SYNTHETIC ROUTES TO HYDROXYALKANEBORONIC ACIDS AND THEIR DERIVATIVES.

by

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ABSTRACT

A study of synthetic routes leading to hydroxyalkaneboronic acids, which were expected to display some useful and interesting biological and chemical properties, has been carried out with reference to reaction sequences involving the hydroboration of alkenes and interaction of Grignard reagents with borate esters.

Hydroboration followed by redistribution with trimethylene borate was carried out on the O-tetrahydropyranyl ethers of prop-2-en-1-ol, pent-4-en-1-ol, pent-4-en-2-ol, but-3-en-2-ol and pent-1-en-3-ol but in most cases a complex product mixture was obtained. However, 2-(3-[2'-tetrahydropyranyloxy]propyl)-1,3,2--dioxaborinane was identified as the major component in the product mixture from 1-(2'-tetrahydropyranyloxy)-prop-2-ene. Evidence was obtained to show that these complex mixtures arose from interaction between trimethylene borate and the tetrahydropyranyloxy functionality. Some mechanistic rationalisation is proposed.

Hydroboration followed by equilibration and hydrolysis to a boronic acid was more successful and thus 5-hydroxypentaneboronic acid was prepared from 1-(2'-tetrahydropyranyloxy)-pent-4-ene, 3-hydroxy-butaneboronic anhydride from 2-(2'-tetrahydropyranyloxy)-but-3-ene, and 3-benzyloxypropaneboronic acid from allyl benzyl ether, although the yields were low. Hydroboration followed by esterification with methanol was carried out on 1-(2'-tetrahydropyranyloxy)-pent-4-ene and dimethyl-1-(5-[2'-tetrahydropyranyloxy])-pentaneboronate was isolated.

The use of Grignard reagents with borate esters as a route to hydroxyalkaneboronic acids was less successful and no such compounds

could be isolated by this preparative method. 1-Hexaneboronic acid and several of its ester derivatives were successfully prepared to check this synthetic route, and samples of 1-hexaneboronic acid were used to investigate the oxidative and hydrolytic stabilities of a typical alkaneboronic acid. The results showed that it was stable under normal storage conditions.

Before proceeding to the study of boronic acid syntheses involving the use of monosaccharide derivatives, a model system, 1,2-O-cyclohexylidene glycerol, was selected for the introduction of an unsaturated site using organocopper reagents. Thus, 1,2-O-cyclohexylidene-3--deoxy-3-vinyl glycerol was shown to be formed by the action of divinylcopper lithium on 1,2-O-cyclohexylidene-3-deoxy-3-iodo glycerol albeit in low yield and its separation and purification could not be effected.

A carbon chain extension process using 1,2-O-cyclohexylidene-3--deoxy-3-iodo glycerol was considered but an easier route to 1,2-O-cyclohexylidene-4-bromobutane-1,2-diol was devised starting from 4-bromobut-1-ene. Attempted boronic acid synthesis *via* a Grignard derivative of this compound was unsuccessful.

Three typical unsaturated monosaccharides namely, 3,4,6,-tri-O-acetyl-D-glucal, 6-deoxy-1,2:3,4-di-O-isopropylidene-β-L--*arabino*-hex-5-enopyranose and 1,2:5,6-di-O-cyclohexylidene-3-deoxy--α-D-*erythro*-hex-3-enofuranose were synthesised and subjected to hydroboration-redistribution processes. Product mixtures were obtained, which were not considered in these cases to arise from interaction of protecting groups with trimethylene borate, and these mixtures were found to contain carbohydrate dioxaborinanes. The major product from

the starting material 3,4,6-tri-O-acetyl-D-glucal was separated, purified, and characterised as a boron-containing monosaccharide.

INTRODUCTION

Organoboron compounds have recently been found to have many interesting physiological properties and industrial uses. Boronic acids (i.e. $R.B(OH)_2$, where R is alkyl or aryl) in particular have been found useful for the control of slime organisms and bacteria in the paper, paint, leather and polymer industries[1] and as chemisterilants for houseflies[2,3]; their anhydrides and esters are added to oils as sludge inhibitors[1]. Benzeneboronic acid has a pronounced reinforcing effect on antiepileptics[4], analgesics[5], and hypnotics[6,7]; it also exhibits a root growth promoting effect[8]. 2-Hydroxybenzeneboronic acid has been shown to be bacteriostatic[8], and 3-amino-4-carboxybenzeneboronic acid mixed with glucose has an appreciable effect on anticoagulant activity[8]. The action of pentaerythritol-di-(p-methylbenzeneboronate) on the cardiovascular system has been studied and a vasodilation effect and inhibition of certain hypertensive agents was observed[9].

One of the most interesting biological applications of boron compounds is their potential use in neutron capture therapy of brain tumors[10] arising from the unique nuclear property of the non-radioactive ^{10}B isotope to absorb thermal neutrons. These two distinct moieties, each innocuous by itself, are capable of destroying cells by their nuclear interaction which releases high energy α-particles:

$$^{10}_{5}B + {}^{1}_{0}n \longrightarrow {}^{7}_{3}Li + {}^{4}_{2}He + \sim 2.4\ Mev$$

A high tumour $[^{10}B]$ to normal tissue $[^{10}B]$ ratio is therefore required for selective tumour destruction. Because of a distinct permeability difference in the brain between neoplasm and normal tissue[11], the

effect of ^{10}B on brain tumours has been studied in detail. However clinical trials carried out using compounds such as 4-carboxybenzene-boronic acid[12,13] have failed due to simultaneous incidence of high blood concentrations of boron with consequent radiation damage to the blood vessels by α-particles generated <u>in situ</u>[14]. A possible solution to this problem and to the notable toxicity of boron compounds, could arise by the use of boron-containing compounds which bind specifically to the neoplasm and are not therefore concentrated in the blood. Such compounds would have to be structurally similar to metabolites present in natural tissue and a range of such compounds containing boron atoms has been prepared and investigated; for example pyrimidines and amino acids containing boronic acid moieties[8] and a copoly (DL-alanyl-DL-4-boronophenylalanyl) bovine γ-globulin[15] containing 36 boron atoms per molecule. However these compounds were found not to be selectively incorporated into tumour tissue and little further work appears to have been published on this aspect of the biological uses of boron-containing compounds.

A severe limitation to the biological uses of areneboronic acids is the ease with which <u>in vivo</u> hydrolytic and oxidative cleavage occurs[16], as exemplified by the following equations.

$$Ar\ B(OH)_2 + H_2O \longrightarrow ArH + B(OH)_3$$

$$Ar\ B(OH)_2 + H_2O + \tfrac{1}{2}O_2 \longrightarrow ArOH + B(OH)_3$$

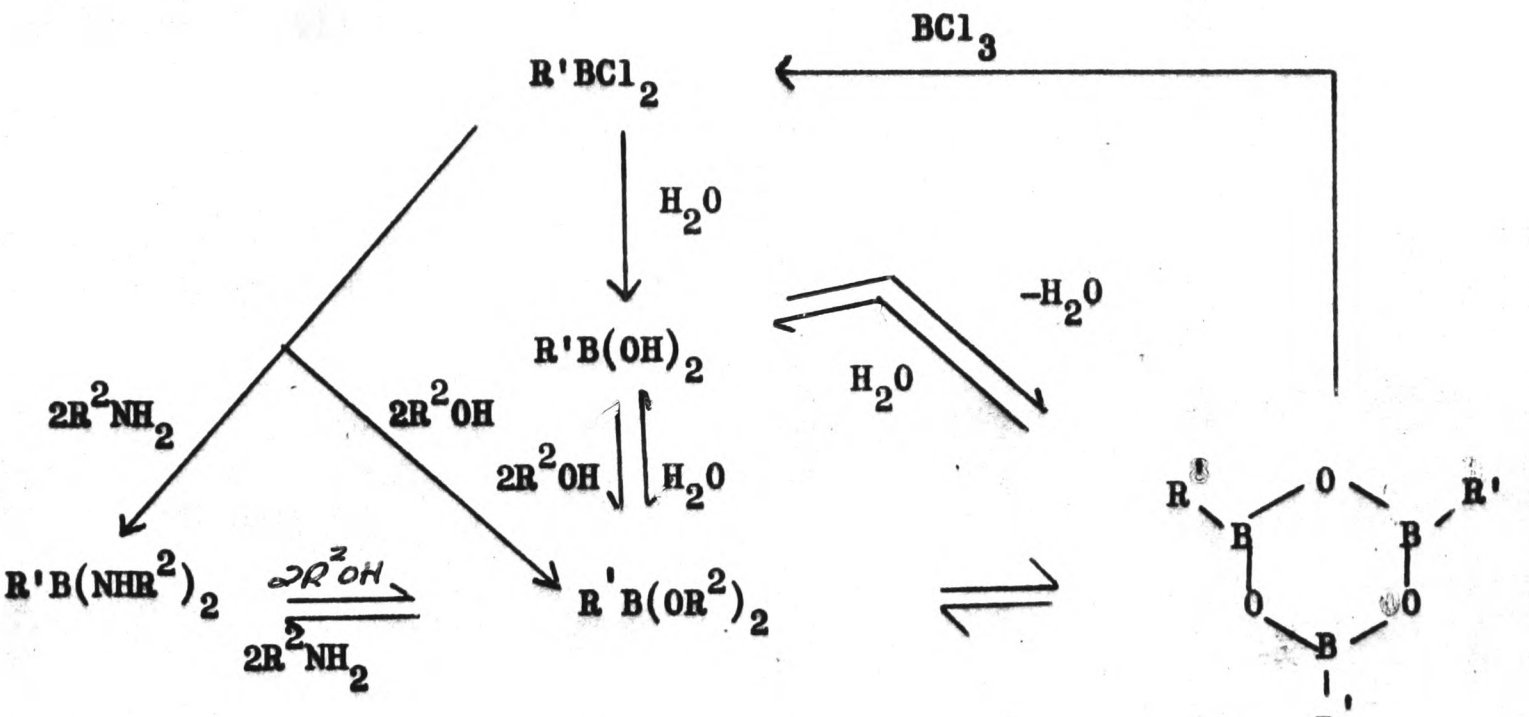
These decomposition routes are not as facile in the case of the alkane-boronic acids although in the dry state[17] and in solution[18] a ready autoxidation has been observed in air.

In recent years some attention has been directed towards the exploration of synthetic routes leading to simple alkaneboronic acids. The study of such routes for the preparation of boronic acids in which additional functionality is present in the alkyl residue has been more restricted. For example, although boron-containing compounds derived from polyhydroxyl compounds have been widely studied, these are the boronate esters (i.e. $R^1B(OR^2)(OR^3)$) and not compounds in which a carbon-boron bond has been formed. These boronate esters of polyhydroxy compounds have been exploited in the carbohydrate field as protecting groups[19], for studies of the conformations which may be adopted by the ring systems[20-23], and for the preparation of volatile derivatives suitable for g.l.c. analysis[24].

A few examples of simple hydroxyalkaneboronic esters and hydroxyareneboronic acids have been reported and it was the purpose of the work described in this thesis to extend these examples and, in particular, to examine the possibility of preparing carbohydrate boronic acid derivatives with the boron directly attached to a carbon atom in the carbohydrate molecule.

(A) PROPERTIES OF ALKANEBORONIC ACIDS AND ARENEBORONIC ACIDS.

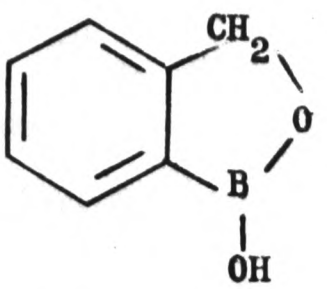
Boronic acids are very weak organic acids but they react to give derivatives analogous to those of carboxylic acids[25]. (Scheme 1, R^1, R^2 -alkyl or aryl).



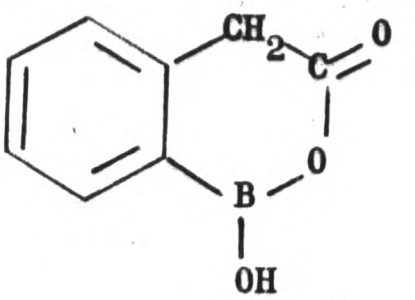
(I)

Scheme 1

In the case of the areneboronic acids, cyclic anhydride formation to give a trimeric anhydride (e.g. I, R^1 = aryl group) proceeds particularly readily[26]. Anhydride formation with alkaneboronic acids has been reported[17] but the process is not as facile. The presence of an appropriately situated hydroxyl group in an areneboronic acid may lead to ready lactone formation, e.g., 2-hydroxymethylbenzeneboronic acid exists entirely in the lactone form (II)[27], and 2-boronophenylacetic acid in the lactone form (III)[28].



(II)



(III)

(B) THE SYNTHESIS OF BORONIC ACIDS.

The known routes to the synthesis of boronic acids may be classified in two general categories, namely, (1) synthetic methods using organometallic reagents with simple borate esters, and (2) synthetic routes employing hydroboration of alkenes.

(1) Synthetic methods using organometallic reagents with simple borate esters.

Although boronic acids were first synthesised by Frankland in 1859 by the partial oxidation of trialkylboranes[29] (equations (1a) and (1b)), and they have also been prepared by the action of metal alkyls or aryls on boron halides[30] (equation (2)), the most frequently used method for the synthesis of boronic acids has been by the interaction of Grignard reagents (alkylmagnesium halides) or alkyllithium reagents with borate esters (equation (3)).

$$3ZnR'_2 + 2B(OR^2)_3 \longrightarrow 2BR'_3 + 3Zn(OR^2)_2 \qquad (1a)$$

$$BR'_3 + O_2 \longrightarrow R'B(OR')_2 \xrightarrow{2H_2O} R'B(OH)_2 + 2R'OH \qquad (1b)$$

$$MR + BX_3 \longrightarrow RBX_2 + MX \xrightarrow{2H_2O} R\,B(OH)_2 + 2HX \qquad (2)$$

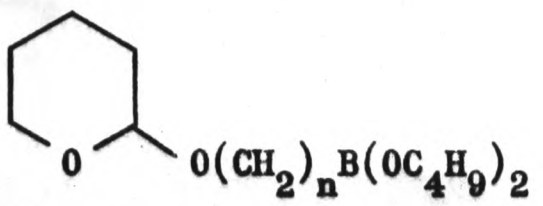
(X = F, Cl, Br; M = metal)

$$R^1MgX + B(OR^2)_3 \longrightarrow [R^1B(OR^2)_3]MgX \xrightarrow{H_3O^+} R'B(OH)_2 + R^2OH + Mg(OH)Br \qquad (3)$$

(X = Br, I.)

For example, a series of simple alkaneboronic acids (butane-, pentane-,

hexane-, tetradecane) was prepared in this way[17], as were the protected α,ω-hydroxyalkaneboronate esters[31] (IV).

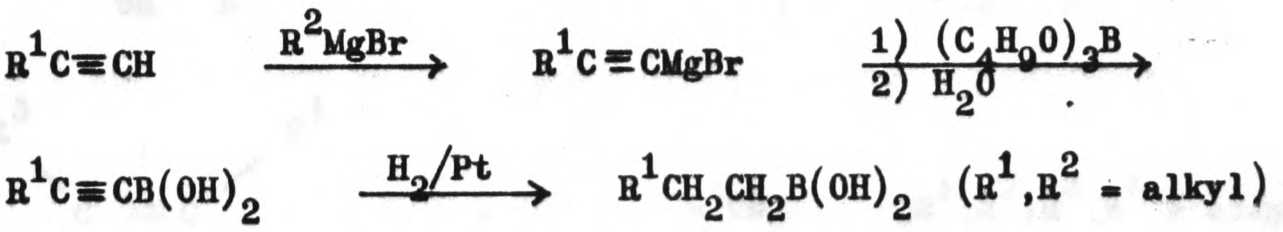


$(n = 4,5,6)$

(IV)

In the aromatic series, benzeneboronic acid[32], the three isomeric tolueneboronic acids[32] and the three isomeric hydroxybenzeneboronic acids[26] have been prepared by the Grignard route; also the 2- and 3-furanboronic acids have been prepared using the appropriate organolithium reagents[33].

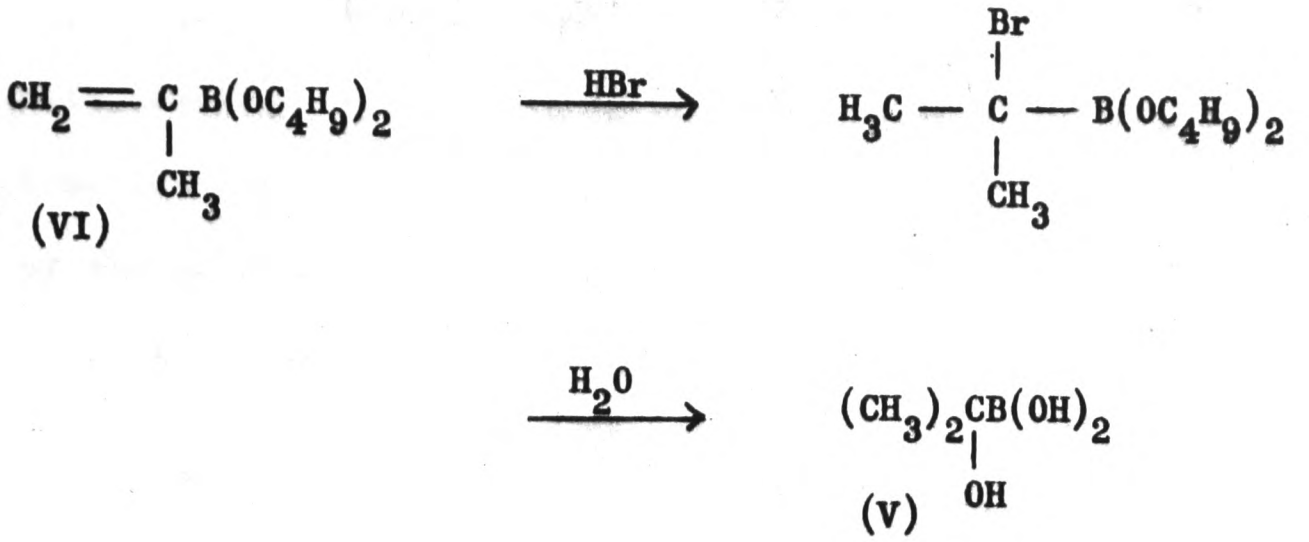
The ready formation of an alkynylmagnesium halide from a terminal alkyne has resulted in the development of a further route to alkane-boronic acids <u>via</u> the corresponding alkynylboronic acid[34] (Scheme 2).



Scheme 2

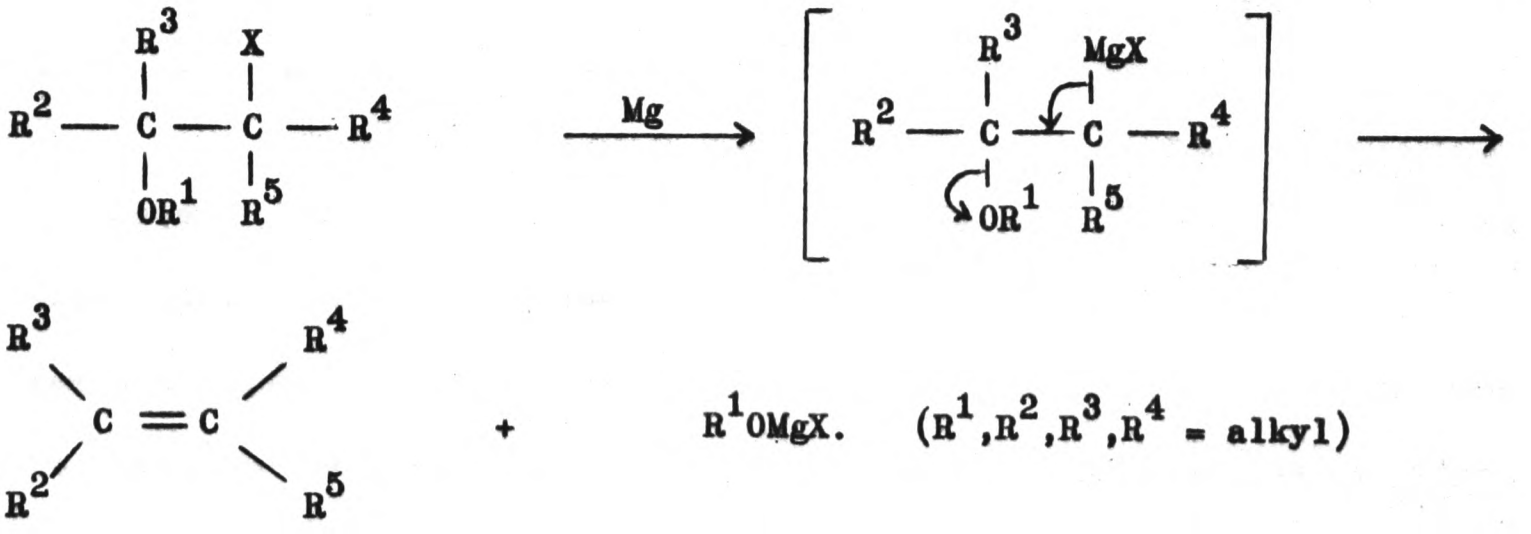
The preparation of boronic acids from organo- sodium, aluminium, tin, zinc, cadmium, and mercury compounds has also been reported[35].

Clearly the presence of reactive neighbouring groups is incompatible with the use of these organometallic reagents and hence 2-hydroxy--propane-2-boronic acid (V) was prepared by hydrobromination of dibutyl-2-propeneboronate (VI) followed by hydrolysis[36].



(VI) (V)

A serious limitation in the application of this general route to compounds in the monosaccharide series is that Grignard reagents cannot be prepared from β - alkoxyhaloalkanes[37]. Attempts to prepare such reagents lead to facile β - elimination processes and the corresponding alkenes are isolated (Scheme 3).



Scheme 3

(2) Synthetic routes employing the hydroboration* of alkenes.

The synthesis of alkaneboronic acids may be achieved via the hydroboration of alkenes[38]. The hydroboration step involves rapid, quantitative addition of diborane to the carbon-carbon double bond to

*The term "Hydroboration" is used in this thesis to denote the addition of diborane or an alkyl-substituted diborane to a carbon-carbon double bond to form a trialkylborane.

form a trialkylborane (<u>i.e.</u>, R_3B). Oxidation of this trialkylborane with alkaline hydrogen peroxide causes cleavage of the carbon-boron bond resulting in formation of the corresponding alcohol; the orientation of the addition step (<u>anti</u>-Markovnikov) is that which is predicted by current mechanistic theory, <u>i.e.</u>,

$$3\ RCH{=}CH_2 \quad + \quad BH_3 \longrightarrow (RCH_2CH_2)_3B$$

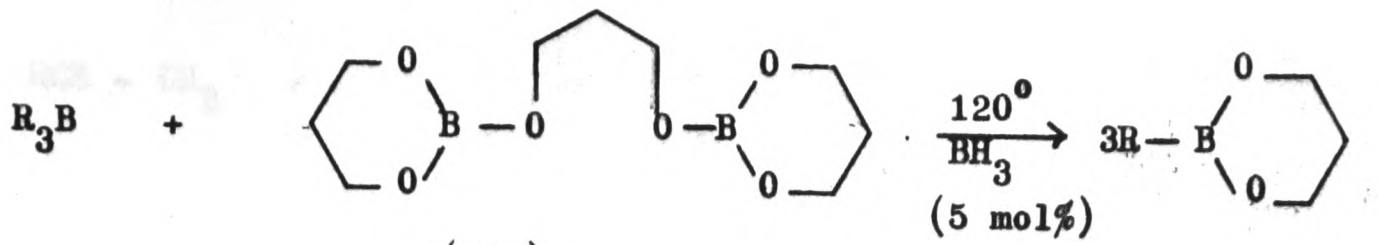
$$(RCH_2CH_2)_3B \quad + \quad H_2O_2 \xrightarrow{OH^{\ominus}} 3RCH_2CH_2OH$$

Conversion of the trialkylborane into a boronic acid is carried out by an equilibration reaction with excess diborane at 50^{o} for six hours to yield predominantly a monoalkylborane (<u>i.e.</u>, RBH_2) which on treatment with an alcohol yields the boronic ester[39].

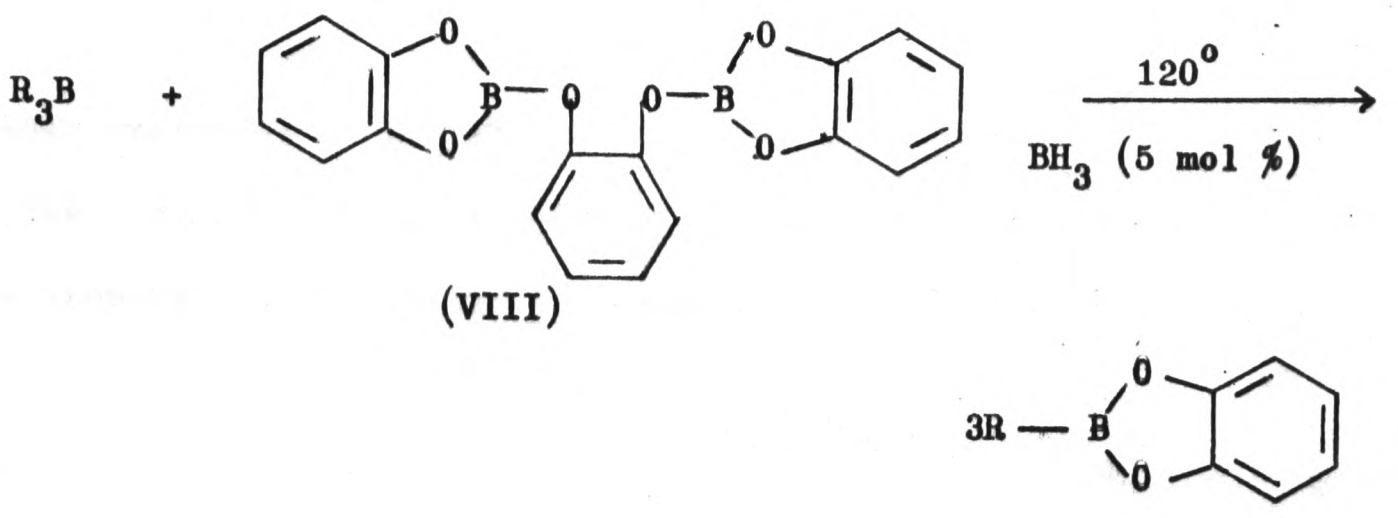
$$R'_3B \quad + \quad 2BH_3 \rightleftharpoons 3R'BH_2 \xrightarrow{2R^2OH} 3R'B(OR^2)_2$$

However, the result of this equilibration is a mixture of products, the composition of which depends on the concentration of diborane, the reaction time, and the temperature. Careful control of these parameters is therefore necessary to achieve optimum yields (<u>e.g.</u> 44–73%) of the boronic ester.

More recently, and with greater success, a redistribution reaction has been effected by heating the trialkylborane with a borate ester such as trimethylene borate[40] (VII) or <u>o</u>-phenylene borate[41](VIII). The reported yields of boronic ester products were typically 80–90%.

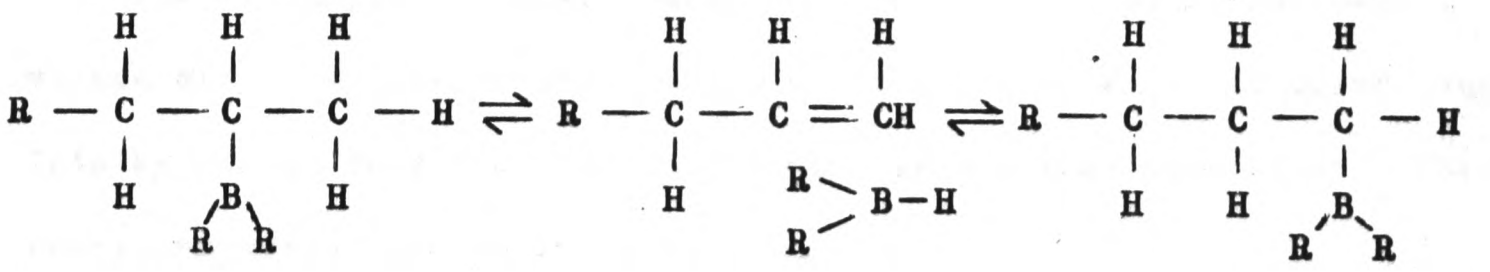


(VII)

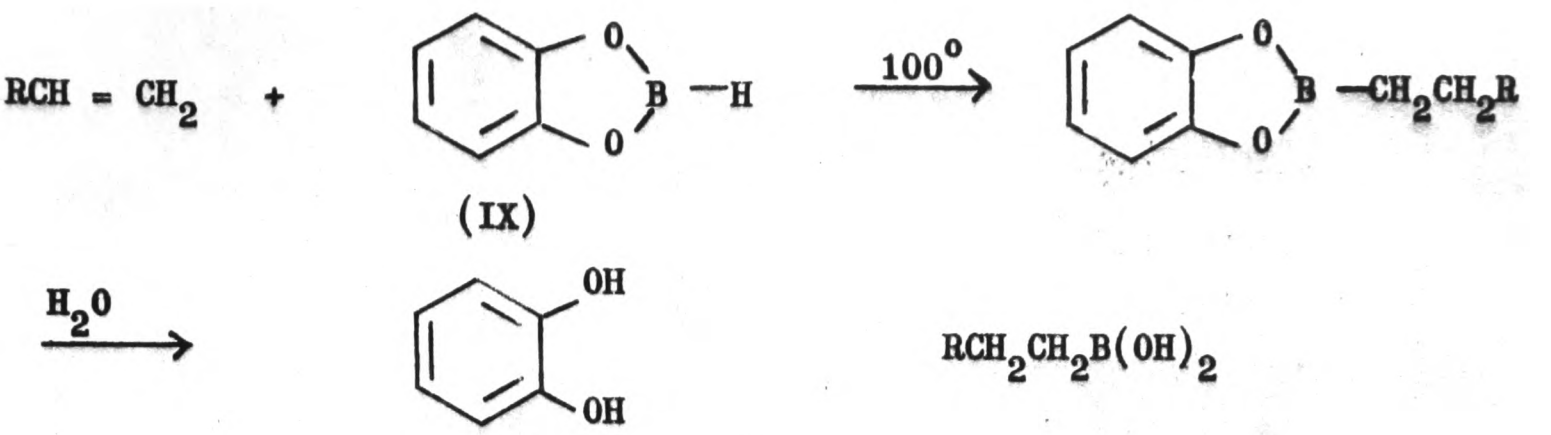


(VIII)

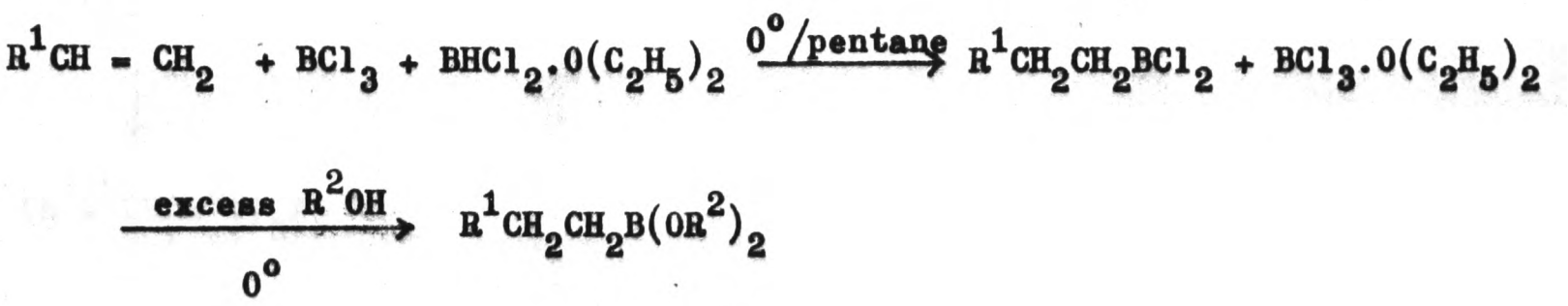
It must be borne in mind, however, that at elevated temperatures secondary organoboranes are isomerised to primary organoboranes and this process is enhanced by the presence of excess diborane[42].



The more general application of this method may not, therefore, be successful. In place of diborane, 1,3,2-benzodioxaborole (IX) has been used as a hydroboration reagent for both alkenes[41] and alkynes[43]. It is advantageous in that it produces a boronic ester directly.

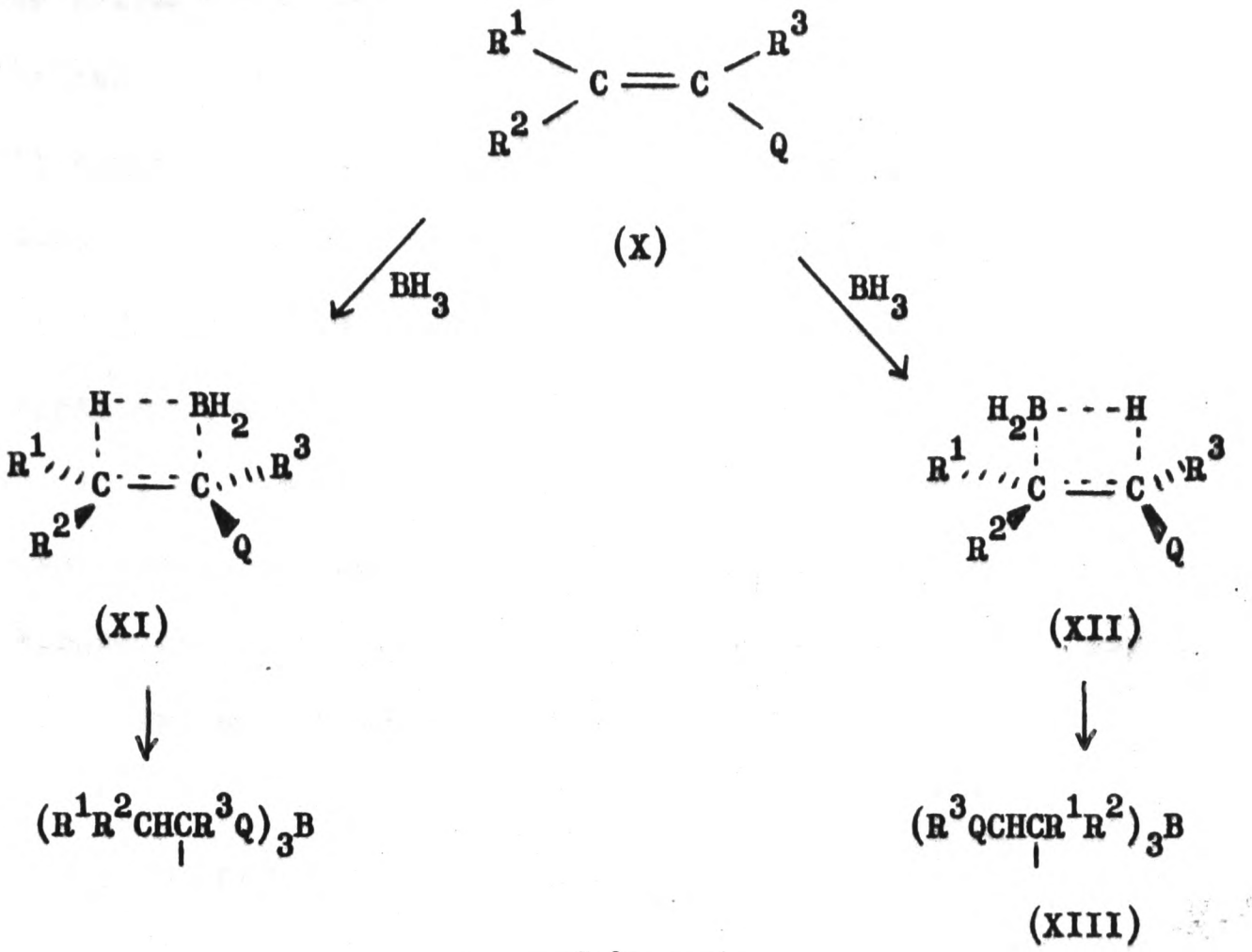


Another variation on the hydroboration theme which has been utilised for the preparation of alkaneboronic esters involves the addition of dichloroborane to an alkene followed by alcoholysis[44].



In the case of polyfunctional systems containing a carbon-carbon double bond, the hydroboration reaction is not as straightforward as in the case of simple alkenes. Substituents near the double bond have a marked effect on the orientation of addition, and as a consequence the trialkylborane intermediate can undergo various side reactions. These reactions are discussed in detail below.

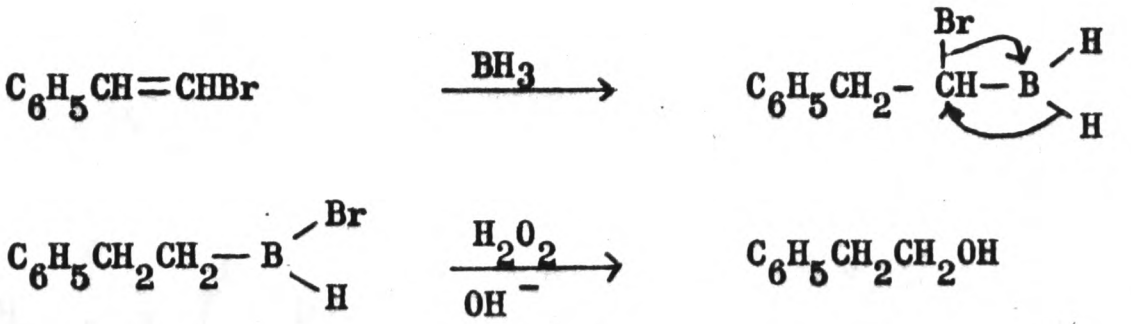
(a) Vinylic systems. The mechanism of hydroboration involves a concerted cis addition of $>B^{\delta\oplus}-H^{\delta\ominus}$ across a carbon-carbon double bond and proceeds via a four-centred transition state. Two such transition states are possible for the reaction of diborane with a vinylic structure (e.g., (X), where Q is a functional group), and therefore a mixture of isomeric products may occur[45] (Scheme 4).



Scheme 4

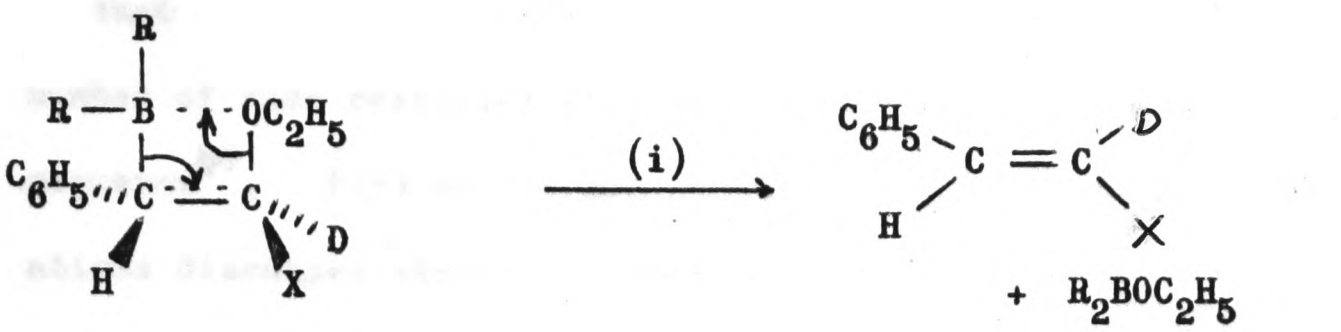
Transition state (XI) is favoured if Q is electron withdrawing (e.g., -Cl) whereas an electron donating substituent (e.g., -OH) favours transition state (XII). An ether substituent (Q= -OR) is reported to exhibit the most marked directive influence due to the mesomeric effect of the oxygen atom[46] resulting in 100% formation of the isomer where boron is attached to the β-carbon atom (XIII). The chlorine substituent in vinyl chloride and the acetoxy substituent (Q= $-OCOCH_3$) in vinyl acetate both direct the boron moiety to the ∝-position. However, in some vinylic compounds which also contain an alkyl substituent (e.g., but-2-en-1-ol) an almost equal mixture of isomers occurs because of the competing influences of the substituents. It is clear that the nature of the products obtained by hydroboration of vinylic compounds is governed by

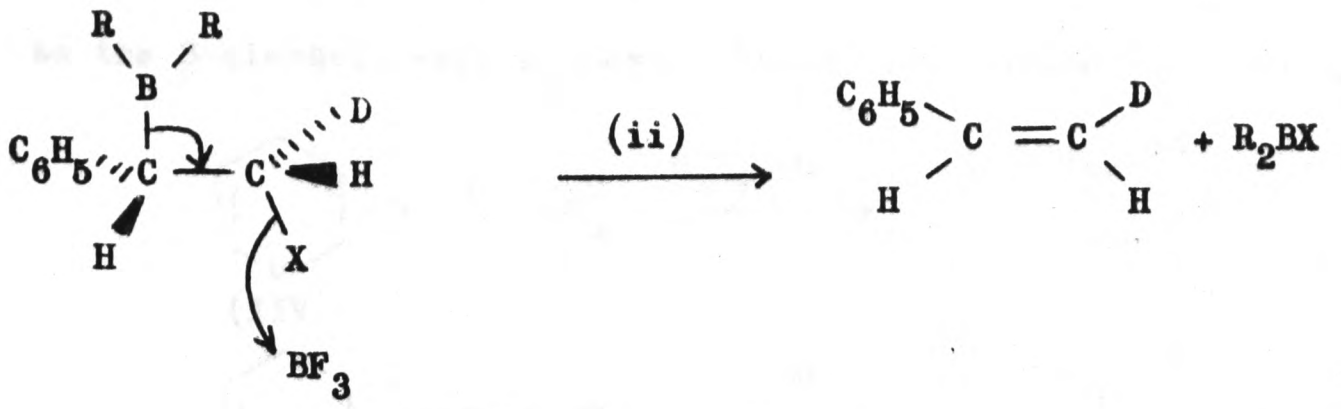
the electronic characteristics of the substituent and that inductive or mesomeric effects may be involved. The situation is further complicated by the ability of the β-trialkylboranes (e.g., XIII) to undergo elimination and subsequent rehydroboration of the resultant alkenes. In addition both α- and β-monoalkylboranes may undergo replacement of a substituent by hydrogen. For example, hydroboration followed by oxidation of trans-β-bromostyrene at 25° was found to give 2-phenylethanol in 79% yield[47] and this was explained by an "α-transfer" process (i.e., the replacement of one of the hydrogen atoms attached to boron in a monoalkylborane by another functional group where the two are geminal) having the following mechanism:

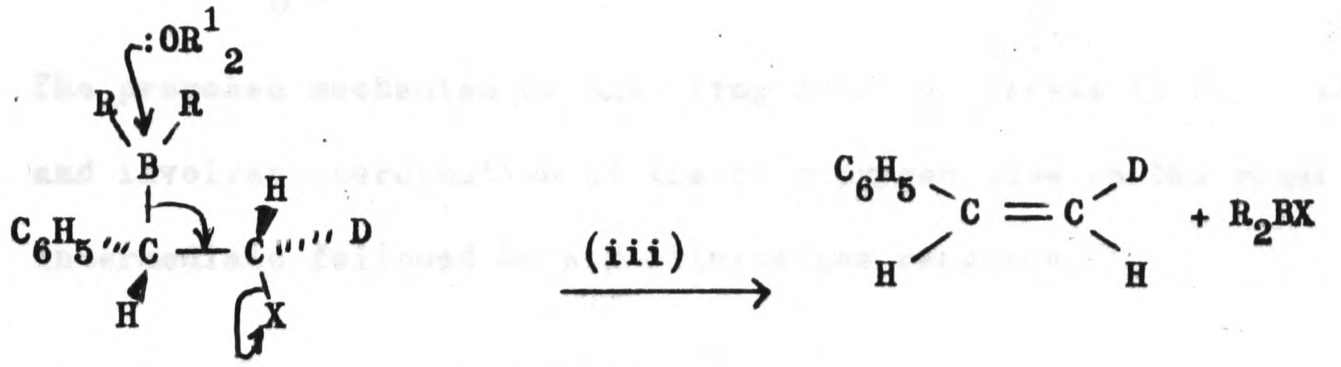


Similarly the intermediate β-trialkylborane formed from the hydroboration of trans-β-ethoxystyrene was shown to undergo competitive transfer and elimination reactions[48]. However, other workers[46] have reported the formation of 2-ethoxy-1-phenylethanol from trans-β-ethoxystyrene in 95% yield and trans-2-ethoxycyclohexanol from 1-ethoxycyclohexene in 97% yield.

Three alternative mechanisms have been proposed for the β-elimination reaction according to whether it is uncatalysed, base or acid catalysed[49], and these mechanisms are shown below.



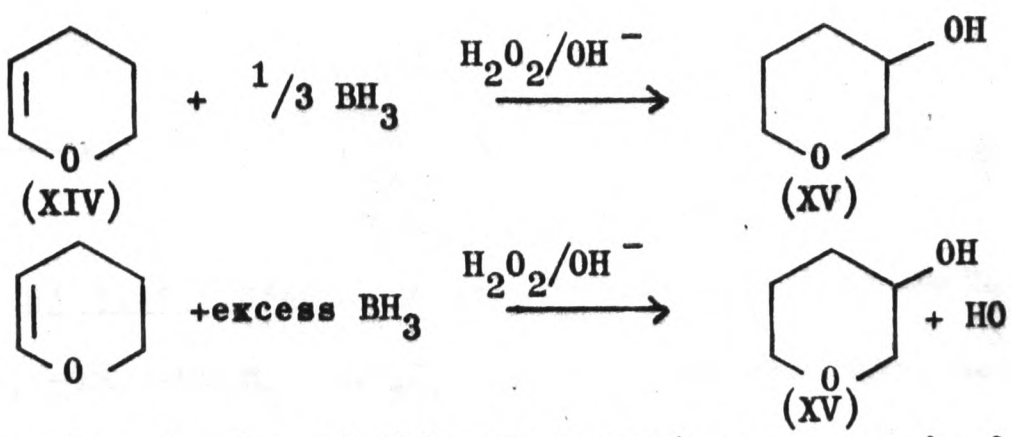




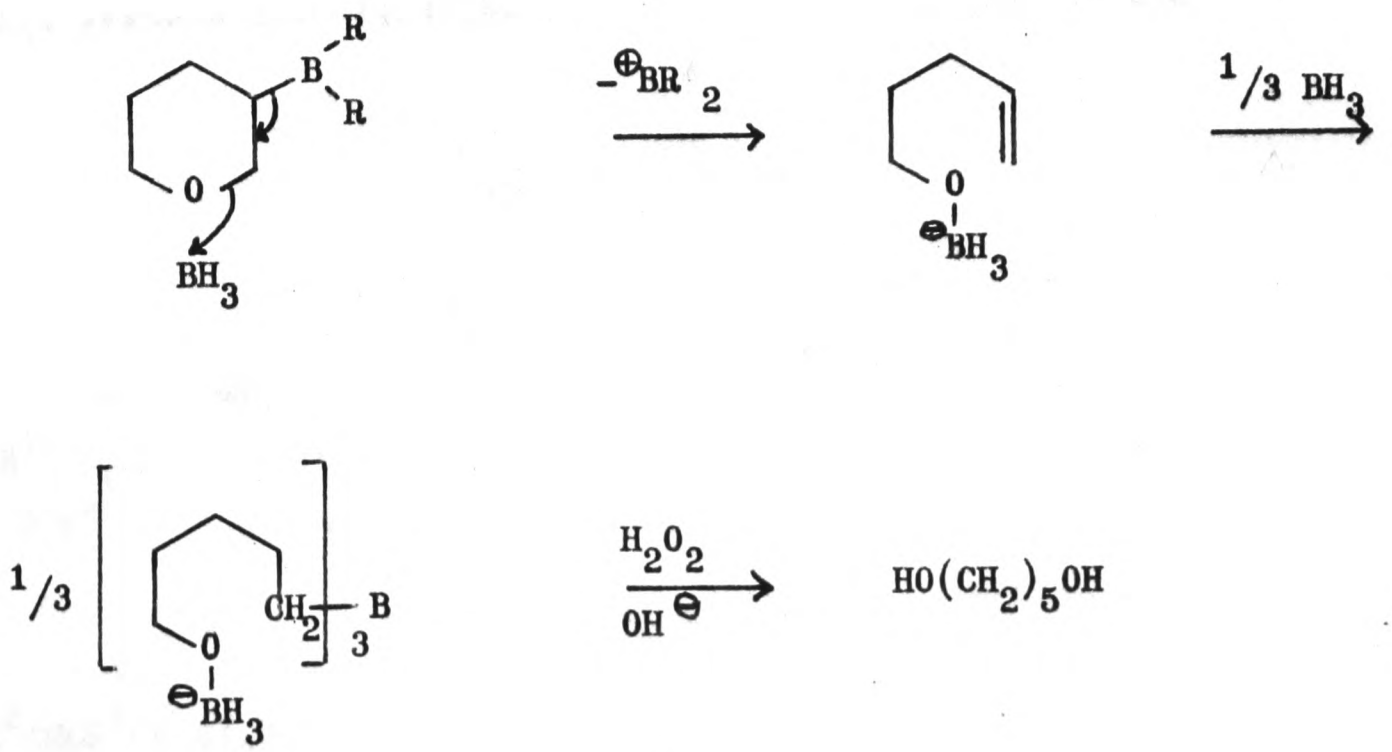
(R = alkyl residue)

(i), the uncatalysed reaction, may occur spontaneously by simultaneous bond breaking and formation and is very temperature dependent, being more facile at higher reaction temperatures. (ii) and (iii) occur by the common trans-β-elimination process and therefore have a stereochemical requirement that the boron moiety and the substituent X must be anti-periplanar. Both these reactions are more facile if X is a good leaving group such as toluene-p-sulphonyl. The catalysts may be either a Lewis acid, for example boron trifluoride, or the ether solvent (OR_2) acting as a base.

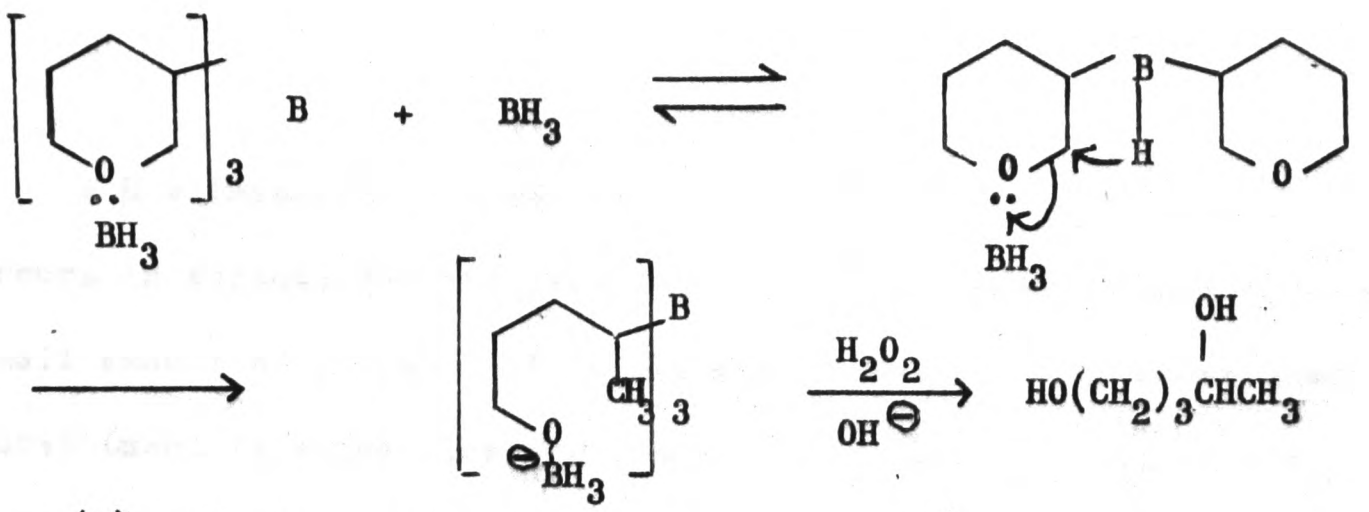
An interesting example of the hydroboration–oxidation reaction is that of the cyclic vinyl ether 2,3-dihydro-4H-pyran (XIV) where a number of side reactions have been shown to develop during the reaction sequence[50]. This may be rationalised using the mechanistic considerations discussed above. The β-alcohol (XV) was isolated in 70% yield by using a stoichiometric amount of diborane, but the use of excess diborane resulted in ring opening and the products isolated, in addition to the β-alcohol, were pentane-1,5-diol and pentane-1,4-diol, i.e.,



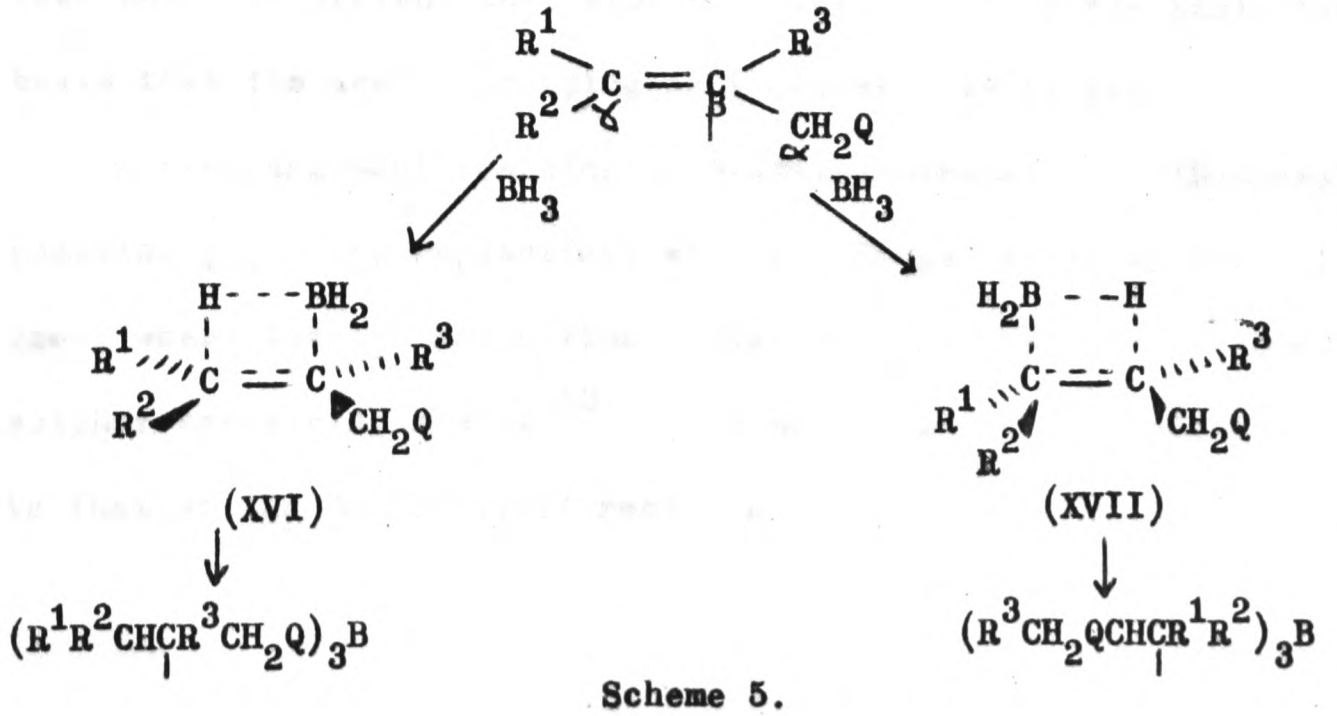
The proposed mechanism of this ring opening process is formulated below and involves coordination of the ring oxygen atom in the organoborane intermediate followed by a β-elimination reaction.



In the presence of excess diborane equilibration takes place which results in the formation of a mixture of intermediates which includes some dialkylborane (i.e., R_2BH) as well as monoalkylborane and trialkylborane. In this case the dialkylborane gives rise to pentane-1,4-diol:



(b) Allylic systems. Allyl derivatives ($CH_2{=}CHCH_2Q$; Q= $-OCOCH_3$, $-OCH_2C_6H_5$, -OH, $-OC_6H_5$, $-OC_2H_5$, $-SC_6H_5$, -borate) have been subjected to hydroboration-oxidation, and mixtures of the β-(XVI) and γ-(XVII) isomers were obtained (Scheme 5) [51], the proportion of the β-isomer decreasing with decreasing electronegativity of the substituent. The electronic effect operating here, in contrast to the corresponding vinylic systems described above, is the inductive effect only.



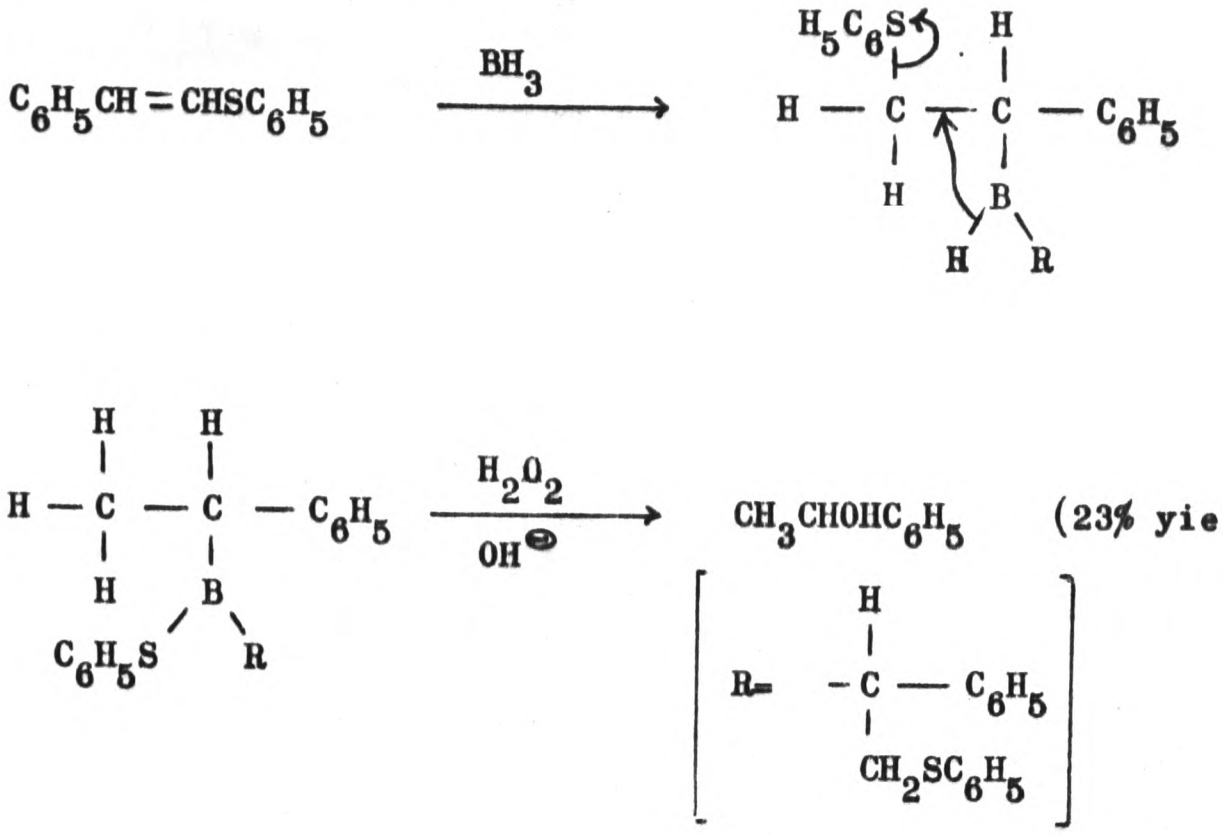
Scheme 5.

For example, hydroboration-oxidation of allyl borate results in the formation of propane-1,3-diol (γ-substituted product, 76%), propane-1,2-diol (β-substituted product, 18%) and propan-1-ol (3%),[45] i.e.,

$$(\overset{\gamma}{CH_2}=\overset{\beta}{CH}-\overset{\alpha}{CH_2}O)_3B \xrightarrow[2)H_2O_2/OH^{\ominus}]{1)BH_3} HO(CH_2)_3OH + HOCH_2\overset{OH}{\overset{|}{C}}HCH_3 + CH_3CH_2CH_2OH$$

A β-elimination process of the type discussed previously(p.23) occurs in boranes derived from allylic systems and accounts for the small amount of propan-1-ol in the above example. In cases where the substituent is a good leaving group (e.g., $-OSO_2C_6H_5CH_3$, $-OCOCH_3$, $-OCH_2C_6H_5$) elimination occurs very readily even at 0^o. With other substituents the elimination reaction is not as facile but does occur readily at 64^o in the presence of excess diborane. In systems such as but-2-en-1-ol the β-substituted trialkylborane is the major product, and β-elimination followed by rehydroboration occurs particularly readily. However protection of the alcohol group by formation of the O-tetrahydropyranyl ether, prior to the hydroboration procedure, has been shown to prevent this side reaction[52]. This was explained on the basis that the acetal grouping is a poorer leaving group.

A rearrangement reaction of β-dialkylboranes (the "β-transfer" reaction i.e., the replacement of the hydrogen atoms by another functional group where the two are vicinal) has been reported in the case of some sulphur-containing systems[53]. The mechanism of this process is analogous to that of the "α-transfer" reaction:



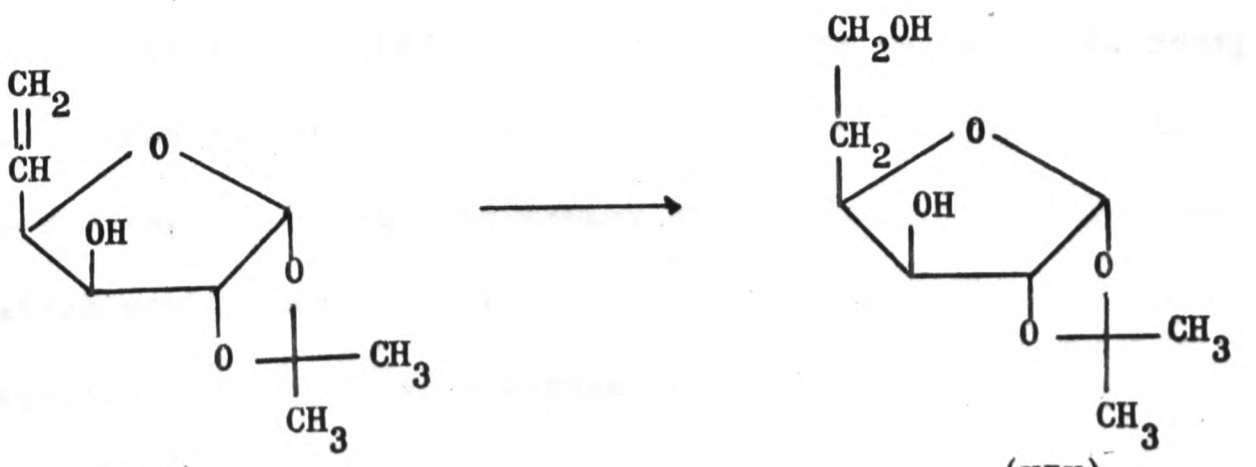
(c) Systems with substituents in positions remote to a double bond.

A study of the system $CH_2=CHCH_2CH_2Q$; Q= $-CH_3$, $-OCH_3$, $-OC_6H_5$, $-OH$, $-OCOCH_3$, $-Cl$, $-NH_2$, $-SCH_3$, revealed 75-100% yields of the terminal alcohol on hydroboration followed by oxidation[54]. No difficulties such as those discussed above were encountered. This result is as expected on the basis of the small influence that a remote substituent can have at the reaction site.

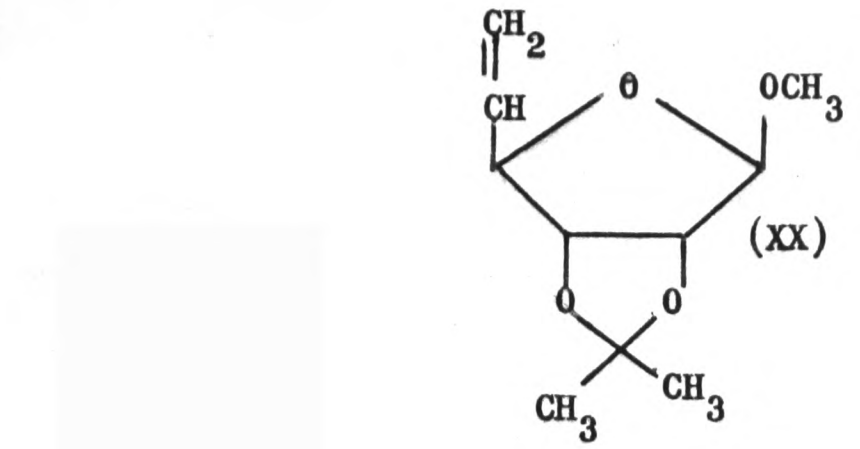
(C) THE HYDROBORATION OF UNSATURATED MONOSACCHARIDES.

Many unsaturated monosaccharides have been prepared[55-7] but there are few examples of their hydroboration followed by oxidation, and none of the preparation of boron-containing compounds *via* initial hydroboration followed by other reactions. In all cases the use of the hydroboration technique has been for the purpose of achieving synthetic pathways to unusual sugars *e.g.* 5-deoxy-D-allose[58], and 9-(3-deoxy-3C-hydroxymethyl-β-(and α)-D-allofuranosyl adenine[59]. Consequently the detailed investigation of the hydroboration step of unsaturated sugar intermediates, which were only part of such pathways, was not undertaken or discussed. However, critical assessment of these reports does reveal some interesting points.

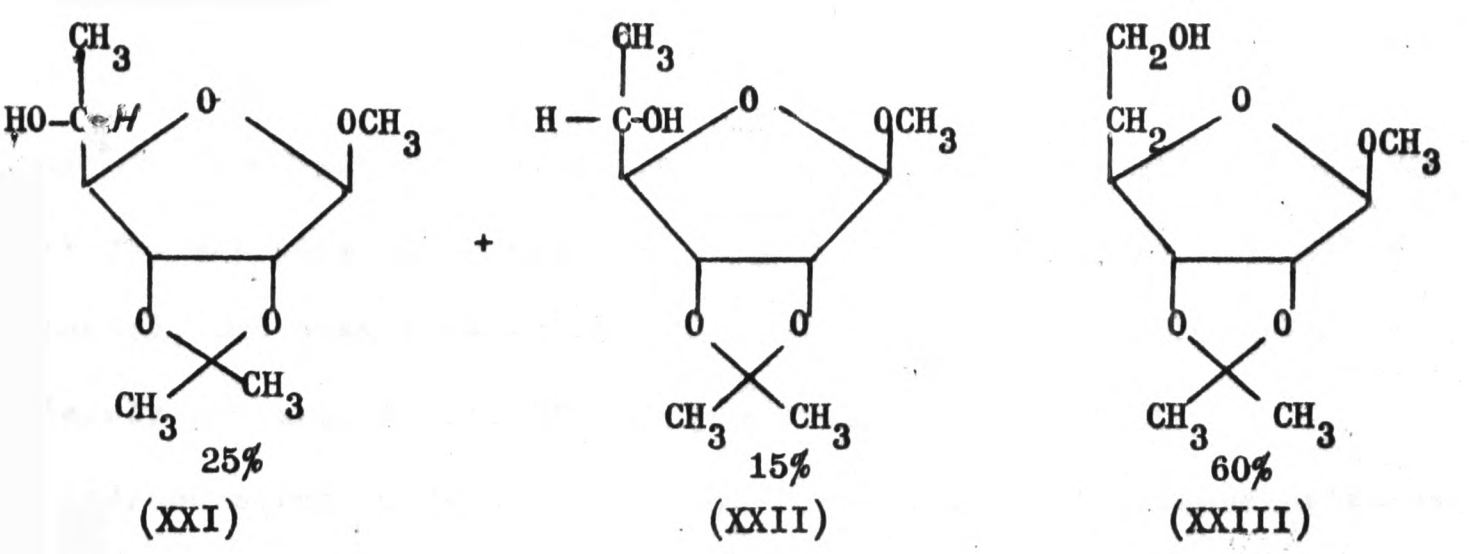
From the hydroboration-oxidation of 5,6-dideoxy-1,2-O-isopropylidene--α-D-*xylo*-hex-5-enofuranose(XVIII) the terminally hydroxylated product (XIX) alone was isolated, although in only 23% yield[60], whereas methyl 5,6-dideoxy-2,3-O-isopropylidene-β-D-~~*ribo*~~-*hex*-5-enofuranoside (XX) gave a mixture of all three possible products[58](XXI, XXII, XXIII). Hydroboration followed by oxidation of 5,6-dideoxy-1,2-O-isopropylidene-3-O-methylsulphonyl-α-D-*xylo*-hex-5-enofuranose (XXIV) gave the product (XXV) in 74% yield[58].



(XVIII) (XIX)



(XX)

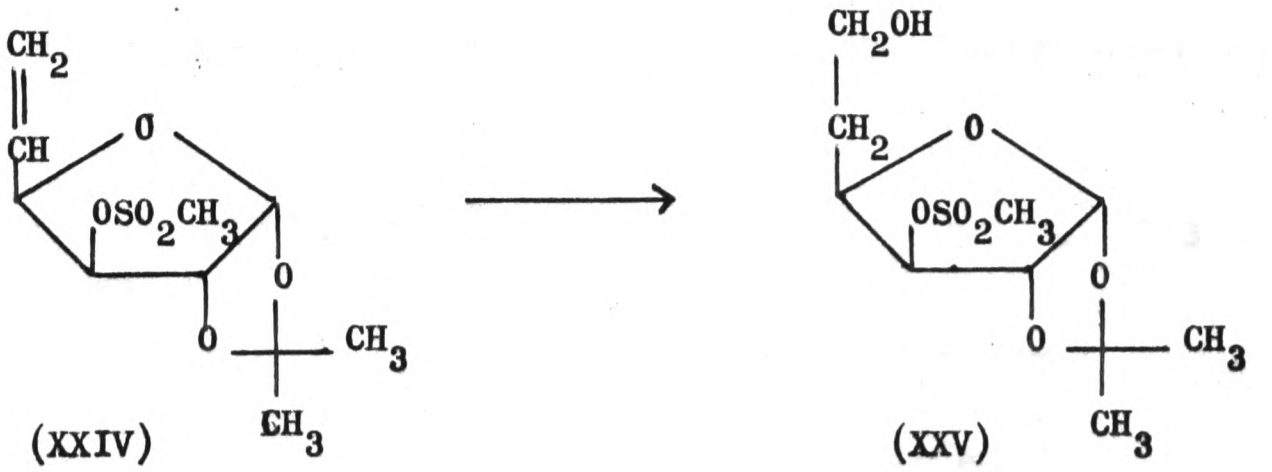


25%
(XXI)

+

15%
(XXII)

60%
(XXIII)



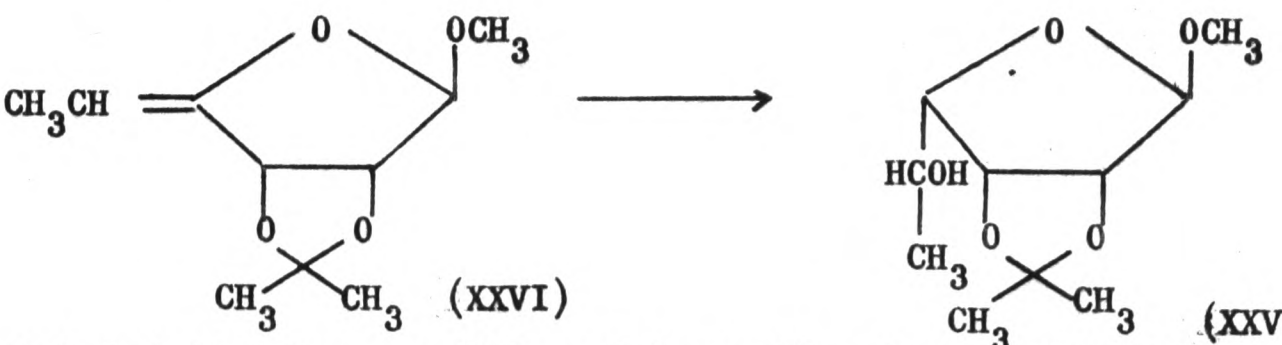
(XXIV)

(XXV)

The authors do not offer a possible mechanistic or stereochemical explanation of their results. The introduction of the terminal hydroxyl group in (XIX), (XXIII) or (XXV) is expected on the basis of the accepted mechanism of hydroboration discussed above. The formation of (XXI) and (XXII) however, represents an interesting stereochemical problem since their formation would have to be rationalised on the basis of the favoured direction of attack of diborane on the unsaturated residue in

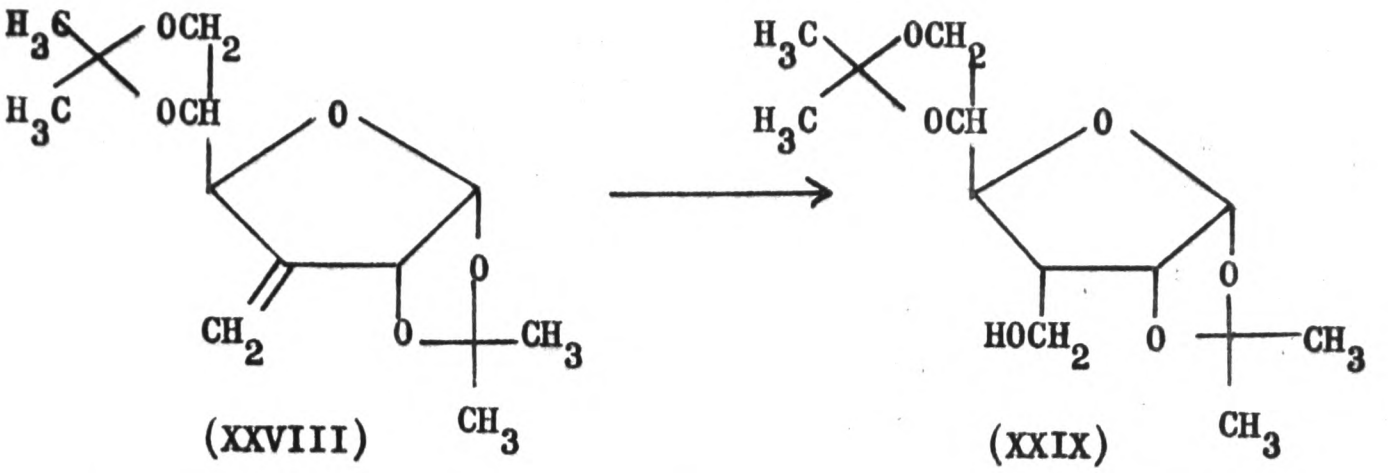
its preferred conformation. Some suggestions along these lines may be envisaged but the reported yields of related monosaccharides, i.e. 74% of (XXV) and 23% of (XIX), suggest that formation of such mixtures of isomers may not be unique. The low yield in the latter case particularly may indicate that other possible products were formed but not isolated. The possible use of a hindered borane as a hydroboration reagent, e.g. bis-(3-methyl-2-butyl) borane was discussed in the literature[58] when it was suggested that a terminal attack of the boron on (XX) to give (XXIII) should then be greatly preferred. In fact the result did not come up to expectation and very little more of (XXIII) was formed, but unexpectedly more of (XXII) and no (XXI). Further work is clearly required to clarify the position.

Hydroboration-oxidation of methyl 5,6-dideoxy-2,3-O-isopropylidene-β-D-~~erythro~~-4-enofuranoside (XXVI) using diborane generated in situ gave methyl 6-deoxy-2,3-O-isopropylidene-β-D-gulofuranoside (XXVII) in 59% yield[61].



(XXVI) (XXVII)

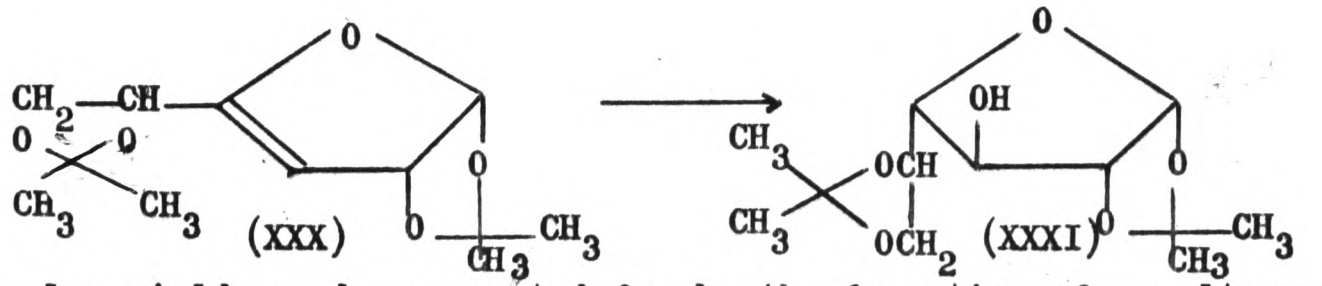
1,2:5,6-di-O-isopropylidene-3-deoxy-3C-methylene-α-D-allofuranose(XXVIII) on treatment with a very large excess of diborane followed by alkaline hydrogen peroxide gave 66% 1,2:5,6-di-O-isopropylidene-3-deoxy-3C-hydroxy-methyl-α-D-allofuranose (XXIX) plus 22% of acetal cleavage products[59].



(XXVIII) (XXIX)

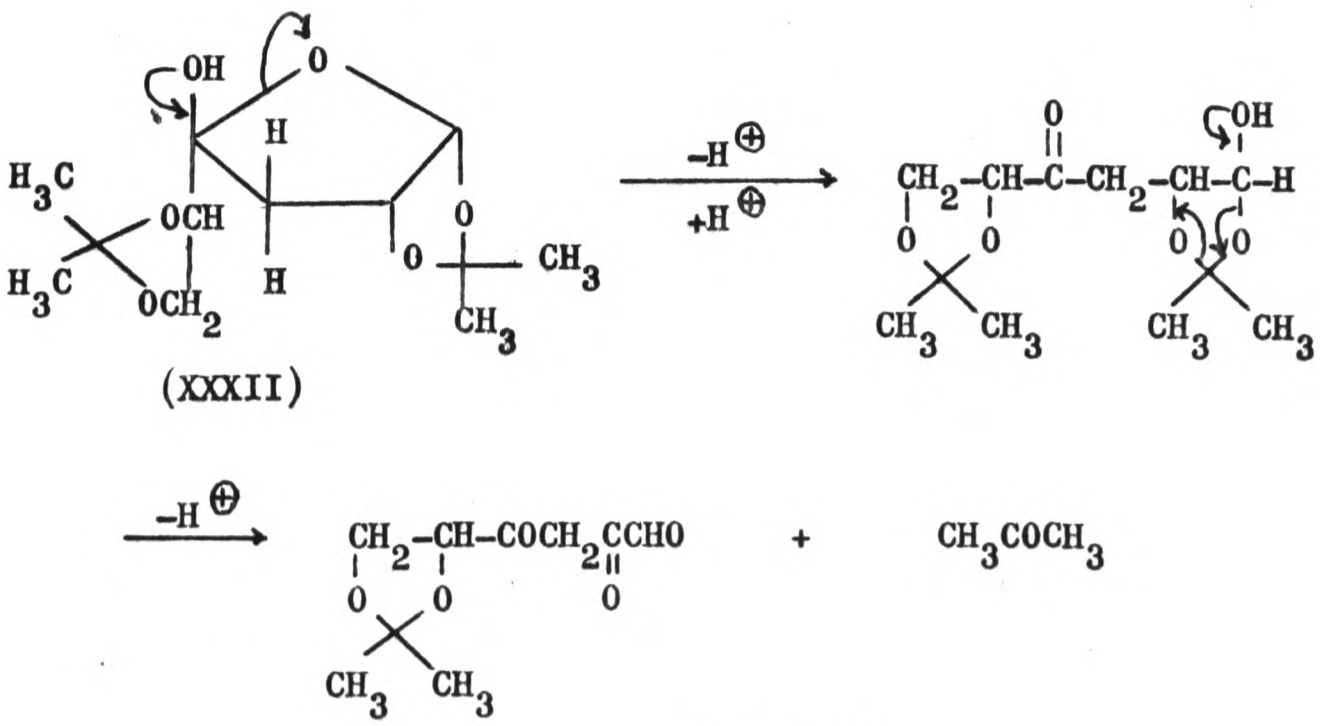
It should be noted that the direction of attack of the boron must have been from the side of the furanose ring opposite to the 1,2-acetal group as has been found for nucleophilic reactions of the carbonyl group in 3-oxo derivatives[70-2].

Hydroboration-oxidation of the internal alkene 1,2:5,6-di-O-isopropylidene-3-deoxy-α-D-erythro-hex-3-enofuranose (XXX) gave the product (XXXI) in 25% yield[62].



(XXX) (XXXI)

The low yield may be accounted for by the formation of an alternative product (XXXII) from the hydroboration which would be unstable (Scheme 6).



(XXXII)

Scheme 6

The analogous di-O-cyclohexylidene compound on hydroboration followed by oxidation gave the 3-hydroxy product of the same configuration as (XXXI) in 38% yield and this increase in yield may be explained by the steric effect of the bulkier cyclohexylidene group as compared with the isopropylidene group, which would be to favour attack at C-3 from above and this is borne out by the results. It is also of importance to note here that the configuration at the reaction site is retained during the oxidation step[64]. No data is available however as to whether this is so during equilibration or redistribution reactions.

(D) SOME SELECTED SYNTHETIC METHODS LEADING TO UNSATURATED MONOSACCHARIDES.

Syntheses of unsaturated monosaccharides have been so numerous[55-7] that only a selective survey is given here. Attention is concentrated on particular structural types, some of which previous workers have subjected to hydroboration procedures, and some of which it was intended to utilise in the present study of carbohydrate boronic acids. Unsaturated monosaccharides may be conveniently classified according to the position of the carbon-carbon double bond in the molecule.

(1) Hex-1-enopyranosides (glycals).

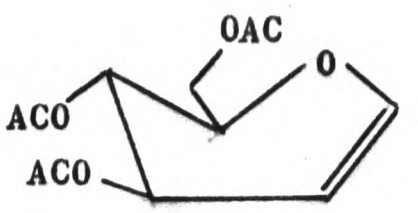
The best known example of this group, and indeed of all unsaturated monosaccharides, is 3,4,6-tri-O-acetyl-D-glucal (XXXIII) which is readily prepared by the action of zinc and acetic acid on 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide[57] (XXXIV). Because of the ready formation of acylglycosyl bromides this general reaction has been applied to most other hexoses and pentoses to give the corresponding unsaturated derivatives. Their stability partially arises from the mesomeric stabilisation of the vinylic ether system, and this structural feature ensures that in many of the reported addition reactions there is a preferred orientation pathway.

(XXXIV) (XXXIII)

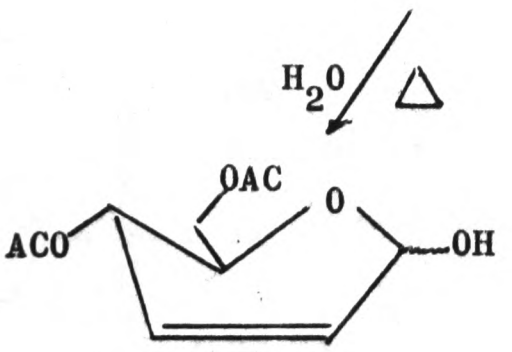
(Ac = $-COCH_3$)

(2) Hex-2-enopyranosides.

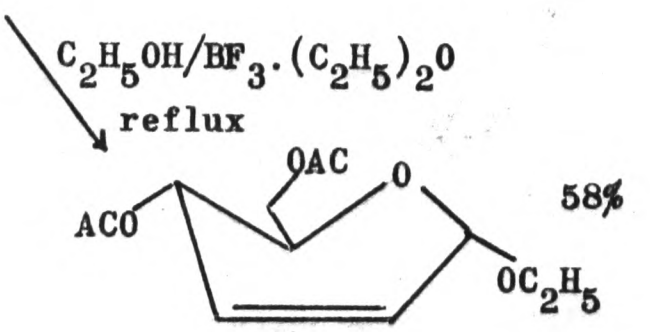
The pioneering transformation of (XXXIII) into (XXXV) with hot water has been capitalised by Ferrier[65] into a direct synthesis of (XXXVI) which, given the ready availability of (XXXIII), makes (XXXVI) the most accesible hex-2-enopyranoside. This latter reaction involves heating 3,4,6-tri-O-acetyl-D-glucal under reflux with boron trifluoride etherate in ethanol.



(XXXIII)

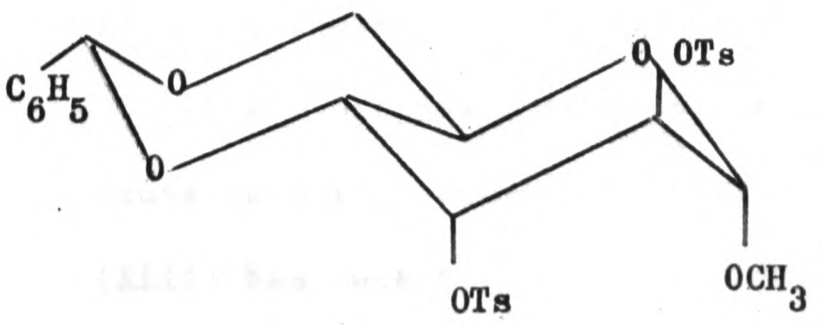


(XXXV)



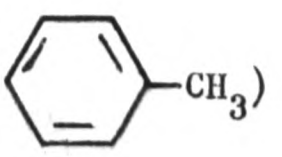
(XXXVI)

The other widely used hex-2-enopyranoside for the study of the reactions of unsaturated monosaccharides is (XXXVIII), which is obtained by the elimination reaction of a trans-di-O-toluene-p-sulphonate (e.g., XXXVII) brought about using the Tipson-Cohen reagent (sodium iodide and zinc dust in dimethylformamide)[66].



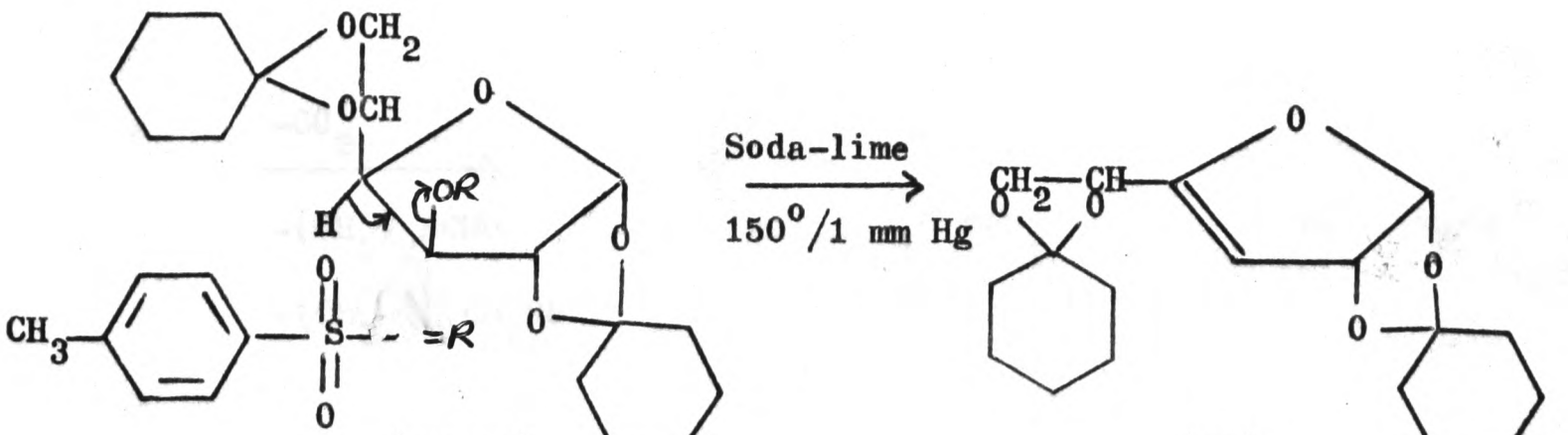
(XXXVII)

(XXXVIII)

(Ts = $-SO_2-$  $-CH_3$)

(3) Hex-3-enofuranosides.

A typical example of this group of unsaturated monosaccharides is 1,2:5,6-di-O-cyclohexylidene-3-deoxy-α-D-erythro-hex-3-enofuranose (XL) prepared by pyrolytic elimination of the corresponding 3-O-toluene-p-sulphonate (XXXIX) employing soda-lime. The yield of product reported for this method is somewhat variable, and attempts to improve this synthesis using as substrates the corresponding acetate, benzoate or xanthate esters were unsuccessful since extensive charring occurred at the temperature required (150-200°) for the reaction[67].

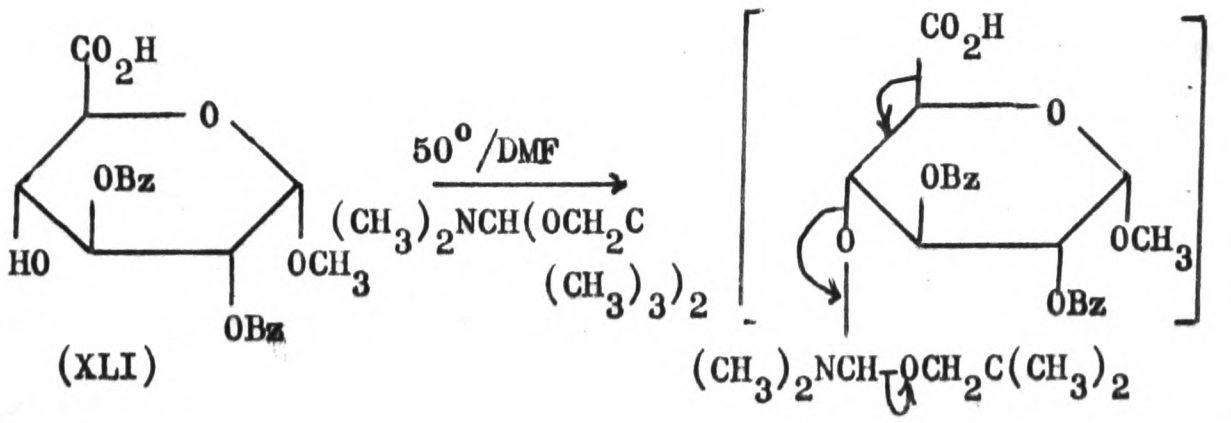


(4) 4-Enopyranoses and furanoses.

Methyl 5,6-dideoxy-2,3-O-isopropylidene-β-D-erythro-4-hex-enofuranoside (XXVI) has been prepared from the corresponding 5-toluene-p-sulphonate by means of an elimination reaction using potassium-t-butoxide[61]. This is another β-elimination reaction with the same mecahnism as that formulated above, and this general reaction has found widespread use in the synthesis of unsaturated monosaccharides due to the ease of preparation of the toluene-p-sulphonate derivatives.

The 4-enopyranose structure is not so common although an interesting route to methyl 2,3-di-O-benzyl-4-deoxy-β-L-threo-pent-enopyranoside (XLII) has recently been described[68]. This procedure involves the

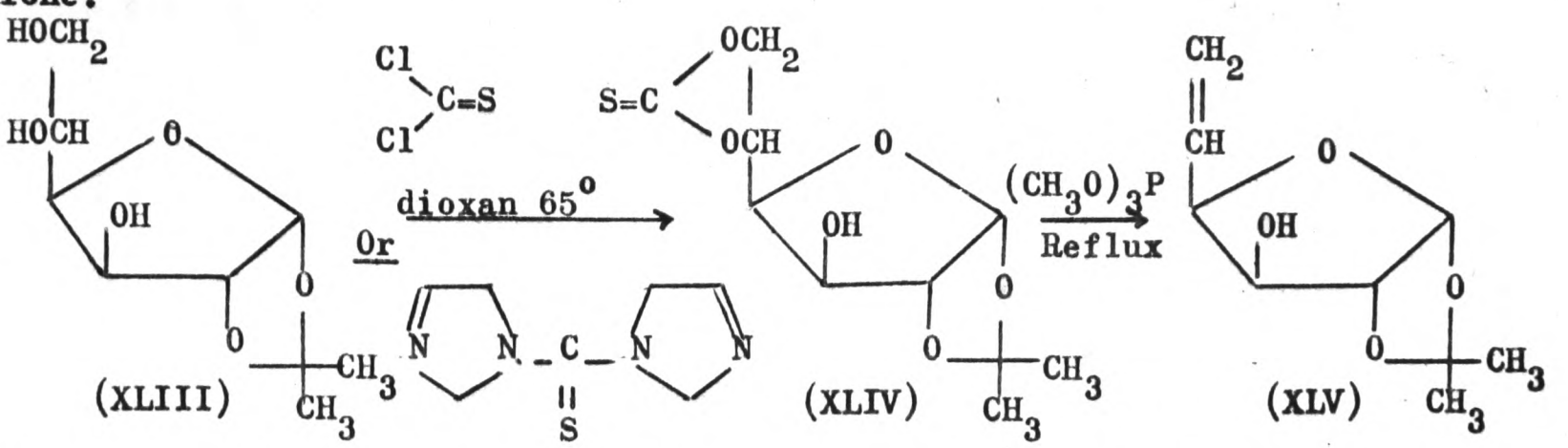
decarboxylative elimination of methyl 2,3-di-O-benzyl-α-D-glucopyranosiduronic acid (XLI) using N, N-dimethylformamide dineopentyl acetal as the reagent.



(5) Hex-5-enopyranoses and furanoses.

Hex-5-enopyranoses (commonly referred to as -osenes, e.g. 5,6-glucosene; 5,6-galactosene, etc.) have been prepared by elimination reactions of the corresponding 6-deoxy-6-iodo compounds using silver (I) fluoride in pyridine[57]. This method has been reported as proceeding in good yield but the cost of silver(I) fluoride makes it an expensive route. Consequently the more recent report[69] of the preparation of 1,2-O-isopropylidene-α-D-xylo-hex-5-enofuranose (XLV) from 1,2-O-isopropylidene-α-D-glucofuranose-5,6-O-thionocarbonate (XLIV) by heating under reflux with trimethyl phosphite (the Corey-Winter synthesis) is of interest. The thionocarbonate was prepared by reaction of 1,2-O-isopropylidene-α-D-glucofuranose (XLIII) (readily available in

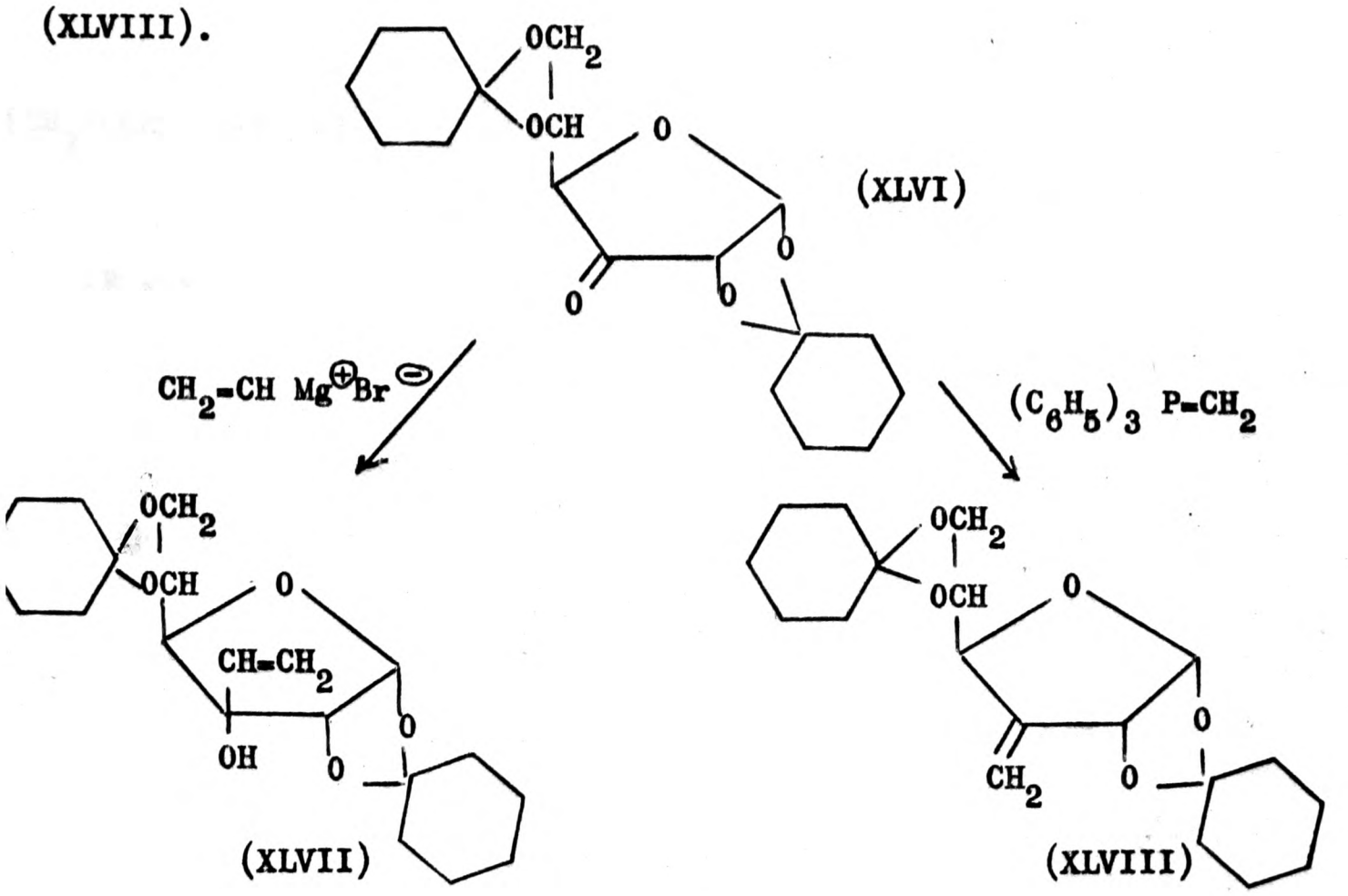
two steps from glucose) with either thiophosgene or bis(imidazol-1-yl)-thione.



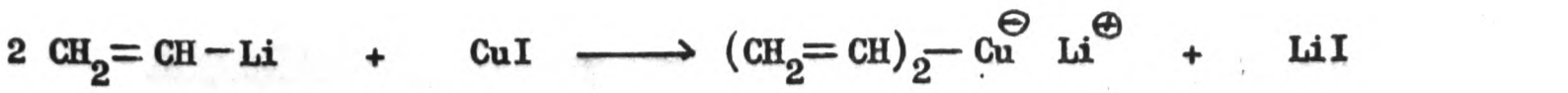
(6) Monosaccharide derivatives with unsaturated side chains.

Organometallic reagents such as Grignard reagents and also phosphonium ylids (i.e. the Wittig reaction), have been used to form monosaccharide derivatives with new unsaturated side chains. These methods could not have been developed without the discovery in the early part of the last decade of a number of useful oxidising reagents which enabled conversion of suitably protected monosaccharides into 2-,3- and 4-oxo sugars. These reagents include ruthenium tetraoxide[70], dicyclohexylcarbodiimide plus orthophosphoric acid in dimethyl sulphoxide (the Pfitzner-Moffatt reagent)[71], and acetic anhydride in dimethyl sulphoxide[72], and they have been exploited in a wide range of interesting synthetic interconversions. The synthesis of monosaccharide derivatives with carbonyl groups sited at C-5, and, where appropriate at C-6, is possible by, for example, a periodate oxidative cleavage reaction. However, this has not been extensively employed synthetically. As an example of this general type of process the reaction of 1,2:5,6-di-O-cyclohexylidene-α-D-ribo-3-hexofuranosulose (XLVI) with vinyl magnesium bromide which results in the formation of 1,2:5,6-di--O-cyclohexylidene-3C-vinyl- α-D-allofuranose[73] (XLVII) can be cited. The same starting material was also used in a Wittig reaction employing

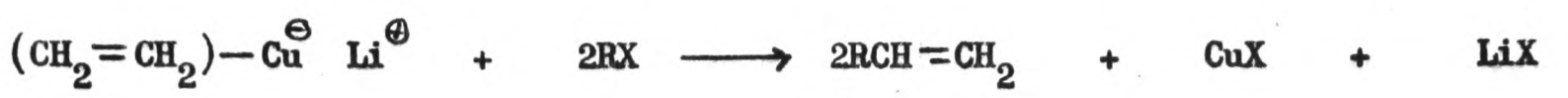
methyltriphenylphosphonium bromide and base to produce 1,2:5,6-di-O-cyclohexylidene-3-deoxy-3C-methylene-α-D-allofuranose[74] (XLVIII).



A possible alternative synthesis of unsaturated monosaccharides using organometallic reagents may also be envisaged. Nucleophilic substitution reactions of compounds containing halide or toluene-p--sulphonyl groups by organometallic reagents (i.e., charge-stabilised or "hidden" carbanions, e.g., vinyllithium (XLIX)) are among the most attractive procedures for the production of new carbon-carbon single bonds. Recently the use of compounds containing carbon-copper(I) bonds has been reported as achieving strikingly successful results in such reactions. In particular, the reactions of lithium diorganocuprates(I) themselves prepared from lithium alkyls, have led to the introduction of unsaturated moieties into a variety of systems[75-80]. The following reaction sequence is a generalised formulation and the details of these reactions will be considered further in the discussion section of this thesis.



(XLIX)



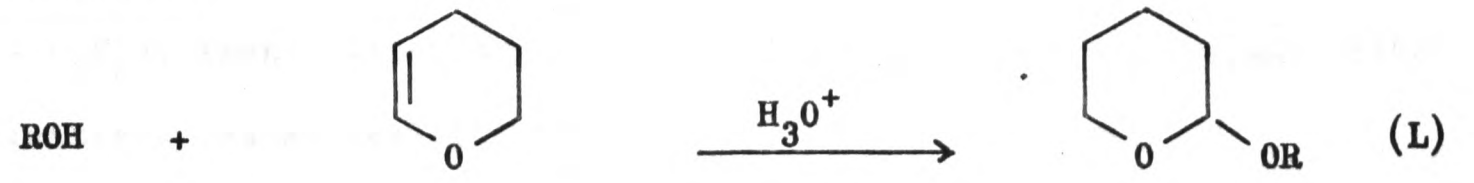
(R = aryl or alkyl; X = Br,I, $OSO_2C_6H_4CH_3$)

(E) PROTECTION OF HYDROXYL GROUPS PRIOR TO ORGANOMETALLIC AND HYDROBORATION REACTIONS[81,82].

The reaction of an organometallic reagent with a substance requires the protection of any active sites (acidic hydrogens) such as hydroxyl groups present in that substance. Effective protecting groups must be easily introduced and removed under mild conditions without affecting other parts of the molecule. They should be stable under the reaction conditions employed and the protected derivatives should be readily purified. Protecting groups for alcohols or diols fall into several categories and the properties of a few selected examples, relevant to the present work,are discussed below.

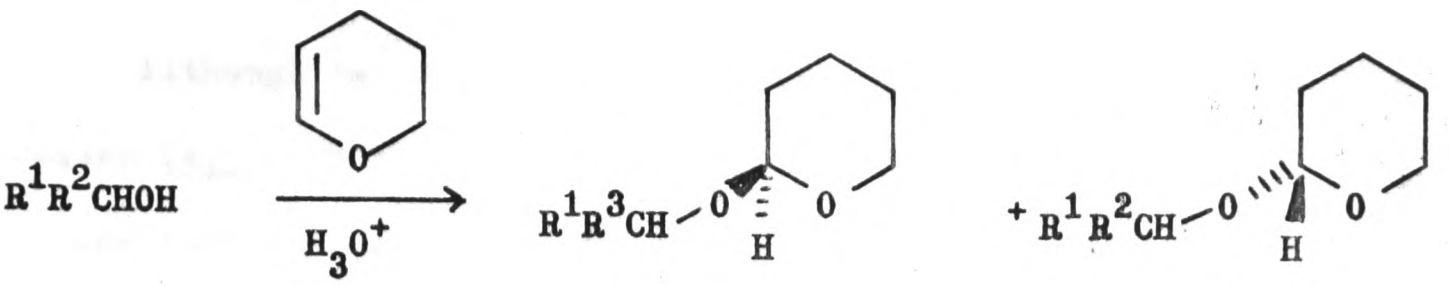
1) Acetals

a) Tetrahydropyranyl ethers (L) may be obtained from monohydric alcohols by reaction with 2,3-dihydro-4H-pyran under acid catalysed conditions.



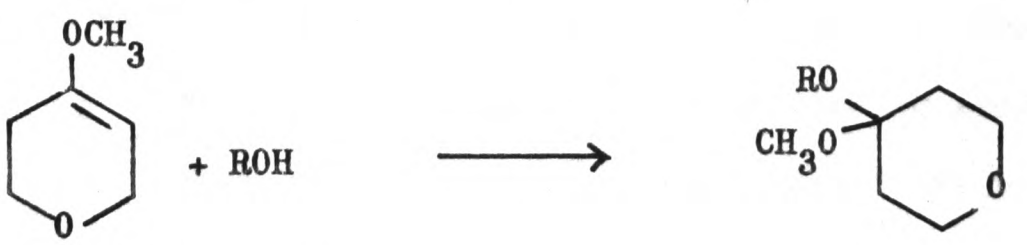
(L)

The system is stable to strong bases, Grignard reagents, lithium alkyls and other organometallic reagents but undergoes acidic hydrolysis under mild conditions. The group has been widely used for protection of hydroxyl functions before subsequent reaction of organometallic reagents. However, in the case of alcohols containing a chiral site, formation of the tetrahydropyranyl ether from the racemic alcohol results in a mixture of diastereoisomers (LI) and (LII).



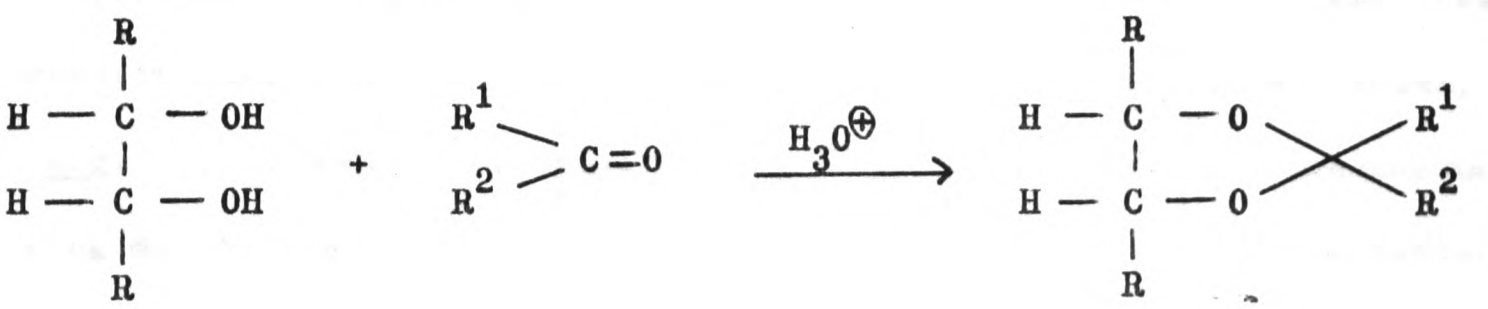
(LI) (LII)

This problem has been avoided by the use of the symmetrical methoxytetrahydropyranyl protecting group (LIII) which is prepared from 5,6-dihydro-4-methoxy-2H-pyran (LIV)[83]. This advantage has been well illustrated by the formation of crystalline ribonucleotide derivatives in good yield[83].

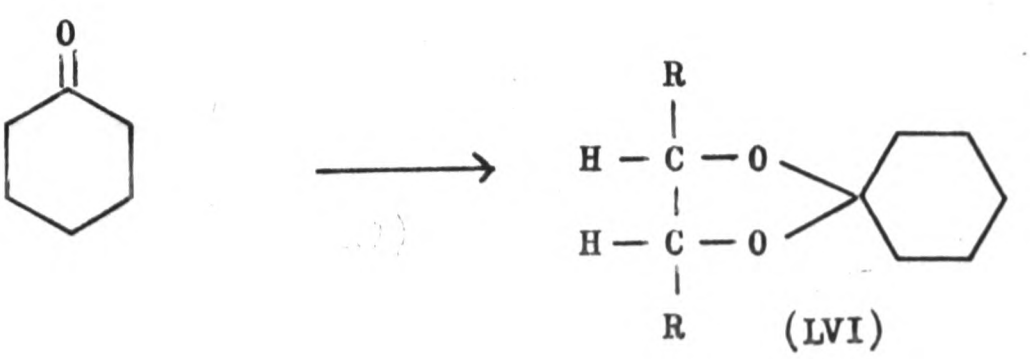


(LIV) (LIII)

b) Cyclic acetals (LV) are prepared by the reaction of 1,2 or 1,3-diols with carbonyl compounds; benzaldehyde, acetone and cyclohexanone commonly being employed to give benzylidene (LV, R^1 = H, R^2 = C_6H_5), isopropylidene, (LV, R^1 = R^2 = CH_3) and cyclohexylidene (LVI) derivatives respectively.



(LV)



(LVI)

Although two diastereoisomers are theoretically possible in some cases (e.g., LV if $R^1 \neq R^2$), very often a pure product is obtained since the condensations are usually carried out under acid catalysed forcing conditions and the thermodynamically favoured product is formed. The ability of a diol system which is part of an alicyclic or heterocyclic (carbohydrate) system to form an acetal is critically dependent on the relative positions of the hydroxyl groups; 1,2-diols react only with ketones but 1,3-diols react with either aldehydes or ketones. In addition, aldehydes preferentially form six membered rings (1,3-dioxanes) while ketones usually form five membered rings (1,3-dioxolanes). If a sugar reacts in the furanose form to produce a dioxolane (e.g., 1,2-O-isopropylidene-α-D-glucofuranose) the ring fusion is usually cis resulting in a V shaped bicyclic system. On the other hand, if the sugar reacts in the pyranose form, the dioxolane ring is also fused in a cis manner but no radical alteration from the chair conformation is involved. In the case of diacetal formation from two cis-α-diols (e.g., 1,2:3,4-di-O-isopropylidene-α-D--galactopyranose) the ring fusion is cis-anti-cis. Although a molecule comprising a six membered ring fused to a furanose ring is formed less readily than a system of five membered rings some examples are known. (e.g., 1,2:3,5-di-O-isopropylidene-α-D-glucofuranose). A dioxane acetal ring may be fused to a pyranose ring in either a cis or a trans manner. In the latter case the chair conformation remains intact (cf., trans--decalin, e.g., methyl 4,6-O-benzylidene-α-D-glucopyranoside). Two possible conformations are feasible with a cis fusion (e.g., 4,6-O--benzylidene-α-D-galactopyranose).

2) **Ethers.**

a) Methyl ethers (LVII) are frequently prepared by the well established Haworth method involving dimethyl sulphate and strong aqueous base. In systems containing functional groups which are sensitive to the action of base (e.g., acyl esters) the procedure may be modified to employ aprotic solvents such as N,N-dimethylformamide and bases such as barium oxide.

$$2\ ROH + (CH_3)_2SO_4 + NaOH \xrightarrow{\text{acetone}/40^{o}} ROCH_3 + Na(CH_3SO_4)$$

$$(LVII) + H_2O$$

The methyl ether group is very stable and is consequently difficult to remove as a protecting group. One facile method of removal exists however involving the use of boron trichloride in methylene dichloride at -80^{o} [84]. In general methyl ethers are not often the derivatives of choice as protecting groups.

b) Benzyl ethers (LVIII), prepared from alcohols using benzyl chloride in the present of strong base (potassium hydroxide) in refluxing toluene, are unsuitable for use with base-labile systems. They are tolerably stable under acidic conditions although they are cleaved using strong mineral acids. Generally the benzyl group is removed by hydrogenolysis over palladium catalysts, or using sodium in ethanol.

$$ROH + C_6H_5CH_2Cl + KOH \longrightarrow C_6H_5CH_2OR + KCl + H_2O$$

(LVIII)

c) β-Methoxyethoxymethyl ethers (LIX) have recently been reported by Corey[141] as a new protecting group. They have the advantages of ready selective cleavage using zinc bromide in methylene dichloride at 25° and that they are devoid of chirality which avoids some of the problems associated with tetrahydropyranyl ethers discussed above. They may be prepared by heating an alcohol under reflux with the triethylammonium derivative of methoxyethoxymethyl chloride in acetonitrile.

$$ROH + CH_3OCH_2CH_2OCH_2N^{\oplus}(C_2H_5)_3Cl^{\ominus} \xrightarrow{CH_3CN} ROCH_2OCH_2CH_2OCH_3 \quad (LIX)$$

In summary therefore, methyl, benzyl, or tetrahydropyranyl ethers are widely used protecting groups for monohydric alcohols in decreasing order of stability. Benzyl ethers may be susceptible to elimination reactions and therefore tetrahydropyranyl ethers, which seem stable enough for use in organometallic and hydroboration reactions and are much more easily removed than the methyl ethers, are the most likely protecting group for this work. In carbohydrates, the cyclic acetals are often the protecting groups of choice since they conveniently condense with pairs of hydroxyls.

DISCUSSION

The purpose of this work was to explore synthetic methods leading to hydroxyalkaneboronic acids, and in particular those derivatives where the residue attached to the boron atom is a monosaccharide unit. The hydroxyl groups in such compounds, hitherto unreported, would be expected to impart increased water-solubility in comparison with simple unsubstituted alkaneboronic acids and thus facilitate pharmaceutical testing proce dures and other possible biological utilisations. Such hydroxyalkaneboronic acids were considered likely to have interesting chemical properties. Specifically their behaviour under dehydrating conditions would merit study since both inter- and intra-molecular anhydride formation is theoretically possible (p.13). Also, the effect of the polyfunctionality on the stability of the boronic acids towards autoxidation would be worthy of attention since the stability of simple alkaneboronic acids depends on the structure of the alkyl residue; in particular the autoxidation process occurs more readily with increasing electron donation[85]. Hence hydroxyalkaneboronic acids might be expected to be less easily autoxidised.

In the monosaccharide series introduction of the boronic acid functional group, resulting from the formation of a new carbon-boron bond, was the prime aim since the only boron-containing monosaccarides which have so far been synthesised are those which involve a boron-oxygen bond[20-24]. It is possible that this new type of compound will have interesting biological uses[1-9]. Thus, in the case of neutron capture cancer therapy discussed on p.11 monosaccharideboronic acids might be expected to become localised in the tumour tissue, and hence overcome the problems so far associated with this technique[12-14]. Also there is the possibility that these compounds could act as antimetabolites,

i.e., they are sufficiently similar to endogenous metabolites that they might be absorbed by the cell where they could block the function of the natural metabolite. Since malignant tumour cells metabolise at a very much faster rate than normal cells these antimetabolites would be absorbed preferentially into, and lead to the selective destruction of, the tumour cells.

The study of synthetic routes employing hydroboration, leading to simple hydroxyalkaneboronic acids, was necessary as a preliminary to the application of these reactions to the more complex unsaturated monosaccharide derivatives. Although much work has been reported on the hydroboration of polyfunctional systems[45,64] and a little on the retention of the boron atom following hydroboration[40,41] (as opposed to oxidative cleavage of the carbon-boron bond) it was thought worthwhile to correlate these two aspects and examine a series of simple unsaturated alcohols as precursors to hydroxyalkaneboronic acids (or esters). Previous work has highlighted many problems in the hydroboration of unsaturated alcohols including powerful inductive and mesomeric effects of the oxygen atom[45], leading to the formation of mixtures of isomeric products, and to various competing side reactions[47-49].

Clearly these aspects needed to be examined in detail before attempting hydroboration of more complicated structures. It must be borne in mind, however, that the more rigid stereochemical requirements of cyclic carbohydrate molecules may prevent some of these complications occurring and therefore it was planned to synthesise and investigate the hydroboration of unsaturated derivatives of 1,2-O-cyclohexylidene glycerol as a simple model system.

Apart from hydroboration, the other important route to boronic acids

namely *via* organometallic reagents, particularly Grignard derivatives[17,30,32] (p.17) was not considered likely to prove fruitful in the monosaccharide series since Grignard reagents cannot be prepared from β-alkoxy halides[37] which is the formal structure of most monosaccharide halides, however this general route was considered worthy of attention in the case of selected model systems.

Thus, the two general methods which were to be investigated as possible ways of obtaining hydroxyalkaneboronic acids were (1) the hydroboration route, and (2) the method utilising organometallic reagents. Whilst ultimately it was intended to employ suitably protected monosaccharide derivatives for (1), it was deemed appropriate to study initially simpler polyhydroxy systems. These were (a) simple hydroxy-alkenes, (b) glycerol derivatives, and (c) butane-1,2-diol derivatives.

(A) SYNTHESIS OF BORONIC ACIDS VIA HYDROBORATION OF SIMPLE HYDROXYALKENES.

Before attempting hydroboration reactions on polyfunctional systems containing a hydroxyl group in addition to a carbon-carbon double bond, protection of the hydroxyl functional site was deemed necessary since diborane reacts rapidly with hydroxyl groups to form the $-OBH_2$ system. In addition, this functionality is a good leaving group[52] and hence undesirable elimination reactions become likely. It has been found, however, that the formation of O-tetrahydropyranyl ethers reduces the possibility of such side reactions[52] in hydroboration reactions. A suitable protecting group should be easily introduced and removed, and be stable to the conditions of the reaction. The protecting group which appeared to satisfy these conditions was the O-tetrahydropyranyl ether (II), and a series of such derivatives of unsaturated alcohols was readily prepared in good yield by stirring the appropriate alcohol with 2,3-dihydropyran (I) in the presence of concentrated hydrochloric acid in accordance with a well established procedure[86].

(I) (II)

A suitable isolation procedure[86] then involved dilution of the reaction mixture with ether, washing with sodium hydrogen carbonate solution to neutralise the acid prior to drying, followed by concentration of the ethereal solution. The products were finally distilled under reduced

pressure and shown to be pure by g.l.c. analysis. Typically these O-tetrahydropyranyl ethers showed i.r. absorption at 820, 875, 1020, 1120, 1180, 1195 cm^{-1} (e.g., I.r. 1) and signals in the n.m.r. spectrum at δ 1.60, 3.3-3.8, and 4.6 (e.g., N.m.r. 1,).

In this way the following compounds were prepared:-

1-(2'-tetrahydropyranyloxy)prop-2-ene (II,R= $-CH_2CH=CH_2$);

1-(2'-tetrahydropyranyloxy)propane (II,R= $-C_3H_7$);

1-(2'-tetrahydropyranyloxy)pent-4-ene (II,R= $-(CH_2)_3CH=CH_2$);

2-(2'-tetrahydropyranyloxy)pent-4-ene (II,R= $-CH(CH_3)CH_2CH=CH_2$);

2-(2'-tetrahydropyranyloxy)but-3-ene (II,R= $-CH(CH_3)CH=CH_2$;

3-(2'-tetrahydropyranyloxy)pent-4-ene (II,R= $-CH(C_2H_5)CH=CH_2$); and

1-(2'-tetrahydropyranyloxy)prop-2-yne (II,R= $-CH_2C\equiv CH$).

The n.m.r. spectrum of 2-(2'-tetrahydropyranyloxy)pent-4-ene (II,R= $-CH(CH_3)CH_2CH=CH_2$) is worthy of comment. In the parent unprotected alcohol, the vinylic proton attached to C-4 appears in the spectrum (N.m.r. 2) as a 12 line multiplet. The derivation of the splitting pattern is shown diagrammatically in Fig. 1.

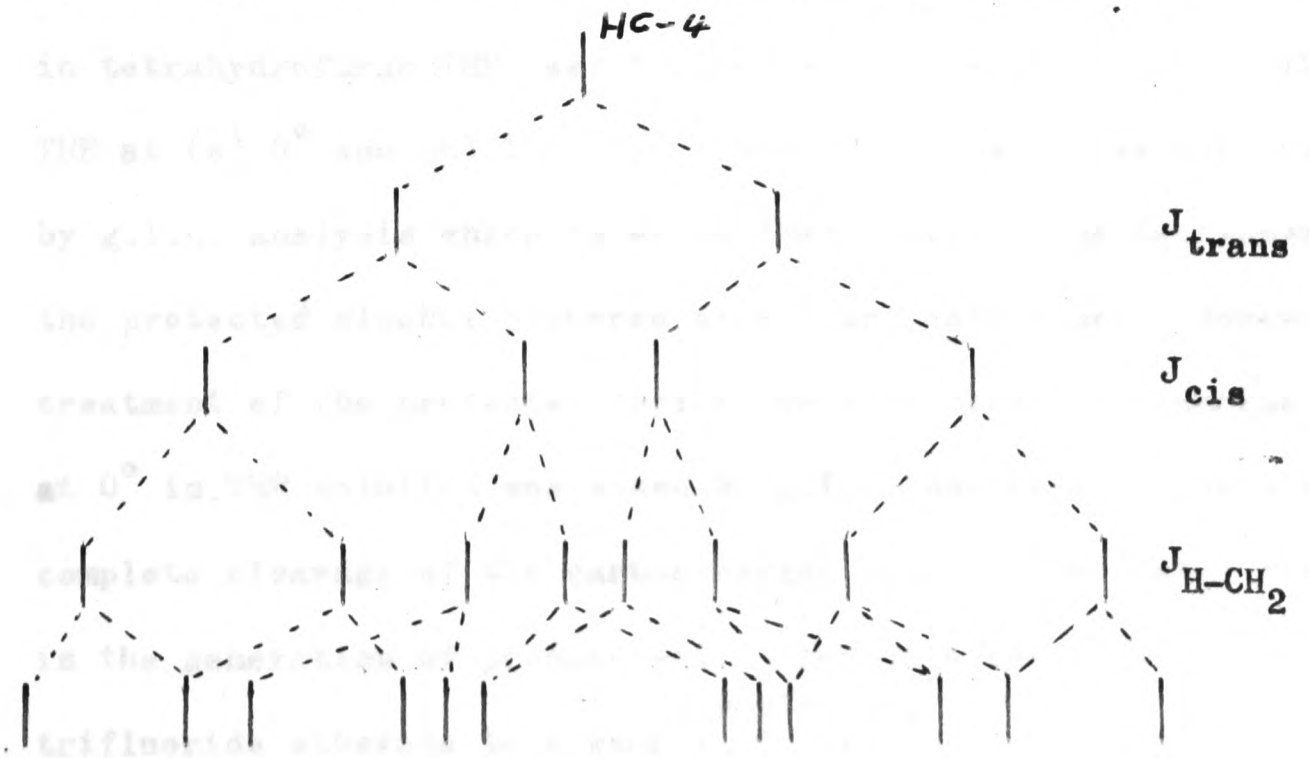


Fig. 1

In the case of the spectrum of the corresponding O-tetrahydropyranyl ether (N.m.r. 3) the splitting pattern for this proton is more complex, but is consistent with the existence of two overlapping 12 line multiplets. Furthermore, the signal due to the C-1 methyl protons appears as a three line signal of 1:1.65:1 ratio instead of the expected doublet. However just as the vinylic proton occurs as two sets of overlapping multiplets, so these methyl protons may occur as two overlapping doublets. This was demonstrated by recording a second spectrum using a field strength of 100 MHz (N.m.r. 4) when the two doublets were separated. The explanation for these effects is that the product exists as a 1:1 mixture of diastereoisomers where the chemical shifts arising from the protons in each case are slightly different.

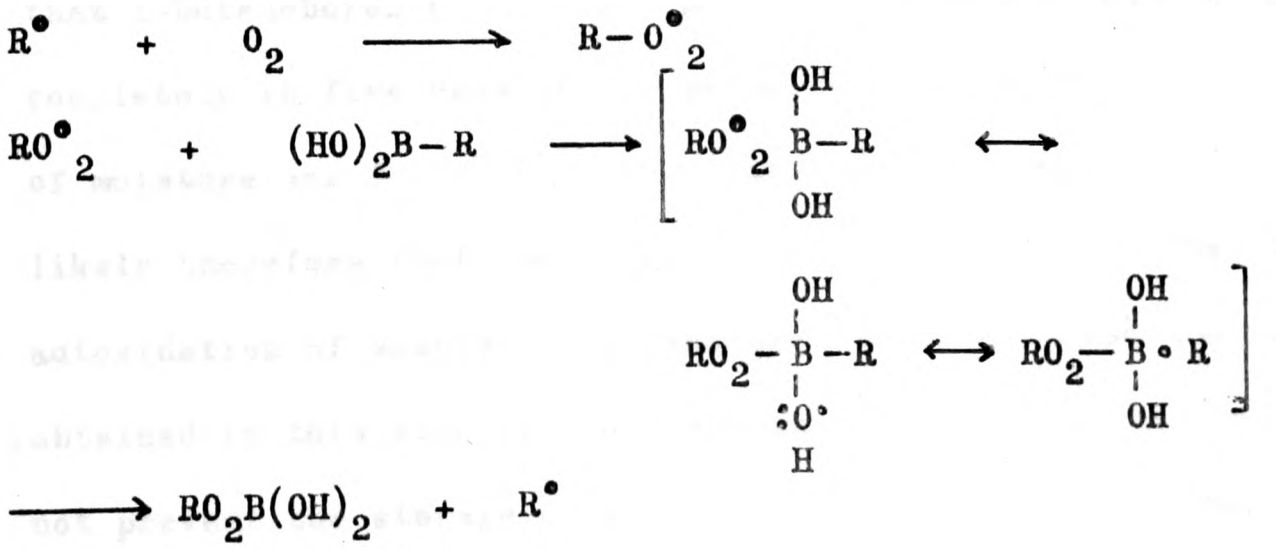
Before initiating a study of the hydroboration of protected unsaturated alcohols, it was considered necessary to study the stability of the protecting group towards the hydroboration reagents and reaction conditions. Hence 1-(2'-tetrahydropyranyloxy) propane in tetrahydrofuran (THF) was treated with a 1M solution of diborane in THF at (a) 0^{o} and (b) 120^{o} for 1 hour. The solution was monitored by g.l.c. analysis which revealed that little or no decomposition of the protected alcohol occurred at either temperature. However, similar treatment of the protected derivative with boron trifluoride etherate at 0^{o} in THF solution was shown by g.l.c. analysis to cause rapid and complete cleavage of the carbon-oxygen bond of the acetal resulting in the generation of propan-1-ol. Nevertheless addition of boron trifluoride etherate to a sample of the protected alcohol in the presence of sodium borohydride at such a rate that the two substances reacted

immediately to form diborane, gave rise to no cleavage reaction.

The next aspect to be considered before proceeding to syntheses of hydroxyalkaneboronic acids is their stability.

Stability of boronic acids.

Alkaneboronic acids in general have been noted in the literature to be unstable, readily undergoing an autoxidation process[17,18]. This results in oxidative cleavage of the carbon-boron bond and is observed with samples in the dry solid state, or with samples in solution shaken under oxygen. The rate of autoxidative decomposition appears to become faster with increasing numbers of electron-releasing alkyl groups at the site adjacent to the boron atom. The mechanism of this autoxidation process is not completely understood despite recent studies in which alkaneboronic acids having a chiral site adjacent to the boron atom were autoxidised to give racemic alcohols[18]. In this study, although the process was established as one involving free radicals, the initiation step for the reaction was not formulated, although the propagation steps were envisagedas:



1-Butaneboronic anhydride was also reported to autoxidise readily by shaking the liquid with dry oxygen[85].

The behaviour of 1-hexaneboronic acid on storage was examined by the author and the following results were obtained. Under normal storage conditions (i.e. the product was dried between filter papers and placed in a stoppered sample tube) the product was stable, and it was also stable when left open to the atmosphere for several weeks. Under desiccating conditions (P_2O_5) in a nitrogen atmosphere the liquid anhydride was formed slowly and complete conversion of the acid was found to take place in 20 days. The same product was also formed by heating the acid in a vacuum pistol at 100° for 8 hours. Anhydride formation was therefore not nearly as facile as is reported to be the case with areneboronic acids[26]. The anhydride was distilled under reduced pressure and its i.r. spectrum (I.r. 5) was significantly different from that of the acid; thus the OH str. was absent and the BO str. band was stronger and broader. The n.m.r. spectrum (N.m.r. 8) showed no signal due to $-B(OH)_2$. It was thus anticipated that spontaneous or facile anhydride formation would probably not be a characteristic of new hydroxyalkaneboronic acids. It has been reported that 1-butaneboronic acid in a pure dry state was found to autoxidise completely in five days in the presence of pure dry oxygen but a trace of moisture was found to inhibit the reaction completely[17]. It is likely therefore that the presence of water vapour in the air prevents autoxidation of samples of alkaneboronic acids. From the results obtained in this work it would appear that the autoxidation process does not prevent the storage of alkaneboronic acids under normal conditions.

Hydroboration techniques.

There are several methods available for the hydroboration of an alkene[38,87]:

(a) Diborane may be generated <u>in situ</u> using boron trifluoride etherate which is added to a stirred mixture of sodium borohydride and the alkene[38]. The rate of addition is such that the diborane formed reacts immediately with the alkene. Although this method is very satisfactory in the case of simple alkenes, it is liable to introduce difficulties with more complex systems. For example the experiments described above indicate the possibility of cleavage of acetal protecting groups by boron trifluoride etherate if the rate of addition is not precisely controlled. Also, boron trifluoride etherate may initiate Lewis acid catalysed elimination reactions of β-organoboranes (see p.23). Finally when the initial hydroboration reaction is to be followed by a redistribution reaction using a borate ester, the sodium borofluoride residue would be present as an insoluble solid material. This residue may hinder isolation of the desired product which would need to be distilled directly from the reaction mixture.

(b) Diborane gas may be generated by the action of boron trifluoride etherate on sodium borohydride and passed into a stirred solution of the alkene in THF using a stream of nitrogen[38]. This is a satisfactory method but not as convenient as method (c).

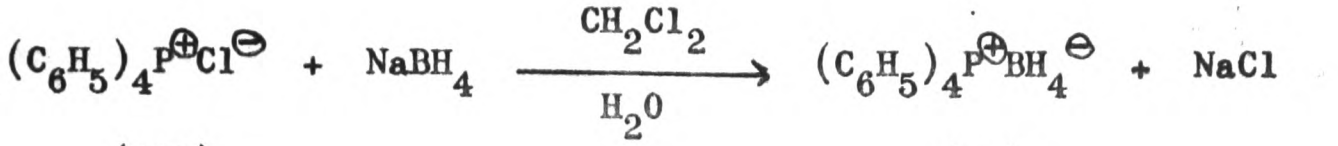
(c) A solution of diborane in THF may be prepared by passing the gas generated as in (b) above into cooled THF. The solution thus obtained may be standardised and will bring about the hydroboration reaction smoothly when added to an alkene. This was the method chosen in the present work because it is the most convenient to perform and there are no by-products in the hydroboration reaction mixture. Solutions of diborane in THF are also available commercially but in the author's hands one of these gave anomalous results which were eventually

traced to the presence of a volatile impurity in the solution. This was detected by g.l.c. analysis and was absent from solutions prepared in the laboratory. In this work satisfactory diborane solutions were prepared by the generation of diborane gas from boron trifluoride etherate and sodium borohydride in diglyme according to the method of Brown[87,88]. Vigorous stirring of the reaction mixture was found to be essential and the gas was passed by means of a nitrogen stream into cooled THF via a Dreschel bottle containing sodium borohydride in diglyme to remove boron trifluoride etherate. When addition of the boron trifluoride etherate was complete the reaction flask was heated at 60° for 1 hour to drive off the residual diborane.

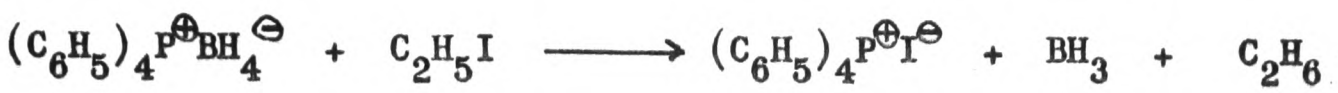
$$3\ NaBH_4 + 4\ BF_3 \longrightarrow 4\ BH_3 + 3\ NaBF_4$$

The concentration of diborane in the THF solution was determined according to a published procedure[89]. An aliquot of the diborane solution was allowed to react with excess acetone and was then hydrolysed with water. The resulting boric acid was estimated in the usual manner[90] by titration against sodium hydroxide solution in the presence of mannitol using phenolphthalein as the indicator.

(d) In a recently (1972) published procedure[91], tetraphenylphosphonium chloride (III) was shaken with sodium borohydride in aqueous sodium hydroxide plus methylene dichloride, and tetraphenylphosphonium borohydride (IV) isolated from the separated organic layer. Treatment of this borohydride salt with ethyl iodide in methylene dichloride gave a diborane solution which was used immediately in an in situ hydroboration procedure.



(III) (IV)

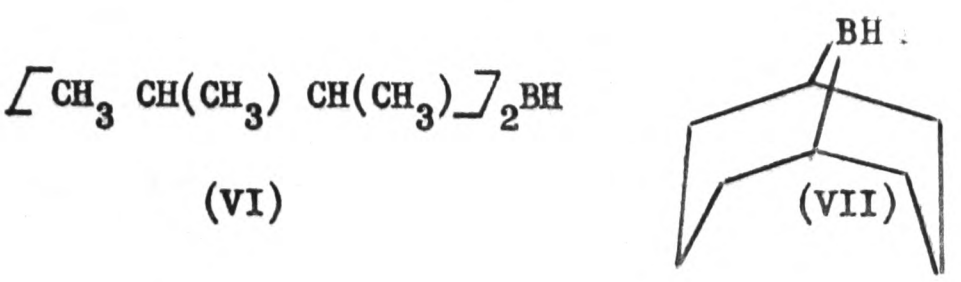


(V)

Phase transfer reaction processes were reported by Starks in 1971[92]. They involve anion transfer in immiscible solvent systems by the use of quaternary ammonium or phosphonium cations. Thus the phase transfer agent serves as a vehicle to bring one reactant into the same phase as the other reactant, allowing rapid production of an active species such as diborane. Although for this work the method was a feasible alternative to the preparation of a diborane solution using boron trifluoride etherate and sodium borohydride, this in situ generation of diborane has the drawback that tetraphenylphosphonium iodide (V) would be present in the reaction mixture. On the other hand it would be possible to filter the diborane solution under nitrogen prior to use but this would render the phase transfer method no more convenient than method (c).

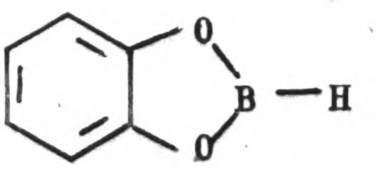
(e) In order to attempt to overcome the difficulties which might be foreseen due to directive effects in the hydroboration of unsaturated alcohols the possible use of selective hydroborating agents was considered. The use of several of these (VI-VIII) has been described[93] and they are obtained by the reaction of diborane with the appropriate alkene (disiamylborane, VI), or diene (9-borobicyclo[3.3.1]nonane, VII), or diol (1,3,2-benzodioxaborole, VIII) to give organoboranes having only one available boron-hydrogen bond. These products will hydroborate

alkenes with a high degree of regiospecificity because of their bulky nature.



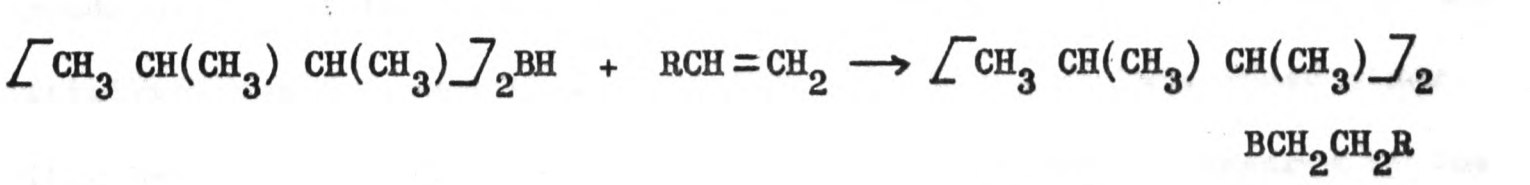
(VI)

(VII)

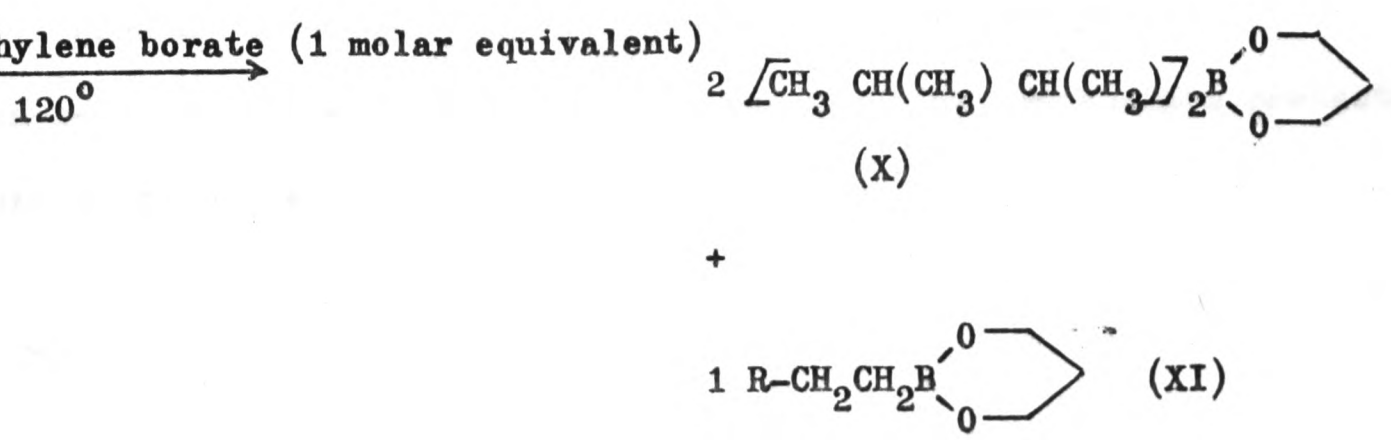


(VIII)

However where a hydroboration reaction is to be followed by a redistribution process, use for example of the organoborane (VI) or (VII), is likely to lead to complications. Thus the intermediate borane (e.g., IX) would redistribute with trimethylene borate to yield two products (X and XI) in the ratio 2:1. Thus for every mole of the desired product (XI) there would also be present in the reaction mixture two moles of a dioxaborinane derived from the reagent. Such a mixture is likely to present difficulties in separation.



(IX)



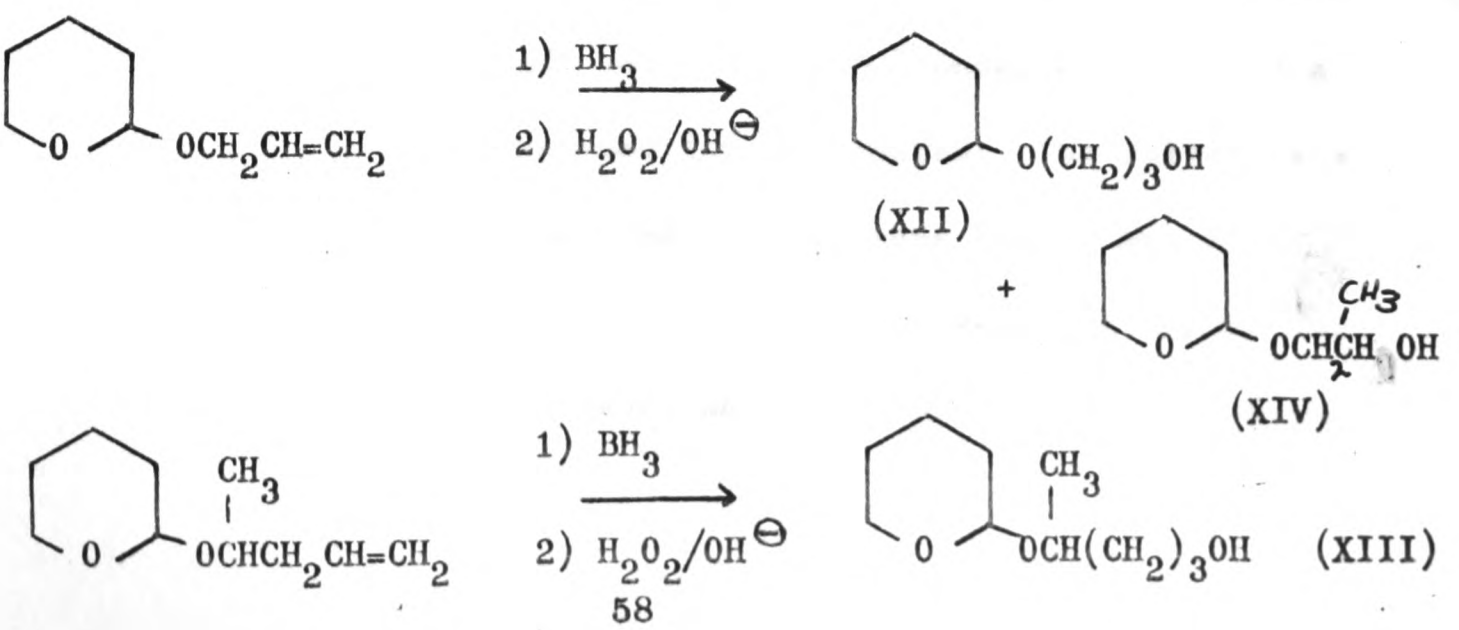
On the other hand the use of 1,3,2-benzodioxaborole (VIII) as a hydroborating agent would be particularly convenient since it would result in the formation of a 2-alkyl-1,3,2-benzodioxaborole, which on

aqueous hydrolysis would yield the alkaneboronic acid directly without the need for a redistribution process[41]. This reagent was prepared by the author by passing diborane gas, generated as previously described, into a cooled (0^{o}) solution of pure, dry 1,2-dihydroxybenzene in THF. The product was distilled under reduced pressure and was shown to be pure by g.l.c. and h.p.l.c. analysis. The i.r. spectrum in solution was identical to that reported in the literature[41].

Hydroboration-redistribution reactions.

As a preliminary study to the attempted synthesis of hydroxy-alkaneboronic acids by the hydroboration-redistribution route, some simple alkenes and tetrahydropyranyloxyalkenes were investigated.

Firstly the progress and efficiency of the hydroboration reactions were followed by oxidation of the reaction mixture with alkaline hydrogen peroxide followed by purification and characterisation of the alcoholic products. In this way it was possible to confirm the formation of the trialkylboranes from the selection of starting materials under study. Thus hexan-1-ol, characterised by g.l.c. analysis, was prepared by the hydroboration-oxidation of hex-1-ene and the monotetrahydropyranyl ether of propane-1,3-diol (XII) and 4-(2'-tetrahydropyranyloxy)--pentan-1-ol (XIII) were similarly prepared from the appropriate protected unsaturated alcohols



In the latter two cases the products were identified by i.r. and n.m.r. spectroscopy, and the yields were 80 and 86% respectively.

G.l.c. analysis of these monotetrahydropyranyl ether products revealed that although that from 2-(2'-tetrahydropyranyloxy)--pent-4-ene was a single component, the product from 1-(2'-tetrahydropyranyloxy)-prop-2-ene was a two component mixture of approximate ratio 9:1. The n.m.r. spectrum of this total crude product clearly showed two doublets (see p.51) at chemical shift values consistent with methyl groups, the integration of which indicated a minor component which is probably 2-(2'-tetrahydropyranyloxy)-propan-1-ol (XIV).

Having confirmed that the trialkylboranes were being readily formed in good yield in these reaction mixtures, attention was then turned to the redistribution reaction using trimethylene borate as reported by Brown[40]. The reagent was prepared in 95% yield by the literature method of azeotropic removal of water from a mixture of boric acid and propane-1,3-diol using a Dean and Stark apparatus. The product was distilled under reduced pressure, and its purity established by g.l.c. and h.p.l.c. analysis. In our laboratory this borate ester was found to be very labile towards moisture and so rigorous precautions in its preparation, purification, storage and use were employed.

In the general procedure adopted for the hydroboration-redistribution reaction, the alkene in THF was added at 0^0 under nitrogen to a diborane solution in THF and stirred for 30 minutes. The solvent was removed in the stream of nitrogen and trimethylene borate was added by syringe through a rubber septum. The mixture was then heated for 4 hours at 120^0 to form the dioxaborinane which was isolated, and on

hydrolysis with water yielded the boronic acid, i.e. in the case of hex-1-ene.

$$3\ C_4H_9CH{=}CH_2 \quad + \quad BH_3 \xrightarrow{0^\circ} (C_6H_{13})_3B$$

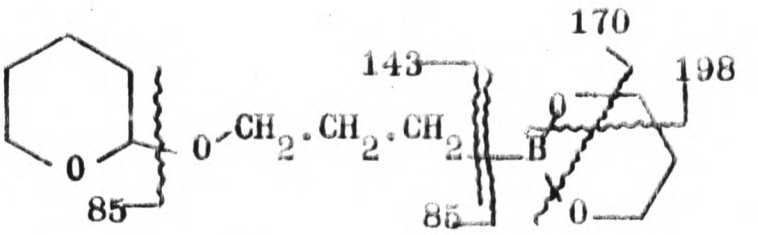
$$\xrightarrow[\substack{1\ \text{TRIMETHYLENE}\\ \text{BORATE}}]{120^\circ} 3\ C_6H_{13}{-}B\begin{array}{l}O\\ \diagup\\ \diagdown\\ O\end{array} \quad \text{(XVI)} \xrightarrow{6\ H_2O} 3\ C_6H_{13}B(OH)_2 \quad \text{(XV)} + 3\ HO(CH_2)_3OH$$

The i.r. spectrum of the product (XV) (I.r.2) showed absorption due to CH str. and B-O str., O-H str., and $(CH_2)_n$ rocking and was very similar to a spectrum of authentic commercial butaneboronic acid. It was identical with the spectrum of 1-hexaneboronic acid obtained by Grignard reaction route from 1-bromohexane (p.74). The n.m.r. spectrum (N.m.r. 5) contained a broad signal due to the $B(OH)_2$ moiety at δ 5.8-6.2 (cf. boric acid δ 5.75), and an unresolved multiplet and distorted triplet due to the alkyl residue. In a further experiment the intermediate boronate ester (2-hexyl-1,3,2-dioxaborinane, XVI) was isolated by distillation under reduced pressure from the reaction mixture and shown by g.l.c. and h.p.l.c. analysis to be identical to that prepared from reaction of 1-hexaneboronic acid with propane-1,3--diol. Its n.m.r. spectrum (N.m.r. 6) showed in addition to the signals described above for the alkyl residue, a quintet and a triplet in the ratio 1:2 due to the methylene protons of the dioxaborinane ring. These signals have the same chemical shift values as those shown in the spectrum of trimethylene borate (N.m.r. 7). The i.r. spectrum (I.r. 3) was completely different to that of trimethylene borate (I.r. 4)

but the B–O str. band at 1350^{-1} was clearly visible.

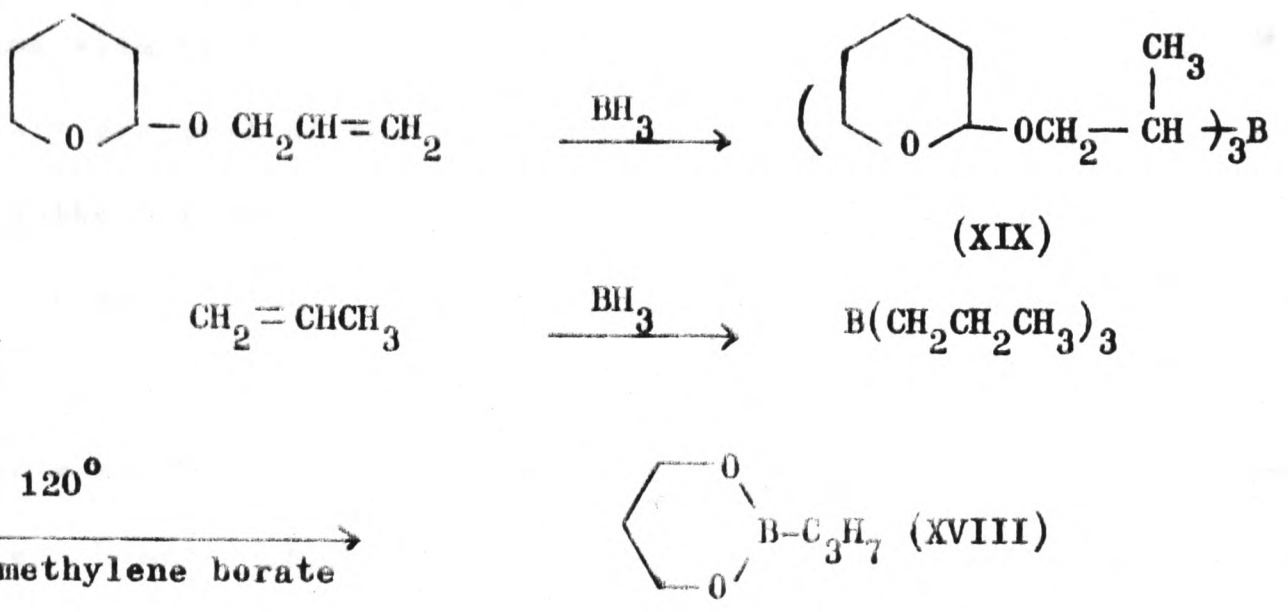
Following these preliminary studies with simple alkenes, each of the series of protected hydroxyalkenes (p.50) was subjected to the hydroboration–redistribution procedure. The reaction mixture arising from 1–(2'–tetrahydropyranyloxy)–prop–2–ene was distilled under reduced pressure and the distillate shown by g.l.c. analysis to consist of a five component mixture in which starting materials were absent. Only three components were demonstrated by t.l.c. and h.p.l.c. analysis, however. When this mixture was submitted to g.l.c./m.s. the results (M.s. 1–5) showed that the major component (66% of the mixture) was 2–(3–[2–tetrahydropyranyloxy]propyl)–1,3,2–dioxaborinane (M.s. 5). The suggested fragmentation pattern is shown in diagram (XVII) to explain the significant ions in the spectrum. This mode of fragmentation is in agreement with that observed by other workers on similar organo–boron heterocycles[94].

(XVII)



In addition, the above fragmentations were confirmed by the measurement of accurate masses of m/e 85, 143, and 170. The mass spectra of the other four components significantly all show m/e 85 as a major fragment which, in this work was found to be characteristic of a dioxaborinane ring and was invariably the most abundant fragment. However the molecular ion values are 101, 128, 187 and 187 which are not consistent with isomers of the major product which might have been expected to arise from the operation of directive effects, but it is likely that if such isomers were formed they would undergo side reactions of the type discussed on p.26 or isomerise to the terminal product (p.19).

The component having M^+ 128 (M.s. 2) could be 2-propyl-1,3,2--dioxaborinane (XVIII, molecular weight 128) which could arise by an elimination reaction of the isomer (XIX) followed by rehydroboration (Scheme 1).

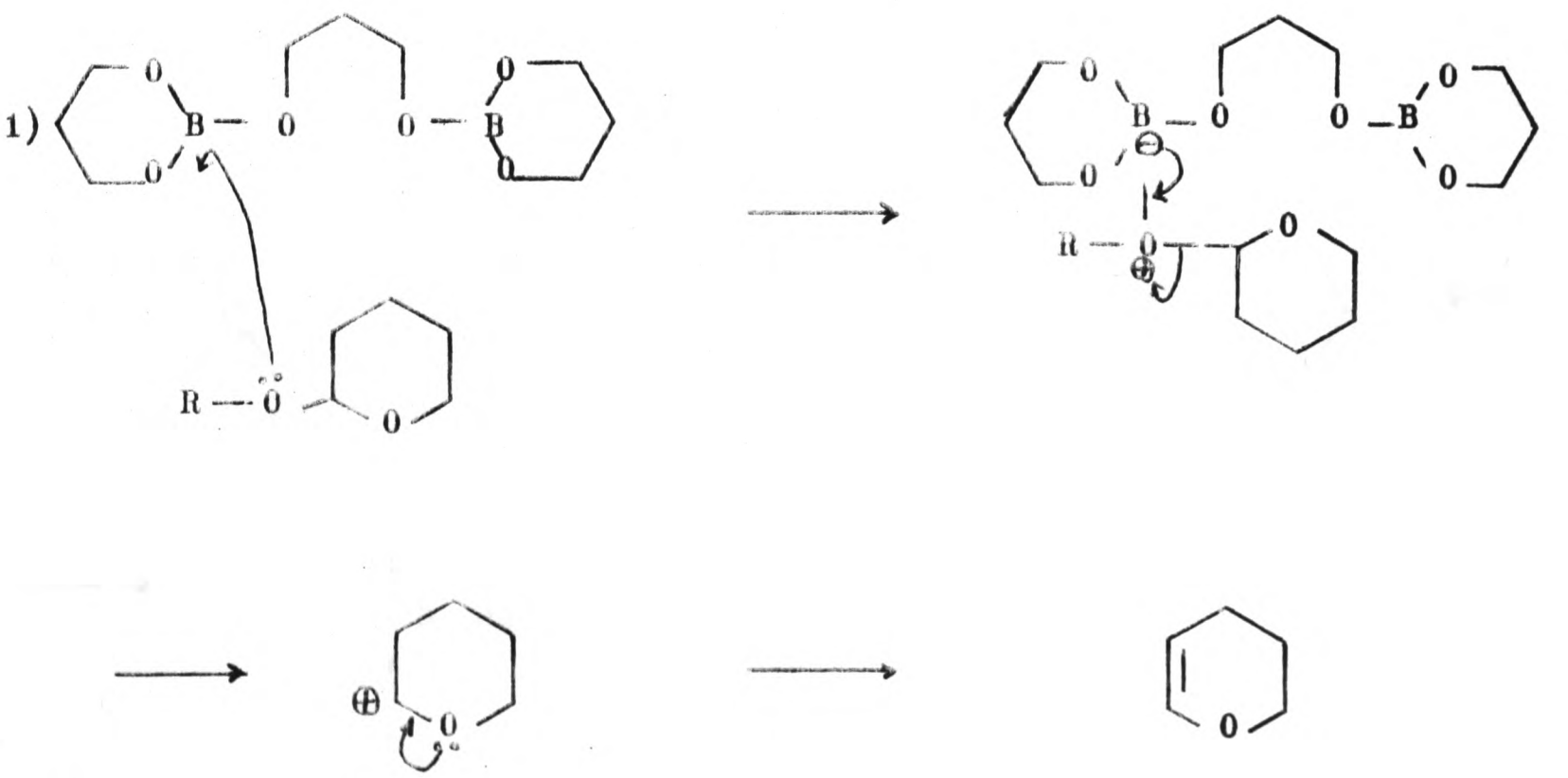


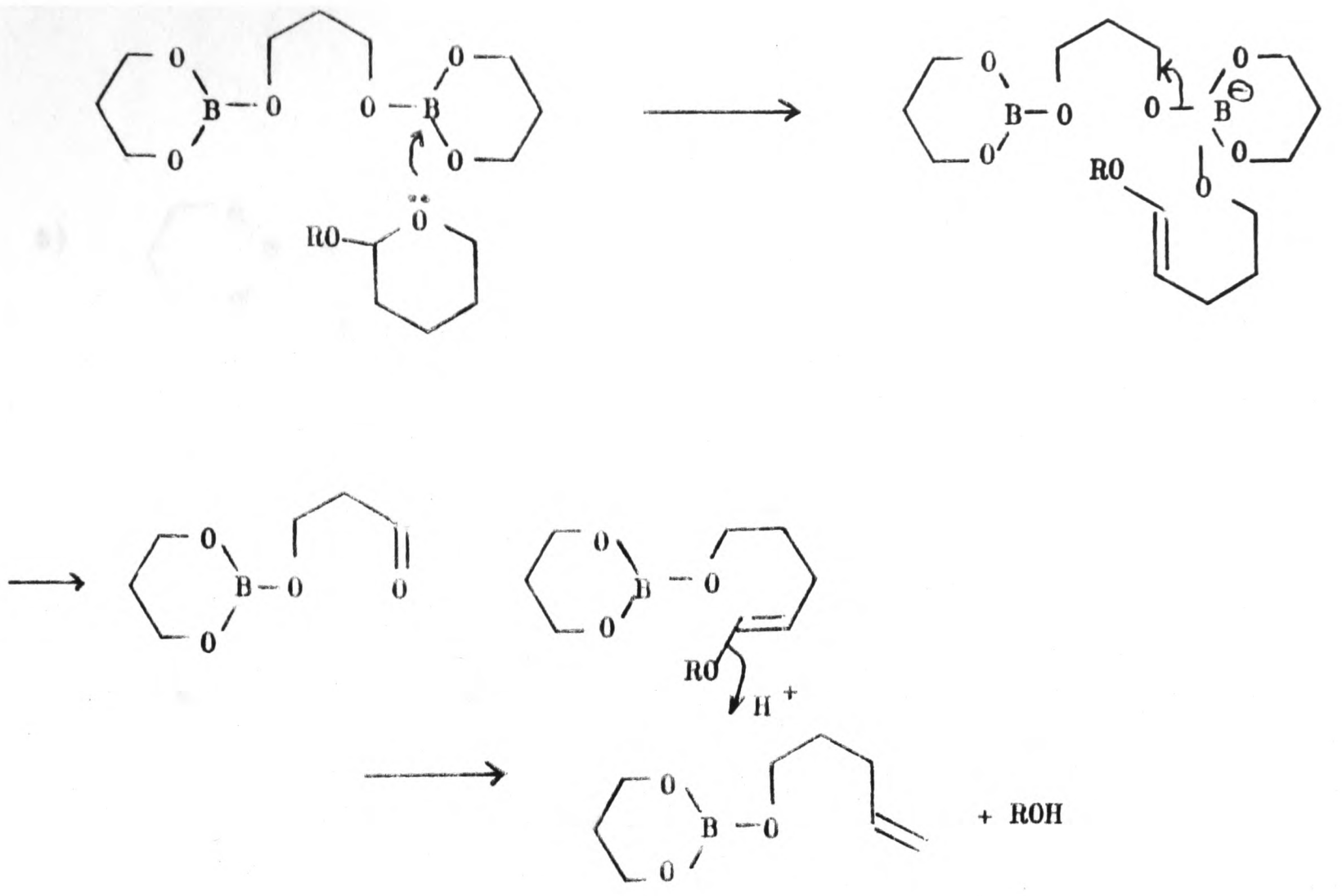
Scheme 1

The other products in this mixture cannot be accounted for as hydroboration by-products, and this led to a more detailed investigation of the stability of O-tetrahydropyranyl ethers to the redistribution reaction conditions. First, trimethylene borate was heated alone, and in the presence of diborane, and in each case g.l.c. analysis revealed an unchanged chromatographic trace. Also the i.r. and n.m.r. spectra of the liquid so treated were identical with those of authentic trimethylene borate. Possible interactions between trimethylene borate and various protected hydroxyl systems (see also p.109) were next investigated. Thus 1-(2'-tetrahydropyranyloxy) propane, 2-(2'-tetrahydropyranyloxy)pent-4-ene, dibenzyl ether, and 1,2-O-cyclohexylidene--3-O-ethyl glycerol (p.87) were each heated at 120° for 4 hours with trimethylene borate, and the reaction was monitored by g.l.c. analysis. The results showed that in the first two examples, although the starting

materials were not completely consumed, several other components appeared in the chromatographic trace. In the last two examples no chromatographic change had taken place.

In the case of the interaction of 1-(2'-tetrahydropyranyloxy) propane with trimethylene borate the presence of dihydropyran and possibly propan-1-ol was demonstrated by comparative g.l.c. analysis with authentic samples and at least four other components were shown to be present in the mixture. It was considered likely that since dihydropyran and propan-1-ol are probably present some of the other products may have arisen by reaction of these compounds with trimethylene borate. Hence, dihydropyran and propan-1-ol were separately heated with trimethylene borate for 4 hours at 120°. Each of these reaction mixtures revealed a chromatographic trace corresponding to two of the products in the original mixture. In the case of propan-1-ol the starting compounds were consumed after 1 hour. The following reactions are postulated for the interaction of trimethylene borate with an O-tetrahydropyranyl ether (Scheme 2).





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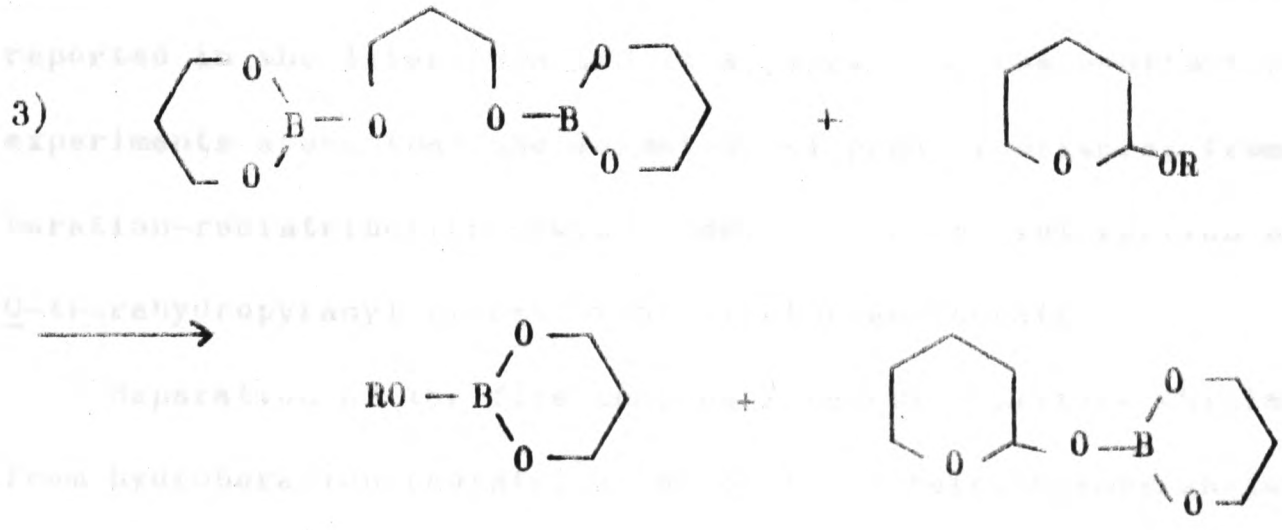

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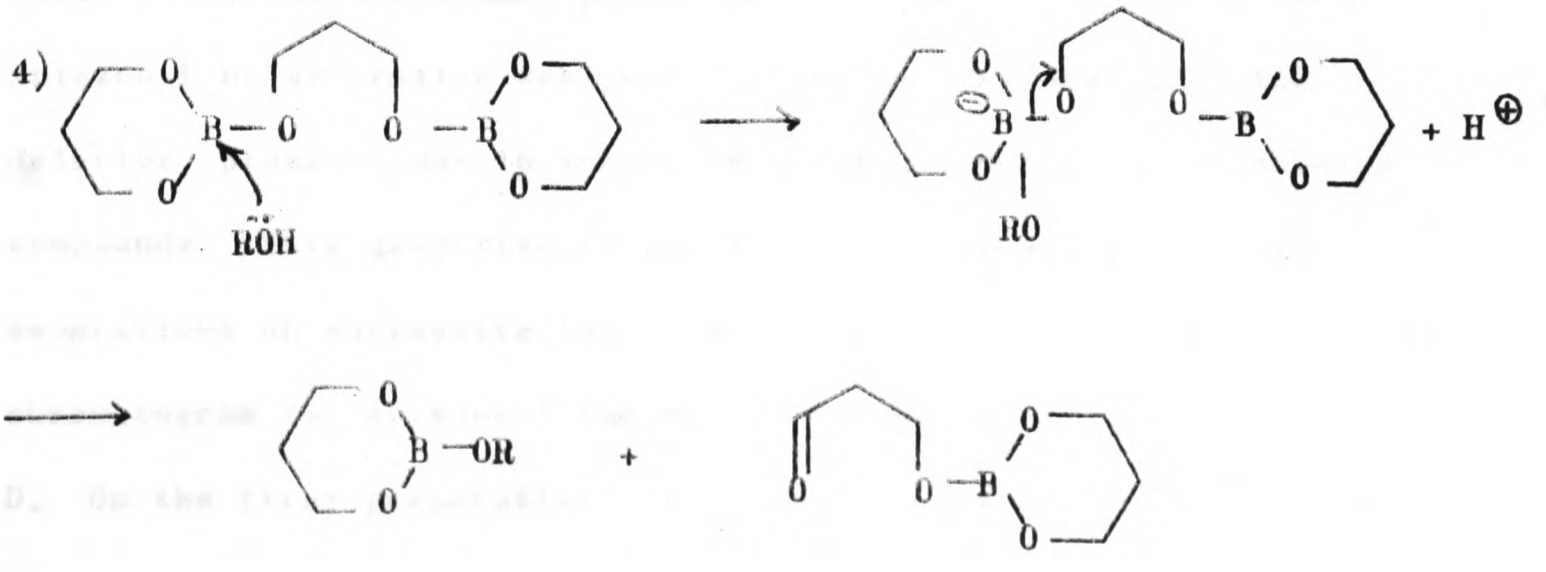
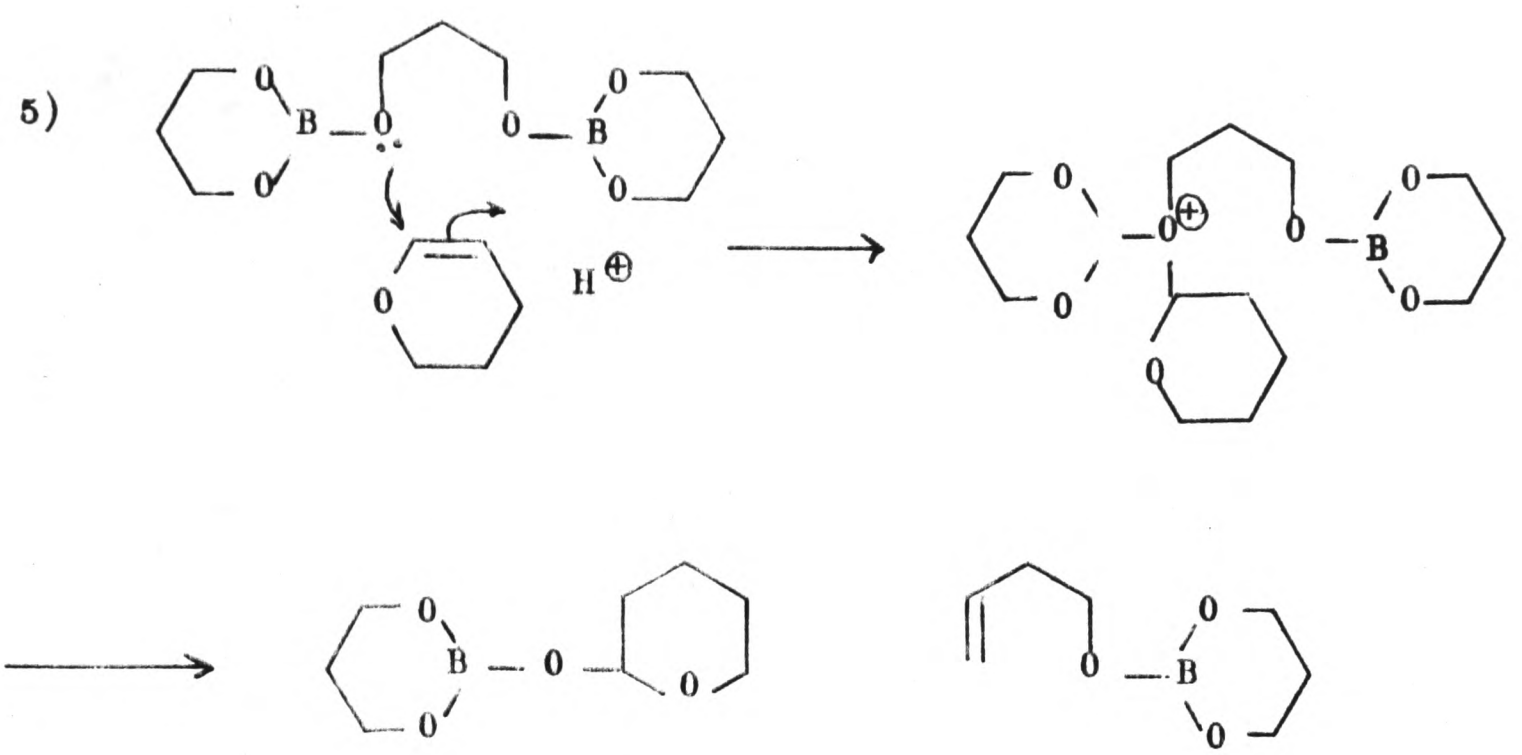




Scheme 2.

Further study of this aspect is clearly required since hydroboration-redistribution of polyfunctional systems has not been reported in the literature and it appears from the preliminary experiments above that the formation of product mixtures from hydroboration-redistribution could be due in part to interaction of O-tetrahydropyranyl ethers with trimethylene borate.

Separation of the five component reaction mixture obtained from hydroboration-redistribution of 1-(2'-tetrahydropyranyloxy)--prop-2-ene was attempted using preparative g.l.c.; the use of three different stationary phases was examined. With SE 52 and Apiezon L no separation was possible due to overloading of the detector, probably due to the build-up of non-volatile organoboron compounds. This gave rise to rapidly declining sensitivity and separations on successive injections. Fig 2(a) shows the analytical chromatogram for Apiezon L the major components are labelled A, B, C, D. On the first preparative chromatograms Figs 2(b) and 2(c) the

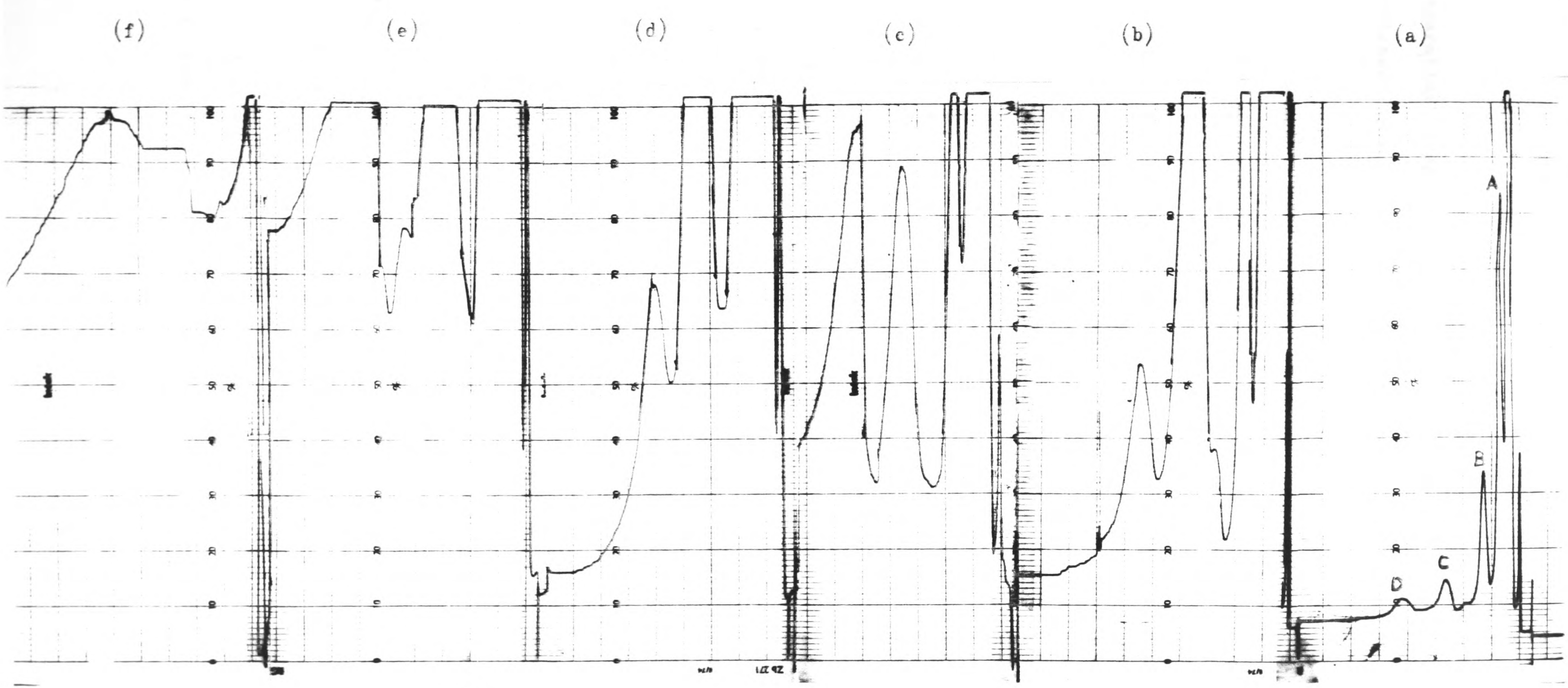


Fig. 2 Successive preparative gas-liquid chromatograms of the product mixture from the hydroboration-redistribution reaction of 1-(2'-tetrahydropyranyloxy)-prop-2-ene.

separation is good except that A is included in the solvent front. On later chromatograms Figs. 2(d) and 2(e) peak B is lost in the solvent front and the resolution is extremely poor. After about eight 100 μl injections all resolution was lost and a trace such as Fig. 2(f) was obtained. With Carbowax as the stationary phase separation of the major product (2-(3-[2'-tetrahydropyranyloxy]-propyl)-1,3,2-dioxaborinane) was achieved, although a white solid material was observed in the collection tubes. It is possible that this dioxaborinane derivative decomposes on the g.l.c. column, although in the case of the chromatography of the simpler 2-hexyl--1,3,2-dioxaborinane only one peak was obtained. The product isolated from the above preparative g.l.c. separation on Carbowax was shown to be a single component on the corresponding analytical column. The i.r. spectrum was consistent with the presence of a dioxaborinane ring and the n.m.r., although poorly resolved due to an insufficient quantity of sample, showed the characteristic dioxaborinane triplet and quintet as well as the tetrahydropyranyloxy signals. This pure product was hydrolysed with warm water and a few white crystals were obtained, the n.m.r. spectrum of which showed signals which were consistent with a trimethylene structure and a $-B(OH)_2$ group. The solid material from the preparative g.l.c. collection tubes was identified as boric acid, which was also obtained by the action of water on the crude five component reaction mixture. When 1-(2'-tetrahydropyranyloxy)-pent-4-ene was subjected to hydroboration-redistribution a single product by g.l.c. analysis was isolated by distillation of the reaction mixture under reduced pressure. The i.r. spectrum had bands consistent with a dioxaborinane but also

an O–H str. band. N.m.r. spectroscopy and m.s. revealed the presence of a tetrahydropyranyloxy group but did not confirm the presence of a boron moiety. Microanalysis results and the molecular weight from the mass spectrum led to a possible empirical formula of $C_{10}H_{20}O_2$ which is not consistent with a product of hydroboration–redistribution of the alkene. The products obtained from application of the hydroboration redistribution producedure to the other protected hydroxyalkenes (p.50) were all multicomponent mixtures by g.l.c. analysis. In all cases the i.r. and n.m.r. spectra were consistent with the present of dioxaborinane ring systems. However, aqueous hydrolysis of the crude mixtures in each case resulted in the formation of crystals of boric acid and an oily liquid which was extracted with ether from the aqueous solution. It was hoped and expected that even with product mixtures the dioxaborinanes would hydrolyse to crystalline boronic acids. However, the effect of the tetrahydropyranyloxy group may be to make the boronic acid products liquids and in this case a mixture of such acids would be more difficult to separate than the esters. The formation of boric acid on hydrolysis of the reaction mixtures indicates that some interaction has occurred between the protecting group and the borate ester reagent. This is because only borate esters and not boronate esters hydrolyse to boric acid and trimethylene borate itself was shown to be absent.

It is concluded from the above study that the best method of analysis of the dioxaborinane mixtures was g.l.c. but separation of such multicomponent mixtures is likely to be best achieved using h.p.l.c. if an appropriate column and solvent system could be found.

It is also envisaged that future work on the hydroboration-redistribution process using hydroxyalkenes would require selection of an alternative protecting group, which would have to be hydrolytically stable, as well as being a poor leaving group to minimise possible elimination reactions. Although the use of methyl ethers might be envisaged the problem of their ultimate removal would need to be borne in mind.

The above results prompted a reappraisal of the older method of synthesis of boronic acids, *via* hydroboration, followed by equilibration of the hydroboration mixture at 50^{o} for 6 hours with a large excess of diborane[39]. The example selected was allyl benzyl ether in which the protecting group was hydrolytically stable. The compound was prepared by the reported reaction of allyl alcohol with excess benzyl chloride and potassium hydroxide in toluene at reflux temperature[95], and the derivative was isolated in 68% yield by fractional distillation. The hydroboration product was subjected to equilibration as described above and then water was carefully added. Crystals formed on cooling and the i.r. and n.m.r. spectra were consistent with a mixture of the required boronic acid (XVIII) and boric acid.

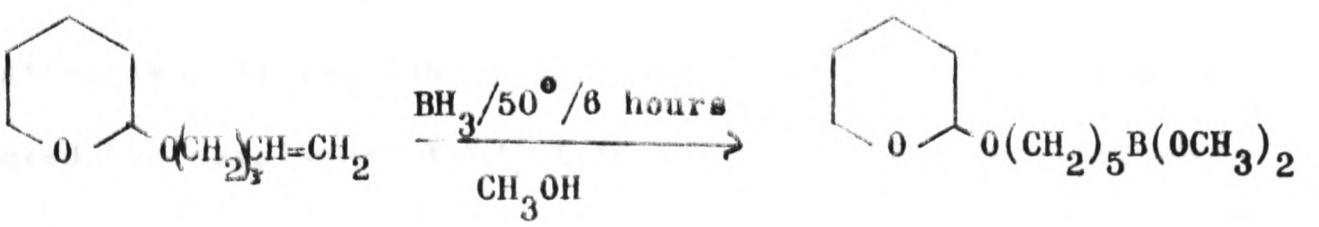
$$C_6H_5CH_2Cl + HOCH_2CH=CH_2 \xrightarrow{KOH} C_6H_5CH_2OCH_2CH=CH_2 + KCl + H_2O$$

$$\xrightarrow{BH_3/50^{o}/6\ hours} C_6H_5CH_2O(CH_2)_3BH_2 \xrightarrow{H_2O} C_6H_5CH_2O(CH_2)_3B(OH)_2$$

(XVIII)

Boric acid cannot be avoided in this reaction since it arises from hydrolysis of excess diborane but a solvent extraction procedure was developed to separate the mixture. This involved shaking the solid mixture with pentane/ether 1:1 v/v and filtering the undissolved boric acid; the resulting solution of the boronic acid was then evaporated. In this way a very small yield of syrupy material was obtained which had i.r. and n.m.r. spectra consistent with the structure (XVIII). The same hydroboration-equilibration procedure was applied to 1-(2'-tetrahydropyranyloxy)-pent-4-ene and 2-(2'-tetrahydropyranyloxy)--but-3-ene and similar results obtained. In the latter case the i.r. and n.m.r. spectra and microanalysis were consistent with the boronic anhydride.

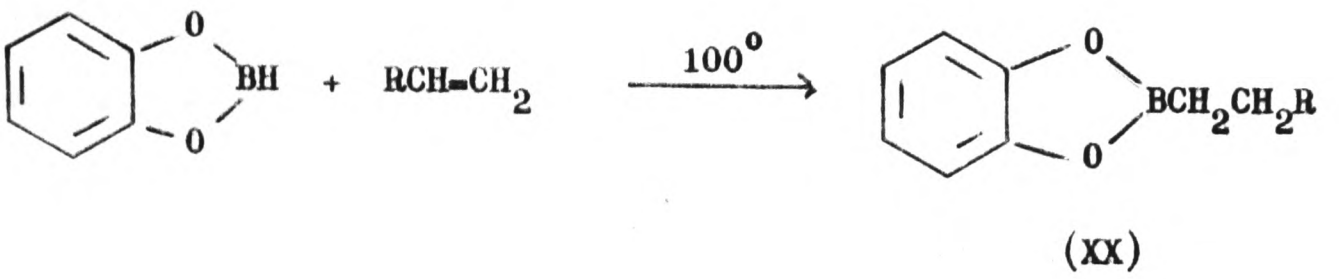
Because the isolation of boronic acids after hydroboration--equilibration was not as efficient as expected, a further experiment was performed to prepare a dimethyl hydroxyalkaneboronate. 1-(2'-tetrahydropyranyloxy)-pent-4-ene was heated at 50^{0} for 6 hours with excess diborane and then methanol was added dropwise to the equilibration mixture. Dimethyl-1-(5-⌈2'-tetrahydropyranyloxy⌋-pentaneboronate (XIX) was distilled under reduced pressure from the final reaction mixture. The product was pure by g.l.c. analysis and was characterised spectroscopically (I.r.6 and N.m.r.9).



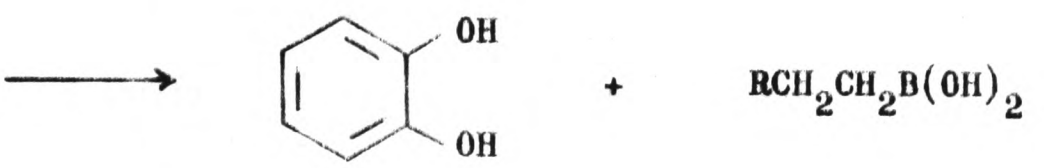
(XIX)

The use of 1,3,2-benzodioxaborole

The following reaction sequence was envisaged as a possible means to overcome some of the difficulties discussed above:



(XX)



That this is a practical possibility was verified in the case of hex-1-ene, which when heated at 100° for two hours with the freshly prepared reagent gave a product in 97% yield consistent with (XX, $R=C_4H_9$). The product was distilled from the reaction mixture and shown to be pure by g.l.c. analysis. The n.m.r. (N.m.r.10) in addition to signals previously described due to the hexyl moiety showed a signal at low field with an AA'BB' splitting pattern due to the aromatic protons. The i.r. spectrum (I.r.7) contained absorption due to B-O str. and aromatic stretching frequencies. microanalysis was not possible because of rapid decomposition to a white solid during weighing. Hydrolysis of an aliquot portion of the product with cold water produced crystals of 1-hexaneboronic acid.

Attempted utilisation of this reagent with an example of a protected hydroxyalkene, 1-(2'-tetrahydropyranyloxy)-prop-2-ene, and a protected hydroxyalkyne, 1-(2'-tetrahydropyranyloxy)-prop-2-yne,

however in each case resulted in a red intractable, non-distillable tar. This result is clearly associated with the presence of a tetrahydropyranyloxy group which may interact with the reagent, as previously postulated for the redistribution reaction, and therefore this route also requires further investigation using alternative protecting groups.

In summary, therefore, the hydroboration route to boronic acids utilising several previously reported procedures[39–41] has been applied in this work to new polyfunctional systems and evidence for the formation of the following compounds has been obtained:

5-Hydroxypentaneboronic acid,

3-Hydroxybutaneboronic anhydride,

3-Benzyloxypropaneboronic acid,

2-(3-⌈2'-tetrahydropyranyloxy⌋propyl)-1,3,2-dioxaborinane, and

Dimethyl-1-(5-⌈2'-tetrahydropyranyloxy⌋)-pentaneboronate.

Because of great practical difficulties in the purification of the compounds only the first two are supported by elemental analysis, characterisation of the others was spectroscopic.

(B) SYNTHESIS OF BORONIC ACIDS VIA ORGANOMETALLIC REAGENTS

This route to alkaneboronic acids involves the reaction of a metal-alkyl reagent such as an alkylmagnesium halide with a borate ester at low temperature followed by hydrolysis of the resulting boronate ester with aqueous acid (Scheme 3). The literature procedures[17,32] recommend an "inverse addition" method under carefully specified conditions.

$$RMgBr + B(OC_4H_9)_3 \longrightarrow BrMg^{\oplus}[RB^{\ominus}(OC_4H_9)_3]$$

$$\longrightarrow RB(OC_4H_9)_2 + MgBr(OC_4H_9)$$

$$\xrightarrow{H_3O^{\oplus}} RB(OH)_2 + 3\ C_4H_9OH + MgBrOH$$

Scheme 3

The preparation of 1-hexaneboronic acid was selected to check the synthetic procedures involved, to gain experience in the appropriate practical techniques and to obtain a supply of a boronic acid for the oxidative studies previously described (p.53). The detailed study of 1-hexaneboronic acid and its derivatives correlated the various synthetic transformations which were being investigated in this project. For example, the optimum conditions and techniques for hydroboration-redistribution (p.60), the preparation of a 2-alkyl-1,3,2-benzodioxaborole (p.71), the preparation of an alkaneboronic acid via a Grignard reagent, and esterification of an alkaneboronic acid (p.75) were established by reference to the synthesis of 1-hexaneboronic acid. Thus

following the reported procedure[17] hexylmagnesium bromide in ether was added dropwise over three hours to tributyl borate in ether at -60 to -70° with vigorous stirring. Dilute sulphuric acid was added after a further 4 hours stirring at the same temperature followed by slow warming to 0°. The mixture was neutralised with sodium hydroxide solution and subjected to repeated evaporation at reduced pressure to remove butan-1-ol as an azeotrope with water. On cooling 1-hexaneboronic acid crystallised in 65% yield. The product had properties consistent with those reported in the literature (see p.60).

In a further experiment to elucidate more fully the optimum isolation procedure, the ethereal solution was evaporated to a thick syrup which was not distillable. This re-dissolved readily in ether and the solution was stirred with water when a white solid formed at the interface between the two layers. The solid was isolated and found to be inorganic, magnesium and bromide being indentified. The alkaline aqueous layer had the smell of butan-1-ol and on evaporation a solid identical to that described above was obtained. The ethereal layer was evaporated and the butan-1-ol was removed azeotropically as before. On cooling 1-hexaneboronic acid was obtained in a 31% yield. Thus, the initial product mixture must have hydrolysed with water as follows and the use of acidic hydrolysis conditions is not therefore necessary to obtain the boronic acid.

$$MgBr(OC_4H_9) + H_2O \longrightarrow C_4H_9OH + MgBrOH$$

$$RB(OC_4H_9)_2 + 2H_2O \longrightarrow RB(OH)_2 + 2C_4H_9OH$$

It should be noted however that definitive characterisation of

alkaneboronic acids is difficult because their i.r. and n.m.r. spectra tend to lack resolution, and melting points are unreliable due to the transition to the liquid anhydride on heating. Indeed it was shown in the present study that thermogravimetric analysis of 1-hexaneboronic acid revealed a continuous weight loss from room temperature to 300° indicating a gradual loss of water through formation of the anhydride probably followed by evaporation of the liquid product. A differential thermal analysis could be usefully performed in the future to confirm that anhydride formation does not occur at a distinct temperature and to check on the sharpness of the melting point.

It was concluded that alkaneboronic acids are likely to be best characterised as volatile ester derivatives (e.g., dioxaborinanes) which have distinctive i.r. and n.m.r. spectra and are amenable to distillation and analysis by g.l.c. and h.p.l.c.

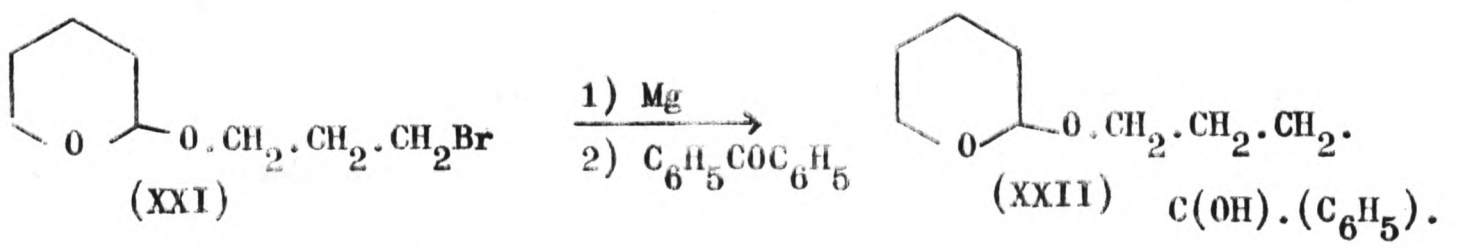
Synthesis of boronic acids from Grignard derivatives of halohydrins.

In the initial studies on the application of the Grignard method to α,ω-halohydrins as starting materials leading to hydroxyalkaneboronic acids, two problems arose. Firstly it is necessary to effect some form of protection of the hydroxyl group, and secondly, the relative positions of the halogen and the protected hydroxyl group prevent the formation of normal organometallic derivatives in some cases. As such difficulties were envisaged with 1,2-bromohydrins[37], the first compound to be studied was 3-bromo-propan-1-ol. The tetrahydropyranyl ether of this bromohydrin (XXI) was prepared in 86% yield by the standard procedure (p. 49), and distilled under reduced pressure. The i.r. and n.m.r. spectra were identical to those previously reported. Cowie[86] reported difficulty with the standard method and speculated, without isolation and

characterisation of any products, that the following reaction sequence occurred:

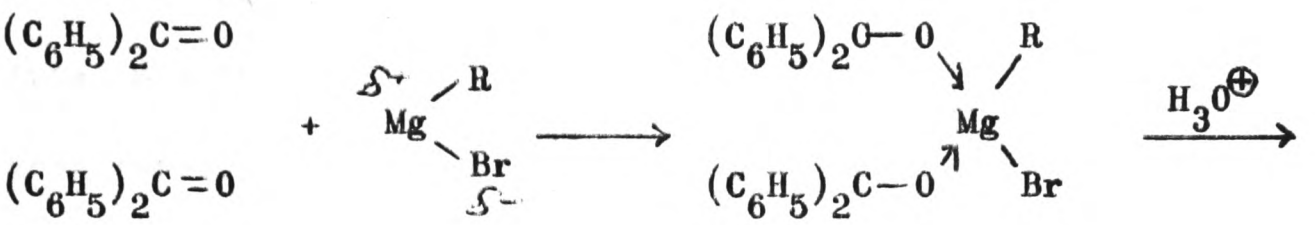
However the product obtained in the present study was found to be pure by g.l.c. analysis, and its i.r. and n.m.r. spectra were identical with those reported by Cowie for a product obtained by an indirect route involving reaction of the bromohydrin with 1-(2'-tetrahydropyranyloxy)-butane.

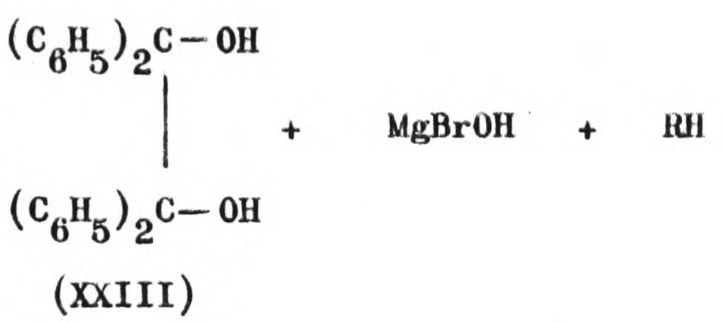
The reaction of 1-(2'-tetrahydropyranyloxy)-3-bromopropane (XXI) with magnesium proceeded smoothly in THF using an entrainment procedure for initiation of the reaction, and when all the magnesium had dissolved, one molar equivalent of benzophenone in THF was added to the solution; the purpose was to isolate and characterise the expected carbinol product (XXII) and thus confirm that the protected 3-bromopropan-1-ol does indeed form a normal Grignard derivative.



However, the addition of benzophenone was accompanied by the appearance of a deep red colouration, which disappeared immediately from a sample when removed for spectroscopic analysis. After work-up by the standard method a crystalline product was isolated and identified as benzopinacol (1,1,2,2-tetraphenylethane-1,2-diol, (XXIII). The yield of this product indicated that at least 50% of the benzophenone had

undergone a radical coupling reaction, and the following mechanism is proposed:



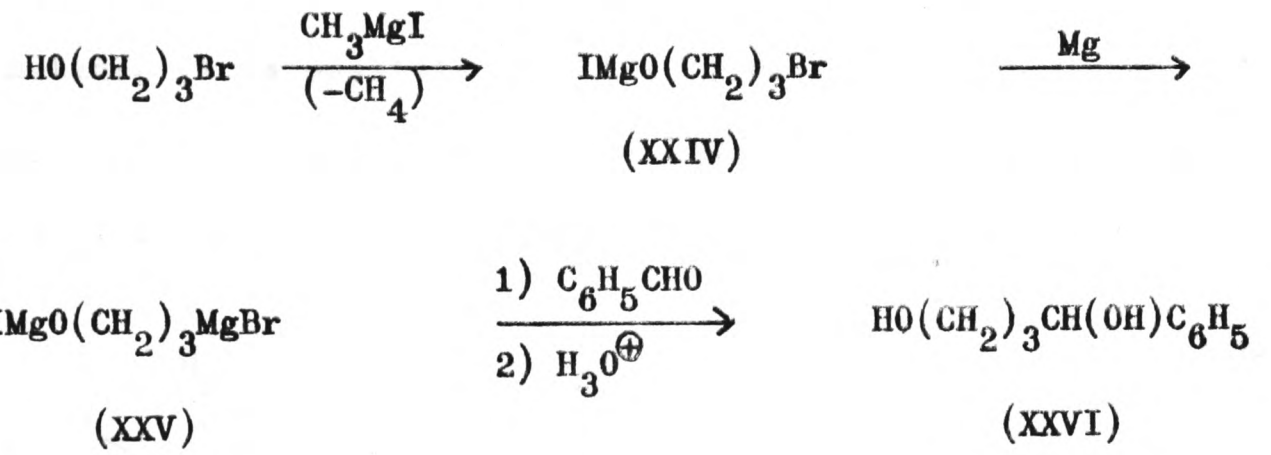


(XXIII)

In addition, a small quantity of a liquid product was isolated which was carefully distilled in a micro apparatus. G.l.c. analysis established purity and the n.m.r. and i.r. spectra were consistent with the product being 1-(2'-tetrahydropyranyloxy)-propane. This was confirmed by g.l.c. analysis of a 1:1 mixture of the product with authentic 1-(2'-tetrahydropyranyloxy)-propane (p. 50) which resulted in a single peak. This product could have arisen from the action of water on 1-(2'-tetrahydropyranyloxy)-propylmagnesium bromide or <u>via</u> the reaction scheme above. Thus although no model derivative (XXII) was obtained from this experiment, it appears probable that the desired Grignard derivative was formed and the protected bromohydrin (XXI) may therefore be a suitable starting material for boronic acid synthesis. In fact, such reaction, when attempted, proved unsuccessful. A few milligrams of a brown sticky oil were isolated, g.l.c. analysis of which revealed the presence of unreacted protected bromohydrin.

As a preliminary to an alternative boronic acid synthesis starting

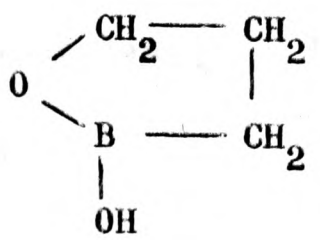
from a bromohydrin the formation of the carbinol (XXVI) was envisaged by the route shown in Scheme 4. Protection of the hydroxyl group in 3-bromopropan-1-ol was achieved by the use of methylmagnesium iodide. This <u>in situ</u> protected intermediate (XXIV) was then subjected to reaction with magnesium to give (XXV) followed immediately by addition of benzaldehyde. After conventional work-up the product isolated was consistent with 1-phenylbutane-1,4-diol (XXVI):



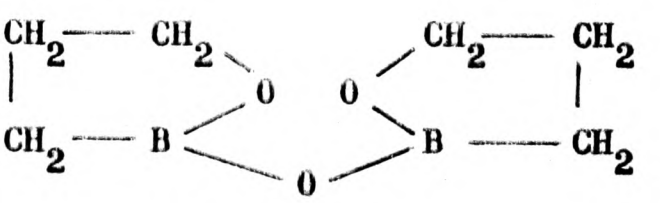
Scheme 4

Reaction of this Grignard reagent with tributyl borate was then attempted. However, using the same conditions as those used successfully for the preparation of 1-hexaneboronic acid no hydroxyalkaneboronic acid could be isolated. On removal of ether the initial product prior to hydrolysis was a yellow syrup which was not distillable. On careful hydrolysis with an excess of water the smell of butan-1-ol was observed and this compound was removed as usual by azeotropic distillation under reduced pressure at room temperature and the crude produce was then stored at 0^{o}. No crystals formed apart from a small quantity of boric acid so the water present was removed by reduced pressure evaporation and the residue thus obtained was entirely inorganic as shown by its i.r. spectrum and failure to produce a black residue on

burning. Clearly the products from this reaction must have been volatile and hence lost during the rotary evaporation procedures. This prompted a re-examination of the 1-hexaneboronic acid synthesis. In this experiment (p. 74) the reaction mixture was subjected to the same work-up and isolation procedure as described above and the boronic acid was finally obtained in average yield (40%). Therefore two possibilities seem likely; (a) the properties of a hydroxyalkane-boronic acid are different from those of an alkaneboronic acid, for instance it is possible that the product may have lactonised (<u>cf.</u> p.14) and such a product of structure (XXVII) or (XXVIII) is likely to be volatile under the conditions of removal of butan-1-ol.

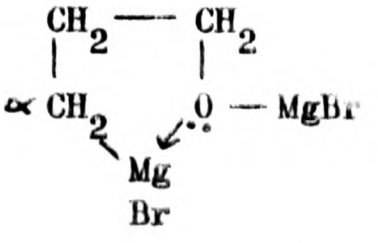


(XXVII)



(XXVIII)

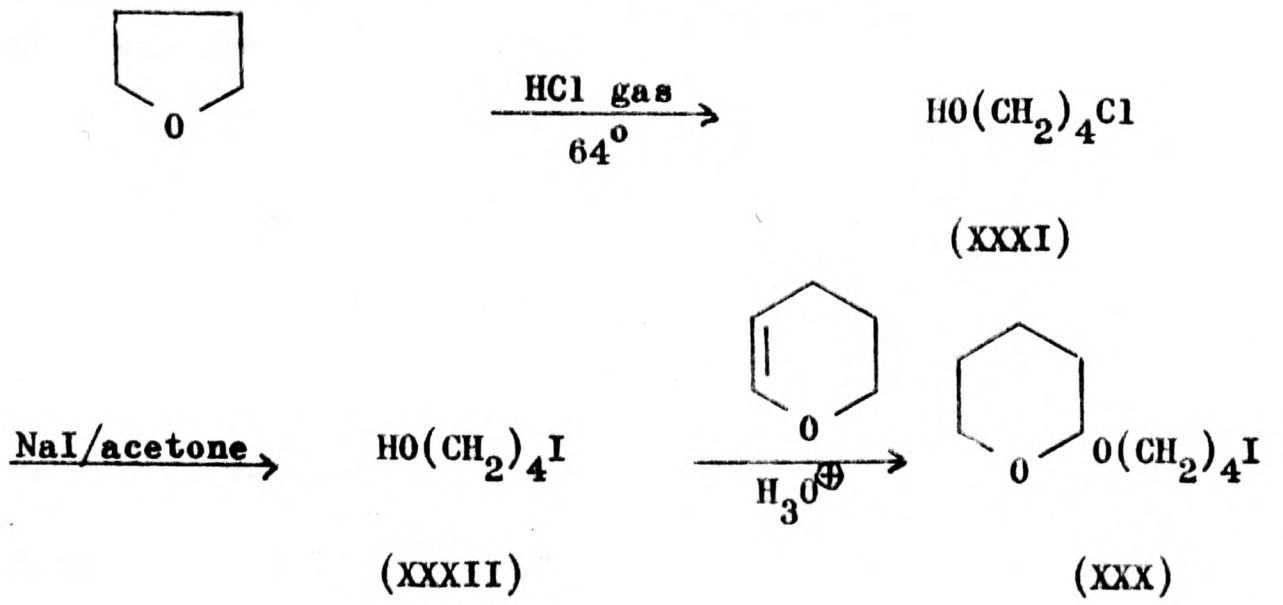
and (b) the above desired Grignard synthesis was not successful although the Grignard reagent (XXV) itself was probably formed. This latter hypothesis may be rationalised by postulating a co-ordinated Grignard derivative in which the oxygen atom donates its lone pair of electrons to the electrophilic magnesium atom resulting in the formation of the five-membered cyclic structure (XXIX). The α-carbon atom, therefore, (which is the reactive site of a Grignard reagent) would become less nucleophilic and less reactive towards a site surrounded by bulky groups such as the boron atom in tributyl borate.



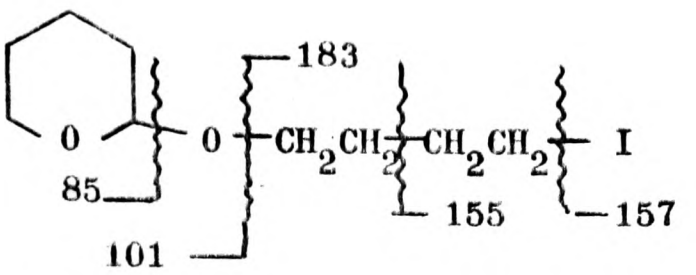
(XXIX)

The volatile product could then have been propan-1-ol arising from aqueous hydrolysis of the unreacted Grignard derivative (XXV).

In the development of this study a 1,4-halohydrin was examined since the formation of a boronate ester (although not the acid) via a Grignard reagent has been described previously for such a system[31]. A convenient route to 1-(2'-tetrahydropyranyloxy)-4-iodobutane (XXX) was achieved starting from tetrahydrofuran:



4-Chlorobutan-1-ol (XXXI) was readily prepared by passing hydrogen chloride gas into boiling tetrahydrofuran for 6 hours[96]. The tetrahydrofuran was evaporated and the product distilled under reduced pressure; it was characterised by g.l.c. analysis, i.r. and n.m.r. spectroscopy. 4-Iodobutan-1-ol (XXXII) was obtained by conversion of the 4-chlorobutan-1-ol using a Finklestein halogen exchange reaction[97]. This was achieved by shaking the chloride with sodium iodide and acetone at room temperature. This product was then further converted into its 2'-tetrahydropyranyloxy derivative (XXX) using the standard method previously described (p. 49) and characterised by mass spectrometry (M.s. 6); the proposed fragmentation pathway is shown below.



The 2'-tetrahydropyranyloxy derivative of 4-chlorobutan-1-ol was also prepared and a Finklestein exchange reaction on the halogen atom was attempted. In this case a mixture of the required product (XXX) and 4-iodobutan-1-ol was isolated from which it was concluded that cleavage of the protecting group had occurred.

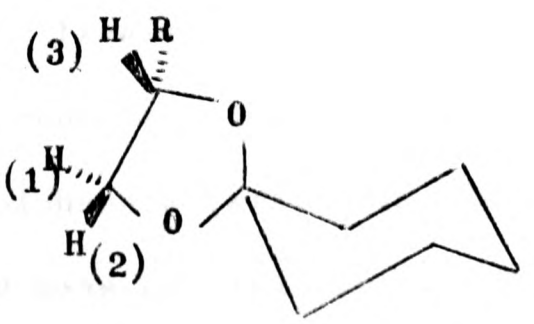
1-(2'-tetrahydropyranyloxy)-4-iodobutane was added in THF to magnesium. After an entrainment procedure that initiated the reaction, most of the magnesium slowly dissolved. Benzaldehyde was added to the reaction mixture which was then heated under reflux for one hour. After a standard isolation procedure the product was distilled under reduced pressure and found to be a single componant, distinct from the starting material, by g.l.c. and t.l.c. analysis. The i.r. and n.m.r. spectra revealed the presence of a hydroxyl group but no aromatic ring. Because of the doubtful result of this reaction, it was decided not to attempt a further reaction with magnesium followed by treatment with tributyl borate.

In conclusion, therefore, the Grignard route has not proved successful for the conversion of 1,3- and 1,4-halohydrins into hydroxyalkaneboronic acids.

(C) SYNTHESIS OF BORONIC ACIDS FROM GLYCEROL DERIVATIVES.

Prior to investigation of the reactions of cyclic systems possessing more rigid structures than simple halohydrins and hydroxyalkenes (e.g., monosaccharides) it was first necessary to examine a simple cyclic compound and 1,2-O-cyclohexylidene glycerol (XXXIII) was selected as a model sugar. It was envisaged that introduction of suitable functional sites for boronic acid synthesis might be achieved by a variety of reactions. For example, introduction of a halogen atom for the preparation of a Grignard derivative might be possible by replacement of a free hydroxyl group. Alternatively, a carbon-carbon double bond might be introduced by an elimination reaction or by chain extension reactions, for example using vinyl- or allyl- organometallic reagents. Since it is well known that cyclic acetals are compatible with such organometallic reagents[81], no problems arising from the presence of the cyclohexylidene protecting group were expected. If these preliminary studies proved informative, the methods used could then be applied to monosaccharides.

Glycerol was treated with cyclohexanone in the presence of sulphuric acid, and 1,2-O-cyclohexylidene glycerol (XXXIII) was obtained in 47% yield.



XXXIII, R = $-CH_2OH$

XXXIV, R = $-CH_2OSO_2C_6H_4CH_3$

XXXV, R = $-CH_2I$

XXXVI, R = $-CH_2B(OH)_2$

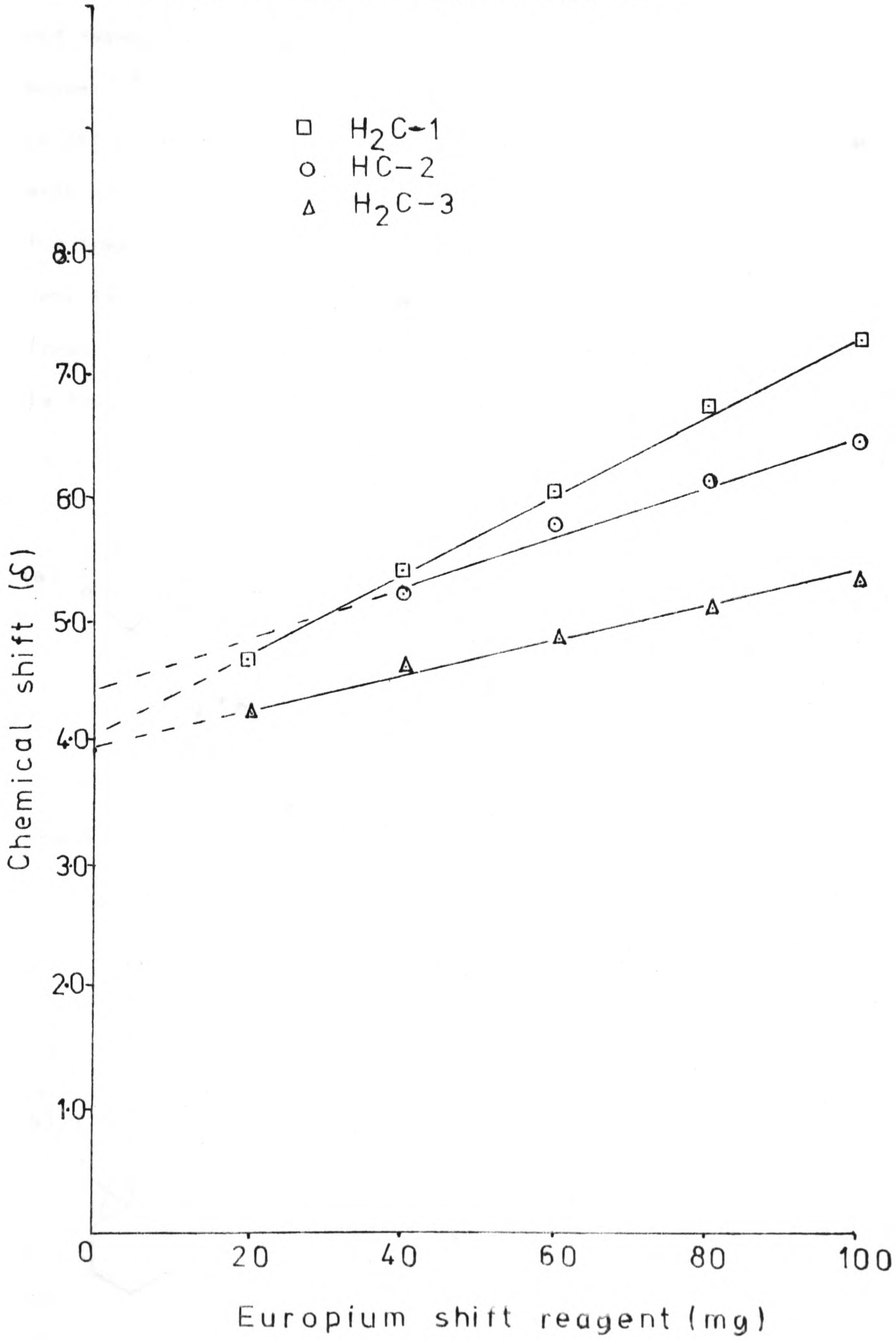
XXXVII, R = $-CH_2CH=CH_2$

XXXVIII, R = $-CH_2CH_2CH=CH_2$

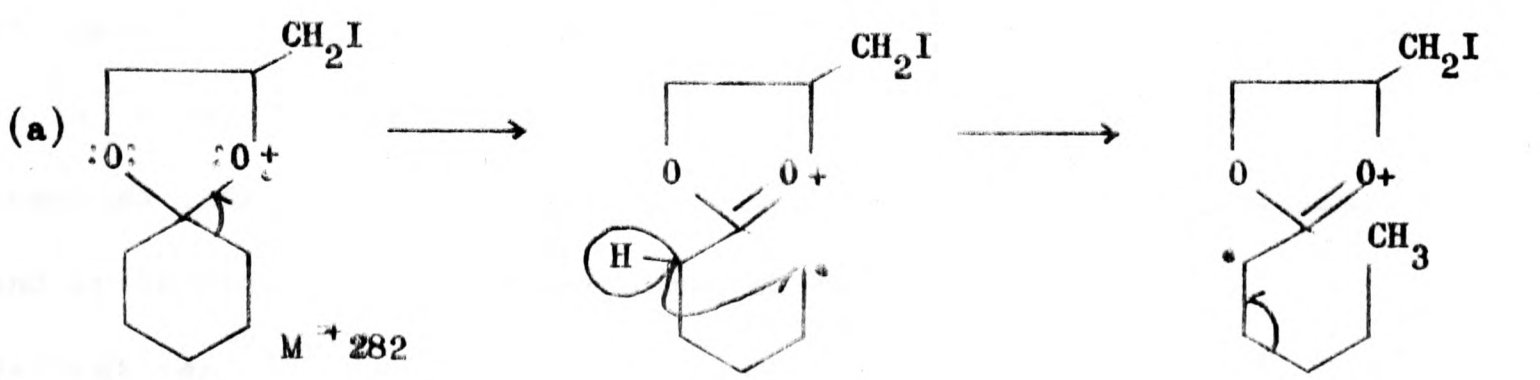
The method and the product have previously been described[98] but further characterisation of the product has been carried out in the present work. Distillation followed by preparative g.l.c. gave a pure sample having i.r. and n.m.r. spectra consistentwith (XXXIII). The n.m.r. spectrum (N.m.r. 11) was interesting since the five protons of the dioxolane ring and CH_2OH group gave rise to a complex multiplet which was capable of simplification and analysis using the technique of addition of a europium shift reagent[99]. In this work the reagent used was tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) europium (III) and it resulted in the resolution of the signal into three distinct sets of lines (N.m.r. 12) due to complex formation between the oxygen and europium atoms resulting in a progressive deshielding effect from C-1 to C-3. The chemical shifts of the protons in the untreated compound, determined by graphical extrapolation (Fig.3), were 4.05(C-1), 4.45(C-2) and 3.95(C-3). The coupling constants were elucidated by computer analysis since the spectrum was non-first order. For this a five proton programme was used and estimated chemical shifts and coupling constants were employed. The following lines were observed in the analysed spectrum 300.3, 307.0, 308.8, 315.3, 336.0, 342.1, 344.1, 350.8, 380.0, 391.5, 397.0, 402.5, 420.0, 426.5, 431.5, 437.5, 442.2, 454.0, 458.8 Hz, and the coupling constants were $J_{1,2}$ 8.37, $J_{1,3}$ 6.09, $J_{2,3}$ 6.35, $J_{3,4}$ 6.35, $J_{3,5}$ 5.33, $J_{4,5}$ 11.64 Hz.

Treatment of XXXIII with toluene-p-sulphonyl chloride in pyridine at room temperature by a reported procedure[100] gave the toluene-p--sulphonate (XXXIV) in 52% yield. The pure compound gave i.r., n.m.r. and mass spectra consistent with the proposed structure.

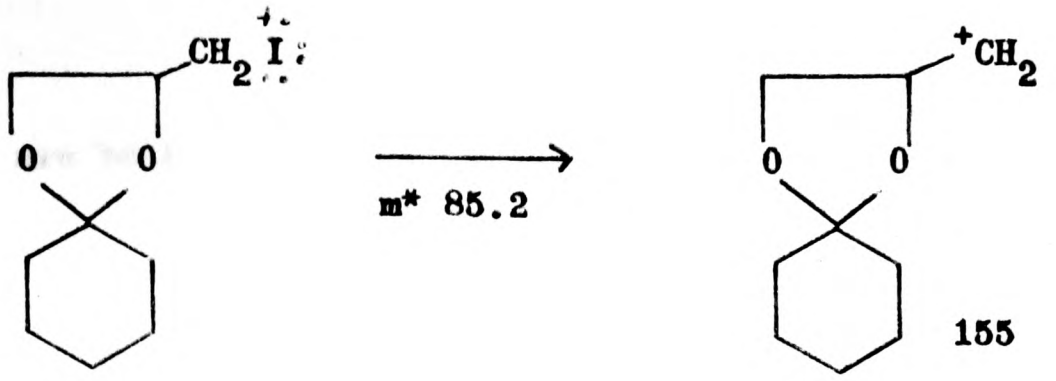
Fig. 3 **The effect of a Europium shift reagent ($Eu(fod)_3$) on the n.m.r. of 1,2-O-cyclohexylidene glycerol.**



Replacement of the tosyl group in (XXXIV) by iodine was effected by heating (XXXIV) under reflux with ground lithium iodide in toluene and hexamethylphosphoramide (HMPT) in accordance with a literature method[101]. Distillation of the reaction mixture yielded a product in 76% yield having an i.r., n.m.r. and mass spectrum (M.s.8) consistent with structure (XXXV). A detailed examination of the mass values of the fragments obtained in the mass spectra of (XXXIV) and (XXXV) revealed some striking similarities. Scheme 5 shows a possible fragmentation pathway for (XXXV); that proposed for (XXXIV, M.s.7) is identical. In particular the metastable peaks observed provide good evidence for the pathway suggested.



(c)



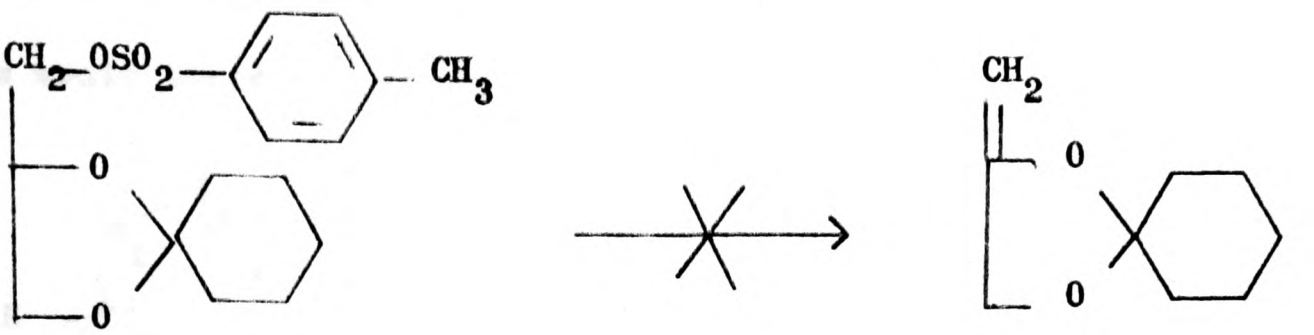
Scheme 5.

The iodo derivative (XXXV) was prepared as starting material for the proposed preparation of a Grignard derivative which hopefully would then react with butyl borate to give a straightforward synthesis of the protected glycerolboronic acid (XXXVI). However, several previous attempts to prepare the Grignard derivative in THF and HMPT resulted in isolation of starting material only[102] and it appears that iodo compound (XXXV) must be regarded as similar to β-alkoxy haloalkanes and epibromohydrins which are known to fail to give Grignard derivatives[37,103](see p.17).

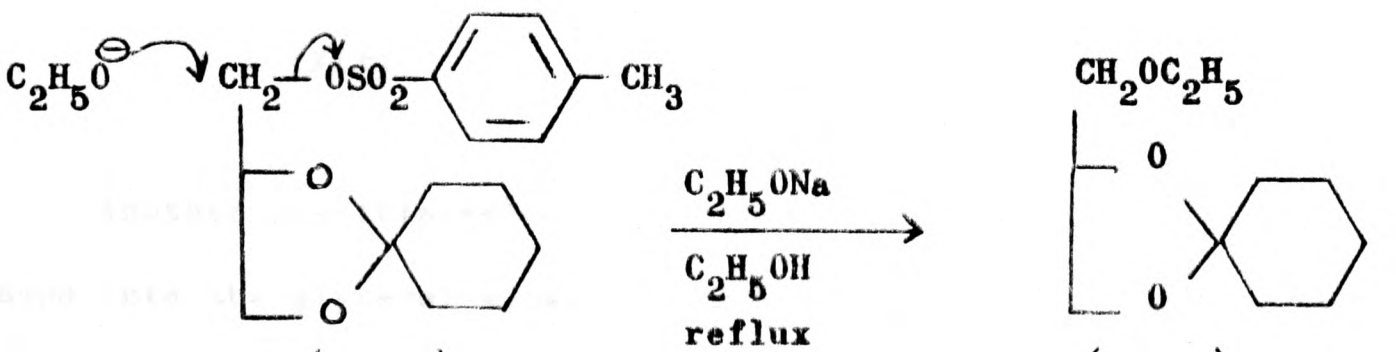
The simplest alternative route to a glycerolboronic acid would be to utilise the toluene-p-sulphonyl and iodo derivatives (XXXIV) and (XXXV) in β-elimination reactions to give the unsaturated compound (XL) which chould then be subjected to the hydroboration-redistribution procedure.

Treatment of 1,2-O-cyclohexylidene-3-O-toluene-p-sulphonyl glycerol with sodium ethoxide in ethanol resulted in isolation of a single product which was identified by i.r. and n.m.r. spectroscopy as 1,2-O-cyclohexylidene-3-O-ethyl glycerol (XXXIX). Clearly substitution of the toluene-p-sulphonyl group by the ethoxide ion has taken place rather than the hoped for elimination reaction. These

reactions are both formulated below:



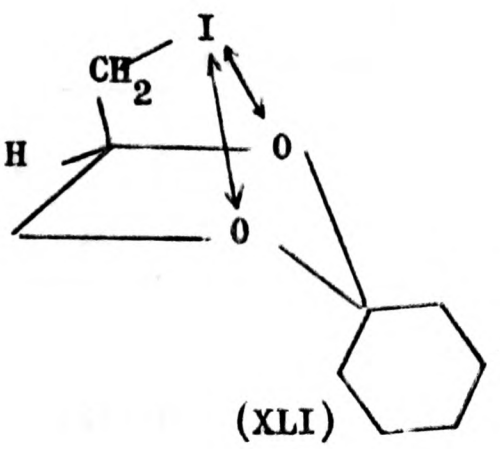
(XL)



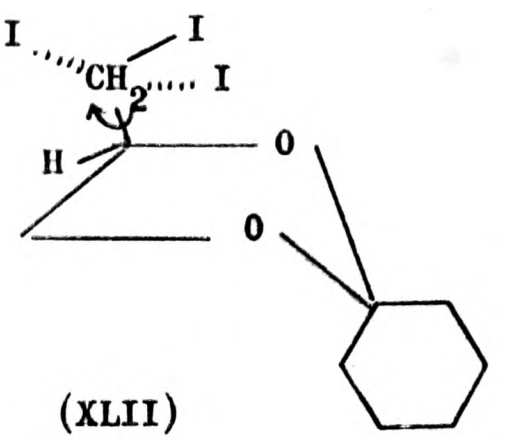
(XXXIV) (XXXIX)

In another experiment cyclohexanone was conclusively identified as the main product from the attempted base induced elimination of 1,2-O-cyclohexylidene-3-deoxy-3-iodo glycerol using potassium hydroxide in ethanol, and also from a similar reaction using the non-nucleophilic base, 1,5-diazabicyclo[3.4.0]non-5-ene. This latter reagent was chosen to minimise competing substitution reaction processes. In order for a β-elimination process to take place, the leaving group (i.e., -I or $-OSO_2C_6H_4CH_3$) and the β-hydrogen must be antiperiplanar to each other and this requires, in the case of this dioxolane system, the bulky leaving group to be closer to the two ring oxygen atoms (conformation XLI) than would be the case when the molecule adopts its probable preferred conformation (XLII). Therefore the preparation of the vinyl ether (XL) is unfavourable because it must proceed via conformation (XLI) which would give rise to a high activation energy due to the

repulsive interactions between the electron-rich oxygen and iodine atoms. If an alternative reaction such as substitution is possible this would therefore proceed more readily.



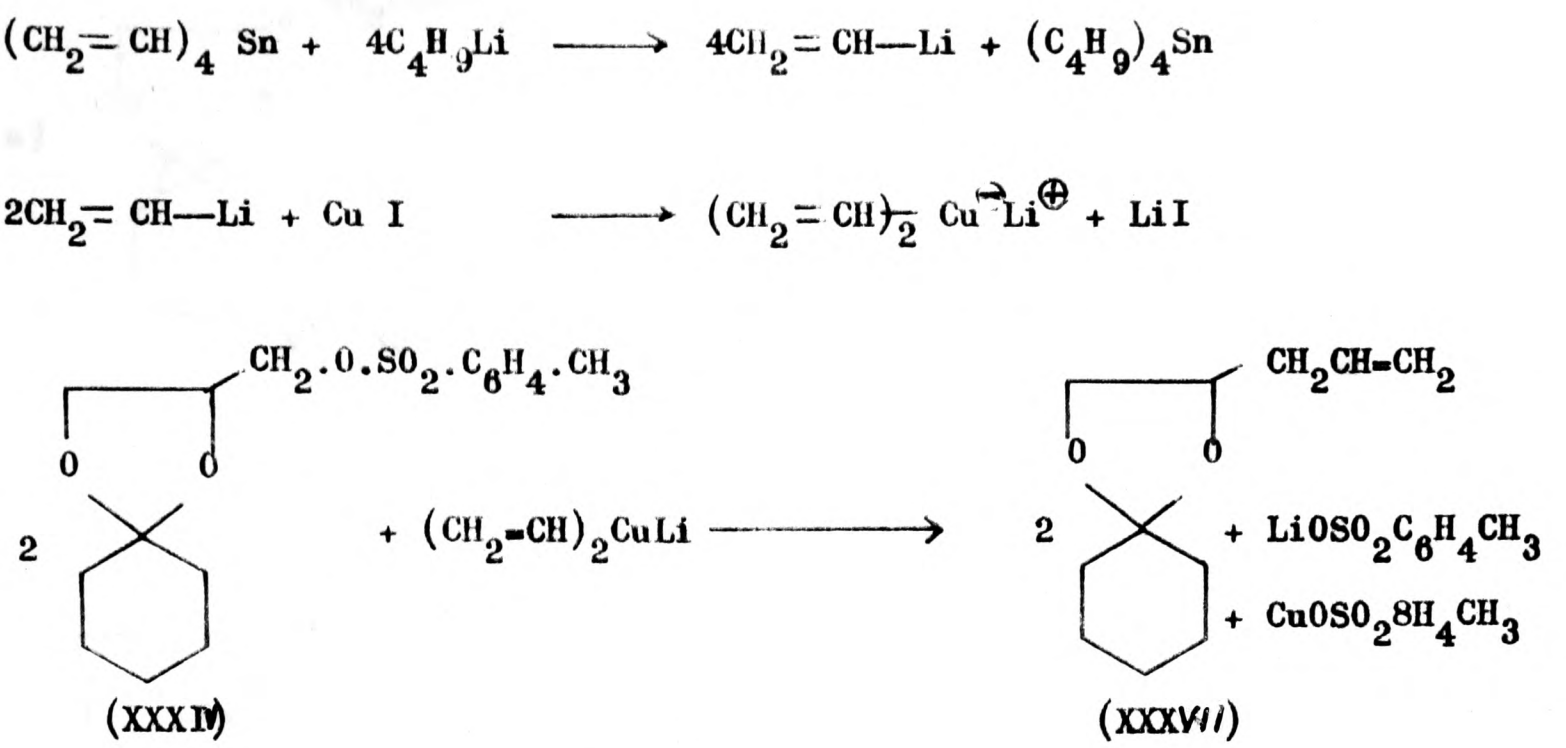
(XLI)



(XLII)

Another possible method of introducing a carbon-carbon double bond into the glycerol system would be by means of a chain extension procedure and it was considered that this could most easily be accomplished by reaction of toluene-p-sulphonate (XXXIV) or iodide (XXXV) with appropriate organocopper reagents as have been developed by Corey[75,76] and by Whitesides[78]. It was thus hoped to attach both vinyl and allyl groups to the glycerol skeleton, once more for the purpose of attempting the hydroboration-redistribution boronic ester synthesis.

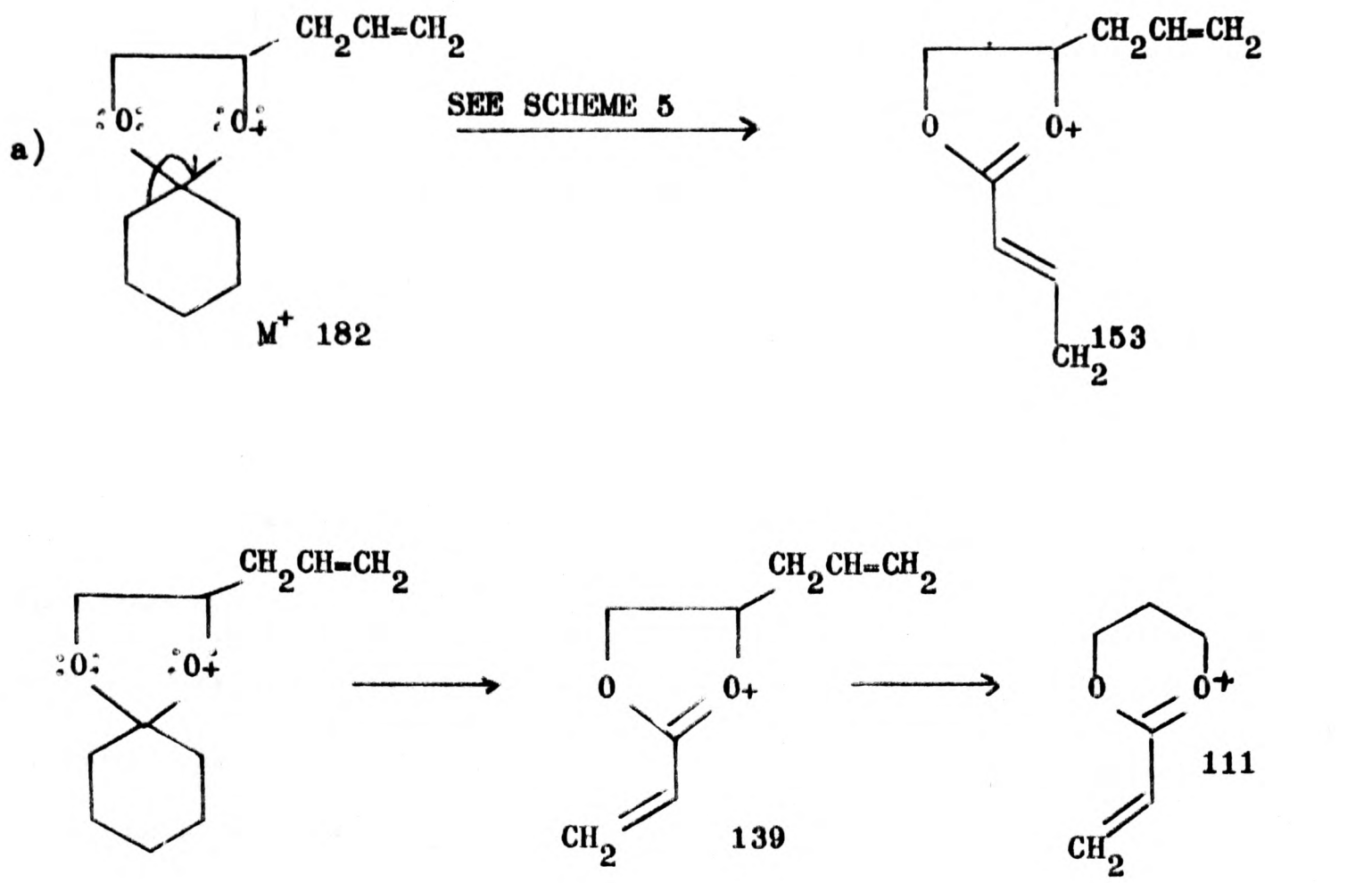
For the attempted preparation of the vinyl compound (XXXVII) a solution of vinyl lithium in THF was first prepared by the reported method, transmetallation of tetravinyl tin with butyl lithium[104]. Treatment of this solution with copper(I)iodide in ether at -60^{o} was expected to yield divinyl copper lithium for subsequent reaction with the tosylate (XXXIV) as outlined in Scheme 6.



Scheme 6.

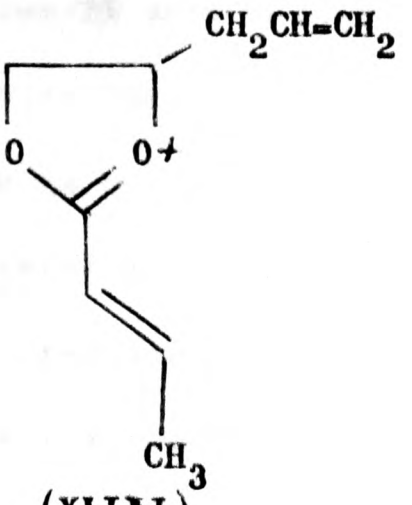
The formation of vinyl lithium was confirmed by titration and by reaction with benzaldehyde. In the latter case the product isolated in 77% yield gave spectroscopic evidence of -OH, aromatic ring and $-CH=CH_2$ which is consistent with reaction of the aldehyde with vinyl lithium.

In the reaction between divinyl copper lithium and the tosylate (XXXIV) at -60 to -70°, the isolation of the reaction product from suitable work-up procedures gave a 25% recovery of the starting material (XXXIV). The remaining organic fraction revealed the presence of some four components by g.l.c. analysis. The desired compound (XXXVII) was found to be one of these components by g.l.c./m.s. The mass spectrum (M.s.9) is of some interest since the proposed fragmentation pattern reveals the dual fragmentations resulting from the loss of an electron either from the ring oxygen or from the carbon-carbon double bond (Scheme 7).



Scheme 7.

It is interesting to note that in the mass spectrum of (XXXVII) there are two fragments having m/e values of 153 but with different postulated structures. It should be possible to confirm these proposed breakdown patterns and to distinguish between the two fragments by the examination of the spectrum of the corresponding derivative arising from the reaction of glycerol with 4-methylcyclohexanone. In such a case the corresponding fragments would be (XLIII) and (XLIV), the latter having a m/e value of 167. However, this experiment was not attempted in the present work.



(XLIII)

(XLIV)

The other products of the reaction of (XXXIV) with divinyl copper lithium were identified as 1,2-O-cyclohexylidene-3-deoxy-3-iodo glycerol (XXXV), tetrabutyltin (M.s. 11), and tin compounds of probable structures $(C_4H_9)_3SnH$ (M^+291), $(C_4H_9)_2Sn(H)CH=CH_2$ (M^+261, M.s. 11). The compound (XXXV) was probably formed during the reaction by nucleophilic substitution of the tosylate group by iodide which would have been present in the reaction mixture. Attempted separation of the mixture by preparative g.l.c. was unsuccessful due to the presence in the reaction mixture of too many structurally related components. It is suggested that in any future development of this promising route the following line of approach might be considered. It has been reported[104] that vinyllithium is insoluble in pentane whereas tetrabutyltin and butyllithium are soluble, therefore if the transmetallation reaction were carried out in that solvent the vinyllithium could be purified by filtration under nitrogen prior to the preparation of the organocopper reagent. It must be borne in mind however that solid vinyllithium is extremely unstable and therefore very rigorous conditions would have to be used in its handling.

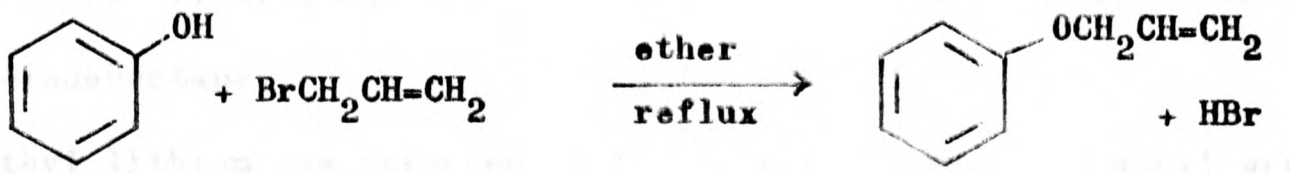
In this work it was decided to attempt to obtain a pure solution of vinyllithium by the reported [126] direct reaction of vinyl bromide

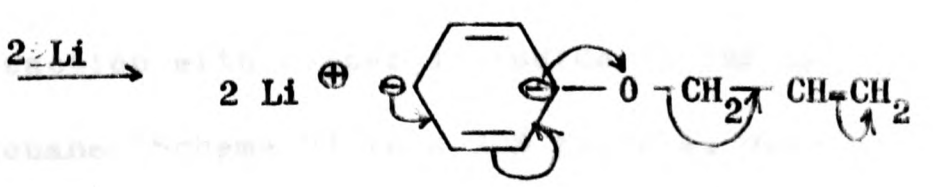
with a lithium/2% sodium alloy but this proved to be unsuccessful. It has recently been reported[105] that such a direct preparation of vinyllithium is only possible starting from vinyl chloride.

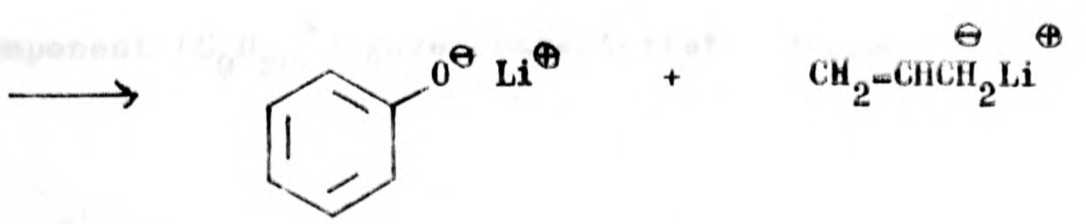
The several attempted preparations of the unsaturated derivative (XXXVIII) by reaction of diallylcopper lithium with the tosylate (XXXIV) were all unsuccessful. Allyllithium was prepared in hexane solution by the reported[106] transmetallation of tetrallyltin with butyllithium (Scheme 8(a)) and subsequently treated with copper(I)iodide followed by the tosylate (XXXIV) (Scheme 8(c)). The only product isolated was tetrabutyltin. A second sample of allyllithium was prepared by the reported[107] cleavage of allyl phenyl ether with excess lithium (Scheme 8(b)) and the yield by titration was 84%. Subsequent reaction as above (Scheme 8(c) resulted in the isolation of cyclohexanone.

(a) $(CH_2=CHCH_2)_4Sn + 4\ C_4H_9Li \longrightarrow 4\ CH_2=CHCH_2Li + C_4H_9Sn$

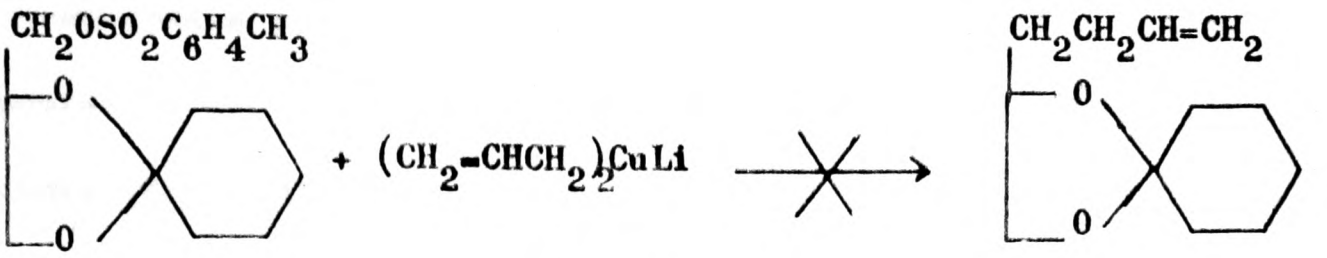
(b)





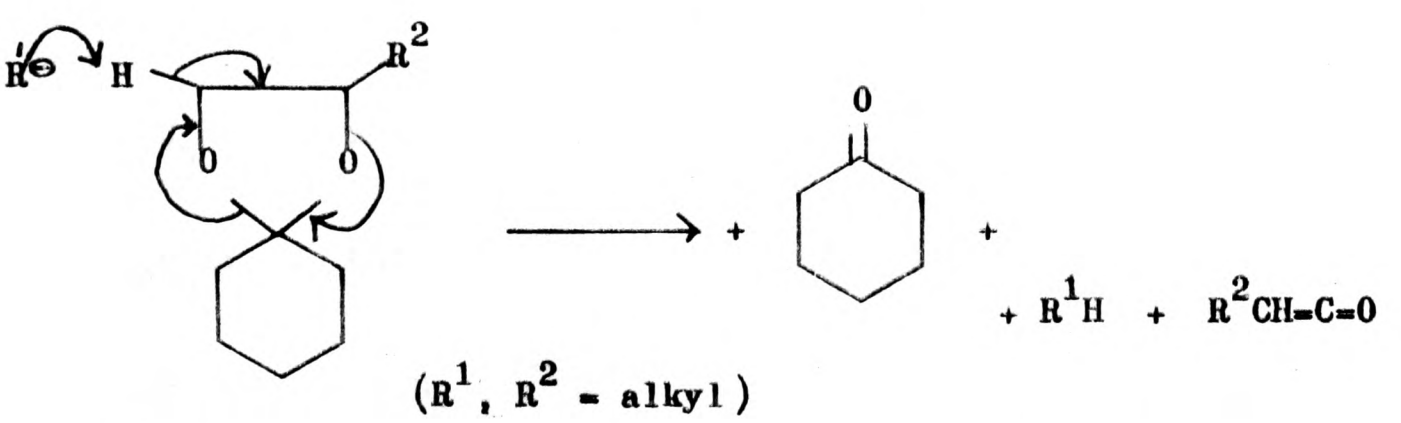


(c) $2\ CH_2{=}CHCH_2{-}Li + CuI \longrightarrow (CH_2{=}CHCH_2)_2CuLi + LiI$



Scheme 8.

It is suggested that the cyclohexanone could have been formed by the following mechanism proposed by Heathcock et al[108].



(R^1, R^2 = alkyl)

In view of the difficulties which had been encountered in these synthetic utilisations of dialkylcopper lithiums some simpler examples were investigated in the hope of unravelling some of the complexities of the coupling reactions involved. These further model systems were diethylcopper lithium and diallylcopper lithium, and both were reacted with 1-iodoheptane.

Ethyl lithium was prepared by the direct method, from ethyl bromide and lithium metal in pentane[109], in 84% yield (by titration). Subsequent reaction with copper(I) iodide in THF and then with 1-iodoheptane gave nonane (Scheme 9) in a 20% yield as determined by g.l.c. analysis. The reaction mixture was submitted to g.l.c./m.s. when the suspected nonane component ($C_9H_{20}^+$) gave characteristic fragments at $C_7H_{15}^+$, $C_5H_{11}^+$,

$C_4H_9^+$, $C_3H_6^+$. The presence of 1-bromoheptane and tetradecane as by-products together with unreacted 1-iodoheptane was also established. 1-Bromoheptane probably originated from a nucleophilic substitution reaction of 1-iodoheptane with the bromide ion present in the reaction mixture (cf. p. 91). Tetradecane must have arisen as the thermal coupling product from the intermediate $C_7H_{15}Cu$. The yield of nonane is consistent with the findings of Johnson and Dutra[110] who reported a 20% yield from the reaction of dibutylcuprate and pentyltosylate in THF; in ether, nonane was obtained by them in a 98% yield.

$$C_2H_5Br + 2\ Li \longrightarrow C_2H_5Li + LiBr$$

$$2\ C_2H_5Li + CuI \longrightarrow (C_2H_5)_2Cu^{\oplus}Li^{\ominus} + LiI$$

$$2\ C_7H_{15}I + (C_2H_5)_2Cu^{\oplus}Li^{\ominus} \longrightarrow 2\ C_9H_{20} + CuI + LiI$$

$$C_7H_{15}I + CuI \longrightarrow C_7H_{15}Cu + I_2$$

$$2\ C_7H_{15}Cu \longrightarrow C_{14}H_{30} + Cu_2$$

$$C_7H_{15}I + LiBr \longrightarrow C_7H_{15}Br + LiI$$

Scheme 9.

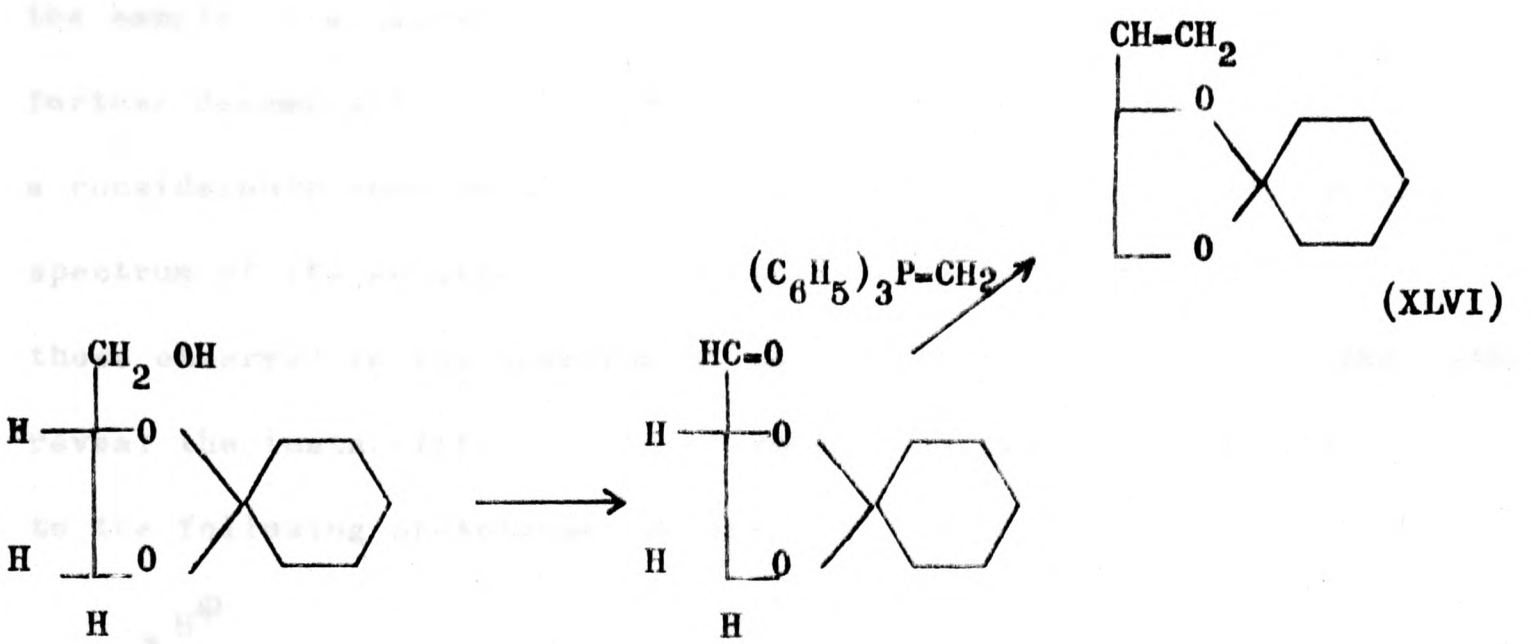
In this work the attempted preparation of dec-1-ene from diallyl copper lithium and 1-iodohoptane in ether resulted in the isolation of a 96% yield of tetradecane presumably by the same mechanism as before, but no dec-1-ene was isolated.

In summary therefore, the use of organocuprates for coupling reactions in the presence of the dioxolane system has been found to be

unsatisfactory because of the instability of such a system to the reactive unsaturated alkyl lithiums, and because of the competing side reactions such as metal-halogen exchange, α-metalation, and thermal coupling[76]. A considerable amount of work has been reported in the literature on the optimisation of conditions for the preparation and reaction of organocuprates and it appears that for the successful preparation and use of these reagents, considerable care, technical skill and experience are required[111]. From these reports it may be concluded that ether is the best solvent medium[80,110,112,113], although some workers have reported a preference for THF[75,76], and the temperature of reaction, which is critical, should be around -60^{o} [80,112]. It has also been reported that the purity of the copper(I) iodide is critical, since traces of copper(II) salts catalyse competitive thermal coupling reactions[80]. It has been reported further[78] that organocuprates may be stabilised as their tributyl phosphine complexes although this was found to offer no advantages and to complicate work-up[80,110]. In any future studies it is suggested that the use of organocuprates to prepare compounds with increased carbon chain lengths and containing new multiple bonds must involve (a) rigorous purification of the cuprous iodide, and (b) special attention to the maintenance of a constant and appropriate reaction temperature, otherwise these methods are thought not likely to be very useful in the carbohydrate field.

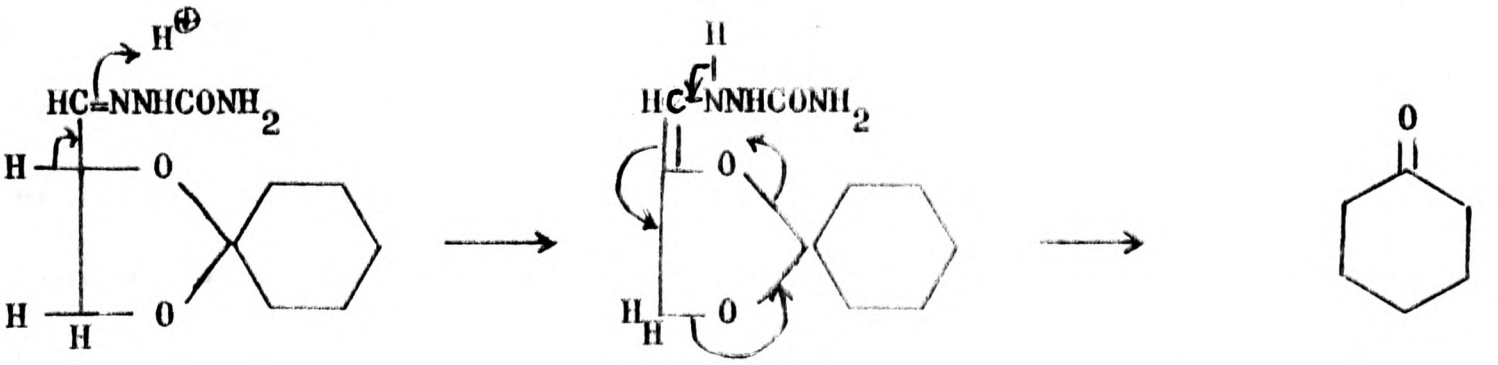
The next approach to the synthesis of unsaturated dioxolane derivatives which was investigated, involved the aldehyde (XLV) which has not previously been reported. It was envisaged that if this compound could easily and quickly be obtained in reasonable quantities,

then application of the Wittig reaction would then lead to the unsaturated glycerol derivative (XLVI). As a first step the preparation of the aldehyde (XLV) by oxidation of 1,2-O-cyclohexylidene glycerol (XXXIII) was attempted. The recently reported reagent chromium trioxide intercalated in graphite ("Seloxcette")[114] was used by heating under reflux in toluene for 24 hours.



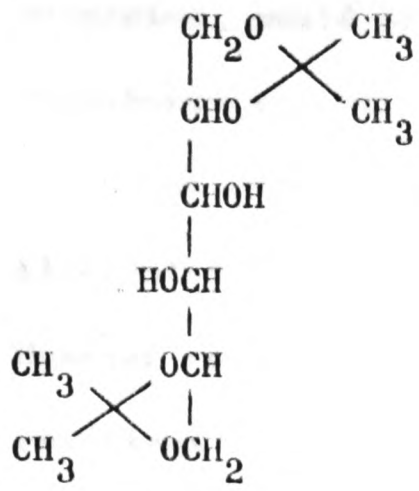
The crude liquid product obtained had i.r. absorption due to C=O str., OC−H str., and O−H str. It gave a strongly positive Schiff's test and was readily converted into a crystalline semicarbazone derivative (XLVII). The i.r. spectrum of this semicarbazone exhibited bands which could be assigned to amide I and II absorption, C=N str., NH_2 str., and NH str. The n.m.r. spectrum also provided evidence for the presence of these groups, and the chemical shifts appeared consistent

with the protons in structure (XLVII). However, the signal at δ 2.45, due to methylene and methine hydrogens, was too large to correspond to the expected number of protons. It was noticed that the stored crystalline sample of the semicarbazone product had an increasing odour of cyclohexanone, the presence of which was confirmed by t.l.c. analysis using two separate solvent systems. Furthermore, heating the sample in a vacuum pistol at 110^{0} for one day appeared to cause further decomposition. The dried material obtained was found to have a considerably reduced solubility in deuterochloroform, and the n.m.r. spectrum of its solution revealed only two broad signals similar to those observed in the spectrum of authentic cyclohexanone. These results reveal the instability of this aldehydic compound which may be due to the following prototropic shifts:

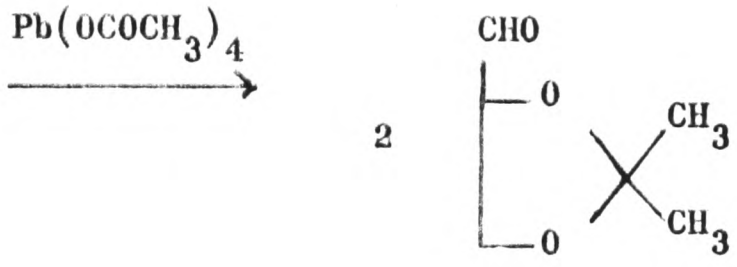


Reported studies[115] on the aldehyde (XLVIII) formed from lead tetracetate fission of 1,2:5,6-di-O-isopropylidene mannitol (XLIX) have also indicated instability. Clearly the milder oxidation conditions

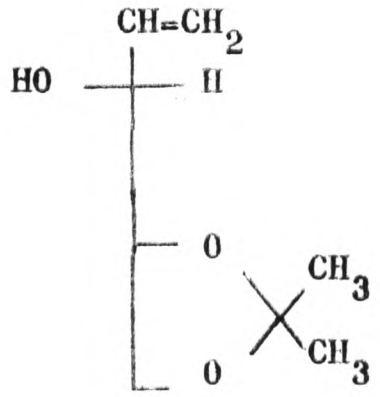
with the mannitol derivative could lead more quickly, and in better yield to the required aldehyde (XLVIII) which could then be used immediately for a Wittig or the already reported[115] Grignard reaction leading to the introduction of a carbon-carbon multiple bond, as in (L) and (LI) respectively. Thus 1,2:5,6-di-O-isopropylidene mannitol (XLIX) was prepared in 60% yield by reaction of mannitol with acetone in the presence of zinc chloride[115]. The product was isolated as white crystals which had a m.p. in agreement with reported values, and i.r. and n.m.r. spectra consistent with the known structure (XLIX). An oxidative diol cleavage reaction was then carried out by the literature method[115] by stirring the product with lead tetracetate in toluene at room temperature. The resulting aldehyde was isolated by filtration of the solution from the sticky precipitate, followed by distillation. The b.p. was in agreement with the literature values [115] and the product had chemical properties and i.r. and n.m.r. spectra consistent with the structure (XLVIII). This aldehyde was then treated with vinylmagnesium bromide as previously reported[115] and the product obtained by standard work-up was found to be a two component mixture by g.l.c. analysis. The retention times of these two components altered on trimethylsilylation of the mixture and the i.r. and n.m.r. spectra of the mixture were consistent with 1,2-O-isopropylidene-3-vinyl glycerol (LI). It is concluded that a mixture of the threo- and erythro- isomers of (LI) has been isolated as found by Horton et al[115].



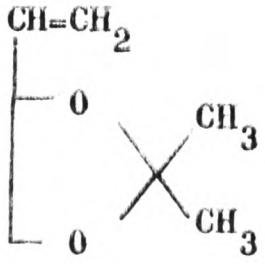
(XLIX)



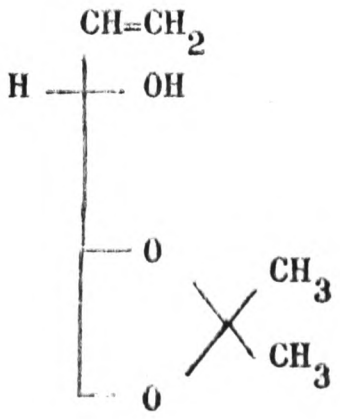
(XLVIII)



(LI)



(L)



$CH_2=CHMgBr$

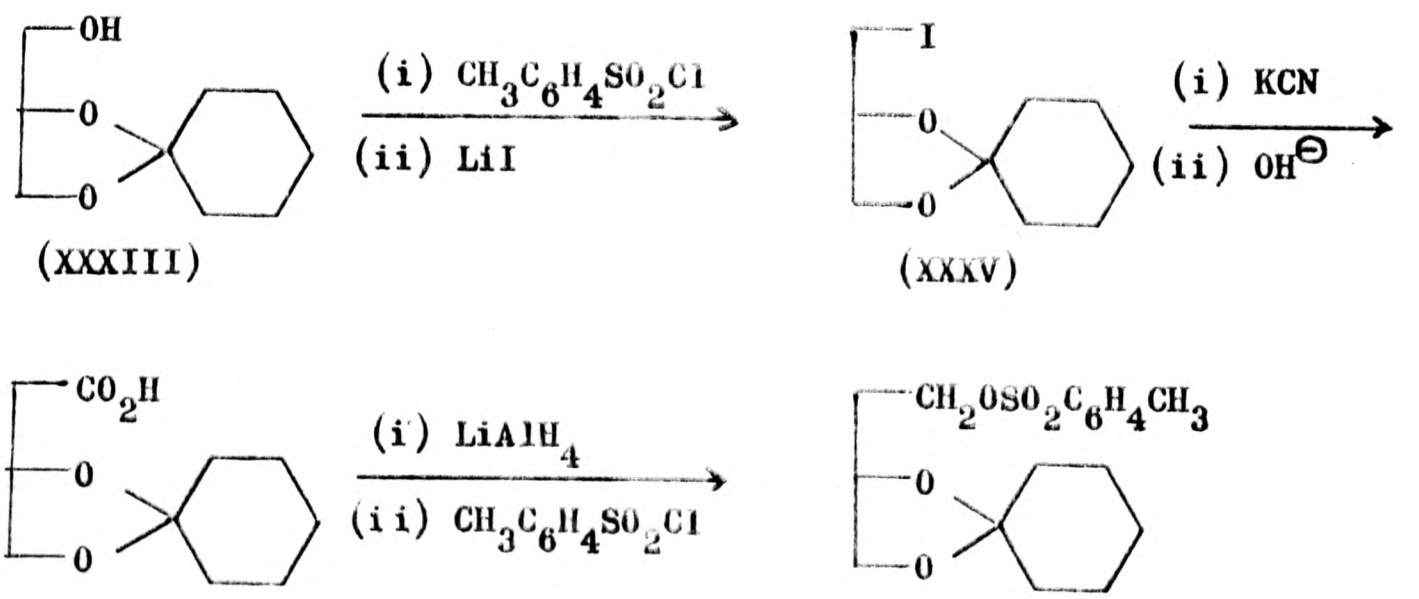
$(C_6H_5)_3P=CH_2$

This route therefore, would seem to be another promising pathway to unsaturated derivatives of glycerol which, provided they could be

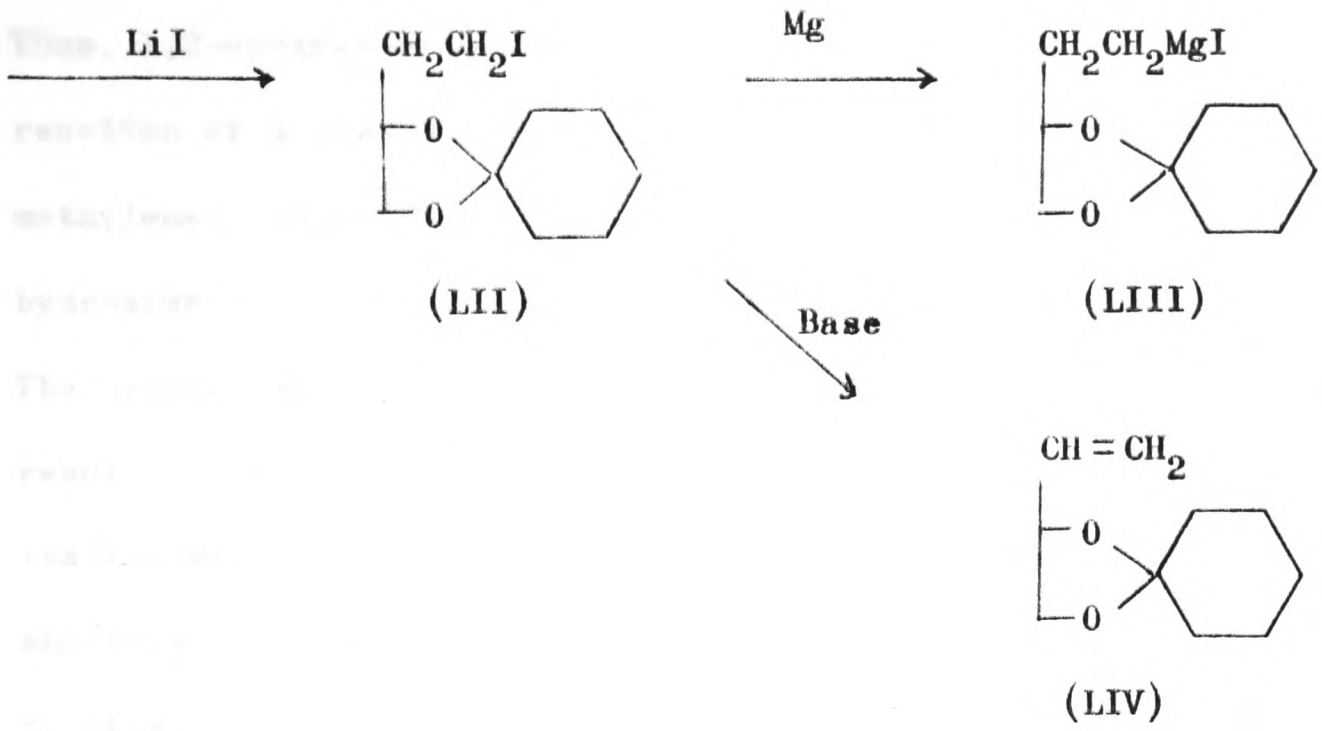
separated, would be suitable for further protection and then the hydroboration-redistribution reaction. In view of the well-known practical difficulties associated with the Wittig reaction, the alternative route leading to (L) was not investigated in this work. However recent phase transfer procedures have enabled some Wittig reactions to be simply performed in aqueous media[116] and the application of such conditions to Wittig reactions of (XLVIII) is an obvious topic for future investigation.

(D) SYNTHESIS OF BORONIC ACIDS FROM BUTANE-1,2-DIOL DERIVATIVES.

Because of the difficulties which were encountered in the preparation of suitable glycerol derivatives, and in their utilisation as synthetic intermediates for the preparation of boronic acids, alternative pathways leading to a protected four-carbon haloalkane-diol were investigated. Such a compound as 1,2-O-cyclohexylidene-4-iodobutane--1,2-diol (LII) would be expected to form the Grignard derivative (LIII) (γ-alkoxyhaloalkanes are known to form normal Grignard derivatives[103]) and might also undergo β-elimination to give the unsaturated derivative (LIV). This latter reaction is likely to be more facile than the dehydrohalogenation already attempted on (XXXV) because in (LII) the reactive sites are one carbon atom further from the dioxolane ring and therefore steric hindrance factors are less likely to operate. The iodide (LII) could be obtained by well-established chain extension procedures (Scheme 10) starting from glycerol but this would have been a very lengthy and inefficient process.

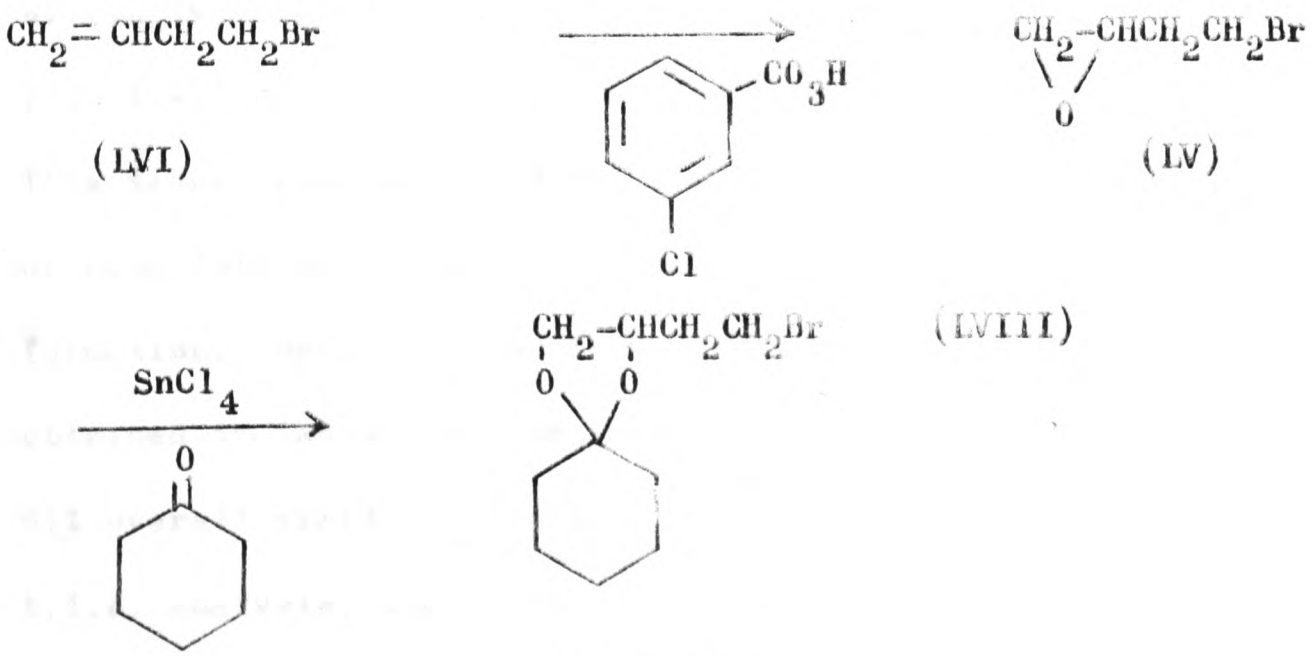


(XXXIII) (XXXV)



Scheme 10

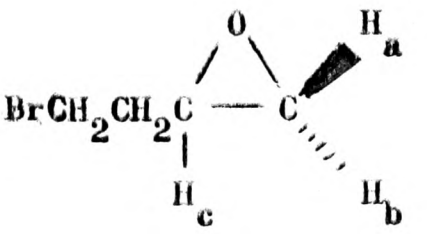
Alternative routes to (LII) or a similar compound were thus sought. 1,2-Epoxy-4-bromobutane (LV) is readily available from 4-bromobut-1-ene (LVI, Scheme 11) according to Cruickshank and Fishman[117] and using the method of Bersin and Willfang[118] (which had been used to prepare 3-chloropropane-1,2-diol-1,2-decyl acetal from decan-1-al and 1,2-epoxy--3-chloropropane) 1,2-O-cyclohexylidene-4-bromobutane-1,2-diol (LVIII) could be obtained directly.



Scheme 11.

Thus, 1,2-epoxy-4-bromobutane (LV) was obtained in 87% yield by reaction of 4-bromobut-1-ene (LVI) with m-chloroperbenzoic acid in methylene dichloride at 0^{o}. The organic layer was washed with sodium hydroxide solution to remove m-chlorobenzoic acid, dried and evaporated. The product was not distilled because it had been reported to decompose readily on attempted distillation[117]. However, an adequate characterisation was carried out; it was shown to be a pure compound by g.l.c. analysis and its i.r. and n.m.r. spectra were identical with those reported[117].

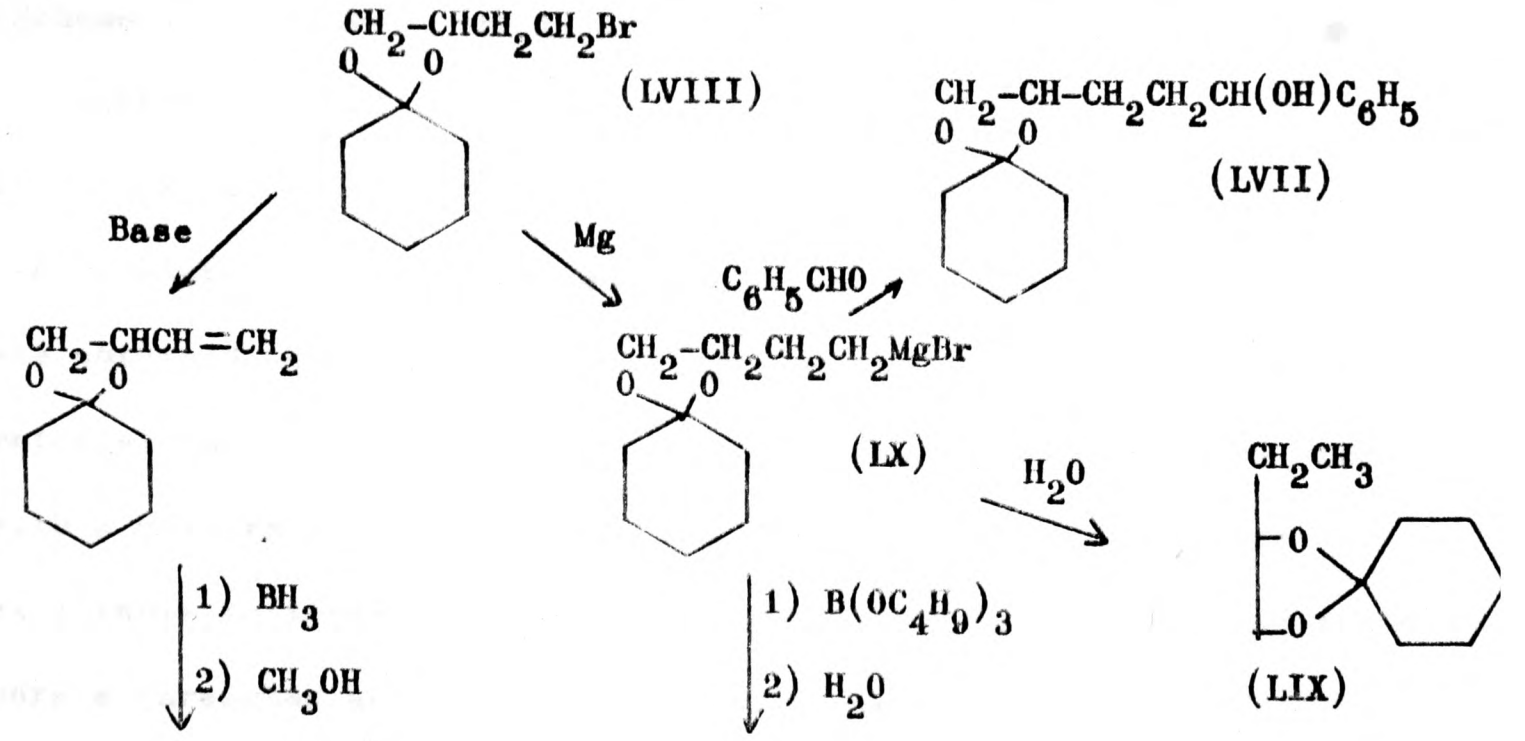
proton	chemical shift	splitting
H_a	2.58	quartet
H_b	2.82	quartet
H_c	3.09	multiplet
H_2C-3	2.10	multiplet
H_2C-4	3.55	triplet



(LV)

This epoxide was then shaken with cyclohexanone in the presence of tin(IV)chloride at room temperature for 24 hours as reported[118] to form the 3,4-O-cyclohexylidene compound (LVIII) directly in 70% yield. This transformation avoided the need to bring about an epoxide ring opening followed by isolation of the diol for subsequent acetal formation. Hence the required bromobutane derivative (LVIII) was obtained in two steps from a readily available starting material in 61% overall yield. The product was shown to be pure by g.l.c. and t.l.c. analysis, and its structure was confirmed by i.r. (I.r.8) and

n.m.r. (N.m.r.13) spectroscopy. The synthetic routes from (LVIII) to boronic acids and esters which were planned for study are shown in Scheme 12.



Scheme 12.

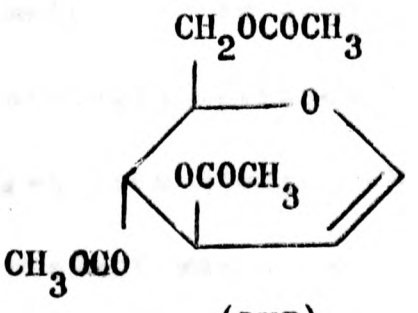
Firstly, 1,2-O-cyclohexylidene-4-bromobutane-1,2-diol (LVIII) in THF was found to react with magnesium only slowly to give a thick grey suspension. Aliquots of this mixture were treated with (a) water and (b) benzaldehyde under reflux for one hour. After conventional work-up procedures the products obtained were identified by i.r. and n.m.r. spectroscopy as 1,2-O-cyclohexylidene-butane-1,2-diol (LIX) and 5-phenyl-1,2-O-cyclohexylidene pentane-1,4,5-triol (LVII) respectively

thus demonstrating the effective formation of the Grignard reagent (LX).

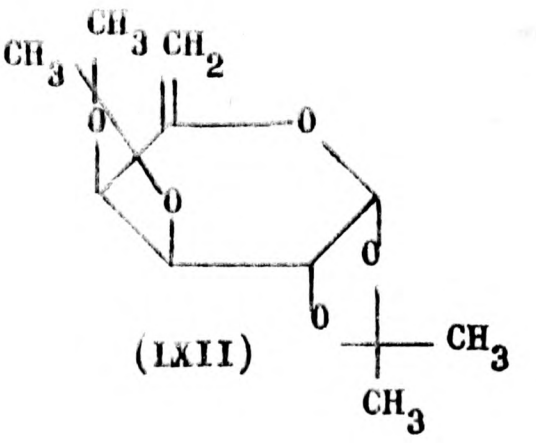
In a separate experiment the Grignard reagent (LX) was added under carefully controlled conditions (see p.73) to tributyl borate (Scheme 12), however, the viscosity of the Grignard solution prevented the maintainence of a constant rate of addition. Product isolation procedures were carried out as for the successful preparation of 1-hexaneboronic acid but only a small quantity of crystalline material was obtained, and evaporation of the aqueous layer gave inorganic material only. The crystals had i.r. and n.m.r. spectra consistent with a mixture of the alkaneboronic acid and boric acid. This is explicable in terms of a low yield of the boronic acid leaving tributyl borate unreacted which would then hydrolyse to boric acid. The low yield may be partly due to the unsteady rate of addition of the Grignard reagent. Further work on this reaction would need to involve exploration of the use of alternative solvents in the formation of the Grignard reagent.

(E) SYNTHESIS OF BORONIC ACIDS VIA UNSATURATED MONOSACCHARIDE DERIVATIVES.

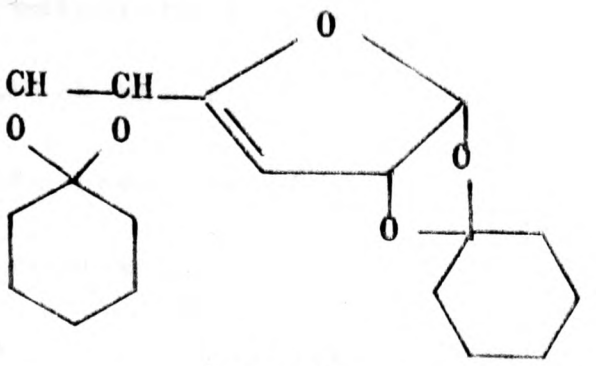
The selection of typical unsaturated monosaccharide systems for use in hydroboration-redistribution studies required that the double bond be situated in a range of different structural environments. Although such compounds may be formally regarded as allyl or vinyl ethers, it is probable that the directive effects exerted by these groups in simple systems would be modified in the more complex case of monosaccharides. Ideally then, a selection of suitable starting materials would include cyclic unsaturated monosaccharides with the double bond in each of the following positions; exocyclic to the ring, endocyclic, in say the 2,3 or 3,4 position, endocyclic in the 1,2 position, and in a side chain. The compounds selected were therefore 3,4,6-tri-O-acetyl-D-glucal (LXI), 6-deoxy-1,2:3,4-di-O-isopropylidene-β-L-arabino-hex-5-enopyranose (LXII), 1,2:5,6-di-O-cyclohexylidene-3--deoxy-α-D-erythro-hex-3-enofuranose (LXIII), and 5,6-dideoxy-1,2-O--cyclohexylidene-α-D-xylo-hex-5-enofuranose (LXIV).



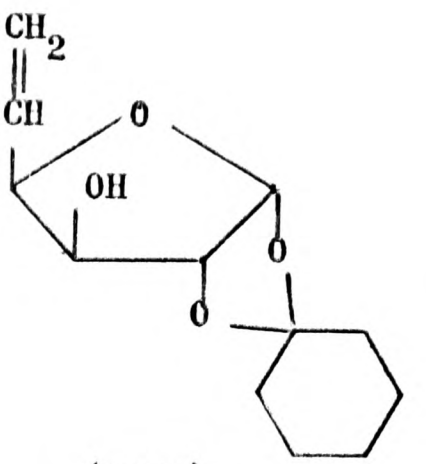
(LXI)



(LXII)



(LXIII)

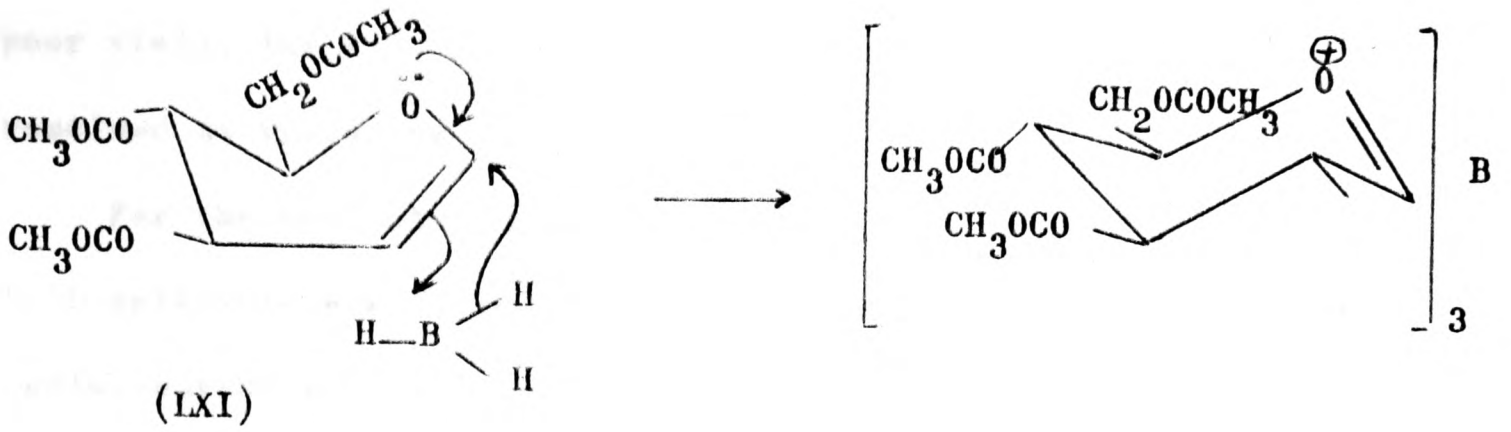


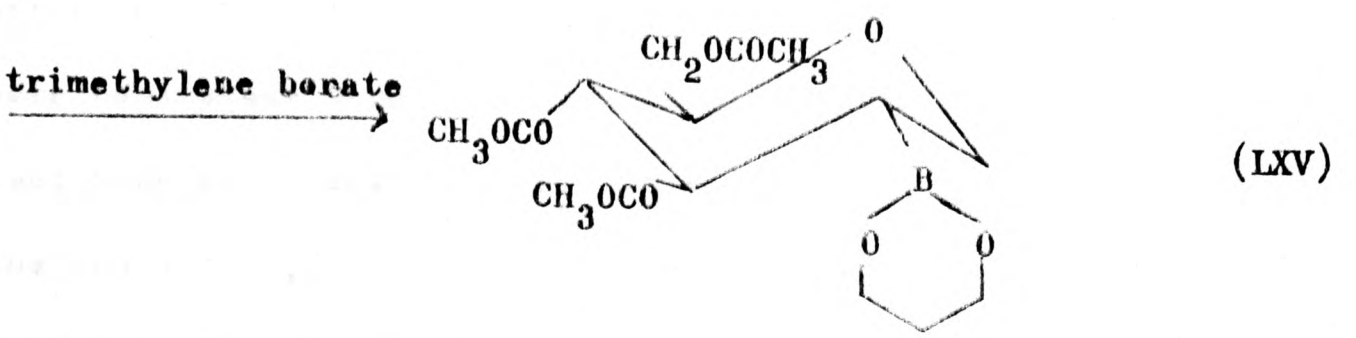
(LXIV)

Compounds (LXI) and (LXII) have not previously been subjected to hydroboration procedures but they are among the most readily obtainable unsaturated monosaccharides. It was throught likely that on hydroboration they would display high regioselectivity owing to the mesomeric stabilisation of the reaction intermediate, provided by the ring oxygen. Compounds (LXIII) and (LXIV) have been subjected to hydroboration processes followed by oxidation[58,63] and the reported results indicate that hydroboration can be successfully accomplished and therefore a reasonable yield of the required product might be expected from a hydroboration-redistribution reaction.

3,4,6-Tri-O-acetyl-D-glucal (LXI) was obtained by the standard method[119] in good yield directly from glucose by formation of the acetoglucopyranosyl bromide immediately followed by an elimination reaction brought about by the action of zinc and acetic acid. The product was shown to be pure by t.l.c. and g.l.c. analysis, and had a m.p. and $[\alpha]_D$ value consistent with literature reports. The i.r. spectrum had absorption bands consistent with structure (LXI) and the n.m.r. spectrum had signals due to the acetyl group with the protons

associated with the double bond appearing as an AB quartet. When this D-glucal derivative was subjected to the hydroboration-redistribution reaction a syrupy three componant mixture was obtained which had i.r. (I.r.9) and n.m.r. (N.m.r.14) spectra consistent with the presence of a dioxaborinane system, and acetyl groups. However, aqueous hydrolysis of the mixture resulted in the formation of boric acid crystals; extraction of the solution with chloroform yielded, after removal of the solvent, a syrup which showed different structural features in its i.r. (I.r.10) and n.m.r. (N.m.r.15) spectra from those of the non-hydrolysed product. In particular the latter product showed absorption due to O-H str., although B-O str., and C=O str. absorption bands were still present in the spectrum. The crude reaction mixture before hydrolysis was submitted to column chromatography on neutral alumina using chloroform as the eluting solvent and one of the components (that with the highest R_f value) was separated as a colourless syrup. The other two components of the original mixture remained unseparated from each other. Purity of the separated colourless syrup was demonstrated by t.l.c. analysis. Its i.r. and n.m.r. spectra were recorded, but because of the small quantity of product, were poorly resolved although B-O str. and C=O str. could be observed. Microanalysis was consistent with the boron-containing sugar $C_{12}H_{22}BO_6$ of possible structure (LXV) based on the known[57] directive effect in addition reactions of the D-glucal system due to the mesomeric influence of the ring oxygen.





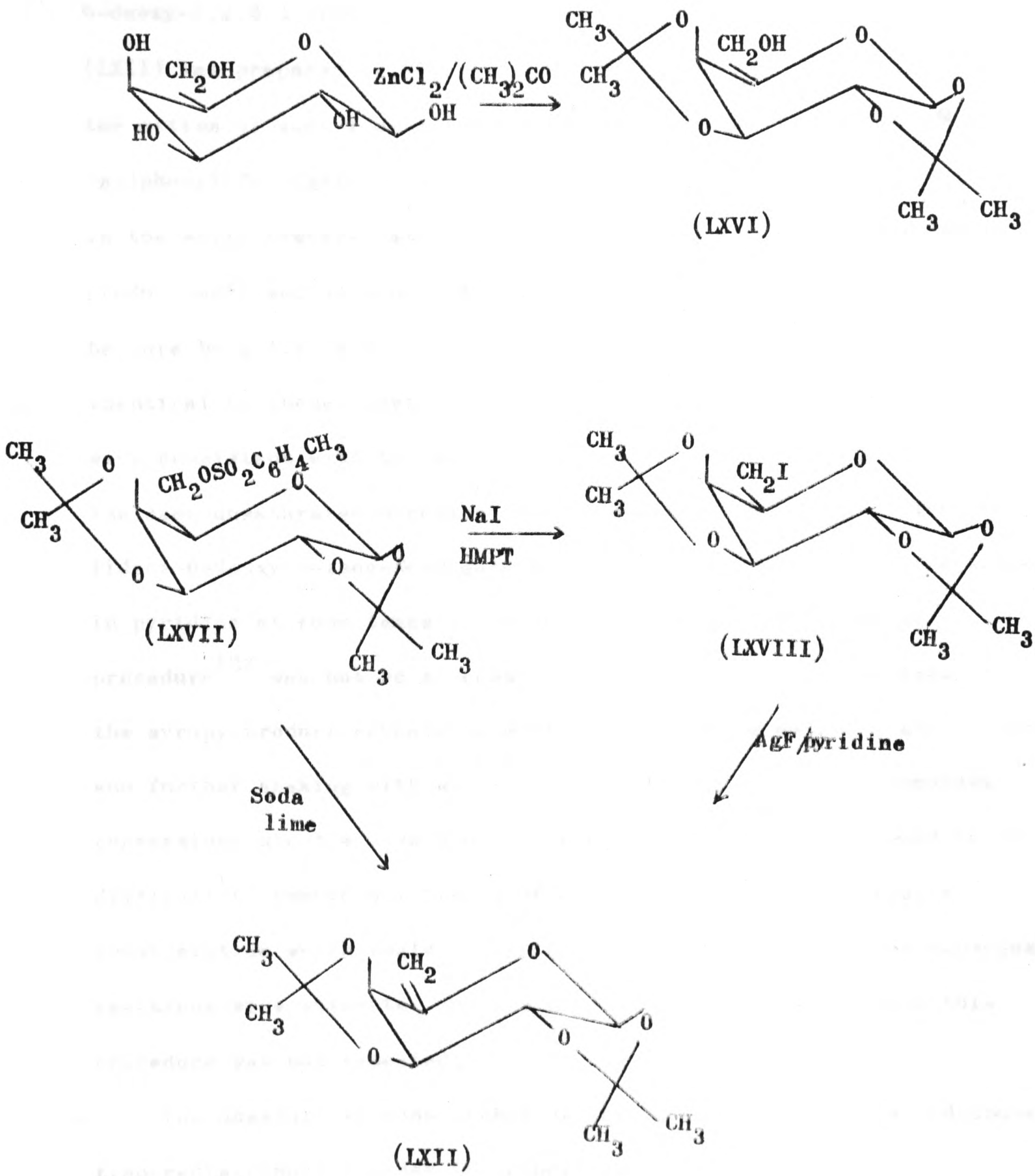
(LXV)

In view of the problems which emerged in the hydroboration--redistribution reactions on simple hydroxyalkenes, particularly the formation of complex reaction mixtures, the possible interaction of 3,4,6-tri-O-acetyl-D-glucal with trimethylene borate itself was studied. The two compounds were heated together at 120° for 4 hours (i.e., the redistribution reaction conditions) and g.l.c. analysis revealed no change in the composition of the mixture, hence such interaction is not responsible for the formation of reaction mixtures in this case.

In a further attempt to prepare a boronic ester from 3,4,6-tri--O-acetyl-D-glucal, it was reacted with 1,3,2-benzodioxaborole (VIII) at 100° for 2 hours. At the end of this time the reaction mixture was a deep red, non-distillable, intractable tar. On trituration with

methylene dichloride however, the material formed sticky crystals in poor yield, the i.r. and n.m.r. spectra of which were too poorly resolved to yield any information.

For the next structural type of unsaturated monosaccharide, α-D-galactose was converted into 1,2:3,4-di-O-isopropylidene-α-D--galactopyranose (LXVI) by stirring with acetone in the presence of zinc chloride at room temperature[120]. The product was isolated as a syrup in 82% yield and the $[\alpha]_D$ value and i.r. and n.m.r. spectra were consistent with those reported for this compound. Toluene-p--sulphonylation was then carried out by a standard procedure[121] and the product (1,2:3,4-di-O-isopropylidene-6-O-toluene-p-sulphonyl-α--D-galactopyranose, LXVII) was finally obtained as white crystals in 89% yield having m.p., $[\alpha]_D$ value and, i.r., and n.m.r. spectra consistent with those reported. The preparation of 6-deoxy-6-iodo--1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (LXVIII) from the above tosyl derivative was effected by the procedure adopted in the glycerol series (p.85), and the product was isolated as a syrup in 93% yield. G.l.c. and t.l.c. analysis showed the product to be pure, and the $[\alpha]_D$ value, i.r., n.m.r. spectra and qualitative elemental analysis for iodine, all confirmed the identity of the product. The overall route is summarised in Scheme 13.


ZnCl2/(CH3)2CO
(LXVI)
NaI
HMPT
(LXVII)
(LXVIII)
Soda lime
AgF/pyridine
(LXII)

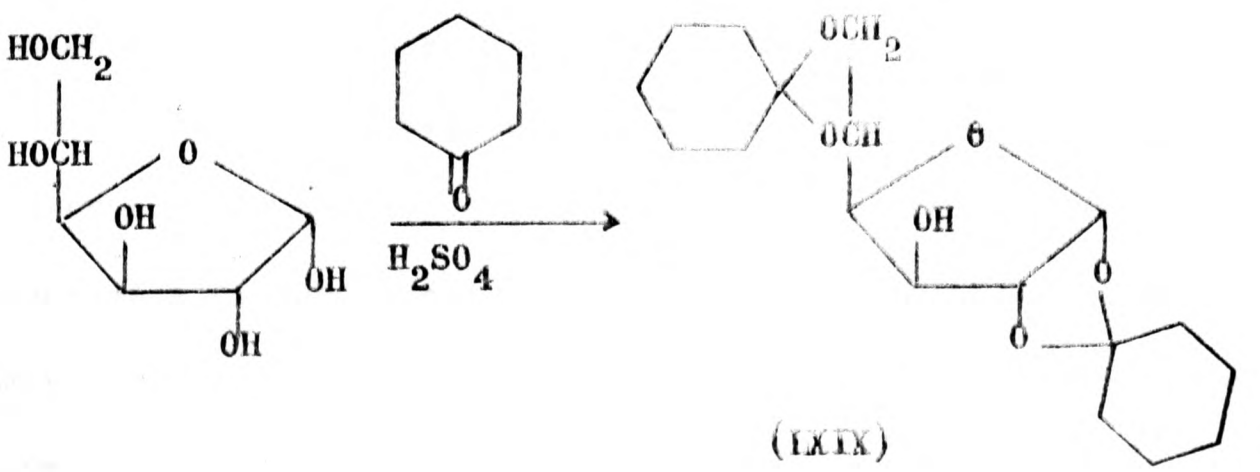
Scheme 13.

The two routes shown in Scheme 13 for the formation of the 5,6-unsaturated derivative (LXII) were both exploited. In the first, 6-deoxy-1,2:3,4-di-O-isopropylidene-β-L-arabino-hex-5-enopyranose (LXII) was prepared in 85% yield by an elimination reaction involving the action of soda lime on 1,2:3,4-di-O-isopropylidene-6-O-toluene-p--sulphonyl-α-D-galactopyranose (LXVII). The reaction was carried out in the solid powdered state at 150° under reduced pressure. The product sublimed onto a "cold finger" in 85% yield and was found to be pure by g.l.c. and t.l.c. analysis. The m.p. and $[\alpha]_D$ value were identical to those previously reported and i.r. and n.m.r. spectra were consistent with the known structure. Attempted preparation of the same unsaturated monosaccaride by shaking 1,2:3,4-di-O-isopropylidene-6-deoxy-6-iodo-α-D-galactopyranose (LXVIII) with silver(I)fluoride in pyridine at room temperature according to another reported procedure[122] was not so successful. G.l.c. and t.l.c. analysis of the syrupy product revealed a mixture of starting material and product and further shaking with silver(I)fluoride did not effect complete conversion into the unsaturated derivative. It was also found to be difficult to remove all traces of silver salt from the syrup, a consideration which could give rise to difficulties if other subsequent reactions were attempted on this material. For these reasons this procedure was not repeated.

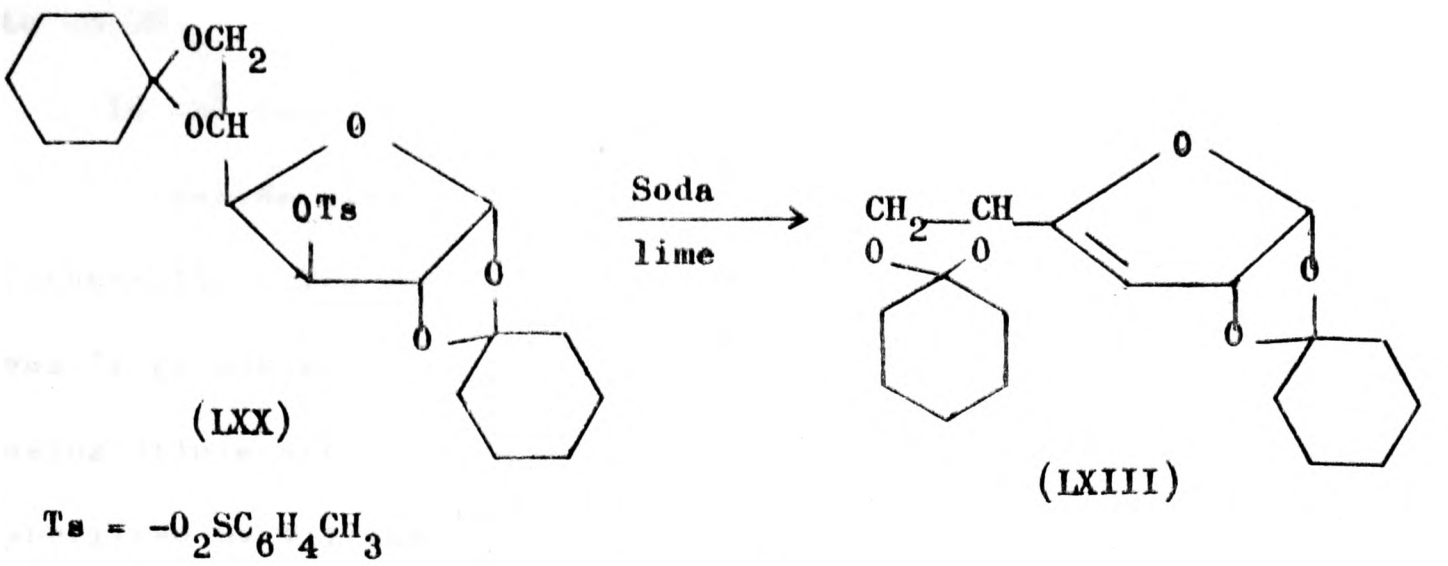
The unsaturated monosaccharide (LXII) was subjected to hydroboration-redistribution under the conditions previously described. A syrupy mixture was obtained which revealed the presence of three components on t.l.c. analysis. Aqueous hydrolysis yielded a product from which only boric acid crystallised; evaporation of the aqueous

solution from which the boric acid had been filtered gave a syrupy residue which had n.m.r. (N.m.r.17) and i.r. (I.r.12) spectra different to those of the mixture prior to the hydrolytic step (N.m.r.16 and I.r.11). Although the i.r. spectrum of the hydrolysed syrup had an absorption band due to O-H str., the n.m.r. spectrum did not contain any signal corresponding to $-B(OH)_2$.

1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranose (LXIX) was prepared from α-D-glucose by stirring with cyclohexanone for 5 hours in the presence of concentrated sulphuric acid[123]. The success of the reaction depends on the maintenance of a low temperature ($0-5^0$) during the initial addition of the sulphuric acid to the cyclohexanone. The product was obtained as white crystals in 40% yield having m.p., $[\alpha]_D$ value, i.r. and n.m.r. spectra, consistent with structure (LXIX). T.l.c. analysis showed the compound to be pure. Toluene-p-sulphonylation of this product in the standard way resulted in a 50% yield of white crystals having m.p., $[\alpha]_D$ value, i.r. and n.m.r. spectra consistent with (LXX); again this compound was confirmed as pure by running as a single spot on t.l.c. analysis.



(LXIX)



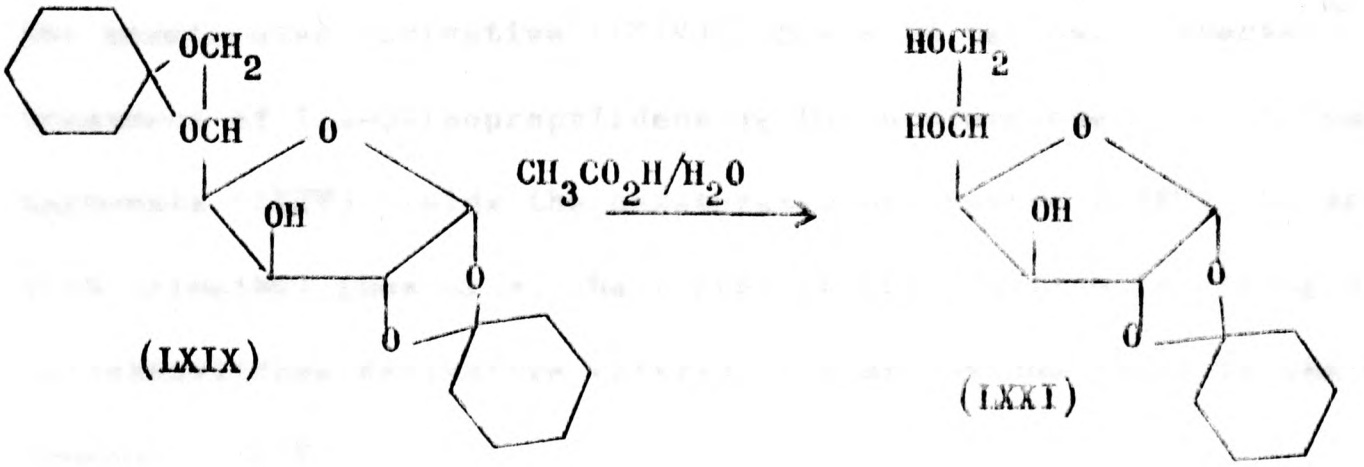
Ts = $-O_2SC_6H_4CH_3$

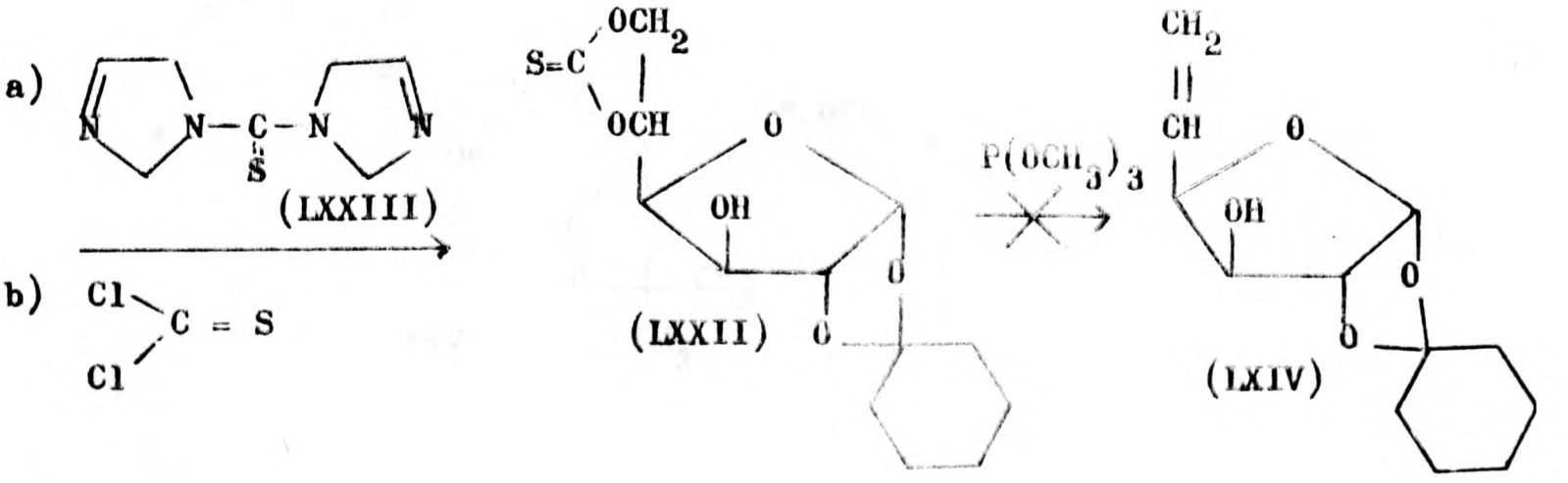
Scheme 14.

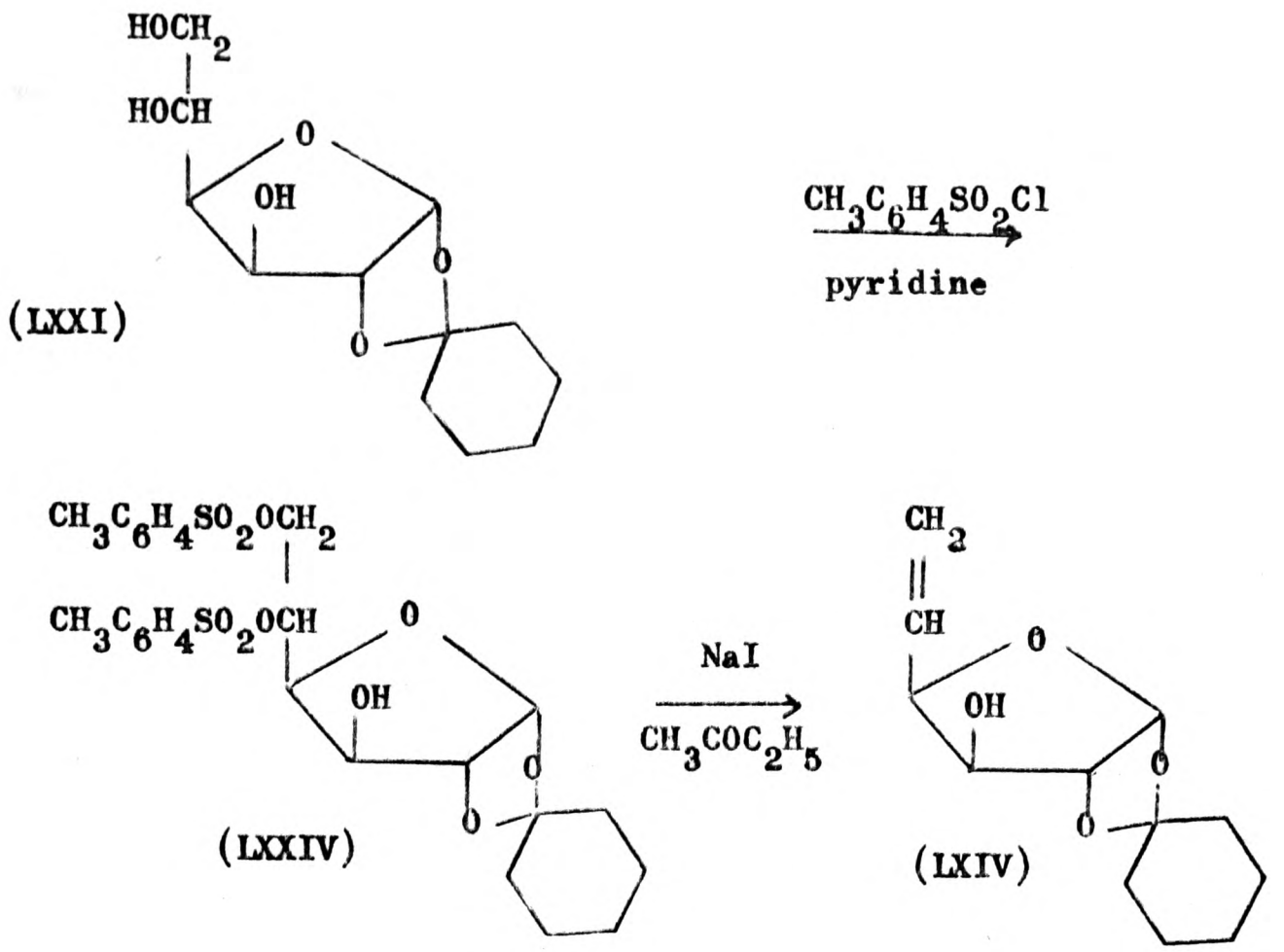
On treatment with soda lime this tosylate (LXX) was converted to the third unsaturated sugar required (Scheme 14), 1,2:5,6-di-O-cyclohexylidene-3-deoxy-∝-D- erythro-hex-3-enofuranose (LXIII). The product from this elimination reaction was purified using column chromatography, and was obtained in a yield of 64%, as a syrup having i.r. and n.m.r. spectra consistent with the structure (LXIII). The yields of both (LXII) and (LXIII) were greatly improved by using freshly prepared soda lime obtained by slaking fresh calcium oxide with concentrated aqueous sodium hydroxide. The hydroboration-redistribution of (LXIII) resulted in a three component syrupy mixture. The i.r. (I.r.13), B-O str., and n.m.r. (N.m.r.18) spectra of this mixture were consistent with the presence of a dioxaborinane system. However, aqueous hydrolysis of the mixture resulted in the formation of boric acid crystals and evaporation of the filtered solution gave a syrup with i.r. (I.r.14) and n.m.r. (N.m.r.19) spectra different to those of the original

mixture. Although the i.r. spectrum showed an absorption band due to O-H str., the n.m.r. spectrum did not contain a signal corresponding to $-B(OH)_2$.

In the reaction sequence leading to the final unsaturated monosaccharide system (LXIV) which had been selected for study (Scheme 15) 1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose (LXIX) was first subjected to partial hydrolysis of the 5,6-acetal grouping using dilute acetic acid under carefully controlled conditions as specified by Williams[124]. The product 1,2-O-cyclohexylidene-α-D--glucofuranose (LXXI), crystallised in 84% yield and the m.p., $[\alpha]_D$ value, i.r. and n.m.r. spectra were consistent with the reported structure. The compound was shown to be pure by t.l.c. analysis.

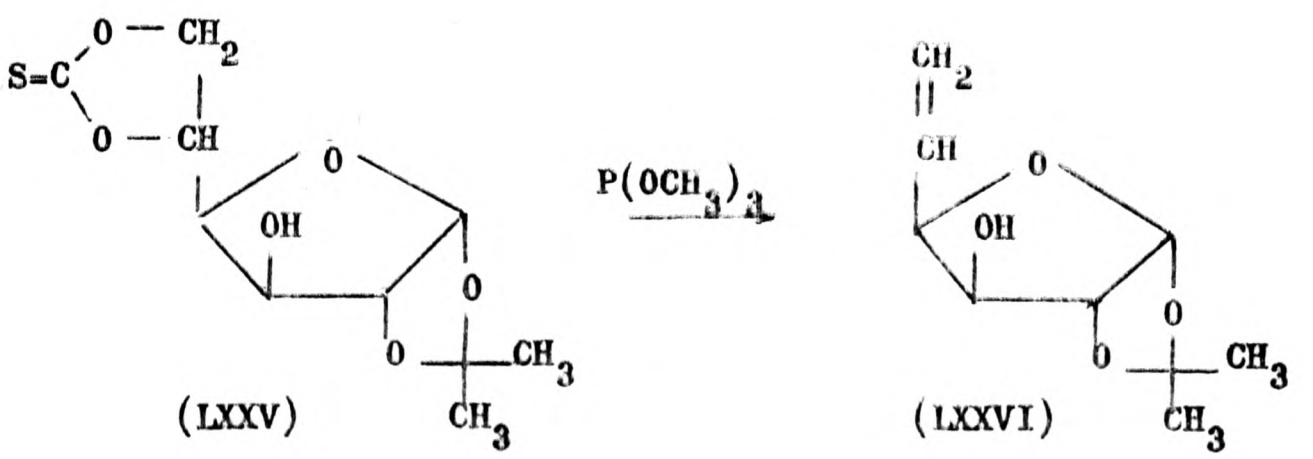






Scheme 15.

Two alternative routes were now available for the synthesis of the unsaturated derivative (LXIV). Since it had been reported[69] that treatment of 1,2-O-isopropylidene-α-D-glucofuranose 5,6-O-thionocarbonate (LXXV) yields the unsaturated derivative (LXXVI) on treatment with trimethyl phosphite, the corresponding reaction involving the cyclohexylidene derivative (LXXII) was an obvious route to the desired compound (LXIV).



The hitherto unreported 1,2-O-cyclohexylidene-α-D-glucofuranose 5,6-O-thionocarbonate (LXXII) was prepared by two different routes. In the first 1,2-O-cyclohexylidene-α-D-glucofuranose (LXXI) was allowed to react with bis(imidazol-1-yl)thione (LXXIII) in warm acetone under nitrogen (Scheme 15,(a)) according to a known procedure[69]. The solution was passed through a charcoal column to decolourise it, evaporated under reduced pressure, and the resulting yellow syrup was then crystallised from methanol. Recrystallisation from methanol afforded white needles (18% yield), the i.r. n.m.r. spectra, and microanalysis of which were consistent with a compound having structure (LXXII). The reagent (LXXIII) was itself prepared by reaction of imidazole with thiophosgene in toluene and methylene dichloride[69]. The thionocarbonate (LXXII) was also prepared in 35% yield by direct reaction of 1,2-O-cyclohexylidene-α-D-glucofuranose (LXXI) with thiophosgene (Scheme 15,(b)) in dioxane and pyridine. The crystals were purified by vacuum sublimation and had properties identical to those of the previous sample.

When the thionocarbonate (LXXII) was treated with trimethyl phosphite under identical conditions to those reported for (LXXV), disappointing and surprising results were obtained. The product isolated was a four component mixture by t.l.c. analysis which had i.r. and n.m.r. spectra which did not contain any evidence for the presence of a double bond. One of the components of the mixture was starting material (LXXII). An alternative route to (LXIV) was therefore selected. The starting material 1,2-O-cyclohexylidene--5,6-di-O-toluene-p-sulphonyl-α-D-glucofuranose (LXXIV) was prepared by treating 1,2-O-cyclohexylidene-α-D-glucofuranose (LXXI) with

toluene-p-sulphonyl chloride (2 molar equivalents) in toluene, pyridine and chloroform. The syrup which was isolated on pouring the reaction mixture into water and evaporating the solvent from the separated organic layer was crystallised readily from ethanol and gave the required product in a 31% yield. The product was shown by i.r. and n.m.r. spectra, and by microanalysis, to be consistent with the proposed structure (LXXIV). This di-toluene-p-sulphonate (LXXIV) was then heated under reflux in butan-2-one with sodium iodide for two hours according to a published procedure[125]. A syrupy product (73% yield) was obtained after purification by column chromatography. The i.r. spectrum had characteristic absorption due to a monosubstituted vinylic compound, in addition to acetal absorption bands. The n.m.r. spectrum was consistent with the structure (LXIV) and was only different to the reported spectrum of the analogous 1,2-O-isopropylidene derivative (LXXVI) in the acetal signal. The product could not be crystallised but was shown to be pure by t.l.c. analysis. Because of the complex results obtained for the three unsaturated sugars previously described, protection of the C-3 hydroxyl group followed by hydroboration-redistribution was not attempted.

Further investigation of the hydroboration-redistribution of unsaturated monosaccharides including (LXIV) would require the separation and identification of all the components of the mixtures arising from hydroboration-redistribution of (LXI), (LXII), and (LXIII). This might be achieved by h.p.l.c. or column chromatography after detailed study of appropriate separation parameters. Reaction mechanisms may then be formulated and conditions modified to achieve

maximum yield of the required products.

(F) CONCLUSIONS AND SUGGESTIONS FOR FUTURE WORK.

The work discussed in this thesis has led to a realisation of some of the problems associated with the synthesis of hydroxyalkaneboronic acids. It would appear that the hydroboration-redistribution and hydroboration-equilibration routes, which have been shown to be successful in these studies, will offer the best general methods of synthesis of hydroxyalkaneboronic acids. However, it was unfortunate that the tetrahydropyranyl ether protecting group logically chosen was not ideal since a complex reaction was found to occur on heating even simple tetrahydropyranyl ethers with trimethylene borate. Further study is clearly needed on the possible interactions with trimethylene borate of a series of protected alcohols having a variety of protecting groups before again attempting the redistribution reaction. It would also be fruitful to perform a parallel series of experiments with 1,3,2-benzodioxaborole to study any possible interactions of this reagent with protecting groups. From the pilot studies undertaken in this work it seems that benzyl or methyl ethers are likely to be the most promising protecting groups and therefore it is suggested that allyl benzyl ether and allyl methyl ether are subjected to hydroboration-redistribution, hydroboration-equilibration and hydroboration using 1,3,2-benzodioxaborole. If any of these routes then appears promising it would be advisable to proceed to monosaccharide derivatives protected as their benzyl or methyl ethers.

Further work on the characterisation and properties of the compounds obtained in this study would also be appropriate, including after further purification, testing for possible biological activity.

These compounds are

5-Hydroxypentaneboronic acid,

3-Hydroxybutaneboronic anhydride,

3-Benzyloxypropaneboronic acid,

2-(3-[2'Tetrahydropyranyloxy]propyl)-1,3,2-dioxaborinane, and

Dimethyl-1-(5-[2'-tetrahydropyranyloxy])-pentaneboronate.

One of the model systems selected for study (1,2-O-cyclohexylidene glycerol) was useful for the attempted formation of unsaturated side chains using organocopper reagents. It is thought that such methods may be suitable but a certain amount of development needs to be carried out to optimise conditions. Study of the stability of 1-hexaneboronic acid towards autoxidation and spontaneous anhydride formation in this work has indicated that the product may be stored without stringent precautions but these aspects would need to be re-investigated in the case of hydroxyalkaneboronic acids.

The Grignard route to boronic acids may be regarded as being generally less satisfactory for the preparation of hydroxyalkaneboronic acids. It would not be applicable to carbohydrates without the prior use of chain extension procedures and it is probably not very useful to carry out further work on the simple model systems.

If further work results in the isolation of hydroxyalkaneboronic acids attention must be turned to their purification and characterisation. Here, it is suggested that h.p.l.c. will assume prime importance and possibly simple acyclic ester derivatives such as benzoates could be prepared. When such pure, fully characterised boronic acids are available they may be subjected to suitable biological screening procedures. Also investigation of their anhydride formation, particu-

larly in the case of carbohydrate derivatives could reveal some interesting chemistry.

EXPERIMENTAL

(A) GENERAL REACTION TECHNIQUES

(i) Solvent purification methods.

Diethylene glycol dimethyl ether (diglyme) was heated under reflux with, and distilled from, calcium hydride.

Diethyl ether was dried over sodium wire.

Dioxan was initially dried with anhydrous sodium sulphate, passed through an alumina column and allowed to stand over potassium hydroxide pellets. It was then decanted from the pellets and distilled under nitrogen.

Light petroleum (b.p. 80-100^{0}) was dried over calcium sulphate, filtered, and redistilled.

Pentane, pyridine and toluene were each dried over anhydrous calcium sulphate.

Tetrahydrofuran (THF) was passed through an alumina column, then heated under reflux with, and distilled from, lithium aluminium hydride.

Benzaldehyde was dissolved in ether, shaken with sodium hydrogen carbonate solution (4 x 20 ml , 10% aq), dried and the solvent evaporated. It was then distilled under reduced pressure.

(ii) Drying and concentration of solutions.

The drying agent utilised in this work, unless otherwise specified, was anhydrous calcium sulphate. All solvent evaporations were carried out using a "Buchi" rotary evaporator under reduced pressure using a water suction pump.

(iii) Chromatographic techniques.

(a) Thin-layer chromatography (t.l.c.) was performed on silica gel G (250μ) and location of spots was by iodine vapour unless otherwise specified, except for monosaccharide derivatives. In these latter cases naphthoresorcinol spray reagent (0.2% w/v in ethanol containing 4.5% orthophosphoric acid) was used and a blue colour was obtained with most of the sugars studied except those specified otherwise.

Solvent system 1 : toluene/methanol (9:1)

Solvent system 2 : acetone/ethyl acetate (1:1)

(b) Gas-liquid chromatography (g.l.c.) using both analytical (5' x $\frac{1}{4}$") and preparative (7' x $\frac{3}{8}$") columns was extensively employed using the following stationary phases:

A SE 30 (5%).

B SE 52 (5% on silanised Chromosob W).

C Carbowax 20M (10%).

D Silicone Oil (10%).

E Apiezon L (10%).

F Poropak Q.

G Dinonyl phthalate (10%).

The instruments used were the Pye models 104 and 105 using nitrogen as carrier gas at 40 ml/minute. Column temperatures were as individually quoted.

(c) High performance liquid chromatography (h.p.l.c.) was carried out on a Carbowax 400/Poracil c 2' x $\frac{1}{8}$" column with chloroform solvent at 0.2 ml/minute using a constant volume pump. The apparatus used was the Walters Associates model 6000 with loop injector and detection was

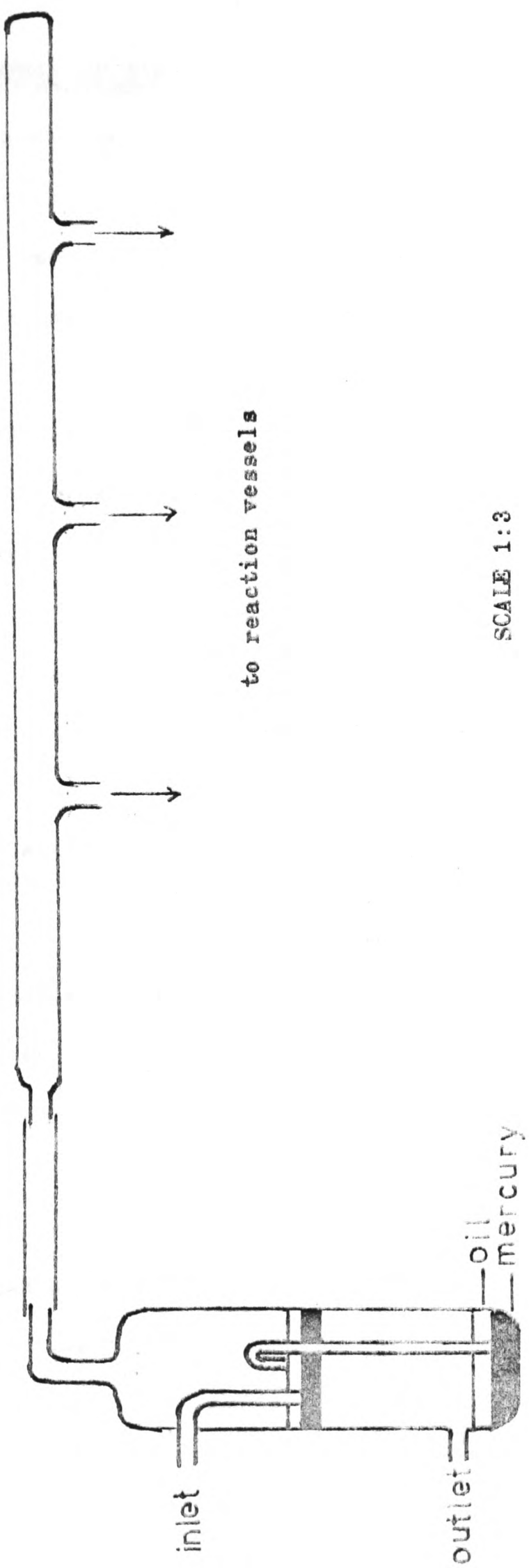
by means of a fixed wavelength ultraviolet detector and differential refractometer.

(iv) Inert atmospheres.

All reactions involving organometallic reagents or intermediates required the use of an inert atmosphere and this was achieved by the use of dry, oxygen-free nitrogen ("white spot"). If the apparatus needed to be flushed with nitrogen, a Pasteur pipette inserted through a 'Quickfit' thermometer holder served as the inlet and this was connected by P.V.C. tubing *via* anhydrous calcium chloride and phosphorus pentoxide tubes to the cylinder head valve. The outlet was usually a calcium chloride tube, but in the case of reactions involving diborane, an acetone bubbler was used to trap any excess diborane gas. An assembly similar to that described by Brown[127] was used to maintain a stationary atmosphere of nitrogen. The essential parts of the apparatus were a glass manifold fitted with stopcocks and a glass constant pressure mercury bubbler (Fig. 1). Each outlet from the glass manifold was connected by P.V.C. tubing to a Quickfit gas inlet which was attached to the reaction flask. All reagent transfers involving air sensitive solutions or liquids were by means of syringe through rubber septa. Addition of solid materials under nitrogen was achieved by attaching a conical flask containing the solid to one neck of the reaction flask by means of a short piece of rubber tubing. After flushing the apparatus with nitrogen the solid could be added at the appropriate moment by inverting the conical flask.

For reactions involving lithium metal, the pieces of metal were hammered out under oil until very thin, then cut into small pieces and

washed with light petroleum immediately before transfer to the reaction vessel under nitrogen.



SCALE 1:3

FIG 1. Constant pressure nitrogen bubbler and manifold.

(B) SYNTHESIS OF SIMPLE HYDROXYALKANEBORONIC ACID DERIVATIVES

(1) Routes via hydroboration of unsaturated alcohols

(a) Protection of hydroxyl functions

2'-Tetrahydropyranyloxy derivatives[86].

In the general procedure the alcohol (0.1 mol), 2,3-dihydropyran (0.105 mol) and concentrated hydrochloric acid (0.2 ml) were mixed at 0^{o}, stirred for 30 minutes and allowed to stand at room temperature overnight. The mixture was diluted with ether (50 ml), washed with sodium hydrogen carbonate solution (25 ml, 5% aq.), dried and distilled under reduced pressure. The products were analysed by g.l.c. and the n.m.r. and i.r. spectra recorded. The latter in all cases contained absorption bands at 820, 875, 1020, 1120, 1180, 1195 cm^{-1}.

alcohol	yield%	g.l.c.			b.p. ^{o}/mm Hg
		t_R minutes	column	temp. ^{o}C	
(i) Prop-2-en-1-ol	99	2.1	C	120	30-2/1
(ii) Propan-1-ol	99	3.6	C	80	50-1/13
(iii) Pent-4-en-1-ol	89	2.7	B	115	42-4/0.4
(iv) Pent-4-en-2-ol	97	2.0	B	115	40-2/0.5
		6.5	C	100	
(v) But-3-en-2-ol	89	2.8	E	145	39-40/4
(vi) Pent-1-en-3-ol	77	5.4	C	100	32-3/3
(viii) Prop-2-yn-1-ol	88	3.0	D	120	46-8/2 (lit.,[128] 65-7/9)

N.m.r. spectra

(i) δ 1.65 (m, 6H, CH_2), 3.3-4.5 (m, 4H, CH_2O), 4.7 (unresolved t, 1H, O-CH-O), 5.0-6.4 (m, 3H, $CH_2=CH$).

(ii) δ 0.9 (t, 3H CH_3), 1.6 (m, 8H, CH_2), 3.0-4.0 (m, 4H, CH_2O) 4.5 (unresolved t, 1H, O-CH-O),

(iii) δ 1.6-2.4 (m, 4H, CH_2), 3.1-4.1 (m, 4H, CH_2O), 4.6 (unresolved t, 1H, O-CH-O), 4.8-6.4 (m, 3H, $CH=CH_2$).

(iv) δ 1.1 (two d, 3H, CH_3), 1.6 (m, 6H, CH_2), 2.2 (q, 2H, CH_2), 3.2-4.1 (m, 3H, CH_2O and HCO), 4.7 (unresolved t, 1H, O-CH-O), 4.8-6.5 (m, 3H, $CH=CH_2$).

(v) δ 1.1 (two d, 3H, CH_3), 1.65 (m, 6H, CH_2), 3.3-4.5 (m, 3H, CH_2O and HC-O), 4.7 (unresolved t, 1H, O-CH-O), 4.9-6.1 (m, 3H, $CH=CH_2$).

(vi) δ 0.95 (t, 3H, CH_3), 1.6 (m, 8H, CH_2), 3.2-4.1 (m, 3H, HC-O and CH_2-O), 4.6 (unresolved t, 1H, O-CH-O), 4.9-6.1 (m, 3H, $CH=CH_2$).

(vii) δ 1.6 (m, 6H, CH_2), 2.55 (t, 1H, $C\equiv CH$), 3.0-3.2 (m, 2H, CH_2O), 4.15 (d, 2H, CH_2O), 4.75 (unresolved t, 1H, O-CH-O).

Stability of O-tetrahydropyranyl ethers towards hydroboration conditions.

(a) Freshly distilled boron trifluoride etherate (2g, b.p. 126°) in THF (10 ml) was added dropwise over 30 minutes to 1-(2'-tetrahydropyranyloxy)-propane (1 g) and sodium borohydride (0.5 g) in THF (20 ml) at room temperature. Aliquots were analysed by g.l.c. (column C, 80°) at 10 minute intervals which revealed small quantities of propan-1-ol being slowly formed (only detected after 1 hour). The i.r. spectrum after solvent evaporation showed characteristic tetrahydropyranyloxy absorption (820, 875, 1020, 1180, 1195 cm^{-1}) together with a small hydroxyl band at 3500-3300 cm^{-1}.

(b) The experiment (a) was repreated without sodium borohydride and g.l.c. analysis revealed the presence of appreciable quantities of propan-1-ol and 2,3-dihydropyran being generated on heating the reaction mixture at 120°. After 1 hour only a small amount of the original O-tetrahydropyranyl ether remained. Propan-1-ol was confirmed by admixture with authentic material and further g.l.c. analysis.

(c) Experiment (a) was repeated using diborane solution (0.4M in THF) in place of sodium borohydride or boron trifluoride etherate. After heating at 120° for 1 hour g.l.c. analysis indicated the presence of only trace amounts of propan-1-ol.

Allylbenzyl ether[95].

Prop-2-en-1-ol (11.6 g, 0.2 mol) was heated under reflux with powdered potassium hydroxide (20 g) and benzyl chloride (40 g) in toluene (100 ml) with vigorous stirring for 6 hours. The mixture was stirred with water (200 ml) and the organic layer separated. The aqueous layer was extracted twice with toluene (40 ml) and the bulked organic layers were washed with water (50 ml), dried and fractionally distilled at atmospheric pressure using a heated Vigreux column. Four fractions were collected and analysed by g.l.c. (column D, 160°) from which the total yield was calculated as 68%. The compositions of the fractions are given in the table below. The i.r. and n.m.r. spectra of fraction (d) was consistent with the proposed structure; δ 7.4 (s, 5H, aromatic); 4.55 (s, 2H, benzyl-CH_2); 5.6-6.5 (m, 3H, $CH=CH_2$).

Fraction	b.p. ^{o}C	Weight g	% allyl benzyl ether by g.l.c.
(a)	110	-	toluene
(b)	176-180	16	35
(c)	198-202	9.2	60
(d)	203-4	5.4	94
residue	-	4.0	91

b) Hydroboration of unsaturated alcohols

Diborane solution in tetrahydrofuran[88].

Freshly distilled boron trifluoride etherate (79 ml) in diglyme (50 ml) was added dropwise over 2 hours to sodium borohydride (19 g, 0.5 mol) in diglyme (100 ml) with vigorous stirring. A nitrogen stream carried the resulting diborane gas through a Dreschel bottle containing diglyme (10 ml) and sodium borohydride (1 g) and thence into a flask containing THF (250 ml) cooled to 0^{o}. After completion of addition the reaction flask was heated to 60^{o} for 1 hour with continuation of stirring and nitrogen flow. The product was standardised[89] by mixing an aliquot (10.00 ml) with acetone (30 ml) and diluting with water to 100 ml in a volumetric flask; 25.00 ml of the latter were mixed with mannitol (1 g) and titrated against 0.100 M sodium hydroxide solution using phenolphthalein indicator[90]. The product was found to be 1.75 M in diborane by this method.

Trimethylene borate[129].

Propane-1,3-diol (114 g, 1.5 mol) and boric acid (61.8 g, 1 mol)

were heated together in toluene (250 ml) and the water formed from the reaction was removed azeotropically using a Dean and Stark apparatus (53 ml recorded, theoretical 54 ml). The solvent was then evaporated to yield a clear liquid (116 g, 95%) which was immediately distilled; b.p. 150-2°/0.5 mmHg (lit.[116], 125°/0.05 mmHg) 86.6 g; ν_{max} 1490, 1420, 1330, 1280 cm^{-1}; δ 4.0 (quin, 12H, CH_2-O), 1.9 (m, 6H, $-CH_2-$); g.l.c. analysis t_R 1 minute (column E, 150°), h.p.l.c. V_R 4.0 ml.

Redistribution reaction of a trialkylborane[40].

The formation of 1-hexaneboronic acid.

Hex-1-ene (1.68 g, 0.02 mol) in THF (10 ml) was added to diborane in THF (20 ml, 1M) at 0° under N_2, and stirred for 30 minutes. The solvent was evaporated by heating in a stream of nitrogen and trimethylene borate (1.5 g) was added by means of a syringe, together with a further portion of diborane solution (5 ml, 1M). The mixture was stirred and heated at 120° for 4 hours when water (10 ml) was added and heated for 1 hour further. White crystals (1.5 g, 68%) formed on cooling, which were filtered and recrystallised from water. The i.r. spectrum was very similar to that of authentic 1-butaneboronic acid -OH str., B-O str., 1310-1450 cm^{-1}; $\lambda_{max}^{CHCl_3}$ 269 nm, ε_{max} 100.

An aliquot portion of the reaction mixture before addition of trimethylene borate was removed and treated with hydrogen peroxide and sodium hydroxide. G.l.c. analysis (columns C, D, 125°) revealed a peak which was identified as hexan-1-ol.

2-Hexyl-1,3,2-dioxaborinane.

Hex-1-ene (4.2 g, 0.05 mol) was treated successively with diborane

in THF (50 ml) and with trimethylene borate (6 g, 0.025 mol) as described above. A colourless liquid (4 g, 75%) was isolated which consisted of one component by g.l.c. analysis, t_R 2.9 minutes (column B, 100°) which was identical to the product obtained by the Grignard reagent route (p.141); ν_{max} B–O str., 1350 cm^{-1}, λ_{max} (cyclohexane) 268, 264, 261, 259, 254 n.m., h.p.l.c. V_R 1.6 ml. Treatment of the liquid product with water gave white hydrophobic crystals having an i.r. spectrum which was identical to that of 1-hexaneboronic acid obtained by the Grignard reagent route.

1-(2'-Tetrahydropyranyloxy)-propane-1,3-diol

1-(2'-Tetrahydropyranyloxy)prop-2-ene (1 g, 0.008 mol) was added to diborane in THF (15 ml, 0.55M) at 0° and stirred for 30 minutes . Sodium hydroxide solution (10 ml, 2.5M) and hydrogen peroxide (5 ml, 30%) were added and the mixture stirred for 1 hour. Water (20 ml) was added and the product was extracted with chloroform (3 x 20 ml). The extracts were dried and the solvent evaporated to give a colourless syrup (1.1 g, 86%), g.l.c. analysis two components (column B, 135°). I.r. ν O–H str., tetrahydropyranyloxy absorption bands, no C=C str.; δ 1.1–2.1 (two d, m, quin, 8H, $-CH_2-$), 3.3–4.6 (m, 7H, $-CH_2O-$, –OH), 4.6 (unresolved t, 1H, O–CH–O).

2-(3-[2'-Tetrahydropyranyloxy]propyl)-1,3,2-dioxaborinane.

1-(2'-Tetrahydropyranyloxy)prop-2-ene (6.3 g, 0.05 mol) was treated with diborane in THF (40 ml, 1M) and trimethylene borate (6.0 g, 0.025 mol) in the same way as for hex-1-ene. The colourless liquid product (10.3 g) was distilled from the reaction mixture

b.p. 108–116°/0.5 mm Hg and found to be a five component mixture which did not correspond to starting materials by g.l.c. analysis (column B, 135°) and three components by h.p.l.c. and t.l.c. (System 2). Mass spectrometry of each component revealed that the major component (60% yield) had a fragmentation pattern m/e 228, 198, 170, 143, 127, 115, 101, 85, 55, 41. The following accurate masses were observed: 85.0461 ($C_3H_6O_2B$ requires 85.0461), 143.0880 ($C_6H_{12}O_3B$ requires 143.0879), 170.1092 ($C_8H_{15}O_3B$ requires 170.1092). Attempted separation of the mixture by preparative g.l.c. (column E, B, 135°) was unsuccessful due to rapid overloading of the detector. However a few milligrammes of the major component were isolated by preparative g.l.c. (column C, 135°). ν_{max} O–H str., B–O str.; δ 1.75 (quin, 2H, $-CH_2-$), 3.8 (t, 4H $-CH_2O-$, CH_2-B), 4.2–5.6 (broad s, 3H, OH and $B(OH)_2$). A white solid material had formed also in the preparative g.l.c. collection tube. Hydrolysis of the crude mixture resulted in the formation of boric acid crystals and an ether-extractable syrup. The latter was established as an organoboron compound by flame test and i.r. spectroscopy, B–O str., O–H str.

4-(2'-Tetrahydropyranyloxy)-pentane-1-ol.

2-(2'-Tetrahydropyranyloxy)-pent-4-ene (1.7 g, 0.01 mol) was treated with diborane in THF (10 ml, 1M) at 0° then stirred at room temperature for 1.5 hours. Water (10 ml) was carefully added followed by sodium hydroxide solution (2 ml, 2.5M) and hydrogen peroxide (1.5 ml, 30%). The mixture was stirred for 1 hour, THF was evaporated and the aqueous residue extracted with ether (3 x 15 ml). The combined extracts were dried and the ether evaporated to give a liquid product

(1.5 g, 80%), g.l.c. analysis showed a single component t_R 2.5 minutes (column B, 135°), ν_{max} O-H str., tetrahydropyranyloxy absorptions; δ 1.1 (t, 3H $-CH_3$), 1.5 (m, 10H, $-CH_2-$), 3.3-3.8 (m, 5H, $-CH_2O$), 3.95 (s, 1H, OH), 4.6 (unresolved t, 1H, O-CH-O).

Attempted preparation of 2-(2-[2'-tetrahydropyranyloxy]butyl)-1,3,2-dioxaborinane.

2-(2'-Tetrahydropyranyloxy)but-3-ene (1.58 g, 0.01 mol) was treated with diborane in THF (10 ml, 1.75M) and trimethylene borate (1.63 g) in the same way as for hex-1-ene. The liquid product (2.4 g) was found to be a multi component mixture by g.l.c. analysis (column C, 160-225°). No separation was attempted, and hydrolysis of the mixture afforded boric acid crystals and an ether extractable syrup.

2-(1-Methyl-4-[2'-tetrahydropyranyloxy]butyl)-1,3,2-dioxaborinane.

2-(2'-Tetrahydropyranyloxy)pent-4-ene (2.53 g, 0.015 mol) was treated with diborane in THF (3 ml, 1.75M) and trimethylene borate (2.44 g) in the same way as for hex-1-ene. The product (3.5 g) was found to be a seven component mixture by g.l.c. analysis (column C, temperature programme 110-220°). No separation was attempted, and hydrolysis of the mixture afforded boric acid crystals and an ether extractable syrup.

Attempted preparation of 2-(5-[2'-Tetrahydropyranyloxy]pentyl)-1,3,2-dioxaborinane.

1-(2'-Tetrahydropyranyloxy)pent-4-ene (9 g, 0.05 mol) was treated with diborane in THF (15 ml, 1.75M) and trimethylene borate (8.1 g) in the same way as for hex-1-ene. The colourless liquid product (11.5 g)

was distilled from the reaction mixture (b.p. 88-9°/4.5 mm Hg) and found to be a single component by g.l.c. (t_{R} 1.6 minutes) (column B, 120°) and h.p.l.c. analysis (V_{R} 1.7 ml). ν_{max} O-H str., tetrahydropyranyloxy absorption bands; δ 1.2-2.0 (m, 10H, CH_2), 3.3-4.2 (m, 8H, CH_2O and OH), 4.6 (unresolved t, 1H, O-CH-O); (Found: C, 62.28, 62.54; H, 10.21, 10.56 %). Mass spectrum M^+ 170, most abundant fragment: measured 85.0654, $C_5H_9O^+$ required 85.0653.

Attempted preparation of 2-(3-[2'-tetrahydropyranyloxy]pentyl)--1,3,2-dioxaborinane.

3-(2'-Tetrahydropyranyloxy)pent-4-ene (1.7 g, 0.01 mol) was treated with diborane in THF (5 ml, 1.75M) and trimethylene borate (1.63 g) in the same way as for hex-1-ene. The product (2.3 g) was found to be a multi component mixture by g.l.c. (column C, 160-225°) and two components by t.l.c. (system 2) analysis. No separation was attempted, and hydrolysis of the mixture afforded boric acid crystals and an ether extractable syrup.

Effect of heating trimethylene borate with various substances.

Trimethylene borate was heated at 120° for 4 hours under nitrogen with each of the substances listed below. The progress of any change was monitored by g.l.c.

Substance	molar ratio	column E, 110°	column B, 135°
Trimethylene borate alone	-	no change	-
Diborane	1:1	no change	-
1-(2'-Tetrahydropyranyloxy)-propane	1:1	propan-1-ol dihydropyran two unknown products	multicomponent mixture
2-(2'-Tetrahydropyranyloxy)-pent-4-ene	1:1	one unknown product	multicomponent mixture
3,4,6-Tri-O-acetyl-D-glucal	1:1	no change*	-
Dibenzyl ether	1:1	no change*	-
Methyl tetra-O-methyl-α-D-glucopyranoside	1:1	no change*	-
1,2-O-Cyclohexylidene-3-O-ethyl glycerol	1:1	no change*	-
Dihydropyran	1:1	starting material consumed	multicomponent mixture
Propan-1-ol	1:2	starting material consumed, two unknown products	multicomponent mixture

* temperature programme used (100-180°)

The two unknown products in the case of 1-(2'-tetrahydropyranyloxy)-propane and propan-1-ol were identical. In the case of trimethylene borate heated alone the result was confirmed by i.r. and n.m.r. spectroscopy. G.l.c. analysis of a series of mixtures of the products obtained by heating trimethylene borate with 1-(2'-tetrahydropyranyloxy)-propane, propan-1-ol, and dihydropyran revealed that two of the components of the last mixture were present in the first and one component

of the second product mixture was present in the first.

5-Hydroxypentaneboronic acid.

1-(2'-tetrahydropyranyloxy)pent-4-ene (4.5 g, 0.025 mol) was heated for 6 hours at 50° with diborane in THF (45 ml, 1.75M). Water (20 ml) was added dropwise and the solution was evaporated under reduced pressure to yield sticky crystals (4.7 g, 87%). ν_{max} O-H str., B-O str.; δ 1.4 (m, 6H, CH_2), 3.3 (t, 4H, CH_2O, CH_2B), 3.8 (broad s, 1H, OH), 5.8 (broad s, 2H, $B(OH)_2$) (Found: C, 50.31; H, 8.91; $C_{10}H_{21}BO_4$ requires C, 55.58; H, 9.80%).

3-Hydroxybutaneboronic anhydride.

2-(2'-tetrahydropyranyloxy)but-3-ene (4.74 g, 0.03 mol) was heated for 6 hours at 50° with diborane in THF (50 ml, 1.75M). Water (25 ml) was added dropwise and the solution was evaporated under reduced pressure to yield a syrup (1.5 g, 25%). ν_{max} OH str., BO str.; δ 0.8 (d, 3H, CH_3), 1.2-1.6 (m, 8H, CH_2), 3.0-4.6 (m, 8H, HC-O-, $-CH_2-$ O-CH-O) (Found: C, 59.35; H, 9.72; $C_{10}H_{19}BO_3$ requires C, 60.64; H, 9.67%). Hydrolysis afforded an ether extractable syrup ν_{max} O-H str., B-O str.

3-Benzyloxypropaneboronic acid.

Allyl benzyl ether (2.98 g, 0.02 mol) was heated for 6 hours at 50° with diborane in THF (40 ml, 1.75M). Water (20 ml) was added dropwise and the solution was cooled in ice. White hydrophobic crystals were obtained (1 g) m.p. 125°; ν_{max} B-O str.; burned with a green flame to a black residue, n.m.r. and i.r. revealed the presence of boric acid so the crystals were shaken with pentane/ether 1:1 and filtration followed by evaporation of the solution gave a syrup (200 mg),

ν_{max} B-O str., O-H str.; δ 1.7 (quin, 4H, CH_2), 3.2-4.1 (m, 8H, CH_2O), 4.5 (s, 2H, benzyl), 7.85 (s, 5H, aromatic).

Dimethyl-1-(5-[2'-tetrahydropyranyloxy])-pentaneboronate.

1-(2'-tetrahydropyranyloxy)-pent-4-ene (4 g, 0.025 mol) was heated with diborane in THF (50 ml, 1M) at 50° for 6 hours. Methanol (15 ml) was then added over 30 minutes. The solvent was evaporated and the liquid product distilled b.p. 48-9°/1.5 mm Hg (2.8 g, 50%), g.l.c. one component, t_R 6 minutes (column E, 135°). I.r. (I.r.6) B-O str., no O-H or C=C; δ 0.8 (t, 6H, $-CH_3$), 1.4-1.8 (m, 12H, $-CH_2-$), 3.1-4.0 (m, 6H, $-CH_2O-$, $-CH_2B$), 4.6 (unresolved t, 1H, O-CH-O) (N.m.r.9). Treatment of the liquid product with water did not produce any crystals; instead a chloroform extract gave a liquid ν_{max} O-H str., B-O str.

1,3,2-Benzodioxaborole[41].

Diborane was generated as described above from sodium borohydride (2.2 g) and boron trifluoride etherate (14 g) and passed into a solution of 1,2-dihydroxybenzene (5.5 g, 0.05 mol) in THF at 0°. The solvent was removed by distillation under nitrogen, then the product was distilled under reduced pressure, b.p. 54-6°/25 mm Hg, (2.5 g, 42%). It was found to be a single component by g.l.c. (column B, 120°), (t_R 2.4 minutes) and h.p.l.c. analysis (V_{lt} 3.2 ml). ν_{max} 2650 (B-H str.), 1470, 1350 (B-O str.), 1240, 1130, 740 cm^{-1}.

2-Hexyl-1,3,2-benzodioxaborole.

1,3,2-Benzodioxaborole (2.4 g, 0.02 mol) was heated with hex-1-ene (1.7 g, 0.02 mol) for 2 hours at 100° under nitrogen. The colourless liquid product (4 g, 97%) was distilled b.p. 96-7°/1.5 mm Hg

and found to be a single component by g.l.c. analysis (column B, 135°) t_R 3.6 minutes. ν_{max} B-O str. (1350 cm^{-1}), absence of O-H str., and B-H str.; δ 0.9 (t, 3H, CH_3), 1.2-1.5 (m, 10H, $-CH_2-$), 6.9-7.1 (m, 4H, aromatic). Treatment of the product with cold water resulted in the formation of white hydrophobic crystals which had an i.r. spectrum and m.p. identical to those of authentic 1-hexaneboronic acid. Microanalysis could not be accomplished due to rapid decomposition of the sample during weighing.

Reaction of 1,3,2-benzodioxaborole with 1-(2'tetrahydropyranyloxy)--2-propene.

On reacting a mixture of 0.01 mol of each of these compounds by the above procedure an intractable red tar was formed.

Reaction of 1,3,2-benzodioxaborole with 1-(2'-tetrahydropyranyloxy)--2-propyne.

On reacting a mixture of 0.01 mol of each of these compounds by the above procedure an intractable red tar was formed.

2) Routes via Grignard reagents of halohydrins.

Butyl borate[130].

Boric acid (61.8 g, 1 mol) was heated under reflux with excess butan-1-ol, and water (50 ml) was removed as an azeotrope with butan-1-ol using a Dean and Stark apparatus. Distillation gave a colourless liquid b.p. 226-230° (lit.[130], 78-80°/0.75 mm Hg), 221 g, 96%; ν_{max} B-O str., no O-H str. G.l.c. analysis t_R 2 minutes (column E, 150°); δ 0.9 (t, 3H, CH_3), 1.45 (m, 4H, CH_2), 3.8 (t, 2H, CH_2B).

1-Hexaneboronic acid[17].

1-Bromohexane, (100 g, 0.6 mol) in ether (100 ml) was added to

magnesium turnings (14.5 g, 0.6 mol) in ether (200 ml) at such a rate that a gentle reflux was maintained. When the magnesium had dissolved (1.5 hours) the ethereal solution was added over 5.5 hours to butyl borate (139 g, 0.6 mol) under a nitrogen atmosphere at -65° to -75°, with vigorous stirring. Stirring was continued for a further 3.5 hours at -65° and the mixture was allowed to warm slowly to 0°. Sulphuric acid (10%, 300 ml) was added with stirring at 0° and the ether layer was separated. The aqueous layer was extracted with ether (2 x 50 ml) and the combined ether layers were evaporated to about 80 ml when an equal volume of water was added. Butan-1-ol was removed as an azeotrope with water and after two further additions of water followed by evaporation, white hydrophobic crystals separated. The crystals were filtered, dried between filter papers (51 g, 65%) and stored under nitrogen. The i.r. spectrum (I.r.2) showed absorption at 3200-3500, 2850, 2930, 2060, 1380, 1365, 1150 cm^{-1} and was identical to that obtained from a sample of hexaneboronic acid from the hydroboration procedure (p.133); λ_{max} 269 nm; δ 0.9 (t, 3H, $-CH_3$), 1.4 (m, 10H, $-CH_2-$), 5.8-6.2 (broad s, 2H, $B(OH)_2$).

In a further experiment this reaction was repeated on a 0.02 mol scale. After completion of the final stirring period the ethereal

solution was evaporated to give a syrup (8.2 g), which was redissolved in ether (50 ml) and a 25 ml aliquot was stirred with water (25 ml) when a white precipitate formed at the interface between the immisible layers. This solid was filtered and dried (0.5 g), ν_{max} O-H str., 1620, 1450, 1250 only. The presence of magnesium was demonstrated using magneson reagent and bromide by the silver nitrate test. When the solid was burned there was no flame colour and no black residue. The aqueous layer was alkaline (pH 9) and the presence of magnesium was confirmed using magneson reagent. The water was evaporated to give a solid (1.9 g): total yield of inorganic material 2.4 g, theoretical yield of Mg(OH)Br (0.02 mol) 2.44 g. The ether layer was evaporated and water was added to the residue and evaporated. This process was repeated until there was no smell of butan-1-ol. On cooling the final residue crystals formed (0.8 g) m.p. 67-70° which had properties consistent with 1-hexaneboronic acid.

1-Hexaneboronic anhydride[17].

A sample of 1-hexaneboronic acid (3.0 g) was placed in a desiccator over phosphorus pentoxide in a nitrogen atmosphere. After a period of 20 days the crystals had been transformed into a colourless liquid (2.3 g, 100%), b.p. 130-2° /1 mm Hg (lit.[17], 149-51/4 mm Hg), ν_{max} B-O str., no O-H str.; δ 0.9 (t, 3H, $-CH_3$), 1.4 (m, 10H, $-CH_2-$).

Preparation and hydrolysis of 2-hexyl-1,3,2-dioxaborinane.

1-Hexaneboronic acid (15.4 g, 0.2 mol) and propane-1,3-diol (15.2 g, 0.2 mol) were heated under reflux in toluene, and water (5.2 ml, theoretical 6.4 ml) was removed as an azeotrope with toluene using a Dean and Stark apparatus. Evaporation of the toluene and

distillation of the residue gave a liquid product b.p. 54–5°/1 mm Hg, 12 g, 54%; ν_{max} B–O str., no O–H str. g.l.c. one component (column B, 100°) t_R 2.9 minutes. (Found: C, 65.37; H, 11.84; $C_9H_{19}BO_2$ requires C, 63.57; H, 11.26%). Treatment of the product with water regenerated 1-hexaneboronic acid.

Stability of 1-hexaneboronic acid.

The acid was slowly transformed into the anhydride after prolonged storage under desiccating conditions as described above. No change was observed after storage in a standard sample tube on the bench: the i.r. and n.m.r. spectra were identical to those of 1-hexaneboronic acid and analysis did not indicate any decomposition (Found: C, 55.88; H, 11.42; $C_6H_{15}BO_2$ requires C, 55.44; H, 11.63%).

1-(2'-tetrahydropyranyloxy)-3-bromopropane[86].

3-Bromopropan-1-ol (13.9 g, 0.1 mol) and dihydropyran (8.8 g, 0.105 mol) were allowed to react in acid and the product (19.4 g, 86%) isolated in the usual manner (p.129). Distillation gave a colourless liquid b.p. 77–8°/2 mm Hg (lit.,[86] 69°/1.2 mm Hg) and g.l.c. revealed one component t_R 2 minutes; ν_{max} tetrahydropyranyloxy absorption bands; δ 1.60 (m, 6H, CH_2), 2.1 (quin, 2H, CH_2), 3.25–4.05 (m, 6H, CH_2O, CH_2Br), 4.6 (unresolved t, 1H, O–CH–O) (Found: C, 43.71; H, 7.08; $C_8H_{15}O_2Br$ requires C, 43.03; H, 6.78%).

1-(2'-tetrahydropyranyloxy)-propylmagnesium bromide.

Addition of 1-(2'-tetrahydropyranyloxy)-3-bromopropane (5 g) in THF (10 ml) to magnesium turnings (0.48 g, 0.02 mol) in THF (10 ml) containing a little ethyl magnesium bromide caused dissolution of the

magnesium in 2 hours. Heating under reflux for 30 minutes was followed by the addition of benzophenone (3.6 g, 0.2 mol) in THF (10 ml) over 15 minutes. A dark red colour developed during the addition, and after 30 minutes reflux, the reaction mixture was poured onto ice and neutralised with hydrochloric acid. Crystals formed immediately which on filtration and recrystallisation from dilute ethanol were identified as benzpinacol (1.8 g, 50%) m.p. 186-7° (lit.[131], 185-6°), δ 3.05 (s, 2H, OH), 7.25 (m, 20H, aromatic); λ_{max} 247, 252, 258, 268 nm. The aqueous filtrate was extracted with ether, dried and the solvent evaporated. The liquid product (5 g) was micro-distilled and g.l.c. revealed the presence of one component which was identified as 1-(2'-tetrahydropyranyloxy)-propane by g.l.c. analysis (column E, 110°) and by its i.r. and n.m.r. spectra.

Attempted preparation of 3-hydroxypropaneboronic acid.

Iodomethane (7.5 g) was added dropwise to magnesium (1.36 g) in THF (25 ml) with stirring. When most of the magnesium had dissolved 3-bromopropan-1-ol (7 g, 0.05 mol) in THF (20 ml) was added dropwise and a vigorous reaction occurred. Magnesium (1.29 g, 0.05 mol) was added which dissolved to leave a thick grey solution. A portion of this was treated with purified benzaldehyde in the same way as before and the product isolated gave an i.r. spectrum containing absorption bands due to an aromatic ring and O-H; δ 1.55 (quin, 2H, CH_2), 2.9-3.8 (m, 6H, CH_2, OH), 4.65 (s, 1H, $CH-C_6H_5$), 7.2-8.1 (m, 5H, aromatic). The remainder of the grey solution was added over 3 hours to butyl borate (11.5 g, 0.05 mol) at -78° while maintaining vigorous stirring and then stirred for 2 hours more. The grey solution thickened

dramatically during addition and a constant rate of addition could not be maintained. The product mixture was subjected to the same isolation procedure as hexaneboronic acid (p.142) but no crystals were obtained. The aqueous residue was evaporated to give inorganic material only.

4-Chlorobutan-1-ol[96].

Hydrogen chloride gas was passed into THF (300 g) heated under reflux for 12 hours. On removal of solvent under reduced pressure distillation a golden yellow liquid (105 g) was isolated. Distillation of this product at a pressure of 13 mm Hg yielded a minor fraction at 50-55° (5 g) and a major fraction at 78-80° (61 g, 10%) which had a purity of 92% by g.l.c. analysis (column A, 150°), t_R 0.72 (major) and 0.56. (lit.[96], b.p. 80-2°/14 mm Hg) ν_{max} O-H str., O-H bend, C-O bend, chlorine was found to be present by sodium fusion; δ 1.7-2.0 (m, 4H, $-CH_2CH_2-$), 3.3-3.8 (m, 5H, -OH, $-CH_2O-$, $-CH_2Cl$).

1-(2'-tetrahydropyranyloxy)-4-chlorobutane.

4-Chlorobutan-1-ol (11 g, 0.1 mol) was stirred with dihydropyran (8.8 g, 0.105 mol) in the presence of acid as above (p.144). The product isolated (17.4 g, 91%) was distilled at 76-8°/1.5 mm Hg and showed to be one component by g.l.c. analysis, t_R 1.7 minutes (column A, 150°). Chlorine was found to be present by sodium fusion, ν_{max} tetrahydropyranyloxy; δ 1.3-2.0 (m, 10H, $-CH_2-$), 3.3-3.7 (m, 6H, CH_2O, CH_2Cl), 4.6 (unresolved t, 1H, O-CH-O).

4-Iodobutan-1-ol.

4-Chlorobutan-1-ol (1.1 g, 0.01 mol) was shaken with sodium iodide (1.5 g) in acetone (20 ml) at room temperature for 5 hours, allowed to stand overnight then heated under reflux for 3 hours [97]. The mixture was poured into water (100 ml), extracted with ether (3 x 20 ml), dried and the solvent removed to give a yellow liquid (1.1 g, 54%). G.l.c. analysis (column A, 150°) revealed a single component having the same t_R as the starting material but iodine was found to be present by sodium fusion.

1-(2'-tetrahydropyranyloxy)-4-iodobutane.

Method (i). 4-Iodobutan-1-ol (2.65 g) was treated with dihydropyran (1.2g) as above (p.144). The product isolated was distilled at 62-4°/1.5 mm Hg (1.73 g, 46%) showed 1 component by g.l.c. analysis (column C, 180°) t_R 3.5 minutes and iodine was found to be present by sodium fusion, ν_{max} tetrahydropyranyloxy absorption bands.

Method (ii). 1-(2'-tetrahydropyranyloxy)-4-chlorobutane (5.4 g) was shaken with sodium iodide (4.2 g) as above and isolation of the product (3.4 g) revealed a 2 component mixture by g.l.c. analysis (column A, 150°) t_R 0.72, 1.7 minutes. ν_{max} -OH str., tetrahydropyranyloxy absorption bands. On treatment of this mixture with dihydropyran (1 g) as above a product (4.1 g, 52%) was obtained which was identical to that obtained by method (i).

Attempted synthesis of 1-(2'-tetrahydropyranyloxy)-butyl magnesium iodide.

1-(2'-tetrahydropyranyloxy)-4-iodobutane (6.7 g, 0.025 mol) was added in portions to magnesium (0.6 g, 0.025 mol) in THF. No visible

reaction occurred after 1 hour from addition of the first portion, then 1,2-dibromoethane (0.5 g) was added. This initiated reflux of the solvent and the iodide was added dropwise. On completion of the addition, purified benaldehyde (1 g) was added and the mixture heated under reflux for 1.5 hours. The product was poured into sulphuric acid and ice water, extracted with ether (3 x 30 ml), washed with sodium bisulphite (4 x 20 ml, 5% aq.) dried over magnesium sulphate and the solvent evaporated. The product was found to be different to the starting material but not consistentwith the required product. ν_{max} OH str., b.p. 68–70°/1 mm Hg, t.l.c. (system 1) R_f 0.56, g.l.c. (column A, 150°) t_R 1.6 minutes, δ 1.3–2.0 (m, 12H, $-CH_2-$), 3.2–4.0 (m, 8H, CH_2O), 4.6 (unresolved t, 1H, O–CH–O).

(C) UNSATURATED DERIVATIVES OF GLYCEROL

1,2-O-Cyclohexylidene glycerol[98].

Concentrated sulphuric acid (7.5 ml) was added to an ice cooled solution of glycerol (92 g, 1 mol) and cyclohexanone (98 g, 1 mol) in light petroleum (200 ml). The mixture was shaken for 18 hours when the petroleum layer was separated and dried (anhydrous potassium carbonate). Distillation of the residue after solvent evaporation yielded a clear liquid (84 g, 49%) b.p. 106-110°/2.5 mm Hg (lit.[98], 118-20°/5 mm Hg; R_F 0.26 (toluene/ethanol, 95:5); t_R 19 minutes (column C, 150°). Trimethylsilylation using hexamethyldisilazane and trimethyldichlorosilane in pyridine[133] followed by g.l.c. analysis revealed one component t_R 2.5 minutes (column A, 180°). (Found: C, 60.58; H, 9.36; $C_9H_{16}O_3$ requires C, 62.76; H, 9.37%). δ 1.60 (m, 10H, cyclohexylidene), 2.70 (s, 1H, -OH) 3.95 (m, 2H $-CH_2-$), 4.05 (m, 2H, $-CH_2-$), 4.45 (quin, 1H, -CH-). The spectrum was simplified and the coupling constants determined using a lanthanide shift reagent followed by computer analysis (p.83).

1,2-O-Cyclohexylidene-3-O-toluene-p-sulphonyl glycerol.

Toluene-p-sulphonyl chloride (7.5 g, 0.04 mol) in pyridine (15 ml) was added to an ice cooled solution of 1,2-O-cyclohexylidene glycerol (5 g, 0.03 mol) in pyridine (5 ml). The mixture was cooled for 2 hours then allowed to stand at room temperature for 5 days. The precipitated pyridine hydrochloride was dissolved by adding water and the mixture was poured into excess ice/water. The oil which separated was extracted with chloroform (2 x 50 ml), and the organic layer was

washed with water (2 x 50 ml) and dried. Evaporation of the solvent gave a crude oil (8.0 g) which crystallised from light petroleum/ methylene dichloride. Upon recrystallisation from the same solvent white crystals (2.1 g) were obtained m.p. 47.5°-48.5°. Evaporation of the mother liquor and recrystallisation of the residue gave a further 3.0 g of product m.p. 47-48°, (combined product 5.1 g, 52%). R_F 0.77 (toluene/methanol, 95.5); (Found: C, 58.74; H, 6.98; S, 9.77. $C_{16}H_{22}S_2O_5$ requires C, 58.88; H, 6.80; S, 9.82%; δ1.60 (m, 10H cyclohexlidene), 2.5 (s, 3H, $-CH_3$), 7.70 (AA' BB', 4H, aromatic), 3.7-4.5 (m, 5H, $-CH_2-CH-CH_2-$); the i.r. spectrum was consistent with the proposed structure; m/e 326, 297, 283, 155, 141, 139, 112, 111, 91, 55.

1,2-O-Cyclohexylidene-3-deoxy-3-iodo glycerol.

Ground lithium iodide (40 g) was added to a solution of 1,2-O-cyclohexylidene-3-O-toluene-p-sulphonyl glycerol (16 g, 0.05 mol) in toluene (200 ml) containing hexamethylphosphoramide (54 g). The mixture was stirred and heated under reflux for 15 minutes, cooled, washed with water (3 x 50 ml) and dried. Upon evaporation of the solvent a product (10.7 g, 76%) was obtained, distillation of which yielded a pale yellow liquid (4.3 g) b.p. 110-114°/1.75 mm Hg which rapidly darkened. Purity was established by t.l.c. and g.l.c. analysis; R_F 0.84 (toluene/methanol 95.5), t_R 8.6 minutes (column C, 170°), 12.0 minutes (column E, 180°), 2 minutes (column A, 180°). (Found: C, 38.80; H, 5.41; I, 47.64. $C_9H_{15}O_2I$ requires C, 38.31; H, 5.36; I, 44.98%). δ 1.6 (m, 10H, cyclohexylidene), 3.0-4.5 (m, 5H, $-CH_2-CH-CH_2-$); m/e 282, 253, 239, 226, 155, 141, 112, 111, 99, 98,

97, 81, 69, m* 51.6 and 85.2.

2,3-O-Cyclohexylidene glyceraldehyde.

1,2-O-cyclohexylidene glycerol (15.7 g) in toluene (50 ml) was heated under reflux with vigorous stirring with chromium trioxide on graphite ("Seloxcette") (25 g) for 24 hours. Evaporation of the solvent gave a liquid product (12 g); ν_{max} 1705, 2740, 3300-3500 cm^{-1}, it gave a positive test with Schiff's reagent.

2,3-O-Cyclohexylidene glyceraldehyde semicarbazone.

The foregoing product (6 g) was shaken with a solution of semicarbazide hydrochloride (6 g) and sodium acetate (9 g) in water (60 ml). On cooling the solution white crystals were formed which on filtration and recrystallisation (dilute ethanol) gave a product (3 g, 39%, m.p. 210-12°) ν_{max} 3500, 3280, 3220, 1700, 1680, 1590, 1090 cm^{-1} there was evidence of facile decomposition by the appearance of insoluble material; t.l.c. on samples stored for a short period of time revealed three components, one of which was identified as cyclohexanone.

1,2 : 5,6-Di-O-isopropylidene mannitol[115].

Anhydrous zinc chloride (70.4 g) was stirred with acetone (352 ml) for 30 minutes when the suspension was filtered into mannitol (36.4 g, 0.2 mol). The mixture was stirred for 2.5 hours in a bath of cold water then poured into potassium carbonate solution (88 ml, 100% aq.). The solid product was filtered and washed with chloroform (3 x 50 ml) and the aqueous layer was also extracted with chloroform (3 x 50 ml). The bulked organic layers were dried and evaporated to

give a white crystalline solid (m.p. 113–6°) which was recrystallised from light petroleum 80–100°/chloroform (9:1) to form white needles (31.5 g, 60%), m.p. 120–2° (lit[115], 120–1°). ν_{max} O-isopropylidene groups (1389, 1372, 1160, 1070, 1040 cm^{-1}).

2,3-O-isopropylidene glyceraldehyde[115].

1,2:5,6-Di-O-isopropylidene mannitol (17 g, 0.065 mol) was suspended in benzene (100 ml) and stirred with lead tetracetate (30 g). The solution was filtered from the sticky precipitate and distilled. After removal of the solvent, the product (7 g, 75%) was collected at b.p. 30–5°/3 mm Hg (lit.[115], 35–42°/11 mm Hg). The presence of H–C=O was confirmed by formation of a 2,4-dinitrophenylhydrazone and a positive Schiff's test; ν_{max} O=C–H str., C=O str.; δ 1.4 (two s, 6H, $>C(CH_3)_3$), 3.8–4.4 (m, 3H, HC–CH_2–), 4.7–5.2 (broad s, 1H, H–C=O).

1,2-O-Isopropylidene-3-vinyl glycerol[115].

Vinyl bromide (10.7 g, 0.1 mol) was added to magnesium (2.4 g, 0.1 mol) in THF at such a rate that a steady reflux was maintained. When all the magnesium had dissolved the solution was stirred for 30 minutes further and then 2,3-O-isopropylidene glyceraldehyde (13 g, 0.1 mol) in THF (50 ml) was added over 30 minutes. After heating under reflux for 1 hour the mixture was cooled in ice and sulphuric acid (50 ml, 2.5M) was added with stirring and the product was then extracted with ether (3 x 50 ml). The combined extracts were dried and the solvent evaporated to yield a yellow liquid (10 g) which consisted of two components by t.l.c. analysis (system 1), R_f 0.17, 0.50. The presence of a carbon-carbon double bond was established by

the decolourisation of potassium permanganate solution; ν_{max} -OH str., C=C str. 1650 cm^{-1}; G.l.c. analysis (column C, 160°) revealed the presence of two peaks which disappeared on silylation (using N, O-bis(trimethylsilyl)acetamide in acetone at room temperature[132]), g.l.c. of the silylated derivatives (column D, 60°) revealed two peaks in the ratio 25:75. These could not be separated by preparative g.l.c.

1,2-O-Cyclohexylidene-3-deoxy-3-vinyl-glycerol.

Butyl lithium (50 ml, 2.1M in hexane) was added over 15 minutes to tetravinyltin (5.7 g, 0.025 mol) in ether (10 ml). The stirred solution of vinyl lithium (77% yield, benzaldehyde) was cooled using dry ice/acetone, dried copper(I)iodide (19 g) was added over 10 minutes, and finally 1,2-O-cyclohexylidene-3-O-toluene-p-sulphonyl glycerol (32.6 g, 0.1 mol) in ether (20 ml) was added. After a further 6 hours stirring at -60 to -70° a saturated ammonium chloride solution (50 ml) was added to the reaction mixture, which was then allowed to warm to 0° and stirred for 15 minutes. The organic layer was separated, washed with saturated sodium chloride solution (2 x 25 ml), dried and the solvent evaporated. The crude product was obtained as an oil (23 g) from which 1,2-O-cyclohexylidene-3-O-toluene-p-sulphonyl glycerol (8.2 g, 25% recovery) crystallised on storage at 5°. Removal of the crystals by filtration under vacuum gave an oily filtrate the i.r. spectrum of which revealed the absence of absorption at frequencies to be expected for the presence of O-toluene-p-sulphonyl groups. G.l.c. analysis of the oil (column A, 120°) revealed at least 4 major components, it decolourised bromine in carbon tetrachloride, and the

n.m.r. spectrum showed signals (δ 5,4–6.4) which were removed on bromination. Attempted separation of the mixture by distillation (1.5 mm Hg) and column chromatography on alumina were unsuccessful, while preparative g.l.c. (column C, 120°) yielded two pure fractions, (a) tetrabutyltin and (b) 1,2-O-cyclohexylidene-3-deoxy-3-iodo-glycerol, identified by n.m.r., mass spectrometry and comparative g.l.c. analysis, and one fraction which was a mixture. G.l.c./m.s. analysis of the crude oil confirmed the presence of (a) and (b) above, as well as two other compounds containing tin and 1,2-O-cyclohexylidene--3-deoxy-3-vinyl-glycerol (M.s.9).

Attempted preparation of 1,2-O-cyclohexylidene-3-deoxy-3-allyl glycerol.

Method (i). Butyl lithium (10 ml, 2.1M in hexane) was added rapidly to tetrallyl tin (1.42 g, 0.005 mol) in ether (10 ml) and stirred for 30 minutes. The mixture was cooled in a dry ice/acetone bath and dried copper(I) iodide (7.6 g, 0.04 mol) was added in portions over 15 minutes. The resultant orange mixture was stirred during the addition of 1,2-O-cyclohexylidene-3-O-toluene-p-sulphonyl glycerol (6.5 g, 0.02 mol) in ether (20 ml), and for 6 hours subsequently. The crude product (8.3 g) was separated in the same manner as for 1,2-O-cyclohexylidene-3-deoxy-3-vinyl glycerol (p.153) and distillation produced a liquid, b.p. 135–140°/2 mm Hg, shown to be 1 component by g.l.c. (column C, 150°) and t.l.c. (toluene/ethanol, 95.5); analysis; δ 0.90 (m), 1.45 (m) ratio (1:1); the mass spectrum gave a measured mass of 287.1132, calculated $C_{12}H_{12}{}^{116}Sn$ 287. 1130.

Method (ii). Allyl phenyl ether (6.7 g, 0.05 mol) in ether (25 ml) was added (45 minutes) to a stirred suspension of lithium

pieces (4.2 g, 0.6 mol) in THF (50 ml), while cooling in ice. The mixture was stirred for a further 15 minutes at room temperature when a pale green colour was observed (yield of allyl lithium by titration, 84%). Dried copper(I) iodide (19 g, 0.1 mol) was added after the mixture had been cooled (dry ice/acetone) and a dark red colour developed. 1,2-O-Cyclohexylidene-3-deoxy-3-iodo glycerol (14.1 g, 0.05 mol) was added and the mixture was stirred for 6 hours. The crude product (8.9 g), was isolated as for the vinyl analogue and was shown to consist of 2 components by g.l.c. (column C, 120° and by t.l.c. (toluene/methanol 95.5) analysis. One of these was identified by comparison with authentic material as cyclohexanone. A 2,4-dinitrophenylhydrazone derivative was prepared and recrystallised from methanol m.p. 154-5°. The crude product was dissolved in ether and washed 5 times with sodium bisulphite solution. After drying the ether layer and evaporating the solvent a product was obtained ν_{max} (OH str.) 3300-3500 cm^{-1}, (C=C$_{H}$) 3030, (C=O str.) 1690, (C=C) 1615; δ 1.50 (m), 2.2 (d), 2.05 (s, removed by D_2O), 3.4-4.2 (m), 4.8-6.1 (m, not removed by bromine).

Allyl phenyl ether[134].

Phenol (40 g, 0.42 mol), allyl bromide (50 g, 0.42 mol), anhydrous potassium carbonate (58 g) and dry acetone (90 ml) were heated under reflux for 8 hours. The mixture was poured into water (200 ml) and the organic layer separated. The aqueous phase was extracted with ether (3 x 50 ml) and the bulked organic layers shaken with sodium hydroxide (2.5M, 50 ml), separated, dried, and the solvent evaporated to yield a product (45.1 g, 80%). Distillation gave a colourless

liquid (41.2 g) b.p. 80–82°/15 mm Hg, n_D^{20} 1.5227 (lit.[135], 1.5223), g.l.c. t_R 1.4 minutes (column D, 170°), λ_{max} 267, 273, 279.5 nm, i.r. consistent with reported structure. δ 4.55 (m, 2H, $-CH_2-$), 5.1–6.5 (m, 3H, CH_2 $CH-CH_2-$), 6.8–7.5 (m, 5H, aromatic).

Nonane.

Ethyl bromide (27.2 g, 0.25 mol) in pentane (80 ml) was added over 4 hours to lithium (3.5 g, 0.5 mol) in pentane (40 ml) which was maintained under gentle reflux[109]. When all the lithium had dissolved (yield of ethyl lithium, 84% by titration) the mixture was cooled in dry ice/acetone and THF (80 ml) and copper(I) iodide (19 g, 0.1 mol) were added with vigorous stirring. 1-Iodoheptane (11.4 g, 0.05 mol) in THF (50 ml) was then added to the black solution over 15 minutes followed by toluene (4.60 g, 0.05 mol internal standard). The reaction mixture was then stirred for 8 hours and allowed to warm slowly to room temperature. The mixture was heated under reflux for 1 hour, water was added and the organic layer separated. The aqueous layer was shaken with pentane (3 x 50 ml) and the combined extracts were dried and evaporated ($<30°$/15 mm Hg) to remove pentane and THF, but not toluene. G.l.c. analysis (column C, 80°) showed the mixture consisted of 5 components which were identified by g.l.c./mass spectrometry as shown below. The yield of nonane was calculated by g.l.c. analysis to be 19%.

Component	t_R (minutes)	m/e
Nonane	0.15	128, 99, 85, 71, 57, 43, 41, 29, 27.
Toluene	0.3	-
1-Bromoheptane	1.0	178, 149, 135, 107, 70, 57.
1-Iodoheptane	2.0	226, 155, 128, 127, 99, 70, 57.
Tetradecane	2.9	198, 169, 155, 141, 127, 125, 113, 99, 85, 71, 57.

Attempted preparation of dec-1-ene.

A solution of allyl lithium (50 ml, 0.84M) was prepared from allyl phenyl ether using the same method and quantities as previously described (p.154), cooled in ice/potassium carbonate, and copper(I) iodide (19 g, 0.1 mol) was added over 15 minutes. 1-Iodoheptane (11.4 g, 0.05 mol) in ether (25 ml) was added over 15 minutes and the mixture was stirred for 8 hours, after which products were isolated as described for 1,2-O-cyclohexylidene-3-deoxy-3-vinyl glycerol (p.153). G.l.c. analysis (column C, 170°) of the product revealed the presence of phenol and this was confirmed by the i.r. spectrum. Phenol was removed by dissolving the mixture in ether and extracting with sodium hydroxide until a sample of the organic layer gave no colour with ferric chloride. Recovery of the purified product gave a liquid which was further purified by preparative g.l.c. (column C, 120°), and was then identified as tetradecane (4.8 g, 96%). δ 0.9 (m, 6H, $-CH_3$), 1.3 (m, 24H, $-CH_2-$); the mass spectrum gave a measured mass of 198.2345, calculated $C_{14}H_{30}$ 198.2347. The i.r. was consistent with

a long chain saturated hydrocarbon ν_{max} $(-CH_2-)_n$ 750 cm^{-1}.

1,2-O-cyclohexylidene-propene-2,3-diol.

Method (i). Sodium (1.2 g 0.04 mol) was dissolved in ethanol (30 ml) and 1,2-O-cyclohexylidene-3-O-toluene-p-sulphonyl glycerol (3.26 g, 0.01 mol) in ethanol (10 ml) was added; the mixture was heated for 3 hours under reflux, poured into water (50 ml) and extracted with chloroform (3 x 30 ml). The bulked extracts were washed with sodium hydroxide (2 x 30 ml, 2.5M), dried, and the solvent removed under reduced pressure to give a liquid (1.7 g). Distillation b.p. 108-110°/12 mm Hg yielded a product (1.2 g) which consisted of a single component by t.l.c. (system 1), R_F 0.82 and g.l.c. (column C, 150°), t_R 4.75 minutes. The i.r. spectrum did not reveal absorption due to the present of a carbon-carbon double bond; δ 1.2 (t, 3H, CH_3), 1.60 (m, 10H, cyclohexylidene), 3.3-4.5 (m, 7H, $-CH_2OCH_2-$, $-CH_2O-$, H-C-O-).

Method (ii). 1,2-O-Cyclohexylidene-3-deoxy-3-iodo glycerol (11.3 g, 0.04 mol) was heated under reflux with potassium hydroxide (5 g) in ethanol (40 ml) for 30 minutes. The mixture was poured into water (50 ml) and extracted with chloroform (3 x 30 ml), the combined extracts dried and the solvent evaporated. The product was identified by g.l.c. (column C, 120°) and t.l.c. (system 1) as cyclohexanone (3.5 g, 89%). The i.r. and n.m.r. spectra were identical to those of authentic cyclohexanone and a 2,4-dinitrophenylhydrazone was prepared, m.p. 154-5° (lit.[136], cyclohexanone-2,4-dinitrophenylhydrazone m.p. 162°).

Method (iii). 1,2-O-Cyclohexylidene-3-deoxy-3-iodo glycerol

(7.0 g, 0.025 mol) was stirred with 1,5-diazabicyclo[4.3.0]non-5-ene (6.2 g, 0.05 mol) at 90° for 20 minutes, then poured into ice/water (50 ml) and extracted with chloroform (3 x 30 ml). The combined extracts were dried and the solvent evaporated to leave a product which was identified as cyclohexanone (2.1 g, 86%) in the same way as above.

(D) BUTANE-1,2-DIOL DERIVATIVES.

1,2-Epoxy-4-bromobutane[117].

m-Chloroperbenzoic acid (16.5 g, 0.075 mol) in methylene dichloride (100 ml) was added dropwise at 0^{o} to 4-bromo-but-1-ene (10 g, 0.075 mol) in methylene dichloride (20 ml). The mixture was stirred at room temperature for 20 hours, then washed with sodium hydroxide (2 x 25 ml, 2.5M) followed by water (3 x 25 ml). On drying the organic extracts, followed by removal of the solvent under reduced pressure on a water bath at $<40^{o}$, a liquid product was obtained (9.8 g, 87%) which gave a single peak, t_R 2 minutes, on g.l.c. analysis (column D, 120^{o}). This product was found to contain bromine by the sodium fusion test; it showed absorption frequencies in the i.r. spectrum corresponding to the presence of an epoxide ring (835, 1270 cm^{-1}) and none due to C=C; δ 1.8-2.2 (m, 2H, CH_2), 2.5 (quin, 1H, CH), 2.7 (quin, 1H, CH), 2.9-3.15 (m, 1H, CH), 3.55 (t, 2H, CH_2Br).

1,2-O-Cyclohexylidene-4-bromobutane-1,2-diol.

1,2-Epoxy-4-bromobutane (9.5 g, 0.063 mol) was mixed with cyclohexanone (6 g, 0.63 mol) at room temperature and a few drops of tin(IV) chloride were added [118]. An immediate exothermic reaction ensued and the mixture darkened. It was then shaken at room temperature for 24 hours after which time it was poured into water, extracted with ether (3 x 30 ml), washed with sodium bisulphite (4 x 20 ml), dried and the solvent removed under reduced pressure. The liquid product (8 g) was then subjected to distillation and a clear colourless liquid, b.p. $114-6^{o}/2$ mm Hg (6.5 g, 42%) single component on g.l.c. analysis

t_R 8 minutes (column D, 170°) and t.l.c. analysis R_f 0.81 (system 1) was obtained. The i.r. spectrum had absorption frequencies due to the acetal group (ν_{max} 1040, 1100, 1160 cm^{-1}) and none due to epoxide; bromine was found to be present by sodium fusion test; δ 1.60 (m, 10H, cyclohexylidene), 1.95-2.3 (t, 2H, CH_2), 3.4-4.4 (m, 5H, H-C-O,-CH_2O, CH_2Br).

Attempted preparation of 1,2-O-cyclohexylidene-butane-1,2-diol--4-boronic acid.

1,2-O-Cyclohexylidene-4-bromobutane-1,2-diol (12.5g, 0.05 mol) in THF (20 ml) was added dropwise to magnesium (1.2 g). 1,2-dibromoethane was used to initiate the reaction which gave finally a thick grey suspension. A portion of this was treated with purified benzaldehyde in the same way as before and the product isolated gave an i.r. spectrum containing absorption bands due to an aromatic ring, O-H and cyclohexylidene; δ 1.60 (m, 10H, cyclohexylidene) 2.15 (quin, 2H, CH_2), 3.3-4.4 (m, 5H, CH, CH_2), 5.4 (s, 1H, OH), 7.3-8.2 (m, 5H, aromatic). The remainder of the grey solution was added over 3 hours to butyl borate (11.5 g, 0.05 mol) at -78° while maintaining vigorous stirring and then stirred for 2 hours further. The grey solution thickened dramatically and a constant rate of addition could not be maintained. The product was subjected to the same isolation procedure as was used for 1-hexaneboronic acid (p. 142) and crystals were obtained; δ 1.5 (m, 10H, cyclohexylidene), 3.3-3.7 (m, 7H, CH_2CH), 5.4 (broad s, OH).

(E) HYDROBORATION REACTIONS OF UNSATURATED MONOSACCHARIDES.

α-D-Glucofuranose derivatives.

1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranose[137].

Concentrated sulphuric acid (31 ml) was added dropwise over 45 minutes to cyclohexanone (500 ml) at 0°. D-glucose (225 g, 1.25 mol) was added in portions with vigorous stirring which was continued for 5 hours, while the mixture was allowed to warm to room temperature. After standing overnight the product was warmed with light petroleum (80-100°), the lower dark oily layer discarded and on storage at 5° white crystals (175 g, 41%) were obtained, m.p. 116-8°. Recrystallisation of the product from light petroleum (80-100°) gave crystals m.p. 130.5°-132° (lit.[123], 131-2°), $[\alpha]_D^{28}$ + 0.55° (c 3, $CHCl_3$), (lit.[123], $[\alpha]_D^{31}$ + 1.65° (c 3, $CHCl_3$), $[\alpha]_D^{24}$ - 2.03° (c 2, C_2H_5OH), (lit.[123], $[\alpha]_D^{31}$ - 2.20° (c 2, C_2H_5OH). t.l.c. (system 1) showed a single component R_f 0.30 and the i.r. spectrum had absorption bands due to -O-H str., and cyclohexylidene; δ 1.6 (m, 20H, cyclohexylidene), 3.1 (broad s, 1H, OH), 3.9-4.4 (m, 5H, CH and CH_2O-), 4.5 (d, 1H, HC-2), 6.0 (d, 1H, HC-1).

1,2-O-Cyclohexylidene-α-D-glucofuranose[124].

1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranose (34 g, 0.13 mol) was heated with acetic acid (180 ml, 75% aq.) at 70-80° for 90 minutes. The mixture was neutralised with sodium hydrogen carbonate and washed with hot heptane (2 x 50 ml). White needles (21.7 g, 84%) crystallised from the aqueous solution upon storage at 5°, m.p. 150-1°, (lit.[122], 151-2°), $[\alpha]_D^{20}$ + 6.8 (c 1, acetone) (lit.[122], $[\alpha]_D$ + 5.9° (c 1,

acetone) + 4.1° (c 1, acetone). The i.r. spectrum was consistent with the reported structure, and the product was a single component by t.l.c. analysis (system 1) R_F 0.15; δ 1.50 (m, 10H, cyclohexylidene), 3.55–4.4 (m, 9H, HC-2, HC-3, HC-4, HC-5, $-CH_2-$ and OH), 5.85 (d, 1H, HC-1).

1,2-O-Cyclohexylidene-5,6-di-O-toluene-p-sulphonyl-α-D-glucofuranose.

1,2-O-Cyclohexylidene-α-D-glucofuranose (5 g, 0.019 mol) in toluene (20 ml) and pyridine (10 ml) was mixed at 0° with toluene-p--sulphonyl chloride (9 g) in chloroform (17 ml) and allowed to stand overnight at room temperature. Water (10 ml) was added to the reaction mixture at 0° followed by hydrochloric acid (50 ml, 2.5M). The product was extracted with chloroform (3 x 50 ml) and the combined extracts were washed with hydrochloric acid (50 ml, 2.5M), sodium hydrogen carbonate (50 ml, 5% aq.) and water (50 ml), dried and the solvent removed. A syrup (8 g) was obtained which crystallised from ethanol (3.4 g, 31%), m.p. 160–1°, $[\alpha]_D^{24}$ + 2.75° (c 1, acetone); the i.r. spectrum showed absorption bands due to OH str., toluene-p-sulphonyl and cyclohexylidene; t.l.c. (system 1) R_F 0.41; δ 1.60 (m, 10H, cyclohexylidene), 2.5 (s, 6H, CH_3), 3.25 (s, 1H, OH), 4.1–5.0 (m, 6H, H-C-O-, CH_2O), 5.85 (d, 1H, HC-1), 7.2–7.9 (m, 8H, aromatic) (Found: C, 55.42, H, 5.72 $C_{26}H_{32}S_2O_{10}$ requires C, 54.92; H, 5.67%).

Bis(imidazol-1-yl)thione[69].

Thiophosgene (39 g) in dry toluene (150 ml) was added over 20 minutes to imidazole (91 g, 1.3 mol) in dry methylene dichloride with stirring in a nitrogen atmosphere. The stirring was continued

overnight, the mixture filtered and toluene (200 ml) added. Crystals formed on storage at 5° which were recrystallised from THF m.p. 97-99° (lit.[69], 100°) (23 g, 37%). The i.r. spectrum was identical to that reported in the literature; δ 7.25-8.25 (m, 0H, aromatic).

1,2-O-Cyclohexylidene-α-D-glucofuranose 5,6-O-thionocarbonate.

Method (i)[69]. Bis(imidazol-1-yl)thione (4 g) was added to stirred 1,2-O-cyclohexylidene-α-D-glucofuranose in warm acetone (80 ml) and heated under reflux in a nitrogen atmosphere for 1 hour. The mixture was passed through a charcoal column and the solvent removed leaving a yellow syrup which was crystalised from methanol. The product was recrystalised from methanol to give white needles (0.9 g, 18%), m.p. 164-5°, $[\alpha]_D^{24}$ -16.2° (c 1, acetone); ν 1230 cm^{-1} (C=S); λ_{max} C_2H_5OH 232 nm, (lit.[69], 234 nm); δ 1.6 (m, 10H, cyclohexylidene), 4.4-5.0 (m, 5H, HC-3, HC-4, CH_2OH), 5.2-5.6 (m, 1H, HC-5), 5.8 (d, 1H, HC-2), 6.15 (d,1H, HC-1) (Found: C, 51.79; H, 6.21. $C_{13}H_{18}SO_6$ requires C, 51.65; H, 6.00%).

Method (ii)[137]. Thiophosgene (10 ml) was added dropwise to 1,2-O-cyclohexylidene-α-D-glucofuranose (10 g) in dioxane (200 ml). An orange precipitate formed which dissolved on heating to 65°. Pyridine (10 ml) was added dropwise and stirring at 65° was continued for 10 minutes, the solvent was removed, and the product crystallised from ethanol. Recrystallisation from ethanol afforded light brown needles (4 g, 35%), m.p. 163-5° which had an i.r. spectrum identical to that of the product above.

5,6-Dideoxy-1,2-O-cyclohexylidene-α-D-xylo-hex-5 -enofuranose.

Method (i)[125]. 1,2-O-Cyclohexylidene-5,6-di-O-toluene-p-sulphonyl-

-∝-D-glucofuranose (3 g, 0.011 mol) and sodium iodide (5.5 g) were heated under reflux in butan-2-one (100 ml) for 2 hours. The product was filtered, the solvent removed and the residue partitioned between sodium thiosulphate (50 ml, 10% aq.) and chloroform (50 ml). The aqueous phase was further extracted with chloroform (2 x 25 ml) and the combined extracts were washed successively with sodium hydrogen carbonate (25 ml, 5% aq.), sodium metabisulphite (4 x 25 ml, 5% aq.), and water (25 ml), dried and the solvent removed. The syrupy product (1 g, 73%) consisted of a single component by t.l.c. analysis R_F 0.26 (system 1), 0.59 (system 2), ν_{max} 3080, 3010, 1645, 1410, 995, 915 cm^{-1}, in addition to O-H str. and cyclohexylidene bands; δ 1.70 (m, 10H, cyclohexylidene), 1.95 (s, 1H, OH), 4.15 (d, 1H, HC-3), 4.6 (d, 1H, HC-2) 4.8 (q, 1H, HC-4), 5.3-5.9 (m, 3H, $CH=CH_2$), 6.05 (d, 1H, HC-1).

Method (ii)[69]. 1,2-O-Cyclohexylidene-∝-D-glucofuranose 5,6-O-thionocarbonate (1.6 g, 0.005 mol) was heated under reflux in trimethyl phosphite (20 ml) in a nitrogen atmosphere for 4 days. Ethylene glycol (20 ml) was added and the mixture extracted with ether (3 x 20 ml). The combined extracts were dried and the solvent removed to give an oil (1.8 g) which on t.l.c. analysis (system 2) was found to consist of at least 4 components. The i.r. and n.m.r. spectra failed to afford any evidence of the required product having been formed.

1,2:5,6-Di-O-cyclohexylidene-3-O-toluene-p-sulphonyl-∝-D-glucofuranose[124].

1,2:5,6-Di-O-cyclohexylidene-∝-D-glucofuranose (3.4 g, 0.01 mol) in pyridine (10 ml) was mixed with toluene-p-sulphonyl chloride (2.4 g) in chloroform (10 ml) at 0^o and the resulting solution allowed to stand at room temperature for 2 days. This solution was poured into ice/water

(50 ml) and extracted with chloroform (3 x 30 ml). The combined extracts were washed successively with hydrochloric acid (2 x 30 ml, 2.5M), sodium hydroxide (2 x 30 ml, 2.5M) and water (2 x 30 ml). Drying and solvent evaporation yielded a syrup which was readily crystallised from methanol m.p. 90-1° (lit.[138], 90.5-91°), (2.4 g, 50%), $[\alpha]_D^{24}$ -70° (c 2, chloroform) (lit.[138], $[\alpha]_D^{20}$ -68° (c 1, chloroform). The i.r. spectrum was consistent with the required compound, δ 1.6 (m, 5H, CH and CH_2O), 4.5 (d, 1H, HC-2), 6.0 (d, 1H, HC-1), 7.65 (q, 4H, aromatic).

Soda lime.

Sodium hydroxide solution (40% aq.) was added to dried calcium oxide until the reaction subsided. The mixture was evaporated to dryness, finely ground, oven dried and stored under nitrogen.

1,2;5,6-Di-O-cyclohexylidene-3-deoxy-α-D-erythro-hex-3-enofuranose[63].

1,2:5,6-Di-O-cyclohexylidene-3-O-toluene-p-sulphonyl-α-D-gluco--furanose (1 g) was mixed with soda lime (2 g) and heated (150-200°) under reduced pressure (1 mm Hg) in a vacuum sublimation apparatus. After column chromatography the colourless syrup (0.4 g, 64%) collected on the cold finger had i.r. and n.m.r. spectrum identical to those previously reported; ν_{max} 1670 cm^{-1}, δ 1.60 (m, 20H, cyclohexylidene), 3.9-4.8 (m, 4H, C_2-H, C_5-H, CH_2), 5.3 (d, 1H, C=C-H), 6.1 (d, 1H, C_1-H), t.l.c. analysis (system 1) consisted of a single component R_F 0.65 (with a trace impurity R_F 0.40), $[\alpha]_D^{22}$ +29° (c 2, chloroform) (lit.[63], $[\alpha]_D^{20}$ +31.2° (chloroform).

Hydroboration of 1,2:5,6-di-O-cyclohexylidene-3-deoxy-α-D-erythro-hex-3-enofuranose.

1,2:5,6-Di-O-cyclohexylidene-3-deoxy-α-D-erythro-hex-3-enofuranose (0.4 g, 1.3 mmol) in THF (5 ml) was treated with diborane in THF (3 ml, 1.75M) and trimethylene borate (0.15 g) in the same way as for hex-1-ene. A syrupy product (0.55 g) was obtained which was found to be a three componant mixture by h.p.l.c. and t.l.c. analysis (system 1). The mixture had i.r. (I.r.13) and n.m.r. (N.m.r.18) spectra consistent with the presence of a dioxaborinane; no bands were observed due to the presence of C=C. Hydrolysis of the product afforded a syrup with different spectra (I.r.14) and (N.m.r.19) to those of the unhydrolysed product.

α-D-Glucopyranose derivatives.

3,4,6-Tri-O-acetyl-D-glucal[119].

α-D-Glucose (55 g, 0.3 mol) was added to acetic anhydride (200 ml) and perchoric acid (12 ml, 0.1M in acetic acid) at 40° over 1 hour. Red phosphorus (15 g) was added and the mixture cooled to 0° then bromine (29 ml) was added over one hour, followed by water (15 ml) over 30 minutes. The solution was allowed to stand at room temperature for 2.5 hours and then added at 0° over 1 hour to a mixture of sodium acetate (200 g), zinc dust (110 g), copper sulphate (11 g), water (290 ml) and glacial acetic acid (200 ml). The resultant mixture was stirred for 2 hours, filtered, and the solid washed thoroughly with acetic acid (50% aq.). Ice-cold water (500 ml) was added to the filtrate, which was extracted with chloroform (5 x 50 ml). The bulked organic

layers were washed successively with ice-water, sodium carbonate solution followed by ice-water again, dried, and the solvent removed under reduced pressure. The syrupy product (56 g, 68%), a single component by t.l.c. analysis R_f 0.36 (system 1), was crystallised from light petroleum (b.p. 60-80°), m.p. 47-9°, and recrystallised from ether, m.p. 47-9° (lit.[125], 54-5°). G.l.c. analysis revealed a single component t_R 1.5 minutes (column A, 200°), t_R 8.8 minutes (column E, 175°), ν_{max} 1660 and 1750 cm^{-1}, $[\alpha]_D^{27}$ -9.5° (c 2, ethanol) (lit.[56], $[\alpha]_D$ -16° ethanol).

Hydroboration of 3,4,6-tri-O-acetyl-D-glucal.

3,4,6-Tri-O-acetyl-D-glucal (2.72 g, 0.01 mol) in THF (10 ml) was treated with diborane in THF (20 ml, 1.75M) and trimethylene borate (1.22 g) in the same way as for hex-1-ene. A syrupy product (3.9 g) was obtained which was found to be a three component mixture by t.l.c. (system 1) and h.p.l.c. analysis. The mixture had i.r. (I.r.9) and n.m.r. (N.m.r.14) spectra consistent with the presence of a dioxaborinane; no bands were observed due to the presence of C=C. The major component of the reaction mixture (0.78 g, 20%) was separated by column chromatography on neutral alumina using chloroform as the eluting solvent, t.l.c. (system 2) R_f 0.51, ν_{max} C=O, B-O (Found: C, 51.03; H, 7.10; $C_{12}H_{23}BO_6$ requires C, 50.30; H, 6.47%). The other two components R_f 0.10, 0.42 could not be further separated. Hydrolysis of the crude product mixture afforded a syrup with different spectra (I.r.10) and (N.m.r.15) from the unhydrolysed product.

Reaction of 1,3,2-benzodioxaborole with 3,4,6-tri-O-acetyl-D-glucal.

On reacting a mixture of 0.01 mol of each of these compounds together

as in the above procedure an intractable red tar was formed.

Methyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside [139].

In a fume cupboard dimethyl sulphate (100 ml, washed with cold water, then sodium hydrogen carbonate solution) and sodium hydroxide solution (150 ml, 50% aq.) were added simultaneously over 1 hour to a stirred solution of methyl α-D-glucopyranoside (9.7 g, 0.05 mol) in acetone (50 ml) at 40°. The mixture was stirred at 40° for 2 hours then poured into ice/water (100 ml) and extracted with chloroform (3 x 50 ml). The extracts were dried and the solvent removed to give an oil which was distilled b.p. 112-114°/1 mm Hg, 6.8 g (55%), n_D^{24} 1.4481 (lit.[139], b.p. 145-50°/13 mm Hg, n_D^{20} 1.4460). The i.r. spectrum was consistent with the desired structure no O-H str., C-O band 1090 cm^{-1}.

α-D-Galactopyranose derivatives.

1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose [120].

Zinc chloride (43.2 g) was dissolved in acetone (450 ml) by stirring for 30 minutes and a few drops of concentrated sulphuric acid were added. D(+) galactose (36 g, 0.2 mol) was added and the mixture stirred for 4 hours. Potassium carbonate (72 ml, 100% w/v) was added with stirring and the mixture was filtered. The precipitate was washed with acetone and the combined filtrate and washings were evaporated under reduced pressure. The mixture was then extracted with ether (3 x 100 ml) and the combined extracts were dried and evaporated to yield a syrup (42 g, 82%). Distillation b.p. 138-40°/ /0.3 mm Hg (lit.[120], 131-5°/0.2 mm Hg) gave a pure product, 1 component

by t.l.c. analysis R_f 0.23 (system 1), R_f 0.69 (system 2), $[\alpha]_D^{20}$ -52^o (c 3.6, chloroform), (lit.[120], $[\alpha]_D^{29}$ -55^o (c 3.6, chloroform), ν_{max} OH str., isopropylidene; δ 1.2-1.5 (m, 12H, $C(CH_3)_2$, 2.5 (broad s, 1H, OH), 3.6-4.7 (m, 6H, -CH), 5.6 (d, 1H, HC-1).

1,2:3,4-Di-O-isopropylidene-6-O-toluene-p-sulphonyl-α-D-galacto-pyranose[121].

1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (40 g, 0.15 mol) was dissolved in acetone (50 ml) and pyridine (35 ml). Toluene-p--sulphonyl chloride (46 g, 0.25 mol) was added over 1 hour at 0^o, and the mixture was allowed to stand overnight at room temperature. Water (20 ml) was added in portions with stirring at 0^o and the mixture was added to ice/water (200 ml), extracted with chloroform (3 x 100 ml), washed with sodium hydrogen carbonate (100 ml, 5% aq.) dried and evaporated. The syrupy product (57.2 g, 89%) was crystallised from propan-1-ol to yield white crystals (51 g), m.p. $90-1^o$ (lit.[121], $89-91^o$) $[\alpha]_D^{20}$ -65^o (c 2, chloroform), lit.[121], $[\alpha]_D$ -63^o (chloroform) t.l.c. one component R_f 0.48 (system 1), ν_{max} toluene-p-sulphonyl, isopropylidene, -OH str., δ 1.2-1.5 (m, 12H, $C(CH_3)_2$, 2.45 (s, 3H, CH_3), 4.0-4.7 (m, 6H, CH), 5.45 (d, 1H, HC-1), 7.65 (ABq, 4H, aromatic).

6-Deoxy-6-iodo-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose[136].

Ground lithium iodide (40 g) was added to a solution of 1,2:3,4-di-O-isopropylidene-6-O-toluene-p-sulphonyl-α-D-galactopyranose (23 g, 0.055 mol) in toluene (200 ml) containing hexamethylphosphoramide (50 ml). The mixture was stirred and heated under reflux for 15 minutes, cooled, washed with water and dried. Upon evaporation of the solvent a syrup (20 g, 93%) was obtained which consisted of

1 component by g.l.c. (column A, 200°) t_R 2 minutes and t.l.c. analysis (system 1) R_f 0.64. Elemental analysis demonstrated the presence of iodine and absence of sulphur and the i.r. spectrum was consistent with the reported structure, $[\alpha]_D^{18}$ -45.4° (c 3.5 chloroform), (lit.[136], $[\alpha]_D^{18}$ -50.4 (methylene dichloride), δ 1.1-1.7 (m, 12H, $C(CH_3)_2$, 2.3-4.7 (m, 5H, CH, CH_2), 5.6 (sext, 1H, HC-1).

6-Deoxy-1,2:3,4-di-O-isopropylidene-β-L-arabino-hex-5-enopyranose[140].

Method (i). 1,2,3,4-Di-O-isopropylidene-6-O-toluene-p-sulphonyl--α-D-galactopyranose (1 g) was mixed with soda lime (2 g) and heated (150°) under reduced pressure (0.2 mm Hg). Crystals (0.5 g, 85%) formed on the "cold-finger" and these were re-sublimed at 80-90° to give white needles, m.p. 86-7° (lit.[130], 86-7°), $[\alpha]_D^{23}$ -157° (c 1, chloroform) (lit.[140], $[\alpha]_D$ -143° (methylene dichloride) t.l.c. 1 component R_f 0.71 (system 1), g.l.c. (column A, 180°) t_R 1 minute, ν_{max} 3020, 1665, 1400, 885 cm^{-1}, δ 1.35 (s, 6H, $C.CH_3$), 1.50 (s, 6H, $C.CH_3$), 4.3-4.7 (m, 5H, HC-2, HC-3, HC-4, $C{=}CH_2$), 5.65 (d, 1H, C.CH).

Method (ii). 6-Deoxy-6-iodo-1,2:3,4-di-O-isopropylidene-α-D--galactopyranose (2.5 g, 0.0065 mol) was shaken for 24 hours with silver(I) fluoride (2.5 g) in pyridine (50 ml). The solvent was removed under reduced pressure and the residue was dissolved in ether (50 ml), filtered and evaporated. This process was repeated several times. Finally an oil (1.7 g) was obtained, which on g.l.c. analysis (column A, 180°) was found to consist of approximately equal amounts of 6-deoxy--6-iodo-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose and 6-deoxy-1,2:3,4-di-O-isopropylidene-β-L-arabino-hex-5-enopyranose. This

product was shaken with silver(I) fluoride (1 g) for 96 hours and treated as before. G.l.c. and t.l.c. (system 1) analysis of the product did not significatnly differ from before.

Hydroboration of 6-deoxy-1,2:3,4-di-O-isopropylidene-β-L-arabino--hex-5-enopyranose.

6-Deoxy-1,2:3,4-di-O-isopropylidene-β-L-arabino-hex-5-enopyranose (0.4 g, 1.7 mmol) in THF (5 ml) was treated with diborane in THF (5 ml, 1.75M) and trimethylene borate (0.3 g) in the same way as for hex-1-ene. A syrupy product (0.7 g) was obtained which was found to be a 3 component mixture by t.l.c. and h.p.l.c. analysis. The mixture had i.r. (I.r.11) and n.m.r. (N.m.r.16) spectra consistent with the presence of a dioxaborinane; no bands were observed due to the presence of C=C. Hydrolysis of the product afforded a syrup with different spectra (I.r.12) and (N.m.r.17) to those of the unhydrolysed product.

(F) SPECTRA

All infra-red spectra were recorded on a Perkin-Elmer model 237 spectrophotometer at fast scan speed and normal slit setting with samples either as liquid films or KBr discs. Nuclear magnetic resonance spectra were recorded with the samples in deutereochloroform solution (except n.m.r. 5, where DMSO was employed) using a Varian A60A 60 MHz analytical n.m.r. spectrometer.

Infra-red (I.r.)

1. 1-(2'-Tetrahydropyranyloxy)-prop-2-ene.
2. 1-Hexaneboronic acid.
3. 2-Hexyl-1,3,2-dioxaborinane.
4. Trimethylene borate.
5. 1-Hexaneboronic anhydride.
6. Dimethyl-1-(5-[2'-tetrahydropyranyloxy])-pentaneboronate.
7. 2-Hexyl-1,3-2-benzodioxaborole.
8. 1,2-O-Cyclohexylidene-4-bromobutane-1,2-diol.
9. Product from the hydroboration-redistribution reaction of 3,4,6-tri-O-acetyl-D-glucal.
10. Product from aqueous hydrolysis of compound 9. above.
11. Product from the hydroboration-redistribution reaction of 6-deoxy-1,2:3,4-di-O-isopropylidene-β-L-arabino-hex-5-enopyranose
12. Product from aqueous hydrolysis of compound 11. above.
13. Product from the hydroboration-redistribution reaction of 1,2:5,6-di-O-cyclohexylidene-3-deoxy-α-D-erythro-hex-3-enofuranose.
14. Product from aqueous hydrolysis of compound 13 above.

Nuclear magnetic resonance (N.m.r.)

1. 1-(2'-Tetrahydropyranyloxy)-prop-2-ene.
2. Pent-4-en-2-ol.

3. 2-(2'-Tetrahydropyranyloxy)-pent-4-ene.

4. 2-(2'-Tetrahydropyranyloxy)-pent-4-ene (100 MHz).

5. 1-Hexaneboronic acid.

6. 2-Hexyl-1,3,2-dioxaborninane.

7. Trimethylene borate.

8. 1-Hexaneboronic anhydride.

9. Dimethyl-1-(5-⌈2'-tetrahydropyranyloxy⌋)-pentaneboronate.

10. 2-Hexyl-1,3,2-benzodioxaborole.

11. 1,2-O-Cyclohexylidene glycerol.

12. 1,2-O-Cyclohexylidene glycerol + 100 mg $Eu(fod)_3$.

13. 1,2-O-Cyclohexylidene-4-bromobutane-1,2-diol.

14. Product from the hydroboration-redistribution reaction of 3,4,6-tri-O-acetyl-D-glucal.

15. Product from aqueous hydrolysis of compound 14. above.

16. Product from the hydroboration-redistribution reaction of 6-deoxy-1,2:3,4-di-O-isopropylidene-β-L-arabino-hex-5-enopyranose

17. Product from aqueous hydrolysis of compound 16 above.

18. Product from the hydroboration-redistribution reaction of 1,2:5,6-di-O-cyclohexylidene-3-deoxy-α-D-erythro-hex-3-enofuranose.

19. Product from aqueous hydrolysis of compound 18 above.

Mass spectra (M.s.)

1-4. Unidentified products from the hydroboration-redistribution reaction of 1-(2'-tetrahydropyranyloxy)-prop-2-ene.

5. 2-(3-⌈2'-Tetrahydropyranyloxy⌋propyl)-1,3,2-dioxaborinane.

6. 1-(2'-Tetrahydropyranyloxy)-4-iodobutane.

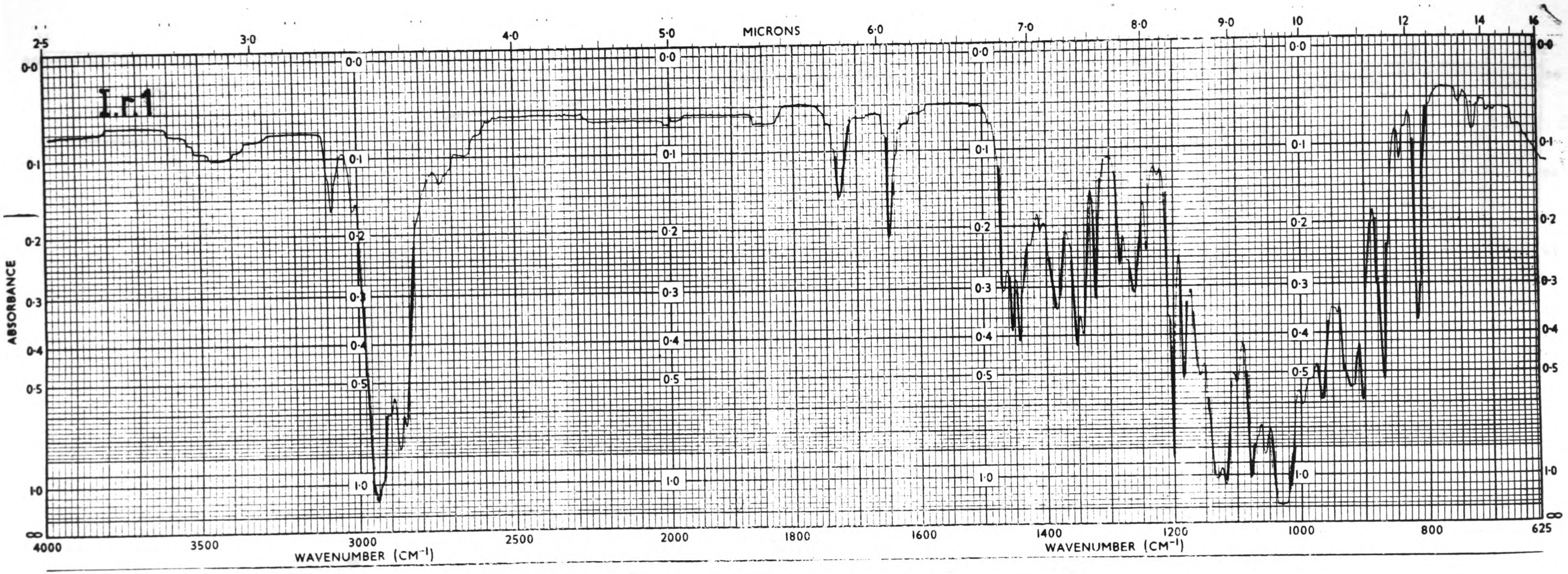
7. 1,2-O-Cyclohexylidene-3-O-toluene-p-sulphonyl glycerol.

8. 1,2-O-Cyclohexylidene-3-deoxy-3-iodo glycerol.

9. 1,2-O-Cyclohexylidene-3-deoxy-3-vinyl glycerol.

10. Dibutyl vinyl tin.

11. Tetrabutyltin.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7·0
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9·0
10
12
14
16
ABSORBANCE
0·0
0·1
0·2
0·3
0·4
0·5
1·0
4000
3500
3000
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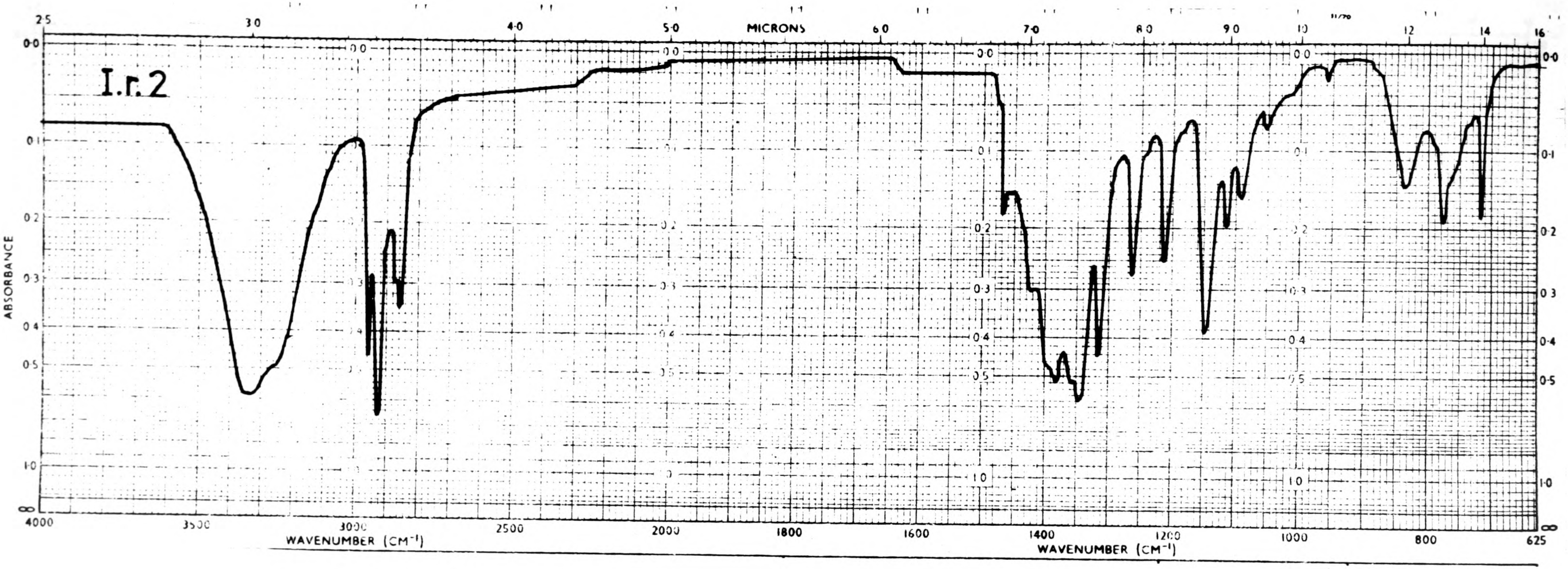
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)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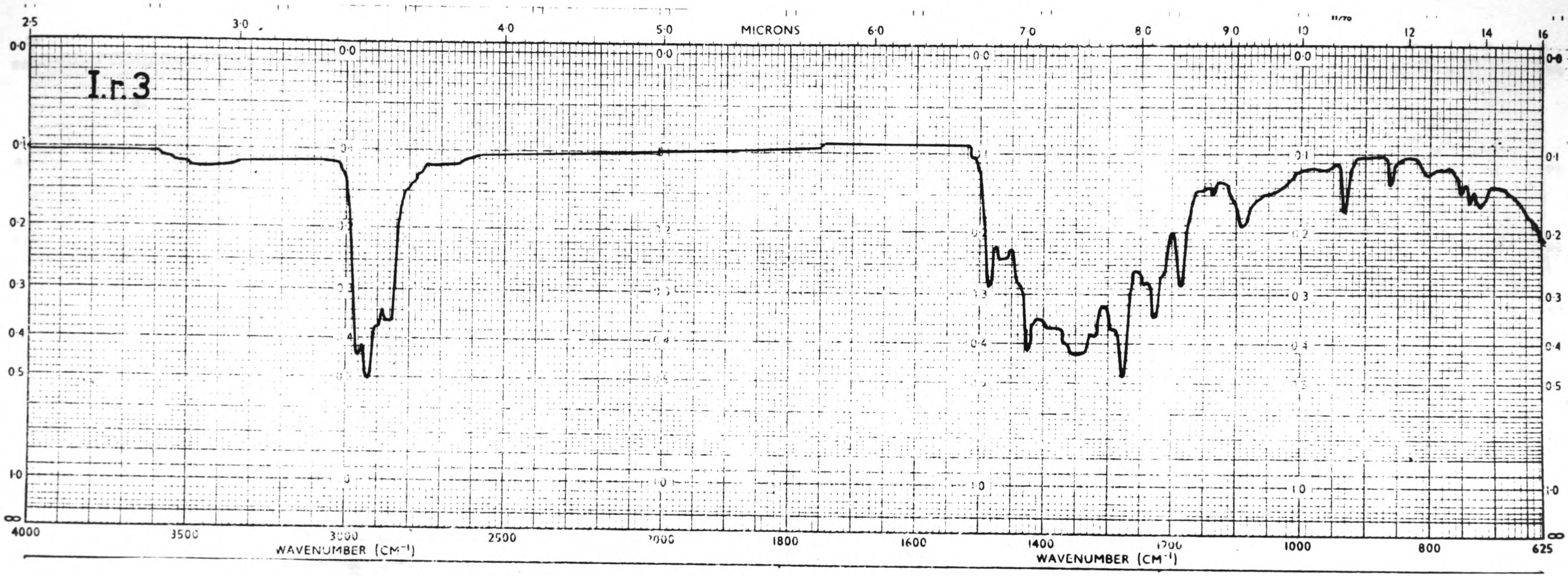
ABSORBANCE
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)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5·0
MICRONS
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7·0
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9·0
10
12
14
16
0·0
0·1
0·2
0·3
0·4
0·5
1·0
4000
3500
3000
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1600
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1200
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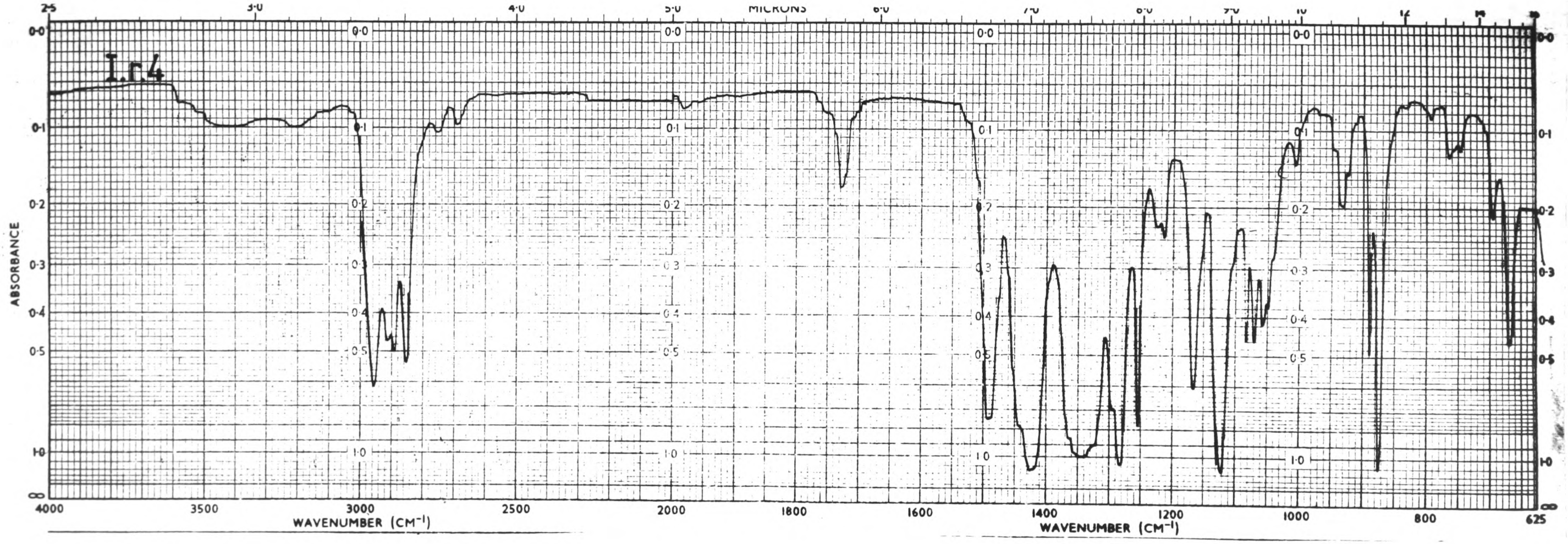
800
625
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)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WAVENUMBER (CM⁻¹)
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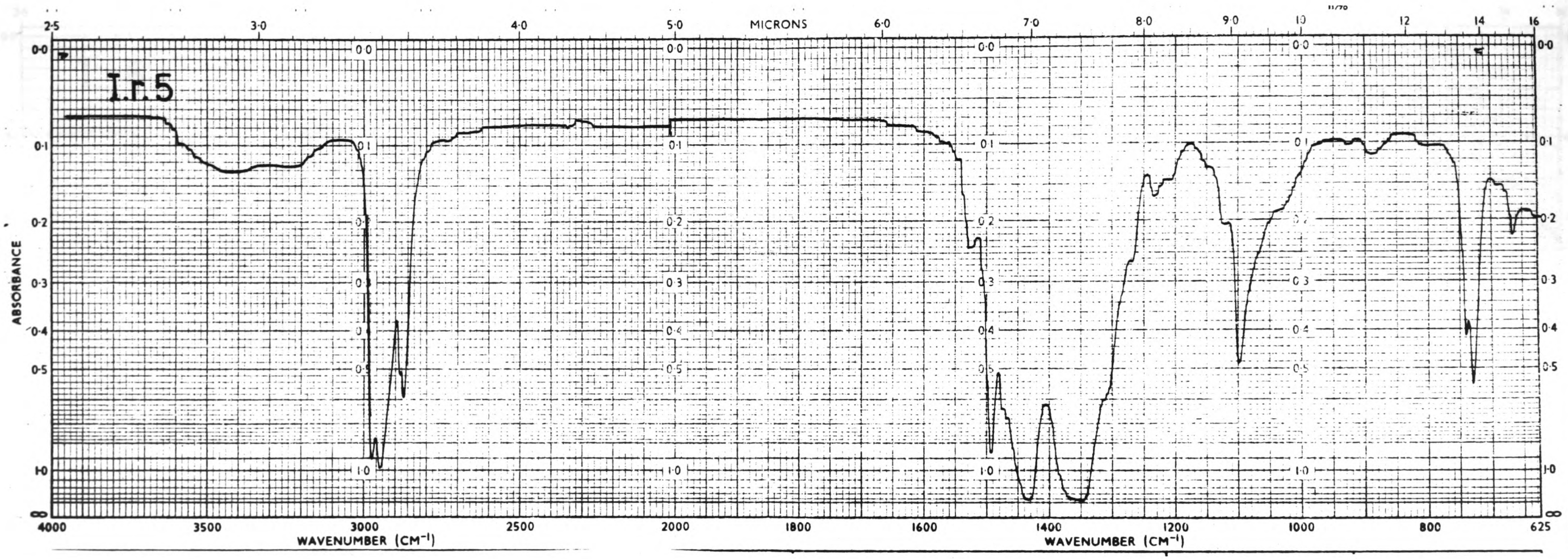
1400
1200
1000
800
625

I.r.5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5·0
MICRONS
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7·0
8·0
9·0
10
12
14
16
0·0
0·1
0·2
0·3
0·4
0·5
1·0
ABSORBANCE
4000
3500
3000
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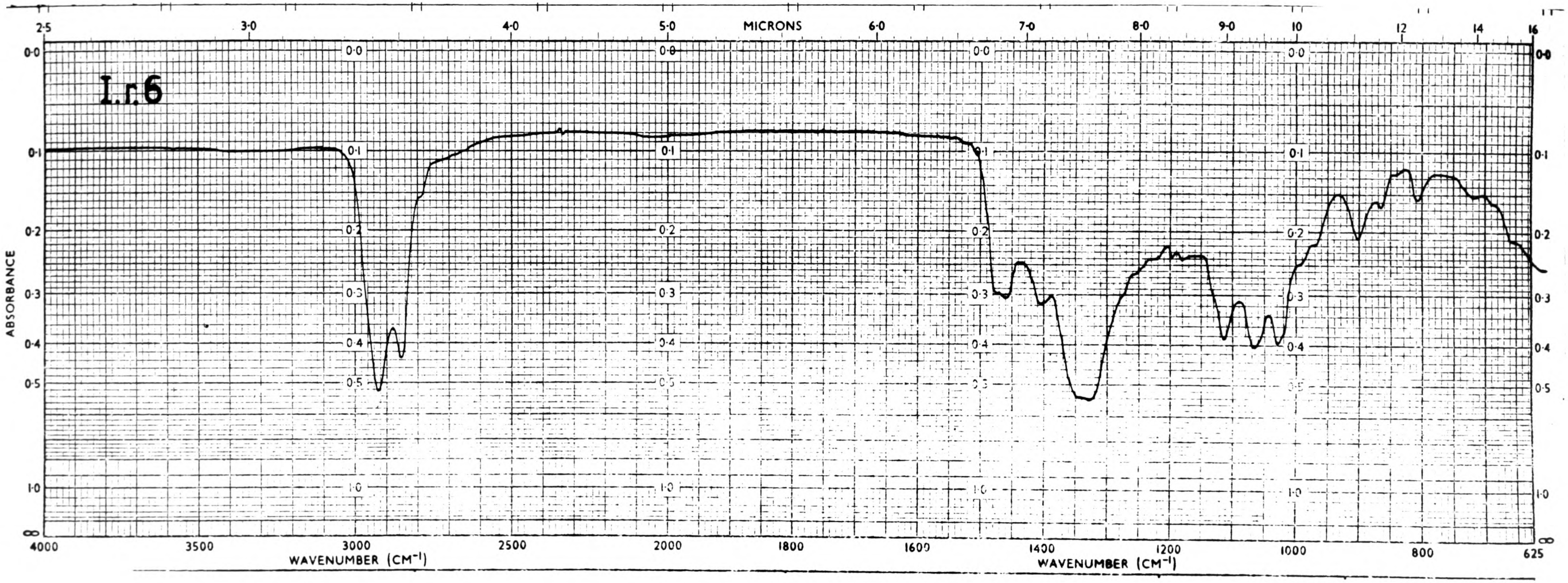
2000
1800
1600
1400
1200
1000
800
625
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)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8·0
9·0
10
12
14
16
ABSORBANCE
0·0
0·1
0·2
0·3
0·4
0·5
1·0
∞
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1200
1000
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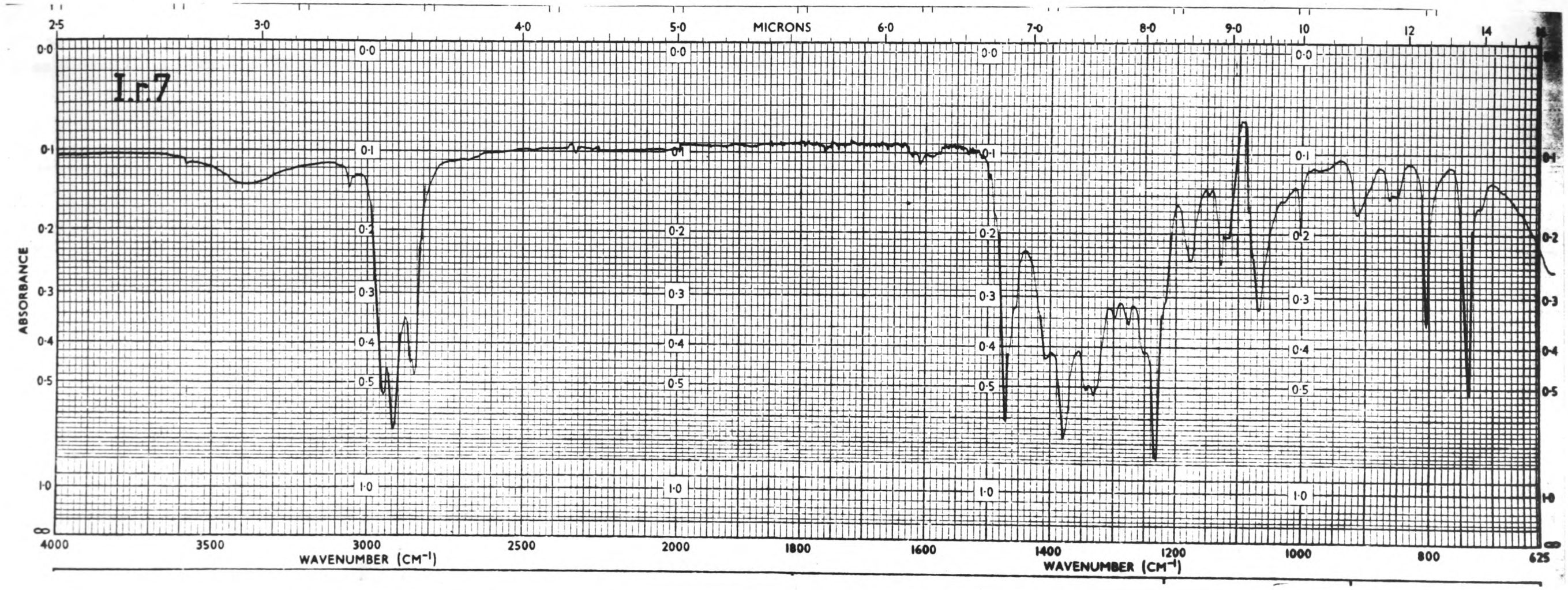
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)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14
ABSORBANCE
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0·1
0·2
0·3
0·4
0·5
1·0
4000
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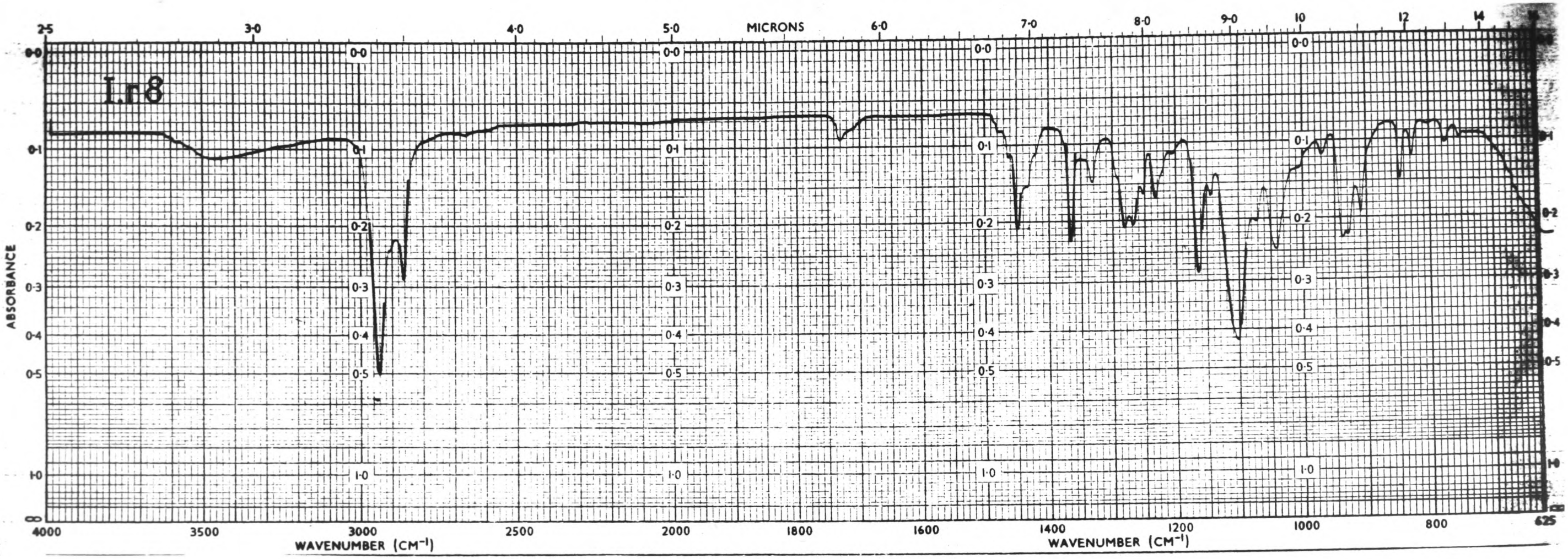
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)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14
ABSORBANCE
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0·1
0·2
0·3
0·4
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800
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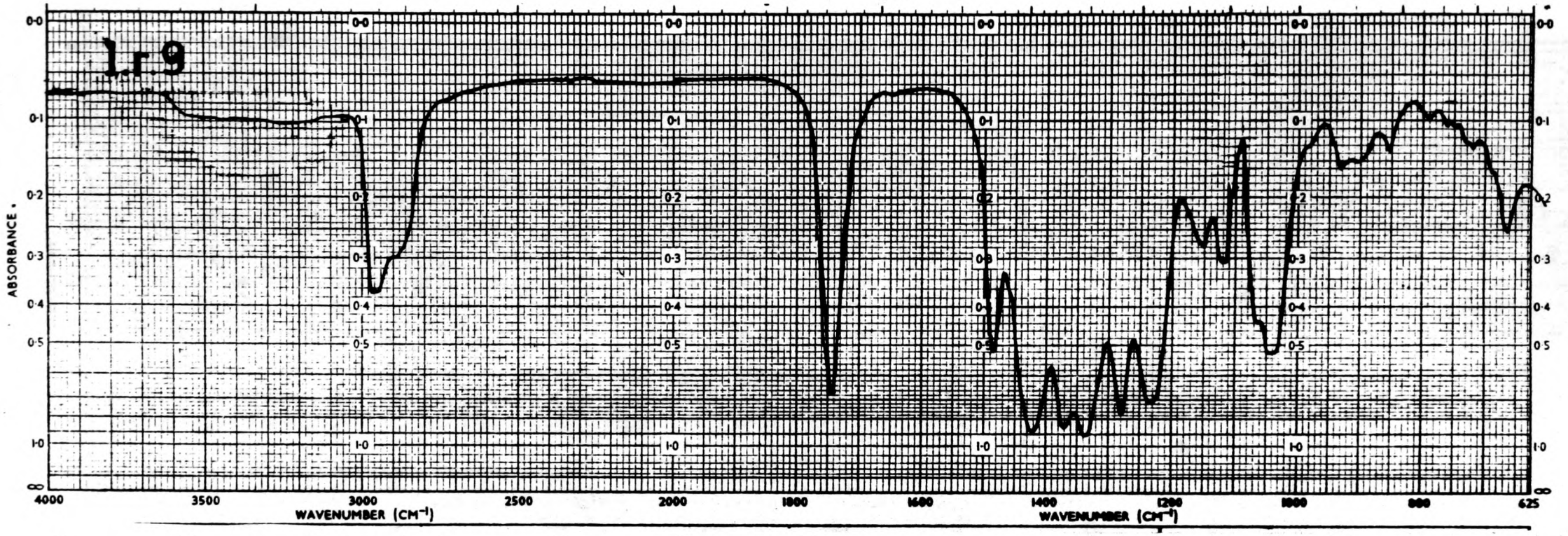
WAVENUMBER (CM⁻¹)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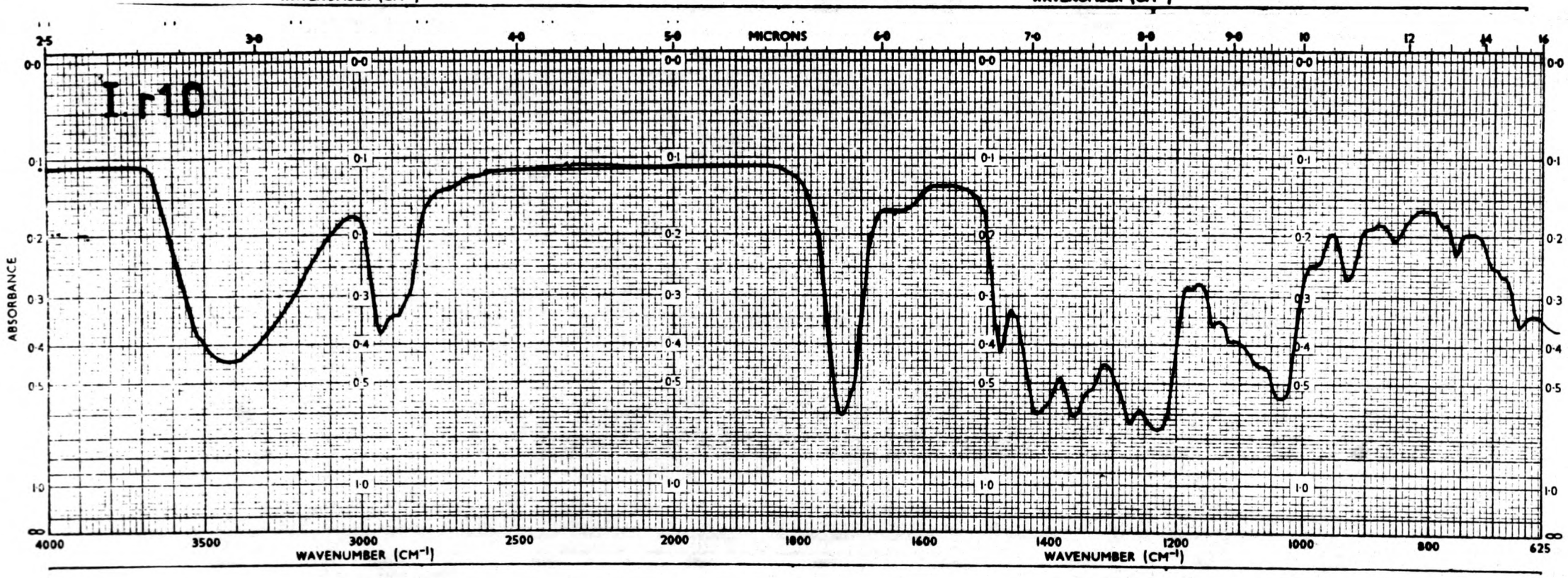
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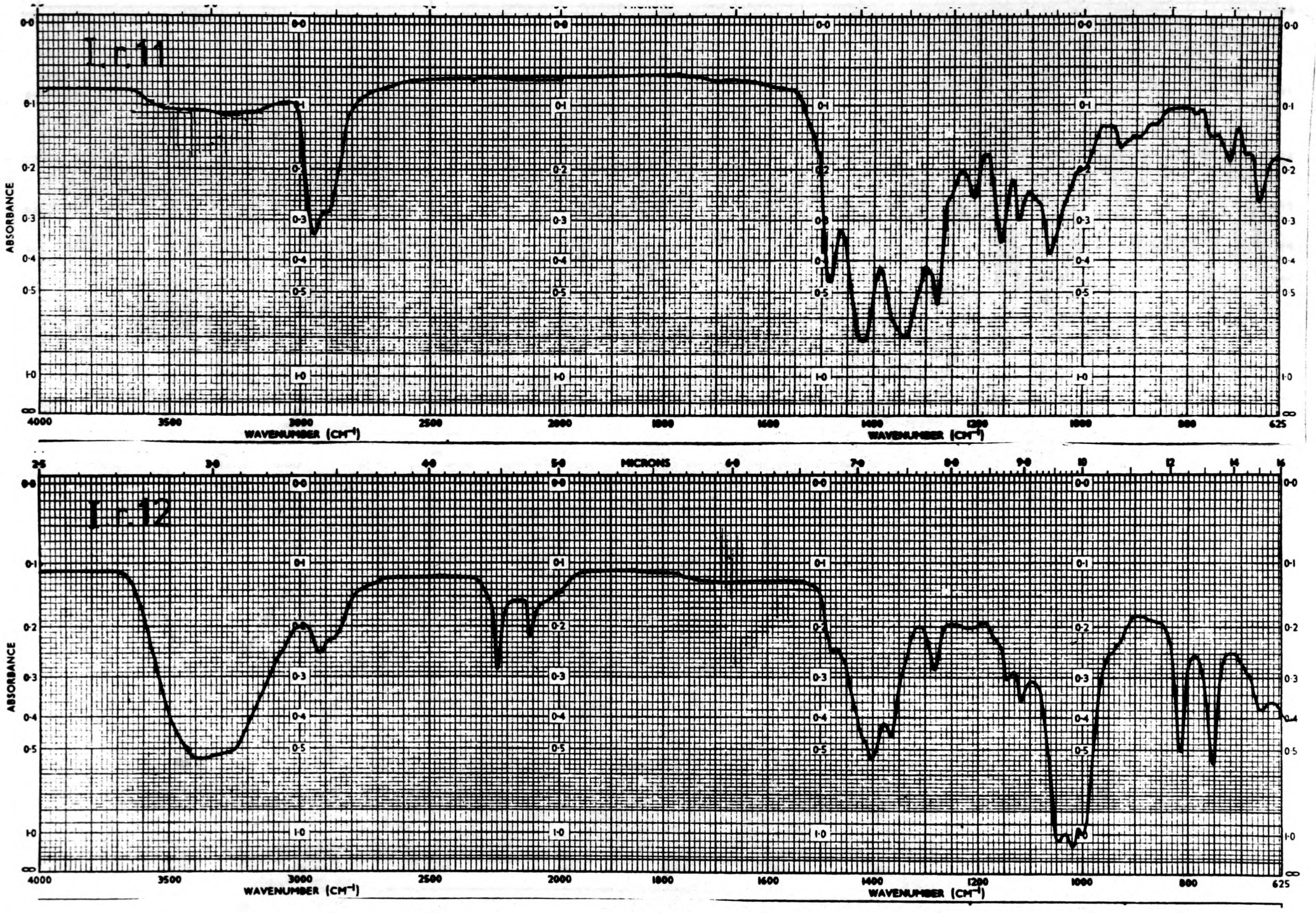
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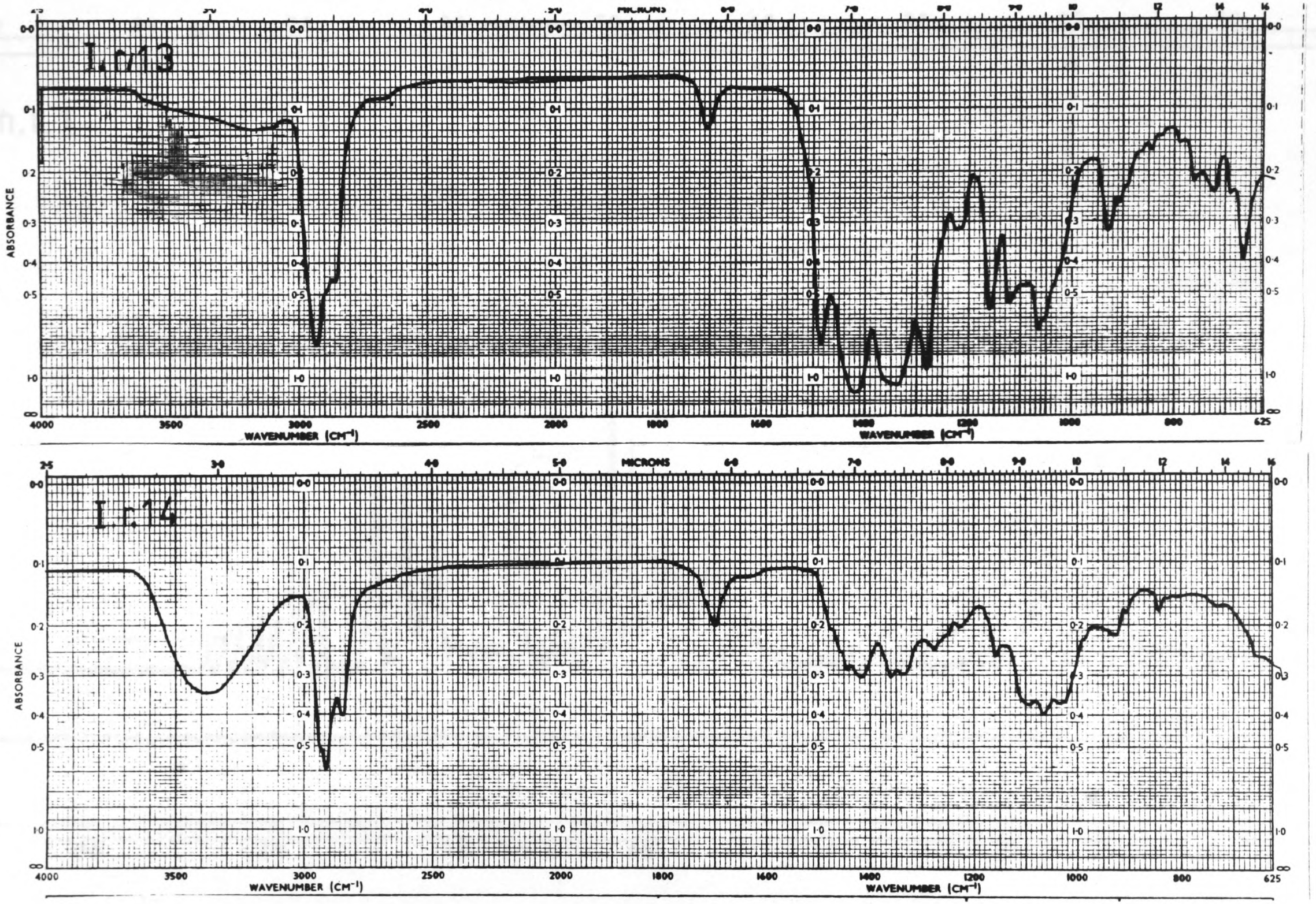
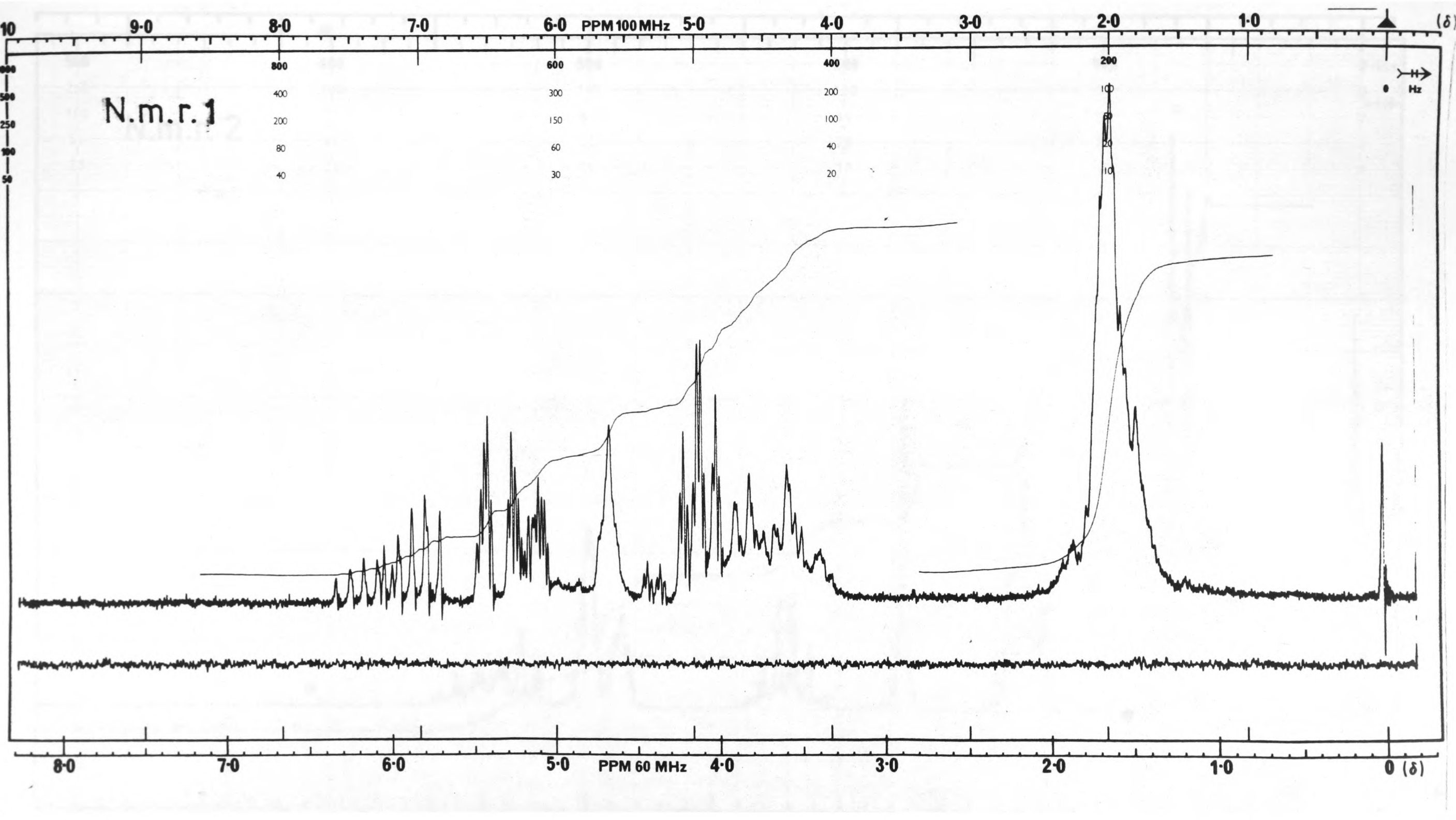

L.r.13
L.r.14
ABSORBANCE
WAVENUMBER (CM⁻¹)
MICRONS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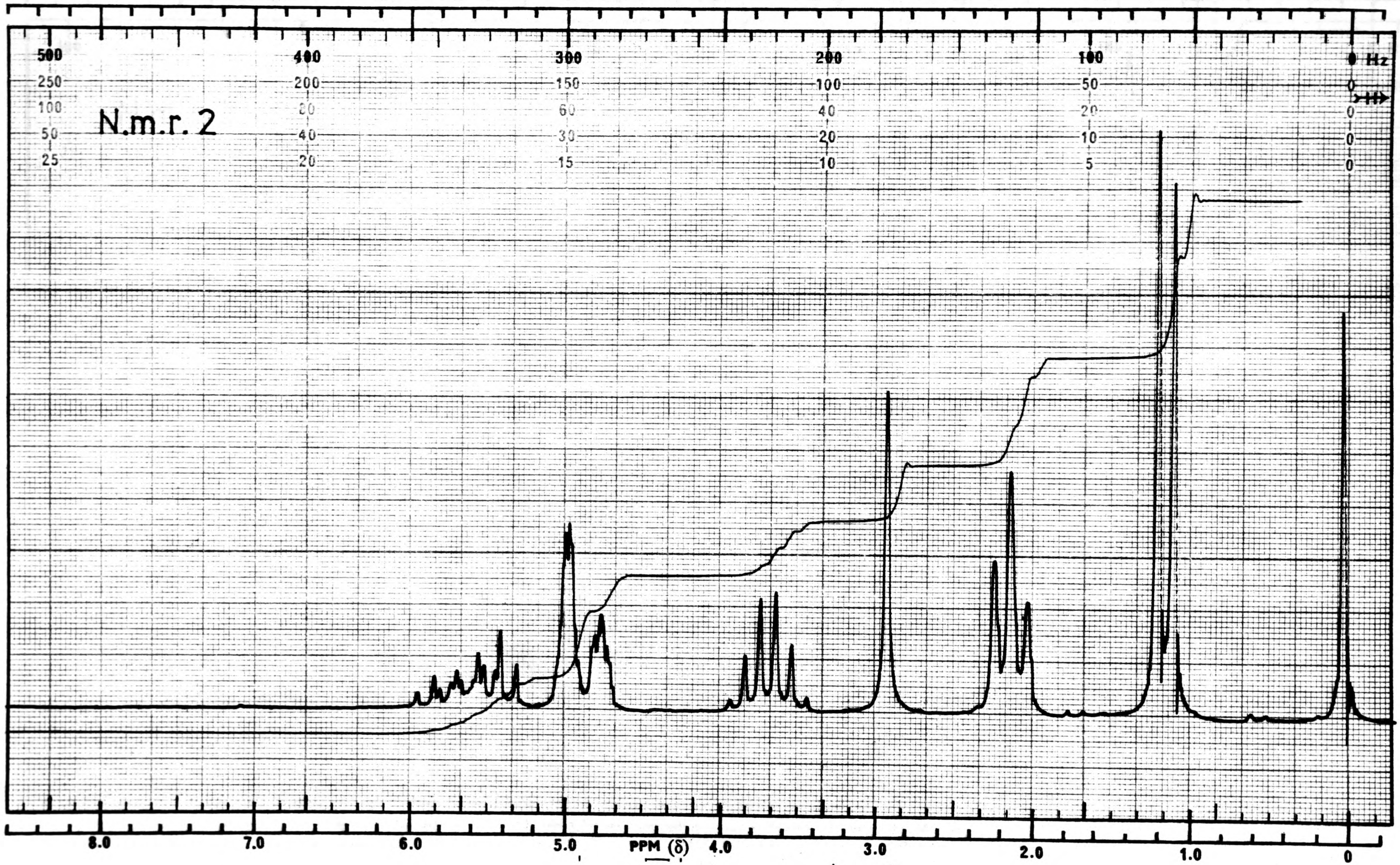
8·0
7·0
6·0
PPM 100 MHz
5·0
4·0
3·0
2·0
1·0
(δ)
1000
500
250
100
50
800
400
200
80
40
600
300
150
60
30
400
200
100
40
20
200
100
80
60
40
20
10
0
Hz
8·0
7·0
6·0
5·0
PPM 60 MHz
4·0
3·0
2·0
1·0
0 (δ)

N.m.r. 2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200
100
40
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100
50
20
10
5
0 Hz
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PPM (δ)
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2.0
1.0
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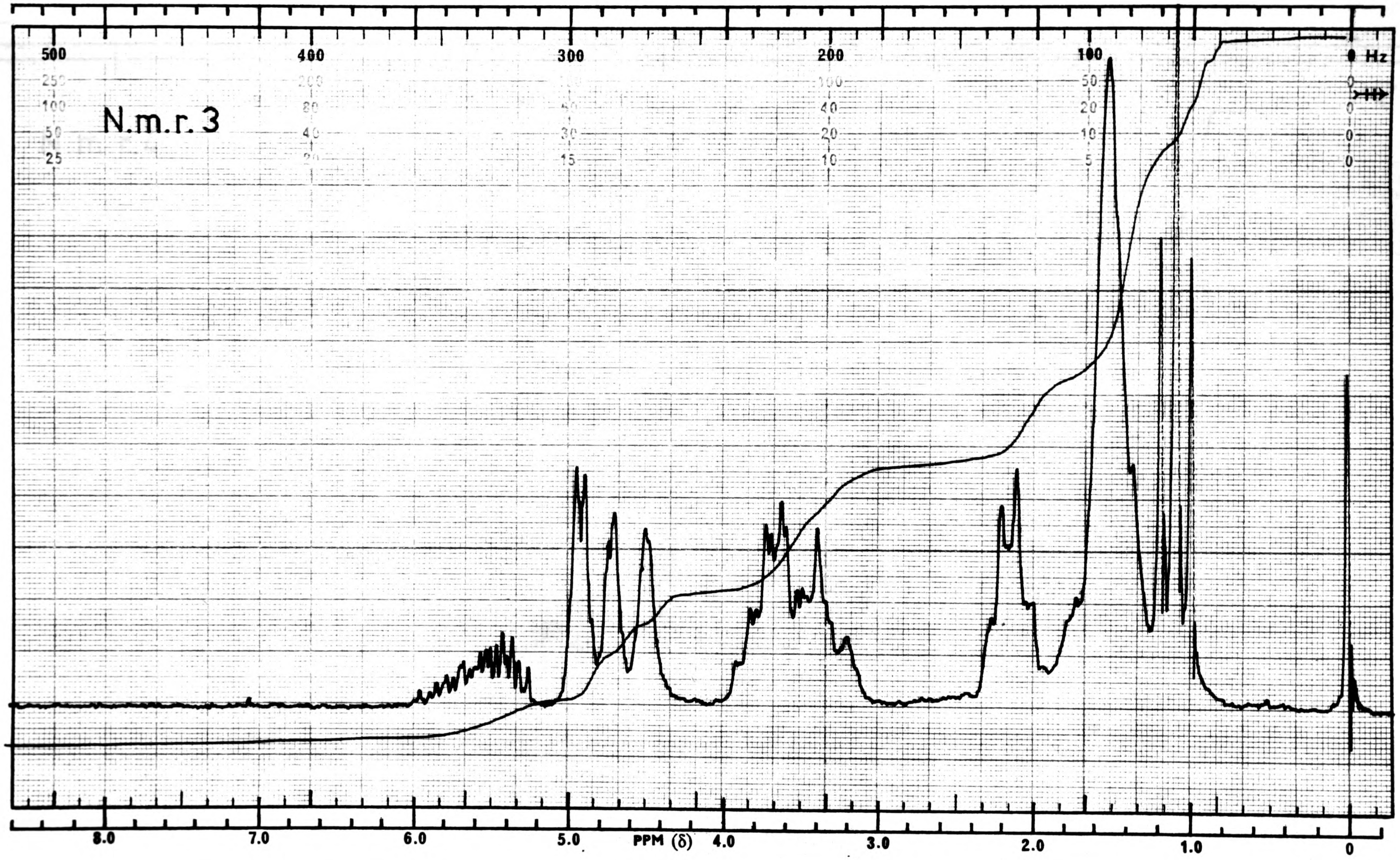
N.m.r. 3
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400
300
200
100
0 Hz
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6.0
5.0
PPM (δ)
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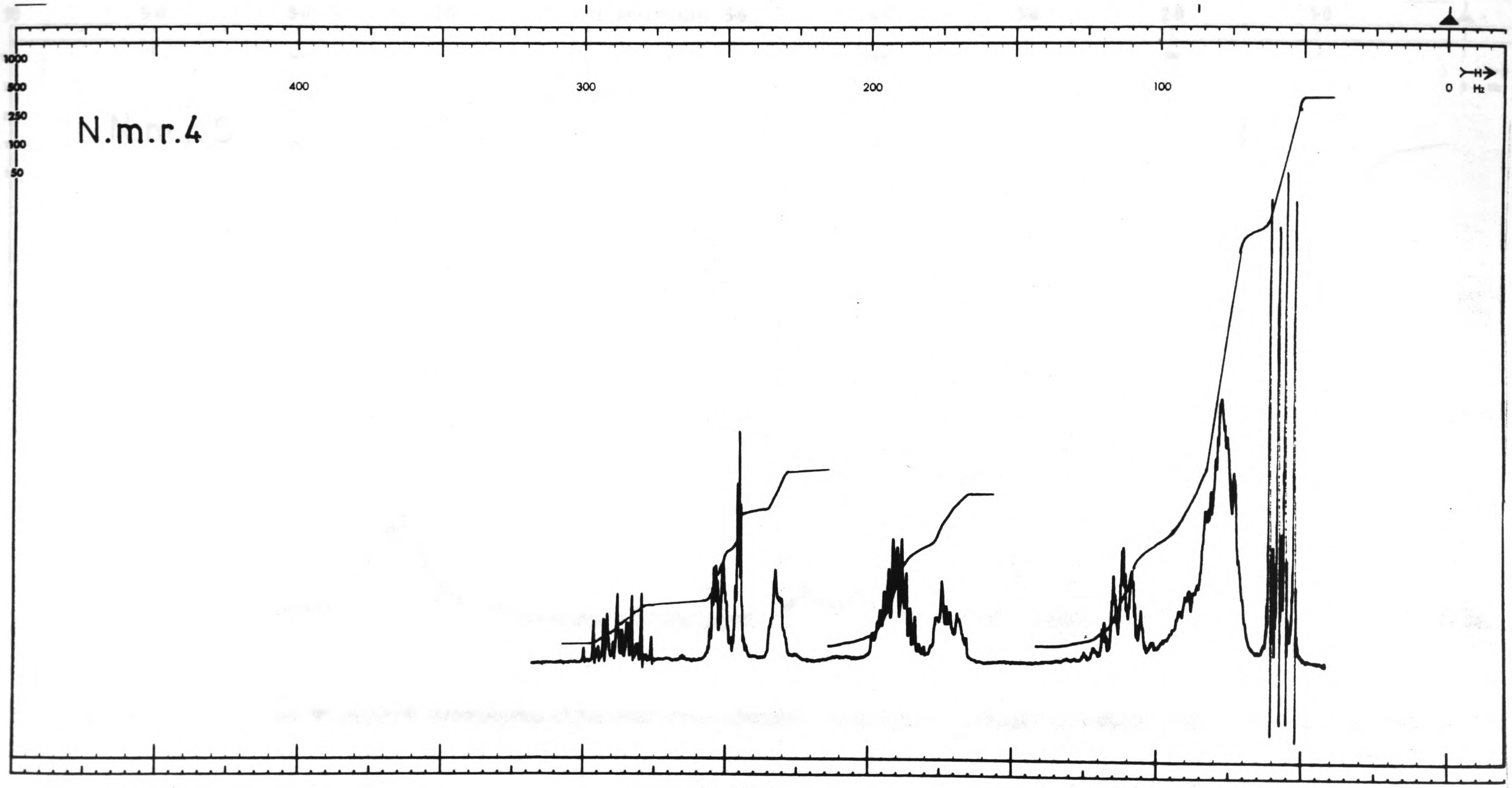
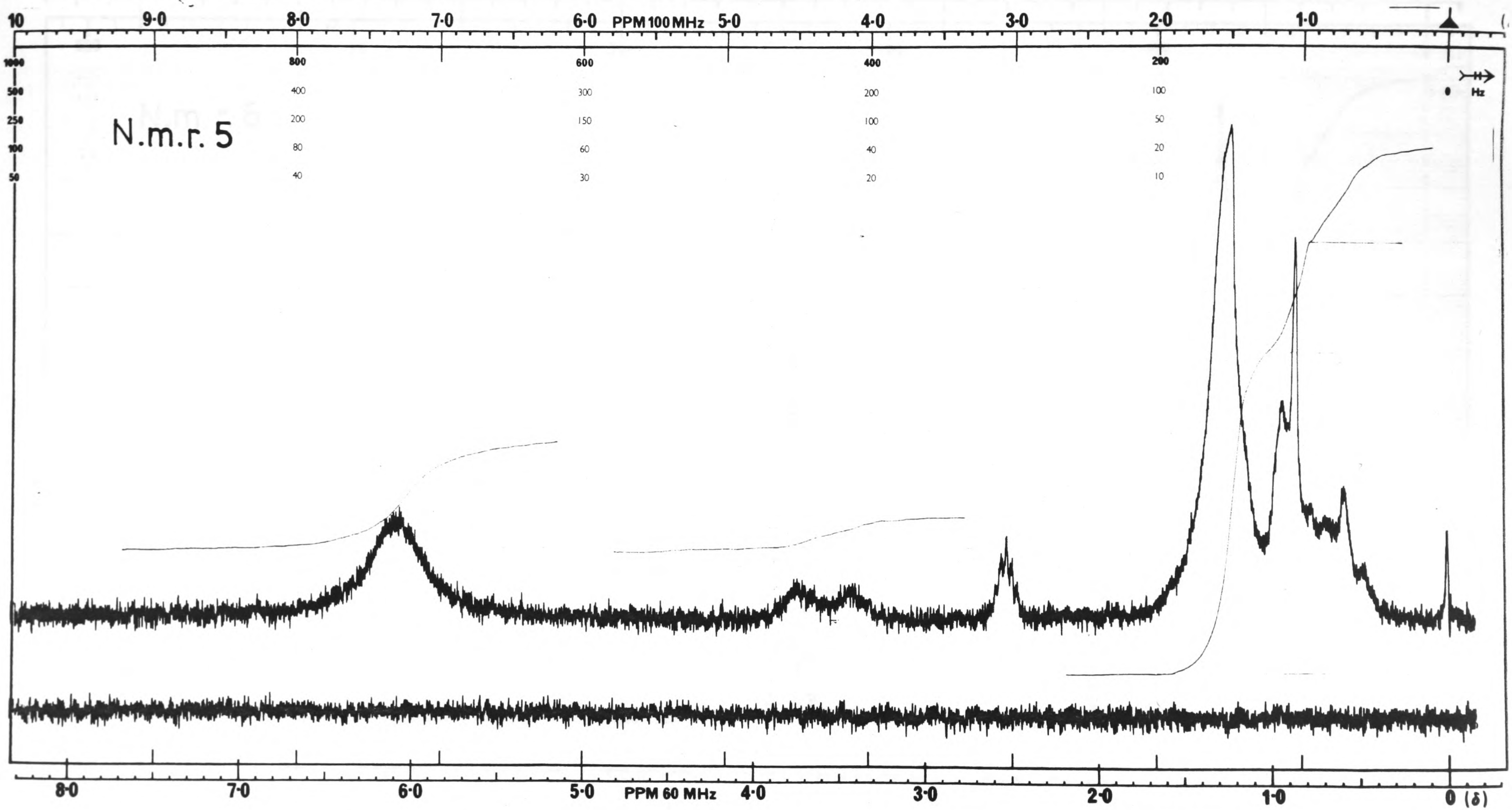
3.0
2.0
1.0
0

N.m.r.4

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7·0
6·0
PPM 100 MHz
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4·0
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2·0
1·0
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200
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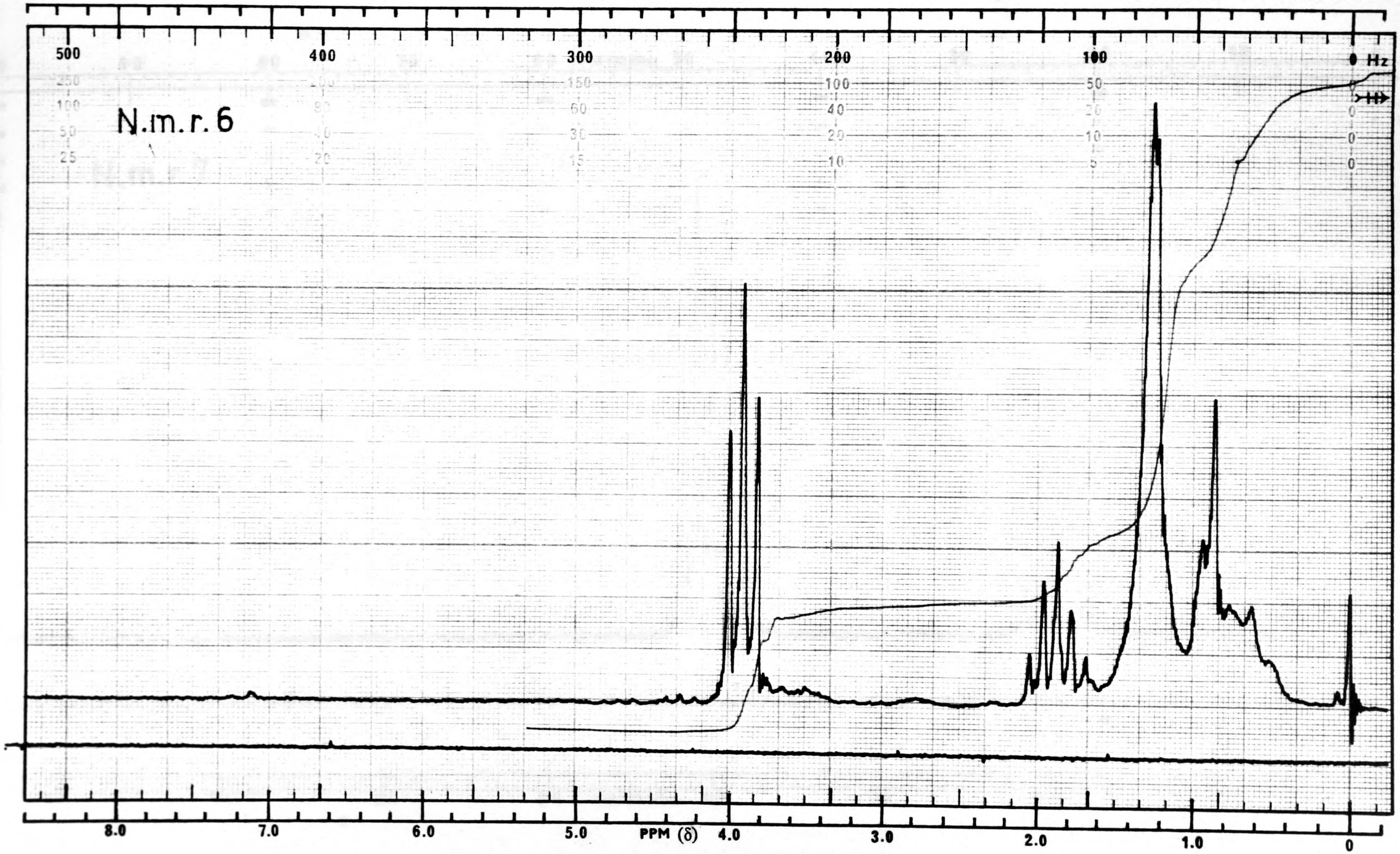
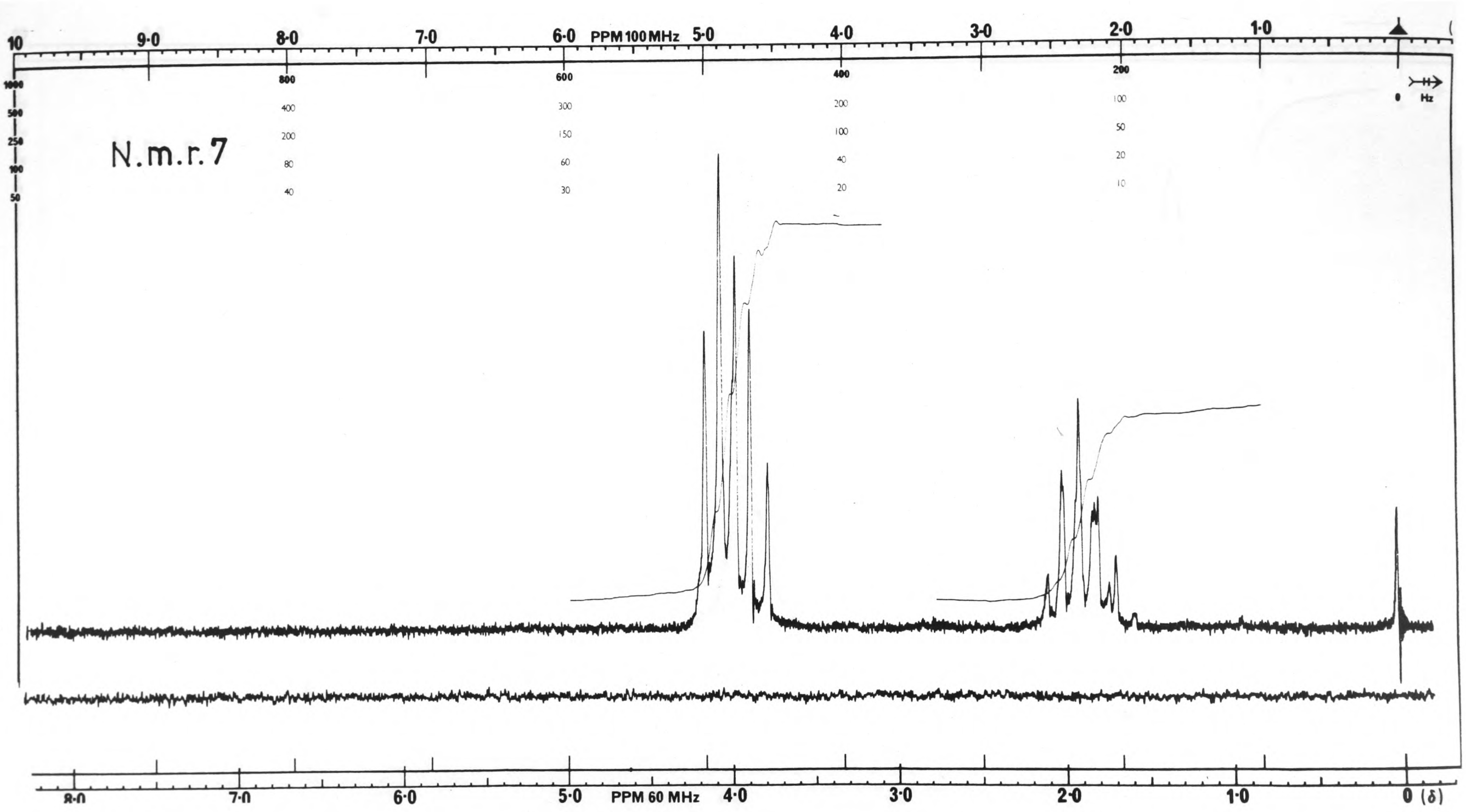
600
300
150
60
30
400
200
100
40
20
200
100
50
20
10
H
0 Hz
N.m.r. 5
8·0
7·0
6·0
5·0
PPM 60 MHz
4·0
3·0
2·0
1·0
0 (δ)

N.m.r. 6

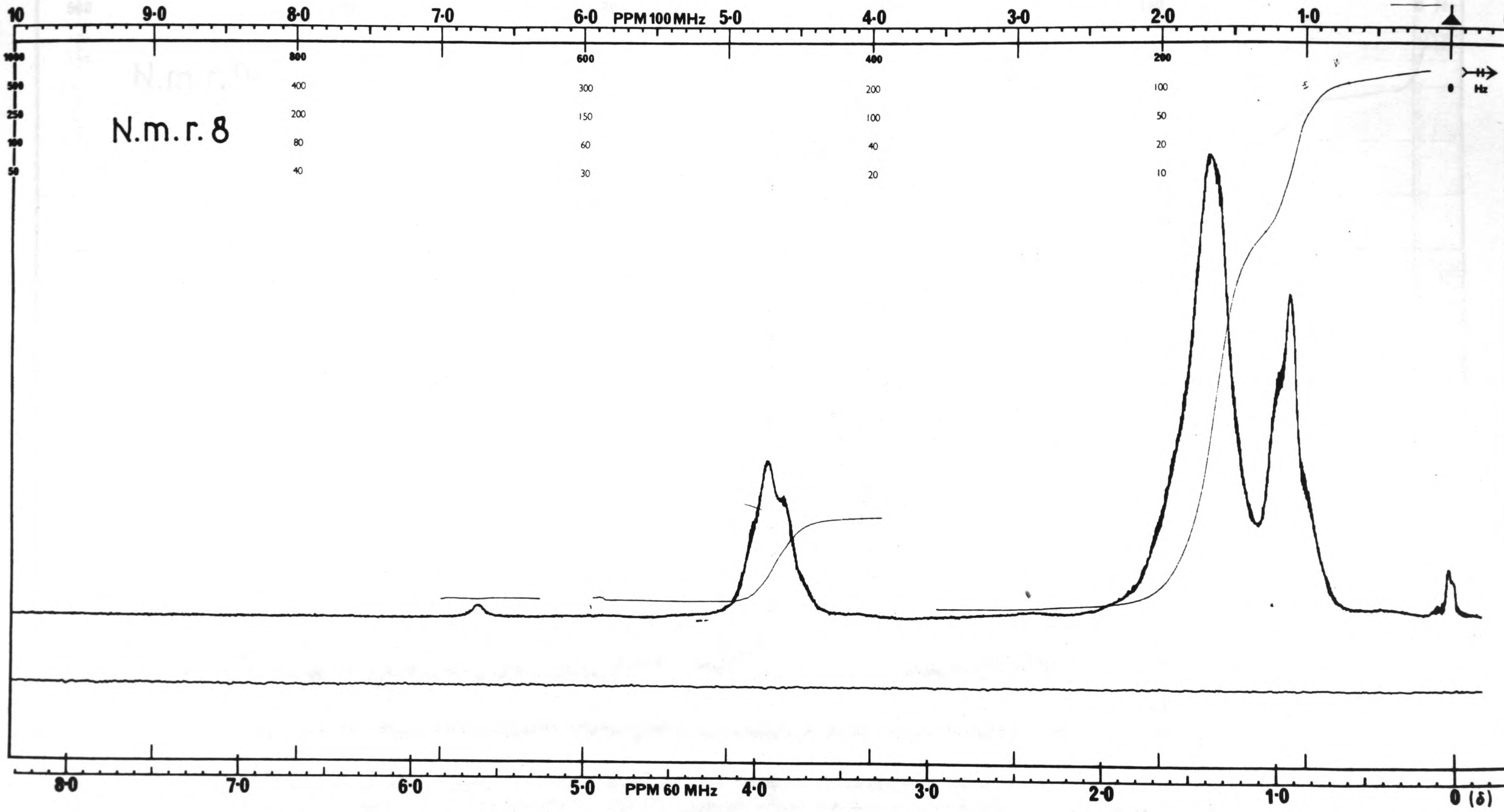


N.m.r.7


10
9·0
8·0
7·0
6·0
PPM 100 MHz
5·0
4·0
3·0
2·0
1·0
0
Hz
1000
500
250
100
50
800
400
200
80
40
600
300
150
60
30
400
200
100
40
20
200
100
50
20
10
9·0
8·0
7·0
6·0
5·0
PPM 60 MHz
4·0
3·0
2·0
1·0
0 (δ)

1988

N.m.r. 8


10
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7·0
6·0
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2·0
1·0
0
Hz
1000
500
250
100
50
800
400
200
80
40
600
300
150
60
30
400
200
100
40
20
200
100
50
20
10
8·0
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5·0
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2·0
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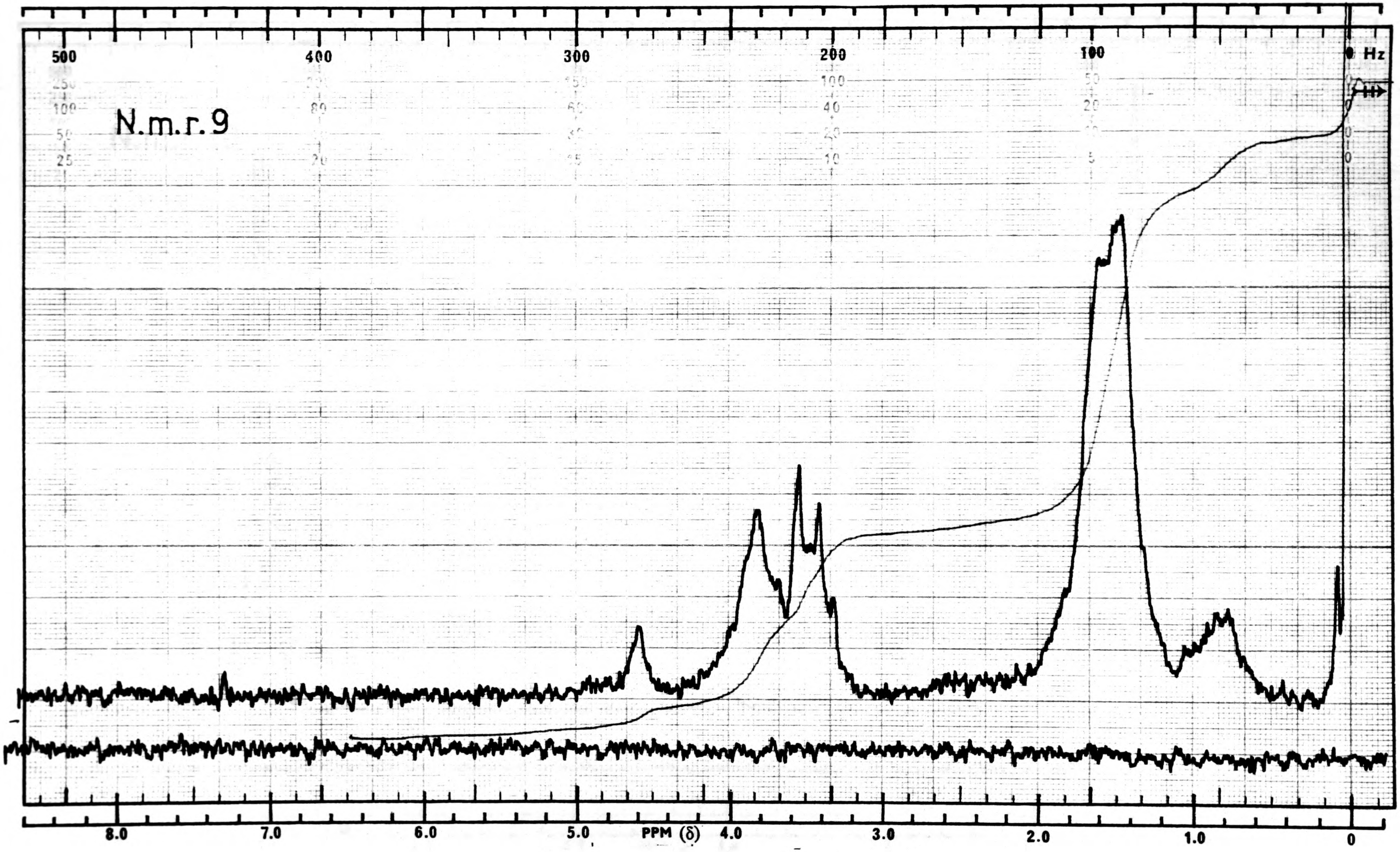
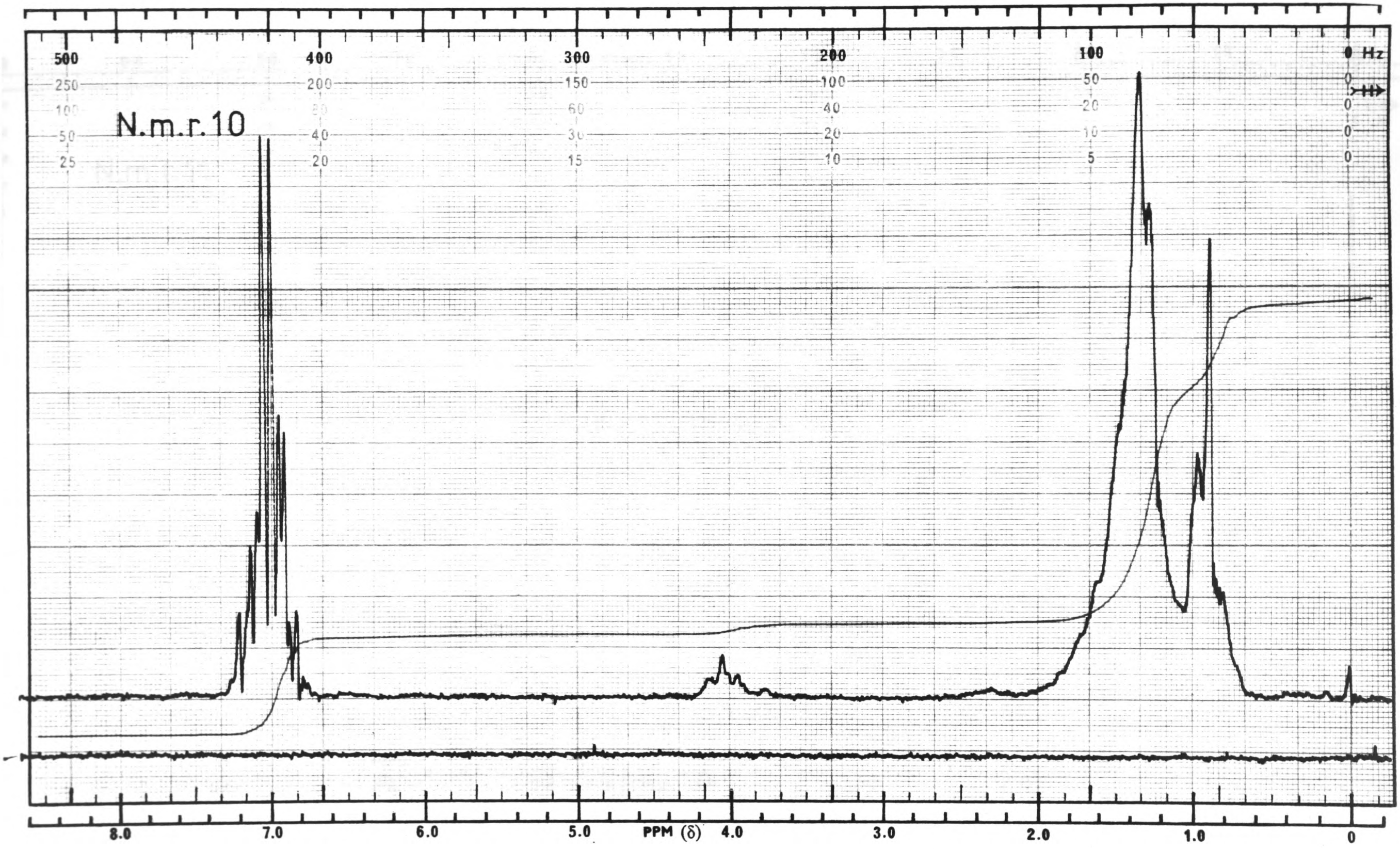
0 (δ)

N.m.r.9

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80
40
20
300
150
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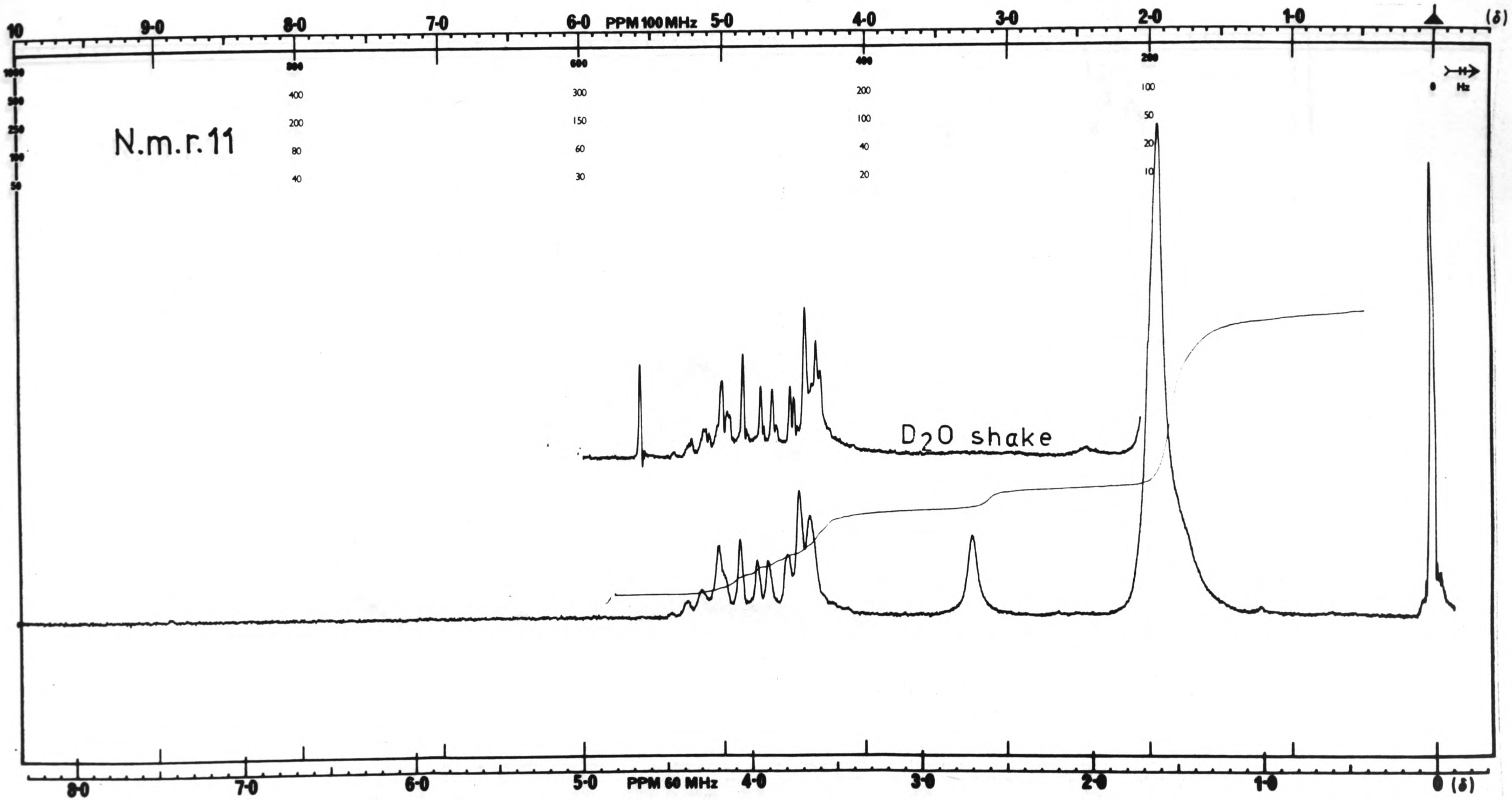
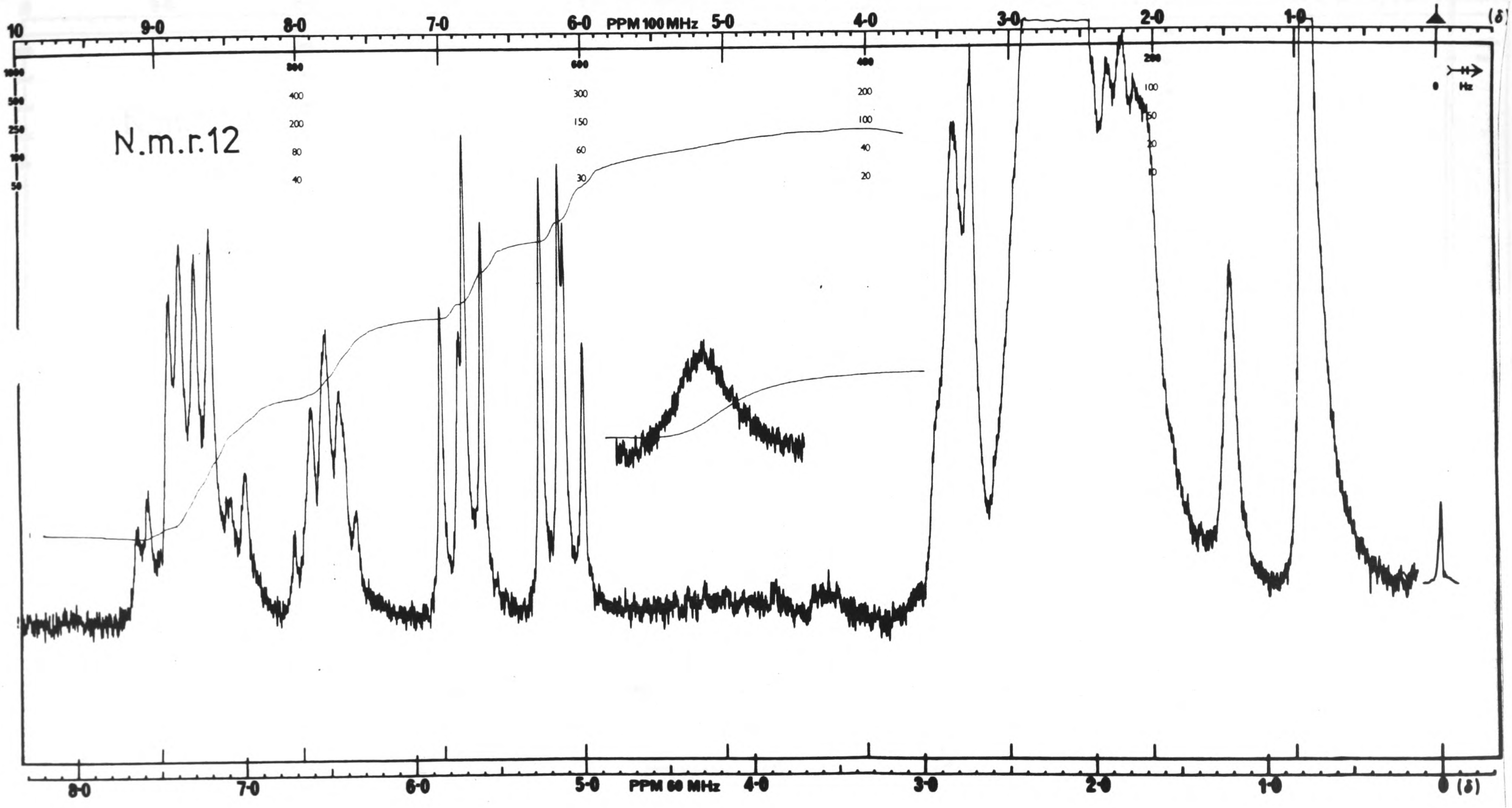
30
15
200
100
40
20
10
100
50
20
10
5
0 Hz
0
0
0
0
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

N.m.r.11


10
9-0
8-0
7-0
6-0
PPM 100 MHz
5-0
4-0
3-0
2-0
1-0
(δ)
0 Hz
800
400
200
80
40
600
300
150
60
30
400
200
100
40
20
200
100
50
20
10
D2O shake
8-0
7-0
6-0
5-0
PPM 60 MHz
4-0
3-0
2-0
1-0
0 (δ)


10
9-0
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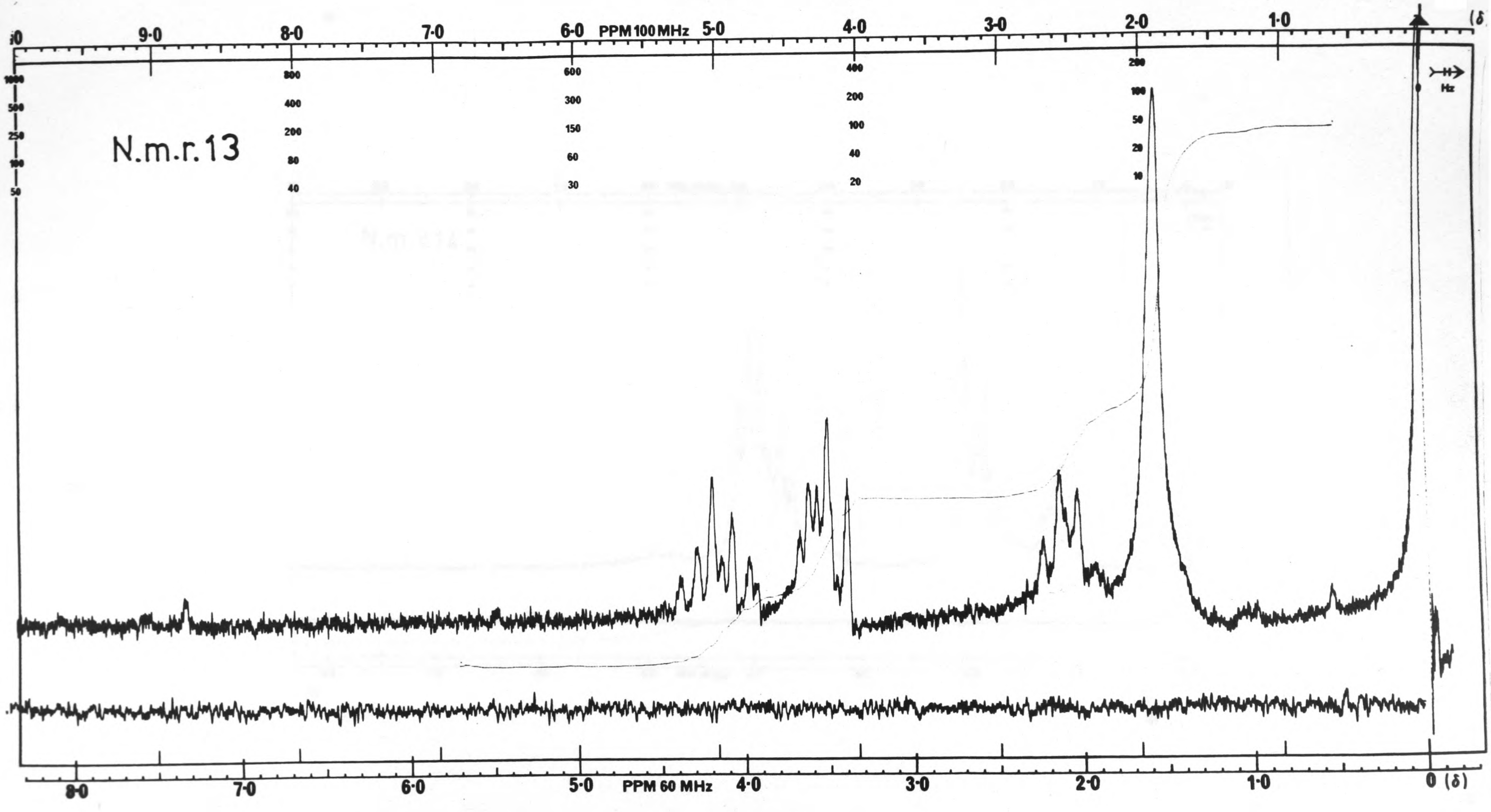
(δ)
N.m.r.12
PPM 60 MHz

N.m.r.13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8·0
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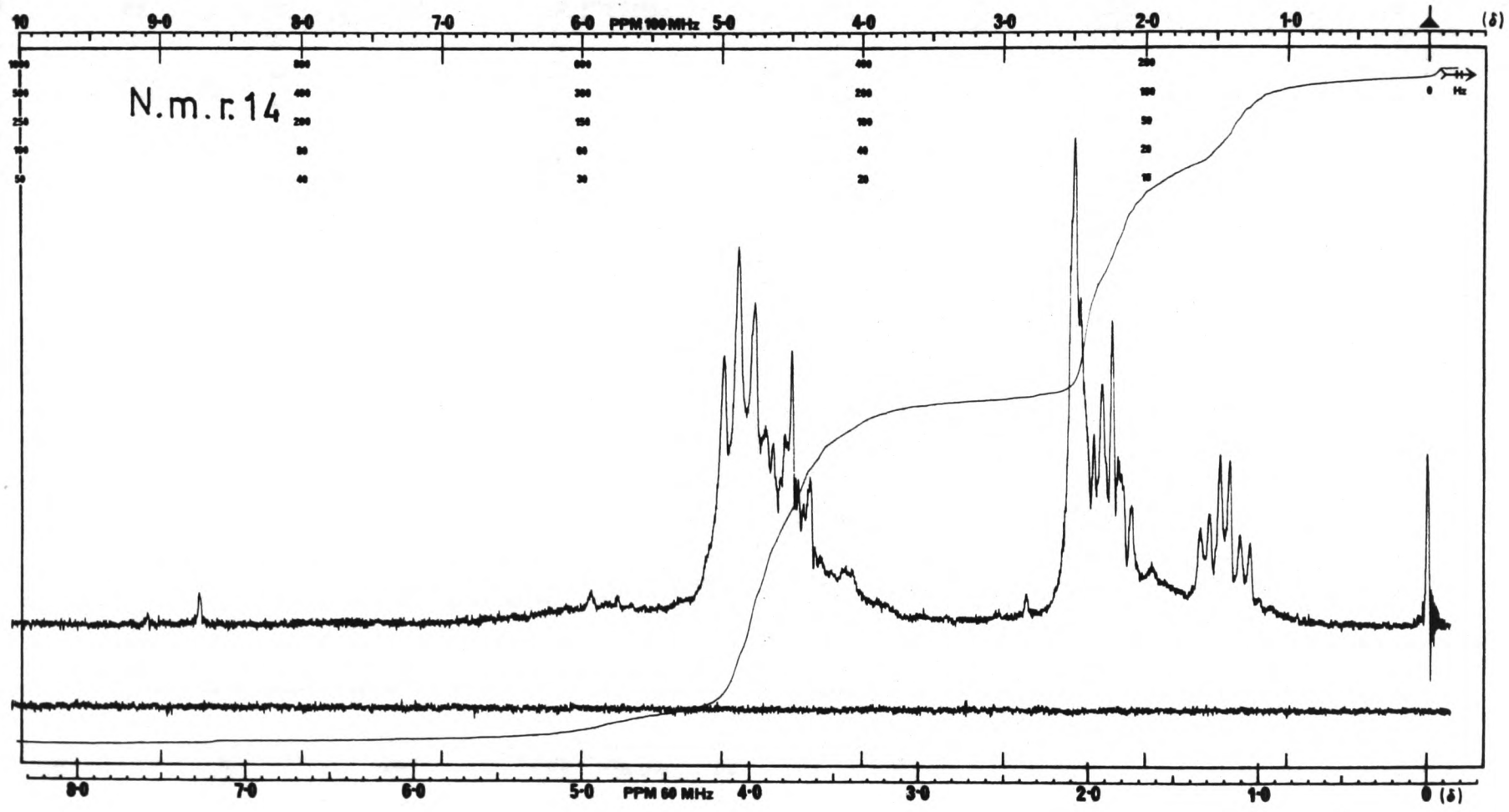
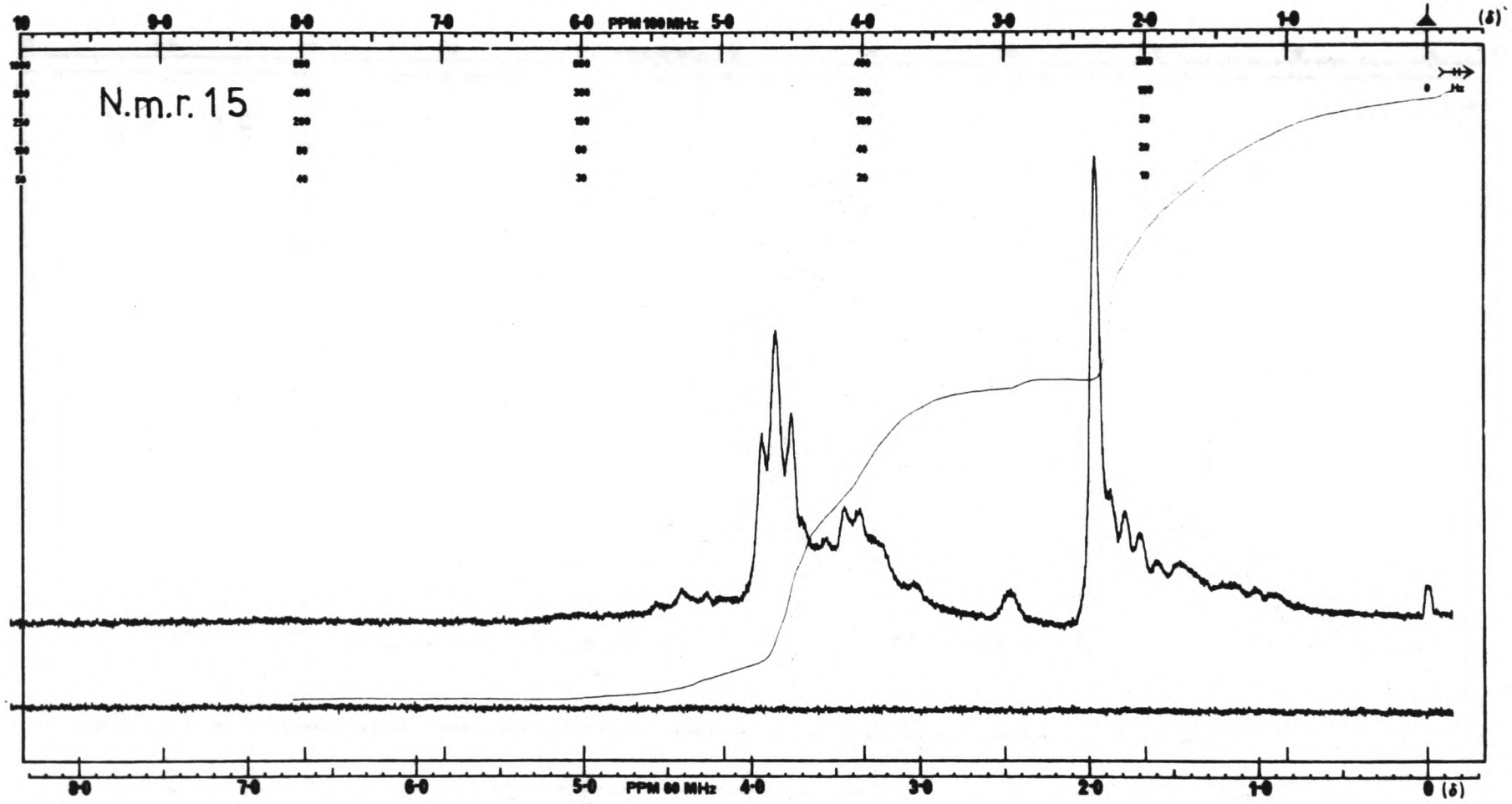
PPM 100 MHz
5·0
4·0
3·0
2·0
1·0
Hz
8·0
7·0
6·0
5·0
PPM 60 MHz
4·0
3·0
2·0
1·0
0 (δ)


N.m.r.14
10
9·0
8·0
7·0
6·0
PPM 100 MHz
5·0
4·0
3·0
2·0
1·0
(δ)
0 Hz
8·0
7·0
6·0
5·0
PPM 60 MHz
4·0
3·0
2·0
1·0
0 (δ)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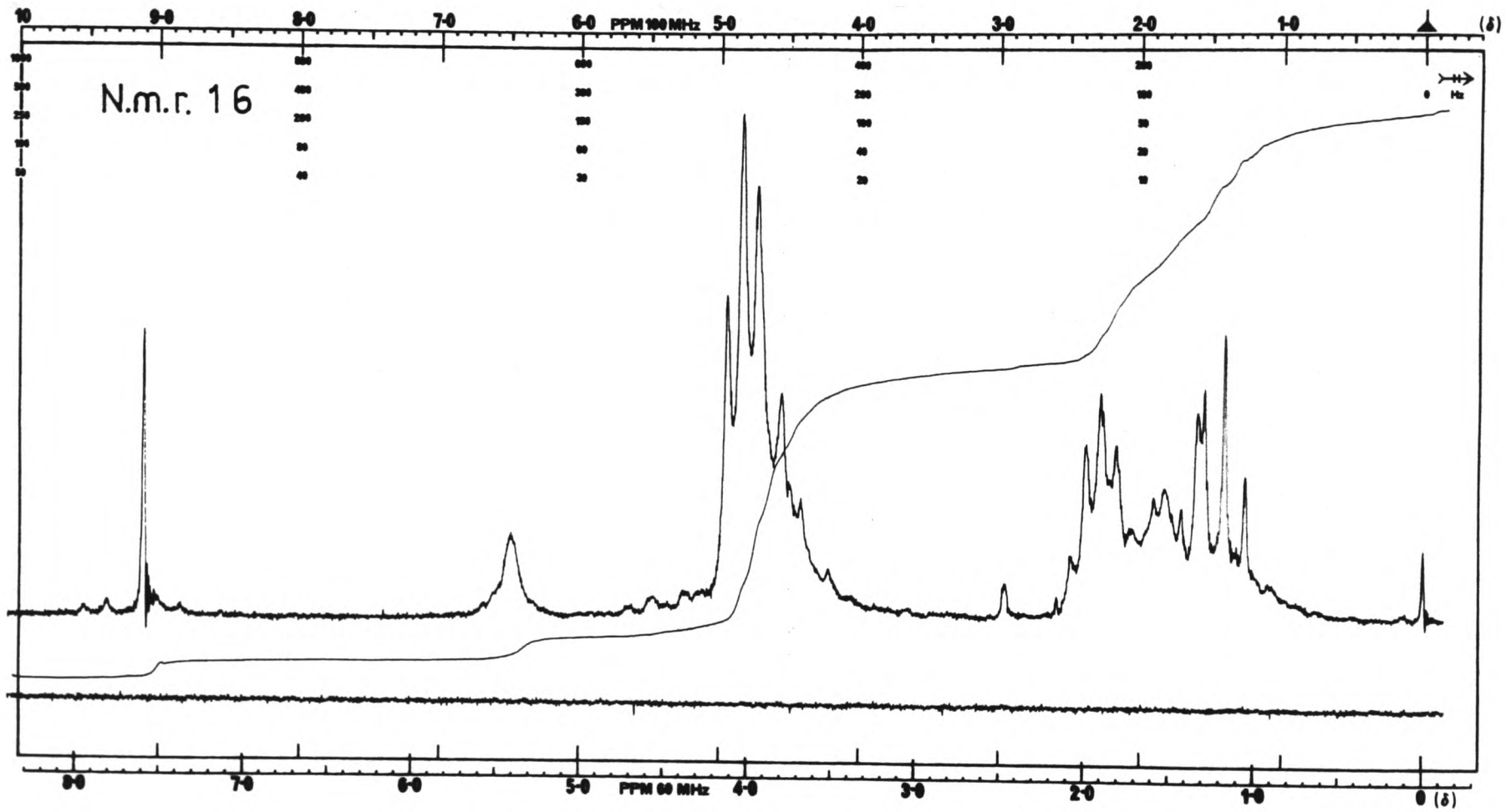
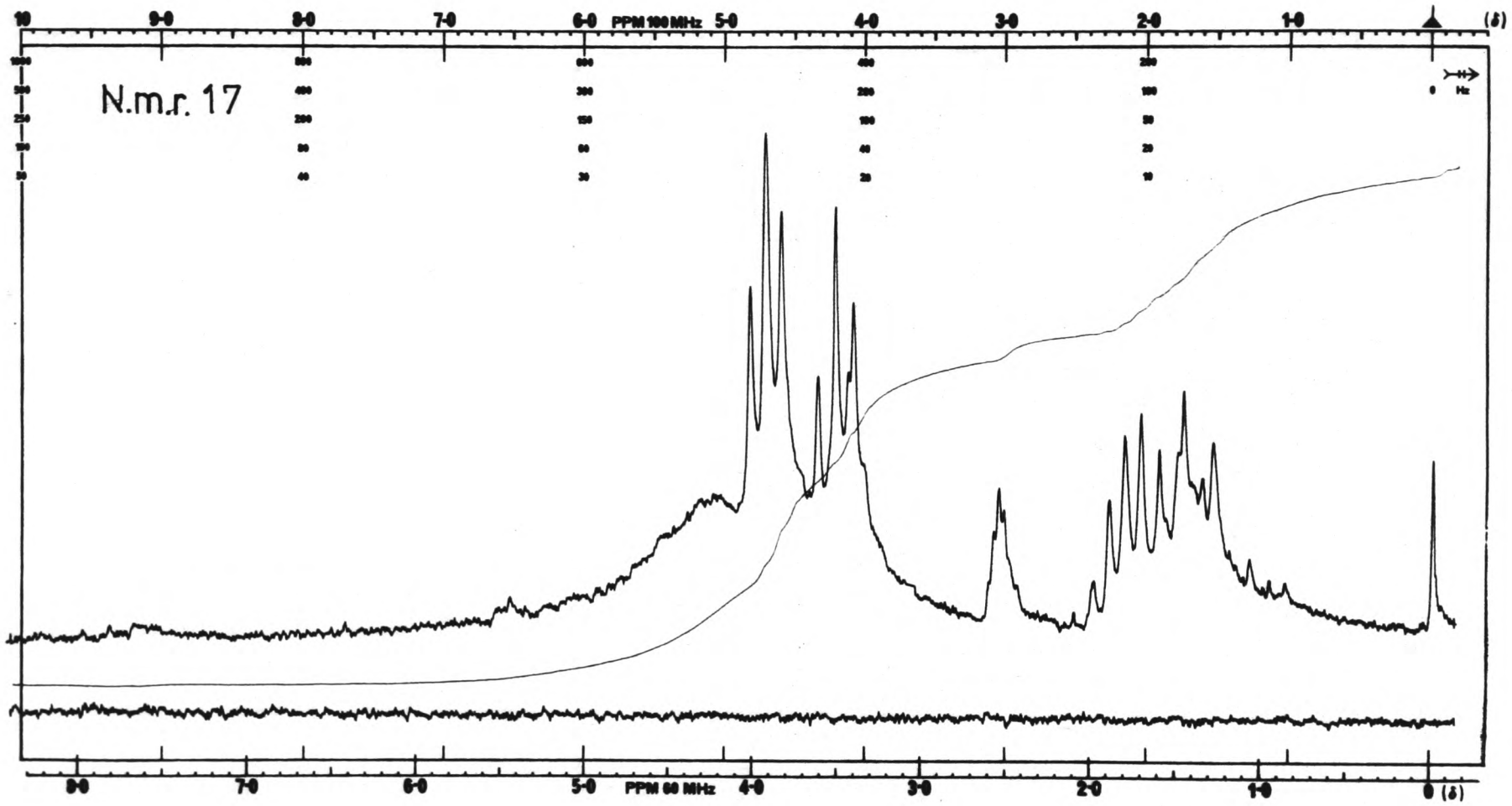
PPM 100 MHz
PPM 60 MHz
(δ)


N.m.r. 16
10
9·0
8·0
7·0
6·0
PPM 100 MHz
5·0
4·0
3·0
2·0
1·0
(δ)
Hz
8·0
7·0
6·0
5·0
PPM 60 MHz
4·0
3·0
2·0
1·0
0 (δ)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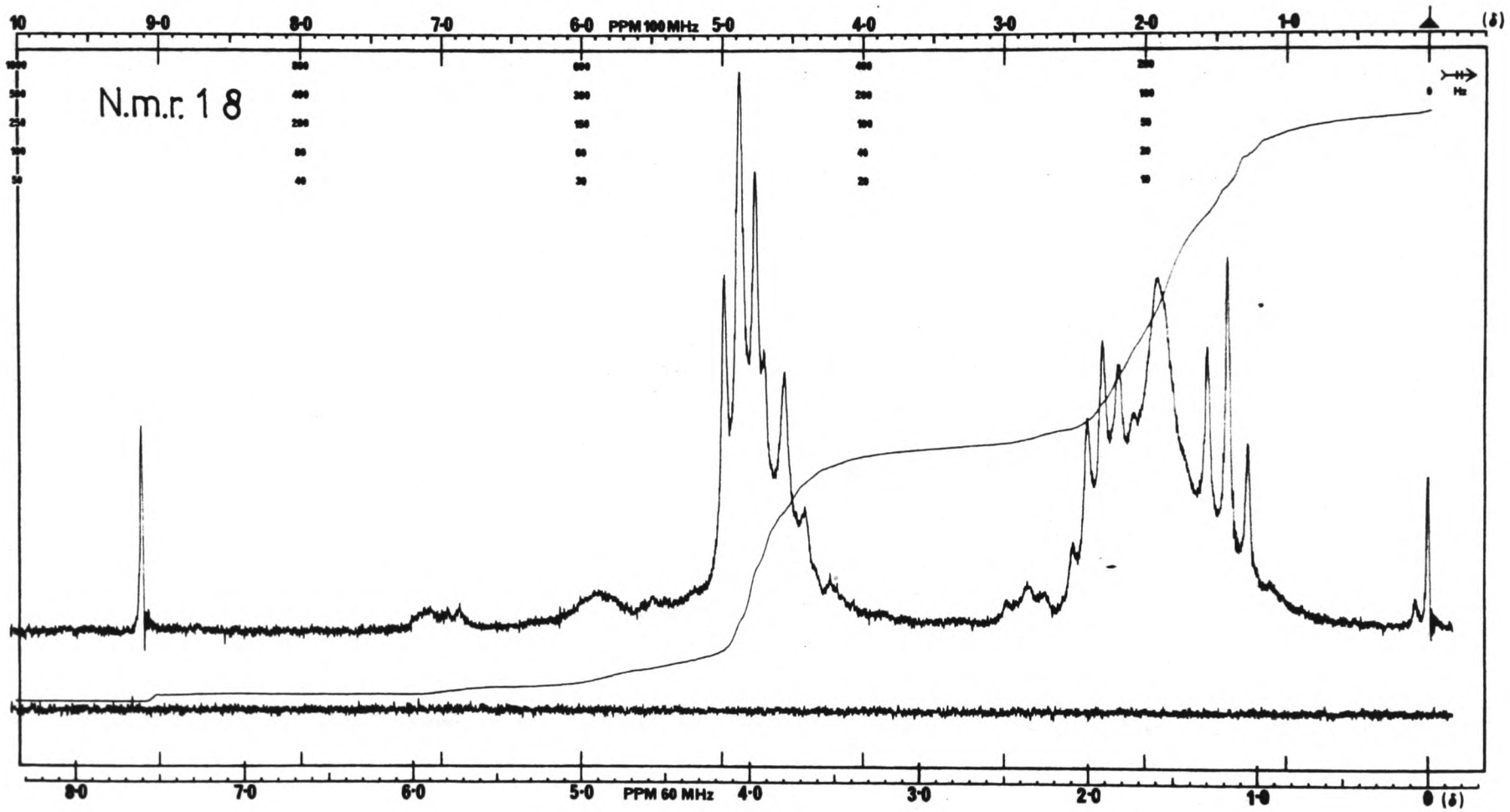
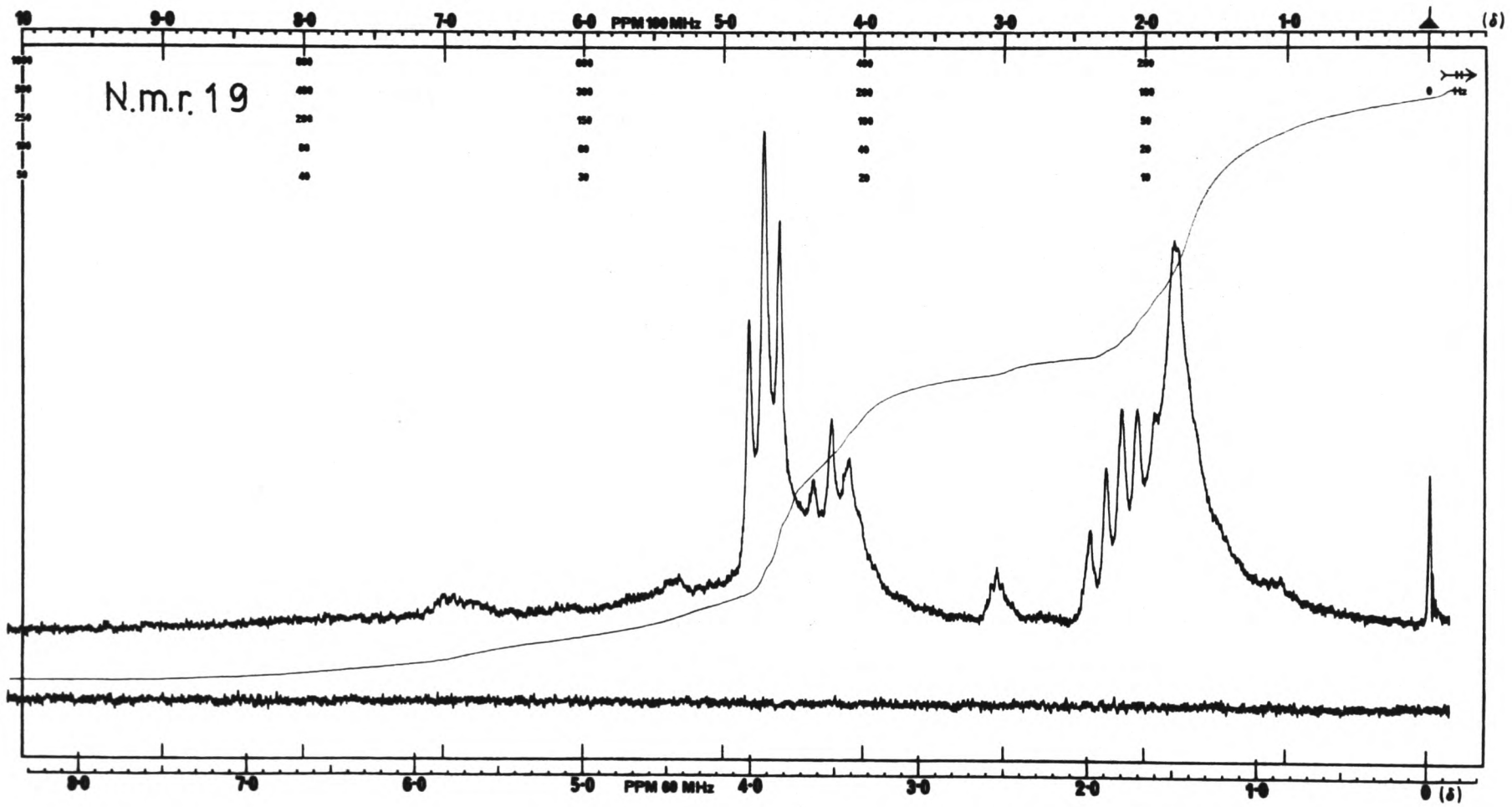
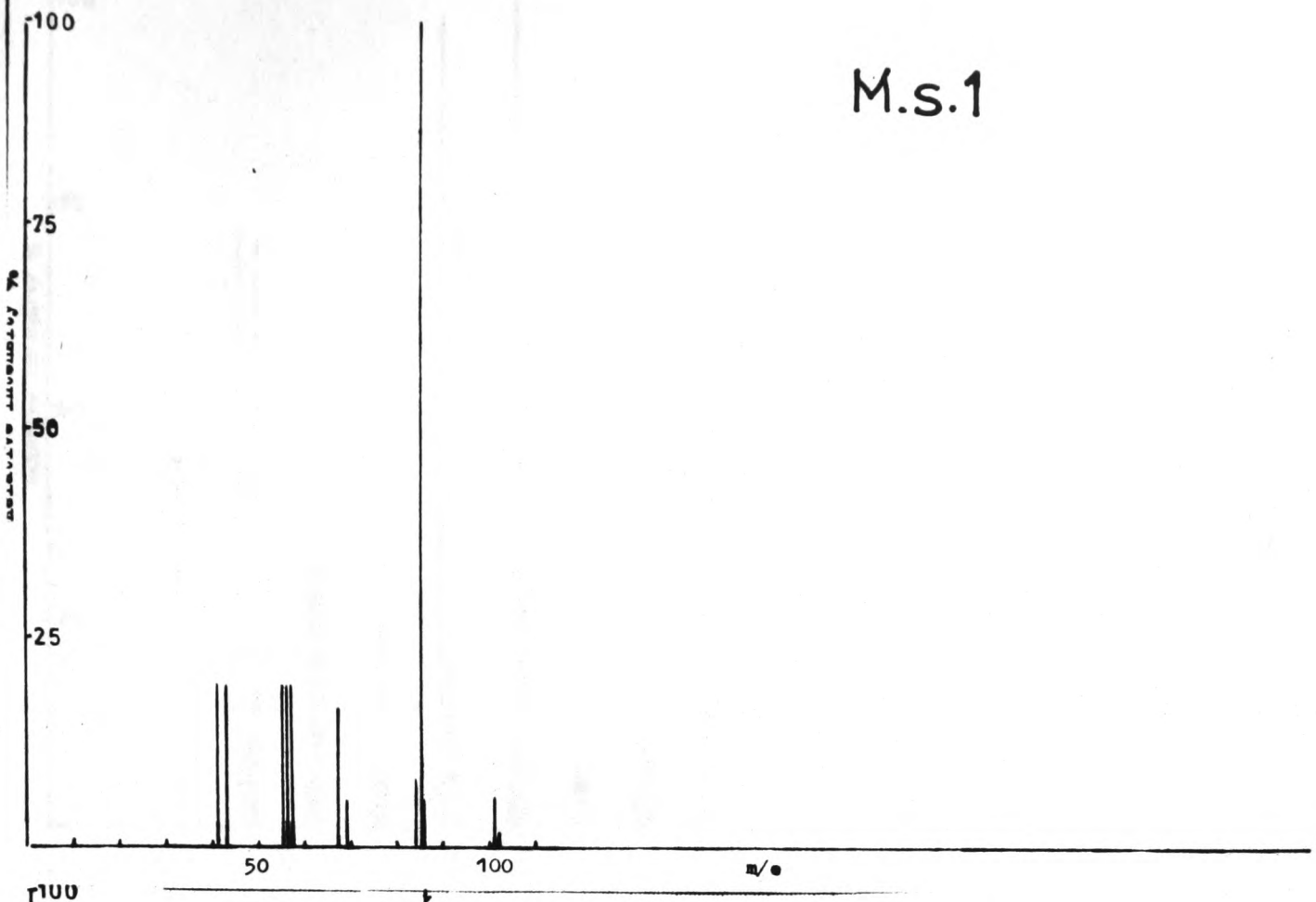
PPM 100 MHz
(δ)
PPM 60 MHz
(δ)

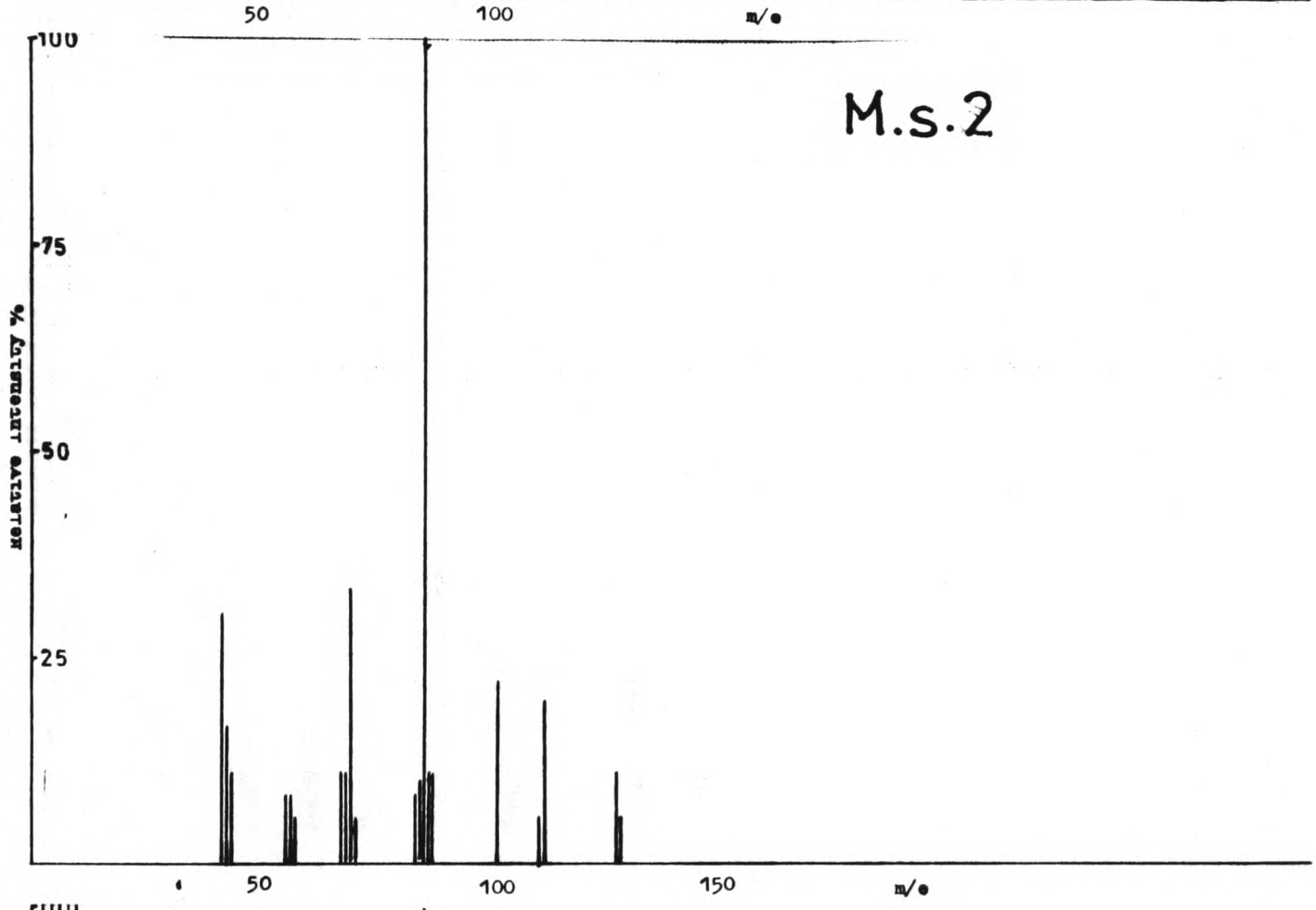

N.m.r. 1 8
10
9·0
8·0
7·0
6·0
PPM 100 MHz
5·0
4·0
3·0
2·0
1·0
(δ)
Hz
8·0
7·0
6·0
5·0
PPM 60 MHz
4·0
3·0
2·0
1·0
0 (δ)


N.m.r. 19
PPM 100 MHz
PPM 60 MHz
(δ)

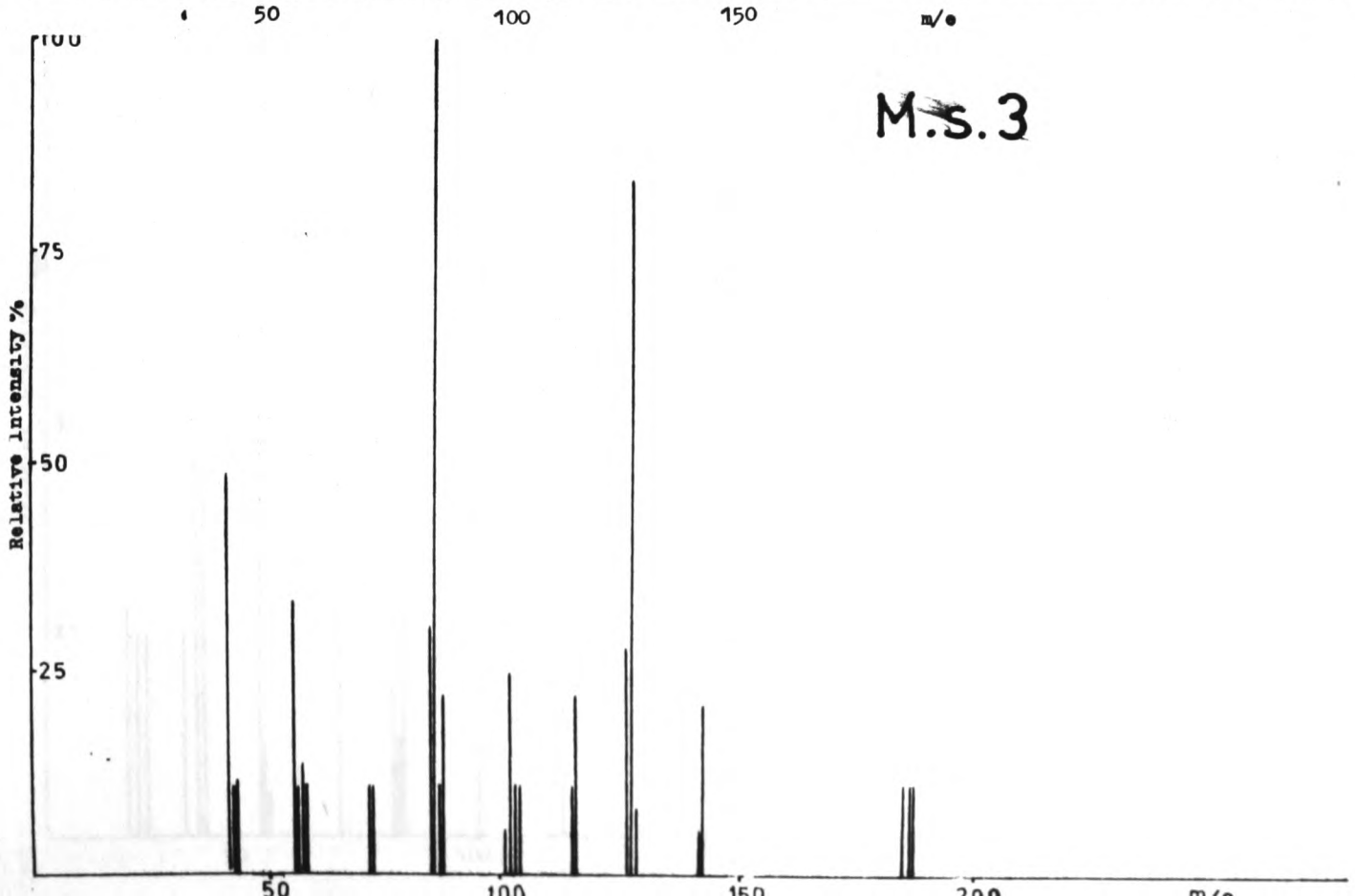
M.s.1


100
75
50
25
% Relative intensity
50
100
m/e

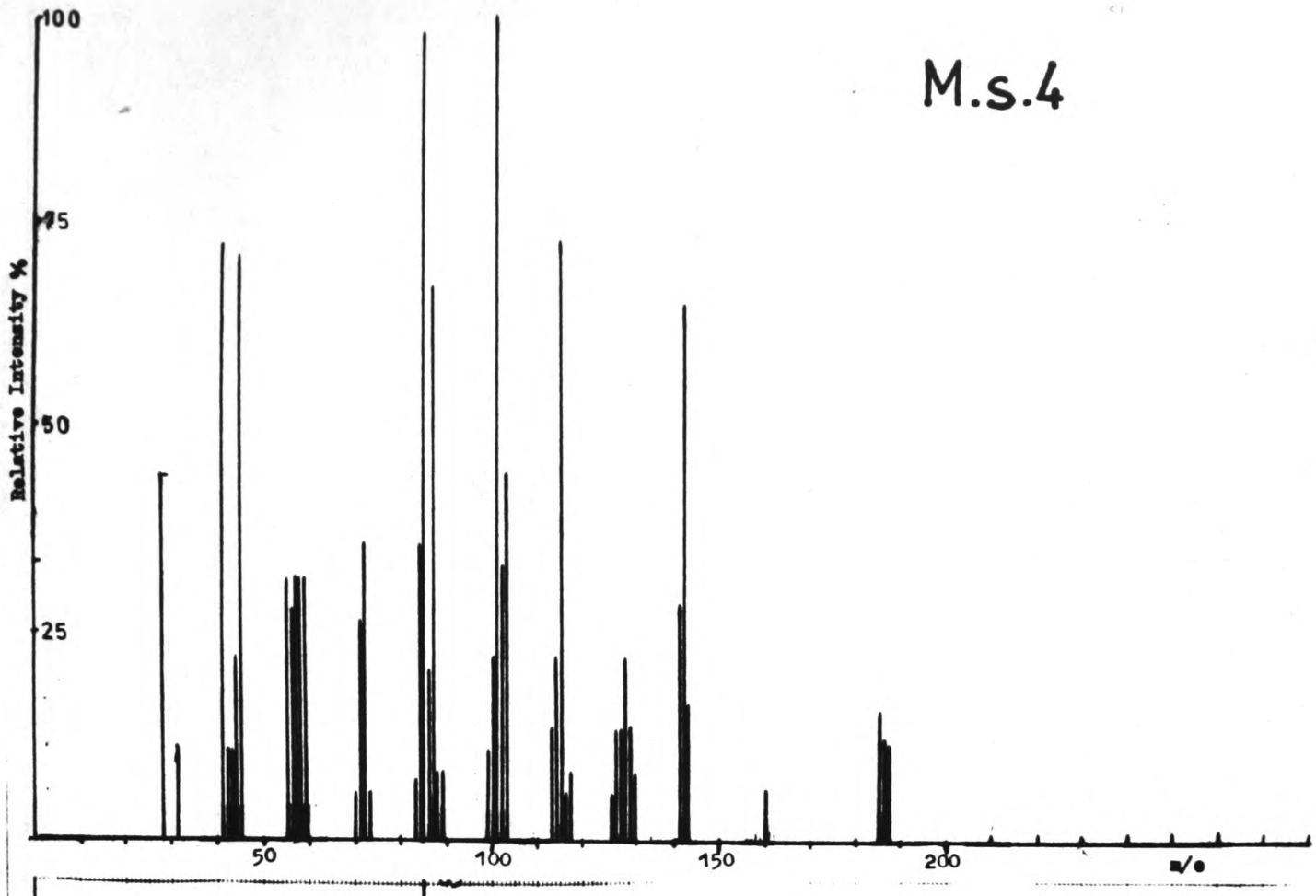
M.s.2


100
75
50
25
% Relative intensity
50
100
150
m/e

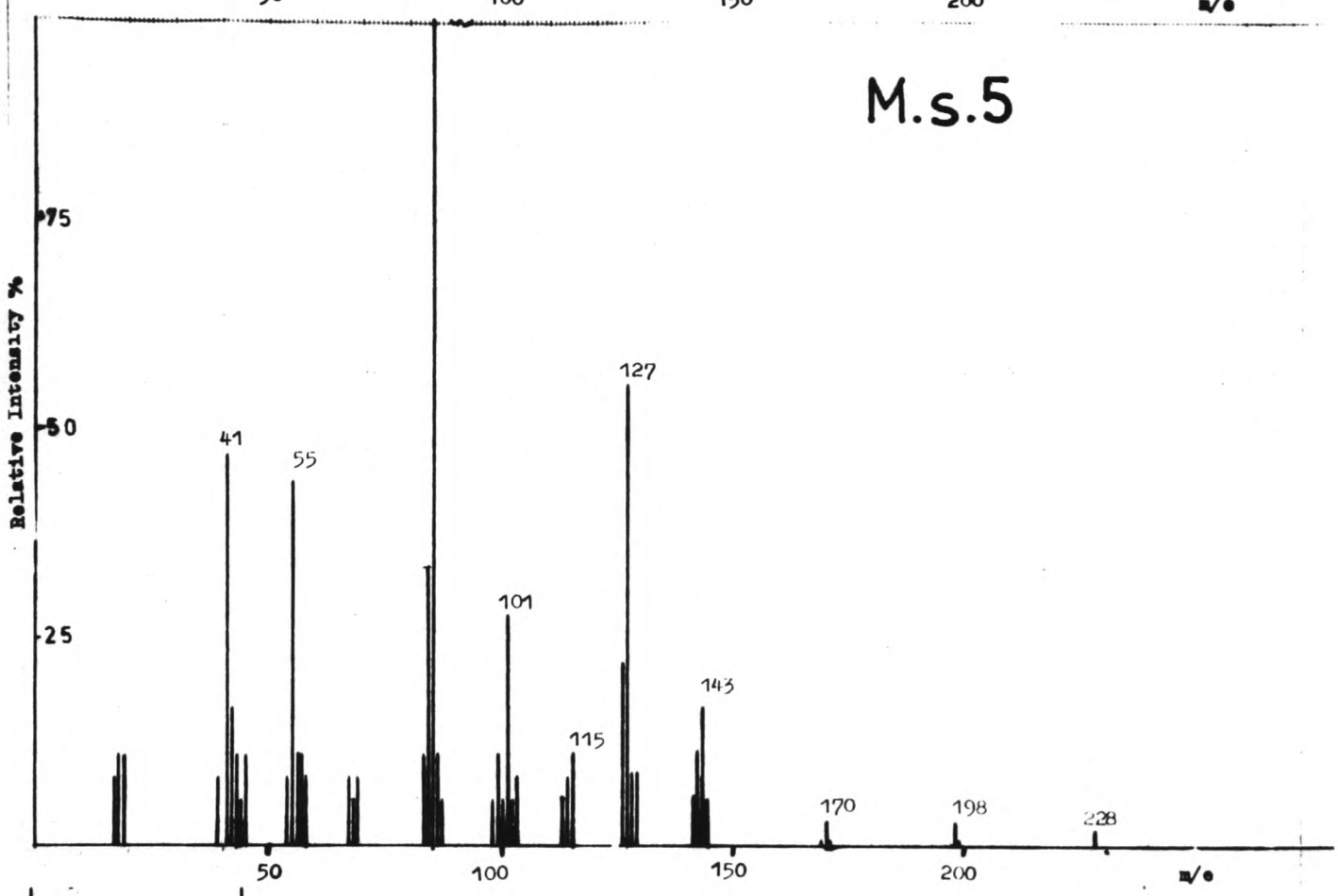
M.s.3


100
75
50
25
Relative intensity %
50
100
150
200
m/e

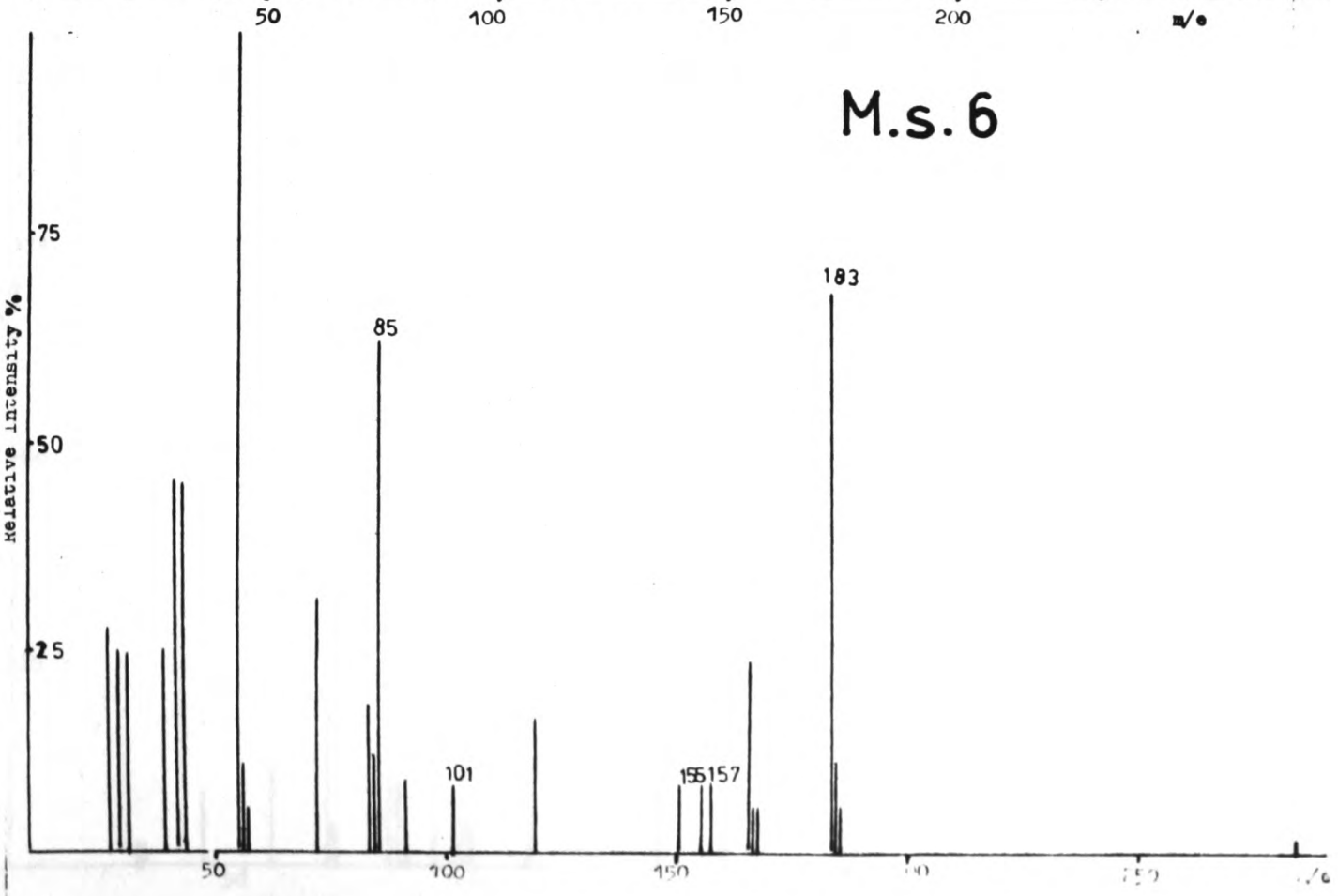
M.s.4

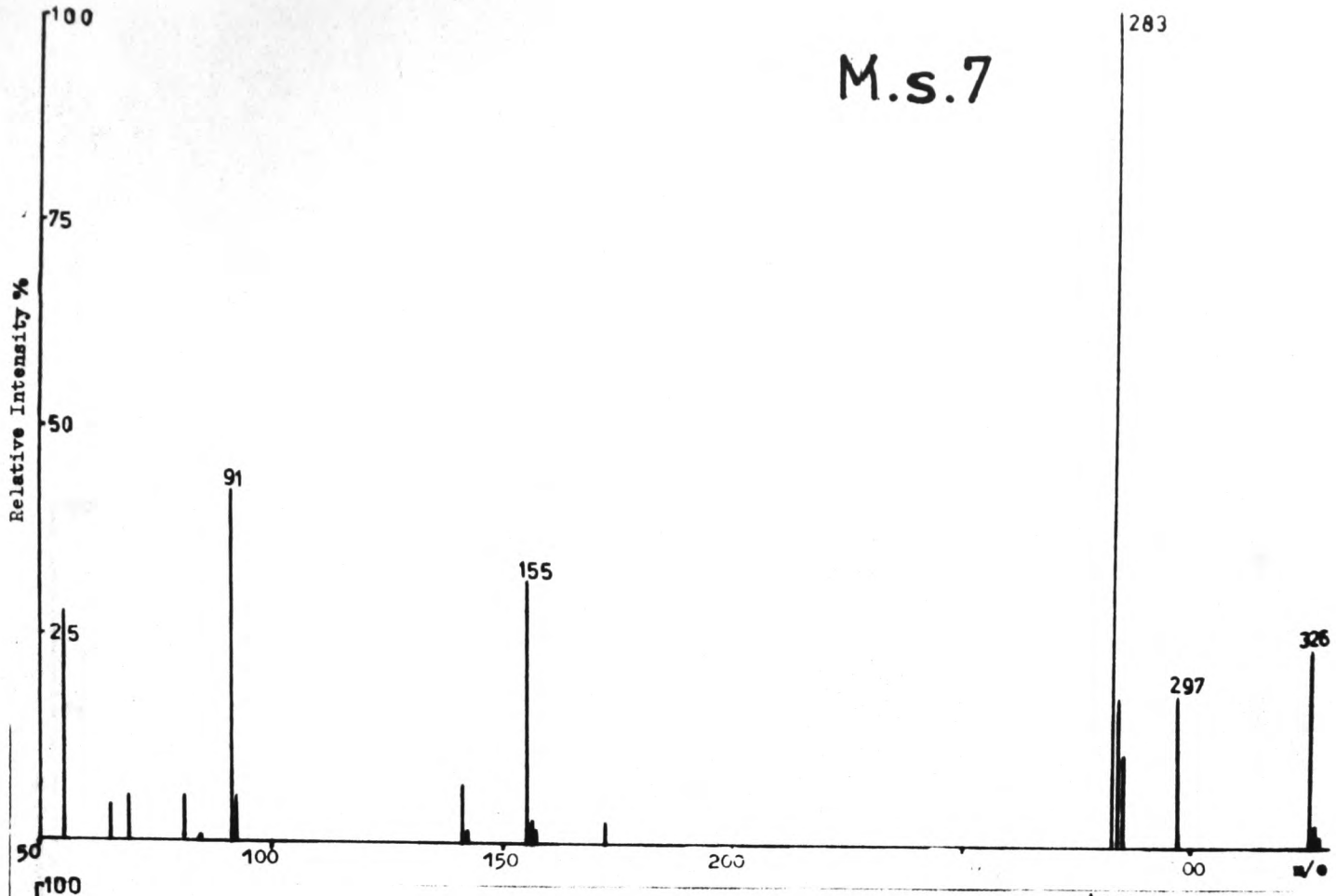

Relative Intensity %
100
75
50
25
50
100
150
200
m/e

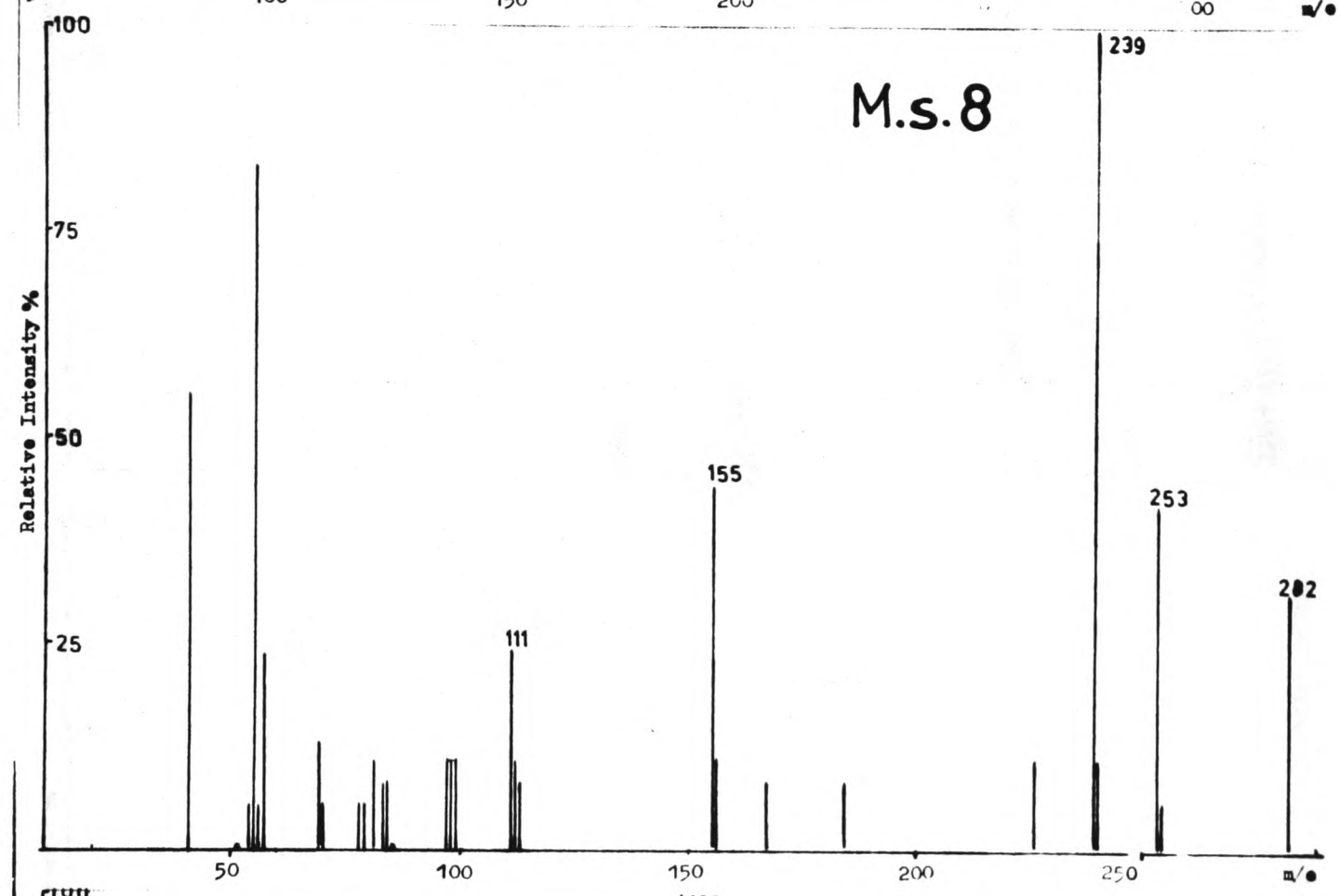
M.s.5

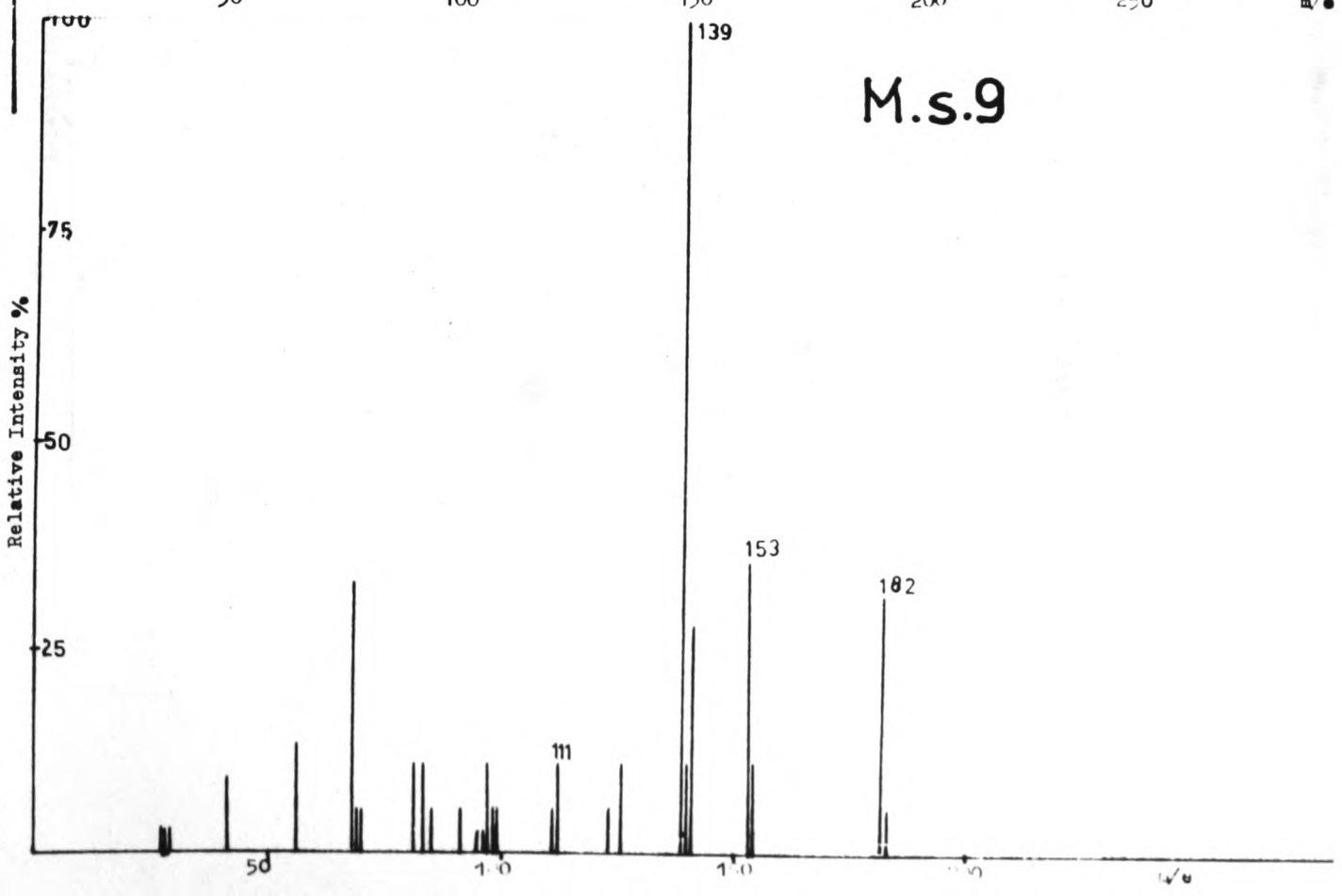

Relative Intensity %
75
50
25
41
55
101
115
127
143
170
198
228
50
100
150
200
m/e

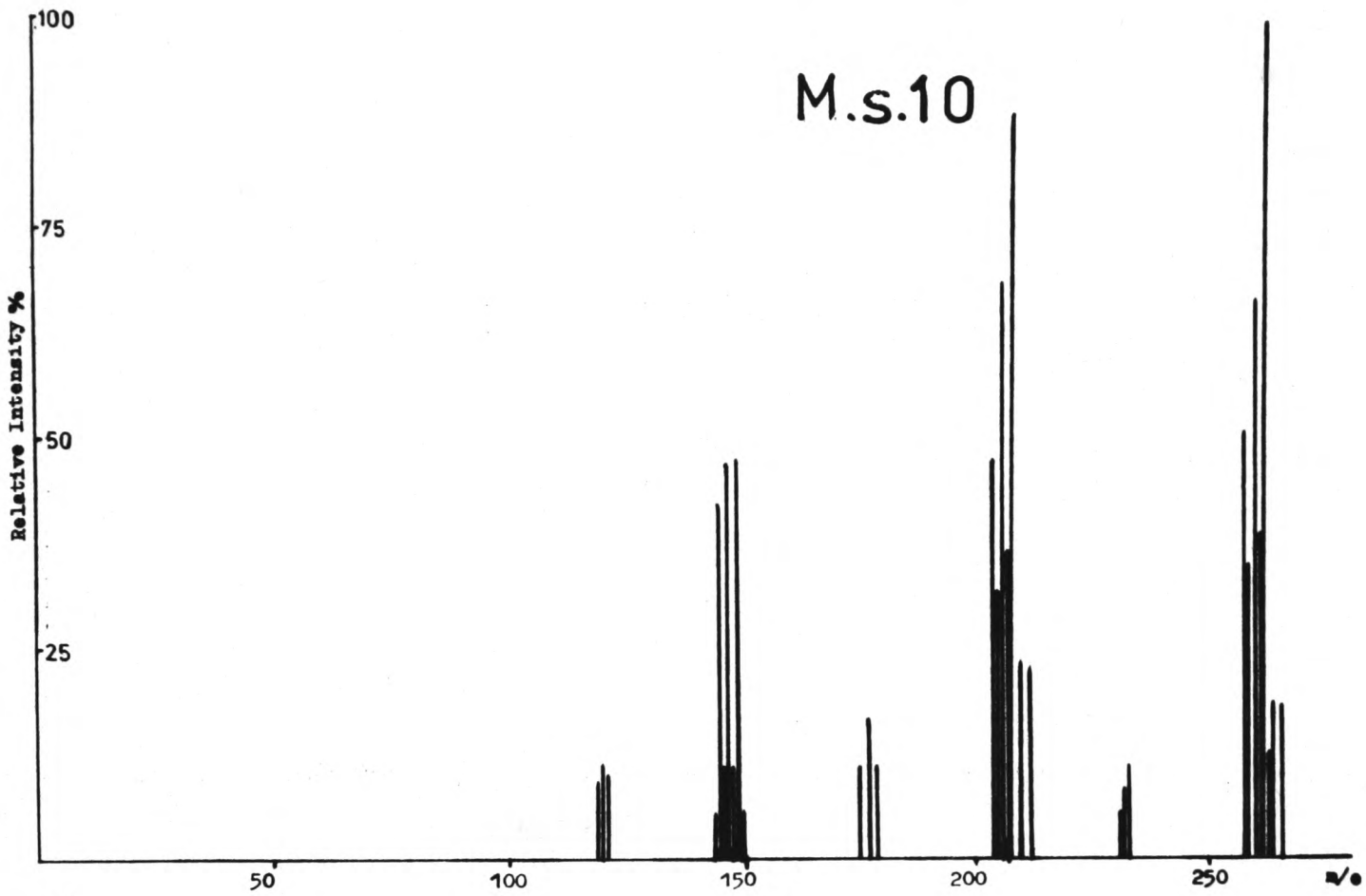
M.s.6

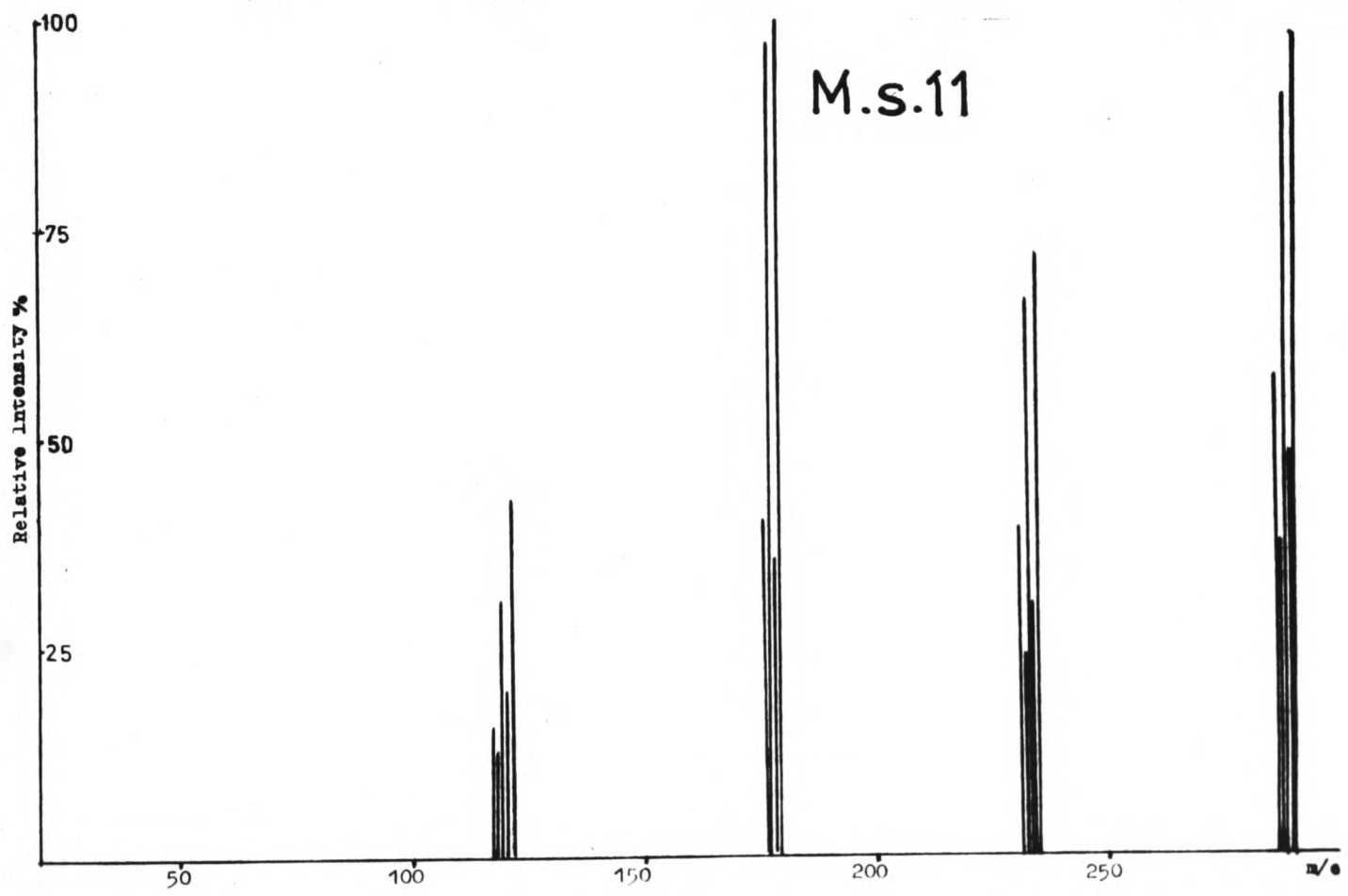

Relative Intensity %
75
50
25
85
101
155
157
183
50
100
150


M.s.7
Relative Intensity %
100
75
50
25
50
91
155
283
297
326
100
150
200
00
m/e


M.s.8
Relative Intensity %
100
75
50
25
111
155
239
253
282
50
100
150
200
250
m/e


M.s.9
Relative Intensity %
75
50
25
111
139
153
182
50
m/e


M.s.10
Relative Intensity %
100
75
50
25
50
100
150
200
250
m/e


M.s.11
Relative Intensity %
100
75
50
25
50
100
150
200
250
m/e

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