. The Rf values were: isomannide 0.34, isosorbide 0.43, isoidide 0.55, pyridinium nitrate 0.10, nitrate esters 0.98.

**Hexane/methanol.** A chromatography tank with a tight fitting lid was set up with two dishes in the bottom, one containing hexane saturated
with methanol, the other methanol saturated with hexane. A piece of filter paper was led up from each of the dishes and fastened to the sides of the tank to facilitate the attainment of equilibrium between the solvent and the vapour in the tank. The paper was spotted with material in the usual way, attached to a glass rod, and placed in the tank suspended from the rod with cotton thread through a hole in the lid. The paper was equilibrated in this way for a period of four to eighteen hours before lowering into a trough of hexane saturated with methanol at the top of the tank. The solvent ran at a rate of about 20–30 cm. per hour.

As the solvent was very volatile it was difficult to remove the paper from the tank quickly enough to mark the solvent front before some evaporation had occurred. Therefore two methods were used to determine the distance the front had travelled. One was to draw a line on the paper at a suitable distance and allow the solvent to reach this front before removing the paper. The other was to observe the distance moved by a series of calibration marks placed on the outside glass of the tank.

Hexane was obtained as commercial grade n-hexane from Phillips Petroleum. It was dried over calcium chloride and distilled through a fractionating column - boiling range 67–69°C. \((n^2 1.3755)\). Some samples of petroleum ether (nominal boiling range 65–110°C.) had 95% boiling in range 65–70°C. and with \(n^2 1.3755\) this was used as n-hexane. Other samples of petroleum ether boiled at 75–85°C. \((n^2 1.3768–1.3807)\) and were probably mixtures of heptanes. These fractions were used with success for chromatography; the \(R_f\) values were lowered
slightly. The methanol was reagent grade and was redistilled before use. After mixing the hydrocarbon and methanol with shaking the mixture was allowed to separate into two layers. The top one was used as irrigating solvent and the bottom one used in saturating the tank.

Rf values in this solvent system and a discussion of the method are given in Appendix II.

Reagents Used for Detection of Materials on Paper Chromatographs

For isohexides -

Iodine vapour. The papers were first exposed to a jet of steam for a short period then placed in a chamber of iodine vapour for about fifteen minutes. The isohexides showed as brown spots on a yellow background.

p-Anisidine/hydrochloric acid (122). The papers were sprayed with the reagent then heated in an oven at 140°C. for five minutes. This reagent detected isohexides as light spots on a brown background only when the solvent system methylethylketone/water was used.

For nitrates -

Diphenylamine/sulphuric acid. A 1% solution of diphenylamine in 50% sulphuric acid (dissolved by warming) was smeared over the paper supported by a glass plate. Nitrate (or nitrite) material showed as dark blue against which background.

Diphenylamine/ultraviolet (148). A 1% solution of diphenylamine in ethanol (95%) was sprayed onto the paper. After drying the treated paper was exposed to ultraviolet light for five minutes. Nitrate
material showed as yellow spots in daylight (dark regions under ultraviolet light) against white or cream background.

**Isohexide Dinitrate-Pyridine Reaction**

**Investigation of Reaction Products**

Various separation procedures were used to investigate the products of the nitrate-pyridine reaction. The general scheme used is shown in Figure XXIII, this was used in most cases with various modifications. Table XV lists the various separations carried out with the main products isolated. The various modifications are described after the table.

**Figure XXIII: General Scheme for the Separation of Reaction Products**
### TABLE XV

**Summary of Separations**

<table>
<thead>
<tr>
<th>No. and Compound</th>
<th>Weight g.</th>
<th>Temp. °C.</th>
<th>Time hrs.</th>
<th>Unreacted dinitrate g.</th>
<th>Insoluble materials A(g)</th>
<th>B(g)</th>
<th>Aqueous solution g.</th>
<th>Alcohol extract g.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 S</td>
<td>0.05</td>
<td>115</td>
<td>6</td>
<td>0.025</td>
<td>0</td>
<td>-</td>
<td>0.011</td>
<td>-</td>
</tr>
<tr>
<td>2 S</td>
<td>0.20</td>
<td>115</td>
<td>7</td>
<td>0.083</td>
<td>0</td>
<td>0.027</td>
<td>0.027</td>
<td>0.020</td>
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<td>3 S</td>
<td>0.01</td>
<td>115</td>
<td>4.5</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4 I</td>
<td>0.01</td>
<td>115</td>
<td>4.5</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5 S</td>
<td>0.10</td>
<td>115</td>
<td>36</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6 S</td>
<td>0.12</td>
<td>115</td>
<td>60</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7 S</td>
<td>0.05</td>
<td>115</td>
<td>72</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8 M</td>
<td>0.24</td>
<td>115</td>
<td>48</td>
<td>0.095</td>
<td>0</td>
<td>0.02</td>
<td>0.090</td>
<td>0.070</td>
</tr>
<tr>
<td>9 S</td>
<td>4.0</td>
<td>115</td>
<td>17</td>
<td>2.50</td>
<td></td>
<td>0.30</td>
<td>1.65</td>
<td>1.25</td>
</tr>
<tr>
<td>10 M</td>
<td>4.0</td>
<td>115</td>
<td>24</td>
<td>2.50</td>
<td></td>
<td>-</td>
<td>-</td>
<td>0.65</td>
</tr>
<tr>
<td>11 S</td>
<td>3.0</td>
<td>115</td>
<td>17</td>
<td>1.10</td>
<td></td>
<td>-</td>
<td>-</td>
<td>1.20</td>
</tr>
<tr>
<td>12 S</td>
<td>0.20</td>
<td>115</td>
<td>36</td>
<td>0.020</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13 M</td>
<td>0.20</td>
<td>115</td>
<td>60</td>
<td>0.050</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14 M</td>
<td>5.0</td>
<td>115</td>
<td>69</td>
<td>1.127</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>1.03</td>
</tr>
<tr>
<td>15 S</td>
<td>4.5</td>
<td>115</td>
<td>48</td>
<td>0.266</td>
<td>1.0</td>
<td>0.4</td>
<td>2.00</td>
<td>1.54</td>
</tr>
<tr>
<td>16 M</td>
<td>0.5</td>
<td>115</td>
<td>72</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17 S</td>
<td>0.5</td>
<td>115</td>
<td>48</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>18 S</td>
<td>1.95</td>
<td>115</td>
<td>48</td>
<td>0.30</td>
<td>0.26</td>
<td>0.14</td>
<td>-</td>
<td>0.62</td>
</tr>
<tr>
<td>19 S</td>
<td>2.40</td>
<td>115</td>
<td>24</td>
<td>0.101</td>
<td>0.57</td>
<td>0.04</td>
<td>0.686</td>
<td>-</td>
</tr>
<tr>
<td>20 I</td>
<td>0.40</td>
<td>87</td>
<td>41</td>
<td>0.282</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>21 S</td>
<td>1.00</td>
<td>87</td>
<td>91</td>
<td>0.640</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>22 M</td>
<td>1.00</td>
<td>87</td>
<td>187</td>
<td>0.876</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>23 I</td>
<td>0.50</td>
<td>87</td>
<td>96</td>
<td>0.261</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>24 S</td>
<td>1.00</td>
<td>87</td>
<td>240</td>
<td>0.494</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>25 M</td>
<td>1.00</td>
<td>87</td>
<td>528</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>26 I</td>
<td>0.50</td>
<td>100</td>
<td>24</td>
<td>0.297</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>27 S</td>
<td>1.00</td>
<td>100</td>
<td>96</td>
<td>0.424</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>28 M</td>
<td>1.00</td>
<td>100</td>
<td>312</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Solutions were evaporated on a rotary type evaporator under reduced pressure. Final traces of pyridine were removed from the residue from the ether solutions by standing over concentrated sulphuric acid in a dessicator under vacuum.
Modifications to Separation Procedures

Separation 1. The recovered isosorbide dinitrate was recrystallised - m.p. 49-50°C, mixed m.p. (isosorbide dinitrate) 50-51°C. Samples of the aqueous solution were run on paper chromatographs (methylethylketone/water solvent) - five spots were visible under ultraviolet light, none reacting with alkaline potassium permanganate.

Separation 2. Ether solution was extracted with sodium bicarbonate solution. The extract was acidified and extracted with ether - the residue of this ether solution was zero. The original ether solution gave isosorbide dinitrate on evaporation, characterised by melting point and mixed melting point.

Separations 3 and 4. The original pyridine solution, the ether solution and the aqueous solution were run on paper chromatographs (methylethylketone/water solvent) and nitrate-containing spots were detected with diphenylamine/sulphuric acid reagent (Table III). The ether solution from the isoidide dinitrate reaction was evaporated and the unreacted dinitrate was recrystallised - m.p. 55-60°C, mixed m.p. (isoside dinitrate) 56-62°C.

Separations 5 and 6. Spots corresponding to a mononitrate derivative were detected in the ether solution using paper chromatography (hexane/methanol solvent).

Separation 7. The pyridine reaction mixture was cooled to 0°C and tosyl chloride (0.150 g.) was added. The mixture was allowed to stand for twenty four hours and was then poured into water and
extracted with chloroform. The chloroform solution was washed, dried and evaporated. Yield - 0.095 g., m.p. 101-103°C, mixed m.p. (isosorbide ditosylate) 80-86°C. This procedure was repeated after first evaporating the original pyridine solution to dryness and adding fresh pyridine. Yield - zero.

Separation 8. Isomannide dinitrate was recovered and characterised by melting point and mixed melting point. The alcohol extract was evaporated; the residue dissolved in pyridine (2 ml.), cooled to 0°C. and tosyl chloride (0.200 g.) was added. After standing for twenty four hours the solution was worked up as before. Yield - 0.015 g., not crystalline.

Separation 9. Isosorbide dinitrate was separated and characterised. The alcohol extract was run on paper chromatographs (methyl ethyl ketone/water and hexane/methanol solvents) and pyridinium nitrate was detected. The alcohol extract was dissolved in water (30 ml.) and passed through ion exchange columns (Dowex I, H⁺ form and Amberlite IR 120, OH⁻ form - both columns 7 mm. x 50 cm.). The eluate was evaporated. Residue - zero.

Separation 10. Isomannide dinitrate was separated and characterised. Alcohol extract - part (0.20 g.) - was tosylated as in Separation 8 to yield 0.045 g. of a syrup which would not crystallise. The remainder (0.35 g.) was chromatographed on a Celite column (Figure XIII).

Separation 11. Isosorbide dinitrate was separated and character-
ised. The alcohol extract was distilled under reduced pressure (0.5 mm. Hg, 100°C.) in a short path distillation apparatus. The distillate obtained was a dark brown and deliquescent liquid.

Separations 12 and 13. Isosorbide (0.500 g.) and isomannide (0.500 g.) were added to the initial reaction mixture in these separations. The alcohol extract was separated and yielded 0.550 g. and 0.550 g. respectively. The fractions were divided into two halves, one half was recrystallised and characterised by melting point and mixed melting point as the unchanged isohexide in each case. The second half was tosylated as described above and gave 0.60 g. (90%) of each of the ditosylates which were recrystallised and characterised.

Separation 14. Insoluble material "A" was tested for solubility in several organic solvents and was found to be insoluble in all of them. Samples (0.10 g.) were heated with concentrated sulphuric acid (3 ml.), concentrated hydrochloric acid (3 ml.) and sodium hydroxide solution (10%) (3 ml.); the material dissolved partially in the sulphuric acid, remained insoluble in the hydrochloric, and dissolved completely in the alkali. The brown-black material was reprecipitated from the alkaline solution on acidification or dilution with ethanol. Part of the alcohol extract (0.400 g.) was subjected to Celite column chromatography (Figure XIII); the remainder (0.300 g.) was chromatographed on an alumina column. From the latter column small amounts of isomannide dinitrate (0.020 g.) and isomannide mononitrate (0.050 g.) (characterised by paper chromatography) were separated. 50% of the original optical activity of the fraction was recovered in these fractions.
Separation 15. 0.30 g. of the alcohol extract was chromatographed on a Celite column (Figure XIII). A further 0.70 g. was chromatographed on an alumina column and gave 0.060 g. of isosorbide mononitrate (characterised by paper chromatography) and pyridinium nitrate (0.400 g.) which was characterised by its melting point and by paper chromatography (methylethylketone/water and hexane/methanol solvents).

Separations 16 and 17. 0.200 g. of isomannide and isosorbide were added to the initial reaction mixtures. The alcohol extracts were isolated and chromatographed on Celite columns (Figure XIII).

Separation 18. Pyridine was first distilled off from the reaction mixture, then fractions were collected and their refractive index was measured. The residue was divided into the ether and aqueous solutions as usual. The aqueous solution was evaporated, dissolved in methanol (20 ml.) and passed through a charcoal column (15 cm. x 9.5 mm.). All the coloured material and some optical activity was removed. Paper chromatography (methylethylketone/water solvent) of the eluate showed nitrate and acid at Rf 0.1.

Separation 19. The pyridine reaction mixture was diluted with chloroform, filtered and distilled. Fractions were collected. The residue was divided into ether and aqueous solutions. The aqueous solution was passed through an Amberlite IR 120 (H⁺ form) column (7 mm. x 50 cm.) and aliquots of the eluate were titrated against bases. Different end points were observed when phenolphthalein or methyl red indicator were used. Part of the eluate was passed through
a Dowex I (OH⁻ form) column (7 mm. x 50 cm.). All the material was retained and was not eluted with 2 Normal acetic acid. The ether fraction was subjected to alumina chromatography - isosorbide dinitrate (0.101 g.) and isosorbide mononitrate (0.080 g.) were isolated. Isosorbide mononitrate gave 5.6% nitrogen on analysis (7.3% required).

Separations 24 and 28. The insoluble materials "B" (0.100 g.) from these reactions were dissolved in sodium hydroxide (1 Normal, 1 ml.). Half of each solution was acidified with sulphuric acid and half treated with ethanol (2 ml.). The reprecipitated materials were separated by centrifugation and washed several times then dried. Infrared spectra of each of these samples and of the original materials were recorded and found to be very nearly the same in all cases.

Nitrate-Pyridine Reactions in the Presence of 3,4-Dimethylphenol

The isohexide dinitrate (0.100-0.010 g.) and 3,4-dimethylphenol (0.250-0.025 g.) were dissolved in pyridine (2 ml.) in a small bulb as used in the rate studies. The solutions were refluxed for various times after which they were poured into sulphuric acid (3 Normal, 150 ml.) and steam distilled as in the colorimetric determination. The distillate was estimated colorimetrically for the presence of nitroxylenol.

A solution of nitroxylenol in pyridine was refluxed for thirty six hours. The nitroxylenol was recovered quantitatively by the steam distillation procedure.
The Determination of Rates of Reaction

The reactions were carried out in glass bulbs with long stems. A water jacket was fitted over the stem and the top enclosed by a drying tube (containing Drierite). The initial concentration used was 0.1 g. of the isohexide dinitrate in 2 ml. of pyridine. The bulbs were heated in an oil bath at 125-130°C. for experiments at reflux (a boiling chip was added in these cases) or in vapour baths for lower temperatures. Samples were removed directly from the bulb by a long-stemmed pipette and then measured out accurately (0.1 or 0.2 ml.) and placed in 2 ml. of distilled water in a test tube. The nitrate ester was extracted with ether (3 x 1 ml.) and the combined ether solutions made up 10 ml. 1 ml. samples of this solution were taken and estimated for nitrate by the colorimetric method.

For some of the slower reactions it was difficult to obtain reproducible results using the bulb method described above. This was probably due to slow evaporation of the pyridine. In these cases the reaction was carried out in sealed tubes (11 x 50 mm.). Pyrex test tubes were used and 0.5 ml. of the initial dinitrate-pyridine solution was introduced before sealing. In these cases it was noted that a pressure formed during the course of the reaction (seen by softening the glass after cooling the reaction mixture—the softened spot was blown out).

In the reactions in which water was added pyridine containing water was prepared in bulk and portions taken for the reactions. For reactions at 100°C. the bulbs or sealed tubes were placed above boiling water. For 87°C. the vapour above a boiling, two layer, mixture of sec-butanol and water was used.
Other Reactions

The Decomposition of Isohexide Dinitrates in Various Solvents

About 50 mg. of the dinitrate was weighed into a small bulb with a long stem and 1 ml. of the solvent added. The top of the stem was well plugged with glass wool and enclosed with a drying tube. The bulb was then heated in a vapour bath (diethyl carbinol, b.p. 113-115°C.) for the required time.

Isolation of unreacted dinitrate was carried out by cooling the bulb then adding 3 ml. ether and introducing the solution onto the top of an alumina column (7.5 mm. by 20 cm.). The bulb was washed out with two 2 ml. portions of ether which were added to the column. A further 15 ml. of ether was passed through the column and then 50 ml. of ether/ethyl acetate (9:1). 5-7 ml. fractions were collected and tested for nitrate (diphenylamine/sulphuric acid). Those fractions containing nitrate were pooled, evaporated and brought to constant weight under vacuum at 40°C. The residual syrups were crystallised by seeding and the melting point of the solids then recorded as a check on their purity.

Solvents Used

Nitrobenzene. Reagent grade - dried over calcium chloride, distilled, redried with phosphorous pentachloride and redistilled (reduced pressure).

m-Xylene. Reagent grade - dried over calcium chloride and distilled.
Diethylcarbinol. Technical grade — dried and distilled (middle 1/3 fraction only used).

Sym-Tetrachloroethane. Technical grade — dried over calcium chloride and potassium carbonate and distilled.

The Determination of the Rate of the Reaction of the Isohexide Dinitrates with Xylenol in Sulphuric Acid

Sulphuric acid containing 100 mg. xylenol in 100 ml. (10 ml.) was placed in a 250 ml. standard taper round bottomed flask and stirred vigorously with a mechanical stirrer. 1 ml. of a standard solution of isohexide dinitrate in ether was added from a pipette (delivery time five seconds). The reaction was quenched by the introduction of water (100 ml. at 0°C). The resulting solution was steam distilled as in the normal nitrate determination, the distillate being collected in sodium hydroxide solution and estimated colorimetrically.

The Reaction of Silver Nitrate with Iodo Derivatives

Times of reaction and temperatures are given in Table X. The solution of iodo compound and silver nitrate in mole proportions 1:2-3 (iodine to silver nitrate) in dry acetonitrile were refluxed (or heated in a water bath) for a given time under anhydrous conditions. The mixture was then cooled and filtered through a sintered glass funnel and the silver iodide washed with a little acetonitrile, dried at 50°C. and weighed. The filtrate and washings were evaporated to small volume then water and chloroform added and the mixture shaken. The layers were separated and the aqueous one re-extracted with a
further portion of chloroform. The combined chloroform extracts were washed with sodium bicarbonate and sodium thiosulphate solutions then water, and finally dried and evaporated.

The residual syrups were dissolved in a little ether and loaded onto alumina columns and the elution carried out with portions of ether/ethyl acetate mixtures. The elution was followed by testing for nitrate and by running paper chromatographs of the various nitrate containing fractions. Those fractions containing single substances were pooled and evaporated. The intermediate fractions were also pooled and evaporated. The relative proportion of the components of these mixtures was estimated by comparison of the intensities and sizes of the spots on paper chromatographs. In this way approximate yields of the various components were obtained.

Reaction of Tosylates with Sodium Iodide

The tosyl compound (0.005 moles) was dissolved in acetic anhydride (dried and redistilled, 25 ml.) and sodium iodide (A.R. grade, 0.0062 or 0.0124 moles) added. The mixture was refluxed for two hours, cooled and left to stand for thirty minutes. The crystalline precipitate was collected by filtration into a weighed sintered glass funnel. The precipitate was washed with acetic anhydride (10 ml.) and dried at 100°C. to constant weight. The filtrate and washings were combined, refluxed for a further two hours and the precipitate collected as before. The solution from this stage was refluxed for four hours before isolation of the final precipitate and the organic products.

The organic products of the reaction were isolated from the final
solution, after removing excess acetic anhydride by distillation under reduced pressure. The mixture was shaken with water and chloroform, separated, and the aqueous layer washed with further chloroform. The combined chloroform extracts were washed with sodium bicarbonate solution (saturated), sodium thiosulphate (10% solution) and water, then dried and evaporated. The resulting syrups usually crystallised on rubbing at 0°C.

The Action of Barium Methoxide on Isomannide and Isoidide Ditosylates

Isomannide ditosylate (2.31 g.) in 0.3 Normal barium methoxide solution (100 ml.) was refluxed for three hours. The mixture was then cooled and titrated against standard sulphuric acid after the addition of indicator. The resulting solution was evaporated nearly to dryness and water (50 ml.) and chloroform were added and the mixture shaken. The chloroform layer was separated, washed, dried and evaporated. Yield - 0.284 g. syrup. This syrup crystallised on seeding and was recrystallised - m.p. 87-90°C., mixed m.p. (isomannide ditosylate) 88-90°C.

Isoidide ditosylate (0.502 g.) was reacted in the same way. The chloroform layer gave 0.280 g. of a syrup which crystallised and was recrystallised - m.p. 103-105°C., mixed m.p. (isoidide ditosylate) 104-105.5°C.

The titration of the solutions showed that 0.0102 equivalents of alkali had been consumed in the case of isomannide ditosylate and 0.00117 in the case of isoidide ditosylate.
Reaction of the Nitrate Esters with Sulphuric Acid in Acetic Anhydride

Isosorbide dinitrate (0.100 g.) was dissolved in acetic anhydride/sulphuric acid (10:1, v/v, 4 ml.) at 25°C. The optical rotation of the solution was recorded at various times until a steady state had been reached. The solution was then poured into water (20 ml.) and extracted with chloroform after standing twelve hours. The chloroform solution was washed, dried and evaporated. The resulting syrup (0.040 g.) was distilled under reduced pressure but would not crystallise.

Isoidide and isomannide dinitrates were reacted in a similar manner.

Hydrogenation of the Isohexide Dinitrates

Palladium-on-charcoal (86) from palladium chloride (0.100 g.) was introduced into the isohexide dinitrate (0.250 g.) in ethanol (95%, 100 ml.), and the mixture hydrogenated at 30 p.s.i. for two hours at 24°C. After this time the catalyst was removed by filtration and the filtrate was evaporated to dryness. The syrups obtained were crystallised by seeding and recrystallised once.

Yields - isomannide 90%, m.p. 85-87°C.
isosorbide 98%, m.p. 61-62°C.
isoidide 95%, m.p. 42-43°C.

Attempt to Prepare Dianhydrodulcitol

Dulcitol (3.6 g.) was dried under vacuum then placed in a Dean-Starke apparatus with xylene (12 ml.) and p-toluenesulphonic acid (0.12 g.). The mixture was refluxed and the water which was removed
was measured at various times (Figure XXIV). After four hours the refluxing was stopped and the xylene removed by distillation under reduced pressure. The residual brown syrup was distilled under reduced pressure but failed to give any distillate.

Mannitol was reacted under the same conditions and gave a 40% yield of isomannide.

![Graph of dehydration of mannitol and dulcitol](image)

**Figure XXIV: The Dehydration of Mannitol and Dulcitol**

**Attempts to Form the Carbonyl Derivative of the Isohexides**

**Catalytic dehydrogenation.** Isomannide (1 g.) and Raney nickel (141) (1 ml. alcoholic sludge) were heated at 150°C. under water pump pressure for two hours. After this time the mixture was dissolved in ethanol (95%, 10 ml.), filtered and its optical rotation measured. Evaporation of this solution gave isomannide. The melting point and mixed melting point were taken.

Isomannide (1 g.) in cyclohexane (15 ml.) with Raney nickel
(from 1 ml. alcoholic sludge – alcohol replaced by acetone) was refluxed for four hours. Samples were removed, centrifuged and their optical rotation measured. No change was noted.

**Chemical oxidation.** The following oxidation procedures were used on isomannide (2 g.). No ether soluble material was isolated from any of the reactions –

1. Isomannide in sulphuric acid (20%, 10 ml.) to which was added potassium permanganate (2%, 45 ml.) slowly with cooling.

2. To isomannide in water (4 ml.) with sodium dichromate (5 g.) at 15-20°C. was added concentrated sulphuric acid (13 ml.). The addition of acid was over one hour and stirring was continued for six hours.

3. Reaction (2) was repeated but with 30 ml. water and 50 ml. of 50% sulphuric acid.

4. To isomannide in water (5 ml.) was added sodium hydroxide solution (500 ml., 2%) containing potassium permanganate (10 g.) and barium nitrate (18 g.). The mixture was stirred for six hours at 24°C.

**Action of Alkali on Diiodoisoidide**

Diiodoisoidide (0.4 g.) in ethanol (3 ml.) was refluxed with potassium hydroxide (30%, 0.5 ml.) for two hours. After this time the solution was evaporated to one third its volume, water (3 ml.) was added and the mixture was extracted with ether (2 x 3 ml.). The ether solution was washed with acid and base then dried over sodium sulphate.
The ether solution was stable indefinitely but on evaporation a colourless oil was left which decomposed spontaneously at room temperature. The oil was reasonably stable at -5°C, was soluble in carbon-tetrachloride and insoluble in water.

The decomposition product was black and contained free iodine (extractable by carbon tetrachloride).
APPENDIX I

The Colorimetric Determination of Nitrates

The colorimetric determination of nitrates utilises the trans-nitration reaction which occurs when nitrate esters are treated with concentrated sulphuric acid solutions containing an easily nitrated compound. The reaction presumably proceeds through the ionisation of the nitrate ester, giving nitronium ions which are available for the nitration. The nitronium ion receiver is selected to give a compound which can be easily separated from the reaction mixture - steam distillation (140) or toluene extraction (95) have been used. The compound must have a high extinction coefficient in a suitable part of the spectrum.

Originally phenoldisulphonic acid (149) was used but this has been superceded by the more sensitive xylenol method. 2,4-Xylenol gives a single product on nitration which is steam volatile (140). However a systematic study of all possible xylenols by Holler and Huch (142) indicated that 3,4-xylenol would be more suitable having a higher extinction coefficient, good steam volatility and being easily nitrated. Although this xylenol gives two isomers, 2- and 6-nitroxylenol, these are formed in constant proportions (1:6). The former has low extinction coefficient at the wavelength used and therefore does not interfere in the estimation.

The method is suitable for the estimation of nitrate esters and nitrate ions. Halogen ions are stated to interfere (140) but only at relatively high concentrations. In the present work tests showed that
pyridine caused no variation in the estimation when present in concentrations up to 0.5 ml. for each estimation. However acetone, which was used as a solvent for the xylenol, caused cloudiness in the final solution if more than 0.2 ml. was present. Up to 3 ml. of ether had no such effect and was therefore used to replace the acetone.

80% (v/w) sulphuric acid has been used generally for the trans-nitration reaction, however no systematic tests on the effect of sulphuric acid concentration have been reported. Table (XVI) shows the results of some tests conducted to test this variation. The reaction was rapid but the rate dropped off rapidly at about 70% sulphuric acid. Very high concentrations of acid tended to cause decomposition after a few minutes. It appears that the range of concentration suitable for the estimation is from 70-85%. In general 75-80% sulphuric acid was used.

Tests were conducted to show that the nitroxylenol was not decomposed in the acid solutions resulting from the dilution of the reaction mixture prior to distillation, even on standing at room temperature for eighteen hours (Table XVII). The alkali solution of the distilled nitroxylenol did not deteriorate in a similar time period (Table XVII). The steam distillation was complete after 20 ml. had been collected (Table XVIII).
### TABLE XVI

**The Effect of Sulphuric Acid Concentration on the Formation of Nitroxylenol**

<table>
<thead>
<tr>
<th>Concentration of sulphuric acid (% (w/w))</th>
<th>0.D. readings of nitroxylenol after distillation</th>
<th>Reaction time at room temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 sec.</td>
<td>45 sec.</td>
</tr>
<tr>
<td>94</td>
<td>0.92</td>
<td>0.90</td>
</tr>
<tr>
<td>89</td>
<td>0.92</td>
<td>0.91</td>
</tr>
<tr>
<td>85</td>
<td>0.86</td>
<td>0.90</td>
</tr>
<tr>
<td>77</td>
<td>0.85</td>
<td>0.91</td>
</tr>
<tr>
<td>70</td>
<td>0.130</td>
<td>0.210</td>
</tr>
<tr>
<td>60</td>
<td>0.005</td>
<td>0.010</td>
</tr>
</tbody>
</table>

These results were obtained using isomannide dinitrate. When isoidide dinitrate was used the results were identical to within + 0.01 O.D. units.

### TABLE XVII

**The Deterioration of Nitroxylenol Solutions**

<table>
<thead>
<tr>
<th>Time of standing</th>
<th>In the diluted reaction mixture (acid) 0.D. (after distillation)</th>
<th>In the distillate (alkali) 0.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample 1</td>
<td>Sample 2</td>
</tr>
<tr>
<td>0</td>
<td>0.660</td>
<td>0.670</td>
</tr>
<tr>
<td>30 min.</td>
<td>0.665</td>
<td>0.670</td>
</tr>
<tr>
<td>60 min.</td>
<td>0.660</td>
<td>0.665</td>
</tr>
<tr>
<td>18 hours</td>
<td>0.660</td>
<td>0.660</td>
</tr>
<tr>
<td>Fraction</td>
<td>100 g. N sample</td>
<td>50 g. N sample</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>0-5 ml.</td>
<td>62</td>
<td>57</td>
</tr>
<tr>
<td>5-10 ml.</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>10-15 ml.</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>15-20 ml.</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>20-25 ml.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>99</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
APPENDIX II

Paper Chromatography

By far the majority of solvent systems used for paper chromatography are only suitable for substances which are more or less hydrophilic in character. This is consequential on the use of filter paper for chromatography. The process of chromatography involves the partition of compounds between the stationary phase, cellulose with its absorbed water, and the moving phase, an organic solvent or mixture of solvents containing water in some proportion. The materials being chromatographed must be soluble, to some extent, in both phases or they will either not be moved off the starting line or will be taken with the solvent front. Thus only relatively hydrophilic substances will chromatograph successfully in the majority of solvent systems.

For a solvent system to be useful it should give $R_f$ values (the ratio of the distances travelled by the solvent front to that which the compound travels) which are in the range 0.1 to 0.9 for the materials being used. The lower limit of this range can be extended somewhat by allowing the solvent to flow off the paper, i.e. letting the solvent front flow much further than normal.

Compounds containing free hydroxyl, amino or carboxyl groups are usually chromatographable in some solvent systems, however non-polar substances generally are not. There have been many attempts to increase the range of compounds to which paper chromatography can be applied. These can be divided into two groups - one where filter paper is used as a base and the other where various other materials are used. The
latter method has only been used recently and there is not very much information yet available. Any fibrous material which can be made into a paper-like sheet can be used provided it has sufficient strength, especially when wet. Among the materials used are asbestos, glass, nylon and several other synthetic fibres. None of these have come into wide usage as yet.

The other approach to the problem is to retain the use of filter paper as a base but in some way reduce its hydrophilic nature. One way in which this can be done is to partially acetylate it. This can be done without breaking down the basic fibres and so the strength of the paper is not lost (150), but it is difficult to obtain even results. Impregnation of the paper with alumina (151) or paraffin (152) has been fairly successful. In the latter case an aqueous solvent is used for irrigation and the system has been called "reverse phase" chromatography as the more hydrophilic phase is the mobile one whereas in ordinary chromatography the more hydrophilic phase is the stationary one.

Finally several solvent systems containing methanol have been reported for use with hydrophobic substances. Rice, Keller and Kirchener (153) first used this type of system to chromatograph 3,5-dinitrobenzoates of alcohols - the solvent system used was 2% methanol in low boiling petroleum ether. Meigh (154) followed up their work but used n-heptane saturated with methanol as an irrigating solvent. Bush (151) working with steroid compounds also reported the use of methanol containing solvents - this work seems to be independent of other reports. In all these methods the paper, after spotting with
the materials to be chromatographed, was hung in the chromatography
tank containing the solvent system in dishes at the bottom and was
allowed to equilibrate for periods from four to eighteen hours before
solvent was added to the top trough and irrigation commenced. It
would appear that the methanol becomes incorporated in the stationary
phase in some way, either displacing the water in the cellulose to
some extent or simply combining with it, thus reducing the hydrophilic
nature of this phase.

The nitrate esters of sugars or sugar alcohols have never been
chromatographed successfully on paper. However the solvent system
of Meigh (petroleum ether/methanol) (154) was found to be very satis-
factor for a number of these derivatives. In particular the isohexide
dinitrates ran well and separated sufficiently to give easy identifi-
cation. Hexane saturated with methanol was used most frequently but
it was shown (Table XIX) that the hydrocarbon used does not have very
much effect on the Rf values so that normal medium boiling petroleum
ether (60-110°C. b.p. range ) could be used more economically.

In this work the chromatographs were always irrigated by the
descending method. Kitchen (155) carried out a study of the chroma-
tographic system using ascending chromatography. He has also deter-
mined conditions which give Rf values which were appreciably more
constant than those normally obtained here. For the purposes of this
work it was sufficient to be able to identify compounds by running
known material along parallel lanes. The Rf values were constant for
the same paper but varied from paper to paper.

The solvent systems of Bush (151) contained methanol and water,
in varying proportions together, with benzene, toluene and petroleum ether either alone or as mixtures. From the reported Rf values of various steroids (151) it was noted that the Rf values increased with an increase in the proportion of water compared to methanol in the solvent system. A series of chromatographs of the isohexide dinitrates were run in solvent systems containing petroleum ether, methanol and water. The ratio of methanol to water was varied but their total volume compared to that of the petroleum ether was kept constant. Table XX shows the variation in Rf obtained. A further series of chromatographs were run in which the methanol/water ratio was kept constant but varying amounts of benzene were added to the petroleum ether (Table XXI).

The above results show that with increasing water content of the solvent system the Rf values are increased. This is to be expected as solvent systems containing water but no methanol give very high Rf values for nitrate esters. The effect of benzene is also to increase the Rf values.

The effect of the addition of water was probably to decrease the solubility of the nitrate in the stationary phase while that of benzene would be to increase their solubility in the moving phase. It is to be expected therefore that the capacity of the former system will be reduced and that of the latter will be increased with respect to the methanol/petroleum ether system. It would seem that the latter systems would be the more desirable due to their higher capacity. It was noted however that the presence of one or two parts of water in ten of methanol greatly decreased the solubility of the
methanolic phase in the hydrocarbon phase. This made the solvents more easily handled, the methanol in these systems did not separate out from the hydrocarbon phase as readily as in the case where no water was added.

The ditosylate derivatives of the isohexides have zero or very low Rf values in the petroleum ether/methanol systems as these derivatives are practically insoluble in petroleum ether. However they are readily soluble in benzene and were found to run quite well in solvent systems containing this solvent. Their Rf values showed similar variations with change of solvent system to those of the dinitrate esters (Table XXI).

From the results the solvent systems D and E are recommended for the isohexide dinitrates and H for the isohexide ditosylates. It can be seen that the systems can be varied readily to suit the particular compounds or derivatives being used.

The tosylate derivatives were detected on the paper chromatographs by spraying these with diphenylamine in ethanol (1% solution), allowing to dry and then exposing to ultraviolet light for five minutes. The tosylates then showed up as strongly fluorescent spots when the chromatographs were viewed under the ultraviolet light.
Solvent Systems

A  n-hexane (10 vol.), methanol (4 vol.)
B  n-heptane (10 vol.), methanol (10 vol.)
C  n-octane (10 vol.), methanol (10 vol.)
D  petroleum ether (20 vol.), methanol (9 vol.), water (1 vol.)
E  petroleum ether (20 vol.), methanol (8 vol.), water (2 vol.)
F  petroleum ether (20 vol.), methanol (7 vol.), water (3 vol.)
G  petroleum ether (18 vol.), benzene (2 vol.), methanol (8 vol.), water (2 vol.)
H  petroleum ether (16 vol.), benzene (4 vol.), methanol (8 vol.), water (2 vol.)
I  petroleum ether (16 vol.), benzene (4 vol.), methanol (9 vol.), water (1 vol.)

TABLE XIX

Rf Values in Petroleum Ether/Methanol Solvent Systems
(Average of four or more chromatographs)

<table>
<thead>
<tr>
<th>Solvent A</th>
<th>Solvent B</th>
<th>Solvent C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ascending (155) (+0.01)</td>
<td>descending (+0.02)</td>
<td>descending (+0.02)</td>
</tr>
<tr>
<td>Isomannide dinitrate</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>0.19</td>
<td>0.175</td>
</tr>
<tr>
<td>Isoidide dinitrate</td>
<td>0.355</td>
<td>0.31</td>
</tr>
</tbody>
</table>
TABLE XX

Rf Values in Petroleum Ether/Methanol/Water Solvent Systems

(Average of three or more chromatographs)

<table>
<thead>
<tr>
<th></th>
<th>Solvent A</th>
<th>Solvent D</th>
<th>Solvent E</th>
<th>Solvent F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isomannide</td>
<td>0.20</td>
<td>0.18</td>
<td>0.25</td>
<td>0.50</td>
</tr>
<tr>
<td>dinitrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide</td>
<td>0.26</td>
<td>0.26</td>
<td>0.34</td>
<td>0.59</td>
</tr>
<tr>
<td>dinitrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoidide</td>
<td>0.42</td>
<td>0.43</td>
<td>0.54</td>
<td>0.72</td>
</tr>
<tr>
<td>dinitrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE XXI

Rf Values in Petroleum Ether/Benzene/Methanol/Water Solvent Systems

<table>
<thead>
<tr>
<th></th>
<th>Dinitrates</th>
<th>Ditosylates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G</td>
<td>H</td>
</tr>
<tr>
<td>Isomannide</td>
<td>0.34</td>
<td>0.49</td>
</tr>
<tr>
<td>Isosorbide</td>
<td>0.45</td>
<td>0.57</td>
</tr>
<tr>
<td>Isoidide</td>
<td>0.60</td>
<td>0.68</td>
</tr>
</tbody>
</table>
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