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REACTIONS OF α-NITROEPOXIDES

AND

SOME STUDIES IN THE 5-THIOGLYCOPYRANOSE SERIES

by

Chukwuemeka B. Madumelu

A thesis submitted to the School of Graduate Studies in partial fulfilment of the requirements for the degree of Ph.D. in Chemistry

UNIVERSITY OF OTTAWA
OTTAWA, CANADA, 1976

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TO MY WIFE AND PARENTS

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PREFACE

This thesis consists of two parts, both being in the domain of synthetic carbohydrate chemistry. Part I, which comprises the main body of research undertaken by the author, deals with chemical transformations in carbohydrate α-nitroepoxides. Part II, a relatively short study, describes some synthetic endeavours in the field of sugars that contain sulfur in the ring.

I gratefully acknowledge my indebtedness to Prof. Hans H. Baer for his guidance, encouragement, and patience throughout the course of this research work and preparation of this thesis.

I would like to thank Dr. J. Kovăr for his interest and helpful discussions, and more especially for guiding me in polarographic measurements.

My sincere appreciation also goes to a colleague, Mr. Fawzy Georges with whom I had a continuous flow of informative exchanges.

The last but not the least is my wife, to whom I owe immense gratitude for her patience, understanding and moral support.

This work was made possible by financial support from the research grants of Prof. Hans H. Baer.

ABSTRACT

Part I

Reactions of carbohydrate α-nitroepoxides with sodium borohydride, catalytically activated hydrogen, dimethylamine, nitromethane, and methylmagnesium iodide are described.

A new route leading to formation of 2-deoxy glycosides resulted from the reaction of 2,3-anhydro-3-nitro glycosides with sodium borohydride. Loss of the nitro function was a common feature. Thus, methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-β-D-allopyranoside (6) and -β-D-talopyranoside (9) reacted readily with sodium borohydride to give methyl 4,6-O-benzylidene-2-deoxy-β-D-arabino- (16) and β-D-lyxo-hexopyranosides (18), respectively. In the case of the epoxide 6, methyl 4,6-O-benzylidene-2-O-ethyl-β-D-mannopyranoside (17) was found as a minor product. Methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-α-D-talopyranoside (7), found to be less reactive towards sodium borohydride in comparison with its stereoisomers 6 and 9, furnished epimeric methyl 4,6-O-benzylidene-2-deoxy-α-D-xylo- (19) and -α-D-lyxo-hexopyranoside (20). The 2,3-anhydro sugar stereoisomers having the α-D-manno (5) and β-D-gulo (8) configuration were inert towards this reagent at room temperature (for steric

reasons) and decomposed upon heating. Also reactive towards sodium borohydride was 5,6-anhydro-1,2-isopropylidene-6-nitro-α-D-glucofuranose (15), which furnished 5-deoxy-1,2-isopropylidene-α-D-xylo-hexofuranose (21). In catalytic hydrogenations of the α-nitroepoxides, a controlling influence of the nitro group was manifest, leading regiospecifically to fission of the α-C-O bond. All the epoxides, including those inert towards borohydride, were cleaved by catalytically activated hydrogen.

Dimethylamine reacted with the 2,3-anhydro glycosides 5 and 6, as well as with 7 and 8, to give novel products (33 and 35, respectively) which arose by loss of the nitro and anomeric methoxyl functions. The products were derivatives of 1,2-unsaturated 3-uloses bearing a dimethylamino substituent at C-2 and carrying a second molecule of dimethylamine as an adduct to the 3-keto group. The 5,6-anhydro sugar 15 furnished with dimethylamine, in a similar reaction, a 5-dimethylamino derivative of a hexodialdo-1,4;6,3-difuranose.

All the 2,3-epoxides investigated were found to be unreactive towards nitromethane in the presence of base whereas the 5,6-anhydro sugar 15 reacted to give 5-deoxy-1,2-O-isopropylidene-5-C-nitromethylhexodialdo-1,4;6,3-difuranose (36).

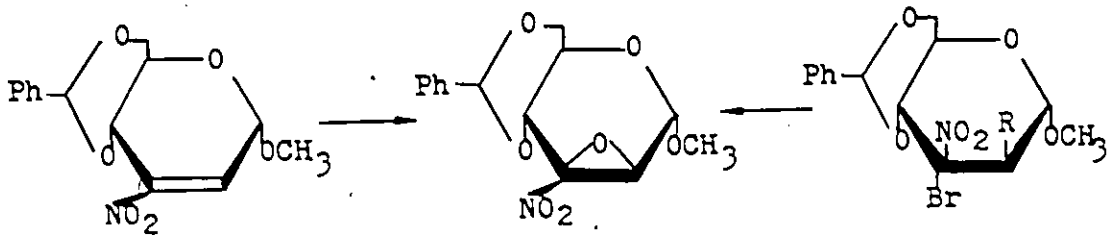
The epoxides 5 and 6 reacted with methylmagnesium iodide to give the 3-C-methyl-3-N-methylhydroxylamino derivatives 37 and 38, respectively. Similar reactions

with compounds 7 and 8 did not lead to identifiable products.

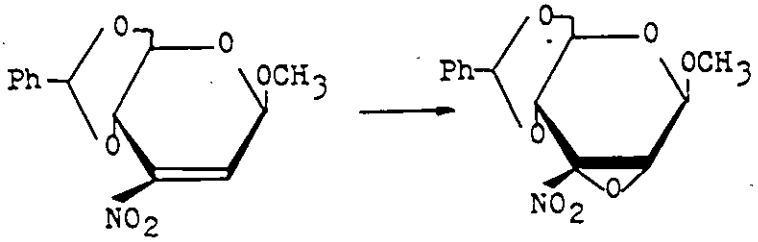
Part II

Glycosylation (methylation) of 1,2,3,4,6-penta-O-acetyl-5-thio-L-ido-hexopyranose (1) and the attempted nitromethane condensation of the oxidation product of the resulting methyl 5-thio-β-L-idopyranoside (6) are described.

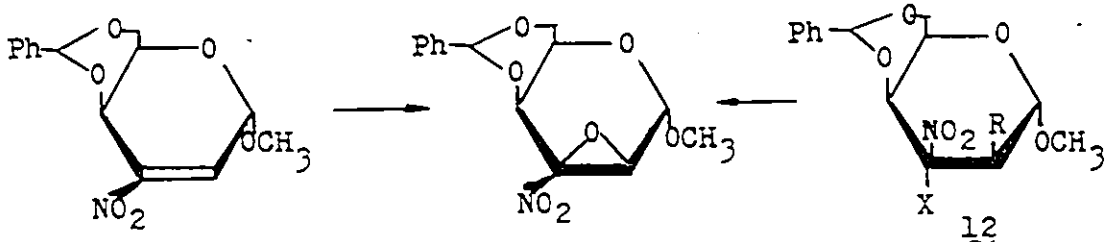
Scheme 1



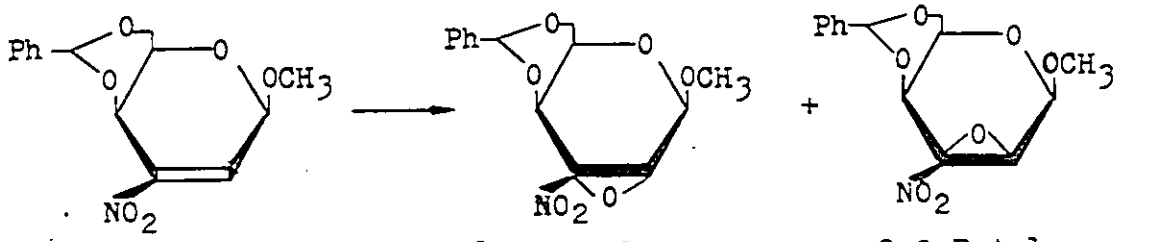
1 α-D-erythro 5 α-D-manno 11 R=OAc



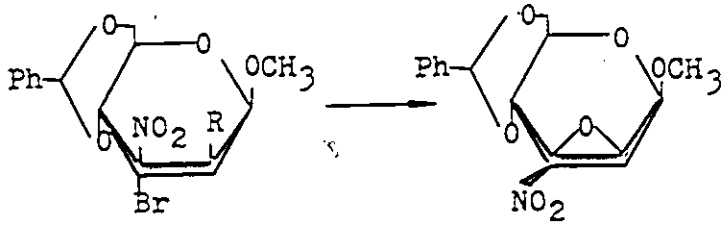
2 β-D-erythro 6 β-D-allo



3 α-D-threo 7 α-D-talo 12 X=Cl or Br; R=OH



4 β-D-threo 8 β-D-gulo (major product) 9 β-D-talo (minor product)



13 R=OAc 10 β-D-manno

PART I REACTIONS OF α-NITROEPOXIDES

INTRODUCTION

Recent History

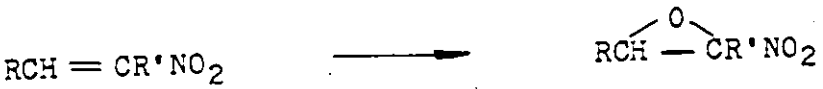
The α-nitroepoxy (α-nitrooxirane) grouping was first described, as a novel functionality in organic chemistry, by Newman and Angier[1,2] some six years ago. These investigators prepared α-nitroepoxides from nitroethylenes substituted by phenyl, methyl and cyclohexyl groups, and they studied some of the chemical transformations which may occur in this novel class of compounds. Independently and beginning about the same time, Baer and Rank[3-6] as well as Nakagawa and his co-workers[7] synthesized various carbohydrate derivatives that possess an α-nitroepoxide function although they did not report on the chemical behavior of their products. At the outset of the present research it could be anticipated on the basis of Newman and Angier's limited data[2] and from a general consideration of organic group reactivity, that α-nitroepoxide derivatives of sugars might undergo interesting reactions and prove to be versatile intermediates for synthesis in the carbohydrate field. It was therefore decided to explore some of the possibilities of chemical transformation offered by these sugar derivatives that had just become available.

As a background, the state of knowledge in the chemistry of α-nitroepoxides existing at the time of

commencement of this work will be reviewed in the following sections. Mention will also be made of some photochemical studies on non-carbohydrate nitro-epoxides published by Japanese authors[8] while this research was in progress. In the meantime, the group of Nakagawa[9] has also continued related investigations in carbohydrates; their preliminary communication disclosed results which complement ours and will be evaluated in the relevant sections of the Discussion.

Synthesis of α-nitroepoxides

α-Nitroepoxides were obtained[1,2] from substituted nitroethylenes (R = phenyl or cyclohexyl, R' = phenyl or methyl) in yields of 67-91% by the action of alkaline, 15% hydrogen peroxide at 0°, employing methanol as the solvent.



In the carbohydrate series, various methyl 4,6-O-benzylidene-3-deoxy-3-nitro-hex-2-enopyranosides[4,5] afforded 2,3-anhydro derivatives by the action of 30% aqueous hydrogen peroxide, employed in excess ethanol as the solvent and in the presence of a small amount of

base (pH 8-9). Reaction times were 0.5-1.5h at room temperature and yields ranged from 75-89%. The unsaturated nitroglycosides having the α-D-*erythro* (1), β-D-*erythro* (2) and α-D-*threo* (3) configurations furnished single epoxide stereoisomers having the α-D-*manno* (5), β-D-*allo* (6) and α-D-*talo* (7) configurations, respectively. Stereoselectivity was less pronounced in the β-D-*threo* olefin (4) which gave a 5 : 1 mixture of the β-D-*gulo* (8) and β-D-*talo* (9) epoxides. In any event, epoxidation occurs preferentially from the side of the ring opposite to the glycosidic methoxyl group (Scheme I).

A second approach to 2,3-anhydro-3-nitro sugars of the type just mentioned departs from saturated 3-nitro sugars, which can readily be converted into geminal 3-halo-3-nitro derivatives by the action of sodium hypochlorite, sodium hypobromite, or *N*-bromoacetamide[6]. Provided these halonitro derivatives possess an antiperiplanar orientation of the halogen atom and the hydroxyl (or acetoxyl*) group at the neighbouring C-2, facile conversion into α-nitroepoxides is brought about by base. Using the halogen derivatives 11, 12 and 13, respectively, this approach made compounds 5 and 7 available in an alternative way and also furnished the

---

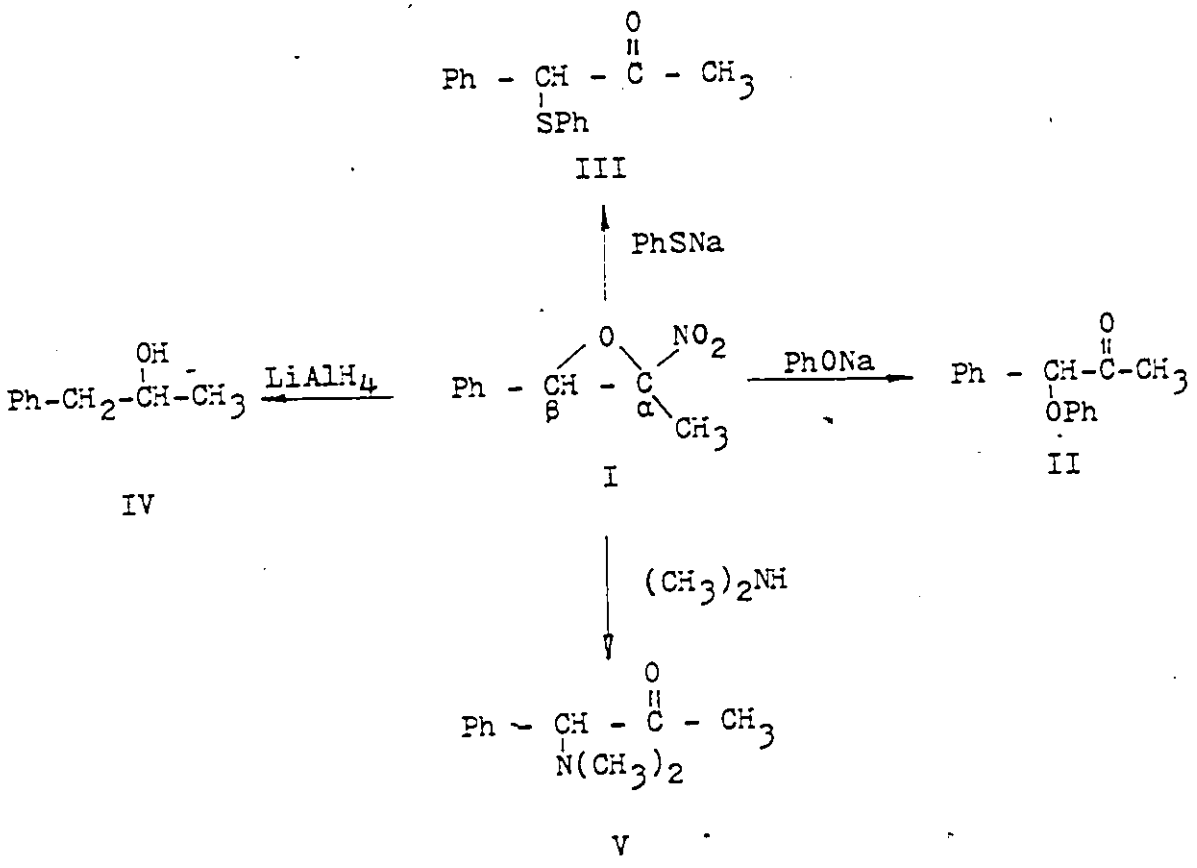
* 2-*O*-Acetyl derivative may be used, in which case saponification occurs in the process.

β-D-manno isomer (10). (Scheme 1).

Reactions of α-nitroepoxides

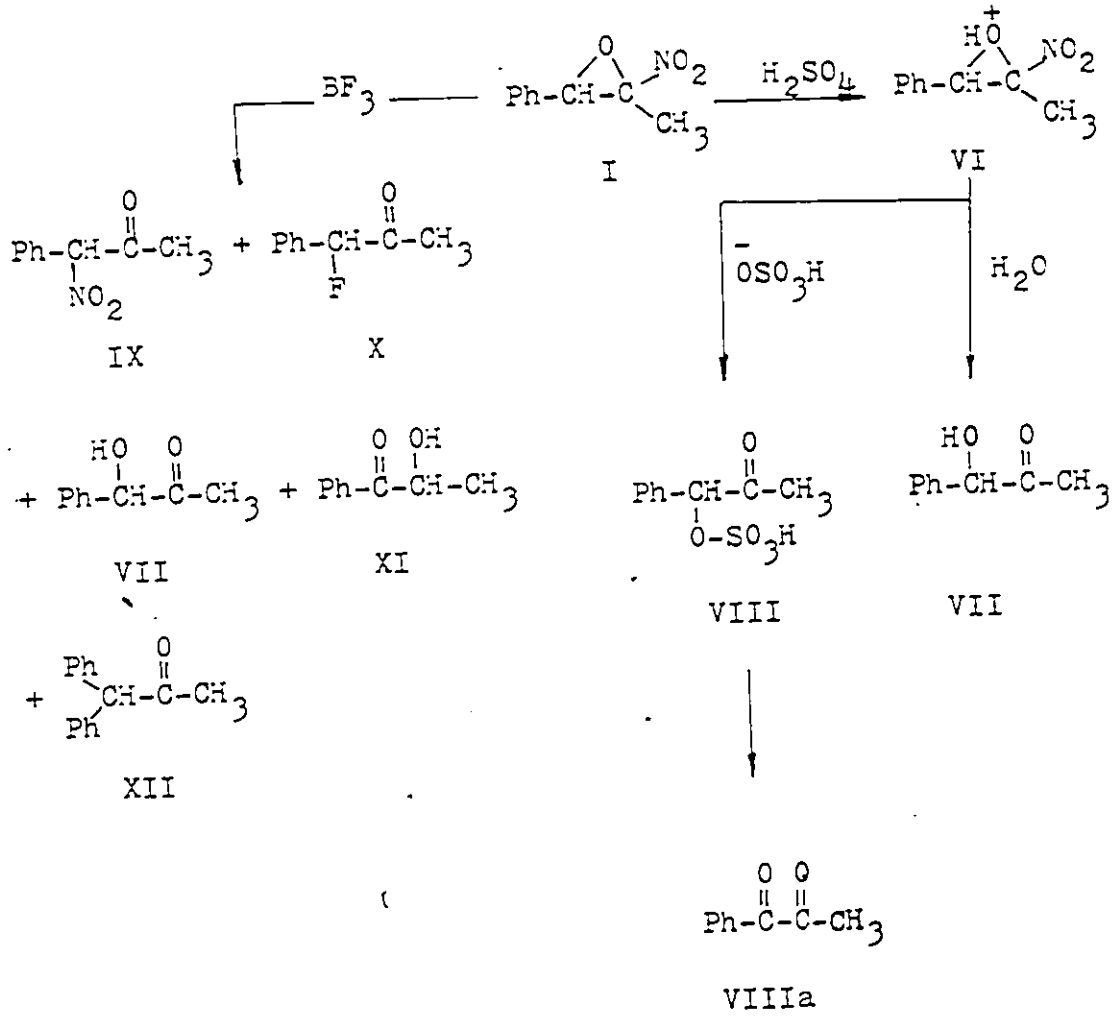
A brief description of reactions carried out by Newman and Angier[2] and Saito and co-workers[8] on some α-nitroepoxides is given in the paragraphs that follow. Roman numerals will be used for this review while Arabic numerals will be reserved for the carbohydrate derivatives.

Action of nucleophiles: The nucleophiles engaged for the investigation included sodium phenoxide, sodium thiophenolate, dimethylamine, and lithium aluminum hydride. The reactions of the nitroepoxide I to give the products II-V are shown:



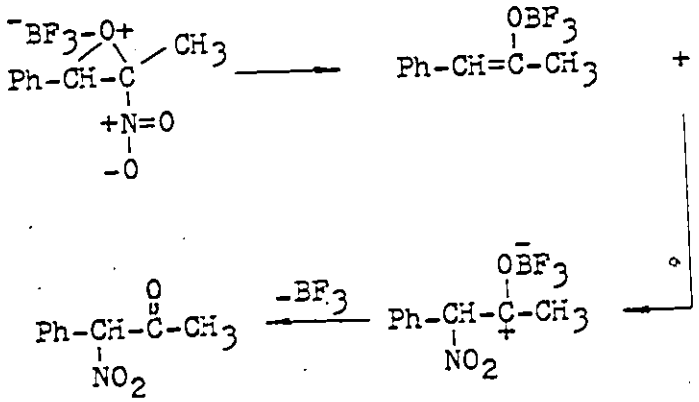
They proceeded by a common path involving S_N2 attack by a given nucleophile from the rear of the oxirane ring, at the carbon atom in β position to the nitro group, leading to loss of nitrite ion. In the case of lithium aluminum hydride, the intermediate ketone was reduced further to the alcohol in the presence of excess reagent.

Action of acids:



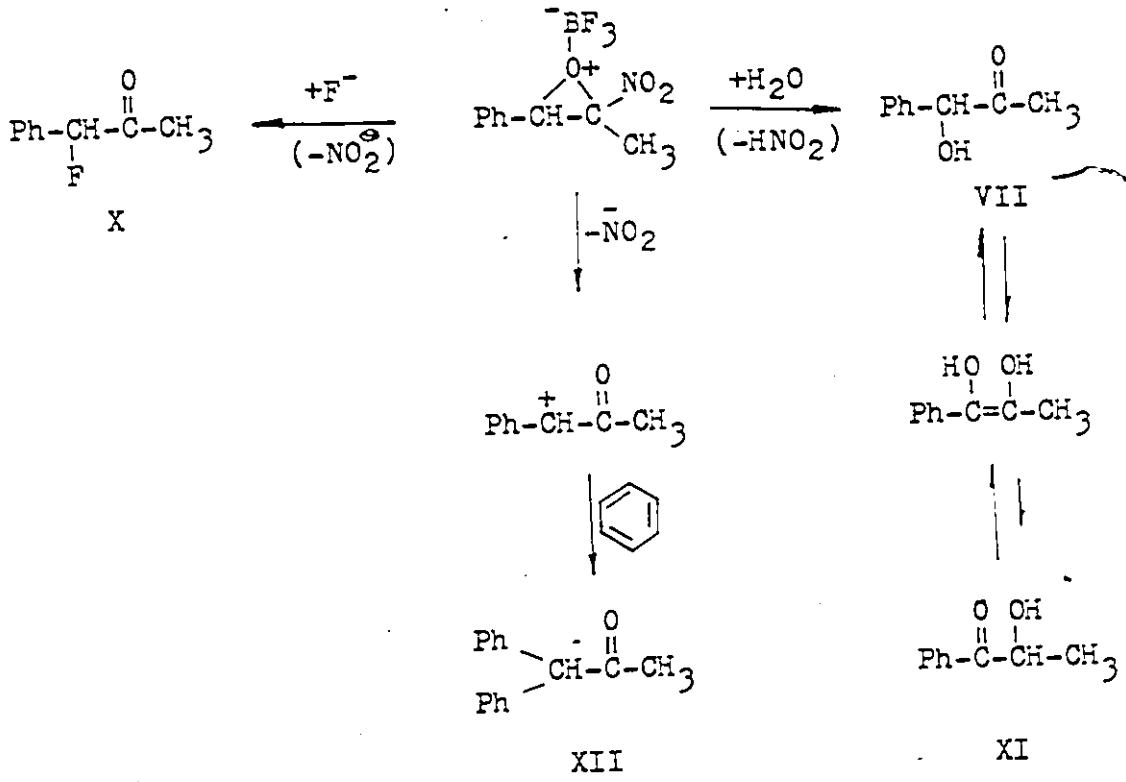
Action of dilute aqueous sulfuric acid on I led to the expected 1-phenyl-1-hydroxyacetone VII along with a small amount of its oxidation product, the diketone VIIIa (ratio 3:1). Mechanistically, this reaction does not differ much from the reaction with nucleophiles described above. Here, protonation of the oxirane oxygen to furnish the intermediate ion VI is followed by nucleophilic opening of the ring by water, leading to the hydroxyketone VII upon denitration. The diketone VIIIa could originate by a ß-elimination in compound VIII which could have arisen by nucleophilic opening of the protonated epoxide VI by hydrogen sulfate anion.

A more complex reaction was encountered with boron trifluoride etherate in dry benzene. The formation of compound IX was particularly interesting and has been suggested[2] to come about by recombination of enol and nitronium ion, formed as a result of Lewis acid-catalyzed decomposition of the α-nitroepoxide, as shown below:

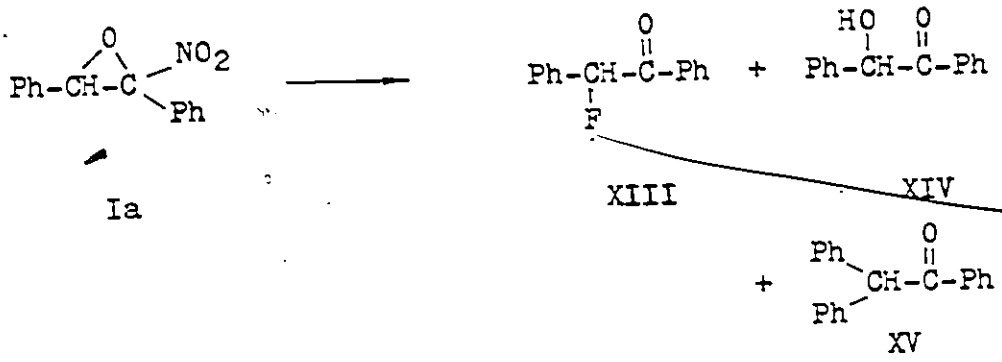


IX

Other components of the mixture can be rationalized to arise from nucleophilic attack by fluoride ion (compd. X); water during work-up (compounds VII and XI); or from electrophilic attack on the benzene solvent (compound XII). In the case of water as the nucleophile, the initially formed major product VII underwent tautomerization in order to give compound XI.



When the starting material was the epoxide Ia, in which the methyl group of the epoxide I is replaced by a phenyl group, compounds XIII, XIV and XV were the only products.



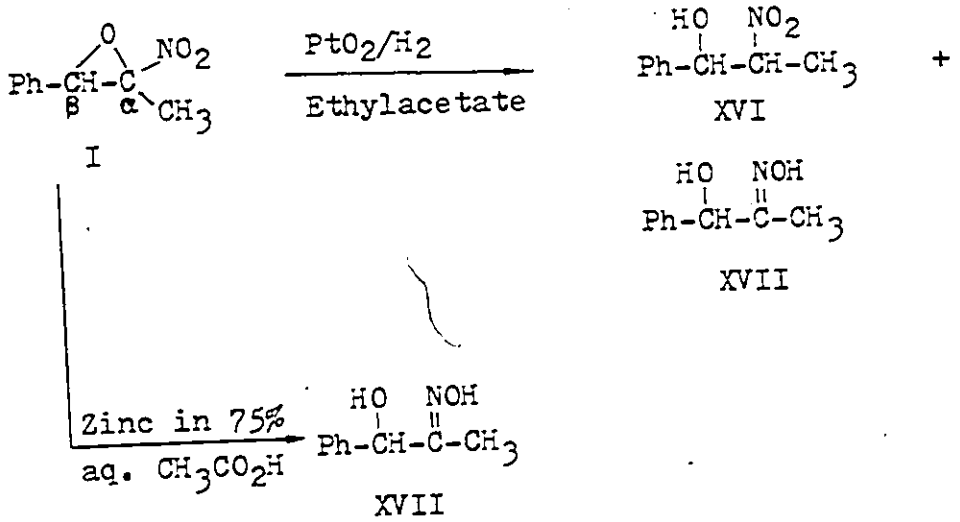
Ia

XIII

XIV

XV

Action of reducing agents:



I

XVI

XVII

XVII

Catalytic hydrogenation of I with platinum dioxide in ethylacetate under pressure for 15min led to cleavage

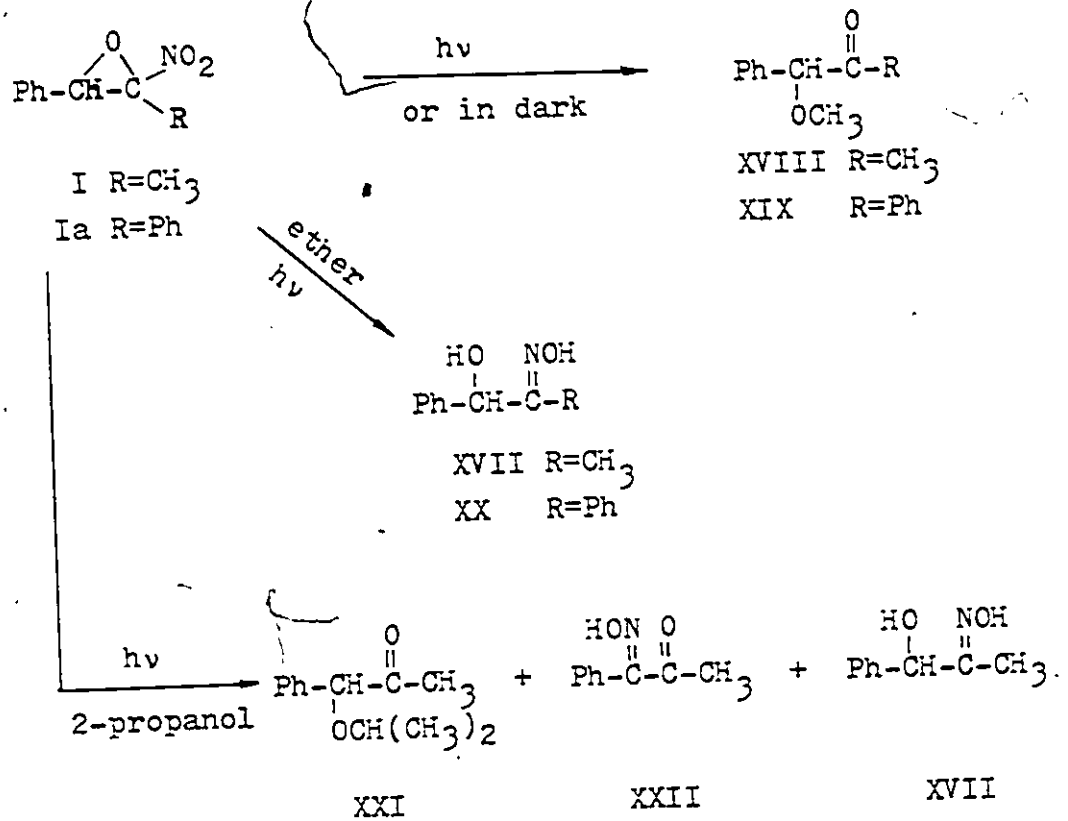
of the α-C-O bond, furnishing as a primary product the nitro alcohol XVI, a large part of which was reduced further to give the oxime XVII. A major difference, in comparison with the nucleophilic reactions treated earlier, is the mode of oxirane ring cleavage. Whereas nucleophiles attack the β-C-O bond with ultimate expulsion of the nitro function, catalytic hydrogenation gives preferential α-C-O bond cleavage with retention of the nitrogenous function. A similar behaviour was observed when zinc dust in 75% aqueous acetic acid was employed as the reducing agent, which gave the oxime XVII as the exclusive product.

Photochemical reactions:

Japanese workers[8] investigated photochemical reactions of (1,2-epoxy-2-nitropropyl)benzene (I) and "α,α'-epoxy-α-nitrobibenzyl" (Ia).* A marked solvent dependence was observed. Reaction of I with methanol, which occurred slowly in the dark, was accelerated by irradiation and gave the methoxy ketone XVIII. In 2-propanol, no reaction took place in the dark, but irradiation gave the isopropoxy ketone XXI together with the oximes XXII and XVII. In pure ether, XVII was the exclusive product while mixtures of the two solvents led to the formation of varying proportions of all three products. Compound Ia reacted readily, in the absence of light, with methanol to give benzoin methyl ether (XIX) whereas irradiation in ether

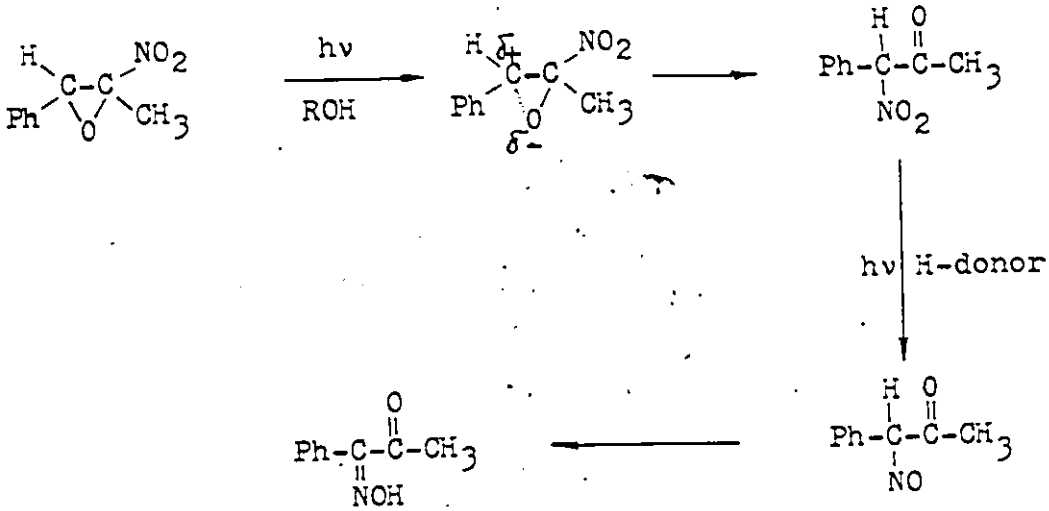
*properly named 1-nitro-1,2-diphenyloxirane

produced a complex mixture from which, however, benzoin oxime (XX) could be isolated. In 2-propanol, Ia also gave a complex mixture and no individual products could be identified. When t-butyl alcohol, acetone, benzene, or n-hexane were used as media, little or no reaction took place with both I and Ia.



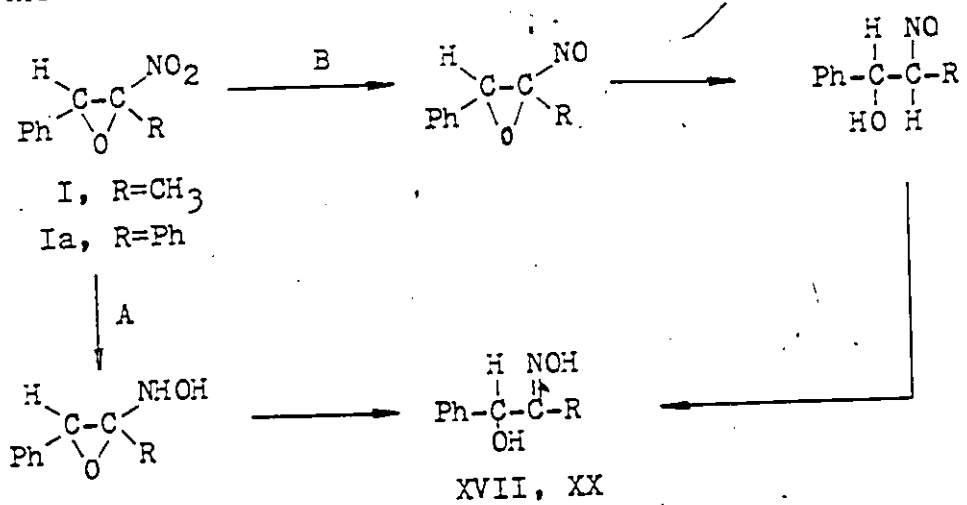
The authors explain the formation of alkoxyketones (XVIII, XIX, XXI) in terms of epoxide ring opening by attack of the alcohol, with subsequent elimination of nitrous acid, by analogy to the nucleophilic reactions mentioned in a

preceding section. It appears reasonable that the efficiency of the reaction should decrease in the order methanol > 2-propanol > t-butyl alcohol. As regards the formation of the oxime XXII, they believe that the nitro epoxide undergoes a 1,2-shift of the nitro group to give a nitro ketone which is then photoreduced, with the solvent serving as the hydrogen donor:



XXII

Two possible pathways were considered for the formation of the oximes XVII and XX:



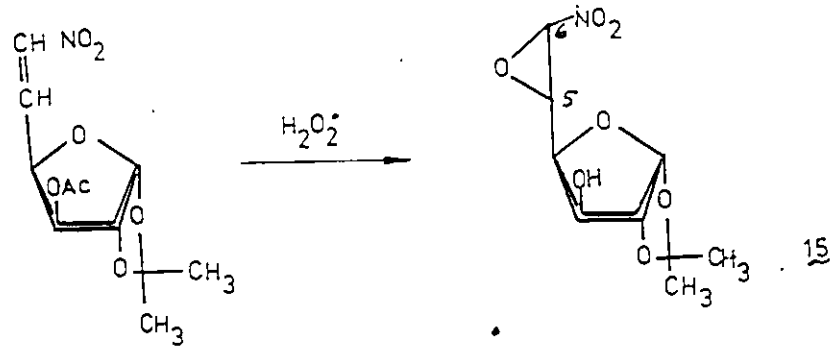
I, $R=CH_3$
Ia, $R=Ph$

XVII, XX

Both pathways involve initial photoreduction of the nitro group leading to a hydroxylamino epoxide (path A) and a nitroso epoxide (path B), respectively. The former will be tautomerized, and the latter first photoreduced further and then tautomerized, to give the observed products.

RESULTS AND DISCUSSION

It was decided to investigate reactions of carbohydrate α-nitroepoxides with sodium borohydride, catalytically activated hydrogen, dimethylamine, nitromethane, and a Grignard reagent. The substrates to be used in these studies were the five stereoisomeric methyl 2,3-anhydro-4,6-O-benzylidene-3-nitrohexopyranosides 5 - 9, which were prepared as described by Baer and Rank[4,5]. In addition, a new epoxide was synthesized for inclusion in the planned series of experiments. It differs structurally from the 2,3-anhydro derivatives just mentioned in that it possesses a terminal α-nitrooxirane grouping: 5,6-anhydro-1,2-isopropylidene-6-nitro-α-D-glucofuranose (15), obtained in 64% yield by alkaline epoxidation of the known[10] nitro-olefinic sugar derivative (14), 3-O-acetyl-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-xylo-hex-5-enofuranose. The configuration of the new chiral centre C-5 in 15 was revealed by chemical evidence as will be shown in a subsequent paragraph, but that at C-6 has not been established.



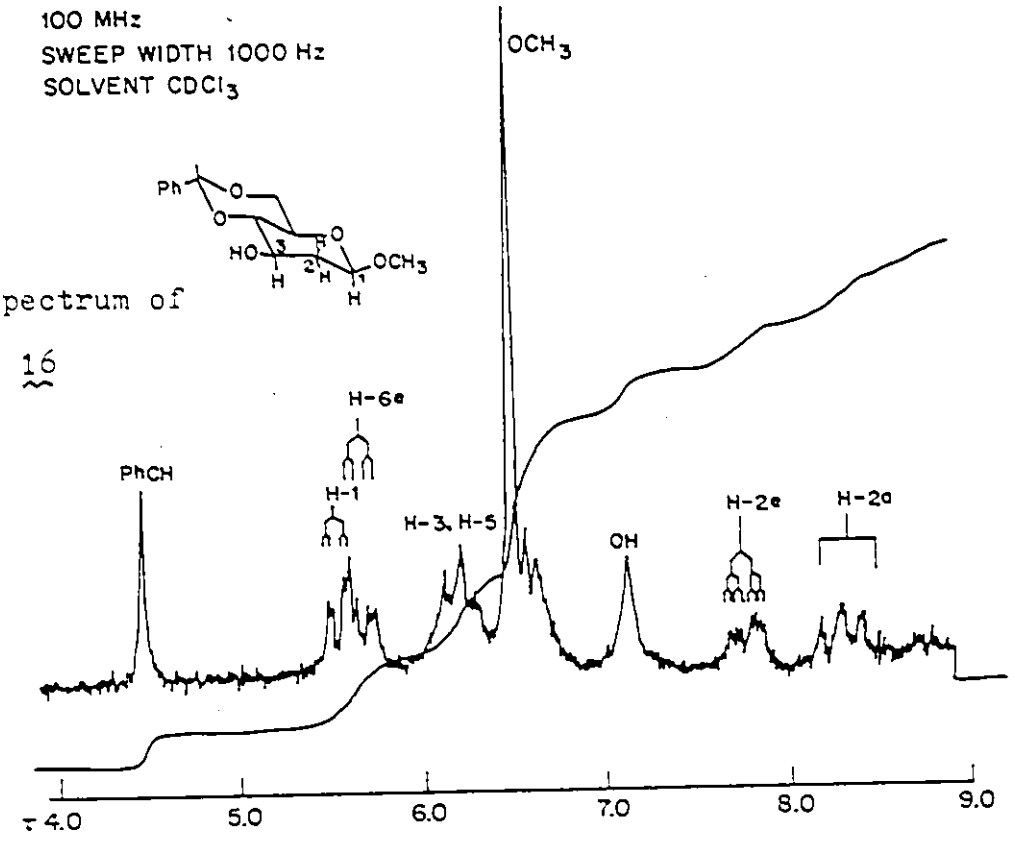
14 15

1. Reduction with Sodium Borohydride

It was found that three of the 2,3-anhydro sugars examined as well as the 5,6-anhydro derivative reacted smoothly with sodium borohydride in ethanolic solution to give high yields of products resulting from reductive denitration, whereas two of the 2,3-anhydro compounds proved unreactive under the same conditions.

Thus, the β-D-allo epoxide 6 reacted completely (according to thin layer chromatography) within 90min at room temperature. Two new crystalline products were isolated in yields of 60 and 20%, respectively. Both were free from nitrogen. The main product proved to be methyl 4,6-O-benzylidene-2-deoxy-β-D-arabino-hexopyranoside (16). Its n.m.r. spectrum (Fig 1a) showed a one-proton octet for each of the C-2 methylene protons, at τ 7.80 (H-2e) and 8.37 (H-2a), and although the signal for H-3 was not resolved from other signals in the τ 6.0-6.8 region, the configuration at C-3 was indicated by the splitting pattern of these octets. Thus, the H-2a octet contained large splittings only (8-10 Hz), requiring an axial H-3, whereas the H-2e octet as expected showed two small splittings (2 and 4 Hz) due to vicinal coupling. The geminal coupling $J_{2a,2e}$ was 10 Hz. The structure of 16 was firmly established by acid hydrolysis giving 2-deoxy-D-arabino-hexose, identified as its known[11] crystalline

a. N.m.r. spectrum of compound 16



b. N.m.r. spectrum of compound 17

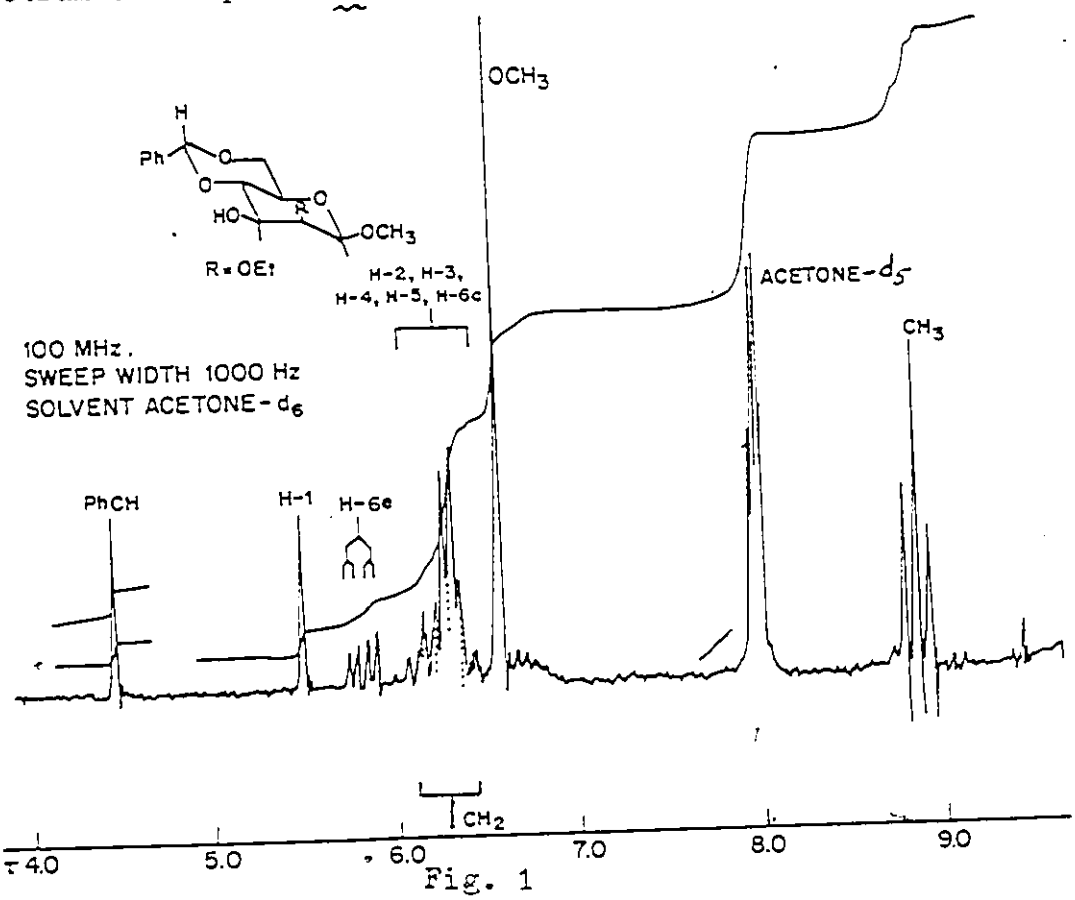
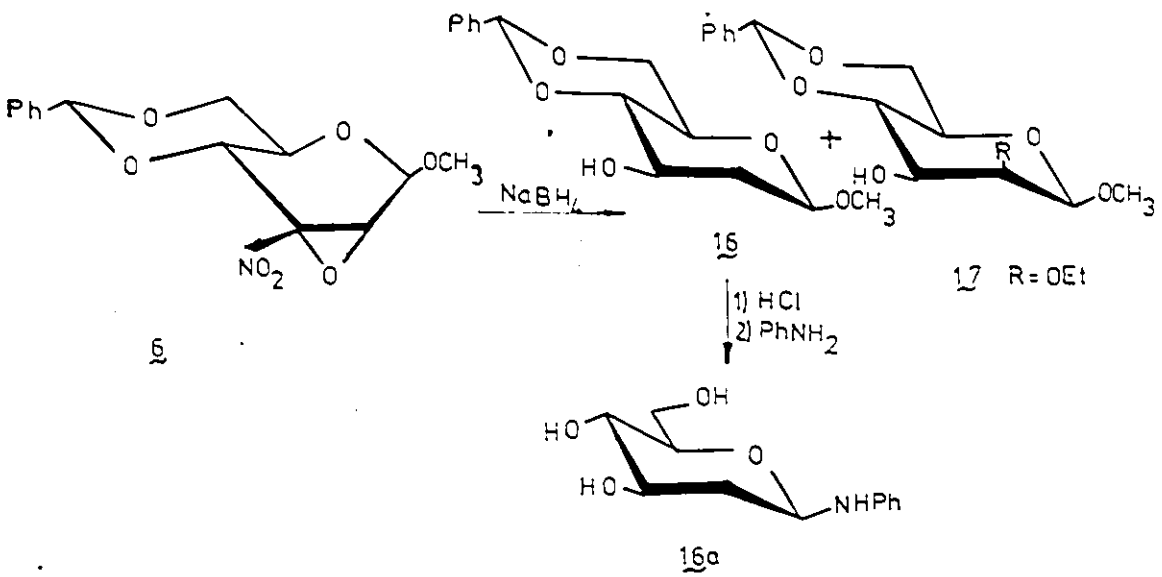


Fig. 1

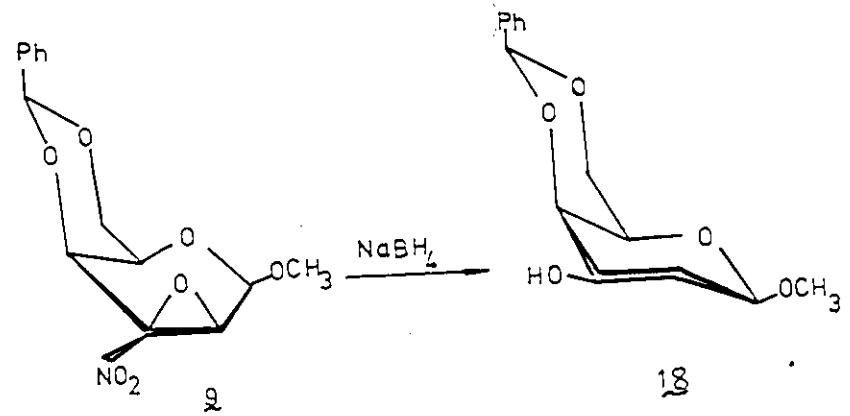
β-anilide 16a.



The minor product isolated from the borohydride reaction of 6 was revealed by its n.m.r. spectrum (Fig 1b) and microanalysis to contain an O-ethyl group but no deoxy function (methylene group). There was a 3-proton triplet at τ 8.86 and 2-proton quartet at τ 6.26, with 6Hz splittings, which indicated this substituent. The anomeric proton gave an apparent singlet ($J_{1,2}$ = 0Hz, at τ 5.48), on account of which an equatorial H-2 had to be postulated. Therefore the product was assigned the structure of methyl 4,6-O-benzylidene-2-O-ethyl-β-D-mannopyranoside (17).

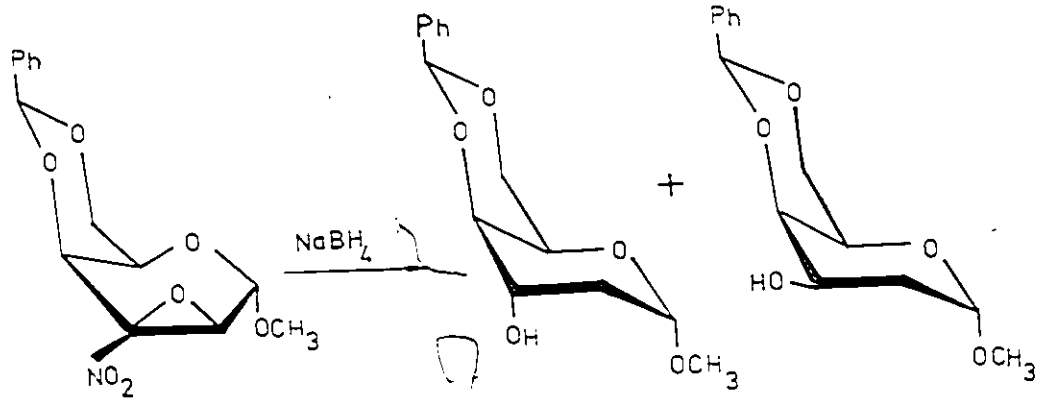
Japanese workers[9] have carried out a similar reductive denitration of 6 using lithium aluminum hydride in tetrahydrofuran (2h at room temperature). They obtained the 2-deoxy glycoside 16 in non-crystalline form and characterized it as a crystalline 3-O-acetyl derivative.

Reduction of the β-D-talo epoxide 9 by sodium borohydride was complete after 30min at room temperature. Crystalline methyl 4,6-O-benzylidene-2-deoxy-β-D-lyxo-hexopyranoside (18) was isolated in 76% yield as the only reaction product. Microanalysis and n.m.r. spectrum were in accord with the structure. The configurational assignment was based on the splitting pattern of the H-3 signal which occurred as an octet at τ 6.21. The signal contained, in addition to small splittings attributable to vicinal couplings with equatorial H-4 and H-2 protons, a large splitting (12 Hz) which required H-3 to be axial and coupled with the axial H-2 proton. The signals for H-1 (a quartet with $J_{1,2a}$ = 12 and $J_{1,2e}$ = 2 Hz) and H-4 (a triplet with $J_{3,4} = J_{4,5}$ =3 Hz) were also readily discernible and in agreement with formula 18.



9 18

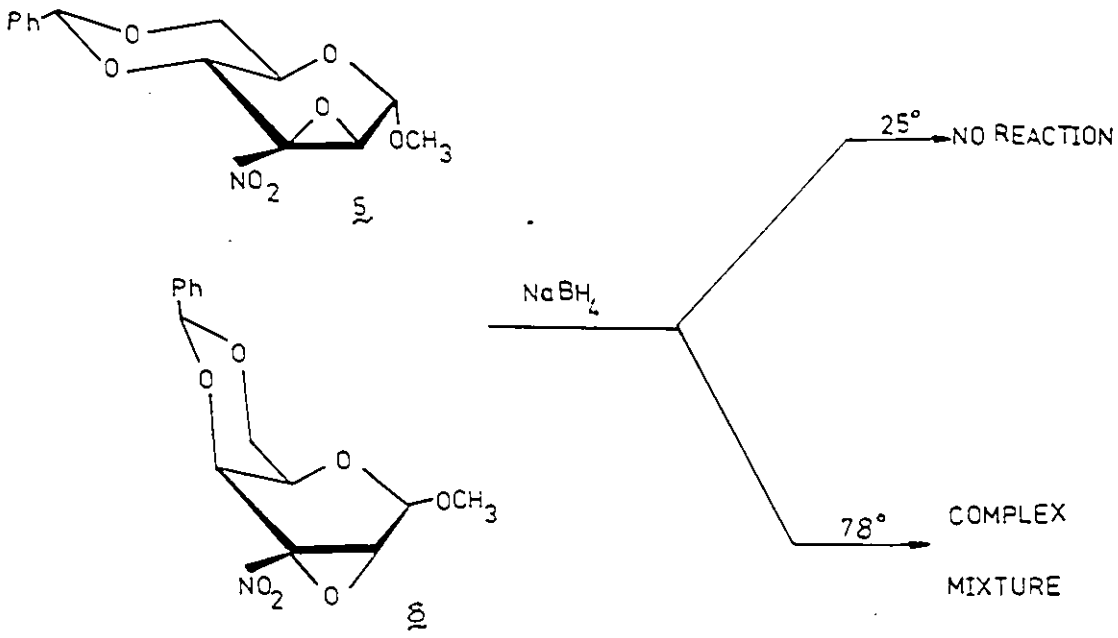
Contrasting with the high reactivity of the epoxides 6 and 9, their α-D-talo stereoisomer 7 did not seem to react under the same mild conditions. However, upon heating of the ethanolic solution to reflux for 50min in the presence of an increased proportion of sodium borohydride, complete consumption of the epoxide and formation of two products was observed. The products were obtained in yields of 40 and 50% and proved on the basis of analysis, n.m.r. spectra and physical constants to be known 2-deoxy glycosides epimeric at C-3, i.e., methyl 4,6-O-benzylidene-2-deoxy-α-D-xylo- hexopyranoside (19)[12] and methyl 4,6-O-benzylidene-2-deoxy-α-D-lyxo-hexopyranoside (20)[13].



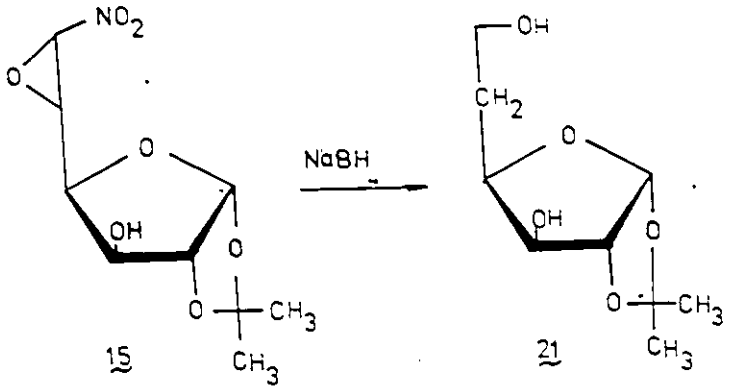
7 19 20

The 2,3-anhydro sugar stereoisomers having the α-D-manno (5) and β-D-gulo (8) configurations were totally

inert towards sodium borohydride at room temperature, even when exposed to the reagent for up to 48 hours. They reacted at reflux temperature but gave complex mixtures of products which could not be unravelled. Attempted reductions with lithium aluminum hydride in ether at ambient temperature failed likewise to give identifiable products.



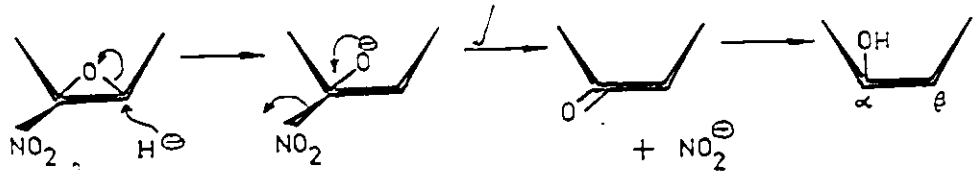
On the other hand, the compound 15 with its terminal nitrooxirane structure was readily reduced within 15 min at room temperature. According to t.l.c., a single product was formed, and this was isolated in crystalline condition in 60% yield and recognized as the known[14] 5-deoxy-1,2-O-isopropylidene-α-D-xylo-hexofuranose (21).



15 21

Mechanistic and stereochemical considerations

The results of the borohydride reactions just described are in line with those obtained with lithium aluminum hydride[2,9]. The α-nitroepoxides are converted into products bearing a hydroxyl group in α- and a deoxy function in β-position. It is assumed that hydride ion attacks the β-carbon atom from the rear of the oxirane ring which results in opening of the ring and formation of a carbonyl group in α-position with concomitant expulsion of a nitrite ion. The carbonyl group so engendered is immediately reduced by excess reagent to give a carbinol.

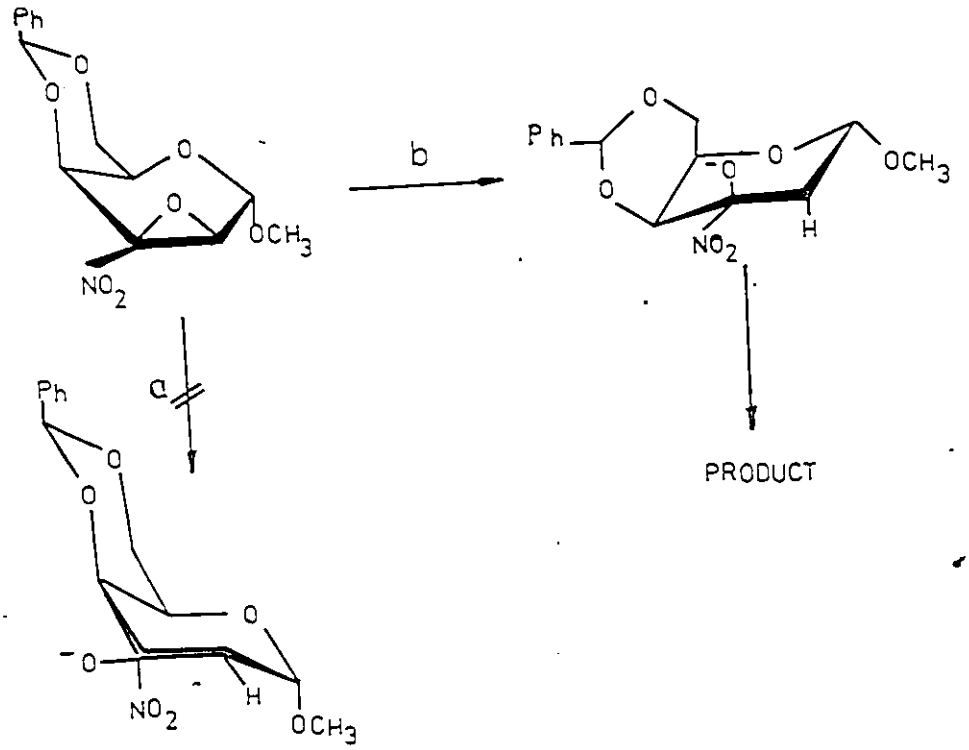


In the case of the epoxide 6, where the 2-O-ethyl derivative 17 was a by-product, it is likely that ethoxide ion from the solvent entered into competition with hydride ion in the ring opening step. The manno- configuration of 17 is in accord with this mechanism.

The strongly electronegative nitro group evidently governs the regioselectivity of nucleophilic attack on the epoxide ring so that the β-carbon appears to be the favoured venue. This effect may reverse the regioselectivity from what would be predicted in the absence of this group.* Thus, where an epoxide ring occupies a terminal position in a chain (as in 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose, the non-nitro analog of 15), almost exclusive nucleophilic attack takes place at the terminal carbon atom [15], whereas 15 was attacked at the penultimate C-5. When an epoxide ring is 2,3-fused to a pyranoside ring which in turn bears a cyclic 4,6-acetal and is thereby rendered conformationally rigid (trans-fused acetals) or at least less flexible (cis-fused acetals), then a nucleophilic reagent gives predominantly one product, namely that which arises from diaxial ring opening (Fürst - Plattner rule)[16]. That is to say, in hydride reductions of non-nitro analogs of 5 - 9 the hydride ion enters axially at C-2 when the epoxy ring is below the pyranose plane, but at C-3 when it is above[16].

*A steric effect of the nitro group may also be operative.

Now in those nitro derivatives which did give identifiable products (6, 7 and 9), attack occurred exclusively at C-2 regardless of the orientation of the epoxide ring. The Fürst-Plattner rule does not appear to hold. This does not necessarily mean that in those cases where the rule is seemingly violated (7 and 9), the ring opening occurs di-equatorially (path a in the accompanying scheme). It may well occur diaxially (path b) through a transition state involving chair inversion. Such inversion, not normally favoured in 4,6-O-benzylidene pyranosides, is possible in the somewhat more flexible cis-fused acetals and may perhaps become operative when reaction at C-3 in the favoured conformation is blocked by electronic reasons.



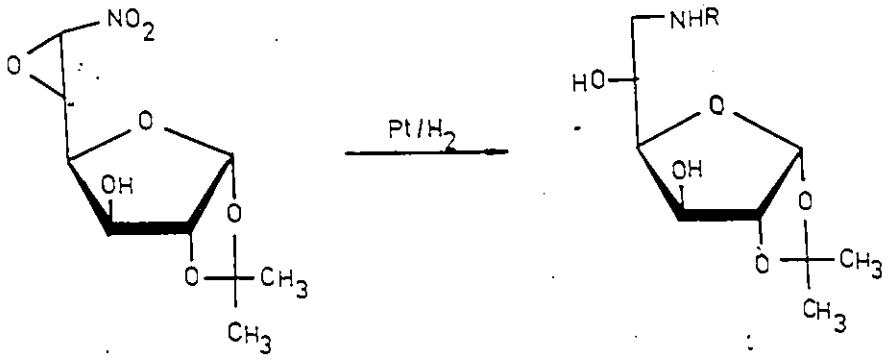
The observation that conformationally rigid, trans-fused benzylidene epoxide 5 was inert towards borohydride could be taken to support the above argument. There remain the questions as to why the reaction of 9 was more facile than that of 7, and why 8 was inert even though it does not require conformational inversion for diaxial ring opening according to these considerations.

It may be suggested that relative facility of approach of the nucleophile is a factor in these reactions. Thus, backside approach at C-2 is unhindered in structures 6 and 9. In compounds 5 and 7, it likely is interfered with by the neighbouring pseudoaxial methoxyl group, which could contribute to their diminished reactivity. Incidentally, it is interesting to note that when 7 did react under forcing conditions, there was practically no stereoselectivity as far as reduction of the intermediary oxo sugar is concerned. Comparable amounts of the two C-3 epimers (19 and 20) were produced whereas single C-3 epimers — those having an equatorial hydroxyl group — arose from 6 and 9. Regarding the lack of reactivity in 8 one is compelled to attribute it to the only feature distinguishing this compound from its reactive isomer 6, namely, the axially oriented oxygen at C-4. Conceivably, this condition is unfavourable for parallel approach of the nucleophile to C-2.

2. Catalytic Hydrogenation

Judging from the work of Newman and Angier[2], an essential difference between hydride reduction of α-nitroepoxides and their reduction by catalytically activated hydrogen is the mode of fission of the oxirane ring. Catalytic hydrogenation causes homolytic cleavage of the bond between the epoxy oxygen and the α-carbon to give, initially, α-nitro-β-hydroxy compounds. The latter may be obtained as such or suffer further reduction of the nitro group but, in any event, a nitrogenous function is retained in contrast to what is observed in hydride reactions (see p 20). It was therefore interesting to examine how the various carbohydrate nitroepoxides would behave in catalytic hydrogenation and whether, in the available stereoisomers, configurational effects might be discerned.

The 5,6-anhydrohexofuranose derivative 15 was hydrogenated in the presence of platinum catalyst in ethanol at ambient temperature and pressure. In line with the above generalization and with experience showing that platinum tends to catalyze reduction of nitro groups to the amine stage[17], an amino alcohol was obtained. The crystalline product was established to be 6-amino-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (22) by conversion into its known[18] N-acetyl derivative (22a). This proved the D-gluco configuration of 15 which had not previously been ascertained.



15

22 R=H

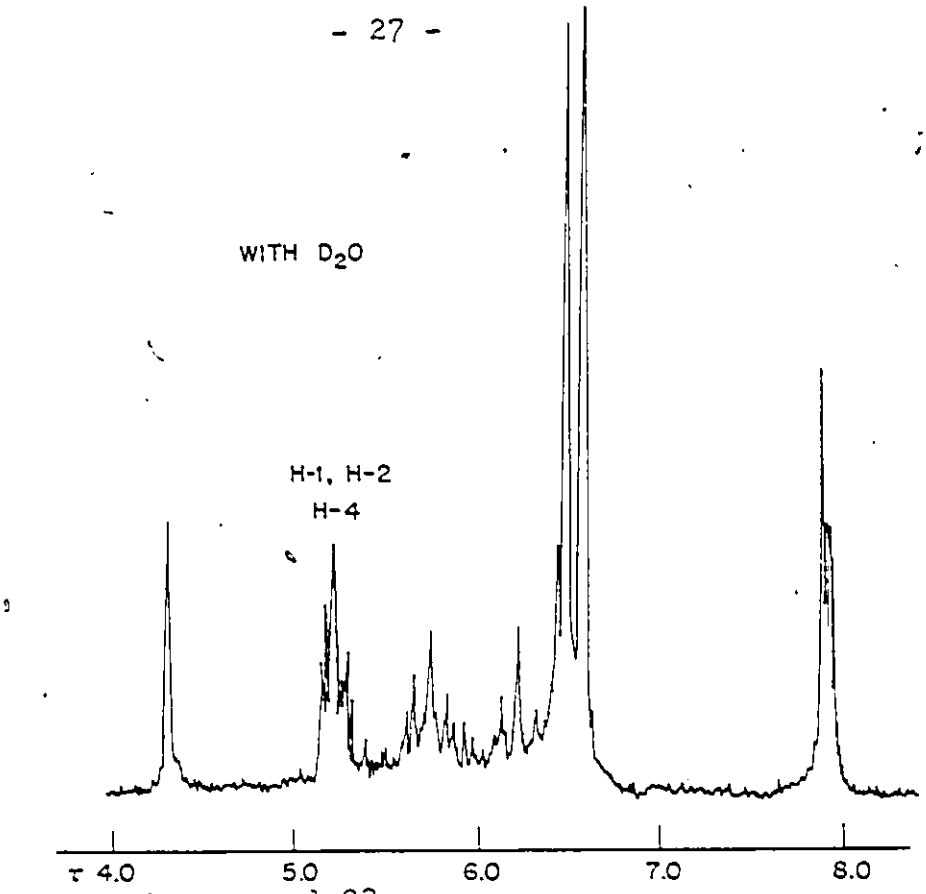
22a R=Ac

Palladium, a less powerful hydrogenation catalyst than platinum, has repeatedly been used to perform selective saturation of the carbon-carbon double bond in nitroolefins with retention of the nitro group[19]. However, by prolonged action the nitro group may slowly be attacked. Thus, in nitroolefinic glycosides which offer steric hindrance to hydrogenation of the double bond, partial reduction of the nitro group became competitive and led to the formation of large proportions of oximes[20].

In view of this, it was considered worthwhile to investigate how the pair of stereoisomeric epoxides 5 and 6 would behave in palladium-catalyzed hydrogenation. We recall that with sodium borohydride the latter compound

reacted smoothly whereas the former was inert. Now it was found that both compounds underwent quantitative hydrogenolysis of the oxirane ring (between the α-carbon and oxygen atoms according to the aforementioned scheme) when hydrogenated with palladium on carbon in ethanol for 24 hours. Yet an interesting difference in the two reactions was seen, which was due to stability factors in the expected products.

The β-D-allo epoxide 6 furnished the known[21], and expected, methyl 4,6-O-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (23), which was obtained crystalline in 90% yield and identified with an authentic sample. A minor by-product, isolated in 7% yield, analyzed as $C_{14}H_{17}NO_6$ which indicated loss of one oxygen atom. The i.r. spectrum (Fig. 3) lacked the strong, characteristic nitro band at 1550 cm^{-1} but showed a weak band at 1570-1600 cm^{-1} which was attributed to a C=N vibration. Presumably the product was methyl 4,6-O-benzylidene-3-deoxy-3-oximino-β-D-ribo-hexopyranoside (23a). Its n.m.r. spectrum (Fig. 2) showed a three-proton unresolved multiplet in the τ 5.09-5.31 region, assignable to H-1, H-2 and H-4 protons. Upon deuterium exchange, this multiplet was simplified as a result of removal of the H-2 coupling with 2-OH. The region τ 5.61-6.41 containing H-5, H-6e and H-6a remained unchanged after deuterium exchange.



N.m.r. spectrum of compound 23a

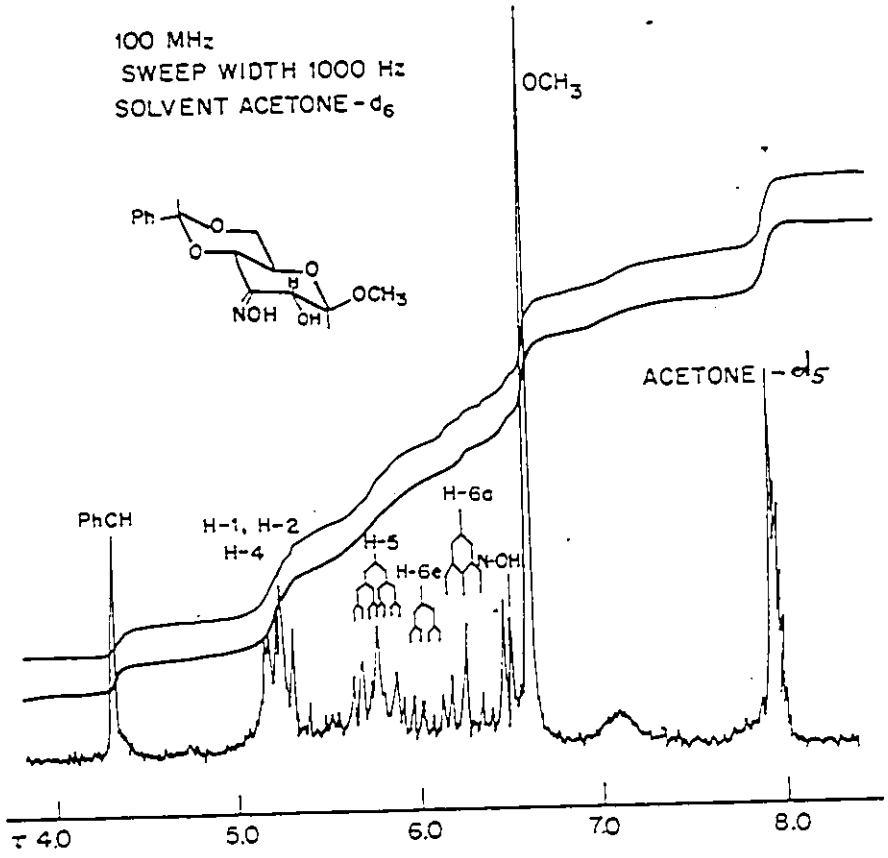


Fig. 2

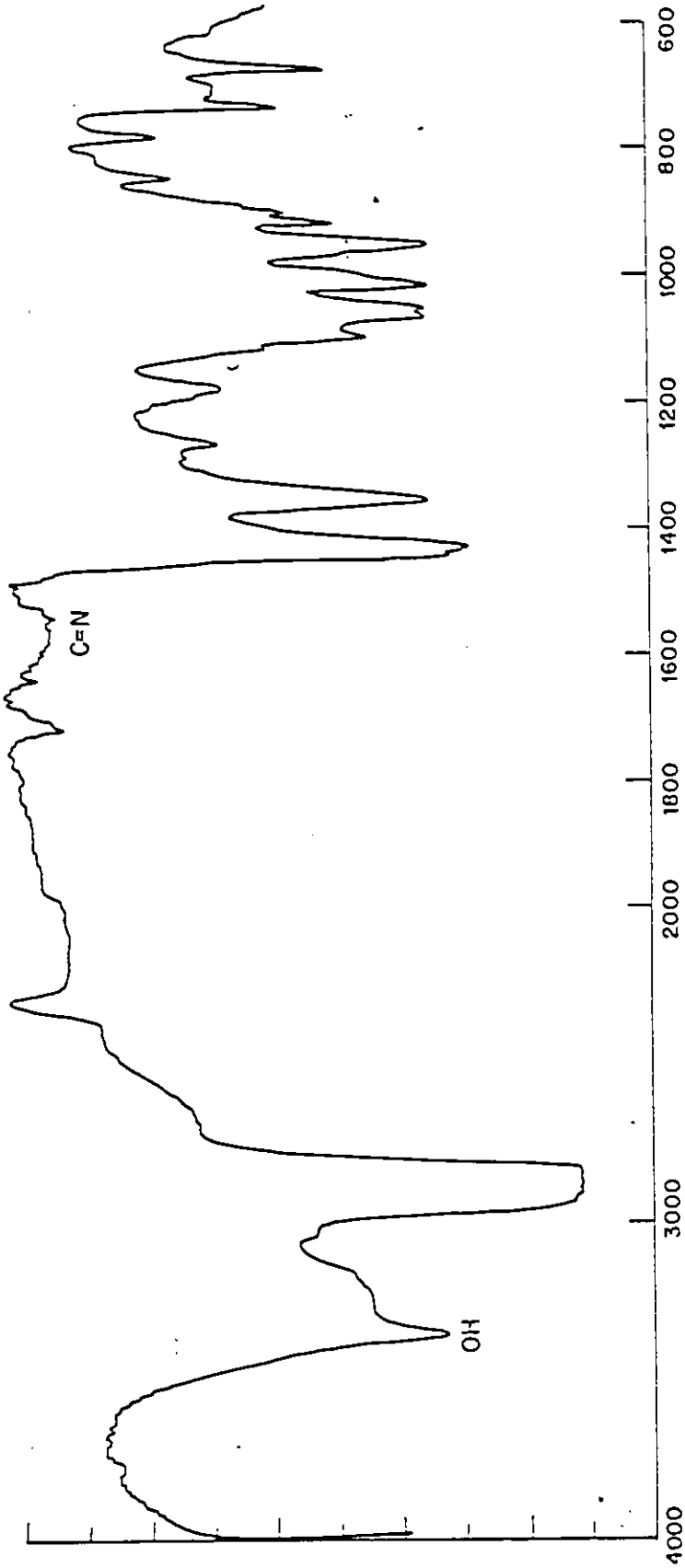
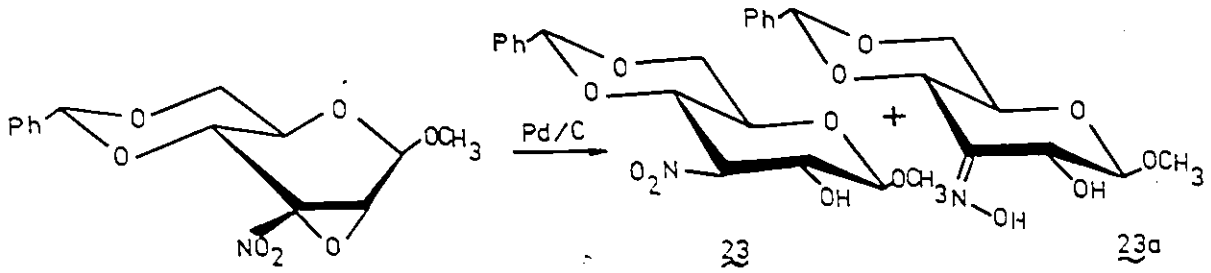


Fig. 3 I.R. spectrum of compound 23a

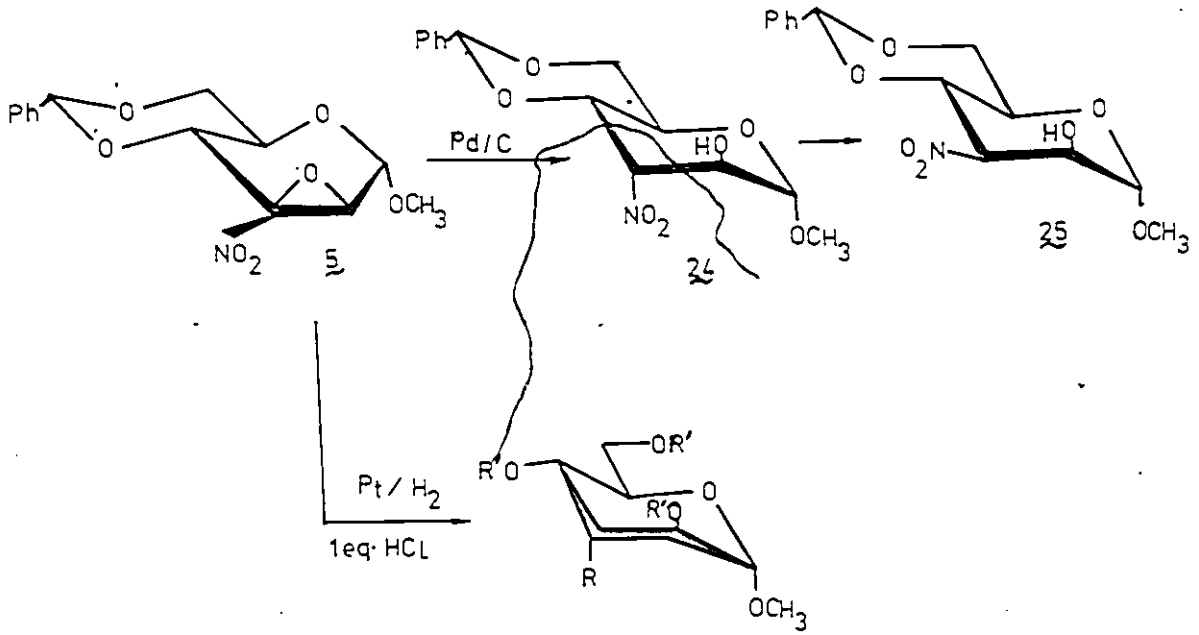


5 23 23a

The α-D-manno epoxide 5 gave almost quantitatively a chromatographically homogeneous hydrogenation product, 70% of which could be crystallized. It was a nitro glycoside, and no oxime or other by-product was observed in this case. However, the product did not have the α-D-altro configuration (24) that was expected to arise by a reaction proceeding in stereochemical analogy to that of 6. Rather, the product was identified (by means of comparison with an authentic sample) as the known[22] α-D-manno isomer 25. It must be assumed that the primary product was in fact the unknown isomer 24 in accordance with the suggested mechanism, but that it epimerized during the process to thermodynamically more stable 25. It is well known[17,23,24] that an axial nitro group on pyranoside and inositol rings is associated with great instability. Traces of base can be expected to promote rapid epimerization to generate a more favoured, equatorial nitro group. In order to prove the point, 5 was

hydrogenated in the presence of 1 equivalent of hydrochloric acid which was to forestall any epimerization of intermediary 24, and platinum was used to effect full reduction to the amine, at which stage epimerization can no longer occur. The conditions chosen caused simultaneous de-O-benzylidenation, but this is not relevant to the point in question. The product proved indeed to possess the D-altro configuration. It was crystalline but very hygroscopic methyl 3-amino-3-deoxy-α-D-altropyranoside hydrochloride (26) which was characterized as its known[25], crystalline tetraacetyl derivative 27.

(Concerning the intermediacy of 24, see also Note 1 on p. 71.)



The second of the 2,3-anhydro glycosides which could not be successfully reduced with sodium borohydride, namely the β-D-gulo isomer 8, was also hydrogenated to an amine by platinum catalysis in ethanol. No acid was provided in this case since it was considered that the nitro intermediate resulting here from oxirane ring opening should have an equatorially oriented nitro group which will not be prone to epimerization. Under the conditions employed, which involved a reaction time of 51 h at ordinary temperature and pressure, the benzylidene group was found to be largely retained. (A trace of by-product detected in t.l.c. might have been due to de-O-benzylidenation). There was isolated over 90% of crystalline, crude product, and 60% of purified material was obtained. It was assumed to be methyl 3-amino-4,6-O-benzylidene-3-deoxy-β-D-galactopyranoside (28). Its n.m.r. spectrum (Fig. 4) showed a five-proton unresolved multiplet in the τ 5.58-6.04 region, attributable probably to H-1, H-2, H-4, H-6e and H-6a protons. A neat quartet at τ 7.20, containing one large and one small splitting was assigned to H-3. The upfield shift of this H-3 signal compared with those of other protons can be explained in terms of the lower electronegativity of nitrogen in comparison with oxygen. In the spectrum of the N-acetyl derivative 29 that was prepared from 28, no signal

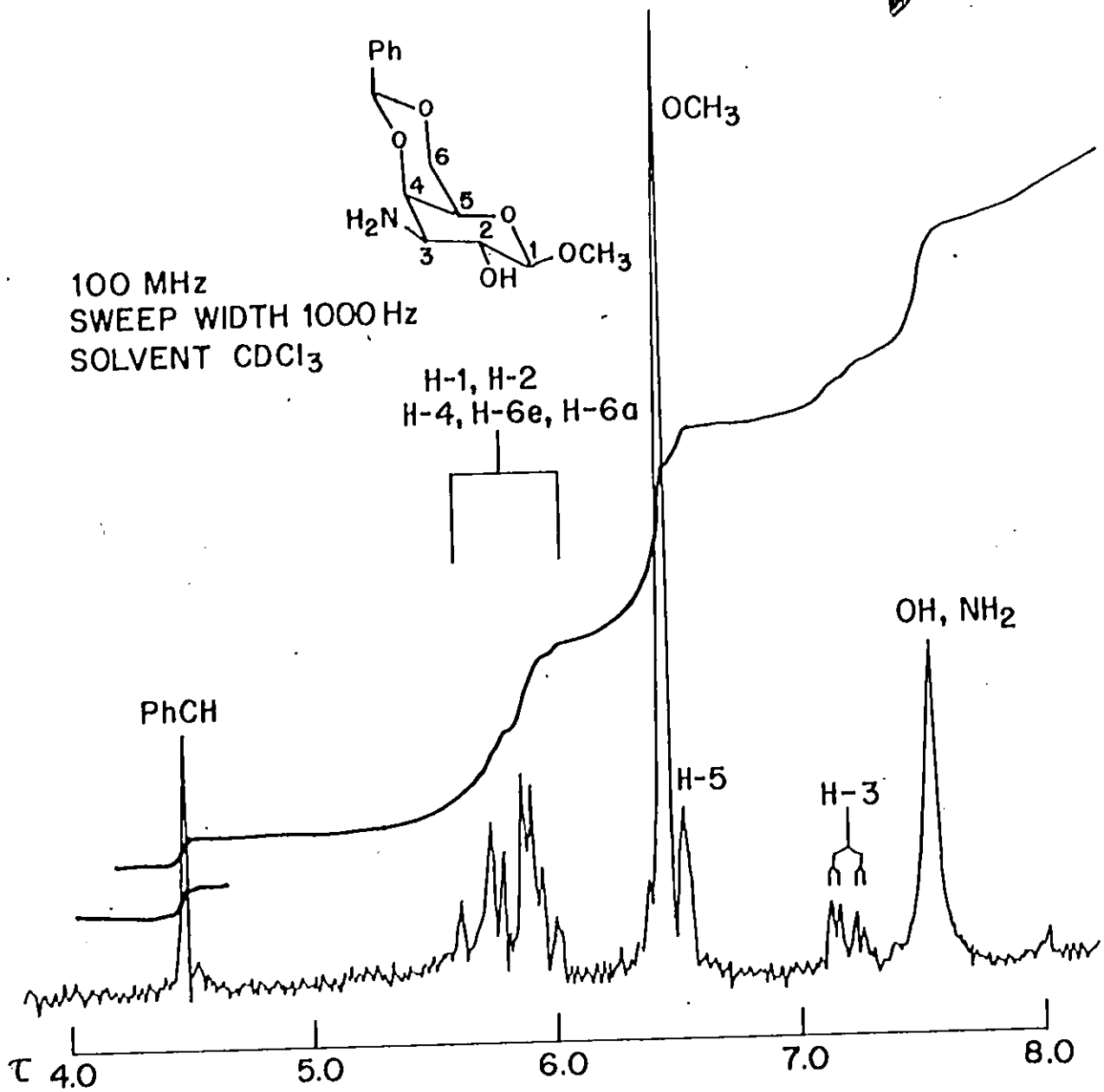
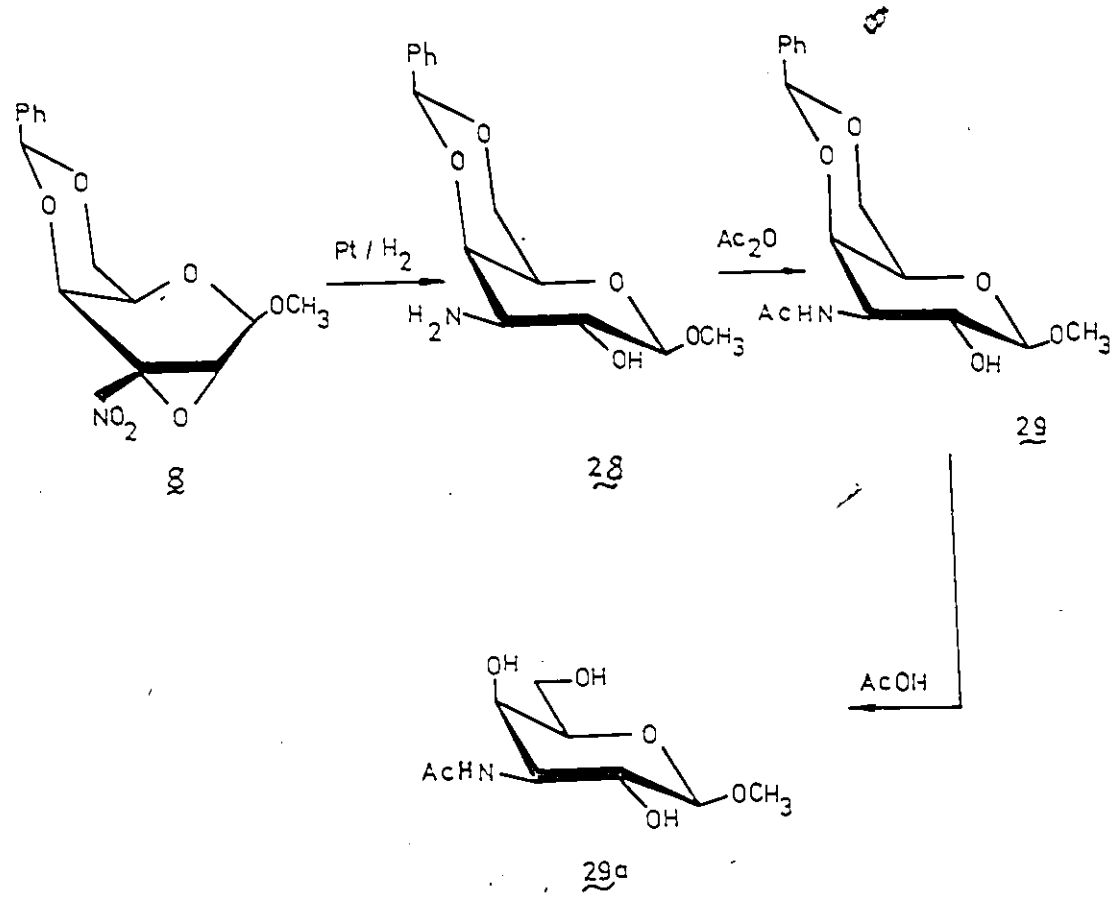


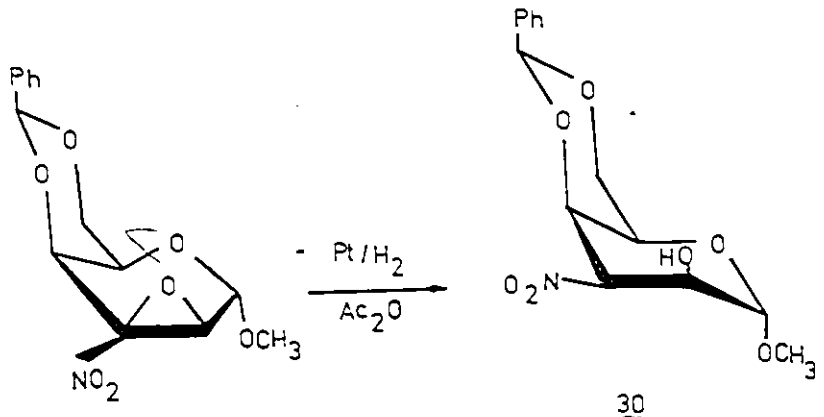
Fig. 4. N.m.r. spectrum of compound 28

appeared in the same region, and H-3 probably resonated at a lower field due to the deshielding effect of the acetyl group. Further structural proof of the compound 28 was provided by acid debenzylidenation of the N-acetyl derivative 29 to give known[26] methyl 3-acetamido-3-deoxy-β-D-galactopyranoside (29a).



Finally, the α-D-talo epoxide 7 (which had been amenable to borohydride reduction but less readily so than 6 and 9) was subjected to catalytic hydrogenation with

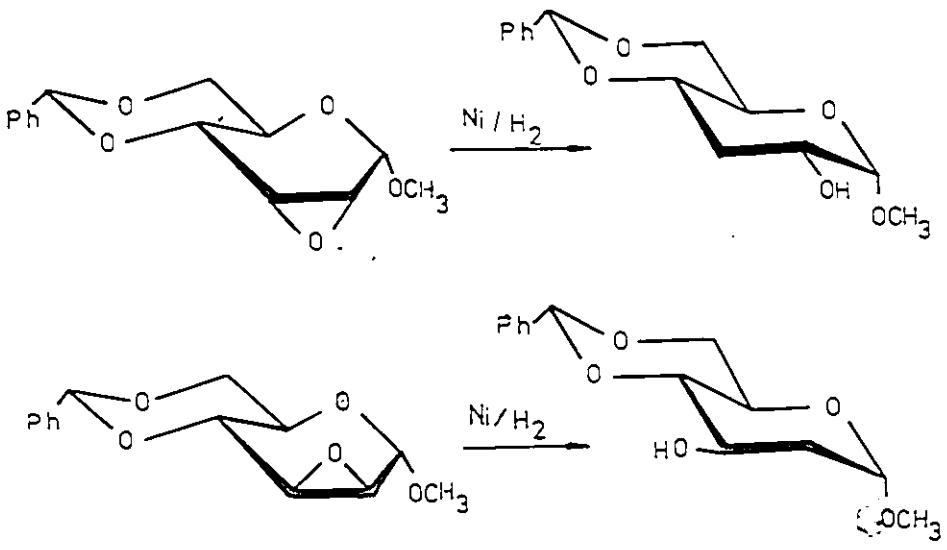
platinum in methanol in the presence of acetic anhydride*. The reaction did not proceed as well as had been hoped, and a substantial part of the starting material was left unreacted and had to be separated from the product by column chromatography. A longer reaction time and increased amount of catalyst effected no noticeable change. Nevertheless, a crystalline reaction product could be isolated in 33% yield. Surprisingly, it was not an amino sugar but proved to be the known[20] methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-talopyranoside (30).



7 30

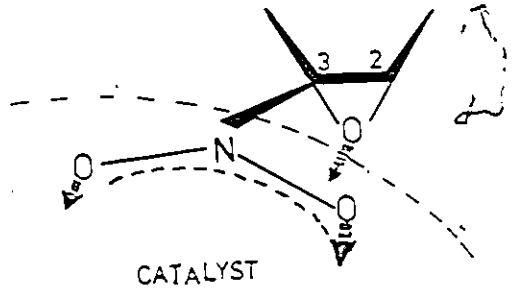
* The acetic anhydride was added in the hope of trapping the expected amine as its N-acetyl derivative, which could facilitate its isolation. Preliminary experiments using no addition, or providing HCl in the medium, had not been promising.

Stereochemical considerations:- Catalytic hydrogenation of epoxides differs stereochemically from metal hydride reduction in that the reductant attacks on the side of the oxygen atom rather than from the opposite side of the ring. It is assumed that the catalyst coordinates with a lone electron pair of the oxygen; then follows homolytic cleavage of one of the C-O bonds. Which one, in the case of asymmetrically substituted epoxide ? The generalization has been made[16] for Raney nickel-catalyzed hydrogenations of non-nitro analogs of our 2,3-anhydro glycosides that scission takes place so as to generate an equatorial hydroxyl group. In other words, the Fürst-Plattner rule is not applicable. For example:



In contrast to this, our nitro epoxides exclusively suffered fission of the O-C_3 bond giving 2-hydroxy derivatives

only, with the hydroxy group oriented equatorially when the epoxide ring was below (6 and 8), and axially when it was above (5 and 7), the plane of the sugar ring. Obviously, the fission is directed by the nitro group. Steric effects due to configuration at C-1 or C-4 were not manifest. One might ascribe the preferential mode of ring opening to a weakening of the $O\text{-}C_3$ bond by the electronegative character of the nitro group. As an alternative hypothesis one might consider a strong co-ordination of the catalyst surface with the nitro oxygens (in addition to the epoxy oxygen), which would "anchor" the catalyst in the proximity of the $O\text{-}C_3$ bond as shown in the diagram below. For yet another explanation see Note 1 on p. 71.



3. The Reaction with Dimethylamine

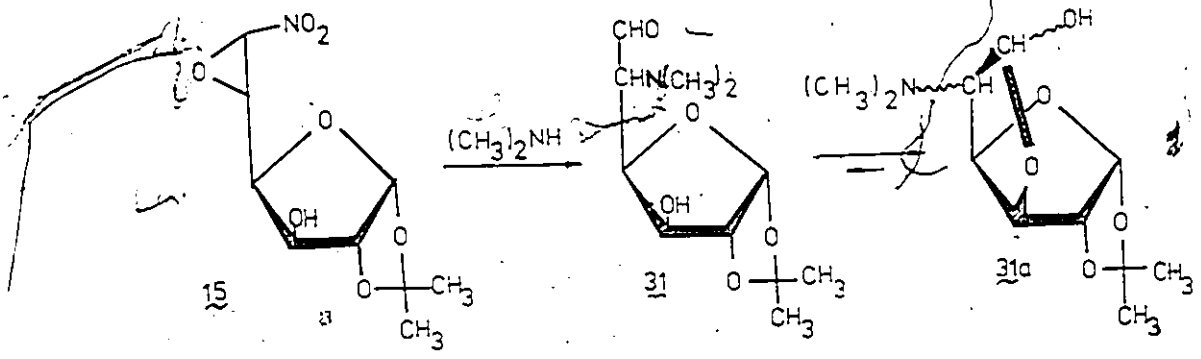
The next subject of study was to be the reaction of carbohydrate α-nitroepoxides with a nucleophilic, electrically neutral base. Dimethylamine was chosen because the synthesis of dimethylamino sugars is of

considerable interest in the chemistry of antibiotics components as exemplified by desosamine, rhodosamine, and angolosamine[27]. As noted in the Introduction, simple α-nitroepoxides furnished dimethylamino ketones with the reagent by way of ring opening at the β-position followed by elimination of nitrite ion from the α-position. It turned out that carbohydrate α-nitroepoxides react correspondingly in an initial phase but complications ensue.

The 5,6-anhydro sugar 15 proved extremely reactive towards aqueous, 25% dimethylamine in which it decomposes immediately. The reaction (1 h at 25°) was moderated in a medium diluted with ethanol, but even then it produced tarry material that rendered isolation of a crystalline product difficult. Eventually, crystals were obtained in a yield of 10% and were revealed by elemental analysis to correspond to the expected structure of a 5-deoxy-5-dimethylamino-1,2-O-isopropylidene-hexodialdose 31.

Aldehyde derivatives of this type may well be expected to be quite sensitive, and this might account for the low yield. There was no carbonyl band in the i.r. spectrum, which is reasonable as internal hemiacetalation to give the 1,4;6,3-difuranose 31a should prevail. Although the substance gave a single spot in t.l.c., it was shown by the n.m.r. spectrum (Fig 5) to contain at least two components, in unequal proportions. At lowest

field, there occurred two 4-Hz doublets (τ 4.01 and 4.12) in an intensity ratio of about 1 : 2, which together integrated to one proton and doubtless represented the anomeric protons H-1 of two stereoisomers. A one-proton signal centred at τ 4.66 was assignable to H-2 but it appeared to consist of two overlapping, unequal doublets rather than a simple doublet*. Similarly there were two separate signals attributable to H-5 of two components, a very narrow multiplet (τ 6.98) and a distinct quartet (τ7.27), with an intensity ratio 1:2. The same ratio was seen in two singlets (τ7.66 and 7.60) of a combined six-proton intensity, belonging to the dimethylamino groups. There was no multiplicity observed in the highfield three-proton singlets of the isopropylidene group. The presence of two components in the product may be due to anomerism at C-6 or, perhaps more likely, epimerism at C-5.



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* In 1,2-O-isopropylidene-α-D-glucofuranose derivatives, H-2 usually gives a doublet due to coupling with H-1 only, as coupling with H-3 tends to be close to zero[28].

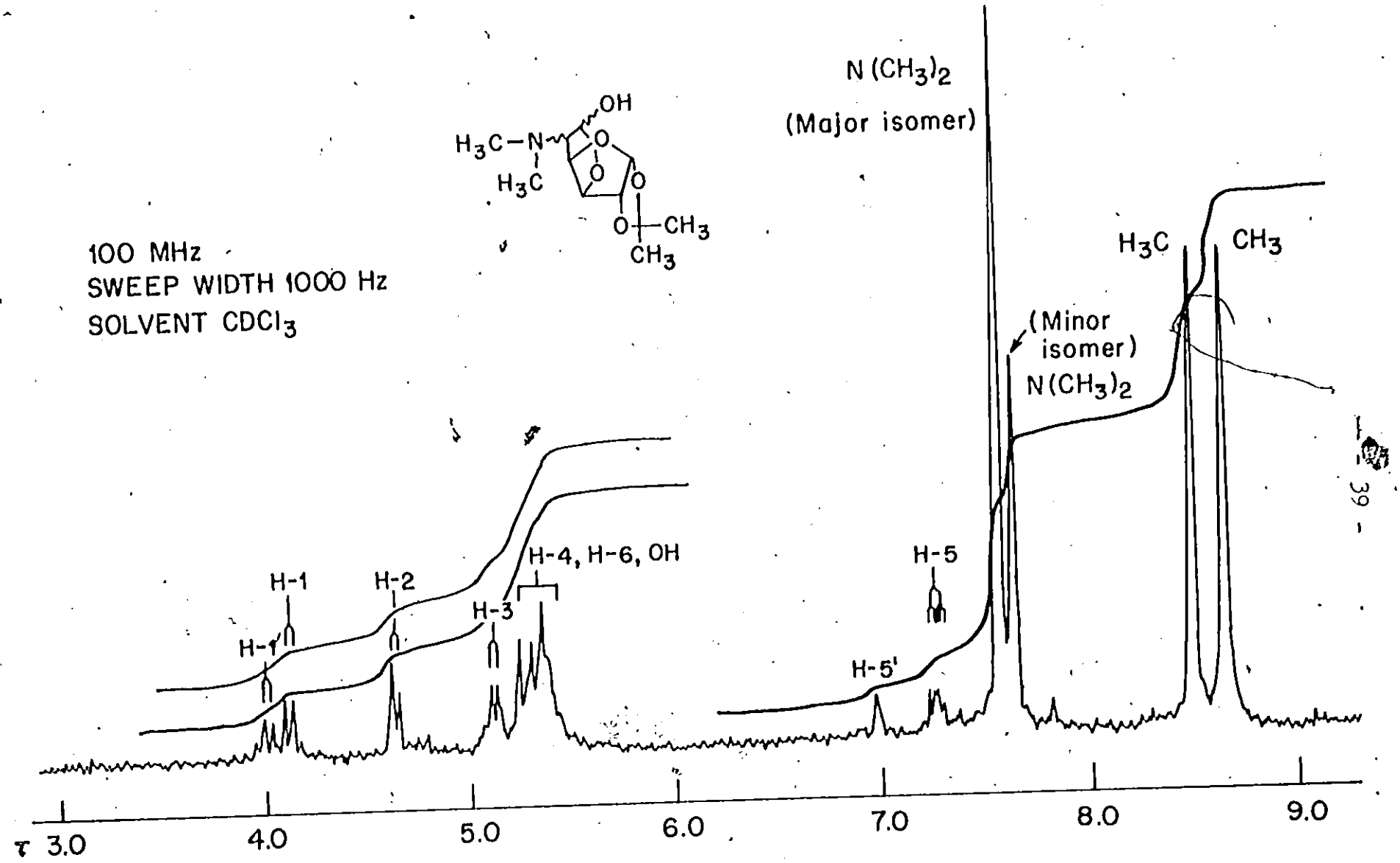
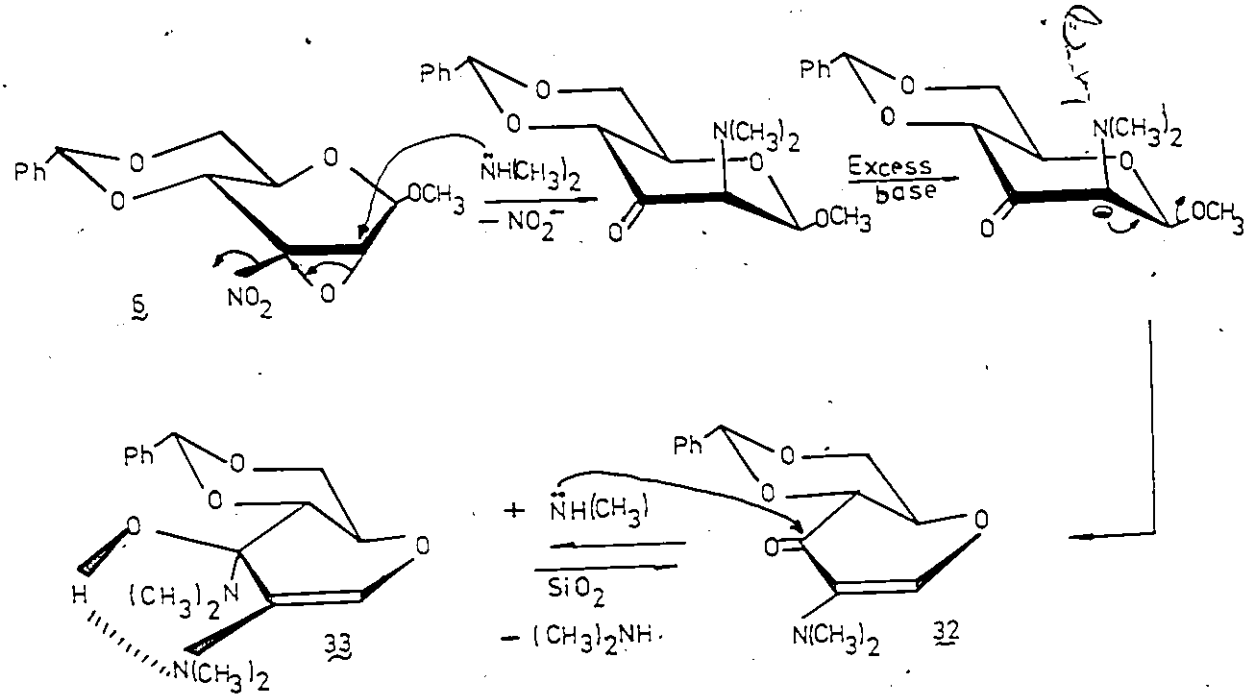


Fig. 5. N.m.r. spectrum of compound 31a.

The study of the interaction of the 2,3-anhydro glycosides 5, 6, 7 and 8 with dimethylamine furnished very interesting results. The reactions were found to yield a novel type of dimethylaminoketones which undoubtedly were primary intermediates. The crystalline products obtained in 50 - 98% yield were 1,5-anhydro-4,6-O-benzylidene-2-deoxy-2,3-bis(dimethylamino)-hex-1-enitols (generally, glycal derivatives). The formation of these hitherto unknown compounds is explainable by the following sequence, using the example of the product 33 generated from the β-D-allo epoxide 6.



Nucleophilic opening of the epoxide ring with ensuing loss of nitrite ion is believed to lead to an intermediate 2-dimethylamino-3-keto glycoside as previously discussed.

This amino ketone under the basic conditions of the medium appears to suffer β-elimination of the anomeric methoxyl group to give the unsaturated ketone, 1,5-anhydro-4,6-O-benzylidene-2-deoxy-2-dimethylamino-D-erythro-hex-1-en-3-ulose (32). The latter forms an adduct with excess dimethylamine, i.e., the bis-dimethylamino compound 33 that was isolated.

The unusual stability of 33 as an isolable, geminal amino alcohol is remarkable. The configuration at C-3 has not been established. However, it is likely that the structure is stabilized by internal hydrogen bonding between the 3-OH and 2-$N(CH_3)_2$ groups, and molecular-models suggest a pseudoequatorial 3-OH group to be in a more favourable position for such bonding than a pseudoaxial one. The presence of chelation is further supported by the i.r. spectrum (in chloroform) showing a broad OH peak at 3400 cm^{-1}. Also supporting our view could be the observed failure of the compound to undergo noticeable deuterium exchange in n.m.r. studies. This could be taken to mean that the hydrogen bonding was strong enough to prevent easy exchange. If this reasoning is correct, the compound as drawn in formula 33 would receive the configurational prefix D-arabino.

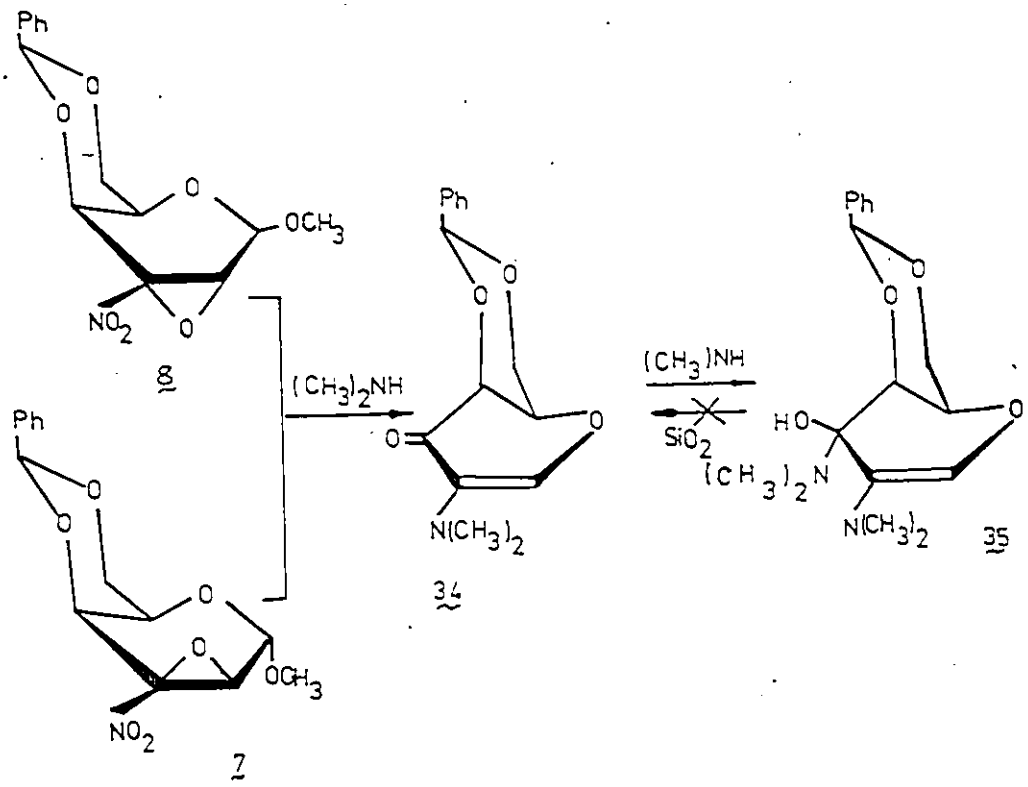
When a chloroform solution of 33 was passed through a column of silica gel, dimethylamine was in part split

off, and the ulose 32 was isolated crystalline in 40% yield.

The most noteworthy feature of the reaction is the loss of the glycosidic methoxyl group, with attendant removal of asymmetry at C-1. In conformity with the mechanistic scheme, the α-D-manno epoxide 5 reacted with dimethylamine, although more slowly, to give the same product 33. (It failed to crystallize in this instance but was readily identified by its n.m.r. spectrum). The observation that α-D-glycoside 5 reacted more slowly (48 h at room temperature after brief initial heating) than the β-D-glycoside 6 (75 min at room temperature) may be attributed to steric hindrance in 5 by the pseudoaxial methoxyl group in the required backside attack of the nucleophile at C-2, or by the need for conformational inversion in the transition state; cf. the discussion of analogous borohydride reactions.

Analogous treatment of the α-D-talo (7) and β-D-gulo (8) epoxides furnished the corresponding bis(dimethylamino)glycal 35, isolated crystalline in both cases. Again, the α-glycoside reacted less readily than the β-glycoside. The former required 48 h at 60° for complete transformation whereas the latter, showing a reasonable rate already at room temperature, was completely reacted in 5 min at 98°. Like in the case of the isomer 33, the configuration at

C-3 in 35 could not be determined. If depicted with a pseudoequatorial hydroxyl group as in the accompanying scheme, the compound would possess the D-lyxo configuration, but the D-xylo configuration (having a pseudoaxial hydroxyl group) cannot be discounted.



Attempted conversion of 35 into the corresponding 3-ulose 34 by passage through a silica gel column in

analogy to the experiment with 33, did not succeed. Nothing at all could be eluted with the chromatographic solvent, ethylacetate-petroleum ether 2 : 3. Similarly, when 35 was stirred for 48 h with a batch of silica gel in the same solvent, it became irreversibly adsorbed. The filtrate was blank and remained so even upon washing of the gel with a more polar solvent, methanol.

The structure of 33 followed from elemental analysis and spectral data. The i.r. spectrum in Nujol (Fig 6) exhibited a broad band at 1640 cm^{-1} for C=C; a strong band at 1560 cm^{-1} attributable probably to $N-CH_3$ vibrations, and a band at 1030 - 1130 cm^{-1} for C-N vibrations. Its i.r. spectrum in chloroform showed a broad band at 3400 cm^{-1} for OH (hydrogen bonded) and a strong absorption at 1600 cm^{-1} for the C=C. The n.m.r. (60 MHz) (Fig 8) spectrum showed a large doublet ($J_{4,5}$ = 8 Hz) at τ 6.24 assignable to H-4; an unresolved four-proton multiplet in the τ 5.37 - 6.10 region attributable probably to H-5, H-6a, H6e and 3-OH; a sharp singlet at τ 2,37 for H-1 followed by the phenyl signal. Two singlets of six-proton intensity each at τ 6.89 and 7.41, respectively belong to the four methyl groups of the dimethylamino groups.

The very low chemical shift (τ 2.37) of the H-1 is surprising. Normally, H-1 would be expected at a much higher field (in the 4.3-5.3 region) as a result of strong

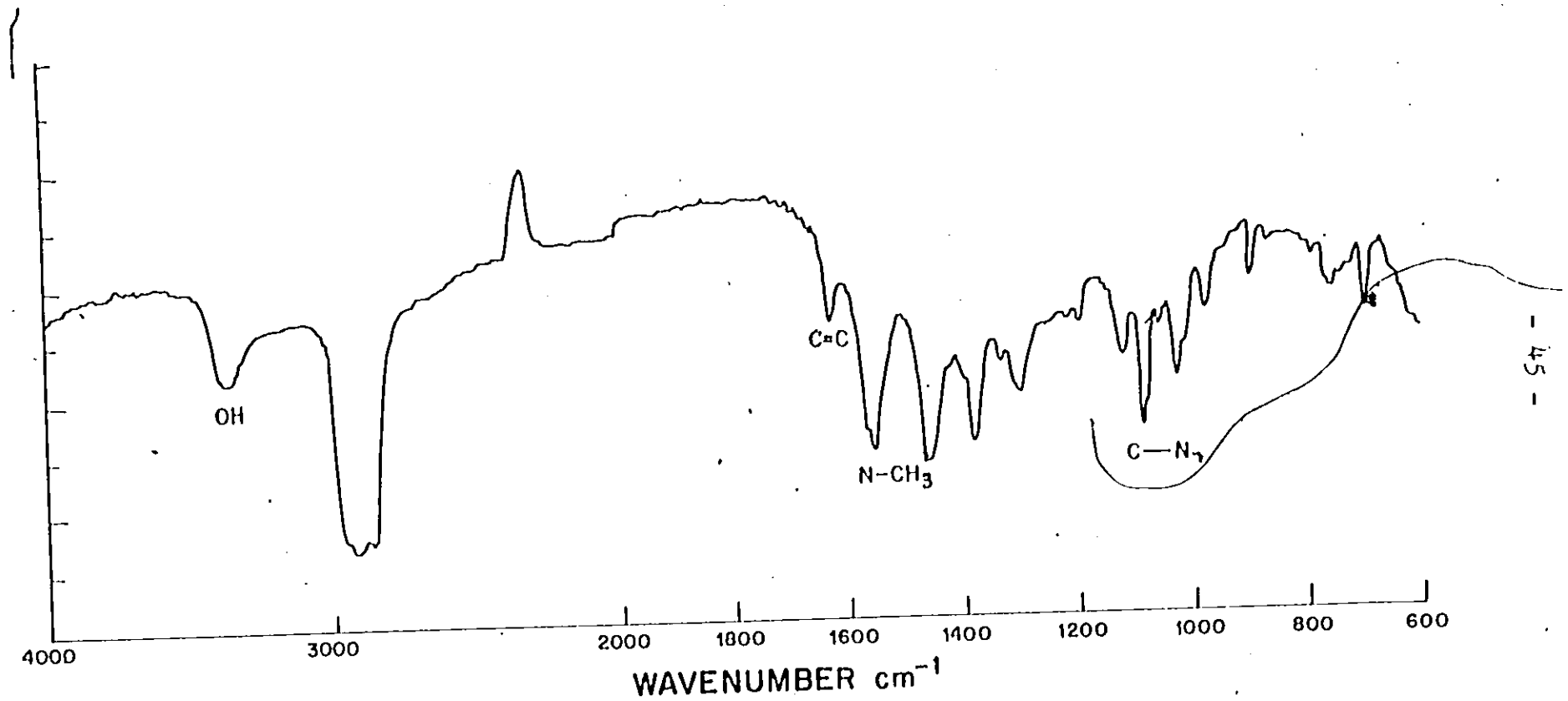


Fig. 6. I.R. Spectrum of compound 33, from Nujol mull.

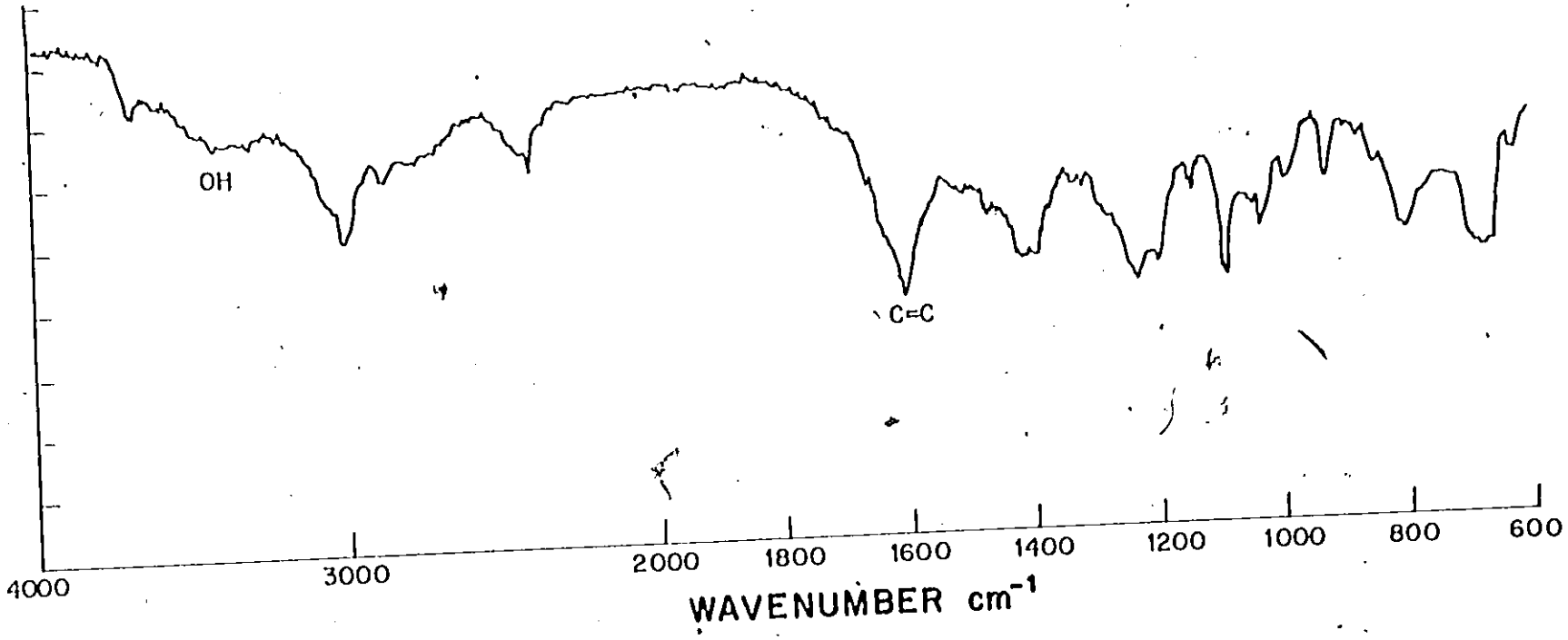


Fig. 7. I.R. Spectrum of compound 33 in Chloroform.

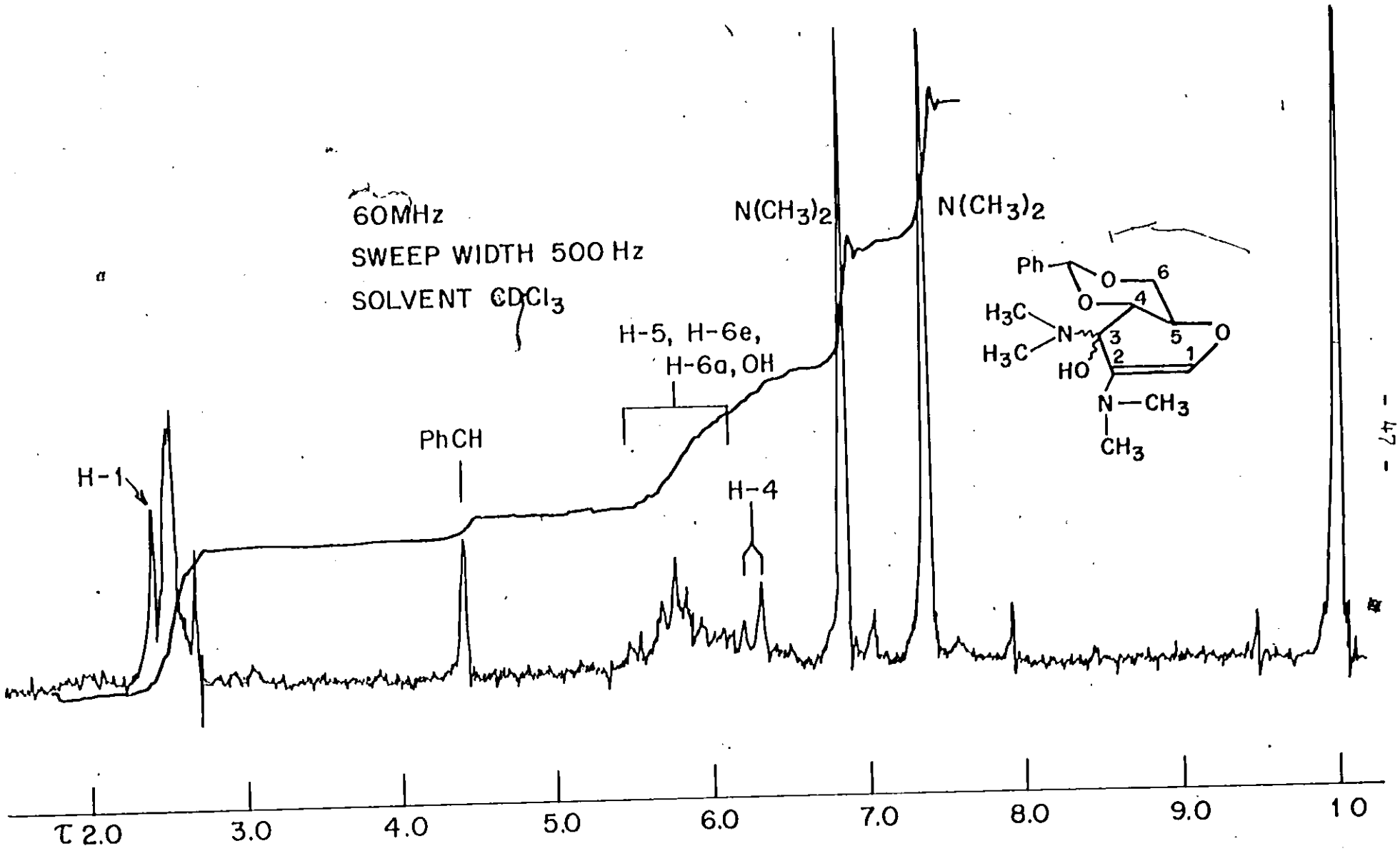
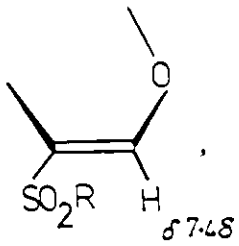


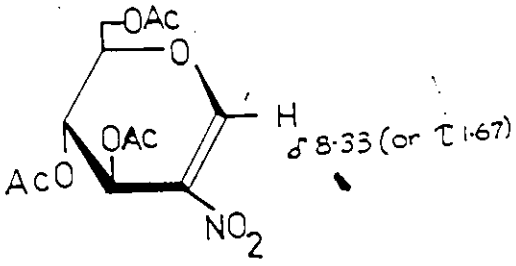
Fig. 8. N.m.r. spctrum of compound 33.

shielding due to a resonance effect between the double bond and the lone pair of electrons on nitrogen of the dimethylamino substituent. The observed low chemical shift could be explained in terms of the chelation suggested above. If the lone pair of electrons on nitrogen was utilized for hydrogen-bonding, resonance effect would be diminished. Furthermore, donation of its lone pair to chelation would give the nitrogen atom a partial positive character, which should lead to a flow of electrons away from C-1 towards the nitrogen. This developing electron-withdrawing effect should reverse the normal effect of the dimethylamino group on the chemical shift of H-1. Obviously, the extent of such deshielding will depend much on the strength of the hydrogen-nitrogen bond in question.

Since no recorded examples could be found of the effect of a quaternary ammonium substituent on the chemical shift of the α-proton in α,β-unsaturated ethers (vinyl ethers), it was difficult to make any direct comparison, but a rough calculation, using a β-sulfonyl substituted α,β-unsaturated ether (shown below) as a model indicated a chemical shift of 7.48 ppm for H-1 (the chemical shift [29] of the α-hydrogen of vinyl ethers is 6.53 ppm; the $-SO_2R$ effect[30] is 0.95 ppm; therefore the resultant shift is 6.53 + 0.95 = 7.48 ppm in the δ scale or 2.52 in τ). This means a difference

of 0.15 ppm in comparison with our observed value of 2.37 τ.

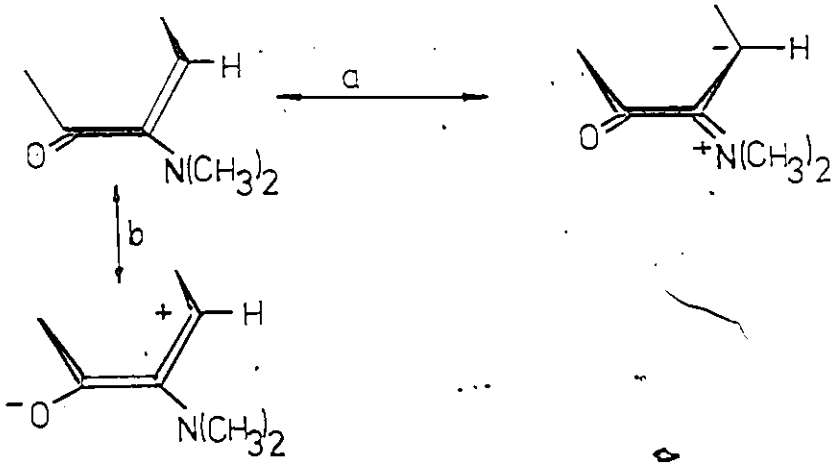




Tri-O-acetyl-2-nitro-D-glucal

A more concrete model, tri-O-acetyl-2-nitro-D-glucal[31] showed a comparable, though lower chemical shift for H-1, reported at τ 1.67.

The i.r. spectrum of the 3-ulose 32 (Fig. 9) had carbonyl absorption at 1725 cm^{-1}. Its n.m.r. spectrum (Fig 10) indicated the presence of only one dimethylamino group, resonating as a sharp six-proton singlet at τ 7.42. H-1 appeared as a sharp singlet at τ 3.03. This higher field shift, compared with that of H-1 in the hydroxy amine 33 (τ 2.37) agrees with absence of chelation in the 3-ulose, the dimethylamino group at C-2 now being free to participate in resonance with the double bond according to a in the scheme depicted:



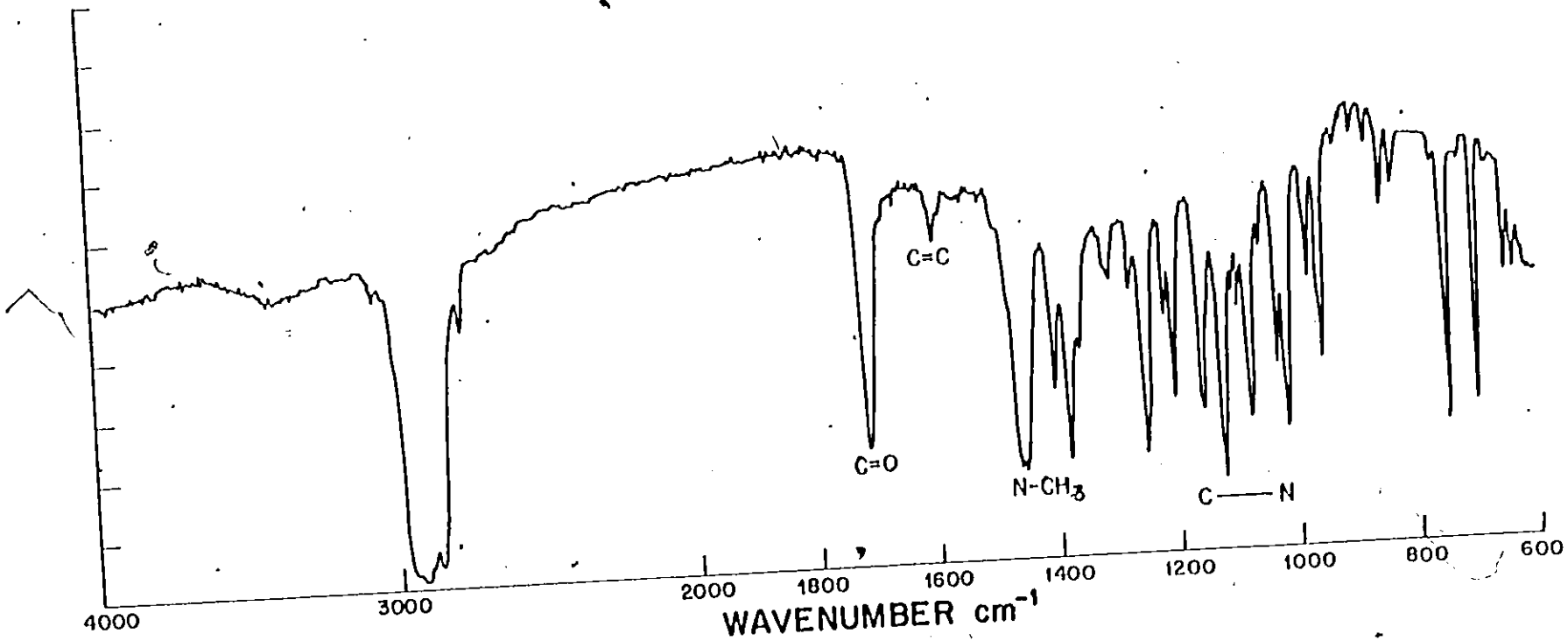


Fig. 9. I.R. Spectrum of Compound 32 from Nujol mull.

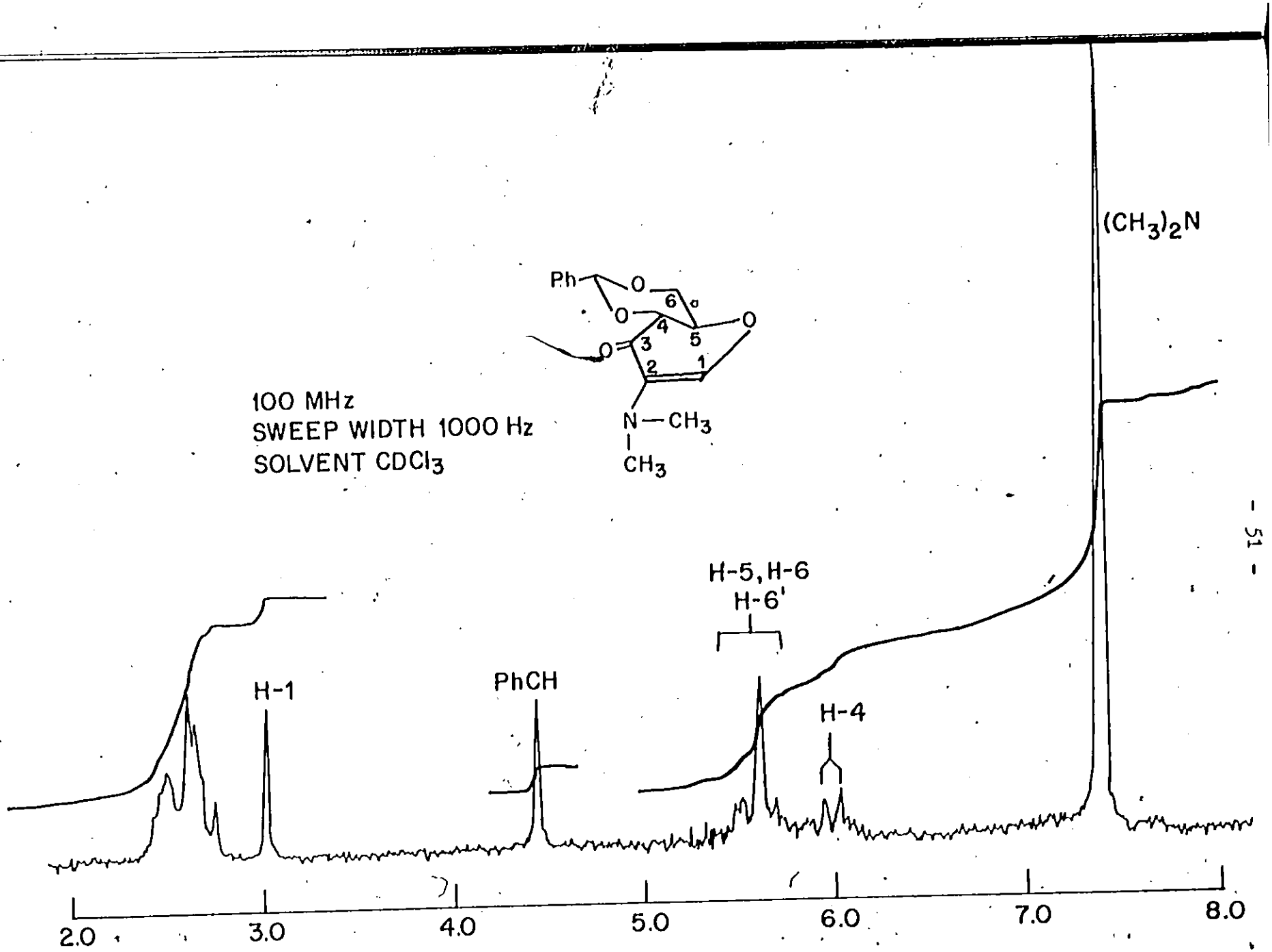


Fig. 10. N.m.r. Spectrum of Compound 32.

This would account for an upfield shift of the H-1 signal. The fact that the shift was less than might have been expected is possibly due to a partial offsetting of the shielding effect by a resonance contribution according to b. A rough calculation, based on Jackman scale[30], taking the substituent coefficient of C=O and $:N(CH_3)_2$ to be 0.81 and -1.31, respectively, showed that the chemical shift of H-1 in 32 should be equal to 6.53 + 0.81 - 1.31 = δ 6.03 or τ 3.97.

The structure of the isomeric bis(dimethylamino) derivative 35 was similarly deduced from its analytical and spectral data. Thus, the i.r. spectrum in Nujol (Fig 11) showed bands at 3340 cm^{-1} for OH, 1625 cm^{-1} for C=C, 1555 cm^{-1} for $N-CH_3$, and 1030 - 1140 cm^{-1} for C-N vibrations. The n.m.r. spectrum (Fig 12) showed a slightly distorted singlet at τ 5.43 which must belong to H-1. A five-proton group of overlapping signals in the τ 5.67 - 6.07 region was assumed to represent H-4, H-5, H-6a, H-6e and OH while the four methyl groups of the dimethylamino substituents gave two singlets of six-proton intensity each at τ 6.90 and 7.40, respectively. The observation that H-1 in compound 35 was much more shielded than that in compound 33 is noteworthy. In light of the previous discussion, which invoked chelation between the 3-OH and 2-$NH(CH_3)_2$ groups in 33 to explain the chemical shift of H-1, one would have to conclude that such chelation is absent in 35. The stability of the geminal amino alcohol

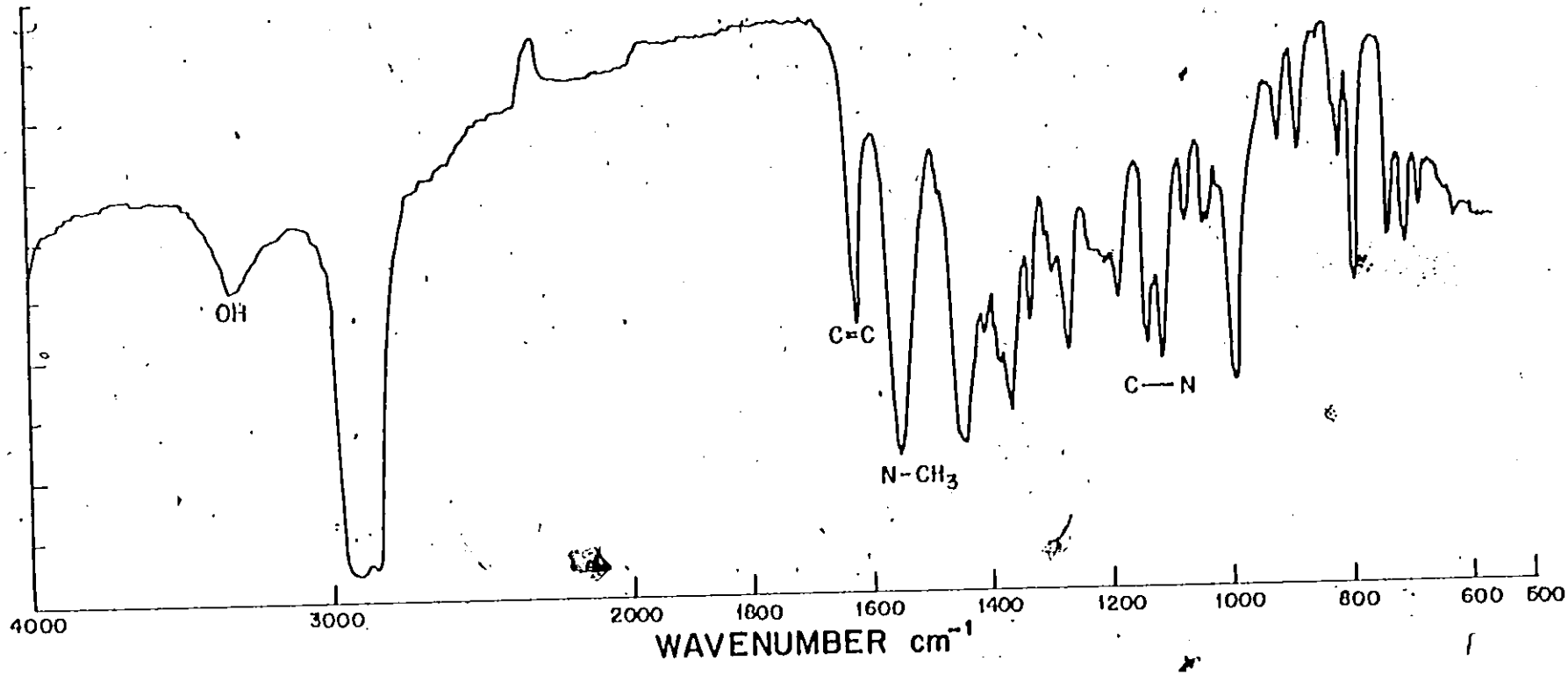


Fig. 11. I.R. spectrum of compound 35 from Nujol mull.

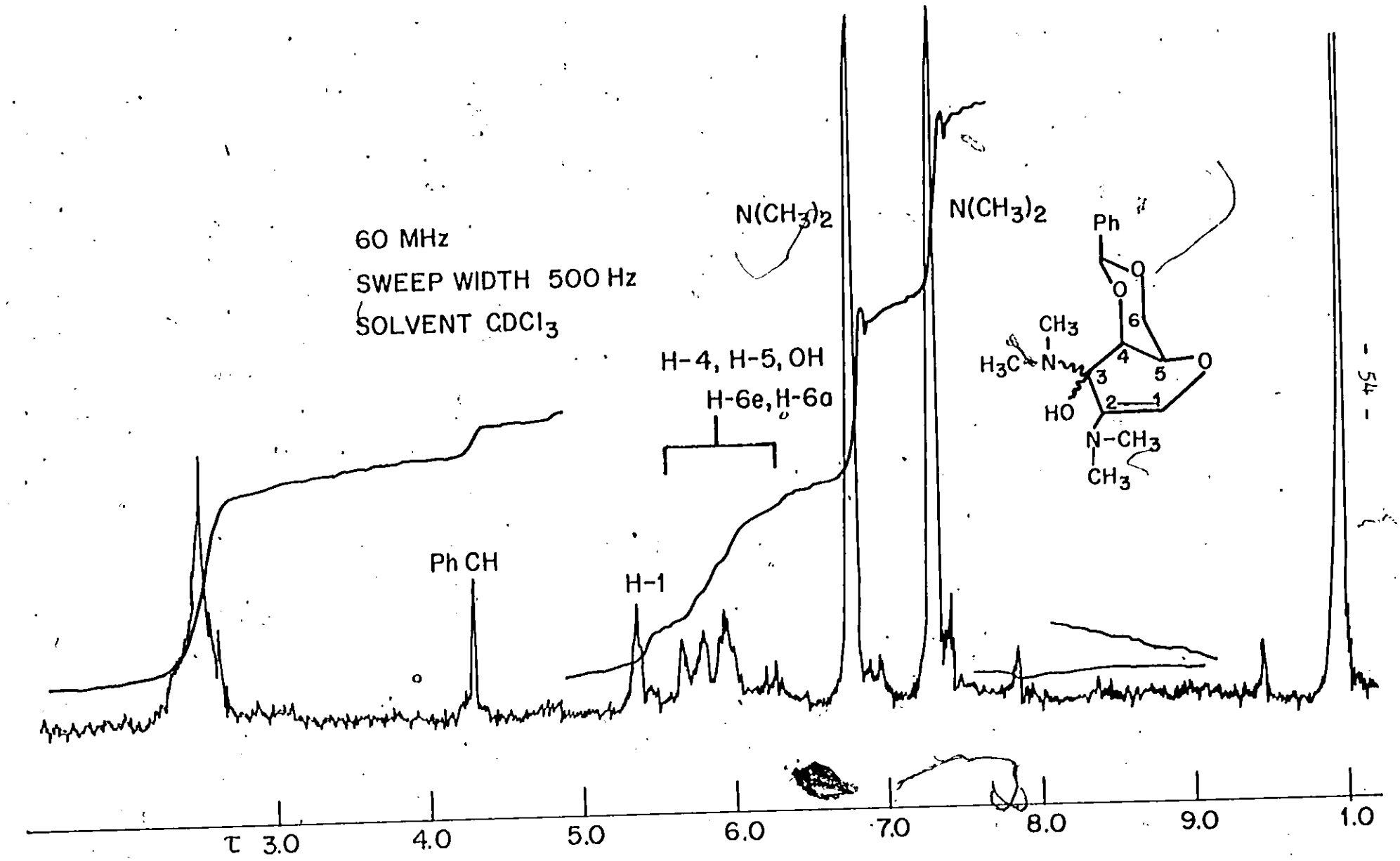
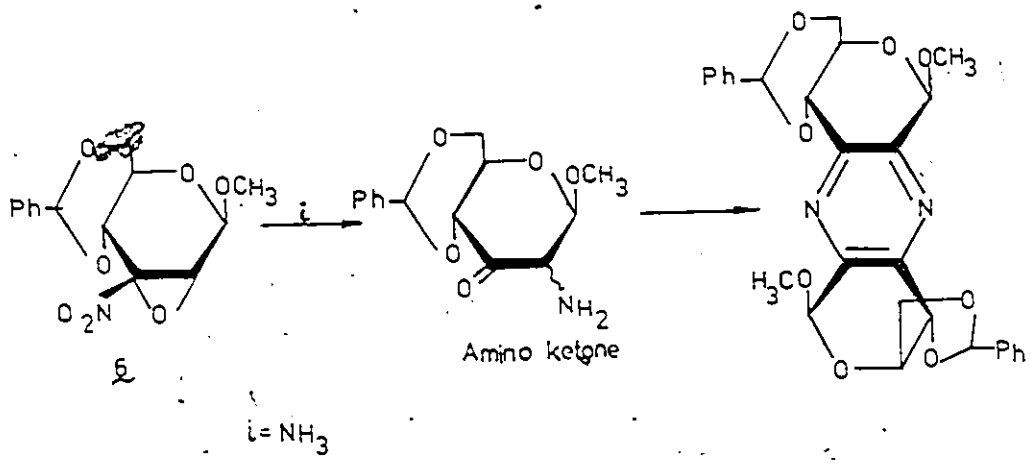


Fig. 12. N.m.r. spectrum of compound 35.

structure, which is a fact nevertheless, could in this instance perhaps be due to hydrogen bonding between the 3-OH group and the neighbouring acetal oxygen atom at C-4.

Contrasting with the foregoing reactions of ~~the~~ α-nitroepoxides with dimethylamine is the behaviour of 6 towards ammonia that was studied by Nakagawa and coworkers[9]. These authors did not observe deglycosylation but obtained, in 78% yield, a condensation product believed to have arisen from a primary amino ketone intermediate. Aromatization of the condensed molecule was attributed to air oxidation.

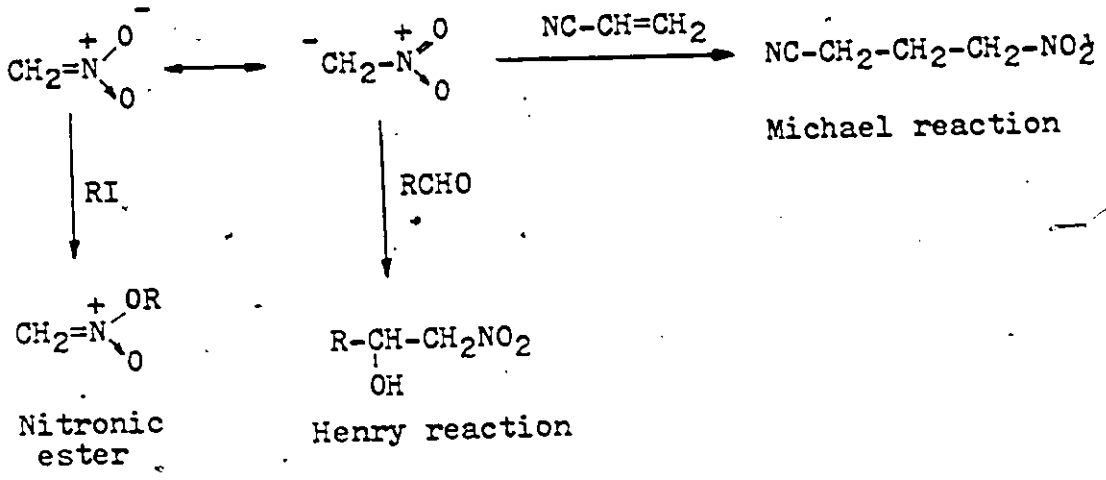


6

4. Reaction with Nitromethane

Nucleophilic opening of oxirane rings by carbanions should lead to branched chain structures. Nitroalkane anions (nitronates) are known to easily react with carbonyl

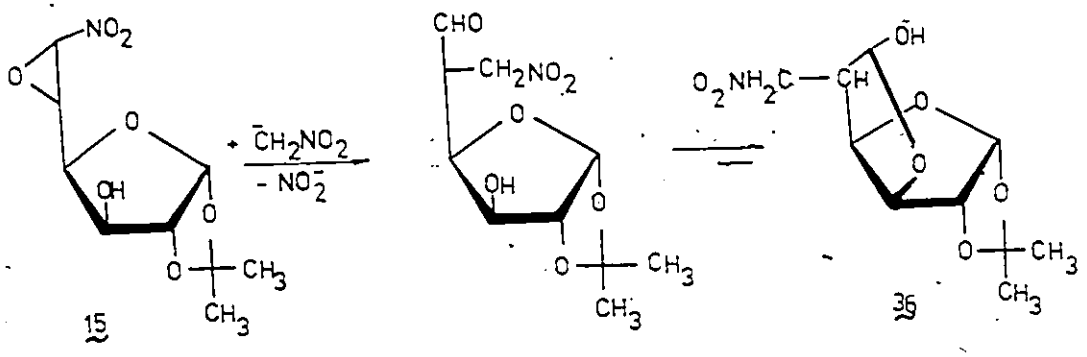
compounds or activated alkenes to form C-C bonds, whereas with alkyl halides they usually undergo O-alkylation:



It was decided to examine how nitromethane would behave in base-catalyzed reaction with our carbohydrate α-nitro-epoxides. The results were disappointing in so far as none of the 2,3-anhydro compounds seemed to react, as evidenced by t.l.c. and recovery of the starting material form the reaction mixtures. The medium employed was saturated barium hydroxide solution (often used for Henry reactions) mixed with small amount of chloroform to dissolve the epoxides. Ambient as well as elevated temperatures were tried. Probably methanenitronate is just too weak a nucleophile for facile epoxide opening, hence no reaction was observed.

The only successful experiment in this series involved the terminal nitroepoxide 15. From its reaction

with nitromethane (26 h at room temperature in methanolic-aqueous barium hydroxide), a crystalline product was isolated in 40% yield. From analytical and spectral data the structure of a 5-deoxy-1,2-O-isopropylidene-5-C-nitro-methyl-hexodialdo-1',4;6,3-difuranose (36) was deduced. The configuration at C-5 remained undetermined. From a mechanism involving backside attack one should expect the product to have the L-ido configuration (barring a secondary epimerization which might well have occurred).



15 36

The i.r. spectrum of 36 (Fig 13) exhibited bands at 3340 cm^{-1} for OH and 1560 cm^{-1} for NO_2 vibrations. The n.m.r. spectrum showed a doublet ($J_{1,2}$ = 4 Hz) at τ 3.71 which doubtless belonged to H-1. An unresolved narrow multiplet (two protons in intensity) appearing in the

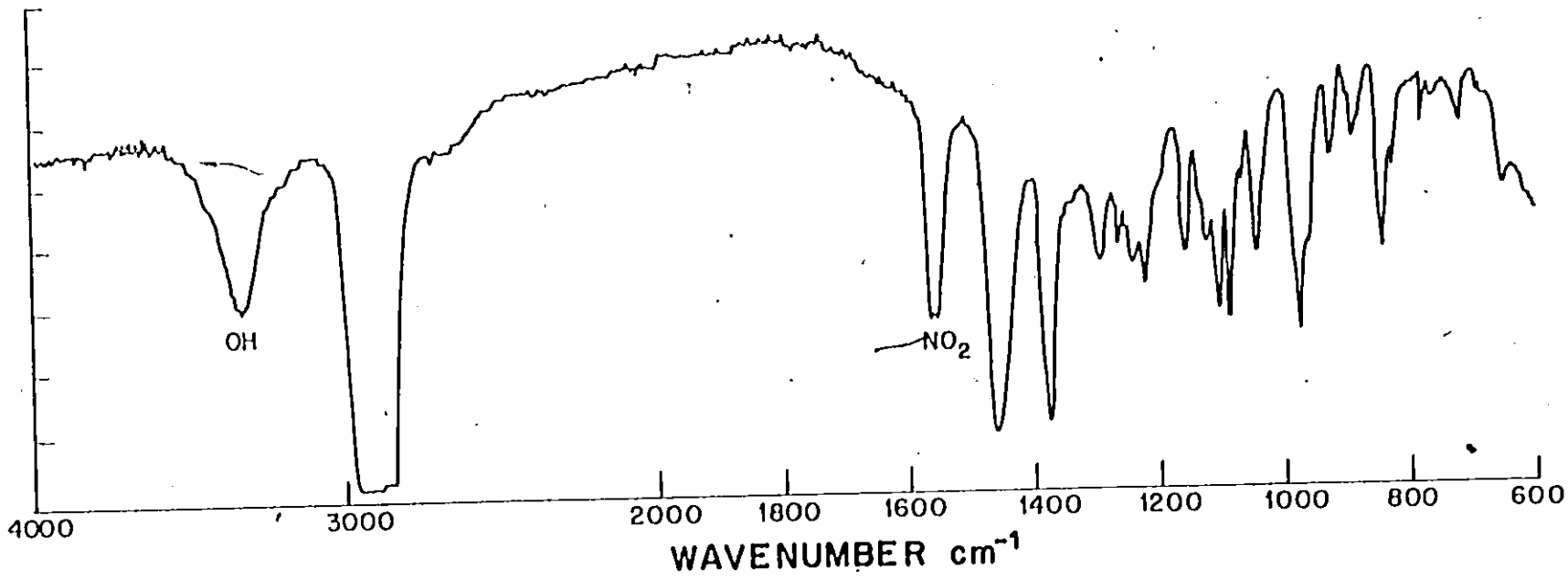
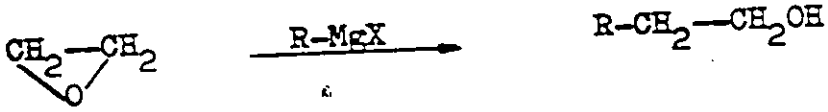


Fig. 13. I.R. Spectrum of compound 36 from Nujol mull.

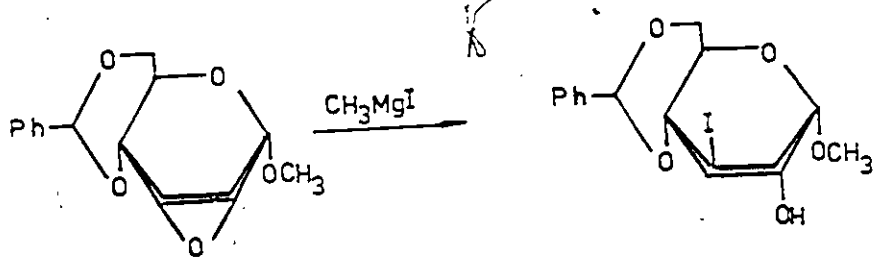
τ 4.72 - 4.90 region could be assigned to H-3 and H-4. The second doublet ($J_{1,2}$ = 4 Hz) at τ 5.28 was assigned to H-2 while an unresolved multiplet (four protons in intensity) in the τ 5.38 - 5.72 region probably could account for H-5, $\underline{CH_2}$-NO_2, and H-6. The 6-OH signal appeared at τ 7.02 as a doublet (J = 4 Hz). The two methyl groups of the isopropylidene function appeared as two almost overlapping singlets at τ 8.62 and 8.64.

5. Grignard Reaction

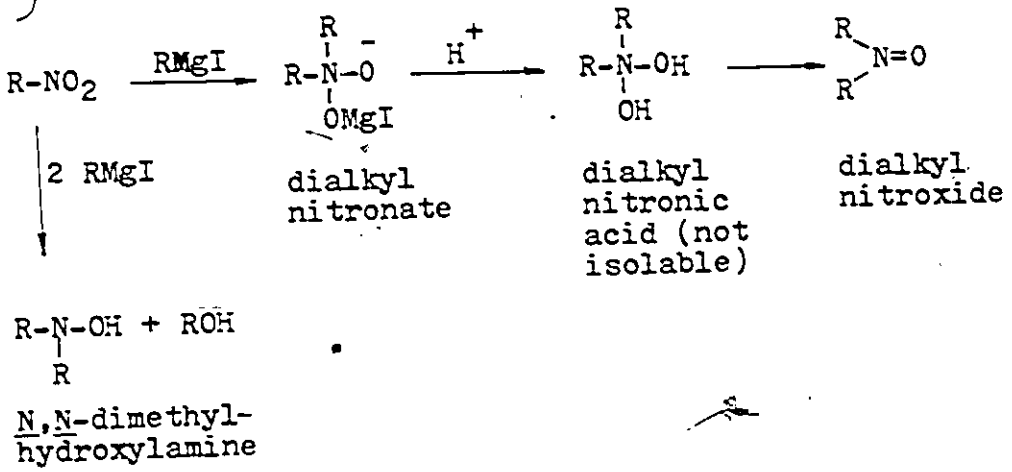
Ethylene oxide reacts with Grignard reagents to afford chain-elongated primary alcohols. Use of higher epoxides is complicated by rearrangements and formation of mixtures.[35]



Certain carbohydrate epoxides have been found[32a,b,c] to give halogeno derivatives. For example, methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside reacted with methylmagnesium iodide to give methyl 4,6-O-benzylidene-3-deoxy-3-iodo-α-D-glucopyranoside:



Aliphatic nitro compounds are known[33] to react with Grignard reagents giving rise to various reduction products. When only one equivalent of organometallic compound is taken, dialkyl nitronates are generally formed in good yields. Acidification of these does not release isolable dialkyl nitronic acids but instead gives rise to dialkyl nitroxides, R_2NO. With more than one equivalent of reagent, oxygen removal may take place, usually to give hydroxylamines.

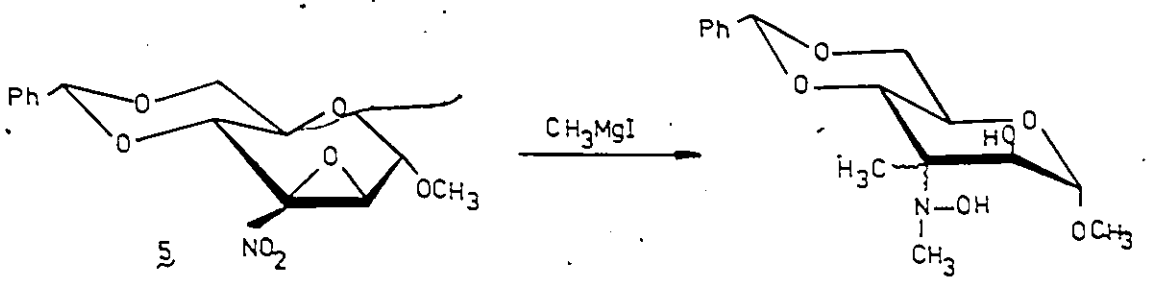


Based on the above considerations, one judiciously may expect that a molecule containing both nitro and epoxy functions can possibly lead to hydroxylamine derivatives when reacted with excess Grignard reagent. It therefore appeared attractive to investigate the behaviour of carbohydrate α-nitroepoxides in the Grignard reaction. Treatment of the α-D-manno and β-D-allo derivatives (5 and 6) with methyl magnesium iodide in ether resulted in complete transformation, according to t.l.c. Crystalline reaction

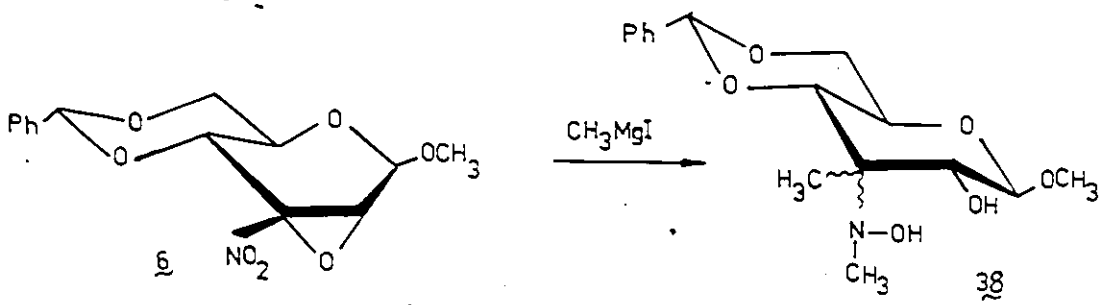
products could be isolated in yields of 40-50%. The α-D-talo and β-D-gulo isomers (7 and 8) as well as the 5,6-anhydro sugar 15 reacted also, as indicated by t.l.c., but processing of the reaction mixture presented difficulties which could not be overcome, and products could not be isolated.

The products obtained from 5 and 6 were shown by chemical analysis to have the composition $C_{16}H_{23}NO_6$ (molecular weight 325.3, verified by the production of molecular ion peaks in mass spectra). Clearly the nitrogen atom was retained but the products contained one less oxygen atom and two more carbon atoms than the starting materials. The i.r. spectra showed hydroxyl bands in the 3400 cm^{-1} region and bands possibly attributable to C-N vibration at 1220 - 1020 cm^{-1}, but they lacked the characteristic nitro group absorptions in the 1550 cm^{-1} region. The n.m.r. spectra, to be discussed in more detail below, showed three methyl singlets with chemical shifts in accord with O-CH_3, N-CH_3 and C-CH_3 groups. The data permitted the products to be assigned the constitution of methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-3-(N-methyl-hydroxylamino)-hexopyranosides (37 and 38). Compound 37 (from 5) possessed an axial hydroxyl group at C-2 whereas compound 38 (from 6) possessed an equatorial one. The configurations at the quaternary carbon C-3 could not be

deduced from available data.



5 37



6 38

Although compounds 37 and 38 gave reasonably good 100-MHz n.m.r. spectra, we shall discuss here their more highly resolved 250-MHz spectra which were obtained by courtesy of Dr. J. Defaye, Grenoble, France, to whom the author expresses his thanks.

The spectrum of compound 37 in $CDCl_3$ (Fig14a) contained two apparent singlets at τ 5.34 and 5.82, taken to represent H-1 and H-2, respectively ($J_{1,2} = 0$ Hz). The very small coupling indicated diequatorial orientations of these protons. There was a sextet for H-5 ($J_{5,6e} = 5$ Hz, $J_{4,5} = J_{5,6a} = 10$ Hz) at τ 5.45, followed by a quartet for H-6e ($J_{5,6e} = 5$ Hz;

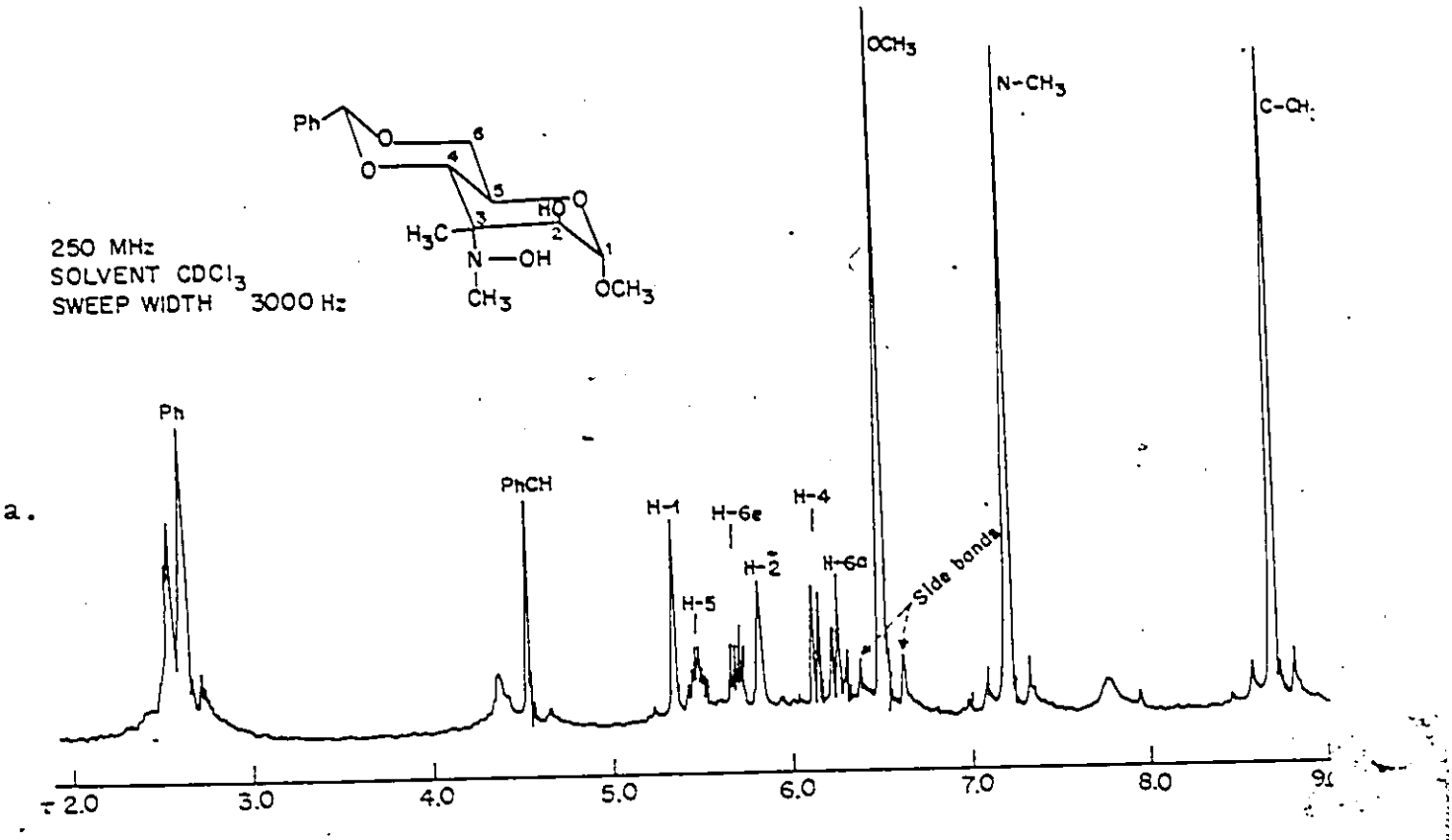
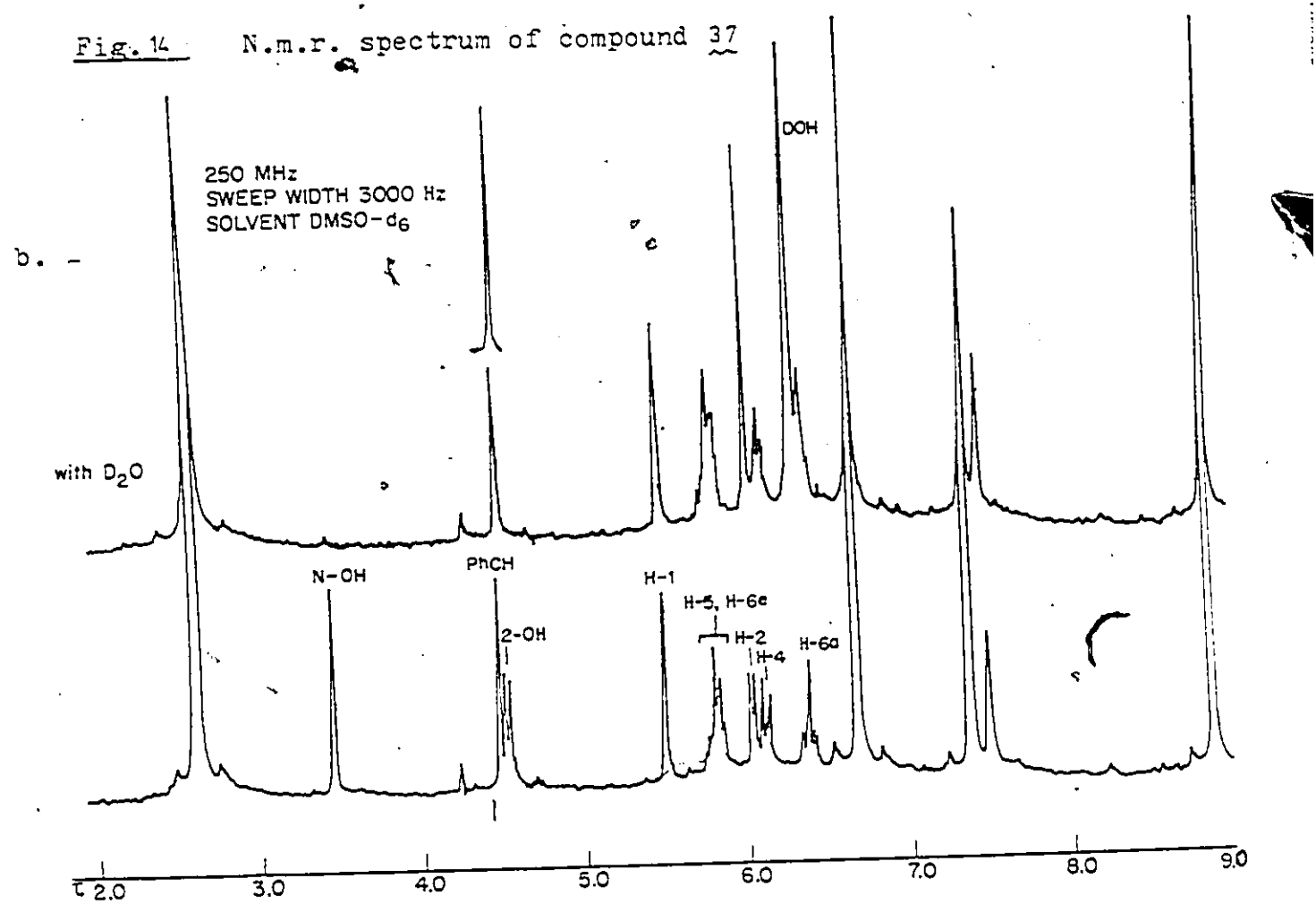


Fig. 14 N.m.r. spectrum of compound 37



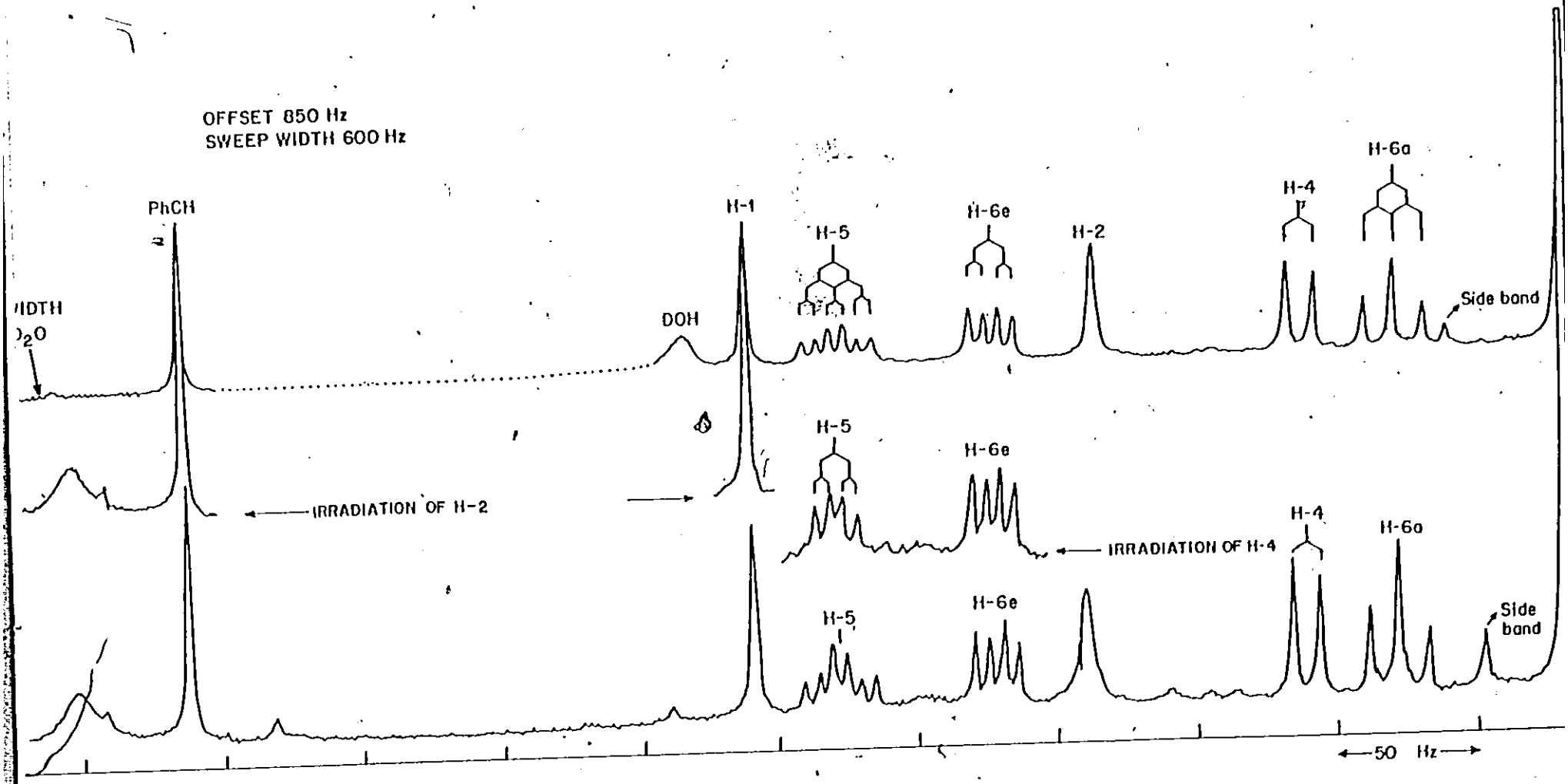


Fig. 15 Expansion and Spin decoupling of N.m.r. spectrum of compound 37

$J_{6a,6e}$ = 10 Hz) at τ 5.69. A doublet ($J_{4,5}$ = 10 Hz) at τ 6.12 and triplet ($J_{5,6a} = J_{6a,6e}$ = 10 Hz) were attributed to H-4 and H-6a, respectively. Signals in the τ 4.20-4.46 region and at 4.70 presumably belonged to 2-OH and N-OH as evidenced from deuterium exchange. In order to resolve them, a similar n.m.r. spectrum was run in DMSO-d_6 (Fig14b). Here N-OH appeared as a sharp singlet at τ 3.44, and 2-OH appeared as a doublet at τ 4.52 with splitting caused by H-2 which gave a doublet at τ 6.20 ($J_{2,OH}$ = 5 Hz). Both the OH singlet and OH doublet disappeared on deuterium exchange while the H-2 doublet collapsed to a singlet. A decoupling experiment involving H-4 substantiated the H-5 assignment. Upon irradiation of H-4, the sextet at τ 5.45 became a quartet ($J_{5,6a}$ = 10 Hz, $J_{5,6e}$ = 5 Hz). Lastly, the three singlets at τ 6.49, 7.20 and 8.68 represented the $\underline{O}$-CH_3, $\underline{N}$-CH_3 and $\underline{C}$-CH_3 methyl groups, respectively.

The n.m.r. spectrum of 38 in $CDCl_3$ (Fig16a) also showed three sharp singlets at τ 6.40, 7.18 and 8.55 for $\underline{O}$-CH_3, $\underline{N}$-CH_3 and $\underline{C}$-CH_3, respectively. Two doublets at τ 5.04 and 6.64 having a large splitting ($J_{1,2}$ = 8 Hz) were assigned to H-1 and H-2, respectively. The large splitting indicated diaxial arrangement of these protons. A quartet at τ 5.63 ($J_{5,6e}$ = 5 Hz, $J_{6a,6e}$ = 10 Hz) and a sextet at 5.84 belonged to H-6e and H-5, respectively. The signal for H-6a near τ 6.34 appeared partly obscured by the $\underline{O}$-CH_3 peak.

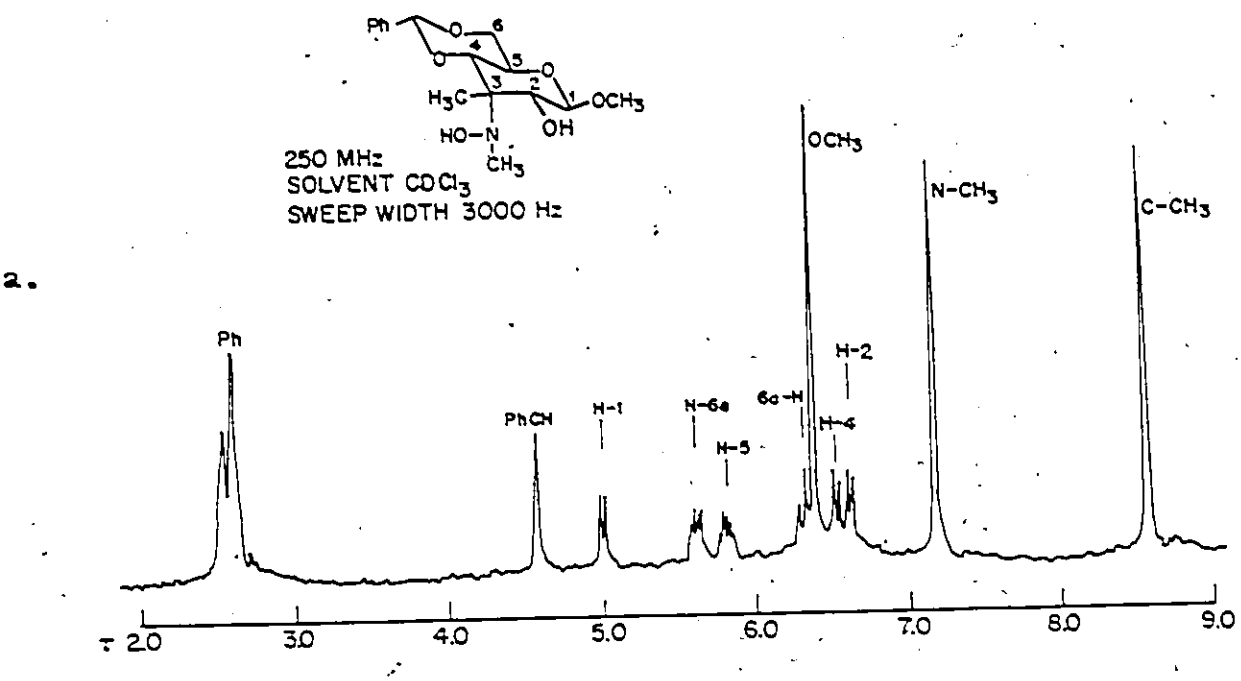
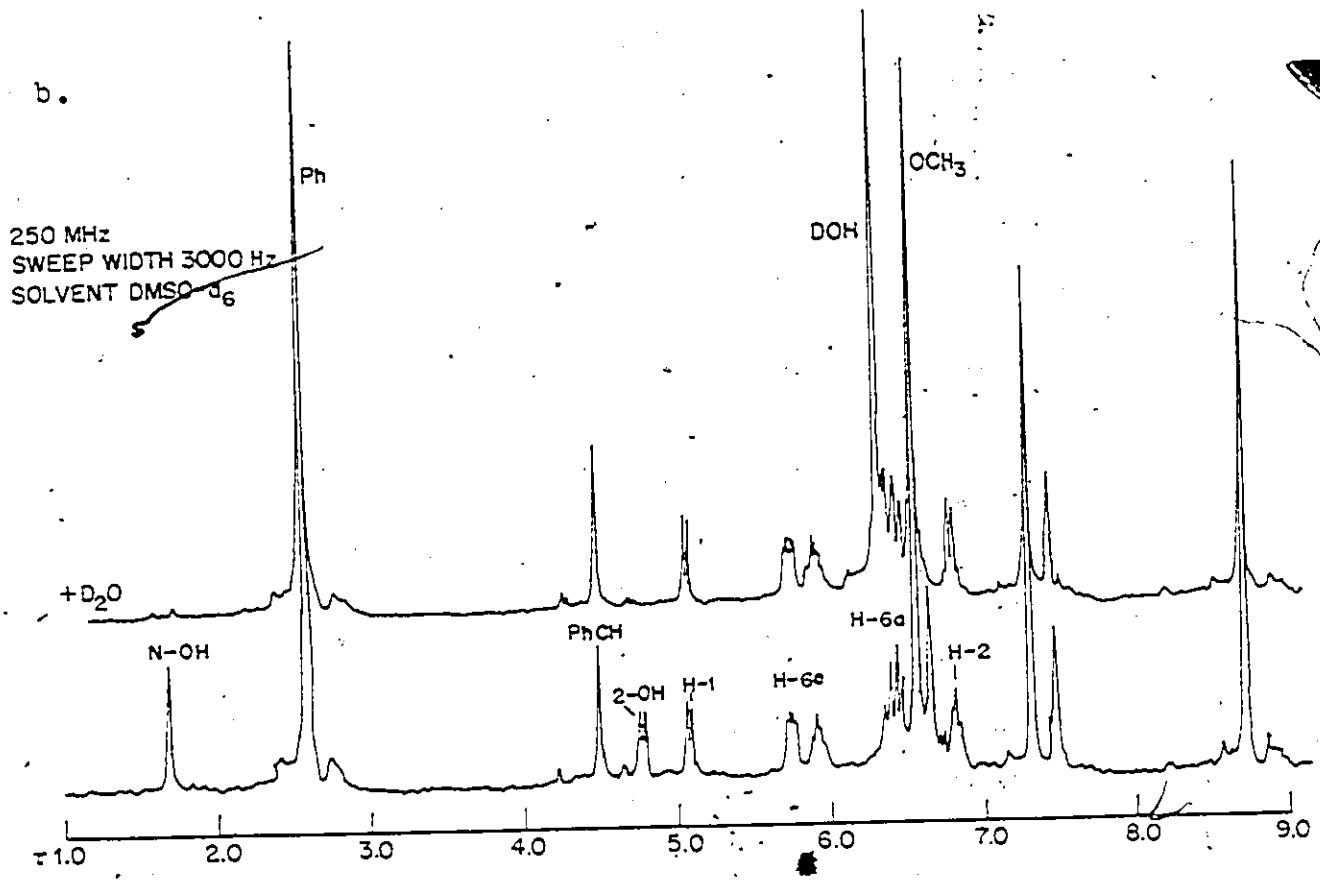


Fig. 16 Nm.r. spectrum of compound 38



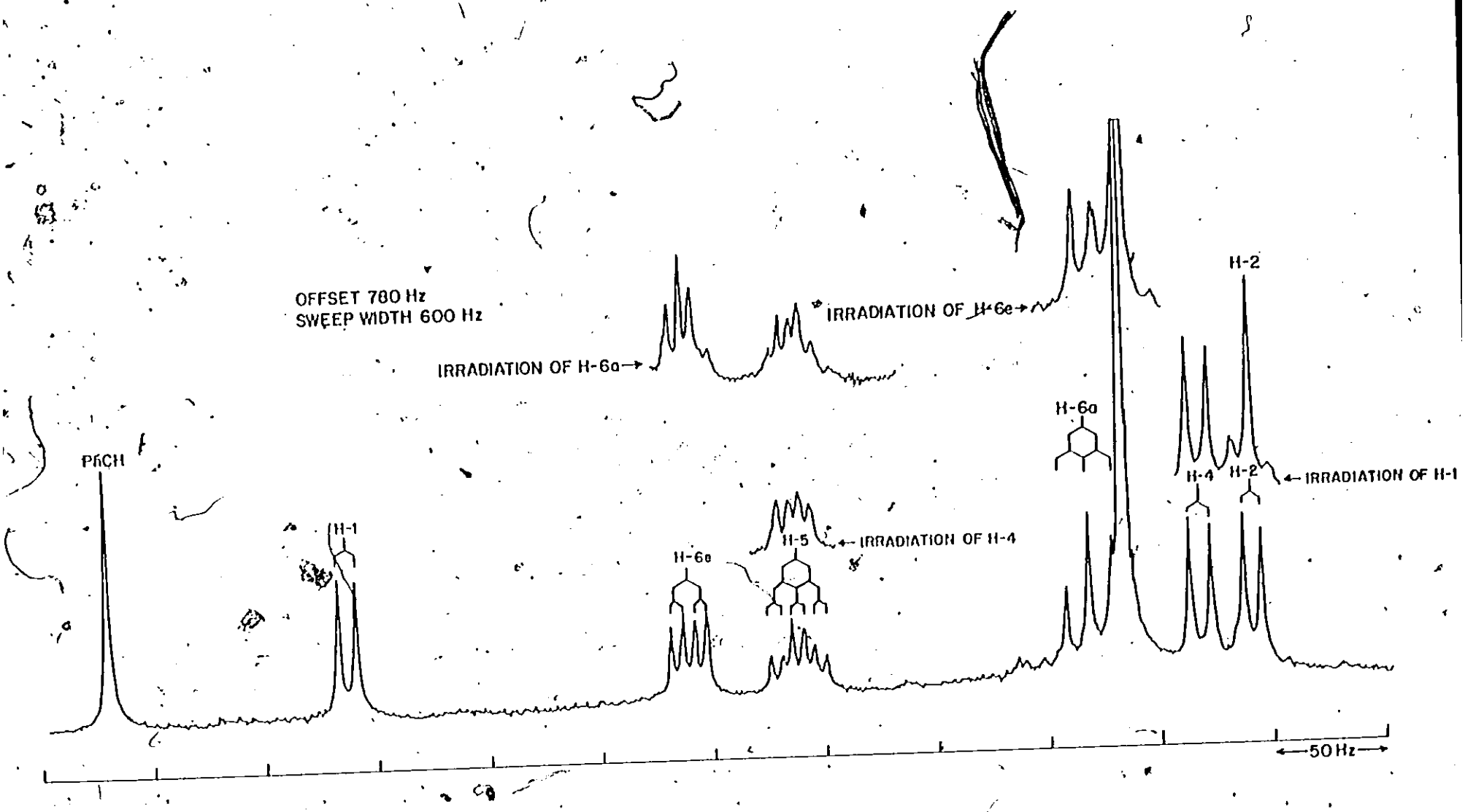


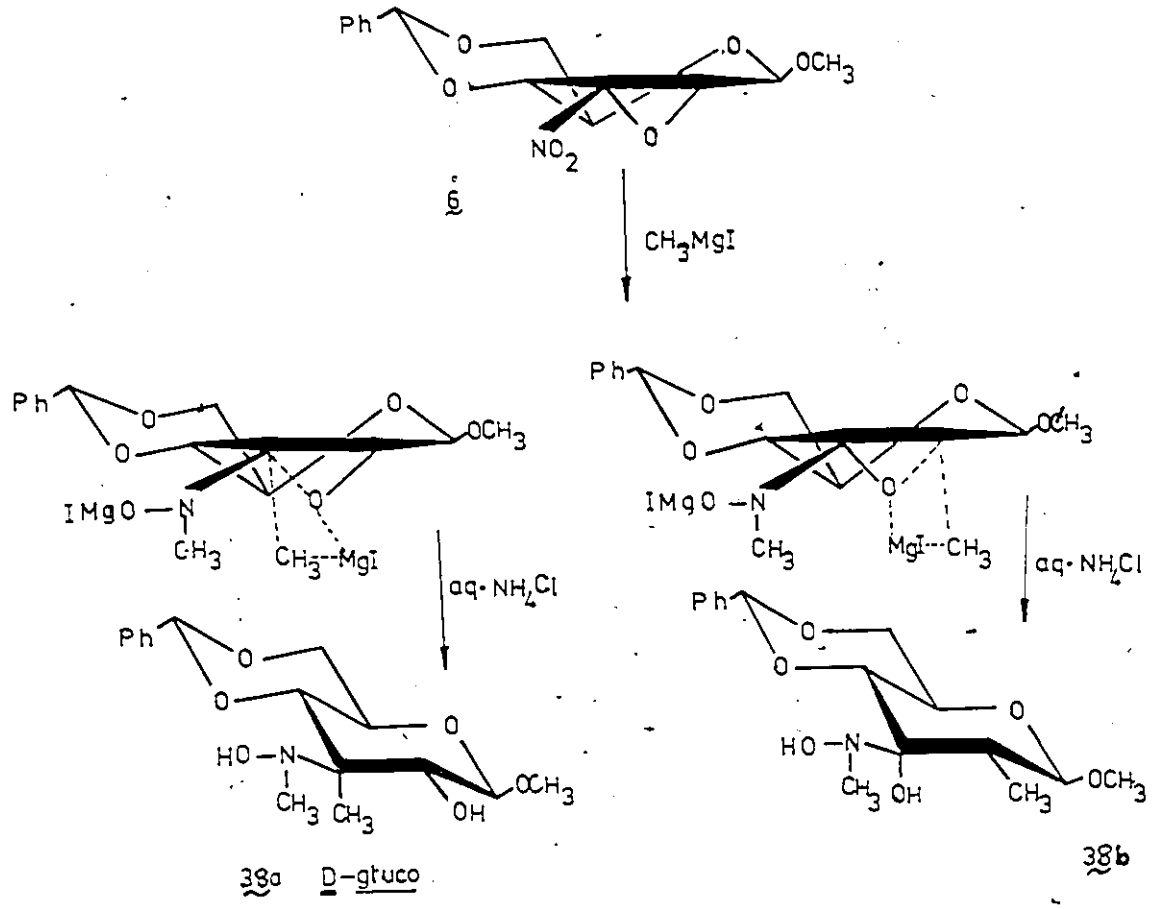
Fig. 17 Expansion and Spin decoupling of N.m.r. Spectrum of compound 38

A doublet attributable to H-4 ($J_{4,5}$ = 10 Hz) appeared at τ 6.55. Collapse of the H-2 doublet at τ 6.64 into a singlet on double irradiation of the H-1 signal supported the assignment of the former. Similarly, the assignment of H-5 was verified by irradiation of H-4, whereby the sextet at τ 5.84 collapsed into a quartet. The triplet at τ 6.34 became a doublet upon irradiation of H-6e to support H-6a assignment. Irradiation of H-6a, on the other hand, did not give a clear picture; H-5, which should have given a quartet, appeared as a quintet and H-6e became more complex. Perhaps the H-6a irradtiation was not carefully performed. For some unknown reason, the 2-OH and N-OH signals could not be accounted for in the spectrum. Therefore, another spectrum of compound 38 was obtained in DMSO-d_6 (Fig16b). This spectrum showed N-OH as a sharp singlet at τ 1.70 and 2-OH as a doublet ($J_{2,OH}$ = 8 Hz) at τ 4.78, split by H-2 which was located at τ 6.82 as a triplet. These assignments followed from the disappearance of the singlet and doublet, and collapse of the triplet into a doublet, upon deuterium exchange.

Mechanistic and Stereochemical Considerations

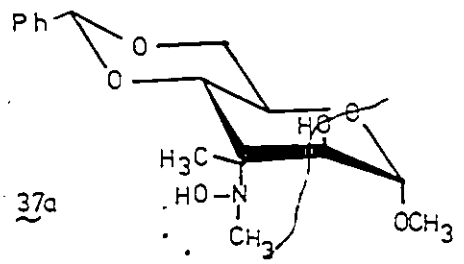
The addition of Grignard reagents to carbonyl compounds is believed to occur by a polar mechanism via a four-centered transition state or by single-electron transfer (or both simultaneously); the pathway seems to depend on the structure of the reactants, the solvent, and the purity of the magnesium metal.[34,36,37] In either event, coordination of the magnesium with the carbonyl oxygen precedes the attachment of the alkyl group to the substrate.

This mechanism could be considered for reactions of the carbohydrate α-nitroepoxides with a Grignard reagent as exemplified by the allo epoxide 6:



If complexation of methylmagnesium iodide with the oxirane oxygen were to involve the β-carbon instead of α-carbon atom, the product would be methyl 4,6-O-benzylidene-2-deoxy-2-C-methyl-3-(N-methyl hydroxylamino)-β-D-allo-pyranoside (38b). That compound 38b was not the reaction

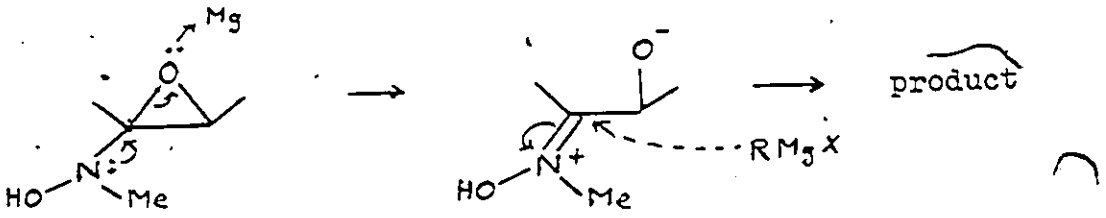
product is evident from the n.m.r. spectrum. Compound 38b would have exhibited a doublet for 2-CH_3 and quartet for H-2. As depicted above, the first step could be reductive attack[33] of the nitro group in excess Grignard reagent to give a methyl hydroxylamino oxirane intermediate, probably because the nitro group is more exposed than the oxirane ring. Complexation of the α-C-O bond in the epoxide with Grignard reagent would lead to a stereospecific opening of the oxirane ring and the product that emerges would have the D-gluco configuration (38a) as shown in the above diagram. A similar mechanism applied to epoxide 5 leads to a suggestion that the product possesses the D-altro configuration (37a).



37a

Although the above hypothesis would predict the (experimentally undetermined) configuration at C-3, it does not explain why the α-C-O bond should be cleaved in preference to the β-C-O bond even though the latter is less hindered sterically. However, one could make the additional assumption that the α-C-O bond is weakened by

the substituent present on C-3; or also, that the substituent contributes to complexing of the Grignard reagent and thus guides it to the neighbouring site of the epoxide ring. Possibly the N-methylhydroxylamino group, which is presumed to be engendered first, causes eliminative opening of the α-C-O bond, and the Grignard reagent would then attack the intermediary hydroxylimmonium species, with methylation at C-3 resulting.



Addendum to p. 29/30 and 36.

Note 1.

Dr. T. Durst has pointed out that the platinum-catalyzed hydrogenation of 5 to give 26 might proceed via an amino epoxide, i.e., with reduction of the nitro group taking place prior to the opening of the oxirane ring. The altroside 24 would then be not involved, and the experiment would not prove its intermediacy in the palladium-catalyzed hydrogenation of 5. The latter could lead directly to the mannoside 25 if one assumes that homolytic cleavage of the α-C-O bond of the oxirane produces a radical at C-3 which, being quite stable due to resonance with the nitro group, could survive until a hydrogen atom is supplied from the lower side of the sugar ring to generate the equatorial nitro group orientation. The stability of such a radical could also explain the regiospecificity of the epoxide opening.

EXPERIMENTAL

General Techniques

Melting points were determined in capillaries in an electric aluminum block apparatus equipped with a calibrated thermometer. Optical rotations were measured at about 25° in a Perkin-Elmer 141 automatic polarimeter. The i.r. spectra were obtained from Nujol mulls on Beckman IR-20 or IR-20A instruments, and significant bands only are reported as ν_{max} values. The mass spectra were obtained with a A.E.I. Ms-90 mass spectrometer. The n.m.r. spectra (100 MHz) were recorded on a Varian HA-100 spectrometer, unless otherwise stated. The t.l.c. was performed on MN-Silica Gel N/UV_{254} (without binder, Macherey & Nagel Co. Germany) with the following solvent systems (v/v): A, ethylacetate-petroleum ether, b.p. 60-80° (1:1); B, ethylacetate-petroleum ether, b.p. 60-80° (1:2); C, ethylacetate-petroleum ether, b.p. 60-80° (2:3); D, methanol-chloroform (1:2); E, methanol-chloroform (1:9); F, carbon tetrachloride-ethylacetate (3:2); G, carbon tetrachloride-ethylacetate (3:1). Column chromatography was run on silica gel 60, particle size 0.063-0.200 mm; 70-230 mesh ASTM, E. Merck AG, Darmstadt, Germany. Evaporations were carried out in vacuo at about 40° in a rotatory evaporator. Catalytic hydrogenations were done at ambient temperature and pressure. Petroleum ether, b.p. 60-80°, was used for recrystallization.

5,6-Anhydro-1,2-isopropylidene-6-nitro-α-D-gluco-furanose (15)

To a solution of 3-O-acetyl-5,6-dideoxy-1,2-O-isopropylidene-6-nitro-α-D-xylo-hex-5-enofuranose (14)[10] (92 mg) in 99% ethanol (10 ml) was added 30% aqueous hydrogen peroxide (0.5 ml). The reaction mixture, stirred at room temperature, had its pH adjusted to between 8 and 9 by dropwise addition of a saturated aqueous solution of sodium bicarbonate. According to t.l.c. (solvent A) the reaction was finished after 50 min, compound 14 having been completely replaced by a single, more slowly moving compound (15). The reaction mixture was extracted several times with chloroform. The combined chloroform extract was washed twice with water and then dried over magnesium sulfate. Upon evaporation, syrupy 15 (65 mg, 78%) was obtained. The syrup crystallized from chloroform-petroleum ether yielding 15 (53 mg, 64%) as needles of m.p. 127-128°, raised on recrystallization from ethylacetate-petroleum ether to 134-135°; $[\alpha]_D$ -5° (c, 0.4 in chloroform). The i.r. data: ν_{max} 3400 (OH); 1560 cm^{-1} (NO_2). The n.m.r. data ($CDCl_3$): τ 4.06 (d, 1H, $J_{1,2}$ = 4 Hz, H-1); 4.48(s, 1H, H-6); 5.46 (d, 1H, $J_{1,2}$ = 4 Hz, H-2); 5.59 (t, 1H, $J_{3,OH} = J_{3,4}$ = 4 Hz, H-3); 5.76 (t, 1H, $J_{3,4} = J_{4,5}$ = 4 Hz, H-4); 6.20 (d, 1H, $J_{4,5}$ = 4 Hz, H-5); 7.48 (d, 1H, $J_{3,OH}$ = 4 Hz, OH); 8.50 (s, 3H, CH_3); 8.66 (s, 3H, CH_3).

Anal. of 15, Calcd. for $C_9H_{13}NO_7$ (247.2): C, 43.7; H, 5.26;

N, 5.66.

Found: C, 43.82; H, 5.34; N, 5.81

Methyl 4,6-O-benzylidene-2-deoxy-β-D-arabino-hexo-pyranoside (16) and methyl 4,6-O-benzylidene-2-O-ethyl-β-D-mannopyranoside (17)

Methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-β-D-allopyranoside[4,5] (6) (1 g, 3 mmole) was dissolved in warm, 99% ethanol (375 ml). The solution was allowed to cool, and sodium borohydride (1.3 g, 30 mmole) was added portionwise, with swirling. According to t.l.c. (solvent C) the reaction was finished after 90 min, compound 6 having been completely replaced by two products of which the more slowly moving one predominated. The reaction mixture was deionized with Amberlite IR-120 (H^+). The resin was filtered off and washed several times with ethanol. The filtrate was evaporated to dryness, and seven 10-ml portions of methanol were successively added to and evaporated from the residue in order to remove the boric acid. A flame test for boric acid was then negative. The resulting oil was crystallized from chloroform-petroleum ether. There was obtained 163 mg of crystalline 16 (the more slowly moving product; m.p. 150-151°), and upon evaporation of the mother liquor, a crystalline mixture of 16 and 17. The mixture was chromatographed on a column (47x2 cm) of silica gel (110 g) by use of solvent B as eluent. The first chromatographically homogeneous fractions yielded

upon evaporation syrupy 17 (182 mg, 20%) which crystallized from the same solvents; m.p. 129°, unchanged on recrystallization; $[\alpha]_D$ -126° (c, 0.4 in ethanol). The yield of crystalline 17 was 155 mg. The n.m.r. data ($CDCl_3$): τ 4.46 (s, 1H, $PhCHO_2$); 5.48 (s, 1H, $J_{1,2}$ = 0, H-1); 5.78 (q, 1H, $J_{6a,6e}$ = 12 Hz, $J_{5,6e}$ = 5Hz, H-6e); 6.26 (q, 2H, J_{CH_2, CH_3} = 6 Hz, CH_2 of ethyl); 5.98-6.46 (m, 5H, H-2, H-3, H-4, H-5 and H-6a); 6.59 (s, 3H, OCH_3); 8.86 (t, 3H, J_{CH_2,CH_3} = 6 Hz, CH_3).

Subsequent fractions from the column furnished another 271 mg of 16; m.p. 148-149°, undepressed upon admixture of 16 previously crystallized. The combined yield of this product was thus 434 mg (60%). Further recrystallization from ethylacetate-petroleum ether raised the melting point of 16 to 155-156°; $[\alpha]_D$ -67° (c, 0.5 in chloroform). The n.m.r. data ($CDCl_3$): τ 4.51 (s, 1H, $PhCHO_2$); 5.57 (q, 1H, $J_{1,2a}$ = 8 Hz, $J_{1,2e}$ = 2 Hz, H-1); 5.71 (q, 1H, $J_{6e,6a}$ = 10 Hz, $J_{5,6e}$ = 6 Hz, H-6e); 6.03-6.79 (m, 4H, unresolved, H-3, H-4, H-5, H-6a); 6.58 (s, 3H, OCH_3); 7.80 (octet, 1H, $J_{2a,2e}$ = 10 Hz, $J_{1,2e}$ = 2 Hz, $J_{2e,3}$ = 4 Hz, H-2e); 8.37 (octet, 1H, $J_{2a,2e}$ = 10 Hz, $J_{1,2a}$ = 8 Hz, $J_{2a,3}$ = 8 Hz, H-2a).

Anal. of 16: Calcd. for $C_{14}H_{18}O_5$ (266.3): C, 63.14; H, 6.81
Found: C, 63.11; H, 6.82

Anal. of 17: Calcd. for $C_{16}H_{22}O_6$ (310.3): C, 61.92; H, 7.15
Found: C, 61.76; H, 7.20

2-Deoxy-β-D-arabino-hexose anilide (16a)

A solution of compound 16 (65 mg) in 0.05 N hydrochloric acid (11 ml) was first stirred for 4 h at room temperature and then heated on a steam bath for 2 h. The t.l.c. (solvent D) of the pale yellow hydrolyzate showed a single spot, which moved more slowly than that of 16. The solution was neutralized with Dowex-1x2(CO_3^{--}) which after filtration was washed several times with water. The filtrate was evaporated, and several portions of added benzene were evaporated from the residue. An oil was obtained (20 mg) whose n.m.r. spectrum in chloroform-d indicated absence of benzylidene and methoxyl groups. The oily product was dissolved in ethanol (2 ml), aniline (0.2 ml) was added, and the mixture was refluxed on a steam bath for 1.5 h. A clean reaction giving a single product was indicated by t.l.c. (solvent D). The reaction mixture was treated with activated charcoal, filtered, and kept in the refrigerator overnight whereby crystalline anilide (20 mg, 74%) was deposited; m.p. 193-194° as reported[11]; $[\alpha]_D$ -162.4° → -103° (c, 1 in pyridine, 2 days); reported[11], $[\alpha]_D$ -138° → -106° (c, 1 in pyridine, 2 days).

Methyl 4,6-O-benzylidene-2-deoxy-β-D-lyxo-hexopyranoside (18)

Methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-β-D-talopyranoside[4,5] (9) (100 mg, 0.4 mmole) was dissolved

in warm, 99% ethanol (40 ml). The solution was allowed to cool, and sodium borohydride (128 mg, 4 mmole) was added portionwise with swirling. According to t.l.c (solvent D) the reaction was finished after 30 min, compound 9 having been completely replaced by a single product. The reaction mixture was deionized with Amberlite IR-120(H^+). The resin was filtered off and washed several times with ethanol. The filtrate was evaporated to dryness, and five 10-ml portions of methanol were successively added to and evaporated from the residue in order to remove the boric acid. The resulting solid residue was passed through a column (19x1 cm) of silica gel (40 g), using chloroform as eluent. Upon evaporation, the fractions yielded crystalline 18 (65.7 mg, 76%); m.p. 200-204°; $[\alpha]_D$ -40.5° (c,0.36 in chloroform). The n.m.r. data ($CDCl_3$): τ 4.43 (s, 1H, $PhCHO_2$); 5.66 (q, 1H, $J_{1,2a}$ = 12 Hz, $J_{1,2e}$ = 2 Hz, H-1); 5.69 (t, 1H, $J_{3,4} = J_{4,5}$ = 3 Hz, H-4); 5.87 (q, 1H, H-6e); 5.99 (q, 1H, H-6a); 6.21 (octet, 1H, $J_{3,4}$ = 3 Hz, $J_{2a,3}$ = 12 Hz, $J_{2e,3}$ = 5 Hz, H-3); 6.51 (s, 3H, OCH_3); 6.57-6.73(m, 1H, unresolved, H-5); 7.83-8.53 (m, 2H,unresolved, H-2a, H-2e).

Anal. of 18; Calcd. for $C_{14}H_{18}O_5$ (266.3): C, 63.15; H, 6.85
Found: C, 63.13; H, 6.86

Methyl 4,6-O-benzylidene-2-deoxy-α-D-xylo-hexopyranoside (19) and methyl 4,6-O-benzylidene-2-deoxy-α-D-lyxo-hexopyranoside (20)

Methyl 2,3-anhydro-4,6-O-benzyliden-3-nitro-α-D-talopyranoside[4,5] (7) (300 mg) was dissolved in warm 99% ethanol (66 ml). The solution was allowed to cool, and sodium borohydride (732 mg) was added. The reaction mixture was refluxed for 35 min. T.l.c. (solvent F) revealed the presence of some starting material 7 and appearance of two faster-moving products. An additional 366 mg of sodium borohydride was added and refluxing continued for another 15 min, at the end of which the t.l.c. (solvent F) showed total consumption of 7. The reaction mixture was deionized with Amberlite IR-120(H^+). The resin was filtered off and washed several times with methanol. The filtrate was evaporated to dryness, and six 10-ml portions of methanol were successively added to and evaporated from the residue in order to remove boric acid. The resulting crude mixture was chromatographed on a column (19x1 cm) of silica gel (40 g) by use of solvent G as eluent. The first chromatographically homogeneous fractions yielded upon evaporation, pure syrupy 19 (93 mg, 40%), which crystallized from chloroform-petroleum ether; m.p. 99-101°, unchanged on recrystallization; $[\alpha]_D$ +78° (c, 0.5 in chloroform); reported[12]: m.p.102-104°, $[\alpha]_D$ +79° (c, 1.190 in chloroform). Yield: 32 mg. The n.m.r. data ($CDCl_3$): τ 4.44

(s, 1H, $PhCHO_2$); 5.24 (d, 1H, $J_{1,2a}$ = 4 Hz, $J_{1,2e}$ = 0, H-1); 5.70 (q, 1H, $J_{6e,6a}$ = 12 Hz, $J_{5,6e}$ = 2 Hz, H-6e); 5.93 (q, 1H, $J_{5,6a}$ = 2 Hz, $J_{6a,6e}$ = 12 Hz, H-6a); 6.02-6.52 (m, 3H, unresolved, H-3, H-4 and H-5); 6.62 (s, 3H, OCH_3); 7.74 (q, 1H, $J_{2e,2a}$ = 14 Hz, $J_{1,2a}$ = 4 Hz, H-2a); 8.19 (d, 1H, $J_{1,2e}$ = 0, H-2e).

Subsequent fractions from the column furnished 106 mg (50%) of 20 as needles; m.p. 167-175°, raised to 186-188° on recrystallization from ethylacetate-petroleum ether; reported[13] m.p. 184-185°; $[\alpha]_D$ +117.5° (c, 0.3 in chloroform), reported[13] $[\alpha]_D$ +104° (c, 0.3 in ethanol) or reported[13a] $[\alpha]_D$ +106° (c, 0.62 in chloroform); m.p. 178-179°. The n.m.r. data ($CDCl_3$): τ 4.43 (s, 1H, $PhCHO_2$); 5.09 (t, 1H, $J_{1,2e} = J_{1,2a}$ = 2 Hz, H-1); 5.54 (q, 1H, $J_{6a,6e}$ = 13 Hz, $J_{5,6e}$ = 2 Hz, H-6e); 5.83-6.09 (m, 3H, unresolved, H-6a, H-5, H-3); 6.33-6.47 (broad peak, 1H, unresolved, H-4); 6.68 (s, 1H, OCH_3); 7.93-8.22 (m, 2H, unresolved, H-2a, H-2e).

Anal. of 19, Calcd.for $C_{14}H_{18}O_5$(266.3): C, 63.20; H, 6.76
Found: C, 63.31; H, 6.91

Anal. of 20, Calcd. for $C_{14}H_{18}O_5$ (266.3): C, 63.20; H, 6.76
Found: C, 63.24; H, 6.94

5-Deoxy-1,2-O-isopropylidene-α-D-xylo-hexose (21)

5,6-Anhydro-1,2-O-isopropylidene-6-nitro-α-D-gluco-furanose (15) (20 mg, 0.09 mmole) was dissolved in 99% ethanol (10 ml) and sodium borohydride (26 mg, 0.68 mmole)

was added portionwise with swirling. T.l.c. (solvent A) after 15 min indicated consumption of the starting epoxide and formation of a single product. The mixture was deionized with Amberlite IR-120(H^+). The resin was filtered off and washed several times with ethanol. The filtrate was evaporated to dryness and three 7-ml portions of methyl alcohol were successively added to and evaporated from the residue in order to remove boric acid. The resulting syrup (17.3 mg) was crystallized from ethylacetate-petroleum ether. There was obtained 10 mg (63%) of crystalline 21; m.p. 92-93°; reported[14], 94°; $[\alpha]_D$ -8° (c, 0.4 in chloroform), reported[14], $[\alpha]_D$ -10° (c, 0.7 in chloroform).

Anal. of 21, Calcd. for $C_9H_{16}O_5$ (204.2): C, 52.94; H, 7.84

Found: C, 52.69; H, 7.82;

Reported[14] C, 53.00; H, 7.98

6-Amino-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (22)

A suspension of platinum dioxide (150 mg) in 99% ethanol (8 ml) was prehydrogenated. Then solid epoxide 15 (300 mg) was added and the hydrogenation continued with vigorous shaking for 26 h. The reaction was complete and t.l.c. (solvent D) indicated replacement of compound 15 by a main product, contaminated in trace amounts by two other, faster compounds. The catalyst was filtered off and washed several times with ethanol. The filtrate was evaporated to dryness and 205 mg of syrup was obtained. The syrup

was purified by eluting it through a column of silica gel (10 g) with solvent D. The fractions containing the faster compounds were discarded (trace amounts). The fractions containing the major product were evaporated and a neat oil was obtained. Crystallization of this oil from methanol-ether furnished pure 22 (85 mg, 31%); m.p. 123-125°; $[\alpha]_D$ -11.3° (c, 0.3 in water). A further crop of 22 (80 mg) was obtained from the mother liquour. The i.r. data: ν_{max} 3440 (broad, OH, NH); 1615 (NH); 1220-1020 and 1390 cm^{-1} (C-N). The n.m.r. data (D_2O): τ (relative to DHO lock signal): 11.29 (d, 1H, $J_{1,2}$ = 4 Hz, H-1); 9.8 (d, 1H, $J_{3,4}$ = 2 Hz, H-3); 9.29 (q, 1H, $J_{4,5}$ = 8 Hz, $J_{3,4}$ = 2 Hz, H-4); 9.11 (sextet, 1H, $J_{4,5}$ = 8 Hz, $J_{5,6}$ = 4 Hz, $J_{5,6'}$ = 8 Hz, H-5); 8.17 (q, 1H, $J_{6,6'}$ = 14 Hz, $J_{5,6}$ = 4 Hz, H-6); 7.97 (q, 1H, $J_{6,6'}$ = 14 Hz, $J_{5,6'}$ = 8 Hz, H-6'); 6.77 (s, 3H, CH_3); 6.62 (s, 3H, CH_3).

Anal. of 22; Calcd. for $C_9H_{17}NO_5$ (219.3): C, 49.30; H, 7.82; N, 6.39

Found: C, 49.31; H, 7.79; N, 6.41

6-Acetamido-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (22a)

To a solution of compound 22 (14.6 mg) in methanol (0.5 ml) was added a few drops of acetic anhydride. The solution was evaporated and the incipient crystals were redissolved in methanol and evaporated several times. The resulting residue was dried in vacuo for several hours and washed thoroughly with ether. Pure crystalline compound 22a,

(16.7 mg, 97%) was obtained; m.p. 166-167°; reported[18] m.p. 165-167°; $[\alpha]_D$ +6° (c, 0.5 in methanol); reported[18] $[\alpha]_D$ +5° (in methanol).

Methyl 4,6-O-benzylidene-3-deoxy-3-nitro-β-D-gluco-pyranoside (23) and methyl 4,6-O-benzylidene-3-deoxy-3-oximino-β-D-ribo-hexopyranoside (23a)

A mixture of methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-β-D-allopyranoside[4,5] 6 (400 mg, 1.3 mmole) and palladium on carbon (96 mg) in 99% ethanol (40 ml) was hydrogenated for 24 h with vigorous shaking. The t.l.c. (solvent C) indicated absence of the starting material and appearance of two new products, of which the faster moving one predominated. The catalyst was filtered off and washed several times with ethanol. The filtrate was evaporated to dryness and a crystalline mixture of 23 and 23a (415 mg) was obtained. The mixture was chromatographed on a column (19x1 cm) of silica gel (40 g) using solvent C as the eluent. The first chromatographically homogeneous fractions yielded upon evaporation crystalline 23 (345 mg, 90%); m.p. 181-183°; undepreesed upon admixture of an authentic sample[21]. Its n.m.r. and i.r. spectra were identical with those of the authentic sample[21].

Subsequent fractions from the column furnished crystalline 23a (27 mg, 7%); m.p. 169° (with decomposition), unchanged on recrystallization from ethylacetate-petroleum ether; $[\alpha]_D$ -55.7° (c, 0.4 in chloroform). The i.r. data:

ν_{max} 3390-3100 (broad, N-OH, OH); 1570-1600 cm^{-1} (weak, C=N). The n.m.r. data (acetone-d_6): τ 4.32 (s, 1H, $PhCHO_2$); 5.17 (d, 1H, $J_{1,2}$ = 7 Hz, H-1); 5.21 (d, 1H, $J_{1,2}$ = 7 Hz, H-2); 5.27 (d, 1H, $J_{4,5}$ = 9 Hz, H-4); 5.77 (m, 1H, $J_{5,6a}$ = 10 Hz, $J_{4,5}$ = 9 Hz, $J_{5,6e}$ = 5 Hz, H-5); 5.86 (q, 1H, $J_{6a,6e}$ = 10 Hz, $J_{5,6e}$ = 5 Hz, H-6e); 6.42 (t, 1H, $J_{6a,6e}$ = $J_{5,6a}$ = 10 Hz, H-6a); 6.61 (s, 3H, OCH_3).

Anal. of 23a; Calcd. for $C_{14}H_{17}NO_6$ (295.3): C, 56.93; H, 5.80; N. 4.74. Found: C, 57.11; H, 5.92; N, 4.60

Methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-manno-pyranoside (25)

A mixture of methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-α-D-mannopyranoside[4,5] (5) (200 mg) and palladium on carbon (20 mg) in 99%ethanol (20 ml) was hydrogenated for 25 h with vigorous shaking. The catalyst was filtered off and washed several times with ethanol. The filtrate was concentrated under diminished pressure to a syrupy product which was purified by eluting it through a column of silica gel (110 g) with solvent C. The fractions upon evaporation yielded syrupy 25 (203 mg, 98%) which was homogeneous as indicated by t.l.c. (solvent C). This syrup crystallized from chloroform-petroleum ether, affording 140 mg (70%) of prisms; m.p. 143-144°, unchanged on re-crystallization from the same solvent, and undepressed on admixture of an authentic sample[22]; $[\alpha]_D$ +27.3° (c, 1.0 in chloroform) ;reported[22], $[\alpha]_D$ +27.7° (c, 0.8 in

chloroform). The i.r. and n.m.r. spectra of 25 were identical with those of the authentic sample[22].

Methyl 3-amino-3-deoxy-α-D-altropyranoside hydrochloride (26) and methyl 3-acetamido-3-deoxy-2,4,6-tri-O-acetyl-α-D-altropyranoside (27)

A suspension of platinum dioxide (100 mg) in 90 % ethanol (5 ml) was prehydrogenated in the presence of hydrochloric acid (0.3 ml, 0.3 mmole). Then a suspension of epoxide 5 (100 mg, 0.3 mmole) in ethanol (4 ml) was added and the hydrogenation was continued. According to t.l.c. (solvent D), the reaction was finished after 20 h, compound 5 having been replaced by three products of which the most slowly moving one predominated and the other two appeared as mere traces. The catalyst was filtered off and washed several times with ethanol. The filtrate was evaporated to dryness. There was obtained a semicrystalline residue (71 mg) which upon crystallization from ethanol-acetone furnished 40 mg of a very hygroscopic solid (26), m.p. 179°; $[\alpha]_D$ +84.2° (c, 0.3 in water); i.r. data: ν_{max} 1600 - 1575 and 1500 cm^{-1} ($\overset{+}{N}H_3\bar{C}l$). A mixture of this solid (30 mg), acetic anhydride (8 ml), and anhydrous sodium acetate (900 mg) was heated on a steam bath for 30 min. A clean reaction giving a single, faster moving product was indicated by t.l.c. (solvent D). The reaction mixture was poured into ice-water and

the oil that separated was extracted with chloroform. An acetylated, oily product 27 (52 mg, still containing some acetic anhydride) was obtained upon evaporation of the extract. Crystallization of this oil from chloroform-petroleum ether furnished pure crystalline 27 in 98 % yield (46 mg); m.p. 176 - 177°; $[\alpha]_D$ +68° (c, 0.8 in pyridine); reported[25], m.p. 175 - 177°; $[\alpha]_D$ +61° (c, 1.0 in pyridine). The i.r. data : ν_{max} 3330 (sharp, NH); 1726 (C=O); 1665 cm^{-1} (N-CO). The n.m.r. data ($CDCl_3$): τ 3.46 (d, 1H, $J_{3,NH}$ = 10 Hz, N-H); 4.92 (q, 1H, $J_{3,4}$ = 6 Hz, $J_{4,5}$ = 10 Hz, H-4); 5.18 (t, 1H, $J_{1,2}$ = 2 Hz, H-2); 5.16-5.44 (m, 2H, unresolved, H-1 and H-5); 5.66 - 5.82 (m, 2H, unresolved, H-6 and H-6'); 5.82 (octet, 1H, $J_{3,NH}$ = 10 Hz, $J_{3,4}$ = 6 Hz, $J_{2,3}$ = 2 Hz, H-3); 6.54 (s, 3H, OCH_3); 7.87 (s, 3H, 2-OAc); 7.91 (s, 3H, 3-NAc); 8.00 and 8.02 (2 s, 6H, 4-OAc and 6-OAc).

Methyl 3-amino-4,6-O-bezylidene-3-deoxy-β-D-galacto-pyranoside (28)

To a suspension of 300 mg of prereduced platinum dioxide in ethanol (15 ml) was added 300 mg of methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-β-D-gulopyranoside 8[4,5], and the mixture was hydrogenated for 51 h. The catalyst was filtered off and washed several times with ethanol. The filtrate was evaporated to give a crystalline residue (260 mg), m.p. 200-206° (with decomposition). The t.l.c. (solvent D) showed the residue to be predominantly a single product, contaminated by a trace of a faster moving compound. The residue was partially dissolved in chloroform, leaving behind needle-like 28 (86.5 mg); m.p. 217-218°. The chloroform solution was evaporated to dryness and the resulting solid was triturated with water in which it was insoluble. A further 90 mg of 28 was thus collected; m.p. 216-217°, undepressed on admixture of needles previously isolated. The total yield was 60%; $[\alpha]_D$ -40° (c, 0.35 in ethanol). The i.r. data: ν_{max} 3380-3040 (broad, NH,OH); 1575 (NH); 1220-1020 cm^{-1} (C-N). The n.m.r. data ($CDCl_3$): τ 4.48 (s, 1H, $PhCHO_2$); 5.58-6.04 (m, 5H,unresolved, H-1, H-2, H-4, H-6e, H-6a); 6.50-6.60 (m, 1H, unresolved but $J_{5,6e}$ small, H-5); 7.20 (q, 1H, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 4 Hz, H-3); 7.53 (broad, NH_2 and OH).

Anal. of 28: Calcd. for $C_{14}H_{19}NO_5 \cdot 1/3\ H_2O$ (287.3): C, 58.52;

H, 6.66; N, 4.87. Found: C, 58.51; H, 6.60; N,5.09.

Methyl 3-acetamido-4,6-O-benzylidene-3-deoxy-β-D-galactopyranoside (29)

Five to six drops of acetic anhydride were added to a solution of the amine 28 (20 mg) in methanol (3 ml). After 5 min the t.l.c. (solvent D) showed complete consumption of 28 and appearance of a single, faster moving product. Upon evaporation of methanol, a crystalline residue of 29 (37.5 mg) was obtained; m.p. 283-285°. Recrystallization from chloroform-petroleum ether increased the melting point to 294-295°; $[\alpha]_D$ +23° (c, 0.5 in ethanol). The i.r. data: ν_{max} 3450 (OH); 3300 (N-H); 1650 (NH-CO); 1555 cm^{-1} (N-H). The n.m.r. data (DMSO-d_6): τ 4.46 (s, 1H, $PhCHO_2$); 5.77 (d, 1H, $J_{1,2}$ =8 Hz, H-1); 5.85-6.07 (m, 3H, unresolved); 6.07-6.81 (m, 8H, unresolved); 8.15 (s, 3H, N-Ac).

Methyl 3-acetamido-3-deoxy-β-D-galactopyranoside (29a)

A solution of 29 (30 mg) in 70% aqueous acetic acid (55 ml) was heated on a steam bath for 20 min. The starting material 29 was completely replaced by a more slowly moving compound as became evident from t.l.c. (solvent D). The reaction mixture was evaporated to dryness with added methanol to give solid 29a, which was recrystallized from methanol-ether. Needles (19 mg, 70%) were collected; m.p. 230-232°, unaltered upon further recrystallization and undepressed upon admixture of an authentic sample[26]. $[\alpha]_D$ +50° (c,0.5in water); reported[26], $[\alpha]_D$ +52° (c,1 in water).

Methyl 4,6-O-benzylidene-3-deoxy-3-nitro-α-D-talopyranoside (30)

A suspension of platinum dioxide (600 mg) in methanol (12 ml) was prehydrogenated in the presence of acetic anhydride (5 ml). Epoxide 7 (300 mg) was added and the hydrogenation continued for 28 h. After this period of time compound 7 had been largely replaced by a more slowly moving product (30) although some 7 remained, according to t.l.c. (solvent B). The catalyst was filtered off and washed several times with methanol. The filtrate was evaporated to dryness to give 275 mg of syrup. A precipitate appeared upon treatment of the syrup with methanol. The isolated solid (52 mg)was a mixture of 7 and the product 30. An oil obtained upon evaporation of the mother liqour partially crystallized from ethylacetate-petroleum ether, but the crystals (50 mg) proved to be inorganic as they did not melt below 320° and left ash on combustion. The mother liqour was evaporated and the resulting , syrupy mixture (160 mg) of 7 and 30 was combined with the aforementioned solid mixture (52 mg) for column chromatography on silica gel (30 g) with solvent B. Evaporation of the first fractions yielded crystalline 7 (22 mg), identical in melting point, m.p. 216-217° (undepressed on admixture) and i.r. data with a sample of the starting material. The subsequent fractions yielded crude crystalline 30 (100 mg) upon evaporation; m.p. 159-161°, raised to 181-182° by recrystallization from ethylacetate-petroleum ether; $[\alpha]_D$ +70.9° (c, 0.4

in chloroform); Reported[20], m.p. 175°; $[\alpha]_D$ +68° (c, 1 in chloroform). The i.r. data: ν_{max} 3510 (OH); 1560 cm^{-1} (NO_2). The n.m.r. data ($CDCl_3$): τ 4.38 (s, 1H, $PhCHO_2$); 4.80-5.08 (m, 2H, unresolved, H-1 and H-4); 5.34 (t, 1H, $J_{3,4} = J_{2,3}$ = 2 Hz, H-3); 5.48 (sextet, 1H, $J_{1,2} = J_{2,3}$ = 2 Hz, $J_{2,OH}$ = 12 Hz, H-2); 5.54 (q, 1H, $J_{6e,6a}$ = 12 Hz, $J_{5,6e}$ = 2 Hz, H-6e); 5.83 (q, 1H, $J_{6e,6a}$ = 12 Hz, $J_{5,6a}$ = 2 Hz, H-6a); 6.20-6.38 (m, 2H, unresolved, H-5 and OH); 6.52 (s, 3H, OCH_3).

5-Deoxy-5-dimethylamino-1,2-O-isopropylidenehexodialdo-1,4:6,3-difuranose (31a)

To a solution of epoxide 15 (300 mg) in 99% ethanol (10 ml) was added 25% aqueous dimethylamine (4 ml). The reaction, which proceeded with change of colour from colourless to yellow, lasted 1 h. The reaction mixture was diluted with water and then extracted with ether. The combined ethereal extract was washed several times with water. The light-yellow extract thus obtained was partially decolourized using activated charcoal and then dried over anhydrous potassium carbonate. The drying agent was filtered off and washed thoroughly with ether. Upon evaporation of the filtrate, a dark oil (228 mg) was obtained. The oil crystallized from hexanes, affording crystalline 31a contaminated by a dark precipitating oil (tar). The tar was separated from the product with a pipette. The dirty product was redissolved in chloroform and more charcoal

added. Upon evaporation of the filtrate, 30 mg (10%) of crude 31a was obtained. Recrystallization from hexanes afforded pure 31a: mp. 142-144°; $[\alpha]_D$ -10° (c, 0.5 in chloroform). The product appeared homogeneous in t.l.c. (solvent B) but n.m.r. data indicated a mixture of two isomers, probably differing at C-5. The i.r. data: ν_{max} 1120-1020 cm^{-1} (C-N). The n.m.r. data ($CDCl_3$) suggested that a major and a minor component were present in a ratio of about 2 : 1. Signals attributable to the major component: τ 4.12 (d, 1H, $J_{1,2}$ = 4 Hz, H-1); 7.27 (q, 1H, J = 2.5 and 4.5 Hz, H-5); 7.60 (s, $N(CH_3)_2$). The corresponding signals of the minor component: τ 4.01 (d, 1H, $J_{1,2}$ = 4 Hz, H-1); 6.98 (m, narrow, H-5); 7.66 (s, $N(CH_3)_2$). The H-2 signals overlapped near τ 4.66, and the H-3 signals, at τ 5.12. An unresolved 3H multiplet was at 5.18-5.50 (H-4, H-6, OH). The isopropylidene resonances (s, 3H) were at τ 8.52 and 8.68.

Anal. of 31a; Calcd. for $C_{11}H_{19}NO_5$ (245.3): C, 53.87; H, 7.75; N, 5.71. Found: C, 53.79; H, 7.94; N, 5.88.

1,5-Anhydro-4,6-O-benzylidene-2-deoxy-2,3-bis(dimethylamino)-D-arabino (?)-hex-1-enitol (33)

From 6: Epoxide 6 (400 mg) was dissolved in 25% aqueous dimethylamine (28 ml) and the solution was stirred at room temperature. There was a colour change from near colourless to yellow as the reaction progressed. According to t.l.c. (solvent B), the reaction stopped after 75 min with the

formation of a main product and a trace of a slightly faster moving second product. The reaction mixture was diluted with some water and then extracted with ether. The combined ether extract was washed twice with water, dried over potassium carbonate, and partially decolourized with activated charcoal. Upon evaporation of the filtrate, 393 mg of syrup, which crystallized on standing, was obtained. Recrystallization from chloroform- petroleum ether furnished 227 mg (53%) of 33 as prisms; m.p. 131-133°; $[\alpha]_D$ -155.5° (c, 0.4 in chloroform); $[\alpha]_D$ -147.3° (c, 0.99 in ethanol). The i.r. data: ν_{max} 3350 (OH); 1625 (C=C); 1560 ($N-CH_3$); 1220-1020 cm^{-1} (C-N). The n.m.r. data (60 MHz, $CDCl_3$): τ 2.37 (s, 1H, H-1) ; 4.37 (s, 1H, $PhCHO_2$); 5.37-6.10 (m, unresolved, 4H, H-5, H-6a, H-6e, OH); 6.24 (d, 1H, $J_{4,5}$ = 8 Hz, H-4); 6.80 (s, 6H, $N(CH_3)_2$); 7.30 (s, 6H, $N(CH_3)_2$).

Anal. of 33; Calcd. for $C_{17}H_{24}N_2O_4$ (320.4): C, 63.72; H, 7.55; N, 8.75. Found: C, 63.92; H, 7.34; N, 8.56.

From 5: To a solution of 200 mg of epoxide 5 in chloroform was added 21 ml of 25% aqueous dimethylamine. The heterogeneous mixture (two layers) was warmed on a steam bath for 5 min and then stirred at room temperature for 48 h. Upon phase separation, the chloroform layer was evaporated to give a crystal-containg syrup which was triturated with ethylacetate. A small amount of insoluble unidentified solid (11 mg, m.p. 360° with decomposition) was removed.

The mother liqour was evaporated, furnishing 210 mg (98%) of a syrup which refused to crystallize. The n.m.r. data were identical to those of the crystalline 33 made from 6.

1,5-Anhydro-4,6-O-benzylidene-2-deoxy-2-dimethylamino-D-erythro-hex-1-en-3-ulose (32)

A solution of 33 (190 mg, from 6) in a small amount of chloroform was passed through a column of silica gel (15 g) with solvent C, The t.l.c. (solvent C) of the fractions from the column indicated the appearance of a faster compound, different from the starting material 33. Evaporation of the fractions gave crystalline 32 (63 mg, 40%); m.p. 128-129°; $[\alpha]_D$ +195° (c, 0.4 in chloroform). A mixture melting point with 33 was strongly depressed. Possibly the product 32 adsorbed fairly strongly on the silica gel, hence the low yield. The i.r. data: ν_{max} 1710 (C=O); 1600 (C=C); 1220-1020 cm^{-1} (C-N). The n.m.r. data ($CDCl_3$): τ 3.04 (s, 1H, H-1); 4.51 (s, 1H, $PhCHO_2$); 5.42-5.90 (m, 3H, narrow, H-5, H-6, H-6'); 5.99 (d, 1H, $J_{4,5}$ = 9 Hz, H-4).

Anal. 32; Calcd. for $C_{15}H_{17}NO_4$ (275.3): C, 65.43; H, 6.22; N, 5.09. Found: C, 65.25; H, 6.31; N, 4.97.

Similarly, syrupy 33 (155 mg from 5) was eluted through a column of silica gel (10 g) using solvent C. Upon evaporation of the fractions, 66 mg (43%) of crystalline residue was obtained, which was recrystallized from ethylacetate-petroleum ether; m.p. 132-134°, un-

depressed on admixture of 32 previously isolated; $[\alpha]_D$ +204° (c, 0.3 in chloroform). The n.m.r. and i.r. spectra were identical with those mentioned above.

1,5-Anhydro-4,6-O-benzylidene-2-deoxy-2,3-bis(dimethylamino)-D-lyxo(?)-hex-1-enitol (35)

From 8: A mixture of epoxide 8 (100 mg) and dimethylamine (7 ml) was heated on a steam bath until the epoxide was completely dissolved. Change of colour was noticed and after 5 min, t.l.c. (solvent A) showed total absence of the starting material 8. The reaction mixture was extracted several times with ether. The combined ether extract was washed with water, and dried over potassium carbonate, and evaporated to dryness. The resulting solid residue (m.p. 124-127°) was recrystallized from chloroform-petroleum ether, furnishing 40 mg of needle-like 35; m.p. 134-136°; $[\alpha]_D$ +28.3° (c, 0.36 in chloroform). The i.r. data: ν_{max} 3340 (OH); 1625 (C=C); 1550 ($N-CH_3$); 1220-1020 cm^{-1} (C-N). The n.m.r. data ($CDCl_3$): τ 4.33 (s, 1H, $PhCHO_2$); 5.40 (s, 1H, H-4); 5.63-6.33 (m, 5H, H-4, H-5, H-6, H-6', OH); 6.87 (s, 6H, $N(CH_3)_2$); 7.37 (s, 6H, $N(CH_3)_2$).

Anal. of 35: Calcd. for $C_{17}H_{24}N_2O_4$ (320.4): C, 63.72; H, 7.55; N, 8.75. Found: C, 63.68; H, 7.41; N, 8.89.

From 7: To a solution of methyl 2,3-anhydro-4,6-O-benzylidene-3-nitro-α-D-talopyranoside[4,5] 7 (100 mg) in chloroform(5 ml) was added 25% aqueous dimethylamine (1 ml). The reaction mixture was heated in a water bath at 60°.

Five additional 2-ml portions of dimethylamine were added at 3-h intervals. T.l.c. (solvent A) showed the reaction to be complete after 2 days. The reaction mixture was diluted with water and the phases were separated. The aqueous layer was extracted twice with chlorofrom. The combined chloroform extract was washed twice with water and dried over magnesium sulfate. After filtration and evaporation, 57 mg of syrup 35 was obtained. Crystallization of the syrup from chloroform-petroleum ether gave 20 mg of crude 35; m.p. 124-126°. Recrystallization from the same solvent raised the melting point to 135-136°. No depression was observed on admixture of the sample previously prepared from 8. Their i.r. and n.m.r. spectra were identical.

5-Deoxy-1,2-O-isopropylidene-5-C-nitromethylhexodialdo-1,4:6,3-difuranose (36)

Epoxide 15 (300 mg) was dissolved in aqueous methanol (10 ml, water-methanol v/v 5:1) and saturated aqueous barium hydroxide (6 ml) was added. The reaction proceeded at room temperature and, according to t.l.c. (solvent A), was finished after 17 h when the starting material 15 was replaced by a single, slightly more slowly moving product. The reaction mixture was extracted with chloroform three times and the combined chloroform extract was washed twice with water, dried over anhydrous sodium sulfate and evaporated to dryness. The very deep-coloured syrup (209 mg) obtained

was dissolved in chloroform and partially decolourized with charcoal. The resulting syrup was crystallized from ethylacetate-petroleum ether, whereby crystalline 36 (43 mg) was collected; m.p. 105-118°. A further crop (80 mg)was collected from the mother liqour, bringing the total yield to 114 mg (40%). Recrystallization of the crude 36 from the same solvent improved the melting point to 117-118°; $[\alpha]_D$ +63.1 (c, 0.4 in chloroform). The i.r. data: ν_{max} 3340 (OH); 1560 cm^{-1} (NO_2). The n.m.r. data ($CDCl_3$): τ 3.71 (d, 1H, $J_{1,2}$ = 4Hz, H-1); 4.72-4.90 (q, 2H, $J_{3,4}$ = 4 Hz, H-3, H-4); 5.28 (d, 1H, $J_{1,2}$ = 4 Hz, H-2); 5.38-5.78 (m, 4H, unresolved, H-5, H-6, CH_2); 7.02 (d, 1H, $J_{6,OH}$ = 4 Hz, OH); 8.62 (s, 3H, CH_3); 8.64 (s, 3H, CH_3).

Anal. of 36; Calcd.for $C_{10}H_{15}NO_7$ (261.2): C, 45.98; H, 5.75; N, 5.37. Found: C, 45.92; H, 5.86; N, 5.24.

Methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-3-(N-methyl-hydroxylamine)-α-D-hexopyranoside (37)

To a solution of freshly prepared methyl Grignard reagent (prepared by addition of 4 ml of methyl iodide to 300 mg of magnesium in ether) was added a suspension of epoxide 5 (200 mg) in 4 ml of ether. The reaction lasted 10 min and according to t.l.c. (solvent A) produced one predominant product contaminated by a trace of faster moving substance. The reaction mixture was treated with a saturated aqueous solution of ammonium chloride until no more effervescence was observed. The ether layer was

separated from the aqueous layer, which in turn was extracted several times with fresh ether. The combined ethereal extract was dried over calcium chloride and evaporated to dryness. The resulting semi-crystalline residue (180 mg) was chromatographed on a column (10x1 cm)of silica gel (10 g) using ethylacetate-petroleum ether (v/v 1:3) as the eluent. A syrupy fast moving material (28 mg) was collected from the first fractions. All attempts to crystallize it failed. No good n.m.r. or i.r. spectrum of the oil was obtained. The major product 37 (110 mg) was collected from subsequent fractions in crystalline form; m.p. 159-162°. Recrystallization of crude 37 from ethylacetate-petroleum ether gave 81 mg (42%) of plates; m.p. 163-165°, unchanged on further purification; $[\alpha]_D$ +62.5° (c, 0.3 in chloroform). The mass spectrum of 37 showed molecular ion peak m/e 325, in agreement with the expected molecular weight. The i.r. spectral data: ν_{max} 3470 (N-OH); 3440 (2-OH); 1220-1020 cm^{-1} (C-N). The n.m.r. data ($CDCl_3$, 250 MHz): τ 4.54 (s, 1H, $PhCHO_2$); 5.34 (s, 1H, $J_{1,2}$ 0, H-1); 5.45 (sextet, 1H, $J_{4,5} = J_{5,6a}$ = 10 Hz, $J_{5,6e}$ = 5 Hz, H-5); 5.69 (q, 1H, $J_{6e,6a}$ = 10 Hz, $J_{5,6e}$ = 5 Hz, H-6e); 5.82 (s, 1H, $J_{1,2}$ = 0, H-2); 6.12 (d, 1H, $J_{4,5}$ = 10 Hz, H-4); 6.29 (t, 1H, $J_{6a,6e} = J_{5,6a}$ = 10 Hz, H-6a); 6.49 (s, 3H, OCH_3); 7.20 (s, 3H, $N\text{-}CH_3$); 8.68 (s, 3H, $C\text{-}CH_3$)

Anal. of 37; Calcd. for $C_{16}H_{23}NO_6$ (325.3): C, 59.07; H, 7.08; N, 4.30. Found: C, 59.32; H, 7.18; N, 4.23.

Methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-3-(N-methyl-hydroxylamino)-β-D-hexopyranoside (38)

The methyl Grignard reagent was prepared as described in the foregoing section. To this reagent was slowly added a suspension of epoxide 6 (200 mg) in 3 ml of ether. The exothermic reaction was finished after 30 min and according to t.l.c. (solvent A) led to total consumption of the starting material and formation of a more slowly moving product. The reaction mixture was evaporated to dryness. The resulting solid residue was redissolved in chloroform and deionized with Amberlite IR-120(H^+) until pH 6-7 was attained. The resin was filtered off and washed several times with chloroform. The combined chloroform washings were evaporated and 180 mg of a partly crystallizing syrup was obtained. Crystallization from chloroform-petroleum ether gave 97 mg (50%) of 38; m.p. 158-160°, unchanged upon recrystallization from the same solvent. From the mother liquor was collected an additional 20 mg; $[\alpha]_D$ -50.7° (c, 0.3 in chloroform). The mass spectrum indicated the molecular ion m/e 325 in agreement with the expected molecular weight of 38. The i.r. data: ν_{max} 3440-3420 (N-OH, 2-OH); 1200-1020 cm^{-1} (C-N). The n.m.r. data ($CDCl_3$): τ 4.60 (s, 1H, $PhCHO_2$); 5.04 (d, 1H, $J_{1,2}$ 8 Hz, H-1); 5.63 (q, 1H, $J_{6e,6a}$ = 10 Hz, $J_{5,6e}$ = 5 Hz, H-6e); 5.84 (sextet, 1H, $J_{4,5}$ = $J_{5,6a}$ = 10 Hz, $J_{5,6e}$ = 5 Hz, H-5); 6.34 (t, 1H, $J_{5,6a}$ = $J_{6e,6a}$ = 10 Hz, H-6a); 6.55 (d, 1H, $J_{4,5}$ = 10 Hz, H-4); 6.64 (d, 1H, $J_{1,2}$ = 8 Hz, H-2); 6.40 (s, 3H, OCH_3);

7.18 (s, 3H, N-CH_3); 8.55 (s, 3H, C-CH_3).

Anal. of 38; Calcd. for $C_{16}H_{23}NO_6$ (325.3): C, 59.07; H, 7.08; N, 4.30. Found: C,57.80; H, 7.01; N, 4.08.

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PART II SOME STUDIES IN THE 5-THIO-GLYCOPYRANOSE SERIES

Introduction

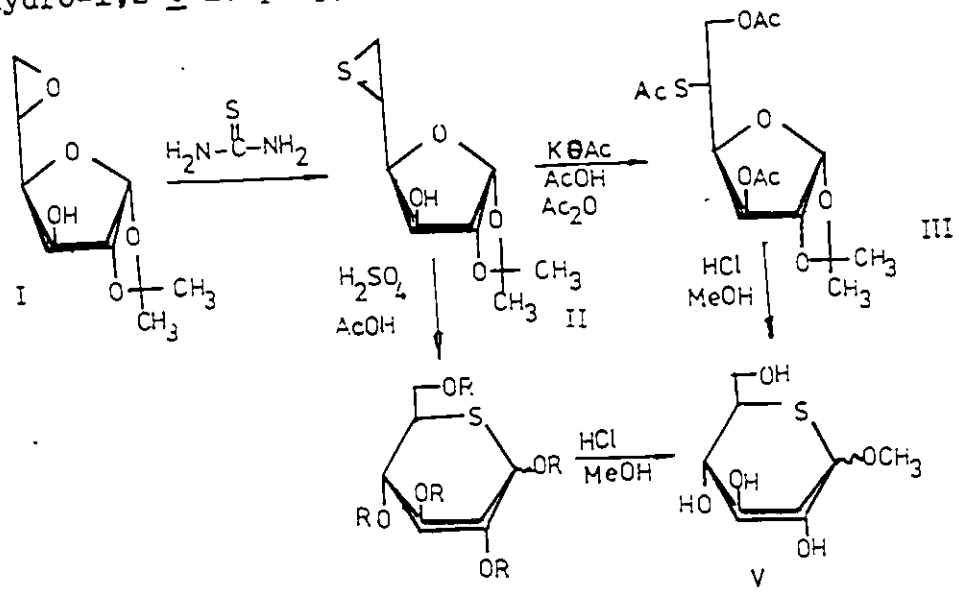
Glycopyranoses in which a sulfur atom replaces the ring oxygen atom are referred to as 5-thio-glycopyranoses or glycothiapyranoses. Prominent among the workers active in studying the chemistry and biochemistry of this class of carbohydrates are R. L. Whistler and his associates[1-9]. 5-Thio-D-glucose, in particular, exhibits interesting biological properties which are connected with its ability to inhibit active transport of D-glucose in biological systems. In low concentration (0.03 M) it prevents the growth of the fruit fly (Drosophila melanogaster) while in high concentrations (in the range of 0.3 M) it prevents development from the larval to the pupal stage[6]. More recently it was found[8] that it reversibly inhibits the maturation of sperm cells in mice at a dose of 50 mg/Kg/day. Withdrawal of the application after a period of as long as two months leads to restoration of fertility. The compound shows no acute toxicity in mice (DL_{50}, 14 g/Kg).

In view of the interesting biological activities of glycothiapyranoses on the one hand, and the well known significance of 3-amino sugars in the chemistry of antibiotics[10] on the other hand, it seemed attractive to attempt the synthesis of sugars that combine these two structural

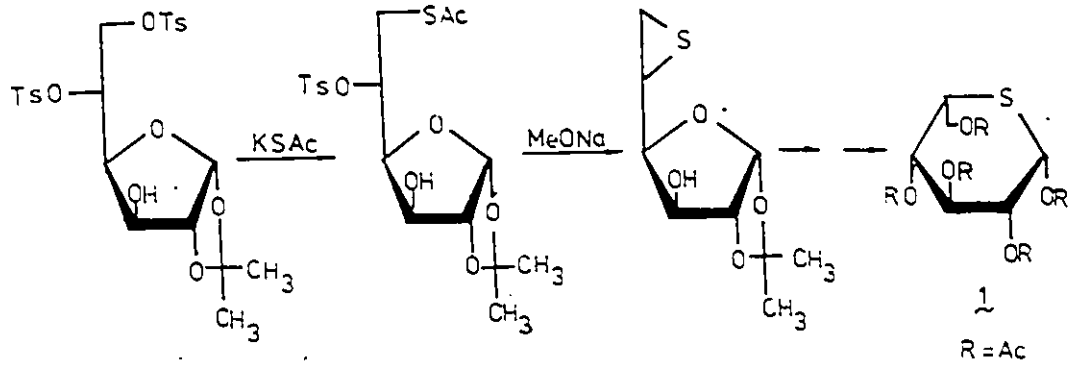
features in the same molecule. No such compounds have hitherto been described. It was therefore decided to prepare a methyl 5-thio-glycopyranoside and to try its utilisation in the general synthesis of 3-amino sugars by nitromethane cyclization[11]. This method involves periodate cleavage of the glycoside followed by ring closure of the resultant dialdehyde with nitromethane; the 3-nitro glycoside so produced is subsequently reduced to the corresponding amine. It was recognized that this procedure could present problems when applied to thiopyranoses since periodate oxidation would not only effect the desired glycol cleavage but would likely oxidize the ring sulfur atom to the sulfoxide or sulfone stage. Indeed, Whistler and co-workers[2] have oxidized with periodate a peracetylated 5-thio-glycopyranoside (which cannot undergo glycol fission) and obtained sulfoxides (two epimers due to sulfoxide asymmetry) and the corresponding sulfone. When a non-acetylated 5-thiopyranoside was oxidized[1], four moles of periodate were consumed and one mole of formic acid was produced. This indicated that ring cleavage by two moles of oxidant must have occurred as in the case of ordinary pyranosides, and that the two additional moles must have oxidized the sulfur function. However it was not established whether the two separate oxidative processes took place at comparable rates or whether one of them was appreciably

faster than the other. If glycol cleavage were the faster reaction it might be possible to elaborate carefully controlled conditions under which a thio sugar dialdehyde could arise, to be then subjected to nitromethane cyclization. Should selective ring cleavage fail it would nevertheless be interesting to see if sulfoxide or sulfone dialdehyde derivatives then expected would be suitable for nitromethane cyclization. Nitrogen-substituted glycosides having an oxidized sulfur function in the ring are likewise unknown.

Hexopyranose derivatives having sulfur in the ring were first prepared by Feather and Whistler[1]. The principle consists of introducing sulfur at C-5 of a blocked hexofuranose derivative, followed by deblocking whereby the 5-thiopyranose ring is formed, as shown in the accompanying scheme of the synthesis of 5-thio-D-glucose from 5,6-anhydro-1,2-O-isopropylidene-β-L-idofuranose:



In analogous fashion, Adley and Owen[12] synthesized 1,2,3,4,6-penta-O-acetyl-5-thio-L-idopyranose (1) from readily available 5,6-epithio-1,2-O-isopropylidene-β-L-idofuranose via the corresponding 6-S-acetyl-6-deoxy-6-thio derivative:



Compound 1 was chosen as a starting material for the present study.

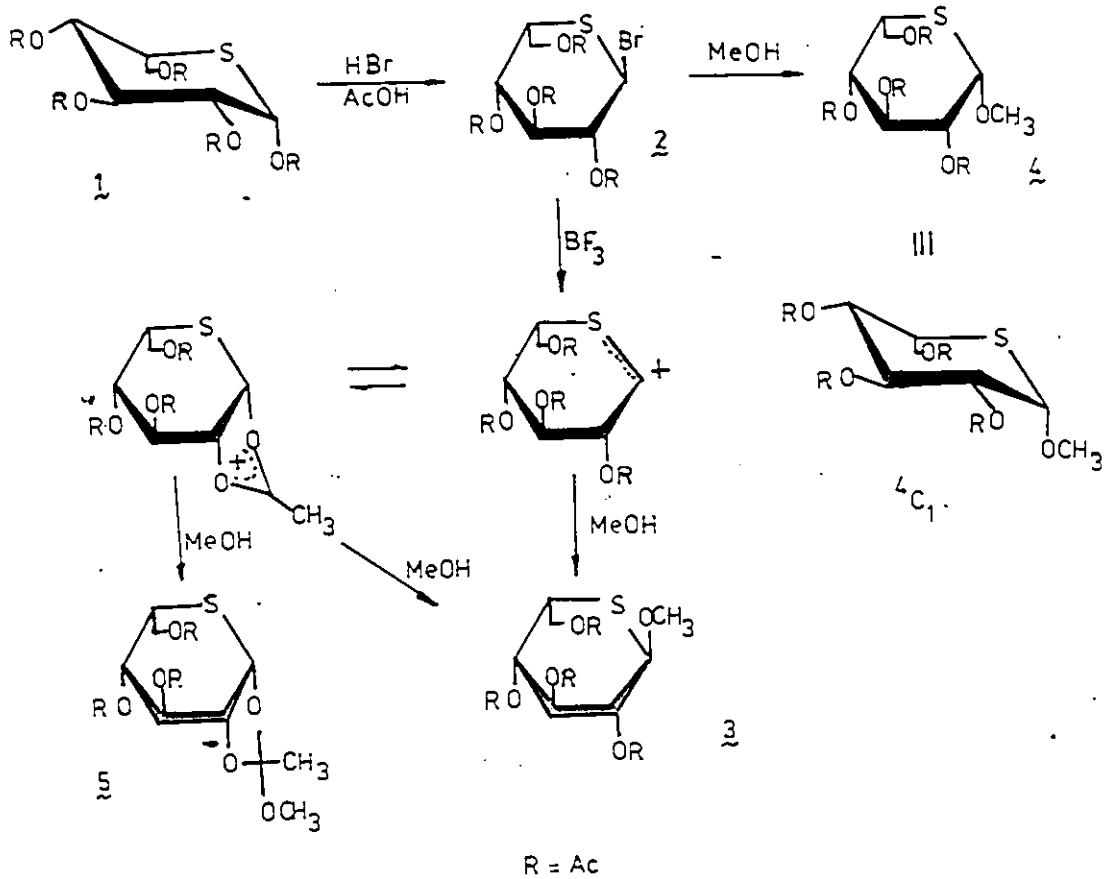
RESULTS AND DISCUSSION

Synthesis of methyl 5-thio-β-L-idopyranoside

Although Owen[12] had not assigned an anomeric configuration to his crystalline pentaacetate 1, the compound is depicted in the following discussion as the β-anomer in the $^4C_1$ (L) conformation. This assignment was based on the n.m.r. spectrum of the compound which we obtained. The ring proton signals attributable to H-2, H-3 and H-4 all contained large splittings (10-11 Hz). One of them (H-3) was a triplet, the others were quartets each containing a small splitting (3-5 Hz) in addition to the large one. The signal at lowest field (H-1) was essentially a doublet (3 Hz) although it appeared to contain additional, very small splitting probably due to long-range coupling with H-5. These data are compatible only with preferential existence of the compound in the form indicated. Furthermore, the specific rotation of 1 ($[\alpha]_D$ +41° in chloroform) suggests a β-L-hexose derivative.

It was necessary to obtain a methyl glycoside from 1. The pentaacetate 1 was treated with methanolic hydrogen chloride but, unlike its D-gluco isomer (see the scheme in the Introduction), it suffered decomposition. More successful was conversion of 1 into the glycosyl bromide 2,

which was achieved by treatment with 30% hydrogen bromide in glacial acetic acid in the presence of acetic anhydride. However, the acetobromo sugar was a syrup that tended to decompose easily when isolated from its ether or chloroform extract, and it could not be stored. It was therefore utilized directly without characterization other than by t.l.c. In view of the powerful anomeric effect in 1-bromo sugars, it is considered likely that 2 was the more stable α-anomer in the $^{1}C_{4}(L)$ conformation with the bromo substituent axially oriented, although no proof for this assumption is available.



Attempts to convert 2 into a methyl glycoside by use of methanol and silver oxide and/or silver carbonate (Koenigs-Knorr conditions) proved futile. However, it was found that glycosylation proceeds well in the presence of Lewis acids. A catalytic amount of aluminum chloride, for example, was effective but in this case a tedious work-up caused the yield of product to be low. This difficulty was by-passed by use of boron trifluoride as a catalyst. After 3 h at room temperature, the bromide 2 was completely consumed, and three new spots were seen in t.l.c. Theoretically one could expect formation of α- and β-glycosides 3 and 4 and possibly some 1,2-ortho-ester (5) by participation of the 2-O-acetyl group. However, two of the spots had low R_f-values and it was therefore suspected that partial de-O-acetylation might have occurred. For this reason the reaction mixture, upon solvent evaporation, was immediately reacetylated with acetic anhydride in pyridine. The two more slowly moving spots disappeared on this treatment, and thereafter, syrupy methyl glycoside was isolated in nearly quantitative yield. It proved to be an anomeric mixture that was not separable chromatographically. The β-anomer (4) could in part be isolated by crystallization (yield, 45%) and was characterized by physical, spectral and microanalytical data. The n.m.r. spectrum of the mother liquor from the crystallization of 4 exhibited two O-CH_3 peaks in nearly

1 : 1 ratio, suggesting the presence of about equal proportions of 4 (τ 6.56) and its α-anomer 3 (τ 6.51). The latter could not be isolated and was not characterized further. The specific rotation of methyl 2,3,4,6-tetra-O-acetyl-5-thio-β-L-idopyranoside (4) in chloroform solution was +75.4°. The rotation of +64° for the oxygen analog (deduced from the value -64° given[13] for the known β-D-enantiomer) supports the anomeric assignment. The n.m.r. data were also in agreement with the structure of 4 and indicated the $^4C_1$(L) conformation. A symmetrical triplet at τ 4.34 with large splitting was assigned to H-3 ($J_{2,3}$ = $J_{3,4}$ = 10 Hz) and indicated axial protons H-2, H-3 and H-4. The doublet at τ 5.50 beloged to the magnetically equivalent* H-6 and H-6' protons ($J_{5,6}$ = $J_{5,6'}$ = 7 Hz, $J_{6,6'}$ = 0). H-5 appeared as a multiplet in τ 6.52 - 6.68 region, overlapping with the O-CH_3 singlet at τ 6.56. The acetyl groups appeared as narrow multiplet in τ 7.91 - 7.96 region.

Finally, the tetraacetate 4 was de-O-acetylated using sodium methoxide in methanol. Methyl 5-thio-β-L-idopyranoside (6) was obtained as a chromatographically homogeneous syrup that failed to crystallize. Its n.m.r. spectrum confirmed

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* The H-6 protons were also found to be equivalent in the n.m.r. spectrum of 1,2,3,4,6-penta-O-acetyl-α-D-idopyranose in acetone-d_6 and chloroform-d, solutions[14].

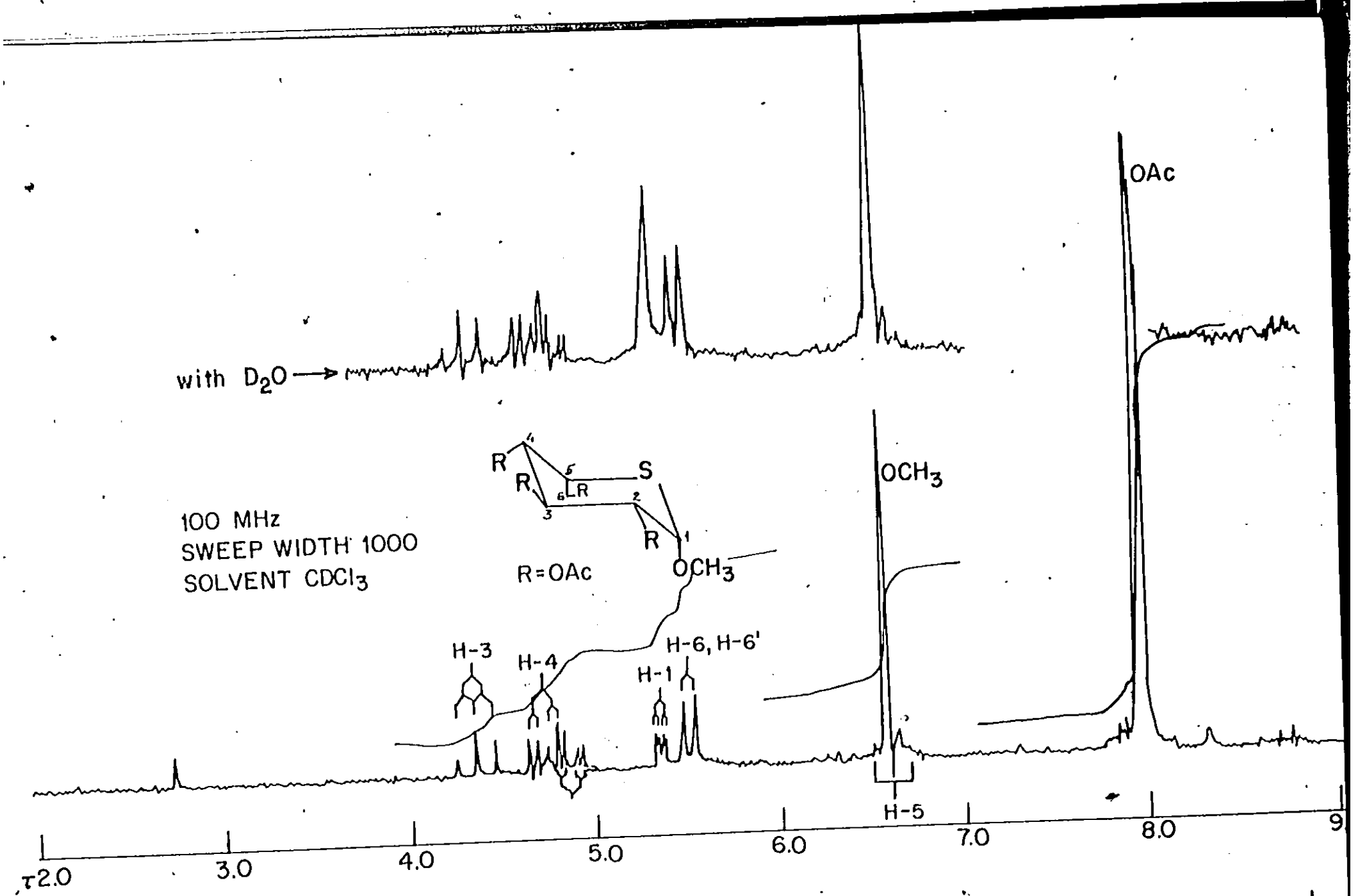


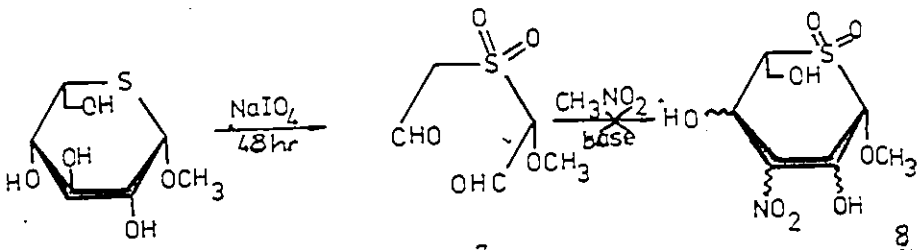
Fig. 18. N.m.r. spectrum of compound 4.

the successful removal of the acetyl groups.

Periodate Oxidation and Nitromethane Condensation

As has been mentioned in the Introduction, Whistler and co-workers[1] have found that methyl 5-thioglycosides (specifically the D-xylosides), react with excess sodium metaperiodate to undergo both glycol fission and oxidation of the sulfur atom. This finding was confirmed in the present work with 6 which was found to consume four moles of the oxidant also. In order to establish whether the two oxidation processes differ in their reaction rates, a polarographic study was undertaken. From the plot of oxidant consumption against time (Fig 19) it became evident that one cannot discern two separate processes of sufficiently different rates. It had to be concluded that it will not be possible to accomplish a selective glycol cleavage.

This being so, attempts were made to cyclize with nitromethane the product of complete periodate oxidation of 6, presumably the dialdehyde 7. Five moles of oxidant, i.e., a 20% excess, was used for these experiments.



6 7 8

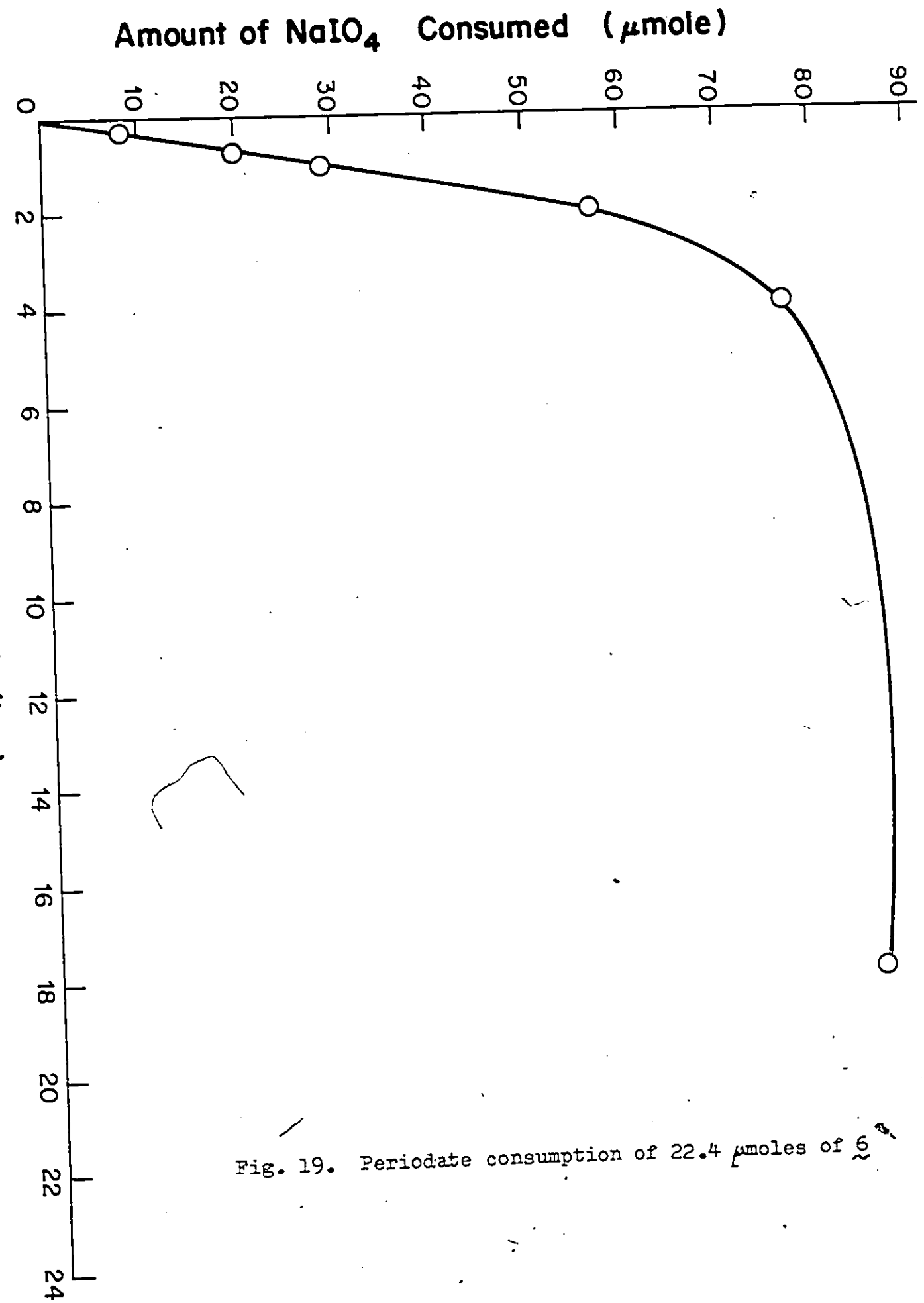
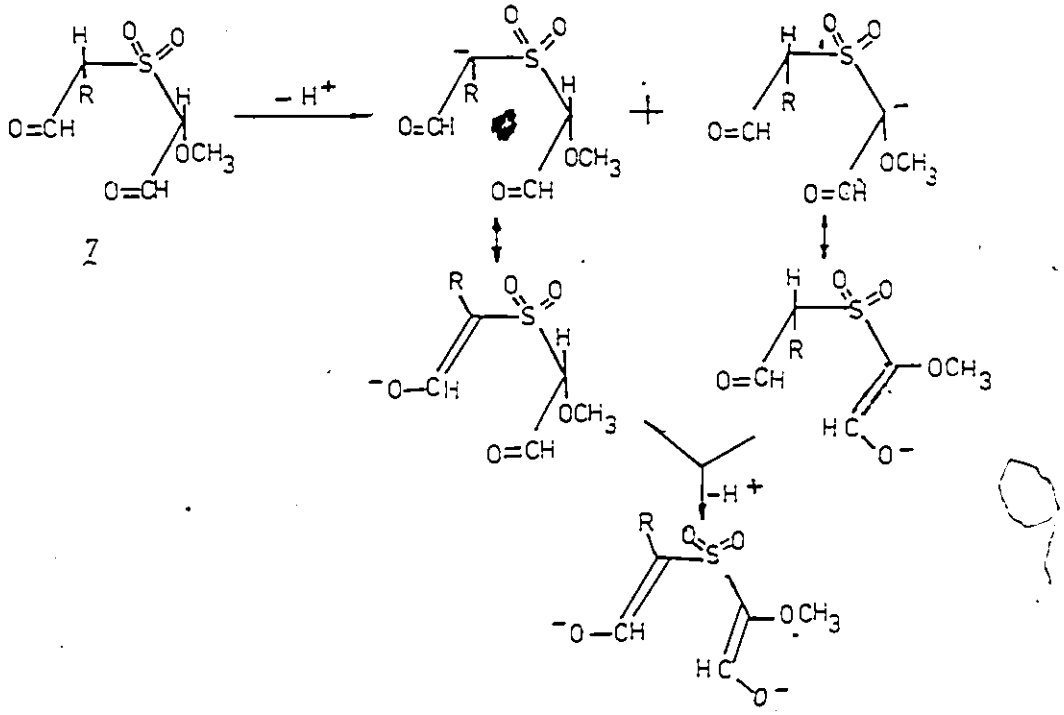


Fig. 19. Periodate consumption of 22.4 μmoles of 6

Fig. 12.

Reactions with nitromethane were carried out in the presence of sodium methoxide or triethylamine as the base, and it was hoped to produce nitro glycosides of type 8. However, very complex mixtures resulted from which no characterizable products could be isolated. It seems possible that no cyclization products (8) were formed at all, and this may be understandable if one considers that the dialdehyde 7 could be subjected to extensive enolization due to the effect of the sulfone group, which could prevent nucleophilic attack of the carbonyl groups by nitronate ion.



It is also possible that 7, in analogy to β-dicarbonyl compounds, is prone to base-induced cleavage reactions which could predominate over the desired nitromethane addition.

EXPERIMENTAL

The general techniques employed were the same as those in part I.

1,2,3,4,6-Penta-O-acetyl-5-thio-β-L-idopyranose (1)

Compound 1 was prepared in a multistep synthesis according to the literature[12]. The crystalline product had m.p. 89-91°; $[\alpha]_D$ +39° (c, 0.5 in chloroform); reported[12] m.p. 90-92°; $[\alpha]_D$ +41° (2.0 in chloroform). The n.m.r. data (in $CDCl_3$): τ 3.90 (d, 1H, $J_{1,2}$ = 4 Hz; H-1); 4.40 (t, 1H, $J_{2,3} = J_{3,4}$ = 10 Hz, H-3); 4.68 (q, 1H, $J_{3,4}$ = 10 Hz, $J_{4,5}$ = 5 Hz, H-4); 4.79 (q, 1H, $J_{2,3}$ = 10 Hz, $J_{1,2}$ = 4 Hz, H-2); 5.22-5.72 (m, 2H, H-6, H-6'); 6.40-6.64 (m, 1H, H-5); 7.83, 7.92, 7.93, 7.95, 8.01, singlets (acetyl groups).

Methyl 2,3,4,6-tetra-O-acetyl-5-thio-β-L-idopyranoside (4)

1,2,3,4,6-Penta-O-acetyl-5-thio-β-L-idopyranose (1) (1 g) was dissolved in acetic anhydride (9.2 ml), and a solution of 30% hydrogen bromide in glacial acetic acid (22 ml) was added. The flask was tightly stoppered and the contents were stirred at room temperature. The reaction was finished after 30 min as shown by t.l.c. (solvent A), the starting material having been completely converted into the faster moving acetobromo sugar (2). Nitrogen was flushed through the reaction mixture for 6 h to remove excess hydrogen bromide. Dry chloroform (40 ml) was added

to the mixture, followed after a few minutes by water (25 ml). The phases were separated and the aqueous layer was extracted twice with chloroform. The combined chloroform extract was washed twice with cold water, dried over potassium carbonate, and evaporated. The resulting unstable oil (2) was quickly dissolved in dry methanol (25 ml) containing seven drops of ethereal boron trifluoride. The flask was tightly stoppered to exclude air and the contents were magnetically stirred at room temperature for 3 h. Three new compounds were detected in t.l.c. (solvent B) but no trace of the bromo intermediate (2) remained. The reaction mixture was neutralized with solid sodium bicarbonate. Methanol was removed by evaporation and the residue was mixed with acetic anhydride (6 ml) and pyridene (10 ml). The mixture was allowed to stand at room temperature for 12 h. T.l.c. (solvent B) thereafter revealed only one spot, which corresponded to the fastest compound present before the acetylation. The reaction mixture was poured into a beaker containg a mixture of crushed ice, concentrated sulfuric acid (6 ml), and chloroform. After vigorous stirring the layers were separated. The aqueous layer was extracted several times with chloroform. The combined chloroform extract was washed with saturated sodium carbonate solution and then with water. After drying over magnesium sulfate, the extract was evaporated to a yellow syrup (1.2 g) which crystallized from ethanol,

furnishing 4 (400 mg, 45%); m.p. 135-136°; $[\alpha]_D$ +75.4° (c, 0.5 in chloroform). The n.m.r. data ($CDCl_3$): τ 4.34 (t, 1H, $J_{2,3} = J_{3,4}$ = 10 Hz, H-3); 4.73 (q, 1H, $J_{3,4}$ = 10 Hz, $J_{4,5}$ = 5 Hz, H-4); 4.85 (q, 1H, $J_{2,3}$ = 10 Hz, $J_{1,2}$ 4 Hz, H-2); 5.35 (q, 1H, $J_{1,2}$ = 4 Hz, $J_{1,2}$ = 1 Hz, H-1); 5.50 (d, 2H, $J_{5,6} = J_{5,6'}$ = 7 Hz, $J_{6,6'}$ = 0, H-6, H-6'); 6.52-6.68 (1H multiplet for H-5 and 3H singlet at 6.56 for OCH_3); 7.91-7.96 (12H, OAc).

The mother liquor was evaporated to give a residual oil (527 mg). Its n.m.r. spectrum revealed two methoxyl groups in almost 1:1 ratio, indicating the presence of α and β anomers. The α-anomer could not be separated from the β-anomer by column chromatography (identical R_f-values) or crystallization, and was not characterized.

Anal. of 4: Calcd for $C_{15}H_{22}O_9S$ (378.4): C, 47.62; H, 5.82; S, 8.65. Found: C, 47.59; H, 5.77; S, 8.69.

Methyl 5-thio-β-L-idopyranoside (6)

Solid sodium methoxide (50 mg) was added to a solution of crystalline 4 (90 mg) in dry methanol (10 ml). The reaction vessel was tightly stoppered and stored in a refrigerator. The reaction was complete after 1 h as evidenced by t.l.c. (solvent E). The reaction mixture was deionized with Amberlite IR-120(H^+). The resin was filtered off and an oil (49 mg, 90%) which failed to crystallize was obtained upon evaporation of the filtrate. The n.m.r. spectrum of the oil in $CDCl_3$ showed absence of acetyl groups. The

specific rotation was $[\alpha]_D$ +78.7° (c, 0.4 in chloroform).

Polarographic monitoring of the oxidation of methyl 5-thio-β-L-idopyranoside 6 with sodium metaperiodate

Calibration was done using standard solutions 1×10^{-3}M, 5×10^{-4}M, 2×10^{-4}M, 1×10^{-4}M, 2.10^{-5}M, and 1×10^{-5}M sodium metaperiodate in 0.1 N aqueous potassium chloride, at -0.35V with a saturated Calomel reference electrode at 5μA current range. It was found that 115 mm (limiting current) was equivalent to 1×10^{-3}M of sodium metaperiodate solution, and that the limiting currents were proportional to concentration used.

A solution of 4.7 mg (0.02 mmole) of methyl 5-thio-β-L-idopyranoside (6) in 10^{-2}M aqueous sodium metaperiodate solution (10 ml, 0.1 mmole) was prepared and stored in the dark. Measurements were taken after 15 min, 60 min, 2 h, 4 h, 18 h, and 48 h, using each time 1 ml of the reaction mixture diluted with 9 ml of 0.1 N potassium chloride (electrolyte) solution. The initial concentration of the sodium metaperiodate solution was 1×10^{-3}M.

The data collected from the polarogram, measured at one and the same potential -0.35 V, are tabulated below:

4.7 mg of the methyl 5-thio-β-L-idopyranoside (M.W. 210) = 0.02238 mmole = 22.4 μmoles.

Time	Height of the limiting current relative to the lower limit, zero (in millimeters)	Amount of IO_4^- remaining (in μmole)	Amount of IO_4^- used up during oxidation (in μmole)	Consumption of IO_4^- per 1 mole of the methyl 5-thio glycoside (6)
0	115	100	0	0
15min	106	92.2	7.8	0.3
45min	92	80.0	26.0	1.2
1 h	81	70.4	29.6	1.3
2 h	49	42.6	57.4	2.6
4 h	26	22.6	77.4	3.5
18 h	16	13.9	86.1	3.8
48 h	12	10.4	89.6	4.0

It was evident from the above table that 1 mole of methyl 5-thio-β-L-idopyranoside (6) consumed 4 mole equivalents of sodium metaperiodate.

Attempted addition of nitromethane to the oxidation product

Syrupy methyl 5-thio-β-L-idopyranoside (6) (488 mg, 2.1 mmole) was dissolved in 50 ml of water and added to a cold, aqueous solution of sodium metaperiodate (2.5 g, 10.2 mmole, 20% excess). The mixture was stored in the dark for 48 h and then poured into 100 ml of cold 99% ethanol. The precipitating inorganic salt was filtered off and washed several times with ethanol. The filtrate was concentrated, and treated again with ethanol to

precipitate more inorganic salt. This operation was repeated until evaporation gave a clear syrup (425 mg) from which no more salt precipitated on addition of ethanol.

To an ice-cold solution of the syrup (425 mg) in methanol (20 ml) containing nitromethane (2 ml) was added dropwise 4 ml of 3% methanolic solution of sodium methoxide. After 2 h, the mixture was deionized with Amberlite IR-120 (H^+). Upon filtration and evaporation, a syrup (225 mg) was obtained which according to t.l.c. (solvent E) was a very complex mixture from which it was not possible to isolate and characterize any products. A similar reaction, in which sodium methoxide was replaced by triethylamine did not change the result.

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CLAIMS TO ORIGINAL RESEARCH

Part I

Reactions of sodium borohydride, dimethylamine, catalytically activated hydrogen, nitromethane, and methylmagnesium iodide with carbohydrate α-nitroepoxides are reported for the first time.

The following new compounds were obtained and characterized:

A From borohydride reactions:

1. Methyl 4,6-O-benzylidene-2-deoxy-β-D-arabino-hexopyranoside (16).
2. Methyl 4,6-O-benzylidene-2-O-ethyl-β-D-mannopyranoside (17).
3. Methyl 4,6-O-benzylidene-2-deoxy-β-D-lyxo-hexopyranoside (18).

B From catalytic hydrogenations

1. 6-Amino-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (22).
2. Methyl 4,6-O-benzylidene-3-deoxy-3-oximino-β-D-ribo-hexopyranoside (23a).
3. Methyl 3-amino-3-deoxy-α-D-allopyranoside hydrochloride (26).
4. Methyl 3-amino-4,6-O-benzylidene-3-deoxy-β-D-galactopyranoside (28).
5. Methyl 3-acetamido-4,6-O-benzylidene-3-deoxy-β-D-

galactopyranoside (29).

C From dimethylamine reactions

1. 5-Deoxy-5-dimethylamino-1,2-O-isopropylidenehexodialdo-1,4;6,3-difuranose (31a)
2. 1,5-Anhydro-4,6-O-benzylidene-2-deoxy-2,3-bis(dimethylamino)-D-arabino(?)-hex-1-enitol (33)
3. 1,5-Anhydro-4,6-O-benzylidene-2-deoxy-2-dimethylamino-D-erythro-hex-1-en-3-ulose (32)
4. 1,5-Anhydro-4,6-O-benzylidene-2-deoxy-2,3-bis(dimethylamino)-D-lyxo(?)-hex-1-enitol (35)

D From the nitromethane reaction

5-Deoxy-1,2-O-isopropylidene-5-C-nitromethylhexodialdo-1,4;6,3-difuranose (36)

E From Grignard reactions

1. Methyl 4,6-O-benzylidene-3-C-methyl-3-(N-methylhydroxylamino)-α-D-hexopyranoside (37)
2. Methyl 4,6-O-benzylidene-3-deoxy-3-C-methyl-3-(N-methylhydroxylamino)-β-D-hexopyranoside (38).

Part II

The synthesis of crystalline methyl 2,3,4,6-tetra-O-acetyl-5-thio-β-L-idopyranose by boron-trifluoride catalyzed reaction of the corresponding tetra-O-acetyl-glycosyl bromide with methanol is reported. The periodate oxidation of the deacetylated 5-thio glycoside was studied and nitromethane cyclization of the oxidation product was attempted.