6200

NATIONAL LIBRARY **BIBLIOTHÈQUE NATIONALE**

OTTAWA **OTTAWA**

CANADA

NAME OF AUTHOR Robert A. Earl

TITLE OF THESIS Studies Related to The Synthesis of Alcohols and Amines from Ulosides

UNIVERSITY of Alberta

DEGREE PHD YEAR GRANTED 1970

Permission is hereby granted to THE NATIONAL LIBRARY OF CANADA to microfilm this thesis and to lend or sell copies of the film.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

(Signed) Robert A. Earl

PERMANENT ADDRESS:

Apt. 206, 756 W. Kilgore
Kalamazoo, Michigan 49001
U.S.A.

DATED March 26 1970

NL-91

THE UNIVERSITY OF ALBERTA

STUDIES RELATED TO THE SYNTHESIS OF ALCOHOLS AND AMINES FROM ULOSIDES

by

Robert A. Earl

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

Department of Chemistry

Edmonton, Alberta

Spring 1970

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled STUDIES RELATED TO THE SYNTHESIS OF AMINES AND ALCOHOLS FROM ULOSIDES submitted by Robert A. Earl in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

R U Lemieux

R. U. Lemieux, (Supervisor)

David Darwish

D. Darwish

JW Lown

J. W. Lown

John E Bertie

J. E. Bertie

D. W. S. Westlake

L. D. Hayward

L. D. Hayward (External Examiner)

March, 1970

DEDICATION

To my wife Pil Soon

ABSTRACT

A model ketone and ketoxime system was constructed for the purpose of examining the effects that polar 2-substituents, such as acetoxy, hydroxy and methoxy, have on the stereochemical course of the sodium borohydride reduction of cyclohexanones and the catalytic hydrogenation of cyclohexanone oximes. Derivatives of 4-_t_-butylcyclohexanone were used for this purpose.

It was found that the presence of an axial 2-acetoxy, 2-benzyloxy, 2-methoxy or an equatorial 2-acetoxy group had little effect on the stereochemical result of the sodium borohydride reduction of 4-_t_-butylcyclohexanone. In all cases the reductions yielded from 86 to 94 % of the equatorial alcohols.

The oxime of 4-_t_-butylcyclohexanone was catalytically hydrogenated using a variety of catalysts and solvent systems. The best yields of 4-_t_-butylcyclohexylamines and fastest rates of reduction were obtained when the reductions were carried out over 5 % palladium on carbon in acidified 90 % ethanol or 5 % rhodium on carbon in 90 % ethanol.

The catalytic hydrogenation of 4-_t_-butylcyclohexanone oxime, with equatorial 2-acetoxy or 2-methoxy substituents, over 5 % palladium on carbon or 5 % rhodium on carbon gave predominantly the axial amines. In contrast to this, axial 2-acetoxy and 2-methoxy substituents enhanced the formation of equatorial amines. It is believed that the polar 2-substituents may act as points of adsorption on the catalyst surface and thereby provide anchoring

effects.

The oxime of 4-t-butylcyclohexanone could not be catalytically hydrogenated over 5 % palladium on carbon in the presence of hydrazine since the oxime was rapidly converted into azine which did not reduce under these conditions. However, when axial or equatorial 2-methoxy substituents were attached to the cyclohexane ring, the oxime was reduced under these conditions, to yield products with approximately the same isomer distribution as when the reductions were carried out over 5 % palladium on carbon in acidified ethanol.

Isopropyl 2-oximino-α-D-arabino-hexopyranoside was catalyticaly hydrogenated under a variety of conditions and provided products with the α-D-gluco and α-D-manno configurations. When the reductions were carried out over rhodium on carbon equal amounts of the gluco and manno products were formed. When 5 % palladium on carbon was used as catalyst the gluco isomer constituted from 80 to 90 % of the product depending on the solvent used. The fraction of gluco product was increased to 95 % if the hydrogenation was carried out in the presence of hydrazine; a result that seemed to involve more than pH effects.

ACKNOWLEDGEMENTS

The author wishes to express his appreciation to Professor R. U. Lemieux for his guidance and encouragement throughout this project.

Appreciation is also extended to the other people with whom I have had the pleasure of working. Particular thanks are due to Drs. K. Clemetson, T. Nagabhushan and M. Robins who have read the manuscript and offered many helpful criticisms.

Lastly and most importantly the author wishes to thank the Canadian people for their generous financial support of this project and for their friendliness that has made his stay in Canada a very enjoyable experience.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Figure Page

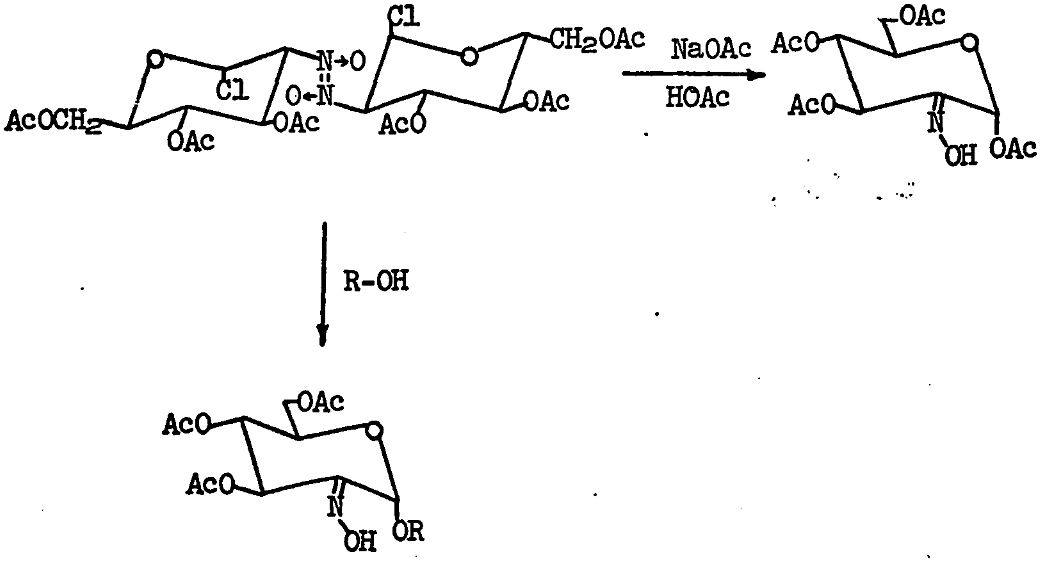
I. INTRODUCTION

The reduction of oximes to amines represents one of the most important procedures for the preparation of primary amines. A wide variety of methods of reduction has been used including catalytic hydrogenation (1), dissolving metals (2) and metal hydrides (3).

The route of reduction of cyclic ketoximes to diastereomeric amines has received considerable attention. In general, dissolving metal reductions give the more stable equatorial amines and catalytic hydrogenations in acid media give axial amines as the predominate products (4). For example, trans-1-decalone oxime gave trans-1-β-decalylamine with sodium in ethanol, whereas hydrogenation over platinum in acetic acid gave mainly trans-1-α-decalylamine (5). Similar results were obtained during the reduction of the oxime of a 3-keto steroid; in this example it was noted that reduction with lithium aluminum hydride gave a high yield of axial amine, the same as catalytic hydrogenation (6). The reduction of cyclohexanone oximes with sodium in ethanol gave mainly the equatorial amines (7, 8, 9, 10, 11), whereas catalytic hydrogenation was shown to give predominantly axial products (7, 8, 9, 12).

The use of oximino sugars as precursors of amino sugars has developed slowly. This was mainly due to the lack of suitable methods for the synthesis of these compounds, since methods were not available for the preparation of keto sugars as precursors of the oximino sugars. Traditional reagents for the conversion of secondary alcohols to ketones, such as chromic acid, are too harsh to be useful for the synthesis of keto sugars; what was needed were oxidizing agents that would work at near neutral pH. Newer reagents such as chromium trioxide in pyridine (13), dimethylsulfoxide-acetic anhydride (14) and ruthenium tetroxide (15) have essentially overcome this problem and made possible the synthesis of a variety of keto sugars from which the oximes are readily prepared. A comparison was made of the relative merits of ruthenium tetroxide and chromium trioxide-pyridine for the preparation of keto sugars and, in general, oxidations with the former were more satisfactory (16). Dimethylsulfoxide-acetic anhydride promises to be a very useful reagent since yields were excellent where it was used for the preparation of keto sugars (17, 18).

Recently, a method has appeared for the synthesis of

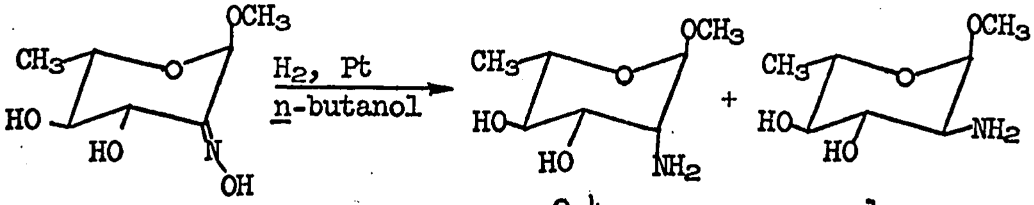


tetra-*O*-acetyl-2-oximino-α-*D*-*arabino*-hexopyranose by reaction of the dimeric nitrosyl chloride adduct of tri-*O*-acetyl-*D*-glucal with sodium acetate in acetic acid (19). Also, by reaction of the dimeric nitrosyl chloride adducts of acetylated glycals with a variety of alcohols and phenols, alkyl and aryl tri-*O*-acetyl-2-oximino-α-*D*-hexopyranosides were produced (19). These reactions were extremely stereospecific and gave good yields of products even with highly hindered alcohols.

It is seen, then, that a variety of oximino sugars have recently become available, therefore opening the way to the synthesis of various amino sugars.

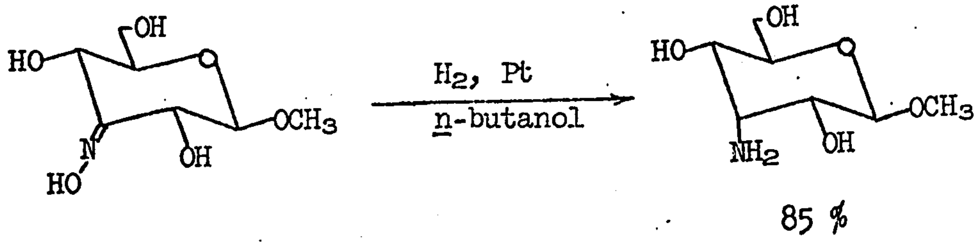
Inososes have also been prepared, generally in low yield, by the platinum catalyzed oxidation of inositols (20, 21, 22, 23). The inososes were converted into oximes and then catalytically hydrogenated over platinum in acetic acid to give good yields of axial amino compounds (20, 21, 22, 23). Anderson and Lardy (20) showed in one case that the catalytic hydrogenation of an inosose phenylhydrazone gave a higher yield of axial amine than the hydrogenation of the corresponding oxime. When inosose oximes were reduced with sodium amalgam they yielded mainly the equatorial amines (20, 21, 23).

The catalytic hydrogenation of oximino-sugars normally gives the axial amines; thus Brimacombe, *et* al. (24) hydrogenated

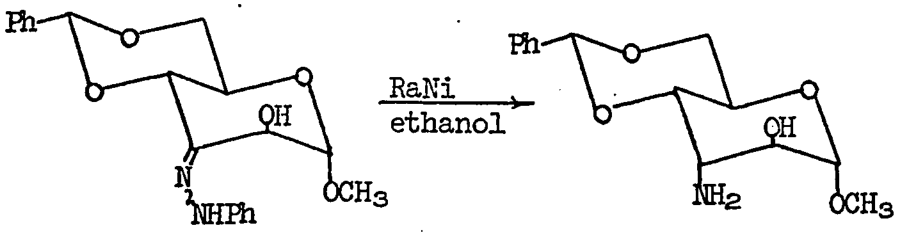


2.4 1

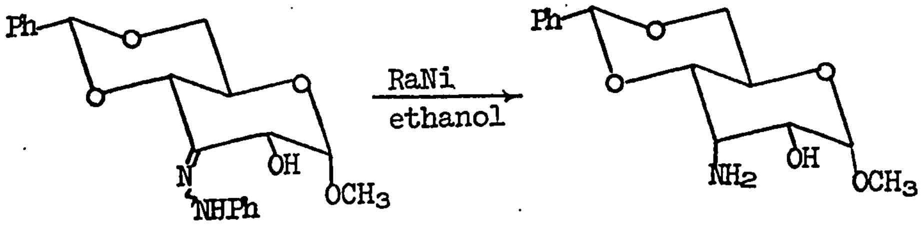
methyl 6-deoxy-2-oximino-α-L-*arabino*-hexopyranoside over platinum in *n*-butanol and obtained a 2.4 to 1 ratio of axial and equatorial amines, respectively. Lindberg and Theander (25) obtained an 85 % yield of axial amine from the catalytic hydrogenation of



methyl 3-oximino-β-D-ribo-hexopyranoside using platinum in *n*-butanol. They also reduced this oxime using sodium amalgam and obtained a 45 % yield of the equatorial amine. Chittenden and Guthrie (26) have catalytically hydrogenated the phenylhydrazones of methyl 4,6-benzylidene-α-D-*arabino* and methyl 4,6-benzylidene-α-D-



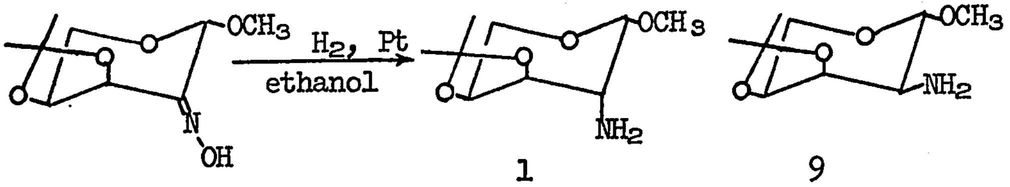
arabino



ribo

ribo-hexopyran-3-ulosides over Raney nickel in ethanol and in both cases they obtained a high yield of the axial amines.

The generality has been made that the catalytic hydrogenation of oximes or hydrazones attached to cyclohexane or pyranose rings usually leads to a preponderance in the isomer having an axial amino group in the stable chair form (24). Several exceptions to this have recently appeared; thus Collins and Overend (27) catalytically reduced methyl 3,4-isopropylidene-2-oximino-β-L-*erythro* pentopyranoside over platinum in ethanol and obtained a 1 to 9

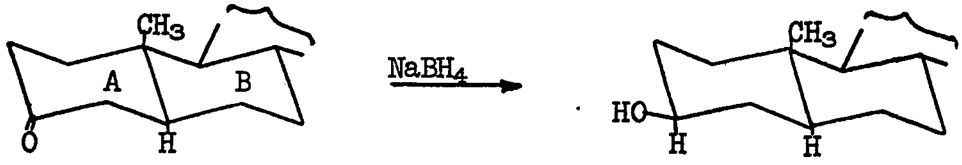


ratio of axial and equatorial amines, respectively. Lemieux and Gunner (28) catalytically hydrogenated a series of alkyl 2-oximino-α-D-*arabino*-hexopyranosides. The reductions were carried out over 5 % palladium on carbon at low pH and produced mixtures of the alkyl 2-amino-2-deoxy-α-D-hexopyranosides, with the *gluco* and *manno* configurations in about 90 % yields. The amount of the *gluco* isomer (equatorial amine) formed varied with the aglycon and was found to be higher (78 %) when the aglycon was isopropyl and lower (62 %) when it was ethyl or *n*-propyl. When the 3,4,6-tri-*O*-acetyl derivative of the isopropyl glycoside was reduced the *gluco* to *manno* isomer ratio was 1:1. Later, Lemieux and Ito (29) found that the ratio of gluco to manno isomers was increased in favor of the former, when the hydrogenations were carried out in the presence of hydrazine. It was also shown, by Lemieux and Nagabhushan (30), that the hydrogenation of penta-O-acetyl-2-oximino-hexopyranoses in acetic acid in the presence of palladium gave over 80 % yields of the axial amines.

Our interest in the reduction of ketoximes to amines is primarily concerned with the preparation of amino-sugars. In particular, the above mentioned development of methods for the synthesis of 2-oximino-hexoses and their α-glycosides (19) warranted an examination of the factors responsible for the observed stereochemical route of their reduction (28, 29, 30). A goal of this research was to construct a model ketoxime system that would enable a study of the effects that α-substituents have on the catalytic hydrogenation of ketoximes. It was of particular interest to examine oximes with polar α-substituents such as hydroxy, alkoxy and acyloxy, since these are the kinds of groups normally situated adjacent to the oximino groups of oximes derived from carbohydrate structures.

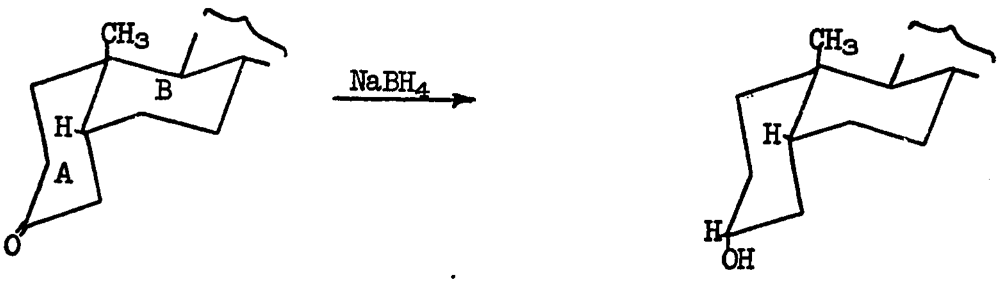
The availability of ulosides has provided a pathway to the epimerization of an alcohol group of a protected carbohydrate, provided that a means is available for the reduction of the carbonyl group to the epimer of the original alcohol. Stereospecific reduction is an important feature in the preparation of α-glycosides by means of the nitrosyl chloride adducts of acetylated glycals (31). Therefore it was also of interest to examine the influence of neighboring substituents on the stereochemical pathway of the reduction of ketones to alcohols. In view of the convenience of sodium borohydride reductions a study was made of the action of this reagent on model α-substituted cyclohexanones. These model compounds were intermediates in the synthesis of the previously mentioned α-substituted ketoximes.

The effects of alkyl substituents on the sodium borohydride reduction of cyclohexanones are better established than are the effects of polar substituents. In the absence of steric hindrance of axial 3-substituents toward the approach of the borohydride ion, the reduction of cyclohexanones gives mainly the equatorial alcohols (4). For example, there is a considerable amount of literature on the sodium borohydride reduction of 3 keto steroids and in each example the equatorial alcohol was the major product (32).



trans

predominant



cis

predominant

It did not matter whether there was a cis or a trans junction between the A and B rings; the equatorial alcohol was the predominant isomer formed. Vail and Wheeler (33) showed that changes in the composition of the solvent had little effect on the stereochemistry of the reduction of 3-cholestanone; the amount of equatorial alcohol that was formed varied between 82 and 94 %.

Table I lists the results of the reduction of a series of substituted cyclohexanones. It is seen that equatorial alcohols predominate in these reductions and that the 3- and 4-substituted cyclohexanones gave nearly identical isomeric ratios on reduction with sodium borohydride. The 2-substituted cyclohexanones gave a lower equatorial to axial ratio. Combe and Henbest (37) studied the reduction of 4-substituted cyclohexanones and found that the isomeric ratios were nearly uneffected by changes in the solvent.

Cyclohexanones with a polar substituent in the 4- or 2-positions show a tendency to produce more axial than equatorial alcohol. Thus, the reduction of 4-chloro, 4-carboethoxy and 4-carbophenoxycyclohexanone has been reported to give 66, 74 and 67 % of the axial alcohols, respectively (34). The reduction of <u>cis</u>-2-chloro-4-<u>t</u>-butylcyclohexanone gave nearly equal proportions of equatorial and axial isomers; whereas, when <u>trans</u>-2-chloro-4-<u>t</u>-butylcyclohexanone was reduced an 87 % yield of the equatorial isomer was obtained (38).

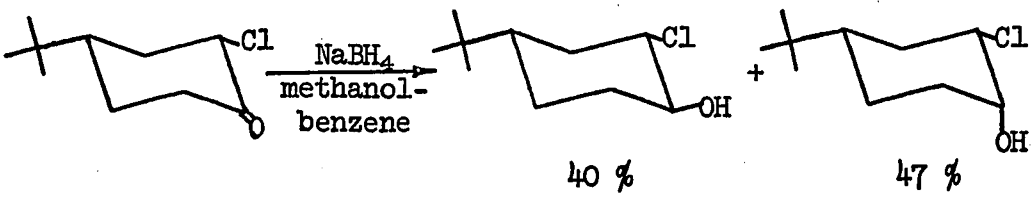
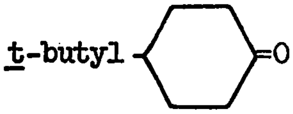
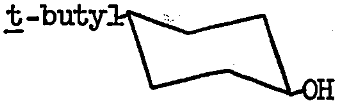
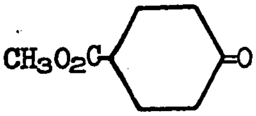
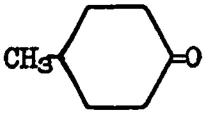
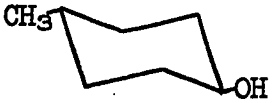
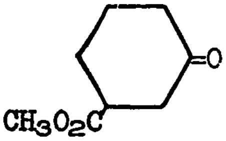
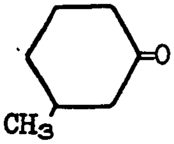
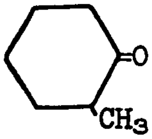
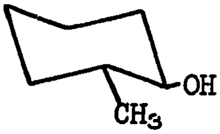
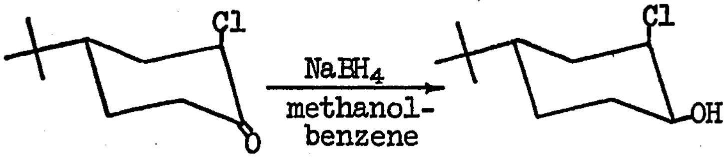


TABLE I

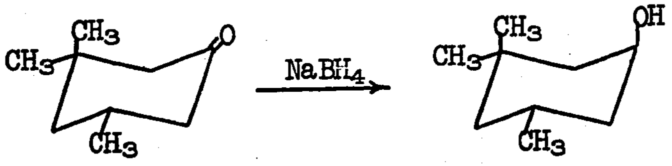
Literature Data for the Sodium Borohydride Reduction of Monosubstituted Cyclohexanones

Ketone		% Equatorial Alcohol (solvent)	Reference	Method of Analysis
		76 (isopropanol)	34	g.l.p.c.
		68 (methanol)	35	g.l.p.c.
		82 (methanol)	36	g.l.p.c.
		75 (methanol-water)	37	density
		78 (isopropanol)	35	g.l.p.c.
		83 (methanol)	35	g.l.p.c.
		83 (methanol)	36	g.l.p.c.
		49 (methanol-water)	37	density
		69 (methanol-water)	37	density



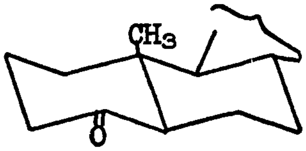
87 %

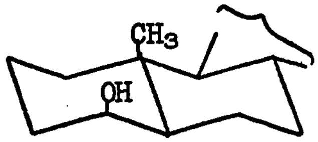
Haubenstock and Eliel (39) showed that the reduction of 3,3,5-trimethylcyclohexanone produced mainly the axial alcohol and that the amount of axial alcohol formed varied by as much as 18 % depending on the solvent employed. In this example the ring



55 - 73 %

is conformationally fixed, since the other chair conformation would required axial methyl groups at the 3- and 5-positions, thereby causing severe syn axial interactions (40). Therefore the axial 3-methyl group should cause hindrance towards axial approach of the borohydride ion accounting for the preponderance in the axial product. Similar effects have been observed for the reduction of 4-keto steroids where the angular methyl group at the 10 position causes hindrance toward approach of the borohydride ion (36).

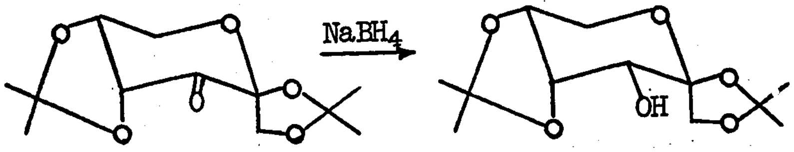




predominant

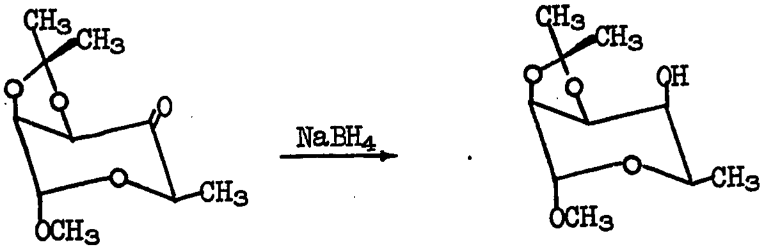
McDonald (17) has reported that the reduction of

1,2;4,5-di-O-isopropylidene-β-D-erythro-2-3-hexodiulose produced mainly the equatorial alcohol. On the other hand, Stevens,

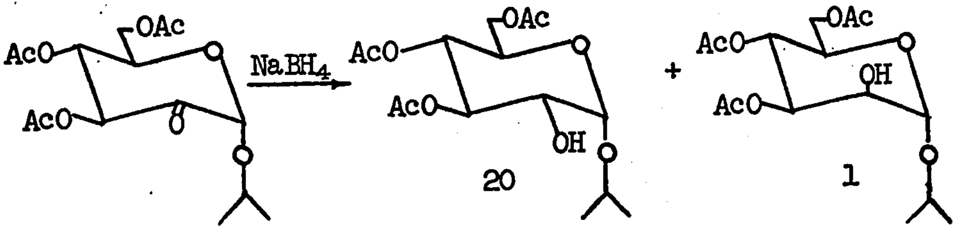


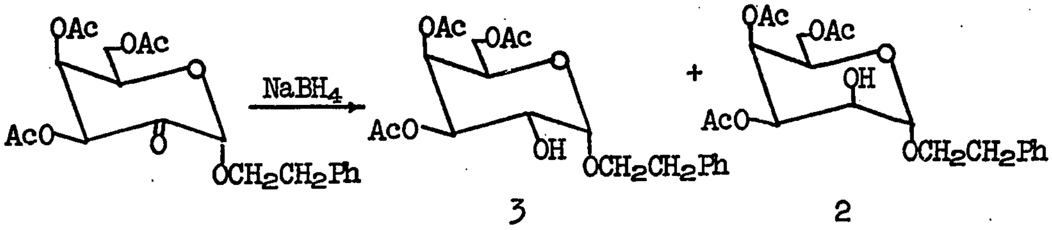
65 % yield

et al. (41) have reported an example of the reduction of a keto sugar that gave a ratio of axial to equatorial alcohol of 45:1. They reduced methyl 6-deoxy-2,3-isopropylidene-α-D-lyxo-hexopyran-4-uloside and obtained a product with the talo configuration.

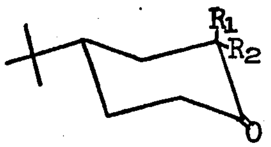


These results are not surprising, however; the endo methyl group of the cis fused 1,3-dioxalane ring must present considerable hindrance toward axial attack by the borohydride ion, thus preventing the formation of equatorial alcohol. Similar, but smaller effects are observed when an axial acetoxy group is attached to a ring carbon atom β to the carbonyl group of a pyranuloside. Thus, Lemieux *et al*. (31) found that sodium borohydride reduction of isopropyl 3,4,6-tri-*O*-acetyl-α-*D*-*arabino*-hexopyran-2-uloside gave a 20:1 ratio of equatorial to axial products, whereas the reduction of β-phenylethyl 3,4,6-tri-*O*-acetyl-α-*D*-*lyxo*-hexopyran-2-uloside gave only a 3:2 ratio of equatorial and axial material (42).

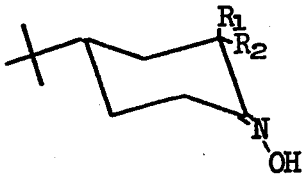




As mentioned above, the goal of this research was to construct a model ketone and ketoxime system that would be useful for the study of the effects of polar α-substituents on the stereochemical route of the sodium borohydride reduction of ketones and the catalytic hydrogenation of ketoximes. Derivatives of 4-*t*-butylcyclohexanone were used for this purpose since the *t*-butyl group is well known to anchor the compound in a specific chair conformation and is sufficiently removed from the reaction center to not directly affect the stereochemical result of the reaction (43). The ketones and ketoximes that were synthesized are shown below. The α-substituted model ketones were reduced



R_1	R_2
H	H
H	OAc
H	OCH_3
OAc	H
OCH_3	H
OCH_2Ph	H

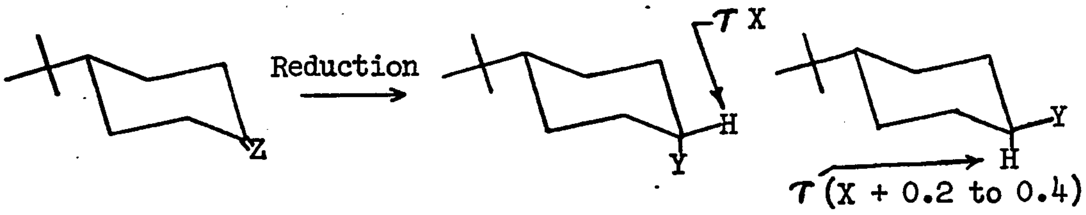


R_1	R_2
H	H
H	OAc
H	OCH_3
OAc	H
OCH_3	H
OCH_2Ph	H
OH	H

under standard conditions and the results compared to those obtained in the reduction of 4-t-butylcyclohexanone. In this way it was possible to assess the effects that the α-substituents had on the course of the reductions. Similarily the α-substituted ketoximes were reduced and the results compared with those obtained in the reduction of the 4-t-butylcyclohexanone oxime. Preliminary studies on the reduction of 4-t-butylcyclohexanone oxime indicated that two catalysts (palladium and rhodium) gave the most satisfactory reductions and therefore these were used for the reductions of the 2-substituted derivatives of 4-t-butylcyclohexanone oxime.

Since our main interest in oxime reductions is connected with the preparation of amino-glucosides, it was of interest that a more thorough study be made of the reduction of a specific oximino-glycoside. For this reason the hydrogenation of isopropyl 2-oximino-α-D-*arabino*-hexopyranoside was carried out under a variety of conditions in order to better evaluate the effects that acidity, catalyst, solvent and in particular hydrazine have on the stereochemical result of the reductions.

An important part of any project of this nature are the tools used for analysis of the results of reactions. In this work gas liquid partition chromatography (g.l.p.c.) and nuclear magnetic resonance (n.m.r.) spectroscopy were ideally suited for this purpose. For the n.m.r. analyses, advantage was taken of the fact that axial hydrogens attached to cyclohexane rings normally produce signals 0.2 to 0.4 τ units up field from the signals produced by equatorial hydrogens in chemically similar environments (44). Therefore it was often possible to determine the ratios of epimeric compounds produced in the sodium borohydride reductions and the catalytic hydrogenations by comparing the intensities of the signals produced by the hydrogens geminal to the newly formed groups (alcohols or amines). Also highly useful was the phenomenon that axial hydrogens produce broader signals (about twice as wide) than do equatorial



Z = N-OH or O

Y = NH_2 or OH

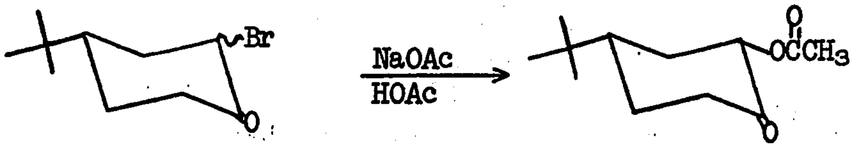
hydrogens, since the former are more strongly coupled to neighboring hydrogens than are the latter (44, 45). Thus it was often possible to assign a configuration to a given group on the basis of the half-band width of the signal produced by the hydrogens geminal to that group. Specific applications of this are discussed in the forthcoming sections.

II. RESULTS AND DISCUSSION

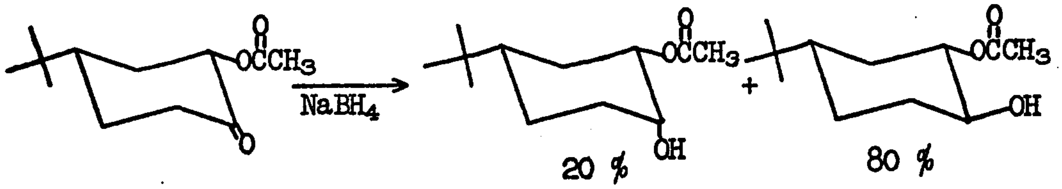
A. Preparation of Model Compounds

1. 2-Substituted 4-*t*-butylcyclohexanones

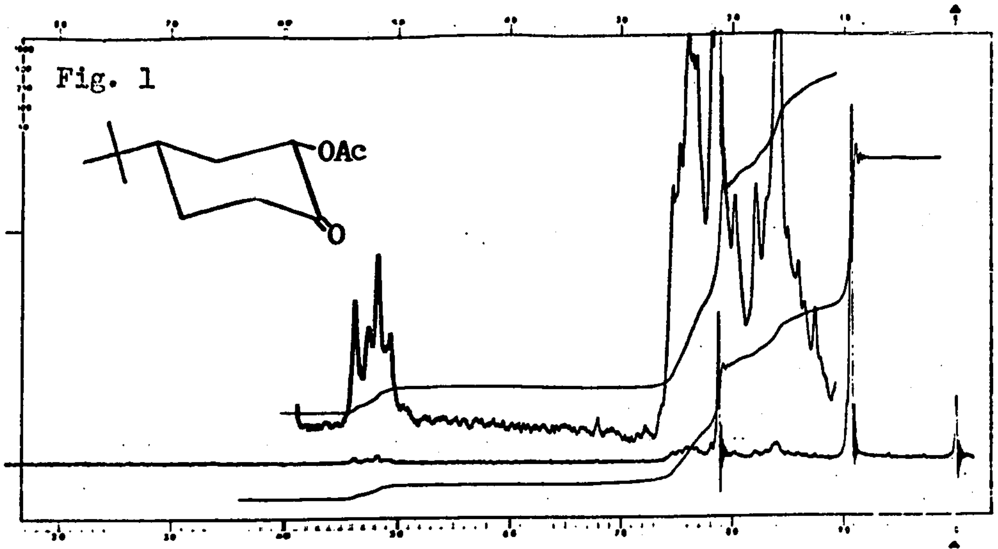
Cis-2-acetoxy-4-*t*-butylcyclohexanone was obtained in 14 % yield by reaction of the readily available 2-bromo-4-*t*-butylcyclohexanone with sodium acetate in acetic acid (46). Several by-products were formed which were not isolated. The n.m.r. spectrum of 1 (Fig. 1) showed a one-proton multiplet at low field, τ4.8, which was assigned to the hydrogen geminal to the acetoxy group. The half-band width of the multiplet (20 Hz) indicated that the hydrogen is axially oriented (44). The multiplet showed some sign of the presence of virtual long range coupling. The configuration of 1 was established as follows. Sodium borohydride reduction of 1 led to a mixture of alcohols. However, as seen from the n.m.r.

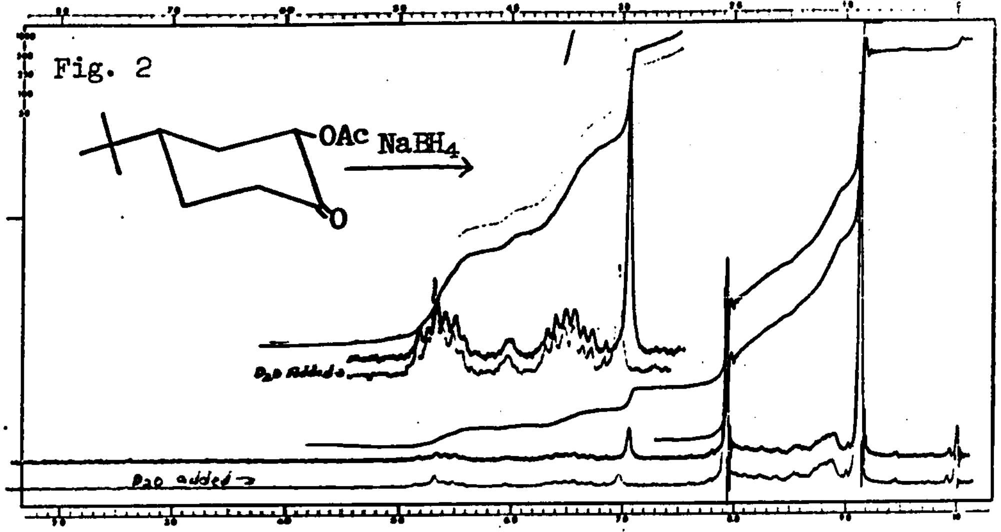


1



1 2 3





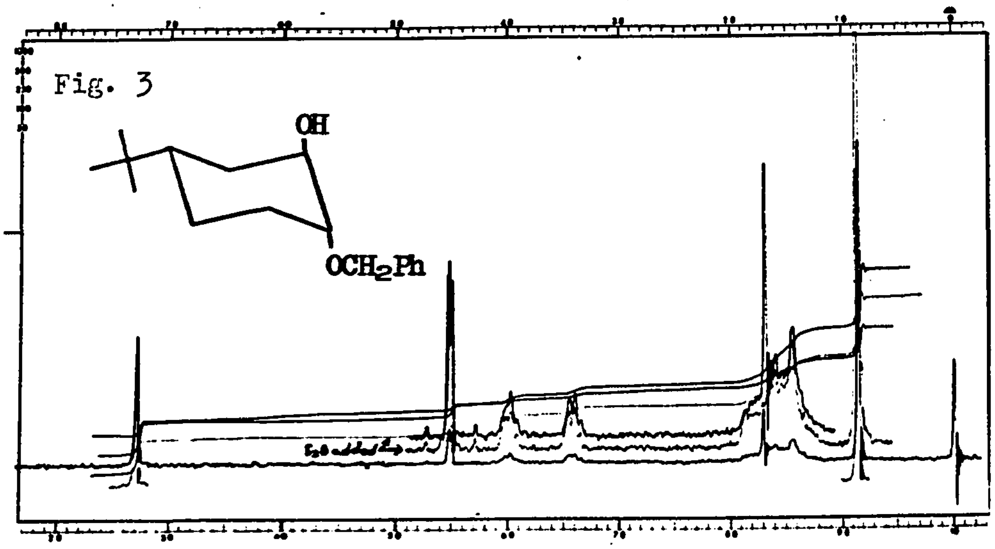
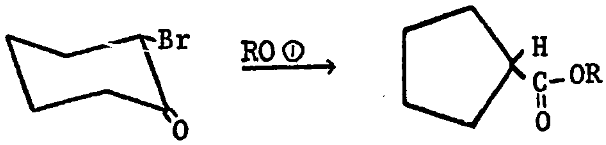


Figure 1. 60 MHz N.M.R. Spectrum of *cis*-2-Acetoxy-4-*t*-butylcyclohexanone (1) in Deuteriochloroform ($CDCl_3$). Figure 2. 60 MHz N.M.R. Spectrum of Product from Sodium Borohydride Reduction of (1) in $CDCl_3$. Figure 3. 60 MHz N.M.R. Spectrum of *trans*-2-Benzyloxy-*trans*-5-*t*-butylcyclohexanol (4) in $CDCl_3$.

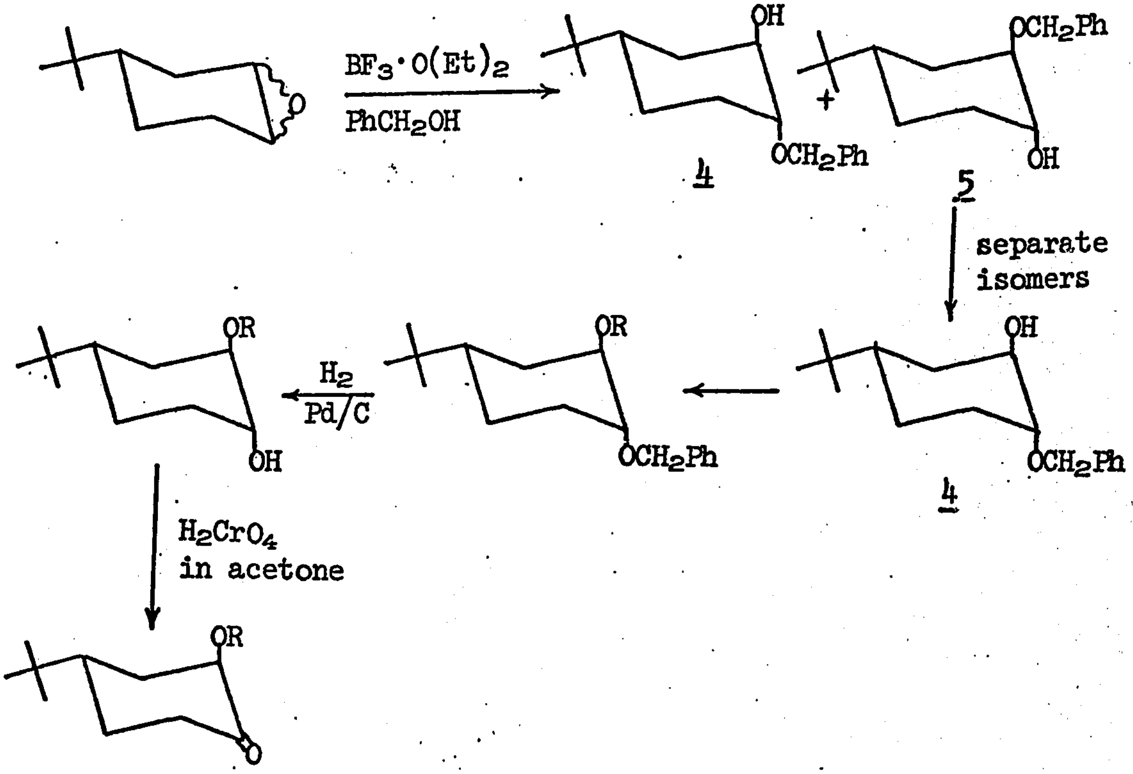
spectrum of the crude product (Fig. 2) one of the isomers comprised about 80 % of the product. The structure of this component was confirmed by the presence of signals, for this isomer, of the hydrogens of an acetoxy group, a hydroxy group and two one-proton sextets at $\tau 5.37$ and $\tau 6.5$. The lower field signal is assigned to the hydrogen at the 2-position which is deshielded by the acetoxy group. Each signal showed two spacings of 9-10 Hz and one of 4-5 Hz which requires both the hydrogens to be axial and coupled with each other and with the hydrogens of a vicinal methylene group. This isomer is therefore, <u>trans</u>-2-acetoxy-<u>trans</u>-4-<u>t</u>-butylcyclohexanol (<u>3</u>). It follows that the parent ketone was indeed the <u>cis</u>-2-acetoxy-4-<u>t</u>-butylcyclohexanone.

When the bromoketone was treated with either sodium methoxide in methanol or sodium benzyloxide in benzyl alcohol, ketonic material could not be readily isolated in a pure state. It is well known (47) that equatorial α-bromocyclohexanones are highly susceptible to the Favorskii reaction (48) and this likely was responsible for



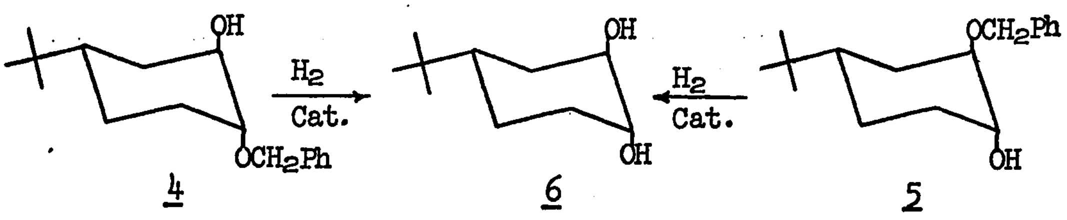
the failure of this approach.

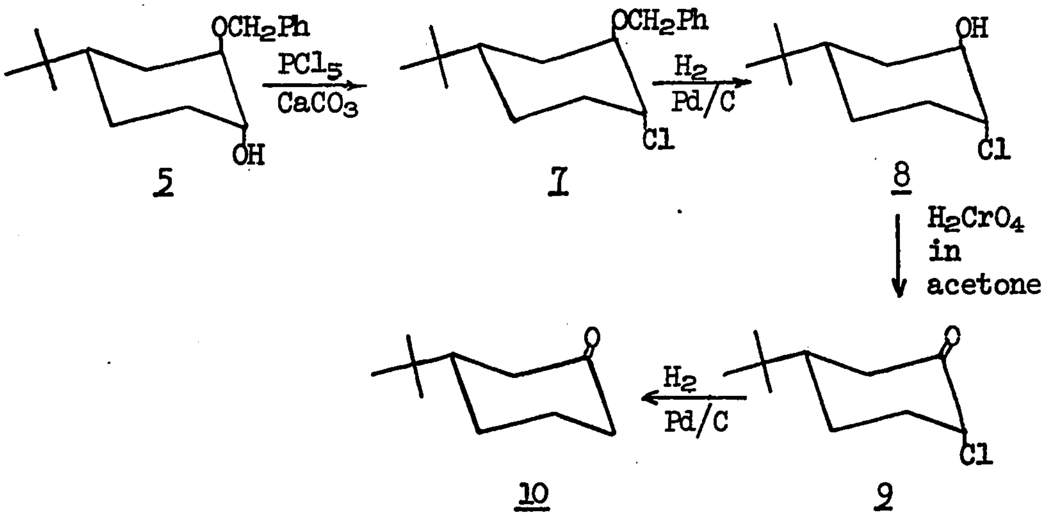
A new approach was needed for the synthesis of 2-substituted 4-<u>t</u>-butylcyclohexanones. A synthetic sequence (outlined below) starting with cis and trans-4-t-butylcyclohexene oxides was used and provided ketones wherein R was acetyl and methyl. The cis and



trans-4-t-butylcyclohexene oxides were prepared (49) and treated with benzyl alcohol in the presence of boron trifluoride etherate; conditions that have been used in the steroid field for the opening of epoxide rings with alcohols (50). A good yield of a mixture of compounds in the ratio of 2:3 was obtained. These were separated by fractional crystallization. The n.m.r. spectra required these to be the expected isomers resulting from opening of the ring by the alcohol and this was confirmed by elemental analysis. The Fürst-Plattner rule (51) predicts the diaxial products 4 and 5 to be the main products from the trans and cis epoxides, respectively.

Each compound showed a pair of one-proton multiplets at low field (Figs. 3 and 4) which could be assigned to the 1 and 2 hydrogens of the cyclohexanol derivative. Since the half-band widths of these multiplets were all less than 10 Hz, clearly the diaxial products were those isolated (44). As expected then, catalytic hydrogenation of both compounds 4 and 5 gave the known trans-2-hydroxy-cis-4-t-butylcyclohexanol (6) (38). The higher melting isomer was shown to be trans-2-benzyloxy-cis-4-t-butylcyclohexanol (5) by chemical degradation as outlined below.





Compound 5 was treated with phosphorus pentachloride and

Fig. 4

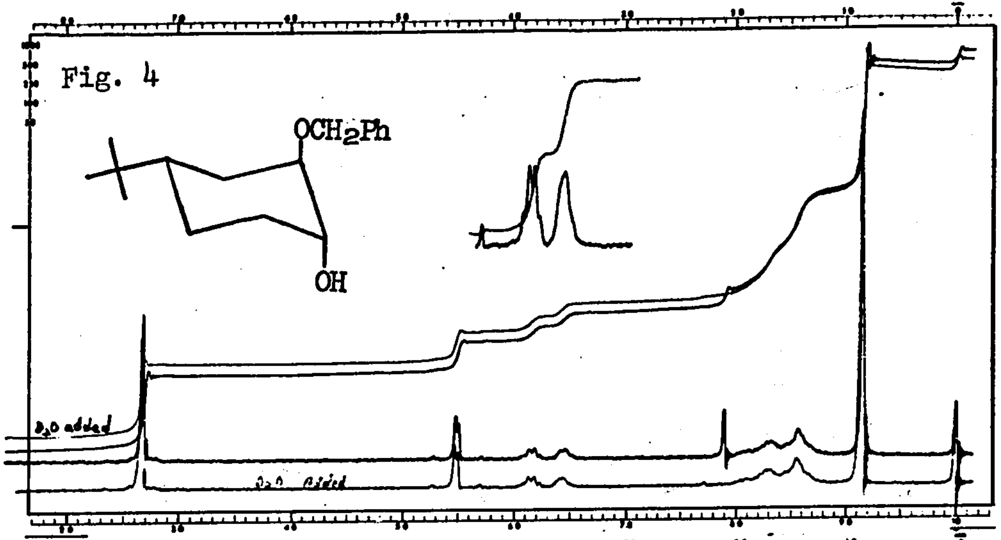


Fig. 5

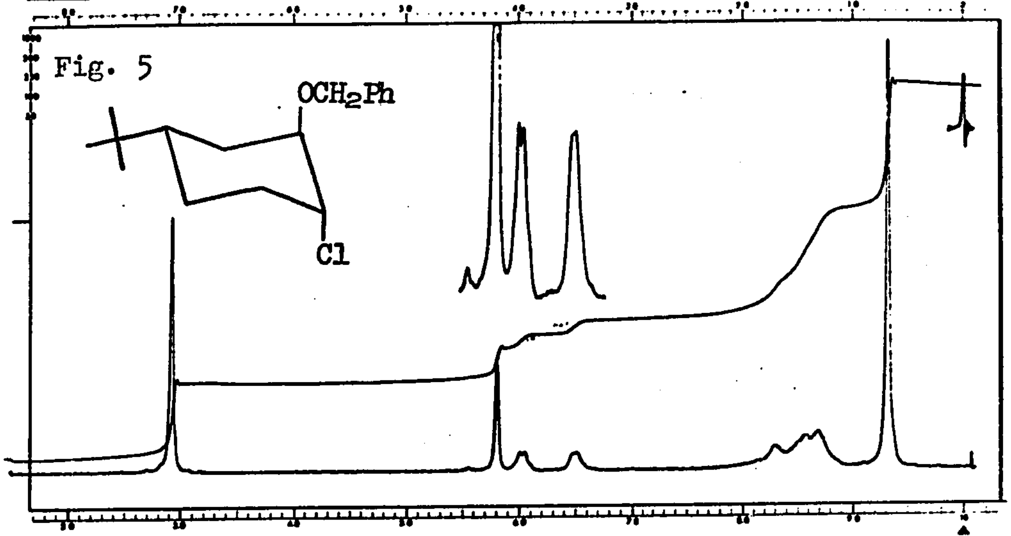


Fig. 6

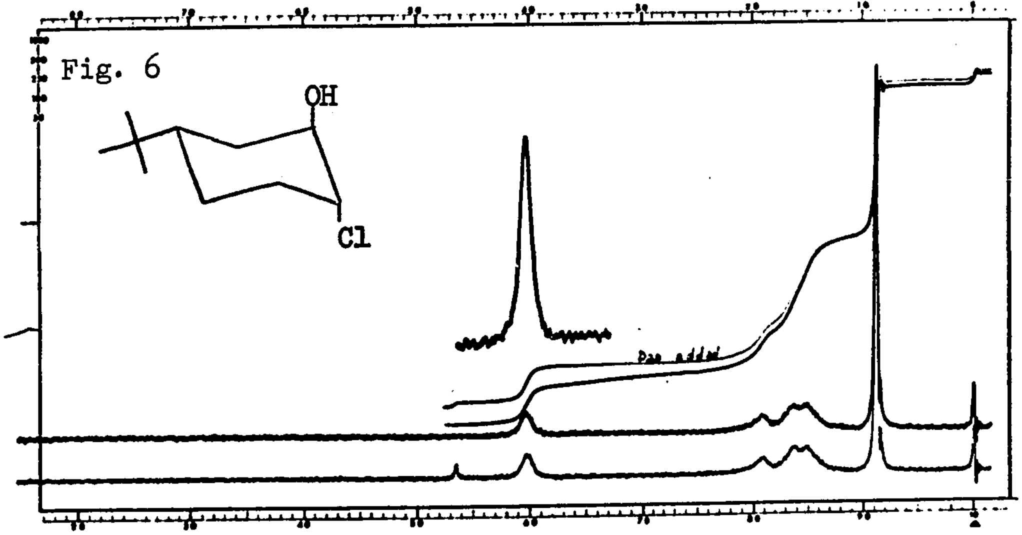
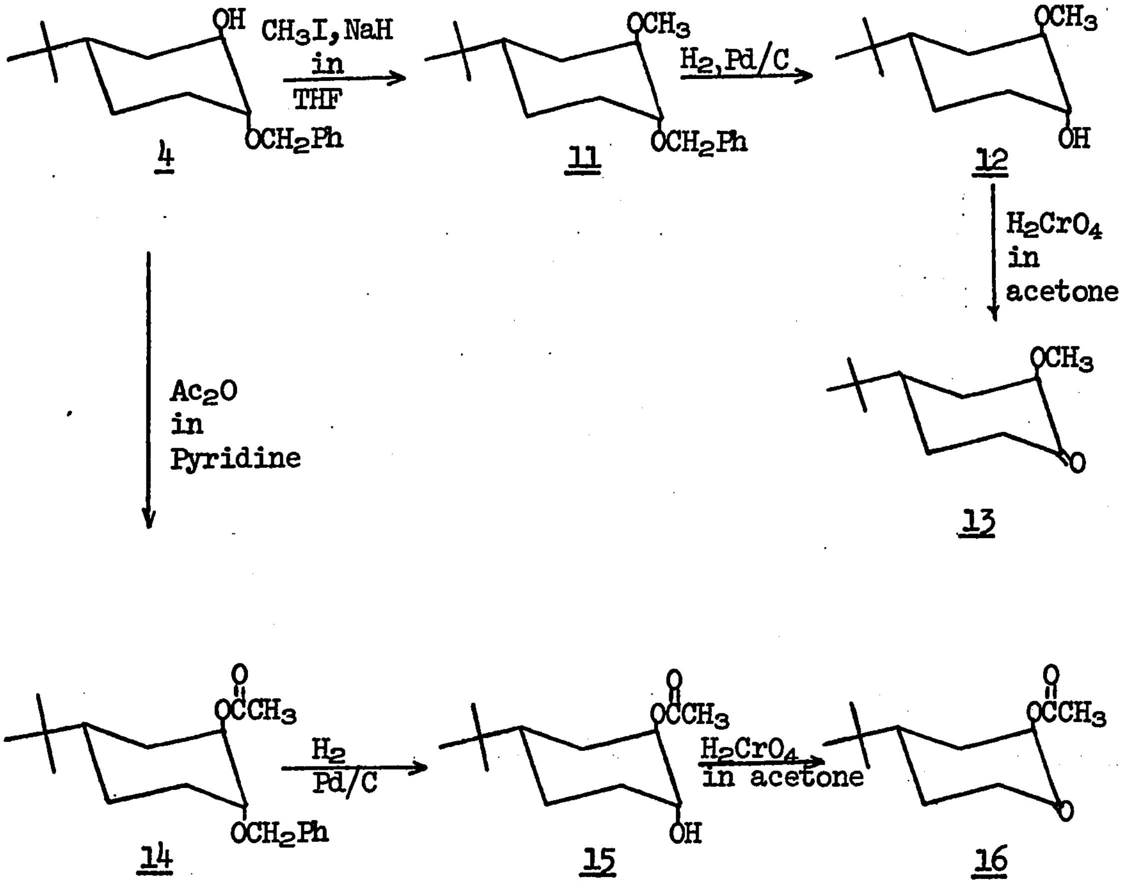


Figure 4. 60 MHz N.M.R. Spectrum of trans-2-Benzyloxy-cis-4-t-butylcyclohexanol (5) in $CDCl_3$. Figure 5. 60 MHz N.M.R. Spectrum of trans-2-Benzyloxy-cis-4-t-butylcyclohexyl Chloride (7) in $CDCl_3$. Figure 6. 60 MHz N.M.R. Spectrum of trans-5-t-butyl-trans-2-Chlorocyclohexanol (8) in Carbon Tetrachloride.

calcium carbonate to produce a compound with a composition suitable for structure **7**. The n.m.r. spectrum of **7** (Fig. 5) showed one-proton doublets at τ6.02 and τ6.5 which are assigned to the hydrogens geminal to the chloro and benzyloxy groups. The half-band width of the signals (7 Hz) indicated that these hydrogens were equatorially oriented (44). Catalytic hydrogenolysis, over 5 % palladium on carbon, converted **7** to a compound (**8**) that had n.m.r. (Fig. 6) and m.p. data the same as those reported (52) for *trans*-3-*t*-butyl-*trans*-6-chlorocyclohexanol. This showed that **5** was *trans*-2-benzyloxy-*cis*-4-*t*-butylcyclohexanol and, therefore, **4** was *trans*-2-benzyloxy-*trans*-5-*t*-butycyclohexanol. However the m.p. reported (38) for *cis*-4-*t*-butyl-*trans*-6-chlorocyclohexanol is also the same as that found for **8**. That **8** was *trans*-3-*t*-butyl-*trans*-6-chlorocyclohexanol was confirmed as follows. Jones oxidation (53) of **8** gave a halogen containing ketone (**9**) which was hydrogenated over 5 % palladium on carbon to yield a ketone (**10**) that was halogen free. The 2,4-dinitrophenylhydrazone and semicarbazone of **10** had melting points the same as those reported (54, 55) for these derivatives of 3-*t*-butylcyclohexanone.

As illustrated below, compound **4** proved useful as a starting material to prepare *trans*-4-*t*-butyl-2-methoxycyclohexanone and *trans*-2-acetoxy-4-*t*-butylcyclohexanone. It was seen above that the latter compound was not available by acetolysis of 2-bromo-4-*t*-butylcyclohexanone.

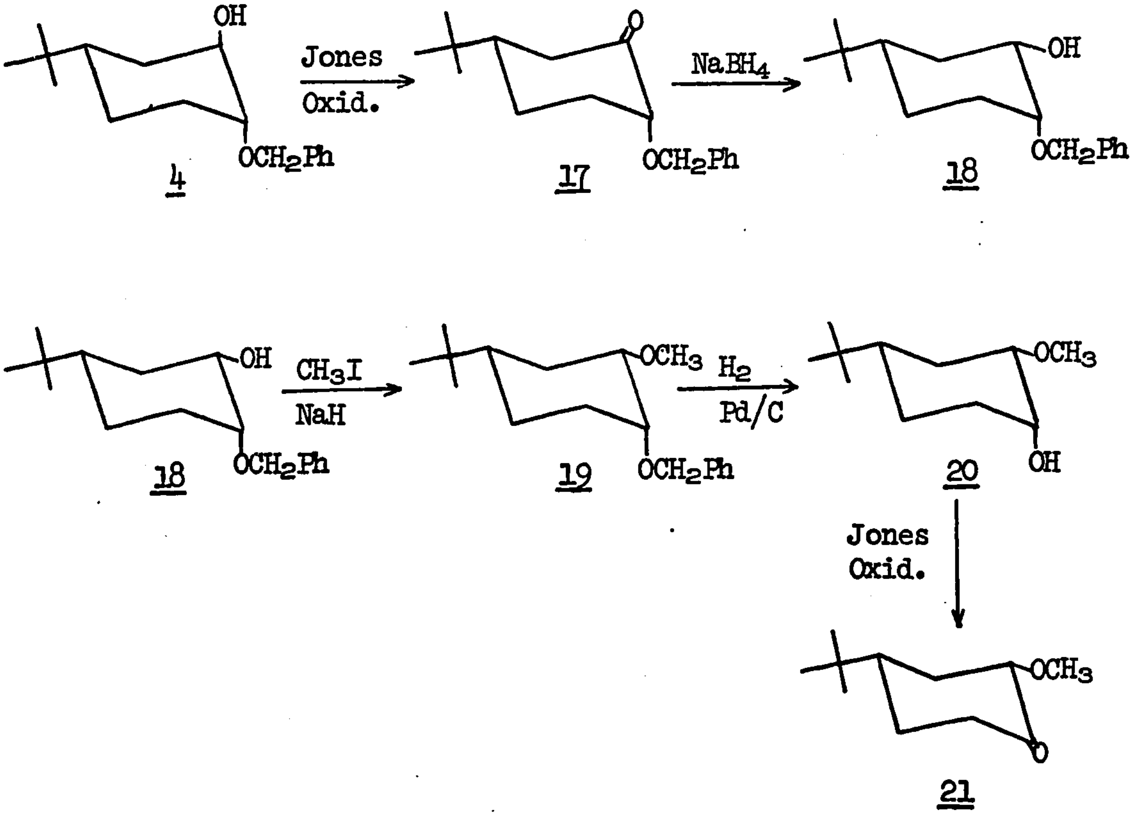
The methylation procedure of Eades and coworkers (56), employing an excess of sodium hydride and methyl iodide in

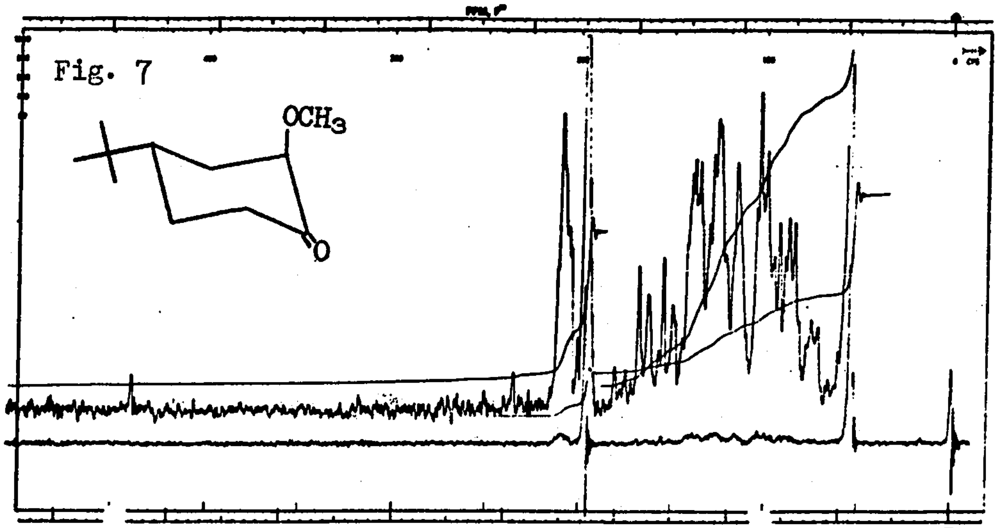


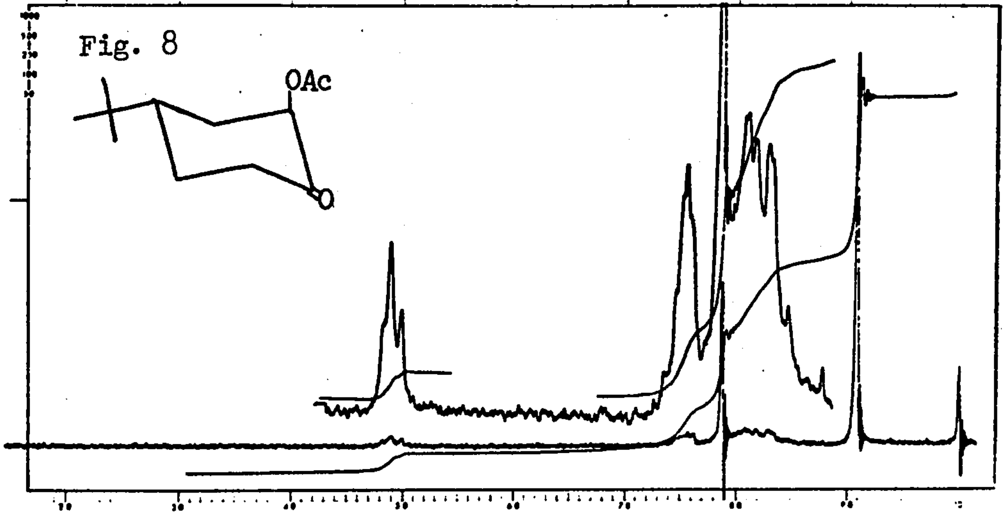
tetrahydrofuran, was used for the preparation of *trans*-2-benzyloxy-*trans*-5-*t*-butylmethoxycyclohexane (11) from 4. Compound 11 was de-O-benzylated by catalytic hydrogenation over 5 % palladium on carbon to produce *cis*-4-*t*-butyl-*trans*-2-methoxycyclohexanol (12). Jones oxidation (53) of 12 produced *trans*-4-*t*-butyl-2-methoxycyclohexanone (13). The n.m.r. spectrum (Fig. 7) of 13 showed signals for the hydrogens of the methoxy group as well as a one-proton multiplet at τ6.53 assigned to the hydrogen geminal to the methoxy group. The half-band width of the signal (7 Hz) indicated that this hydrogen was equatorially oriented (44), therefore confirming that this was the *trans* isomer.

Acetylation of **4** produced *trans*-2-acetoxy-*cis*-4-benzyloxy-*t*-butylcyclohexane (**14**). Compound **14** was de-*O*-benzylated by catalytic hydrogenation over 5 % palladium on carbon to produce *trans*-2 acetoxy-*cis*-4-*t*-butylcyclohexanol (**15**). *Trans*-2-acetoxy-*cis*-4-*t*-butylcyclohexanone (**16**) was obtained by Jones oxidation (53) of **15**. The n.m.r. spectrum of **16** (Fig. 8) showed signals for the hydrogens of the acetoxy group as well as a low field one-proton multiplet at τ4.91 which was assigned to the hydrogen geminal to the acetoxy group. The half-band width of this signal (11 Hz) required that this hydrogen be equatorial (44).

Compound **4** was also a convenient starting material for the synthesis of *cis*-4-*t*-butyl-2-methoxycyclohexanone (**21**). Jones







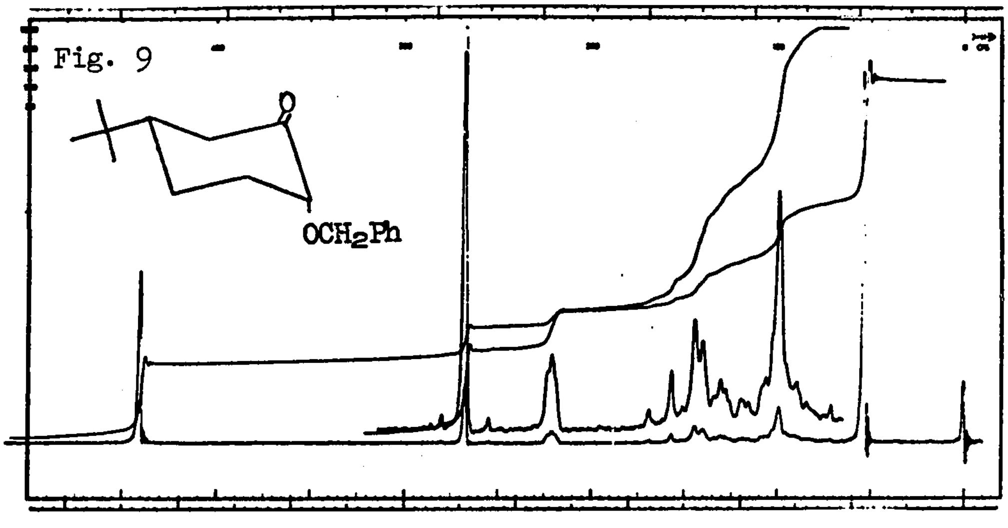


Figure 7. 60 MHz N.M.R. Spectrum of trans-4-t-Butyl-2-methoxycyclohexanone (13) in $CDCl_3$. Figure 8. 60 MHz N.M.R. Spectrum of trans-2-Acetoxy-4-t-butylcyclohexanone (16) in $CDCl_3$. Figure 9. 60 MHz N.M.R. Spectrum of cis-2-Benzyloxy-5-t-butylcyclohexanone (17) in $CDCl_3$.

oxidation (53) of **4** produced *cis*-2-benzyloxy-5-*t*-butylcyclohexanone (**17**). The n.m.r. spectrum of **17** (Fig. 9) showed signals for the hydrogens of a phenyl group, of the methylene group of a benzyl group, an hydroxy group and a one-proton multiplet at $\tau 6.31$ that was assigned to the hydrogen geminal to the benzyloxy group. The half-band width of the multiplet (6 Hz) indicated that this hydrogen was equatorial (44). Reduction of **17** with sodium borohydride produced a mixture of alcohols in the ratio 4.9:1. The predominant isomer **18** was obtained in 45 % yield by fractional crystallization. The n.m.r. spectrum (Fig. 10) of **18** showed the presence of signals for the hydrogens of a phenyl group, an AB quartet for the hydrogens of the methylene group of a benzyl group and a complex two-proton multiplet in the region $\tau 6.22$ to $\tau 6.78$ that was attributed to the hydrogens geminal to the benzyloxy and hydroxy groups. The multiplet appeared to be a composite of a narrow multiplet, half-band width 7-8 Hz, centered at $\tau 6.35$ and a broad multiplet somewhat up field from this with a half-band width of at least 20 Hz. This indicated that one hydrogen was axial and one equatorial (44) and that **18** was *cis*-2-benzyloxy-*cis*-5-*t*-butylcyclohexanol.

Compound **18** was methylated to give *cis*-2-benzyloxy-*cis*-5-*t*-butylmethoxycyclohexane **19**. De-O-benzylation of **19** was accomplished by hydrogenation over 5 % palladium on carbon and produced *cis*-4-*t*-butyl-*cis*-2-methoxycyclohexanol **20**. The n.m.r. spectrum of **20** (Fig. 11) showed the presence of signals for the hydrogens of a hydroxy group, a methoxy group as well as one-proton multiplets at $\tau 5.91$ and $\tau 6.86$ that were assigned to the hydrogens geminal to

Fig. 10

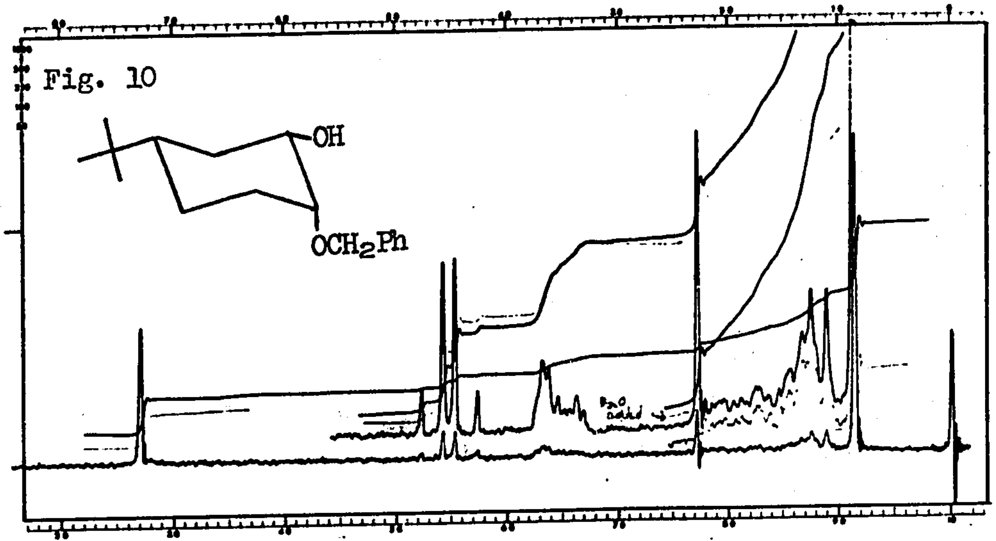


Fig. 11

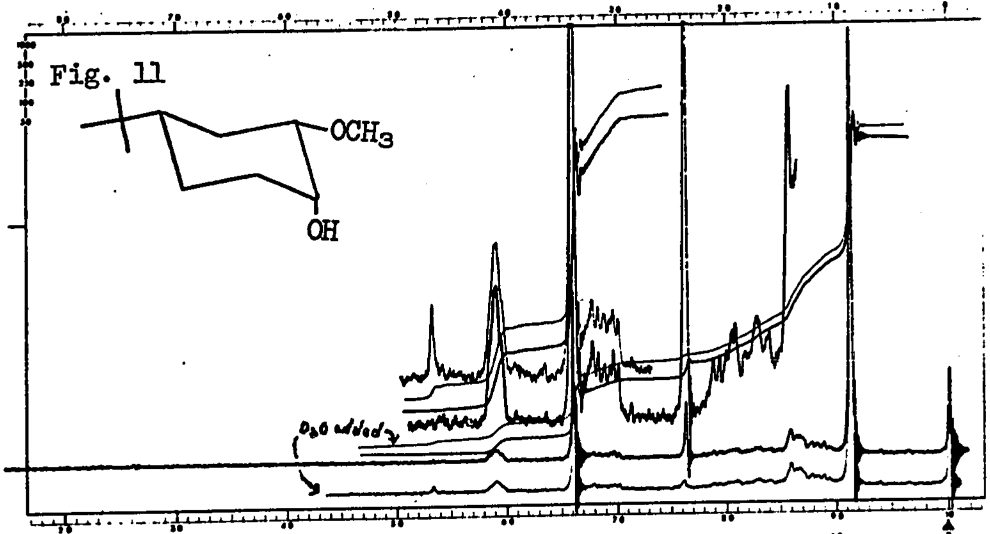


Fig. 12

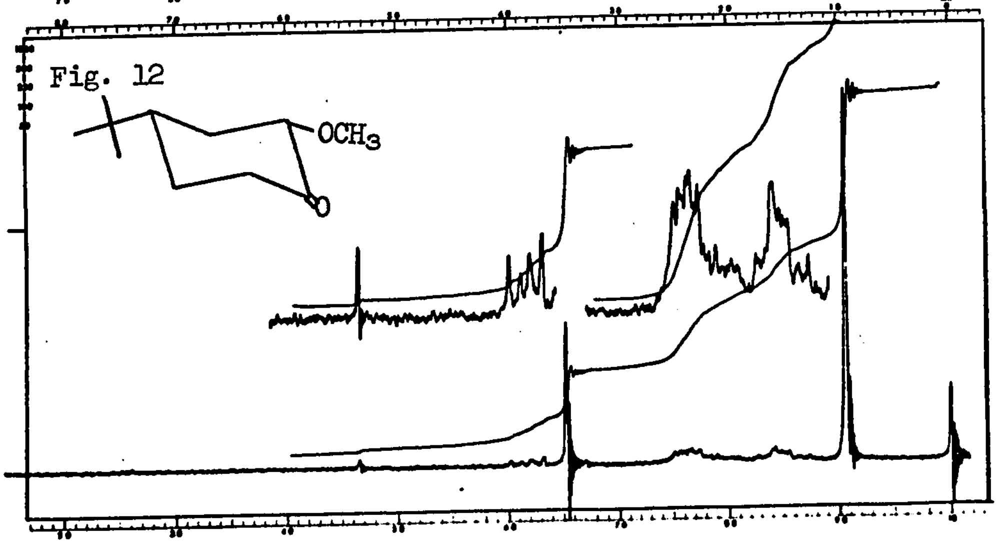
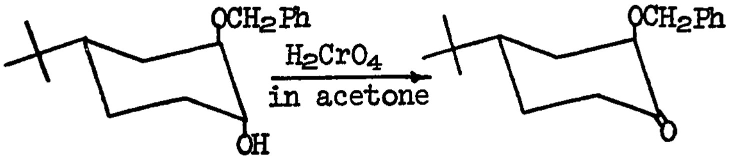


Figure 10. 60 MHz N.M.R. Spectrum of cis-2-Benzyloxy-cis-5-t-butylcyclohexanol (18) in CDCl$_3$. Figure 11. 60 MHz N.M.R. Spectrum of cis-4-t-Butyl-cis-2-methoxycyclohexanol (20) in CDCl$_3$. Figure 12. 60 MHz N.M.R. Spectrum of cis-4-t-Butyl-2-methoxycyclohexanone (21) in CDCl$_3$.

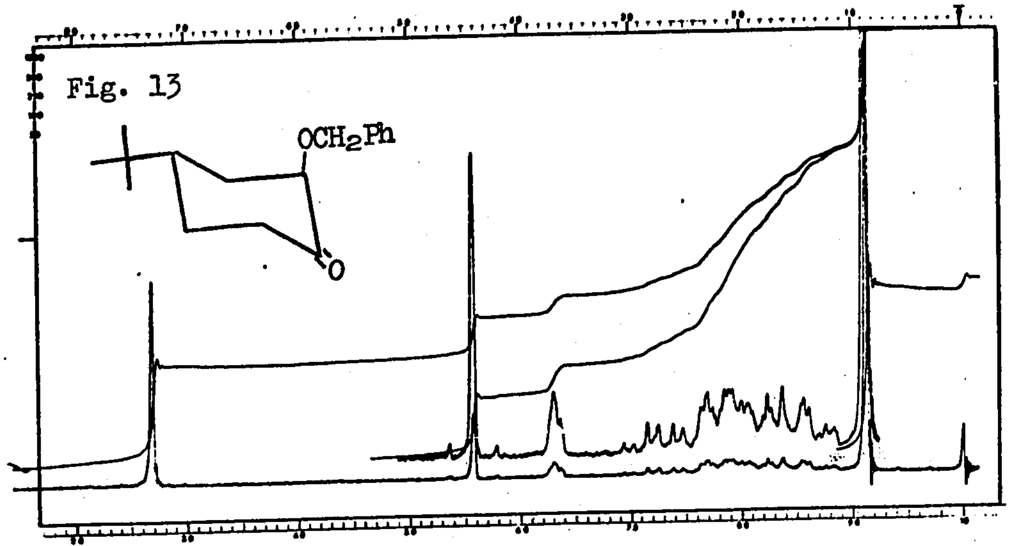
the hydroxy and methoxy groups, respectively. The half-band width (8 Hz) of the signal at τ5.91 required that this hydrogen be equatorial and the half-band width (20 Hz) of the signal at τ6.86 indicated that this hydrogen was axial (44). Jones oxidation (53) of 20 produced *cis*-4-*t*-butyl-2-methoxycyclohexanone 21. There was present in the n.m.r. spectrum of 21 (Fig. 12), a signal for the hydrogens of a methoxy group and a one-proton multiplet at τ6.14 (half-band width 20 Hz) that was attributed to the hydrogen geminal to the methoxy group. The multiplet showed a spacing of 12-13 Hz and one of 5-7 Hz which indicated that this hydrogen was axial and coupled with the hydrogens of the vicinal methylene group.

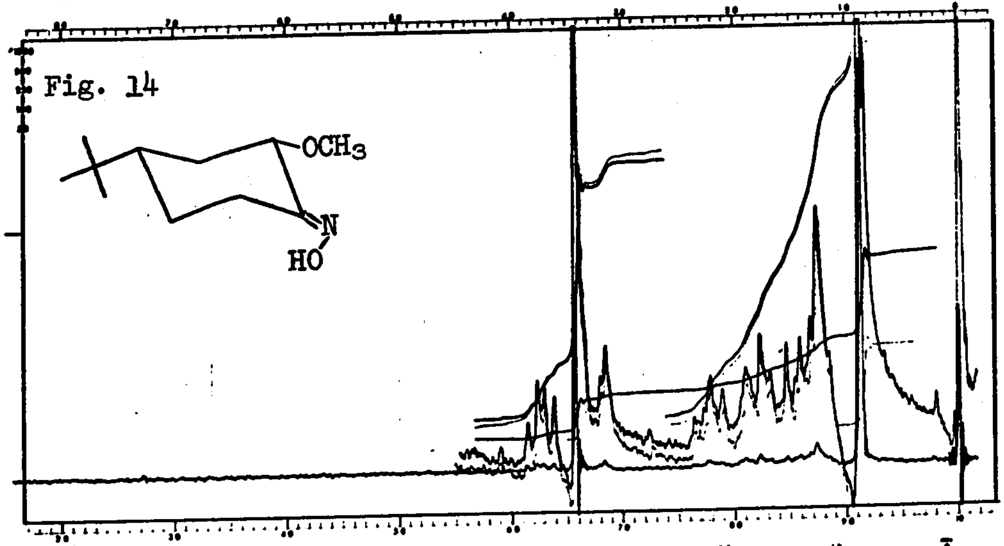
Trans-2-benzyloxy-4-*t*-butylcyclohexanone 22 was obtained, directly, by Jones oxidation of *trans*-2-benzyloxy-*cis*-4-*t*-butylcyclohexanol (5) as shown below. The n.m.r. spectrum (Fig. 13) of



5 22

22 showed the expected signals for the hydrogens of the phenyl group and for the hydrogens of the methylene group of the benzyl group. Also present in the spectrum was a one-proton multiplet at τ6.3 that was attributed to the hydrogen at the 2-position of the cyclohexane ring. The half-band width of this signal (7 Hz)





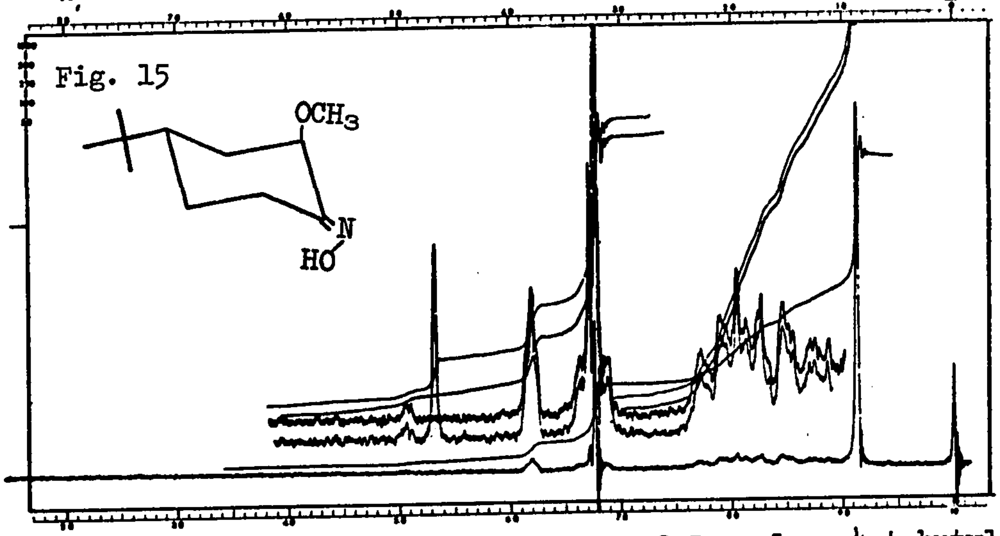


Figure 13. 60 MHz N.M.R. Spectrum of trans-2-Benzyloxy-4-t-butylcyclohexanone (22) in $CDCl_3$. Figure 14. 60 MHz N.M.R. Spectrum of cis-4-t-Butyl-2-methoxycyclohexanone Oxime (25) in $CDCl_3$. Figure 15. 60 MHz N.M.R. Spectrum of trans-4-t-Butyl-2-methoxycyclohexanone Oxime (26) in $CDCl_3$.

required that the benzyloxy group be axial. All attempts to de-O-benzylate 22 by catalytic hydrogenation, over 5 % palladium on carbon, produced intractible products.

2. 2-Substituted 4-t-butycyclohexanone oximes

Table II lists ketones and their oxime derivatives along with n.m.r. parameters for these compounds. The ketones were easily converted into oximes by reaction with hydroxylamine acetate.

The low field signal in the spectrum was assigned, in each case, to the hydrogen geminal to the 2-substituent. It is noted that the chemical shifts of the hydrogens at the 2-position of the epimeric 2-substituted ketones are reverse to the normal in that the equatorial hydrogen is upfield from the chemically similar but axially oriented hydrogen (44). This effect was first observed by Nickon (57) for a series of α-halo steroidal ketones. In his study he showed that, for cyclohexane derivatives, the net effect of a ring carbonyl group is to deshield vicinal axial hydrogens and shield vicinal equatorial hydrogens.

It is of interest to note that, as seen in Table II, oximes do not show this effect for hydrogens <u>anti</u> to the hydroxyl group and which, therefore, should be influenced by the pi-bond system of the oxime in a manner similar to that for the ketones. Apparently the electronic currents caused by the applied magnetic field in the C=N bond are not as strong as those for the C=O bond (58).

When the n.m.r. parameters for the 2-substituted 4-t-butylcyclohexanones are compared with those of their <u>anti</u> oximes it is seen that the signals for the hydrogens at the 2-positions are generally shifted down field on going from ketone to oxime. This is likely an electronegativity effect.

The oximes are assigned the <u>anti</u> configuration on the following

TABLE II

N.M.R. Parameters[a] for α-Substituted 4-t-Butylcyclohexanones and their Oximes in Deuteriochloroform

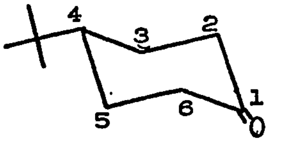
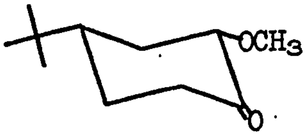
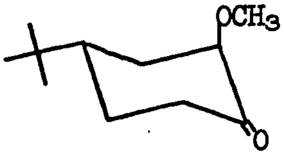
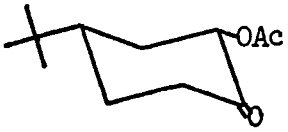
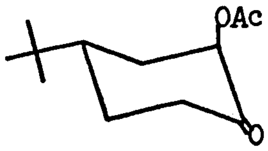
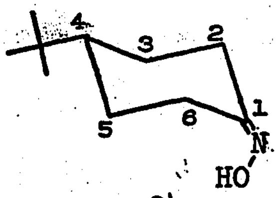
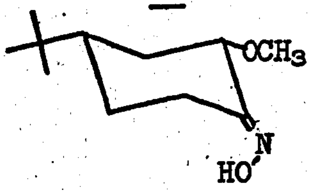
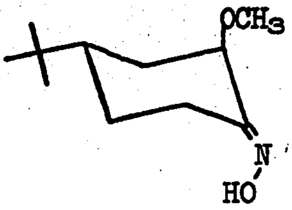
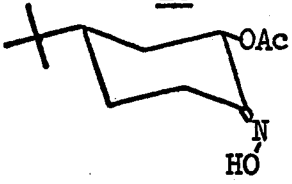
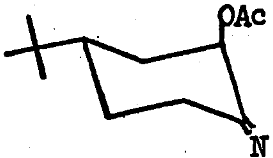
Compound	Chemical Shifts, τ-Units			
	H_2		H_6	
	Axial	Equatorial	Axial	Equatorial
 23	~ 7.5-7.8	~ 7.5-7.8	~ 7.5-7.8	~ 7.5-7.8
 21	6.22 (20)	-	7.5-7.8	7.5-7.8
 13	-	6.53 (7)	7.25	7.7
 1	4.77 (20)	-	7.5-7.7	7.5-7.7
 16	-	4.91 (11)	7.5	~ 7.6

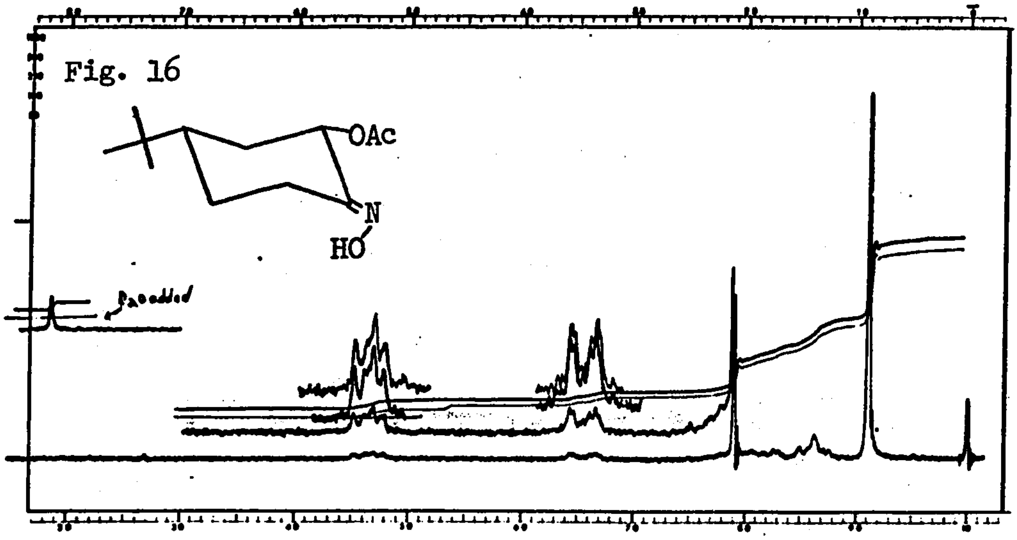
TABLE II (Cont.)

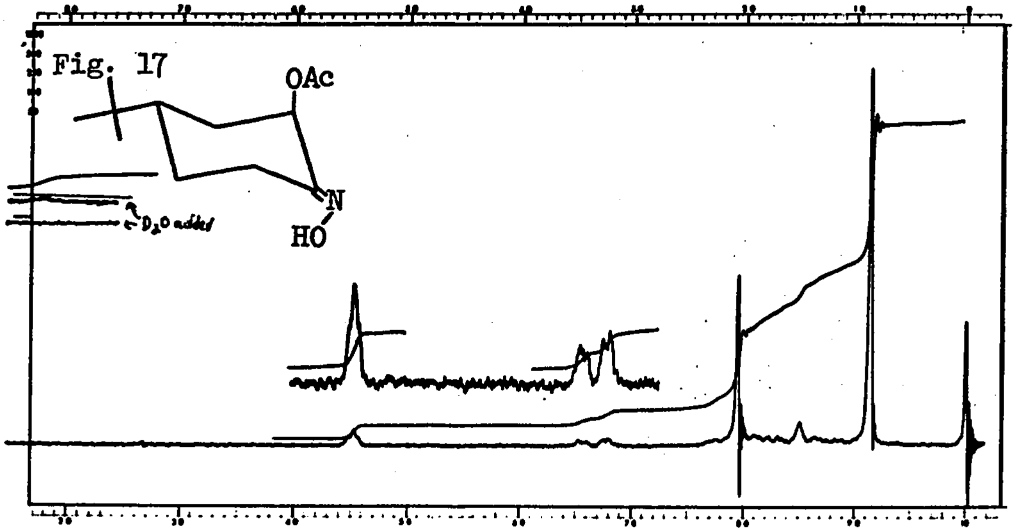
N.M.R. Parameters[a] for α-Substituted 4-t-Butylcyclohexanones and their Oximes in Deuteriochloroform

	Chemical Shifts, τ-Units			
	H_2		H_6	
Compound	Axial	Equatorial	Axial	Equatorial
 24	~ 8-8.3	~ 7.5	~ 8-8.3	6.61
 25	6.28 (15)	-	~ 7.8	6.73
 26	-	6.18 (7)	~ 7.7	6.76
 27	4.65 (17)	-	~ 7.8	6.57
 28	-	4.52 (7)	~ 7.7	6.67

---

a. The n.m.r. spectra of ketones 1, 13, 16 and 21 are shown in Figs. 1, 7, 8 and 12, respectively. The n.m.r. spectra of oximes 25, 26, 27 and 28 are shown in Figs. 14, 15, 16 and 17, respectively. The numbers in parentheses are the half-band widths (in Hz) of the signals.





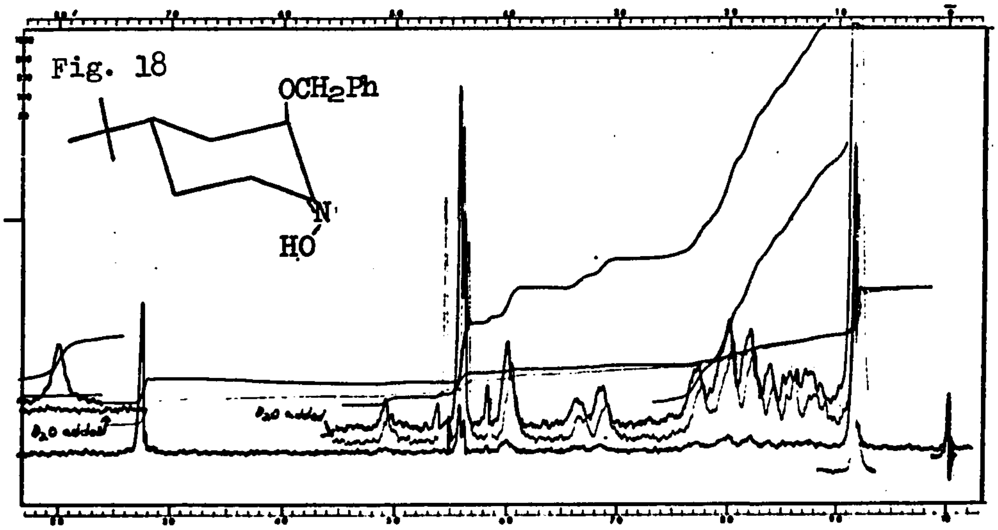
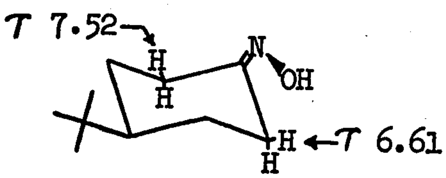
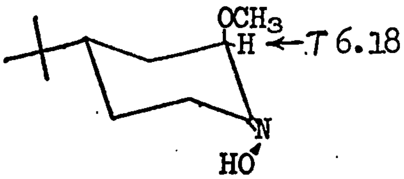


Figure 16. 60 MHz N.M.R. Spectrum of cis-2-Acetoxy-4-t-butylcyclohexanone Oxime (27) in CDCl$_3$. Figure 17. 60 MHz N.M.R. Spectrum of trans-2-Acetoxy-4-t-butylcyclohexanone Oxime (28) in CDCl$_3$. Figure 18. 60 MHz N.M.R. Spectrum of trans-2-Benzyloxy-4-t-butylcyclohexanone Oxime (31) in CDCl$_3$.

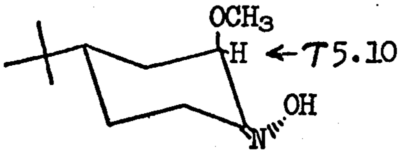
basis. In addition to the low field signal attributed to the hydrogen geminal to the 2-substituent, each oxime displayed a one-proton doublet that was centered in the region τ6.5 to 6.8. Trager and Huitaic (59) have shown that one of the equatorial hydrogens vicinal to the oximino group in 4-*t*-butylcyclohexanone oxime appears as a doublet at τ6.61, 0.91 τ-units down field from the other. Others have observed similar results for a variety of oximes and have shown that it is the equatorial hydrogen *syn* to the hydroxyl group of the oxime that appears down field in the spectrum (60,61). Because the signal for the hydrogen at the 2-position in the 2-substituted 4-*t*-butylcyclohexanone oximes has already been accounted for, the one-proton doublet in the region τ6.5-6.8 must be due to the presence of a deshielded equatorial hydrogen at the 6-position and, therefore, the hydroxy group of the oxime must be *syn* to the 6-position and *anti* to the 2-position. It should be noted that the n.m.r. spectrum (Fig. 15) of *trans*-4-*t*-butyl-2-methoxycyclohexanone oxime indicates the presence of some (approximately 15 %) *syn* oxime. This is indicated by the presence of a signal at τ5.10 (half-band width 7 Hz). The difference (1.08 τ-units) between the chemical shifts of the equatorial hydrogen at the 2-position in the



syn and *anti* oximes is in agreement with the above observations.

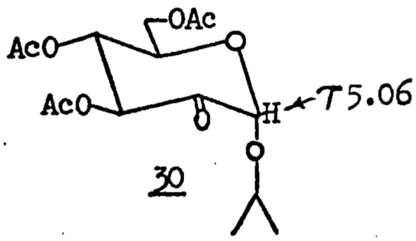


anti isomer

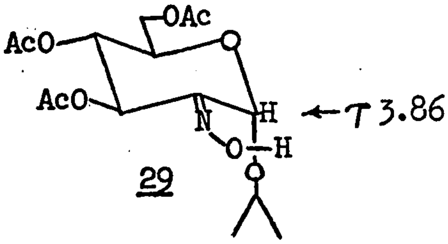


syn isomer

Obviously, therefore, when the chemical shift for an equatorial hydrogen α to a keto group is known then it is possible to determine the configuration of its oxime since its signal will be shifted about one τ-unit down field if the hydroxyl is *syn* to the hydrogen. Thus, it is possible to assign a configuration to the oximino group in isopropyl tri-O-acetyl-2-oximino-α-D-*arabino*-hexopyranoside (**29**) obtained by Lemieux, *et al*. (19). The signal for the anomeric hydrogen in isopropyl tri-O-acetyl-α-D-*arabino*-hexopyran-2-uloside (**30**) was shown to appear at τ 5.06 in the n.m.r. spectrum (31). On the other hand, **29** showed an anomeric signal at τ 3.86. The large downfield shift of the anomeric signal on going from ketone to



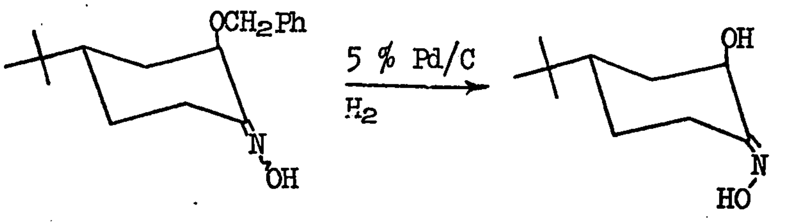
30



29

oxime requires the oxime to have the *syn* configuration as shown above for 29. The alkyl and aryl 3,4,6-tri-O-acetyl-2-oximino-α-*D*-*arabino*-hexopyranosides described in reference 19 all have similar chemical shifts for the anomeric hydrogens and it seems likely that all of these oximes have the *syn* configuration. This result had been predicted on the basis of mechanistic considerations (19).

Not listed in Table II are the oximes of *trans*-2-benzyloxy-4-*t*-butylcyclohexanone and *trans*-2-hydroxy-4-*t*-butylcyclohexanone. *trans*-2-Benzyloxy-4-*t*-butylcyclohexanone oxime (31) was prepared from *trans*-2-benzyloxy-4-*t*-butylcyclohexanone in the usual manner. The n.m.r. spectrum of 31 (Fig. 18) indicated that this was a mixture of the *syn* and *anti* isomers. Signals at τ4.93 (half-band width 7 Hz) and τ6.02 (half-band width 7 Hz) were attributed to the hydrogens at the 2-position of the cyclohexane ring in the *syn* and *anti* isomers, respectively. As shown below 31 was used as starting material for the preparation of the oxime of *trans*-2-hydroxy-4-*t*-butylcyclohexanone (32). The hydrogenation was stopped after slightly more than one equivalent of hydrogen had been absorbed to prevent hydrogenation of the oximino group. The n.m.r. spectrum of 32 (Fig. 19) showed a one-proton multiplet at τ5.56 which was



31　　32

assigned to the hydrogen at the 2-position of the cyclohexane ring. The half-band width of this signal (7 Hz) indicated that the 2-hydroxy group was axial (44).

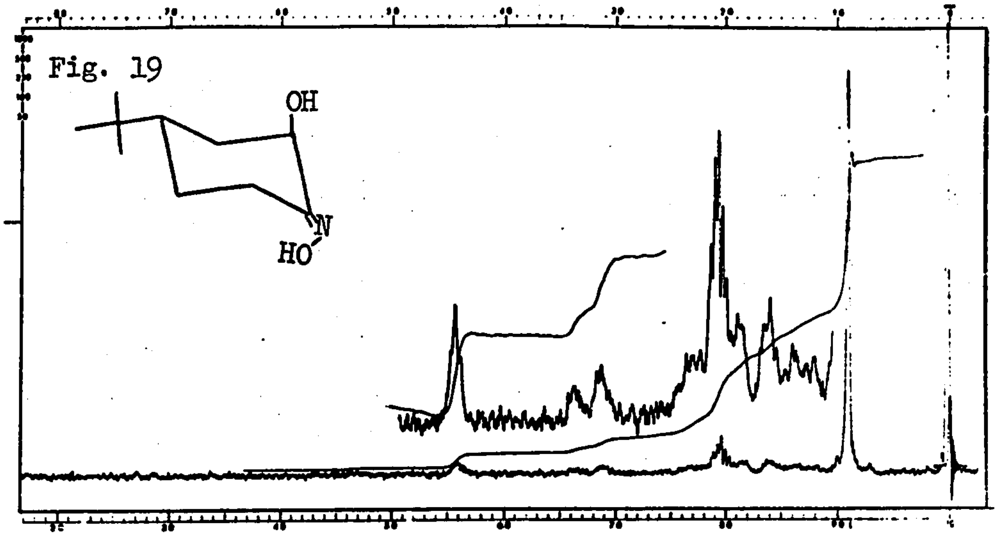
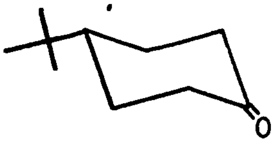


Figure 19. 60 MHz N.M.R. Spectrum of trans-4-t-Butyl-2-hydroxycyclohexanone Oxime (32) in D_4-Acetic Acid.

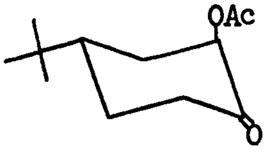
B. Reduction Studies

1. Sodium Borohydride Reduction of 2-Substituted 4-*t*-Butylcyclohexanones

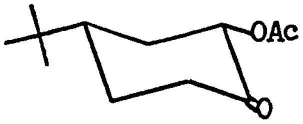
As pointed out earlier, an objective of this research was also to construct model ketones that could be used to study the effects, that 2-substituents have on the stereochemical result of the sodium borohydride reduction of ketones. Particular emphasis was placed on the preparation of ketones with polar 2-substituents, since these are the kinds of groups normally found adjacent to the carbonyl group of ketones derived from carbohydrate structures and information was not available in the literature on what effects these kinds of substituents have on the course of ketone reductions. For this reason the following compounds of fixed conformation were synthesized.



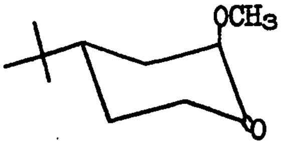
23



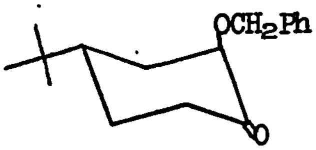
16



1



13



22

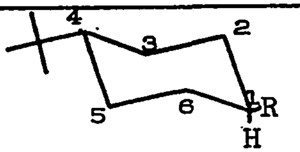
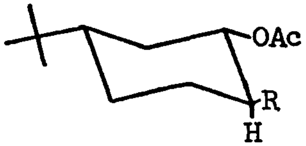
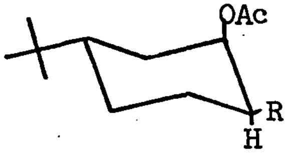
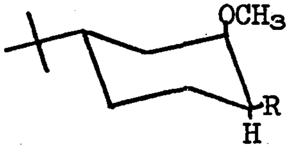
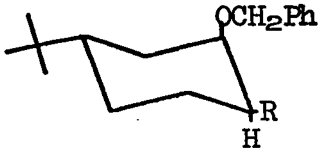
The borohydride reductions were performed under standard conditions at 0° using a 5:1:1 mixture of tetrahydrofuran, ethyl acetate and water as solvent. Nearly quantitative yields of a mixture of epimeric alcohols were produced in each case. The ratios of equatorial to axial alcohols were obtained by a combination of n.m.r. and gas chromatographic analysis and the results are shown in Table III along with appropriate n.m.r. parameters. The reduction of ketones 1 and 23 gave alcohol mixtures that were easily analyzed by n.m.r. because the chemical shifts of the hydrogens at the 1-positions of the epimeric alcohols were well separated in the spectrum. However, this was not so for the pairs of epimeric alcohols obtained from the reduction of ketones 13, 16 and 22 since there was little difference between these chemical shifts.

In Table III it is seen that the products from the reduction of ketones 13 and 22 were acetylated prior to n.m.r. analysis. This was necessary since there was little difference between the chemical shifts for the hydrogens at the 1- and 2-positions of the cyclohexane ring of the unacetylated products.

The pair of epimeric alcohols obtained from the reduction of 16 was separated by column chromatography. The n.m.r. spectrum of the predominant isomer (Fig. 20) contained signals for the hydrogens of an acetoxy and a hydroxyl group in addition to one-proton multiplets at $\tau 4.82$ (half-band width 8 Hz) and $\tau 6.38$ (half-band width 20 Hz) which were assigned to the hydrogens geminal to the acetoxy and hydroxy groups, respectively. The large spacings present in the signal at $\tau 6.38$ confirmed that, indeed, the major product of the reduction was the equatorial alcohol, trans-2-acetoxy-

TABLE III

Sodium Borohydride Reduction of 2-Substituted 4-*t*-Butylcyclohexanones

			Major Product		Chemical Shifts, τ-Units [a]			
					Major Product		Minor Product	
Ketone			R	Yield (%)[b]	H_1	H_2	H_1	H_2
23	$\xrightarrow{NaBH_4}$		OH	94	6.51 (25)[c]	-	6.00 (7)	-
1	$\xrightarrow{NaBH_4}$		OH	86	6.50 (27)	5.37 (25)	5.98 (7)	5.37 (25)
16	$\xrightarrow{NaBH_4}$		OH	86	6.38 (20)	4.82 (8)	6.30 (8)	5.07 (8)
13	$\xrightarrow{NaBH_4}$ $\xrightarrow{Ac_2O}$		OAc	90	5.29 (20)	6.33 (8)	5.01 (7)	~6.60
22	$\xrightarrow{NaBH_4}$ $\xrightarrow{Ac_2O}$		OAc	86	~ 5.2	6.16 (12)	~ 5.2	6.40 (12)

a. The n.m.r. spectra of the crude products obtained from the sodium borohydride reduction of ketones 1, 13 and 16 are shown in Figs. 2, 25 and 21, respectively. The values in parentheses are the half-band widths (in Hz) of the signals. b. As determined by g.l.p.c.

trans-4-t-butylcyclohexanol. In Fig. 21 is seen the n.m.r. spectrum of the corresponding axial alcohol, trans-2-acetoxy-cis-4-t-butylcyclohexanol (15), which, as pointed out earlier, was an intermediate in the synthesis of trans-2-acetoxy-4-t-butylcyclohexanone. It is seen that for this compound, the signals for the hydrogens geminal to the acetoxy and hydroxy groups appear at τ5.07 (half-band width 8 Hz) and τ6.30 (half-band width 8 Hz), respectively. In Fig. 22 is seen the n.m.r. spectrum of the crude product obtained in the borohydride reduction of ketone 16. The spectrum shows clearly that both the equatorial and axial alcohols were present. This was indicated by the presence of multiplets at τ4.82 (half-band width 8 Hz) and τ5.07 (half-band width 8 Hz) which, as was shown above, could be assigned to the signals produced by the hydrogens geminal to the acetoxy groups in the equatorial and axial isomers, respectively. It is apparent from the relative intensities (5.7:1) of these signals that the equatorial product was predominent.

The product from the reduction of trans-2-benzyloxy-4-t-butylcyclohexanone (22) was analyzed in a manner similar to that described above and again the equatorial alcohol was the predominant product. It is seen in Table III that the chemical shifts for the equatorial hydrogens, geminal to the benzyloxy groups were different in the two epimers. This effect has been noted by others (62) and, in general, an equatorial hydrogen vicinal to an axial acetoxy group produces a signal with a chemical shift that is upfield (approximately 0.25 τ-units) from the signal produced by such a

Fig. 20

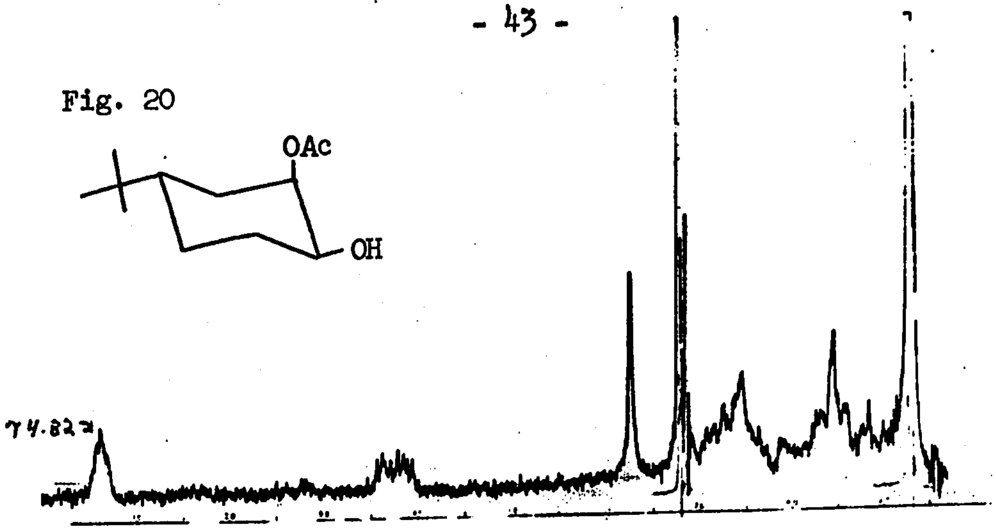


Fig. 21

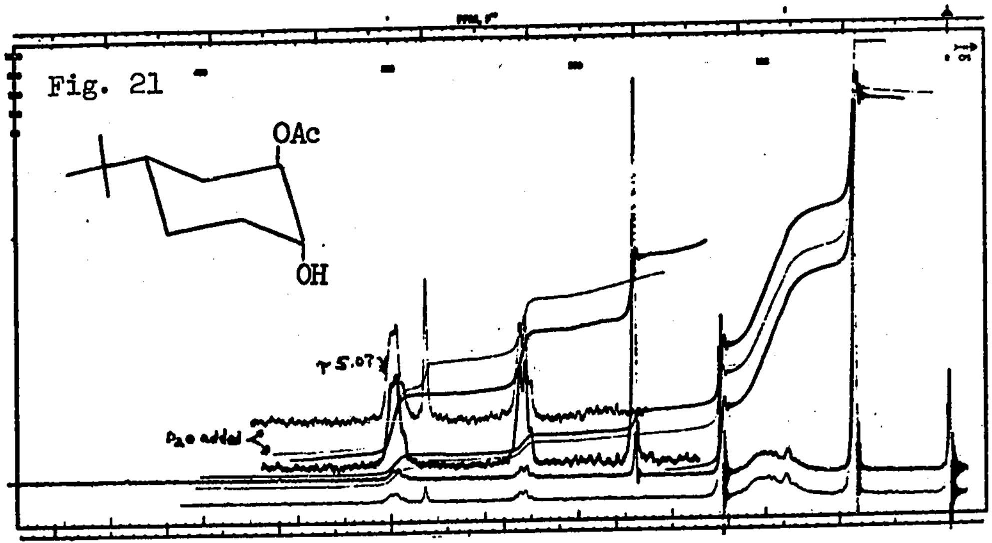


Fig. 22

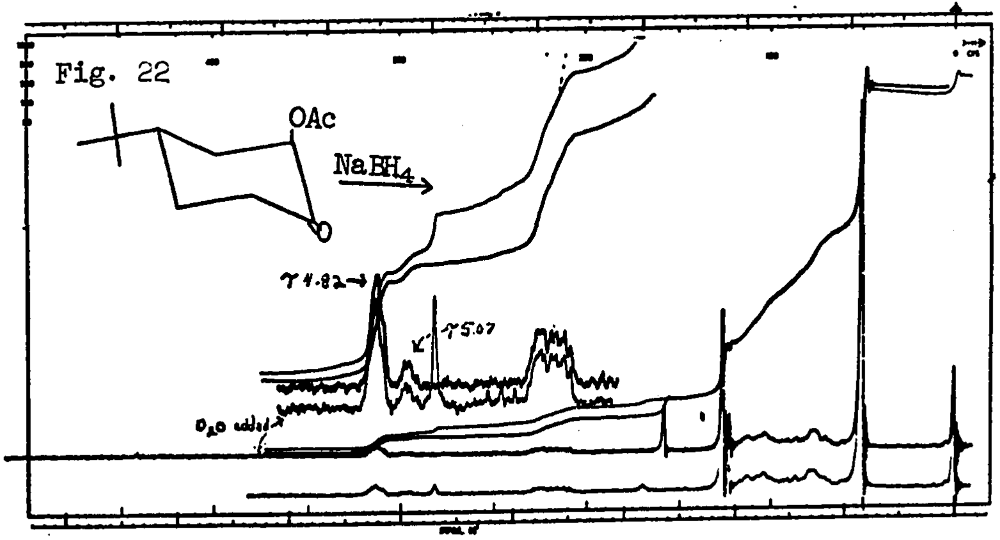
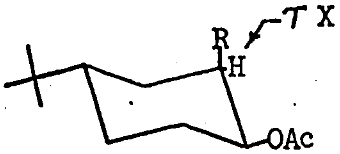
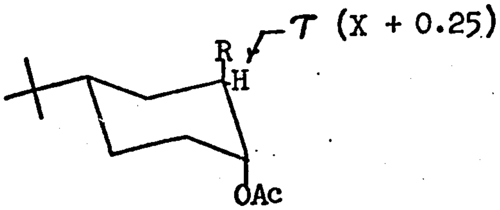


Figure 20. 100 MHz N.M.R. Spectrum of cis-2-Acetoxy-trans-4-t-butylcyclohexanol in $CDCl_3$ (Sweep width 1000 Hz, offset 50 Hz). Figure 21. 60 MHz N.M.R. Spectrum of trans-2-Acetoxy-cis-4-t-butylcyclohexanol (15) in $CDCl_3$. Figure 22. 60 MHz N.M.R. Spectrum of Product from Sodium Borohydride Reduction of trans-2-Acetoxy-4-t-Butylcyclohexanone (16) in $CDCl_3$.

hydrogen when the vicinal acetoxy group is equatorial.





The alcohol mixtures, obtained from the reduction of the ketones, were trifluoroacetylated and examined by g.l.p.c. and in each case produced two well resolved peaks that showed a ratio of intensities in close agreement with the epimeric ratios obtained by n.m.r. analysis. Authentic axial alcohols were available in three cases for trifluoroacetylation and comparison of retention times. In each case the axial alcohol was found to be the minor component and had the shorter retention time.

The results of the reductions show that the addition of polar 2-substituents to 4-t-butylcyclohexanone had the effect of slightly decreasing the amounts of equatorial alcohol produced. The configuration (axial or equatorial) and the nature of the 2-substituents had little effect on the isomeric ratios. In all cases the yield of equatorial alcohol was 86-90 %.

These results seem to parallel the examples found in the literature for the sodium borohydride reduction of ulosides. It was seen in the introduction that, when there are no axial substituents β to the keto group, the borohydride reduction of ulosides normally gives the equatorial alcohol as the predominant product.

2. Catalytic hydrogenation of 4-t-butylcyclohexanone oxime, azine and hydrazones

As has already been discussed, a model oxime system based on derivatives of 4-t-butylcyclohexanone was constructed for the purpose of examining the effects of polar 2-substituents on the catalytic hydrogenation of ketoximes. This Section is concerned, mainly, with the hydrogenation of 4-t-butylcyclohexanone oxime.

The hydrogenations could be carried out under a very wide range of conditions including changes in acidity, catalyst, pressure, solvent and temperature. However, it was desired to obtain at least a semi-quantitative assessment of the effects that acidity, catalyst, solvent and changes in structure have on the rates of the reductions. This was most conveniently achieved by carrying out reactions at 25 ± 1° and using an all glass atmospheric pressure hydrogenator fitted with a gas burette (63). In all cases hydrogenation was continued until hydrogen uptake had ceased. The 4-t-butylcyclohexylamines formed in the reductions were trifluoroacetylated and examined by g.l.p.c. employing cyclohexylamine as internal standard. The results obtained in the hydrogenations are listed in Table IV.

It is seen in Table IV that the reduction of 4-t-butylcyclohexanone oxime over 5 % rhodium on carbon in 90 % ethanol (run 3) gave a lower yield of amine than when the reduction was carried out in absolute ethanol containing 2 % benzene (run 4). Rylander (1) has pointed out that when oximes are hydrogenated in aqueous solvents the yields of amines are often low due to the formation

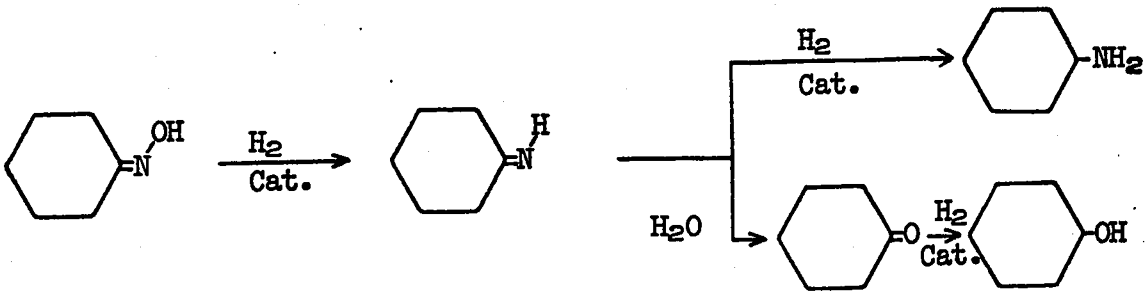
TABLE IV

Catalytic Hydrogenation of 4-t-Butylcyclohexanone Oxime[a]

			4-t-Butylcyclohexylamines Formed				
Run	Catalyst	Solvent	% Conversion[b]	% Yield[c]	% Cis	$t_{1/3}$ (min.)	Rel. Rate
1	5 % Ru/C	90 % EtOH	40	32	67	370	3.2
2	5 % Ru/Al_2O_3	90 % EtOH	9	7	46	860	1.4
3[d]	5 % Rh/C	90 % EtOH	–	51	74	12	100
4	5 % Rh/C	98 % EtOH[e]	71	68	88	66	18
5	5 % Rh/Al_2O_3	98 % EtOH[e]	69	60	91	270	4.5
6	5 % Rh/C	1.1 eq. HCl in HOAc	66	54	80	100	12
7[d]	5 % Pd/C	1.1 eq. HCl in 90 % EtOH	–	55	56	190	6.3
8	5 % Pd/C	1.1 eq. HCl in HOAc	50	32	98	1300	0.9
9	5 % Pd/C 5 % Pt/C (19/1 w/w)	1.1 eq. HCl in HOAc	78	65	69	490	2.5
10	5 % Pt/C	1.1 eq. HCl in HOAc	86	82	69	12	100

a. Two mmoles oxime, 10 ml solvent and 169 mg catalyst at 25 ± 1° and atmospheric pressure and employing cyclohexylamine as internal standard. b. Internal standard added before work up of hydrogenation product. c. Internal standard added after work up and before g.l.p.c. analysis. d. One mmole oxime, 10 ml solvent and 183 mg of catalyst. The yield was determined from the weight of isolated amine. e. Absolute ethanol containing 2 % benzene.

of alcohol and ketone side products. Breitner et al. (64) have suggested that the first step in the hydrogenation of oximes may be the cleavage of the nitrogen-oxygen bond giving rise to an imine. The imine can then be hydrogenated to amine or hydrolyzed to ketone which if hydrogenated would give an alcohol.



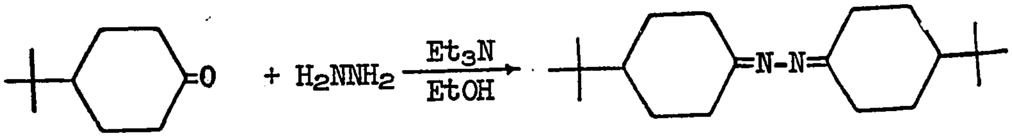
The reductions with ruthenium (runs 1 and 2) were found to be very unsatisfactory giving low yields of amines and very slow rates of reduction. Rylander (1) encountered similar problems when he used ruthenium as catalyst for the reduction of oximes. He observed that the main products of these reactions were alcohols and ketones.

It has been reported that when two platinum catalysts are used together (physical mixture) the hydrogenation rates may be faster than when either catalyst is used individually (65). Synergism by mixtures of two catalysts has been accounted for by the assumption that hydrogenation may involve two or more discrete stages or intermediates (as discussed above), some of which may be reduced more easily by one catalyst and some by the other (66). Run 9 (Table IV) was carried out using a nineteen to one mixture of 5 % palladium on carbon and 5 % platinum on carbon, respectively. It is seen that synergism did not take place since the rate of hydrogenation was intermediate between the rates for palladium (run 8) and platinum (run 10) under the same conditions. However, there is some sign that the hydrogenation does occur in stages since the rate of the reduction was similar to that found when 5 % palladium on carbon was used as catalyst in run 8 whereas the stereochemical result of the reduction was identical to that found for the corresponding reduction employing 5 % platinum on carbon as catalyst (run 10).

The catalyst support may influence the stereochemistry of oxime reduction, but no investigation of the effect of support seems to have been made (1). Since aluminum oxide is commonly used as a catalyst support (66, 67), it was of interest to test the influence of this support on the stereochemical outcome of oxime reductions. It is seen in Table IV that the stereochemical results of reductions using aluminum oxide as catalyst support were nearly the same as when carbon was used as the support. The rates of reduction, however, were slower when aluminum oxide was used as the catalyst support. Thus, the rate of reduction over 5 % ruthenium on carbon in 90 % ethanol (run 1) was about twice as fast as the corresponding reduction over ruthenium on aluminum oxide (run 2). Similarly, the reduction of 4-_t_-butylcyclohexanone oxime over 5 % rhodium on carbon (run 4) was four times as fast as the corresponding reduction using aluminum oxide as the support (run 5). In general, the reductions over the aluminum oxide supported catalysts were unsatisfactory since the yields of amines were also lower than those obtained in the corresponding reductions using carbon supported catalysts.

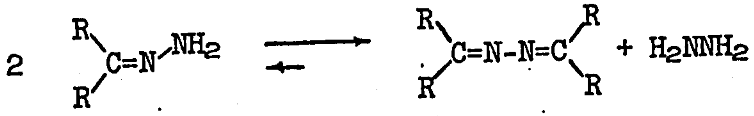
The results in Table IV indicated that catalytic hydrogenation of 4-t-butylcyclohexanone oxime gives predominately axial amine under a variety of conditions. The reduction of 4-t-butylcyclohexanone oxime over 5 % palladium on carbon in glacial acetic acid containing hydrochloric acid (run 8) yielded nearly pure axial amine; whereas, when the reduction was carried out in 90 % ethanol containing hydrochloric acid (run 7) or in glacial acetic acid without mineral acid (experimental, section C-4) nearly equal amounts of the cis and trans amines were formed. This serves to demonstrate the extreme sensitivity of catalytic hydrogenation towards solvents and pH. Although the reduction of 4-t-butylcyclohexanone oxime over palladium in acetic acid containing hydrochloric acid gave a high percentage of axial amine, it is seen that this reduction was about 7 times slower and gave lower yields than that when the hydrogenation was carried out using acidified 90 % ethanol as solvent. Similar results are noted for reductions using rhodium as catalyst (runs 3 and 6). As mentioned before, our main interest in oxime reductions is connected with the synthesis of amino sugars. Since sugar molecules are sensitive to extremes in pH it is desirable that their reductions be carried out under mild conditions and as fast as possible in order to minimize side reactions. The most satisfactory reductions of 4-t-butylcyclohexanone oxime, from the standpoint of mildness of conditions and rapidity of reductions, were those using either rhodium or palladium on carbon as the catalyst and 90 % ethanol as solvent. These conditions are more likely to be used for the reduction of sugar oximes and therefore these conditions were used during the reductions of 2-substituted 4-*t*-butylcyclohexanone oximes, which are discussed in the next Section.

It was shown that the hydrogenation of isopropyl 3,4,6-tri-*O*-acetyl-2-oximino-α-D-*arabino*-hexopyranoside in the presence of an excess of hydrazine gave a good yield of the equatorial amine (*gluco* configuration) (29). It was hoped that the hydrazone of 4-*t*-butylcyclohexanone would show similar effects during hydrogenation; that is the formation of an increased amount of equatorial amine as compared to that obtained on hydrogenation of the oxime. However, treatment of 4-*t*-butylcyclohexanone with an excess of hydrazine, by the procedure of Barton *et al*. (68), led to the formation of azine instead of the desired hydrazone. The tendency towards azine formation is great. When 4-*t*-butylcyclohexanone oxime was hydrogenated (5 % palladium on carbon) in 90 % ethanol containing 10 moles of hydrazine, no hydrogen was absorbed. The n.m.r. spectrum of the crude product showed that it was nearly pure azine. It was reported by Biel *et al*. (69) that certain hydrazones tend to



23 33

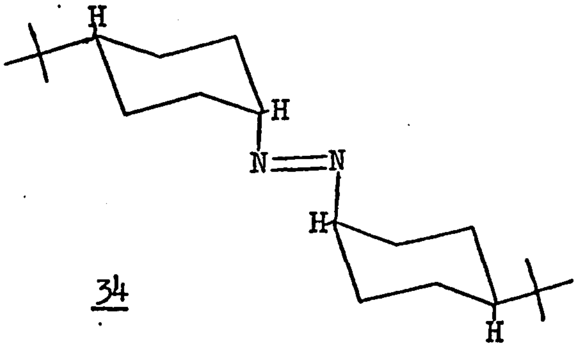
disproportionate to form azine and that this reaction can be



$$2\ R_2C{=}N{-}NH_2 \rightleftarrows R_2C{=}N{-}N{=}CR_2 + H_2NNH_2$$

responsible for the slow and incomplete reduction of hydrazones.

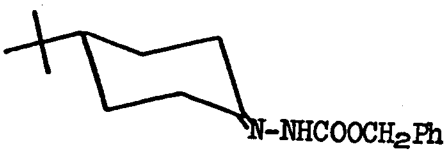
Although the azine was not reduced under the above conditions it was reduced in acid medium. Thus, when the reduction was carried out in acetic acid containing 1.1 equivalents of hydrochloric acid and using 5 % palladium on carbon as catalyst, a reduction product was obtained that contained at least three new components. One nonbasic component was isolated and appeared to be the azo compound shown below. The structure was supported by elemental analysis, an



34

i.r. spectrum that showed no absorption for a carbon-nitrogen double bond and the presence of a 2-proton down field signal in the n.m.r. spectrum at τ6.45 (half-band width 7 Hz) that indicated the presence of two deshielded equatorial hydrogens.

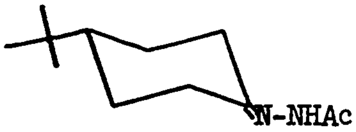
The N-carbobenzyloxyhydrazone of 4-t-butylcyclohexanone was synthesized and hydrogenated over 5 % palladium on carbon in 90 %



35

ethanol and at neutral pH. It was hoped that, as the carbobenzyloxy group was hydrogenolyzed, the hydrazone that was set free would reduce to give amine before it had a chance to form azine. However, the hydrogenation produced only a low yield (5 %) of amines which were a mixture of cis and trans 4-t-butylcyclohexylamine in the ratio 1.3:1, respectively. In addition to the amines, a 10 % yield of azo compound 34 was isolated, indicating that some azine may have been produced during the reaction.

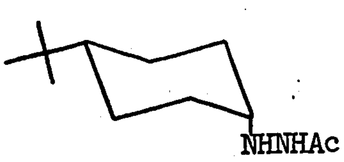
The N-acetylhydrazone (36) of 4-t-butylcyclohexanone was



36

synthesized. It was shown (70) that hydrogenation of acetylhydrazones stops at the hydrazine stage, so it was anticipated that some information might be gained on the stereochemistry of hydrazone reduction from the results of the reduction of this compound. The reduction of 36 over 5 % palladium on carbon in acetic acid containing 1.1 equivalents of hydrochloric acid gave nearly pure 1-N-acetyl-2(cis-

4'-*t*-butylcyclohexyl) hydrazine (37). When the reduction was carried out in 90 % ethanol a 1.8:1 ratio of (37) and the equatorial isomer,



37

38

1-*N*-acetyl-2-(*trans*-4'-*t*-butylcyclohexyl) hydrazine (38) was obtained. As noted before, the reduction of 4-*t*-butylcyclohexanone oxime over 5 % palladium on carbon in 90 % ethanol containing 1.1 equivalents of hydrochloric acid (run 2, Table IV), gave a 1.3:1 ratio of *cis* to *trans* 4-*t*-butylcyclohexyl amines (56 % *cis*). It appears, therefore, that *N*-acetyl hydrazones have a greater tendency to give axial products during hydrogenation than do the corresponding oximes. It was pointed out earlier that the hydrogenation of a inosose phenylhydrazone gave a higher yield of axial amine than the reduction of the corresponding oxime (20).

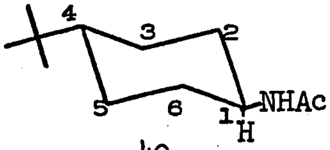
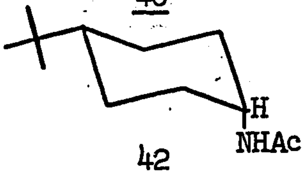
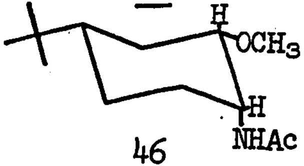
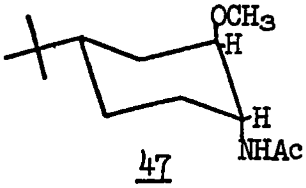
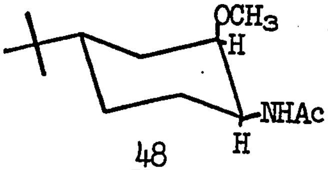
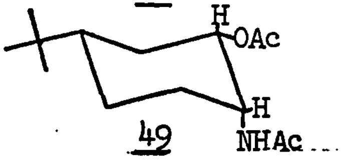
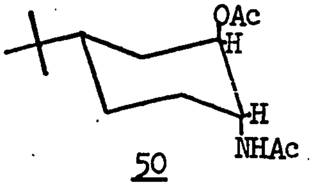
3. Catalytic hydrogenation of 2-substituted 4-t-butylcyclohexanone oximes

The hydrogenations of the 2-substituted 4-t-butylcyclohexanone oximes were carried out in a manner similar to that described in the preceding Section for the reduction of unsubstituted 4-t-butylcyclohexanone oxime. The reductions were effected over 5 % palladium on carbon (in acidified 90 % ethanol) and 5 % rhodium on carbon (in 90 % ethanol) for reasons discussed in the preceding Section. The products of hydrogenation were analyzed by a combination of n.m.r. and g.l.p.c. G.l.p.c. was carried out on the trifluoroacetyl derivatives of the reduction products since these derivatives were far more volatile and showed better separation in the gas chromatogram than the corresponding acetyl derivatives. The products of hydrogenation were acetylated prior to analysis by n.m.r.

The more abundant isomers were isolated from the reaction mixtures (in the form of their acetyl derivatives) either by direct crystallization or by preparative g.l.p.c. The orientations of the acetamido groups and the 2-substituents in these compounds were determined from the half-band widths of the signals for the hydrogens geminal to these groups. Signals with half-band widths of 8 - 9 Hz were assigned to equatorial hydrogens and those with half-band widths of 20 - 25 Hz were assigned to axial hydrogens (44). N.m.r. parameters and m.p. data for these compounds are summarized in Table V.

Special problems were encountered during the reduction of trans-2-acetoxy-4-t-butylcyclohexanone oxime using rhodium as catalyst. A major, fast moving peak was present in the gas chromatogram that

TABLE V
N.M.R. Parameters[a] and M.P. Data[b] for Acetylated
4-t-Butylcyclohexylamines

Compound	Chemical Shifts — In τ-Units —		M.P., °C
	H_1	H_2	
 40	6.35 (25)		
 42	5.91 (9)		
 46	5.62 (8)	~ 6.7	122.5-125
 47	5.85 (8)	6.57 (8)	130-131.5
 48	6.18 (25)	6.55 (8)	121.7
 49	5.60 (8)	5.20 (20)	161-162
 50	5.97 (8)	5.10 (8)	157.5-158.5

---

a. In deuteriochloroform. b. M.P.'s are uncorrected. The values in parentheses are the half-band width (in Hz) of the signals.

did not correspond to the trifluoroacetyl derivative of any of the expected reduction products. The n.m.r. spectrum of the acetylated reduction product indicated that there were three times as many N-acetyl groups as there were O-acetyl groups. It was found that the fast moving peak in the gas chromatogram had a retention time identical to that of the N-trifluoroacetyl derivative of cis-4-t-butylcyclohexylamine and, indeed, it was shown that signals for cis-4-acetamido-t-butylcyclohexane were present in the n.m.r. spectrum. There was also gas chromatographic and n.m.r. spectral evidence that trans-4-t-butylcyclohexylamine had been produced during the reduction.

The gas chromatographic data could not be used for the assignment of the isomeric ratios since it appeared that all of the trifluoroacetylated reduction products were not resolved in the chromatogram. The n.m.r. spectrum of the acetylated reduction product (Fig. 23) showed clearly that one of the products of reduction was trans-2-acetoxy-cis-4-t-butylcyclohexylamine (axial amine). This was evidenced by the presence of signals at τ 5.10 (half-band width 8 Hz) and τ 5.97 (half-band width 8 Hz) which are also present in the spectrum (Fig. 24) of pure cis-4-acetamido-trans-3-acetoxy-t-butylcyclohexane (50). These signals were assigned to the hydrogens geminal to the acetoxy and acetamido groups, respectively, in 50. The n.m.r. spectrum of the acetylated reduction product also showed a narrow multiplet at τ 4.95 (half-band width 8 Hz) which was rationalized as belonging to the hydrogen

Fig. 23

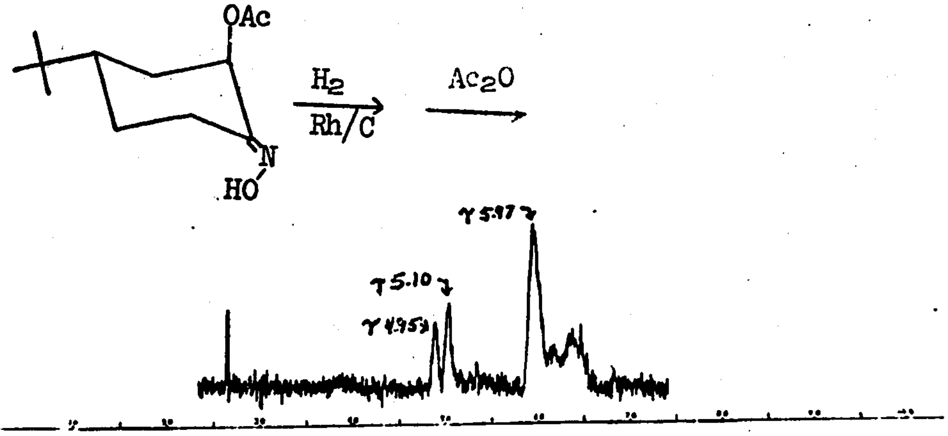


Fig. 24

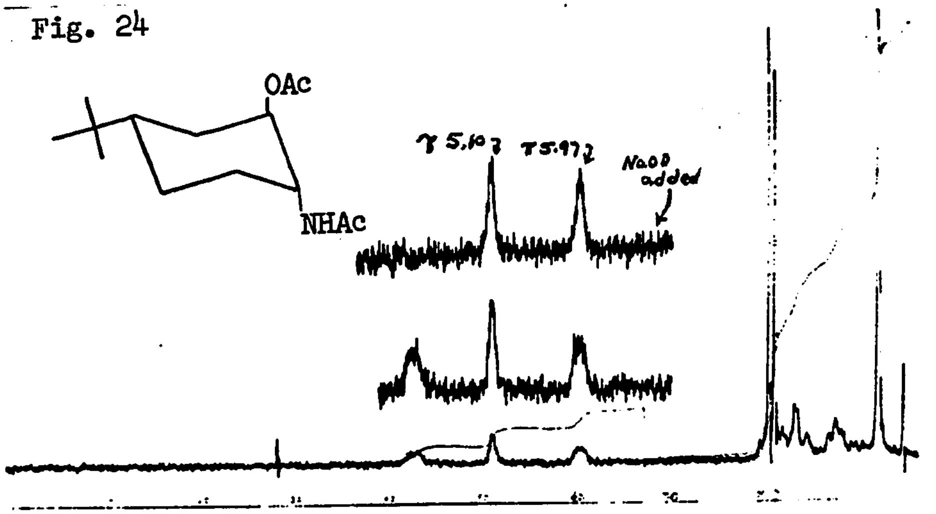


Figure 23. 100 MHz N.M.R. Spectrum of the Acetylated Product from Catalytic Hydrogenation of trans-2-Acetoxy-4-t-butylcyclohexanone Oxime (28) over 5 % Rhodium on Carbon, in 90 % Ethanol. (In $CDCl_3$, Sweep width 1000 Hz and in the range τ2.3 - τ7.4). Figure 24. 100 MHz N.M.R. Spectrum of cis-4-Acetamido-trans-3-acetoxy-t-butylcyclohexane (50) in $CDCl_3$ (Sweep width 1000 Hz).

geminal to the acetamido group in the diastereoisomeric compound, trans-4-acetamido-trans-3-acetoxy-t-butylcyclohexane. The ratio of axial to equatorial amines was therefore assigned on the basis of the ratio of the intensities of the signals at τ 5.10 and τ 4.95, respectively. It was shown earlier that an equatorial hydrogen, vicinal to an equatorial acetoxy group, produces a signal with a chemical shift that is downfield from the signal produced by such a hydrogen when the vicinal acetoxy group is axial and in the next Section it is seen that this is often the case when the vicinal group is an acetamido group.

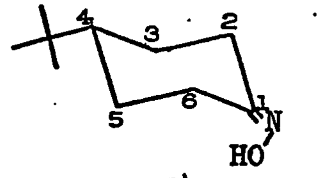
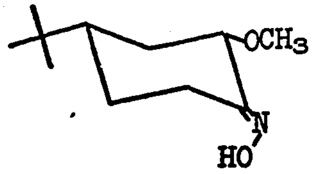
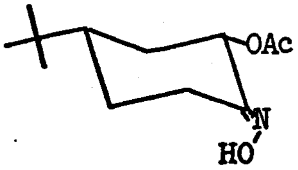
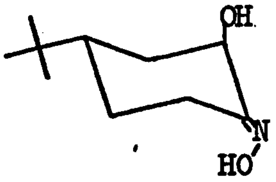
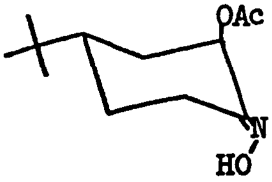
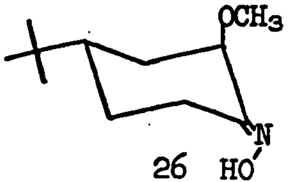
The catalytic hydrogenation of trans-2-acetoxy-4-t-butylcyclohexanone oxime over 5 % palladium on carbon (in acidified 90 % ethanol) also yielded cis and trans 4-t-butylcyclohexylamine, but in much smaller amounts than the corresponding reduction over 5 % rhodium on carbon. As in the previous example the isomeric ratio was determined from the n.m.r. spectrum of the acetylated reduction product. It is interesting to note that these are the first observations of the hydrogenolysis of a group, α- to an oximino group, other than halogen atoms (71).

Tables VI and VII list the oximes, one third reduction times and the percentage axial amines produced during the reductions using 5 % palladium on carbon and 5 % rhodium on carbon as catalysts, respectively.

It is seen in Table VI that the hydrogenation of both the cis-2-methoxy and cis-2-acetoxy derivatives of 4-t-butylcyclo-

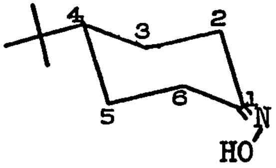
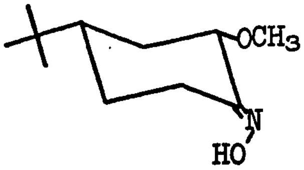
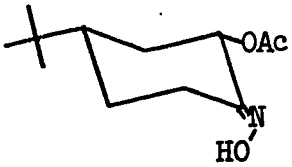
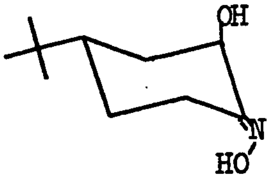
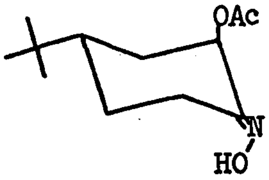
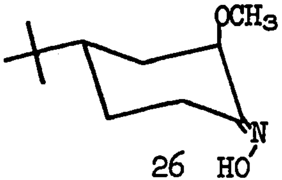
TABLE VI

Catalytic Hydrogenation[a] of 2-Substituted 4-t-Butylcyclohexanone Oximes in 90 % Ethanol containing 1.1 mmoles of Hydrochloric Acid, using 5 % Palladium on Carbon as Catalyst

Oxime	t 1/3 (min.)	% Axial Amine[b]	% Yield[c]	% Epimerization[d]
 24	190	56	55	-
 25	8.6	96	75	-
 27	12	94	46	-
 32	200	94	58	-
 28	46	70	89	-
 26	610	32	62	6

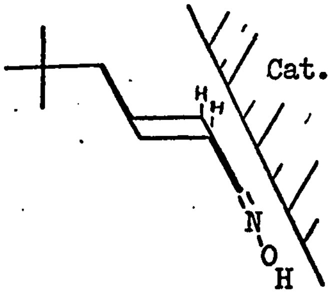
a. One mmole oxime, 10 ml solvent and 184 mg catalyst at 25 ± 1° and atmospheric pressure. b. Determined from the ratio of axial to equatorial amines (in which the 2-substituents were not epimerized). c. Percentage yield of total amines present. d. Percentage of material in which the 2-substituent had epimerized.

TABLE VII
Catalytic Hydrogenation[a] of 2-Substituted 4-*t*-Butylcyclohexanone Oximes in 90 % Ethanol, using 5 % Rhodium on Carbon as Catalyst

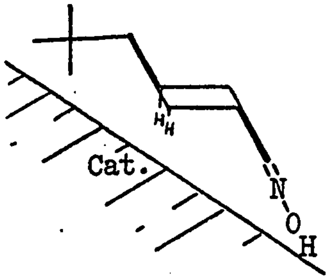
Oxime	t 1/3 (min.)	% Axial Amine[b]	% Yield[c]	% Epimerization[d]
 24	12	74	51	-
 25	62	86	64	7
 27	58	85	25	8
 32	12	96	38	-
 28	52	60	36	-
 26	62	39	58	28

a. One mmole oxime, 10 ml solvent and 184 mg catalyst at 25 ± 1° and atmospheric pressure. b. Determined from the ratio of axial to equatorial amines (in which the 2-substituents were not epimerized). c. Percentage yield of total amines present. d. Percentage of material in which the 2-substituent had epimerized.

hexanone oxime over 5 % palladium on carbon, proceeded under the standard conditions much (about 20 times) more rapidly than the parent compound. These results show that an equatorial α-substituent provides assistance for hydrogenation either through anchoring or inductive effects. The importance of inductive effects is evident from the relatively high rate of hydrogenation (factor of four) found for trans-2-acetoxy-4-t-butylcyclohexanone oxime (28) as compared with the parent compound. However, trans-4-t-butyl-2-methoxycyclohexanone oxime (26) was reduced three times slower than the parent oxime and about 70 times slower than its epimer which had the methoxy group in an equatorial orientation. This latter result seems to require a steric influence of vicinal α-substituents which retards the reaction when they are in axial orientation. This is in accord with the fact that equatorial approach of the



Equatorial approach

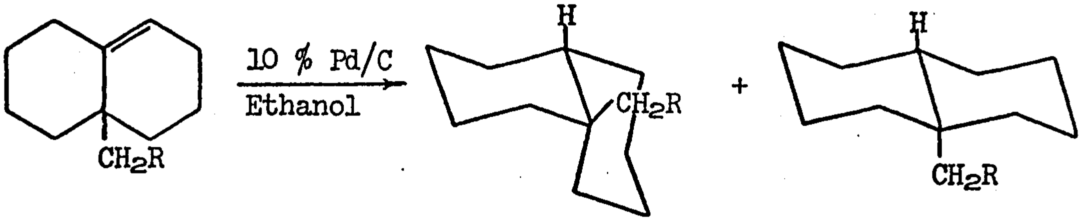


Axial approach

hydrogenated catalyst is the preferred route (4) and that an axial α-substituent is in a cis relationship to this approach. Indeed, both axial acetoxy and methoxy substituents retarded the rate of reaction involving equatorial attack as compared to axial attack. Thus, it is seen in Table VI that there was a substantial increase in the amount of equatorial amine produced during the hydrogenation of the trans-2-acetoxy and the trans-2-methoxy derivatives of 4-t-butylcyclohexanone oxime as would be expected from an increased amount of axial attack by the catalyst.

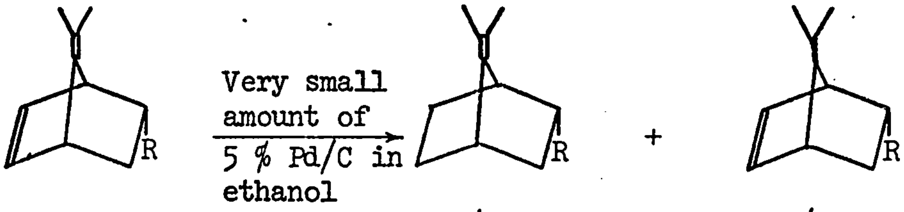
Examination of the results presented in Table VII show that the rates of hydrogenation using rhodium on carbon as catalyst were quite insensitive to the nature or configuration of the α-substituent which is in direct contrast to the results found for the palladium catalyzed reactions. Again it is seen that axial, polar 2-substituents such as acetoxy and methoxy groups, retarded equatorial approach of the catalyst and as a result there was an increased amount of equatorial amine formed during the reduction of 28 and 26. The introduction of an axial hydroxy substituent has little effect on rate but resulted in the formation of nearly pure axial amine. The possible significance of this result will be discussed later.

Burgstahler and Nordin (72) have shown that the stereochemistry of the hydrogenations of a number of substituted octalins were highly dependent on the nature of the angular substituents. Thus,



	Cis	Trans
R = CH_3	3	4
= CHO	5	2
= CO_2H	Main product	

when R was methyl nearly equal proportions of cis and trans decalins were formed but when R was a carboxaldehyde or carboxyl group the cis-decalin constituted the bulk of the product. Similarly, Depuy and Story (73) have shown that the course of the reduction of the diene, shown below, was highly dependent on the nature of R. When



	%	%
R = =O	70	30
= -OAc	95	5
= -OTs	>95	-

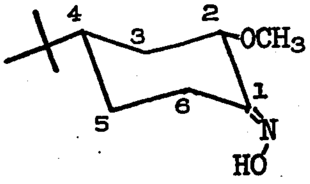
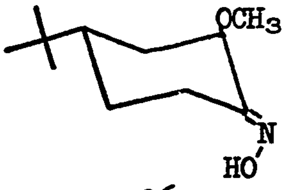
R was a keto group the reduction was relatively nonselective but when R was acetoxy or tosyloxy the reduction was highly stereoselective giving almost pure material in which the endo double bond was reduced. These authors believed that the substituents (CHO, CO_2H, OAc, and OTs) served as points of adsorption on the catalyst surface and provided what might be termed anchimeric assistance to the reactions (74). The effects noted in Tables VI and VII of introducing methoxy and acetoxy substituents, especially in equatorial orientation, are probably related phenomena. Also, the formation of nearly pure axial amine, during the hydrogenation of the trans-2-hydroxy derivative of 4-t-butylcyclohexanone oxime, seems to agree with this concept. The adsorption of the hydroxy group on the catalyst surface and concurrent cis transfer of hydrogen from the catalyst to the oxime would be expected to result in the formation of axial amine.

In addition to palladium catalyzed hydrogenations in acidic medium, the cis and trans 2-methoxy derivatives of 4-t-butylcyclohexanone oxime (25 and 26, respectively) were also hydrogenated over 5 % palladium on carbon in the presence of hydrazine. The results of these reductions are shown in Table VIII. It is seen that the presence of hydrazine had little effect on the amount of axial amine that was formed when these results are compared to those listed in Table VI. It is interesting that the reductions did occur, since under similar circumstances 4-t-butylcyclohexanone oxime reacted with the hydrazine to give azine and no hydrogenation took place. Therefore, the fact that the 2-substituted compounds were reduced indicates that either azine formation was very slow as compared with the rate of hydrogenation of oxime, or that the azines of these compounds do reduce under these conditions to give amines.

One effect, of the presence of hydrazine, was to cause a

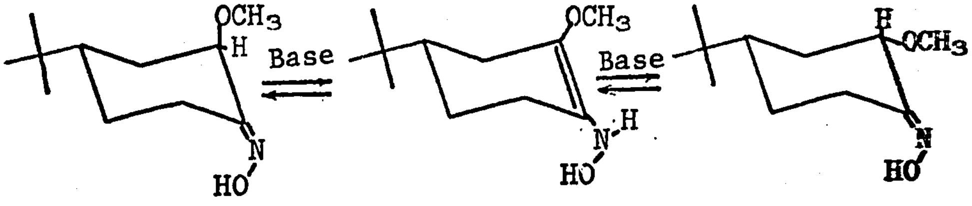
TABLE VIII

Catalytic Hydrogenation[a] of 2-Substituted 4-*t*-Butylcyclohexanone Oximes in 90 % Ethanol, containing 4 mmoles of Hydrazine, using 5 % Palladium on Carbon as Catalyst

Oxime	t 1/3 (min.)	% Axial Amine[b]	% Yield[c]	% Epimerization[d]
 25	130	88	62	-
 26	120	34	37	28

a. One mmole oxime, 10 ml solvent and 184 mg catalyst at 25 ± 1° and atmospheric pressure. b. Determined from the ratio of axial to equatorial amines (in which the 2-substituents were not epimerized). c. Percentage yield of total amines present. d. Percentage of material in which the 2-substituent had epimerized.

considerable amount of epimerization of the methoxy group in trans-4-t-butyl-2-methoxycyclohexanone oxime (26). As depicted below, epimerization might occur by a process similar to that for the epimerization of ketones. The intermediate cycloalkene,



26

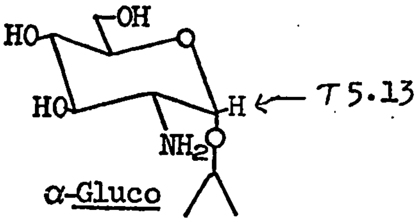
25

a structure analogous to the enol form of a ketone, could isomerize either to trans-4-t-butyl-2-methoxycyclohexanone oxime (26) or to cis-4-t-butyl-2-methoxycyclohexanone oxime (25). As would be expected, epimerization was most favored by a basic reaction medium. Indeed, little epimerization was noted when the hydrogenation was carried out in the absence of hydrazine and in an acid medium (Table VI). Epimerization of 2-substituents also occurred during reductions using rhodium as catalyst (Table VII). No acid was present during these reductions; therefore the pH of the solutions would be expected to rise, as the product amine concentration increased, leading to conditions favoring epimerization. Itis noteworthy that the literature makes no mention of side products, arising during the catalytic hydrogenation of oximes, which were attributable to epimerization of substituents α- to the oximino groups.

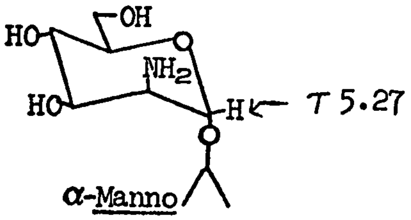
4. Catalytic hydrogenation of isopropyl 2-oximino-α-D-*arabino*-hexopyranoside and isopropyl 3,4,6-tri-O-acetyl-2-oximino-α-D-*arabino*-hexopyranoside

Isopropyl 2-oximino-α-D-*arabino*-hexopyranoside was reduced under a variety of conditions in order to assess the effects of catalyst, solvent, pH and hydrazine on the stereochemical outcome of the hydrogenations. A study of the hydrogenation of this compound was expected to provide information useful for anticipating the stereochemical outcome of the hydrogenation of more complex 2-oximino-α-D-*arabino*-hexopyranosides. Complex 2-oximino-α-D-*arabino*-hexopyranosides are currently being synthesized in this laboratory as precursors of 2-amino-2-deoxy-α-D-*gluco*-pyranosides with antibiotic-like structures.

The reductions of isopropyl 2-oximino-α-D-*arabino*-hexopyranoside produced products with the α-D-*gluco* and α-D-*manno* configurations. The crude reduction mixtures were examined by n.m.r. and the ratios of *gluco* to *manno* products determined by comparison of the intensities of the signals produced by the anomeric hydrogens of these compounds. The anomeric hydrogen of the *gluco* compound produced a doublet at τ 5.13 with a splitting of 3.5 Hz whereas the *manno* compound produced a doublet at τ 5.27 with a splitting of one Hz for H_1. In several



α-*Gluco*



α-*Manno*

cases the crude reduction products were N-acetylated prior to the n.m.r. analyses. In these cases the anomeric signals appeared at τ5.33 and 5.49 for the gluco and manno compounds, respectively.

Some of the amino sugar mixtures were trifluoroacetylated and analyzed by g.l.p.c. The trifluoroacetylated products showed two major peaks in the gas chromatogram that had ratios of intensities that corresponded well with the gluco to manno ratios determined from the n.m.r. spectra. Table IX lists the substrate, solvent system and catalyst used for the reductions. The one third reduction times are given as well as the percentage of gluco product.

It is seen in Table IX that, when palladium was used as catalyst for the reduction of isopropyl 2-oximino-α-D-arabino-hexopyranoside (56), the amount of equatorial amine (gluco product) produced, varied between 79 and 95 %. The studies of the model oximes had indicated that palladium catalysed hydrogenations of oximes produced larger proportions of equatorial amines than did the corresponding reductions over rhodium. The same effect is noted here. Thus it is seen that when the hydrogenation of 56 was carried out in water using palladium as catalyst the percentage of gluco product was about 80 % whereas the corresponding hydrogenation over rhodium produced only 54 % of the gluco product. Similar differences between these catalysts were noted when the reductions were carried out in the presence of hydrazine.

The presence of hydrazine had a profound influence on the stereochemical course of the hydrogenations. When 56 was hydrogenated over 5 % palladium on carbon in 90 % ethanol, containing 4 mmoles of hydrazine, the ratio of gluco to manno products was about 19:1.

TABLE IX

Catalytic Hydrogenation[a] of Isopropyl 2-oximino-α-*D*-*arabino*-hexopyranoside (56) and Isopropyl 3,4,6-tri-O-acetyl-2-oximino-α-*D*-*arabino*-hexopyranoside (29).

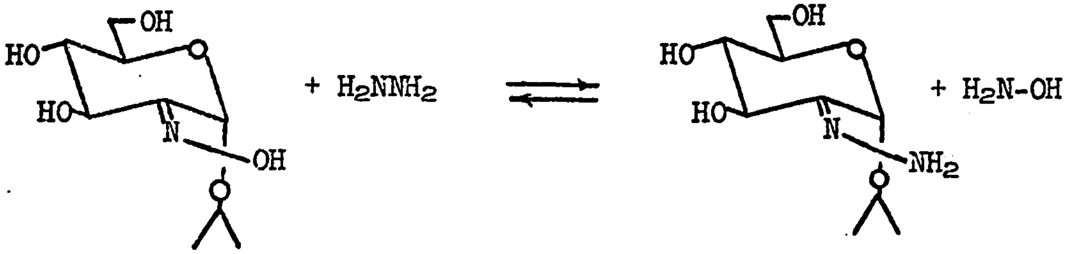
Substrate	Conditions	t 1/3 (Min.)	% Gluco
56	5 % Pd/C, 1.1 mmoles HCl in MeOH	-	79[b]
	5 % Pd/C, H_2O	30	67[c] 80[d] 80[e]
	5 % Pd/C, 4 mmoles hydrazine in H_2O	-	86[c] 86[e]
	5 % Pd/C, 4 mmoles hydrazine in 90 % EtOH	14	100[c] 95[e]
	5 % Pd/C, 4 mmoles Et_3N in 90 % EtOH	21	90[c] 86[e]
	5 % Rh/C, H_2O	132	48[c] 62[d] 54[e]
	5 % Rh/C, 20 mmoles hydrazine in 95 % EtOH	-	79[d]
29	5 % Pd/C, 1.1 mmoles HCl in MeOH	-	50[b]
	5 % Rh/C, 1.1 mmoles HCl in MeOH	-	56[d]

---

a. One mmole oxime, 10 ml solvent and 184 mg catalyst at 25 ± 1° and atmospheric pressure. b. Taken from data in reference 28. c. From n.m.r. of reduction product. d. From n.m.r. of N-acetylated reduction product. e. From g.l.p.c. analysis of trifluoroacetylated reduction product.

Indeed, after N-acetylation, pure isopropyl 2-acetamido-2-deoxy-α-D-gluco-pyranoside could be isolated in 58 % yield by crystallization.

When the above reaction was repeated, using 4 mmoles of triethylamine instead of hydrazine, the ratio of gluco to manno product was about 6:1. This seems to indicate that the effect of hydrazine is not simply one of pH since the pH of the solution containing triethylamine was 11.4 compared to 8.6 for the solution containing hydrazine. It seems likely that the effects noted are due to the formation of a new compound which, when hydrogenated, gives a higher yield of equatorial amine than does the parent oxime. Some indication of this is given in the relative rates of the reductions. As seen in Table IX, the palladium catalyzed hydrogenation of isopropyl 2-oximino-α-D-arabino-hexopyranoside (56) proceeded faster (factor of two) when carried out in the presence of hydrazine as compared to similar reductions carried out in the presence of triethylamine ("pH" 11.4) or in water at an initial "pH" of 7. Very likely the oximinoglycoside reacts with the hydrazine to give a hydrazone and it is mainly this



compound that is being reduced. Another possibility is that the azine of the sugar may have been formed; however, the rapid rates of hydrogenation does not support this since azines are known to be reduced only with difficulty (69).

Lemieux and Gunner (28) had noted that the reduction of isopropyl 3,4,6-tri-O-acetyl-2-oximino-α-D-arabino-hexopyranoside (29) over 5 % palladium on carbon in acidified methanol gave equal amounts of the α-gluco and α-manno products. It is seen in Table IX that nearly identical results were obtained when the reduction was carried out using 5 % rhodium on carbon as catalyst. These results bear a certain resemblance to those found during the reduction of the α-substituted 4-t-butylcyclohexanone oximes. It was seen that the hydrogenation of 4-t-butylcyclohexanone oxime yielded higher proportions of axial amines when an acetoxy group was introduced into the equatorial, 2-position of the cyclohexane ring.

5. Summary

In conclusion, it seems appropriate to compare the results of the reductions of 4-t-butylcyclohexanone and 4-t-butylcyclohexanone oxime with the results of similar reductions of ulosides and oximino-sugars.

The results of the sodium borohydride reduction of 2-substituted 4-t-butylcyclohexanones were very similar to those found for the sodium borohydride reduction of ulosides. It was noted in the introduction that the sodium borohydride reduction of ulosides normally gives an equatorial alcohol as the predominant product except in those cases where there is a bulky substituent β to the carbonyl carbon of the uloside; a result that suggests that polar substituents, α- to the carbonyl group, have little effect on the stereochemical result of the reductions. This study shows that this is true for cyclohexanones, at least, since substituents such as axial 2-acetoxy, 2-benzyloxy, 2-methoxy or equatorial 2-acetoxy had little effect on the stereochemical result of the sodium borohydride reduction of 4-t-butylcyclohexanone. Indeed, in all cases the reductions gave from 86 to 94 % of the equatorial alcohols.

The stereochemical outcome of the catalytic hydrogenation of 2-substituted 4-t-butylcyclohexanone oximes was found to be highly sensitive to the nature and configuration of the substituents. Although hydrogenation of 4-t-butylcyclohexanone oxime over 5 % palladium on carbon (in acidified 90 % ethanol) gave nearly equal amounts of axial and equatorial amines, the corresponding reductions of 4-t-butylcyclohexanone oximes with equatorial 2-acetoxy, 2-methoxy or axial 2-hydroxy substituents gave nearly pure axial amines. These findings suggest that the polar substituents offer assistance to the reactions possibly through anchoring effects. These results closely paralleled those reported for the hydrogenation of inosose oximes and oximino-sugars. As mentioned in the introduction these reductions do normally give axial amine products.

When axial acetoxy or methoxy substituents were placed in the 2-position of the cyclohexane ring of 4-t-butylcyclohexanone oxime, the amount of axial amine produced was only 60-70 %. This result is similar to those found in the reduction of oximino sugars that had bulky, axial substituents α-to the oximino group. It appears, therefore, that axial substituents, α-to the oximino group, offer steric hindrance towards equatorial approach of the catalyst. In agreement with this, the rates of the hydrogenations of 4-t-butylcyclohexanone oximes with axial 2-substituents were considerably less than those for the corresponding reductions where the 2-substituents were equatorial.

The reduction of Isopropyl 2-oximino α-D-arabino-hexopyranoside, over 5 % palladium on carbon yields from 79 to 85 % of the equatorial amine, depending on the solvent employed and the acidity of the reaction mixture. When the reductions were carried out in the presence of hydrazine, the yields of equatorial amine were highest. No such increase in equatorial amine formation was observed when the cyclohexanone oximes were catalytically hydrogenated over 5 % palladium on carbon in the presence of hydrazine. Although 4-t-butylcyclohexanone oxime with axial or equatorial 2-methoxy substituents did hydrogenate in the presence of hydrazine to give amines, the stereochemical results of the reductions were the same as the corresponding reductions that were carried out in the presence of acid and in the absence of hydrazine. In contrast to this, it was found that unsubstituted 4-t-butylcyclohexanone oxime reacted with hydrazine to give azine and that this compound was resistant towards hydrogenation.

III. EXPERIMENTAL SECTION

A. Methods

Thin layer chromatography (t.l.c.) was carried out routinely for monitoring reactions and for following the progress of column chromatography. Unless otherwise noted, t.l.c. was carried out using Silica Gel G and one of the following solvent systems: Solvent system A -- benzene and methanol (9:1, v/v); Solvent system B -- chloroform and Skelly B (4:1, v/v); Solvent system C -- Skelly B and ethyl acetate (7:3, v/v).

Gas liquid partition chromotography (g.l.p.c.) was carried out using a F & M (model 500) gas chromatograph fitted with a thermal conductivity cell. Helium was used as the carrier gas and all determinations were carried out isothermally with a flow rate adjusted to 66 ml/min. Analyses were carried out using the following columns: Column A -- a 6 ft x 0.25 in (O.D.) copper tube packed with 20 % butanediol succinate (LP 23) on non acid washed Chromosorb W (30-60 mesh); Column B -- a 5 ft x 0.25 in (O.D.) copper tube packed with 15 % ethyleneglycol succinate (LP 71) on non acid washed Chromosorb W (30-60 mesh); Column C -- a 6 ft x 0.25 in (O.D.) copper tube packed with 20 % silicone gum rubber (SE 30) on acid washed Chromosorb P (40-60 mesh). Column D -- a 21 ft x 0.25 in (O.D.) copper tube packed with 20 % silicone gum rubber (SE 30) on acid washed Chromosorb P (40-60 mesh). Relative (g.l.p.c.) peak intensities were determined by comparing the weights of traces made of the peaks.

All solutions were dried over anhydrous sodium sulfate and all concentrations were carried out in vacuo (water aspirator) and at 30° unless otherwise stated.

Elemental analyses were performed by the departmental service laboratories. Infra red (i.r.) spectra were recorded using a Perkin Elmer 337 grating infra red spectrometer. Nuclear magnetic resonance (n.m.r.) spectra were carried out using deuteriochloroform (1 % tetramethyl silane (TMS) as internal standard) as solvent and at 60 MHz unless otherwise stated. Unless noted otherwise, pyrazine (chemical shift τ1.55 referred to external TMS) was used as internal standard for runs in deuterium oxide. All chemical shift are reported in τ-units. Varian A-60, A-56/60 and HR-100 spectrometer were used for the analyses. Mass spectra were obtained using an A.E.I. Ltd., MS9 double focussing mass spectrometer (ionizing energy 70 ev).

Melting points were determined in capillaries and are not corrected.

B. Materials

Reagent pyridine and 2,6-lutidine were stored over potassium hydroxide pellets. Tetrahydrofuran and Skelly B (boiling range 64-67°) were dried by distillation from lithium aluminum hydride. All other reagent grade solvents were used as obtained without further purification.

Palladium (5 % on carbon) was purchased from Matheson, Coleman and Bell. Rhodium (5 % on carbon), rhodium (5 % on alumina), ruthenium (5 % on carbon), ruthenium (5 % on alumina), and platinum (5 % on carbon) were purchased from Engelhard Industries. The catalysts were stored in a desiccator over potassium hydroxide pellets.

C. Standardized Procedures

1. Acetylation procedure A

A solution of one mmole of the alcohol (or amine) was dissolved in a ml of acetic anhydride pyridine (1:1, v/v) and let stand for 12 hr. Unless otherwise stated, the work up procedure was as follows: methanol (2 ml for 1 ml of acetylation mixture) was added to destroy excess acetic anhydride. After 20 min the solution was concentrated. The residue was dissolved in methylene chloride and washed in succession with 2.5 N hydrochloric acid solution, water, saturated aqueous sodium bicarbonate solution and again water. The solution was dried followed by removal of the solvent *in vacuo*.

2. Acetylation procedure B

A solution of one mmole of the alcohol (or amine) was dissolved in a ml of acetic anhydride containing 200 mg of anhydrous sodium acetate. The solution was warmed at 80° for 4 hr. Unless otherwise stated, the work up procedure was as follows: methanol (2 ml for one ml of acetic anhydride) was added and after 20 min the solvent was removed *in vacuo*. The residue was partitioned between methylene chloride and water. The methylene chloride solution was washed first with saturated aqueous sodium bicarbonate solution and then with water. The solution was dried and then concentrated.

3. Trifluoroacetylation procedure

One mmole of the alcohol (or amine) was dissolved in one ml of acetonitrile-trifluoroacetic anhydride (1:1, v/v) and let stand for 10 min and then concentrated. For g.l.p.c. analysis, the residue was dissolved in a small amount of methylene chloride.

D. Syntheses

1. Synthesis of 4-t-butylcyclohexanone (23)

The procedure used was that described by Hussey and Baker (75) for oxidation of cyclohexanols to cyclohexanones. A mixture of cis and trans 4-t-butylcyclohexanol, 100 g, gave 87.8 g (90 %) of 23 which distilled in the range 103-107.5° at 8-11 mm. The material crystallized to a camphor-like solid characterized as follows.

2. Synthesis of 4-t-butylcyclohexanone oxime (24)

The addition of a solution of 8.4 g (0.21 mole) of sodium hydroxide in 20 ml of water to a mixture of 4-t-butylcyclohexanone (30.8 g, 0.2 mole) and hydroxylamine hydrochloride (14.6 g, 0.21 mole) in 95 % ethanol (150 ml) resulted in the separation of 24 as a white solid. Two recrystallizations from ethanol-water gave the pure oxime 24 (27 g, 82 %) as white platelets: m.p. 137.5-139° (lit. (76) m.p.

133-134°).

3. Synthesis of *trans*-4-*t*-butylcyclohexylamine (*39*)

The title compound was prepared in 62 % yield by sodium-ethanol reduction of 4-*t*-butylcyclohexanone oxime, using the procedure of Hückel and Heyder (76) and converted into *trans*-4-acetamido-*t*-butylcyclohexane (*40*) (acetylation procedure A), m.p. 96-101° (lit. m.p. (76) 117.2-118.1°). The n.m.r. spectrum of the *N*-acetate (Fig. 25) showed a multiplet at τ 6.35 with a half-band width of 25 Hz which was assigned to the axial hydrogen geminal to the *N*-acetyl group.

4. Synthesis of *cis*-4-*t*-butylcyclohexylamine (*41*)

Hydrogenation of 4-*t*-butylcyclohexanone oxime in glacial acetic acid using Adam's catalyst was carried out as described (76). From 8.45 g of oxime there was obtained 7.6 g of crude amine. Acetylation of this (procedure A) gave a solid derivative which was examined by n.m.r. and found to be a 1.3:1 mixture of the *N*-acetates of *cis* and *trans* 4-*t*-butylcyclohexylamine, respectively, as determined by comparing the intensities of the signals at τ 5.91 and τ 6.35 for the hydrogens geminal to the *N*-acetyl groups. Three recrystallizations of this product from ethyl acetate gave *cis*-4-acetamido-*t*-butylcyclohexane (*42*): m.p. 170.5-172° (lit. m.p. (76) 170.3-171.2°). The n.m.r. spectrum (Fig. 26) showed a multiplet at τ 5.91 (half-band width 15 Hz) which is assigned to the equatorial hydrogen geminal to the *N*-acetyl group.

Fig. 25

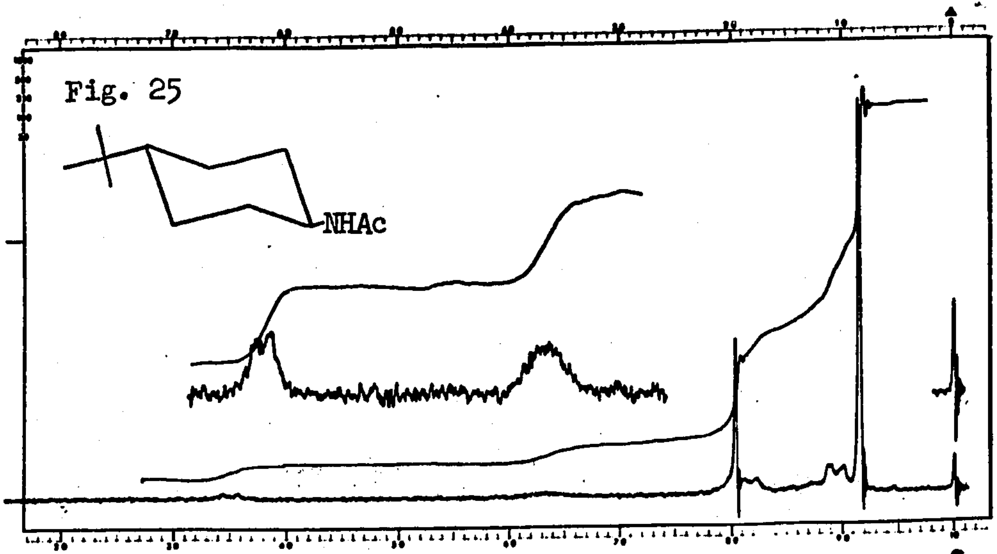


Fig. 26

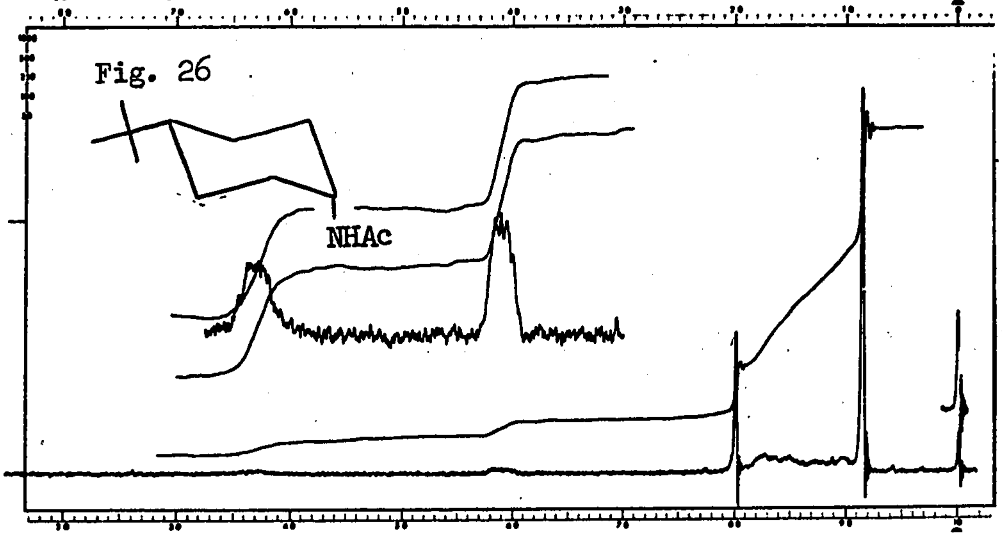


Fig. 27

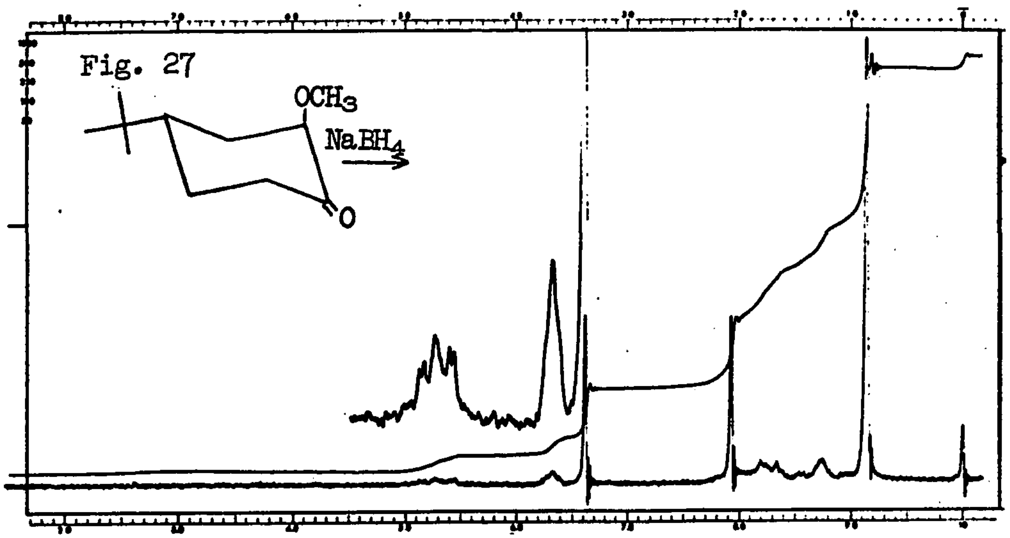


Figure 25. 60 MHz N.M.R. Spectrum of trans-4-Acetamido-t-butylcyclohexane in $CDCl_3$. Figure 26. 60 MHz N.M.R. Spectrum of cis-4-Acetamido-t-butylcyclohexane in $CDCl_3$. Figure 27. 60 MHz N.M.R. Spectrum of the Product from Sodium Borohydride Reduction of trans-4-t-Butyl-methoxycyclohexanone (13) after Acetylation (in $CDCl_3$).

5. Synthesis of cis-4-trifluoroacetamido-t-butylcyclohexane (43) and trans-4-trifluoroacetamido-t-butylcyclohexane (44)

Crude cis and trans-4-t-butylcyclohexylamine (1.3:1 mixture) obtained from above was trifluoroacetylated and the mixture of cis and trans-4-trifluoroacetamido-t-butylcyclohexanes separated into its components by preparative g.l.p.c. G.l.p.c. was carried out on a 208 x 1.8 cm stainless steel column, packed with 20 % 1.4-butanediol succinate on non-acid washed Chromosorb W (10-60 mesh), with a flow rate of 0.4 l/min (N_2) and at 160°. The gas chromatograph used was a Hewlet-Packard model 766 Prep Master Jr. fitted with a hydrogen flame ionization detector.

The cis isomer (43) had a m.p. of 109-111.5° after two recrystallizations from methanol-water. A satisfactory carbon hydrogen analysis was not obtained for this material and the analysis was not reproducible. Anal. Calcd. for $C_{12}H_{20}F_3NO$: N, 5.57. Found: N, 5.51 %.

The compound was examined by n.m.r. and there was present in the spectrum a narrow multiplet at τ5.83 (half-band width 16 Hz) which indicated that the hydrogen geminal to the N-trifluoroacetyl group was equatorial (44).

The trans isomer (44) had a m.p. of 138-140° after two recrystallizations from ether-Skelly B. Although an acceptable carbon, hydrogen analysis was obtained, the analysis was not reproducible. Anal. Calcd for $C_{12}H_{20}F_3NO$: C, 57.35; H, 8.02; N, 5.57. Found: C, 57.16, 58.86; H, 8.35, 8.52; N, 5.39 %. The n.m.r. spectrum showed a multiplet at τ6.30 (half-band-width

28 Hz) which indicated that the hydrogen geminal to the N-trifluoroacetyl group was axial (44).

The mass spectra of the cis and trans compounds were very similar except for the relative intensities of the peaks. In both case, the parent peak (M^+) was observed at M/e 251. The expected major fragments were present at: M/e 194 = $M^+ - C(CH_3)_3$, M/e 139 = $M^+ - CF_3COHN$, M/e 69 = CF_3 ion and M/e 57 = $C(CH_3)_3$ ion.

6. Synthesis of N-trifluoroacetamidocyclohexane (45)

Cyclohexylamine (7 g) was trifluoroacetylated to give N-trifluoroacetamidocyclohexane in 87 % yield: m.p. 94.5-96° (Skelly B) (lit. m.p. (77) 94-95°).

7. 4-t-Butylcyclohexanone azine (33)

Azine was obtained during the attempted preparation of the hydrazone of 4-t-butylcyclohexanone.

Experiment 1: A solution of 15.8 g (0.102 mole) of 4-t-butylcyclohexanone (23) in 20 ml of ethanol was added, dropwise, to a stirred solution of 6.4 g (0.2 mole) of 98 % hydrazine in 20 ml of ethanol. The mixture was warmed gently on the steam bath for 5 min. Ethanol and excess hydrazine were removed in vacuo leaving a semisolid material which completely solidified during trituration with water. The solid was recrystallized from boiling ethanol and yielded 11 g of white, needle-like crystals: m.p. 169-170.5° (dec.). A sample for analysis was recrystallized two times from Skelly B: m.p. 170-172-5° (dec.). Anal. Calcd. for $C_{20}H_{36}N_2$ C, 78.93;

H, 11.92. Found: C, 78.97; H, 11.95 %.

Experiment 2: An attempt to prepare the hydrazone of 4-t-butylcyclohexanone by the method of Barton and coworkers (68) was also unsuccessful.

A solution of 0.51 g (3.3 mmole) of ketone 23 and 2.25 ml of triethylamine in ethanol (6 ml) was prepared. Hydrazine hydrate (3 ml of a 64 % solution, 60 mmoles) was added and the solution heated under reflux for 2 hr. The solution was then cooled to room temperature and poured over an ice-water slurry. The white solid that formed was collected by vacuum filteration and dried over potassium hydroxide pellets for 4 days. The solid had a m.p. of 159-162° (dec.). The n.m.r. spectrum (60 MHz) of this solid was identical to that of pure azine.

8. Synthesis of 4-t-butylcyclohexanone N-benzyloxycarbonylhydrazone (35)

N-Benzyloxycarbonylhydrazine was prepared from dibenzylcarbonate and hydrazine hydrate (78). A solution of 0.831 g (5 mmoles) of benzyloxycarbonylhydrazine and 0.786 g (5.1 mmoles) of 4-t-butylcyclohexanone in 20 ml of ethanol was heated under reflux for one hr. The solution was allowed to stand at room temperature for 16 hr and then concentrated to give a clear oil that crystallized. The solid was recrystallized from ethanol-water and yielded 1.32 g (88 %) of white, needle-like crystals: m.p. 131.2-133°. A sample for analysis was sublimed (90°/0.02 mm) and recrystallized from methanol-water: m.p. 137-138.5°. Anal. Calcd. for $C_{18}H_{26}N_2O_2$:

C, 71.48; H, 8.67; N, 9.26. Found: C, 71.68; H, 8.76; N, 9.41 %.

9. Synthesis of 4-t-butylcyclohexanone N-acetylhydrazone (36)

Acetylhydrazine was prepared from ethyl acetate and hydrazine hydrate (79). A solution of 2 g (27 mmoles) of acetylhydrazine and 4.16 g (27 mmoles) of 4-t-butylcyclohexanone in 15 ml of ethanol was heated under reflux for 15 min and then let stand at ambient temperature for 16 hr. The solution was concentrated to yield a white solid. Recrystallization from Skelly B gave 4.15 g (73 %) of 36 as fine, white needles: m.p. 147.4-150°. A sample for analysis was recrystallized three times from ethanol-water: m.p. 154-155°. Anal. Calcd. for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.55; N, 13.32. Found: C, 68.76, 68.86; H, 10.71; N, 13.43 %.

10. Synthesis of cis-2-acetoxy-4-t-butylcyclohexanone (1)

A mixture of cis and trans α-bromo-4-t-butylcyclohexanones was prepared by bromination of 4-t-butylcyclohexanone (154 g, 1 mole) (46). The crude undistilled product was dissolved in 500 ml of glacial acetic acid. Anhydrous sodium acetate (180 g, 2.2 mmoles) was added and the mixture heated under reflux for 4 days with vigorous stirring and with protection from moisture. After cooling, the mixture was poured into 600 ml of cold (0°) water in a separatory funnel. The mixture was extracted with methylene chloride (3 x 170 ml). The combined extracts were washed three times with water and then with saturated sodium bicarbonate solution until neutral.

The solution was dried and concentrated. Fractional distillation yielded two low boiling fractions, which were discarded, followed by a fraction boiling at 93-97°/1.0 mm (39 g) and a fraction boiling at 102-107°/1.0 mm (51.1 g). The n.m.r. spectrum of fraction 4 indicated that it was mainly an acetoxy compound. Gas chromatographic analysis of fraction 4 on column A (200°) indicated the presence of one major component with a retention time of 12 min. Fraction 3 also contained this component (with several minor components of shorter retention time). Fractions 3 and 4 were combined and redistilled through a short Vigreux column (15 cm). Two low boiling fractions were obtained which were discarded. The bulk of the material distilled at 98.5-101.5°/0.8 mm and weighed 68.7 g. This material crystallized. The solid was recrystallized twice from hexane and yielded 30.4 g (14.3 %) of white crystals: m.p. 64-65.8°. Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.49. Found: C, 67.64; H, 9.71 %. The i.r. spectrum (chloroform solution) showed carbonyl absorptions at 1724 (ketone), 1732 (ester) and 1751 cm^{-1} (ester) The n.m.r. spectrum (Fig. 1) of this material showed a one-proton multiplet at τ4.8 (half-band width 20 Hz) that was assigned to the hydrogen geminal to the acetoxy group. The width of the signal indicated that the hydrogen was axial and that the material must be cis-2-acetoxy-4-t-butylcyclohexanone.

11. Synthesis of cis-2-acetoxy-4-t-butylcyclohexanone oxime (27)

A solution of 4.92 g of hydroxylamine hydrochloride (75 mmoles) and 5.8 g (75 mmoles) of anhydrous sodium acetate in 20 ml of water was added to a solution of cis-2-acetoxy-4-t-butylcyclohexanone in 100 ml of methanol. The resultant solution was heated on the steam bath and water added to insipient turbidity. The mixture was then allowed to stand at 0° overnight. The oxime separated out as flat spear-like crystals (15.5 g, 96 %): m.p. 152-154°. A sample was recrystallized twice from methanol for the analytical sample: m.p. 154.5-156.5°. Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.40; H, 9.31; N, 6.16. Found: C, 63.40; H, 9.60; N, 6.37 %. The n.m.r. spectrum is shown in Fig. 16.

12. Synthesis of cis and trans methylsulfonyloxy-4-t-butylcyclohexane

The procedure of Sicher, et al., (80) was used for the preparation of the title compounds with the following modifications: A 20 % excess of methylsulfonyl chloride was used. At the end of the reaction the mixture was poured into an ice-water mixture containing sufficient sulfuric acid to neutralize the pyridine.

From 300 g (1.92 moles) of a mixture of cis and trans-4-t-butylcyclohexanols was obtained 463 g (100 %) of a mixture of the cis and trans methane sulfonates.

13. Synthesis of 4-t-butylcyclohexene

The title compound was prepared by the method of Sicher et al., (80) except that 2,6-lutidine was used as the base in place of collidine.

From 463 g (1.92 moles) of a mixture of cis and trans methylsulfonyloxy-4-t-butylcyclohexanes was obtained 266 g (99 %) of 4-t-butylcyclohexene: b.p. 60-61°/15 mm (lit. (80) b.p. 60-65°/ 20 mm).

14. Synthesis of cis and trans 4-t-butylcyclohexene oxide

The procedure of Jones and coworkers (49) was used for the preparation of this compound except that methylene chloride was used as the solvent and a 30 % excess of peracetic acid was used.

From 216 g (1.89 moles) of 4-t-butylcyclohexene was obtained 240.5 g (83 %) of the epoxides which distilled in a range of 85-90°/ 11 mm.

15. Synthesis of trans-2-benzyloxy-trans-5-t-butylcyclohexanol (4) and trans-2-benzyloxy-cis-4-t-butylcyclohexanol (5)

To a cold (0°) and stirred solution of 3.5 ml of boron trifluoride etherate in 800 ml (7.7 moles) of freshly distilled benzyl alcohol was added, dropwise during 40 min, 210.8 g (1.4 moles) of 4-t-butylcyclohexene oxide (cis and trans mixture). The temperature was maintained at 7-13° during the addition by external cooling with an ice-water bath. After the addition was completed the somewhat viscous mixture was stirred for a further 10 min at ambient temperature. No starting material was detected by t.l.c. (solvent system A). Aqueous ammonia (15 ml of a 6 N solution) was added and the mixture dissolved in one l of ether. The ethereal solution was then washed in succession with water (100 ml) and saturated sodium chloride solution (30 ml). The solution was then dried and concentrated to give a residue which was fractionally distilled under vacuum to yield 650 ml of benzyl alcohol b.p. 47-49°/0.5 mm followed by product weighing 319.2 g (90 %) which distilled in the range 128-139°/0.08-0.12 mm and which crystallized. The n.m.r. spectrum indicated that the product was a mixture of isomers. Analysis by g.l.p.c. on column B at 205° gave two overlapping peaks with retention times of 27.0 min and 28.6 min in the ratio of 3:2 respectively.

The crystalline material obtained was separated into its components by fractional crystallization from Skelly B. The most abundant isomer and the fastest moving (g.l.p.c.) had a tendency to crystallize as a hard shell on the sides and bottom of the flask. By decantation of the mother liquors, this isomer was obtained in fairly pure form. After two more recrystallizations the material had a m.p. of 61-64°. This isomer was later shown to be trans-2-benzyloxy-cis-4-t-butylcyclohexanol (5). Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.86 H, 9.99. Found: C, 77.63; H, 9.71 %. The n.m.r. spectrum (Fig. 4) of this material showed one-proton multiplets at τ6.16 (half-band width 7.5 Hz) and τ6.44 (half-band width 7.5 Hz) that were attributed to the hydrogens geminal to the benzyloxy group and hydroxy group. The small half-band widths indicated that both of these hydrogens were equatorial.

The other isomer, trans-2-benzyloxy-trans-5-t-butylcyclohexanol (4), crystallized in the form of a voluminous precipitate that required five recrystallizations before it was obtained pure. The pure material had a m.p. of 79.5-81.7°. Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.86; H, 9.99. Found: C, 78.01; H, 9.79 %. The n.m.r. spectrum of this material showed one-proton multiplets at τ6.01 (half-band width 10 Hz) and τ6.6 (half-band width 8 Hz) that were attributed to hydrogens geminal to the benzyloxy group and the hydroxy group. The half-band width of these signals indicated that both of the hydrogens were equatorial.

16. Structure proof of trans-2-benzyloxy-cis-4-t-butylcyclohexanol (5) by chemical degradation

a. Synthesis of trans-2-benzyloxy-cis-4-t-butylcyclohexyl chloride (7).

Trans-2-benzyloxy-cis-4-t-butylcyclohexanol was chlorinated using the following adaption of the procedure of Bridgewater and Shoppe (81) for the conversion of cyclohexanols to cyclohexylchlorides.

A solution of 4 g (15.3 mmoles) of the low melting (61-64°) and fast running isomer (g.l.p.c.) in 10 ml of dry Skelly B was added, dropwise during 25 min, to a cold (0°) stirred suspension of 7 g (33.6 mmoles) of phosphorus pentachloride and 5 g of anhydrous calcium carbonate in 30 ml of Skelly B. After addition, the mixture was stirred for 1.6 hr at ambient temperature. Analysis by t.l.c. (solvent system A) indicated that the reaction was complete after one hr.

The reaction mixture was cautiously poured into a separatory funnel containing ice and water. Sufficient sodium carbonate was added to neutralize the solution. The Skelly B layer was separated and the aqueous layer extracted twice with 10 ml portions of Skelly B. The Skelly B extracts were combined and washed with 5 ml of saturated sodium bicarbonate solution followed by two washings with water. The Skelly B layer was separated and dried. The solution was concentrated and the residue distilled under vacuum to give 3.57 g (86 %) of a colorless oil: b. p. 105-106°/0.05 mm. The oil gave strongly positive Beilstein and silver nitrate tests (81) for halogen. Anal. Calcd. for $C_{17}H_{25}ClO$: C, 72.69; H, 8.87. Found: C, 72.63; H, 8.87 %. The n.m.r. spectrum of this compound (Fig. 5) showed narrow one-proton multiplets at τ 6.03 and τ 6.5 attributed to the hydrogens geminal to the benzyloxy and chloro groups. The half-band width (7 Hz) of these signals indicated that both of these hydrogens were equatorial.

b. Synthesis of <u>trans</u>-5-<u>t</u>-butyl-<u>trans</u>-2-chlorocyclohexanol (<u>8</u>).

A solution of 3.02 g (10.6 mmoles) of <u>trans</u>-2-benzyloxy-<u>cis</u>-4-<u>t</u>-butylcyclohexyl chloride (<u>7</u>) in 15 ml of glacial acetic acid containing 1.64 g (20 mmoles) of anhydrous sodium acetate and 300 mg of 5 % palladium on carbon was stirred overnight under an atmosphere of hydrogen. The reaction mixture was filtered through Celite and the filter cake washed with glacial acetic acid (5 ml). The colorless filtrate was poured into a separatory funnel containing 100 ml of water and extracted with methylene chloride (3 x 20 ml). The methylene chloride extracts were combined, washed with water and then dried. The solution was concentrated leaving a crystalline residue.

Recrystallization from a small amount of Skelly B gave 1.67 g (80 %) of material: m.p. 76-78.5°. A sample of this was recrystallized twice from Skelly B to give colorless crystals: m.p. 78.5-80°. The material gave strongly positive Beilstein and silver nitrate tests (82) for halogen. Anal. Calcd. for $C_{10}H_{18}ClO$: C, 62.98; H, 10.04. Found: C, 63.19; H, 10.09 %. The 60 MHz n.m.r. spectrum of this material (Fig. 6, in carbon tetrachloride solution) showed a 2-proton singlet at τ 5.97 (half-band width 7 Hz, attributed to the hydrogens at the 1 and 2-positions of the cyclohexane ring) and the _t_-butyl signal at τ 9.11. _Trans_-5-_t_-butyl-_trans_-2-chlorocyclohexanol is reported (52) to have a m.p. of 74-76° and to show a 2-proton singlet at τ 5.99 and the _t_-butyl signal at τ 9.11 in the n.m.r. spectrum (60 MHz, in carbon tetrachloride solution).

c. Synthesis of _cis_-5-_t_-butyl-2-chlorocyclohexanone (_9_).

A solution of one g (5.2 mmoles) of _trans_-5-_t_-butyl-_trans_-2-chlorocyclohexanol (_8_) in 5.9 ml of acetone was cooled to 0°. A slight excess of chromic acid (2 ml of 3 M aqueous solution) was added, dropwise, to the stirred and cooled solution of _8_. Ten min after addition, no starting material could be detected by t.l.c. (solvent system A). The reaction mixture was poured into a separatory funnel containing cold water (10 ml) and Skelly B (10 ml). The Skelly B layer was washed twice with water followed by saturated sodium bicarbonate solution and then dried. After drying the solvent was removed _in vacuo_ leaving 0.99 g of a clear oil. The i.r. spectrum showed a sharp carbonyl absorption at 1725 cm^{-1}, but no absorption in the region 3100-3600 cm^{-1} (hydroxy). The material gave strongly positive Beilstein and silver nitrate tests (81) for halogen. This compound was used without further characterization.

d. Synthesis of 3-t-butylcyclohexanone (10).

The α-chloroketone obtained above (0.99 g, 5.2 mmoles) was dissolved in 10 ml of anhydrous methanol and transferred to a flask containing 0.434 g (5.3 mmoles) of anhydrous sodium acetate and 0.25 g of 5 % palladium on carbon. The mixture was stirred under an atmosphere of hydrogen until it absorbed 80 ml. The reaction mixture was filtered through Celite and the filter cake washed with methanol (5 ml). The filtrate and washings were combined and partially concentrated in vacuo to 3 ml. The concentrate was dissolved in methylene chloride (10 ml) and washed once with saturated sodium bicarbonate solution. After drying the solvent was removed in vacuo. Short path distillation of the residue yielded 0.51 g (64 %) of a ketonic material that gave a single spot by t.l.c. (solvent system A). The i.r. spectrum of this compound showed a sharp carbonyl absorption at 1718 cm^{-1}. The n.m.r. and i.r. spectra of this compound were not identical with those of authentic 4-t-butylcyclohexanone. The material gave negative Beilstein and silver nitrate tests (82) for halogen. The 2,4-dinitrophenyl hydrazone (2,4-DNP) was prepared (83) and melted at 164-166° after two recrystallizations from ethyl acetate-ethanol and was in the form of short, orange needles (lit. (54) m.p. 161-162.5° (from ethanol) for the 2,4-DNP derivative of 3-t-butylcyclohexanone). The semicarbazone was prepared (83) and had a m.p. of 206.7-208° (dec.) (inserted at 200°) after two recrystallizations from ethanol-water and was in the form of lustrous, white plates (lit. (55) m.p. 205-206° (inserted at 200°) for the semicarbazone of 3-t-butylcyclohexanone).

The 2,4-DNP of authentic 4-t-butylcyclohexanone was prepared and had a m.p. of 155-156° after two recrystallizations from ethanol-ethyl acetate and was in the form of long, dark, orange, needle-like crystals. The mixture m.p. of the 2,4-DNP of authentic 4-t-butylcyclohexanone and the 2,4-DNP of the ketone derived from 9 was 125-127°. The semicarbazone of authentic 4-t-butylcyclohexanone had a m.p. of 214.5-216° (dec.) (inserted at 205°) after two recrystallizations from ethanol-water and was in the form of small, white plates. A mixture m.p. of this semicarbazone with the semicarbazone derived from 9 was 192.5-204° (dec.).

17. Synthesis of cis-4-t-butyl-trans-2-hydroxycyclohexanol (6) from:

a. Trans-2-benzyloxy-cis-4-t-butylcyclohexanol (5).

A solution of 300 mg (1.15 mmoles) of trans-2-benzyloxy-cis-4-t-butylcyclohexanol in 10 ml of 90 % ethanol was placed in a flask containing 100 mg of 5 % palladium on carbon. Concentrated hydrochloric acid (0.1 ml, 1.2 mmoles) was added and the mixture stirred under an atmosphere of hydrogen for 18 hr. The reaction mixture was filtered through Celite, the filter cake washed with ethanol and the filtrate and washings concentrated in vacuo. The powder-like residue (197 mg, 100 % yield) was recrystallized twice from acetone-Skelly B and yielded 150 mg of small, white platelets, m.p. 143.5-146°.

b. Trans-2-benzyloxy-trans-5-t-butylcyclohexanol (4).

De-O-benzylation of trans-2-benzyloxy-trans-5-t-butylcyclohexanol was carried out as above. From 300 mg (1.15 mmoles) of 4 was obtained 190 mg of product which had a m.p. of 144-146°, after two recrystallizations from methyl ethyl ketone-Skelly B, and an i.r. spectrum identical to the i.r. spectrum of the product of the previous experiment (the lit. (38) m.p. for cis-4-t-butyl-trans-2-hydroxycyclohexanol (6) is reported to be 141-142°). A mixture of this material with the product of the previous experiment gave an undepressed m.p.

18. Synthesis of trans-3-acetoxy-cis-4-benzyloxy-t-butylcyclohexane (14)

Trans-2-benzyloxy-trans-5-t-butylcyclohexanol (8.0 g, 30.6 mmoles) was acetylated (procedure A) to yield 9.33 g (100 %) of 14. A one g sample of 14 from a similar preparation was subjected to short path distillation and boiled at 95-105°/0.08 mm. Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.02; H, 9.27 %.

19. Synthesis of trans-2-acetoxy-cis-4-t-butylcyclohexanol (15)

A solution of 9.33 g (30.6 mmoles) of trans-3-acetoxy-cis-

4-benzyloxy-t-butylcyclohexane (14) in 50 ml of glacial acetic acid was added to a flask containing one g of 5 % palladium on carbon. The mixture was stirred under an atmosphere of hydrogen until no more hydrogen uptake could be detected (43 hr). The reaction mixture was filtered through Celite and the filter cake washed with glacial acetic acid. The filtrate was concentrated and the residue dissolved in methylene chloride. The methylene chloride solution was washed with water followed by saturated sodium bicarbonate solution. The methylene chloride solution was dried and then concentrated. The 6.6 g of residue contained a small amount of 14 which could be detected in the n.m.r. spectrum.

For the purpose of analysis a one g sample was rehydrogenated under identical conditions using fresh catalyst. Work up as before yielded an oil that was free of starting material. Evaporation at reduced pressure yielded 594 mg of material: b.p. 70°/0.05 mm. Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.42; H, 10.38 %. The n.m.r. spectrum (Fig. 21) showed one-proton multiplets at τ 5.07 and 6.30 which are assigned to the hydrogens geminal to the acetoxy and hydroxy groups, respectively. Also present in the spectrum was a one-proton singlet at τ 7.18 (hydrogen of the hydroxy group), a 3-proton singlet at τ 7.95 (hydrogens of the acetoxy group) and a 9-proton singlet at τ 9.12 (hydrogens of the t-butyl group).

20. Synthesis of trans-2-acetoxy-4-t-butylcyclohexanone (16)

The title compound was prepared from trans-2-acetoxy-cis-4-t-butylcyclohexanol (15) using a procedure analogous to that used for the preparation of 9. From 5.6 g of 15 was obtained 4.71 g of a clear oil, which contained benzyloxy compound 14 as an impurity. A crystalline sample of ketone 16 was obtained by column chromatography of a small sample on Silica Gel G using solvent system A.

The remaining crude ketone was dissolved in 10 ml of Skelly B and seeded with the crystals obtained from chromatography. Cooling to 0° resulted in the deposition of 2.6 g of ketone that was recrystallized twice from Skelly B yielding 1.37 g: m.p. 52-57°. A small sample was sublimed at 35°/0.06 mm for analysis: m.p. 52.2-54.5°. Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.73; H, 9.39 %. T.l.c. behavior of sublimed and unsublimed ketone was identical. The n.m.r. spectrum (Fig. 8) of the pure ketone showed the expected signals for the hydrogens of an acetoxy and a t-butyl group. Also present in the spectrum was a low field one-proton multiplet at τ4.91 (half-band width 11 Hz) which is assigned to the hydrogen geminal to the acetoxy group. The i.r. spectrum showed a broad carbonyl absorption in the region 1725-1745 cm^{-1}.

21. Synthesis of trans-2-acetoxy-4-t-butylcyclohexanone oxime (28)

A solution of 0.222 g (3.2 mmoles) of hydroxylamine hydrochloride and 0.262 g (3.2 mmoles) of anhydrous sodium acetate in 3 ml of water was added to a solution of trans-2-acetoxy-4-t-butylcyclohexanone (636 mg, 2 mmoles) in 25 ml of methanol-water

(2:3, v/v). After 5 min the mixture was heated on the steam bath for 15 min. The solution was cooled and poured into a separatory funnel containing water (15 ml). The mixture was extracted with methylene chloride (3 x 7 ml). The methylene chloride extracts were combined and washed with water (7 ml), saturated sodium bicarbonate solution (7 ml) and then water (7 ml). The methylene chloride solution was dried and then concentrated. The residue was recrystallized from Skelly B and yielded 570 mg of white, needle-like crystals (84 %): m.p. 113.2-116°. A sample sublimed (80°/0.06 mm) for analysis had the same m.p. Anal. Calcd, for $C_{12}H_{21}NO_3$: C, 63.40; H, 9.31; N, 6.16. Found: C, 63.30; H, 9.46; N, 6.03 %. The n.m.r. spectrum (Fig. 17) showed signals for the hydrogens of an acetoxy group (τ 7.95) and a t-butyl group (τ 9.08) as well as a one-proton multiplet at τ 4.52 (half-band width 7 Hz) which was assigned to the hydrogen geminal to the acetoxy group.

22. Synthesis of cis-2-benzyloxy-5-t-butylcyclohexanone (17)

The title compound was prepared from trans-2-benzyloxy-trans-5-t-butylcyclohexanol (4) using a procedure similar to that used for the preparation of 9. From 1.5 g (5.75 mmoles of) 4 was obtained 1.4 g of ketone. A sample of the ketone was distilled (85-90°/0.07 mm) for the analytical sample. Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.40; H, 9.31. Found: C, 78.18; H, 9.50 %. The n.m.r. spectrum (Fig. 9) showed a 5-proton singlet at τ 2.67 (hydrogens of the phenyl group), a two-proton singlet at τ 5.53 (hydrogens of the methylene group of the benzyl group) and a 9-proton singlet (hydrogens of the t-butyl group). A one-proton multiplet at τ6.31 (half-band width 8 Hz) was assigned to the hydrogen geminal to the benzyloxy group.

23. Synthesis of cis-2-benzyloxy-cis-5-t-butylcyclohexanol (18)

A solution of 3.18 g (84 mmoles) of sodium borohydride in 20 ml of cold (0°) water was added in one portion to a stirred solution of 15.89 g (61.3 mmoles) of cis-2-benzyloxy-5-t-butylcyclohexanone (17) in 130 ml of a cold (0°) mixture of tetrahydrofuran and 32 ml of ethyl acetate. The temperature of the reaction mixture rose to 15° and then slowly dropped back to 0°. The mixture was stirred for one hr and then 10 ml of glacial acetic acid was added slowly, while stirring and cooling were continued. The mixture was then diluted with water (100 ml) and extracted with Skelly B (3 x 25 ml). The combined extracts were washed successively with water (25 ml), saturated sodium bicarbonate solution (10 ml) and then saturated sodium chloride solution (10 ml). The solution was dried and then concentrated. The oily residue (16 g) crystallized. The solid residue was melted by warming on the steam bath and a sample withdrawn for analysis by g.l.p.c. The sample was trifluoroacetylated and analyzed using column B at 205°. Two peaks appeared after the solvent peak with retention times of 6.6 min 7.9 min in the ratio 1:4.9, respectively.

The oily residue resolidified on cooling and was recrystallized three times from Skelly B to yield 7.3 g (45 %) of pure cis-2-benzyloxy-cis-5-t-butylcyclohexanol (18): m.p. 55.5°-58° (softening at 52.5°). Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.86; H, 9.99. Found: C, 78.08; H, 9.96 %. The n.m.r. spectrum (Fig. 10) showed signals for the hydrogens of a phenyl group (τ 2.71), the methylene group of a benzyl group (AB quartet centered at τ 5.52), a hydroxyl group (τ 7.74) and a t-butyl group (τ 9.18). A complex two-proton multiplet centered at τ 6.50 was assigned to the hydrogens at the 1 and 2-positions of the cyclohexane ring.

24. Synthesis of cis-2-benzyloxy-cis-5-t-butylmethoxycyclohexane (19)

Cis-2-benzyloxy-cis-5-t-butylcyclohexanol (18) was methylated using the methylation procedure of Eades and Coworkers (56). Sodium hydride (2.4 g, 0.1 mole) was obtained by washing the mineral oil from 4.6 g of a 52.3 % dispersion of sodium hydride in mineral oil with dry Skelly B. A solution of 6.55 g (25 mmoles) of 18 and 15 ml (0.24 mole) of methyl iodide in 200 ml of anhydrous tetrahydrofuran was kept under a nitrogen atmosphere while the sodium hydride was added in one portion. The slurry was stirred with protection from moisture for 20 hr, after which no starting material could be detected by t.l.c. (solvent system A). Methanol was then added, dropwise, to destroy unreacted sodium hydride followed by the addition of sufficient glacial acetic acid to neutralize the solution. The solution was concentrated to 60 ml and then transferred to a separatory funnel containing an equal amount of water. The aqueous solution was extracted with Skelly B (3 x 25 ml). The extracts were combined and washed successively with 2 N aqueous hydrochloric acid, water, saturated sodium bicarbonate solution and again water. The solution was then dried and concentrated leaving a residue weighing 7.06 g (100 %). A sample was distilled for analysis: b.p. 65-70°/0.02 mm. Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.16; H, 10.04 %.

25. Synthesis of cis-4-t-butyl-cis-2-methoxycyclohexanol (20)

A solution of 6.5 g (23.5 mmoles) of cis-2-benzyloxy-cis-5-t-butylmethoxycyclohexane (19) in 240 ml of 95 % ethanol containing 2 ml of concentrated hydrochloric acid (24 mmoles) was poured into a flask containing 600 mg of 5 % palladium on carbon. The mixture was stirred under an atmosphere of hydrogen for 17 hr. The reaction mixture was filtered through Celite and the filter cake washed with ethanol (5 ml). The filtrate was concentrated in vacuo to a volumn of 15 ml. The concentrated solution was diluted with water (30 ml) and extracted with Skelly B (3 x 20 ml). The Skelly B layers were combined and washed successively with water, saturated sodium bicarbonate solution and again water. The Skelly B solution was then dried and concentrated, leaving a sweet smelling liquid weighing 4.3 g (98 %). A sample was distilled for analysis: b.p. 60°/0.06 mm. Anal. Calcd. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.73; H, 11.61 %. The n.m.r. spectrum (Fig. 11) showed signals for the hydrogens of a methoxy group (τ6.63), a hydroxy group (τ7.64) and a t-butyl group (τ9.17). There was also present in the spectrum a one-proton multiplet at τ5.91 (half-band width 8 Hz) and at τ6.86 (half-band width 20 Hz) which are assigned to the hydrogens geminal to the hydroxy and methoxy groups, respectively.

26. Synthesis of cis-4-t-butyl-2-methoxycyclohexanone (21)

Cis-4-t-butyl-cis-2-methoxycyclohexanol (20) was converted to the title compound using a procedure analogous to that used for the preparation of 9. From 4.0 g (21.5 mmoles) of 20 was obtained 3.48 g of a water-white liquid. Analysis by t.l.c. (solvent system A) indicated that no starting material was present and that there was one major substance present and several minor components. A sample was distilled for analysis. Anal. Calcd. for $C_{11}H_{20}O_2$; C, 71.69; H, 10.94. Found: C, 71.64; H, 10.99 %. The i.r. spectrum showed a sharp carbonyl absorption at 1726 cm^{-1} (ketone). The n.m.r. spectrum (Fig. 12) showed a 3-proton singlet at τ 6.52 (hydrogens of the methoxy group) and a 9-proton singlet at τ 9.07 (hydrogens of the t-butyl group). There was also present in the spectrum a one-proton multiplet at τ 6.22 (half-band width 20 Hz) which is assigned to the hydrogen geminal to the methoxy group.

27. Synthesis of cis-4-t-butyl-2-methoxycyclohexanone oxime (25)

The oxime of cis-4-t-butyl-2-methoxycyclohexanone was prepared in a manner analogous to the procedure used for the preparation of oxime 28. From 2.78 g of ketone was obtained 2.9 g of a solid oxime, which was recrystallized twice from methanol-water to yield 2.13 g of white crystals which were sublimed (80°/0.04 mm) to yield 2.03 g (66 %) of crystalline material: m.p. 166-168°. Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.47;

H, 10.48; N, 7.29 %. The n.m.r. spectrum (Fig. 14) supported the assigned structure. Signals for the hydrogens of the methoxy and *t*-butyl groups were present at τ6.60 and τ9.19, respectively. A one-proton multiplet appeared at τ6.28 (half-band width 15 Hz) and is assigned to the hydrogen at the 2-position of the cyclohexane ring.

28. Synthesis of *trans*-2-benzyloxy-*trans*-5-*t*-butylmethoxycyclohexane (**11**)

Trans-2-benzyloxy-*trans*-5-*t*-butylcyclohexanol (**4**) was methylated using a procedure analogous to that used in the preparation of **19** except that a smaller proportion of sodium hydride and methyl iodide to alcohol was used. From 8.62 g (33 mmoles) of **4**, 2.16 g (90 mmoles) of sodium hydride, and 15 ml (240 mmoles) of methyl iodide was obtained 9.11 g (99 %) of the title compound as a clear oil. An earlier, smaller scale preparation yielded material that was distilled (b.p. 80-85°/0.05 mm) for the analytical sample. Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.50, H, 10.28 %.

29. Synthesis of *cis*-4-*t*-butyl-*trans*-2-methoxycyclohexanol (**12**)

The title compound was prepared from *trans*-2-benzyloxy-*trans*-5-*t*-butylmethoxycyclohexane (**11**) using a procedure analogous to that used for the preparation of **20**. From 9.11 g of **11** was obtained 5.75 g (88 %) of crude **12**. A sample for analysis was distilled: b.p. 55-63°/0.06 mm. Anal. Calcd. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 69.85. 69.95; H, 11.99, 11.80. The phenylurethane was prepared and had a m.p. of 152-153° after recrystallization once from methanol-water and once from Skelly B. Anal. Calcd. for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 71.10; H, 9.16; N, 4.80 %.

30. Synthesis of trans-4-t-butyl-2-methoxycyclohexanone (13)

The title compound was prepared from cis-4-t-butyl-trans-2-methoxycyclohexanol (12) using a procedure analogous to that used for the preparation of 9. From 5 g (26.8 mmoles) of 12 was obtained 4.73 g (96 %) of a mobile, water-white liquid. A sample was distilled for analysis and had a b.p. of 90-100°/15-20 mm. Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.49; H, 11.16 %. The i.r. spectrum showed a sharp carbonyl absorption of 1726 cm^{-1}. The n.m.r. spectrum (Fig. 7) showed signals for the hydrogens of the methoxy and t-butyl groups at $\tau 6.75$ and $\tau 9.15$, respectively. There was also present in the spectrum a one-proton multiplet centered at $\tau 6.53$ which is assigned to the hydrogen at the 2-position of the cyclohexane ring.

31. Synthesis of trans-4-t-butyl-2-methoxycyclohexanone oxime (26)

The preparation of the oxime of trans-4-t-butyl-2-methoxycyclohexanone was carried out in a manner analogous to that used for the preparation of 28. From 3.5 g of 13 was obtained 3.5 g of a gummy solid. The solid was sublimed (50°/0.02 mm) and afforded 2.7 g of crystalline material that was recrystallized from methanol-water to give 2.36 g of white, spear-like crystals with a m.p. of 64-81°. The crystals were sublimed and afforded 2.1 g (55 %) of a white, crystalline solid: m.p. 66-73°. Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.41; H, 10.82; N, 7.31 %. The n.m.r. spectrum (Fig. 15) showed a 3-proton singlet at τ6.79 (hydrogens of the methoxy group) and a 9-proton singlet at τ9.18 (hydrogens of the *t*-butyl group). Narrow multiplets were present at τ5.10 (half-band width 7 Hz) and 6.18 (half-band width 7 Hz) (in the ratio 1:5.6, respectively), which were assigned to the hydrogens at the 2-position of the cyclohexane ring in the *syn* and *anti* oximes, respectively.

32. Synthesis of *trans*-2-benzyloxy-4-*t*-butylcyclohexanone (**22**)

Trans-2-benzyloxy-*cis*-4-*t*-butylcyclohexanol (**5**) was converted to the title compound using a procedure analogous to that used in the preparation of **9**. From 13.07 g of (**5**) was obtained 11.63 g of ketone. The ketone contained benzaldehyde as an impurity, detectable by its odor. Fractional distillation gave 10.5 g (81 %) of pure ketone: b.p. 115-117°/0.08 mm. Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.40; H, 9.31. Found: C, 78.38; H, 9.08 %. The i.r. spectrum showed a sharp carbonyl absorption at 1726 cm^{-1} (ketone). The n.m.r. spectrum (Fig. 13) showed a 5-proton singlet at τ2.70 (hydrogens of the phenyl group), a 2-proton singlet at τ5.60 (hydrogens of the methylene group of the benzyl group) and a 9-proton singlet at τ9.15 (hydrogens of the *t*-butyl group). A one-proton multiplet was present at τ6.30 (half-band width 7 Hz) and this is assigned to the hydrogen geminal to the benzyloxy group

33. Synthesis of *trans*-2-benzyloxy-4-*t*-butylcyclohexanone oxime (*31*)

Oximination of *trans*-2-benzyloxy-4-*t*-butylcyclohexanone (*22*) was carried out by a procedure analogous to that used in the preparation of *28*. From 5.2 g (2 mmoles) of *22* was obtained 4.67 g of oxime. Recrystallization twice from nitromethane yielded 4.1 g (74 %) of oxime: m.p. 83-90°. A sample was sublimed for analysis (75°/0.02 mm) and had a m.p. of 86.5-88.5°. Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.13; H, 9.39; N, 5.15 %. The n.m.r. spectrum (Fig. 18) showed a 5-proton singlet at τ2.75 (hydrogens of the phenyl group), an AB quartet at τ5.65 (hydrogens of the methylene group of the benzyl group) and a 9-proton singlet at τ9.15 for the hydrogens of the *t*-butyl group. Multiplets were present at τ4.93 (half-band width 7 Hz) and τ6.02 (half-band width 7 Hz) in the ratio 1:5.7 which are assigned to the hydrogens at the 2-position of the cyclohexane rings in the *syn* and *anti* oximes, respectively.

34. Synthesis of *trans*-2-hydroxy-4-*t*-butylcyclohexanone oxime (*32*)

A mixture of 1.38 g (5 mmoles) of *trans*-2-benzyloxy-4-*t*-butylcyclohexanone oxime (*31*) and 200 mg of 5 % palladium on carbon in 50 ml of 90 % ethanol containing 0.458 ml (5.5 mmoles) of concentrated hydrochloric acid was stirred under an atmosphere of hydrogen. Hydrogen uptake was rapid until 147 ml of hydrogen had been absorbed when the rate of absorption suddenly slowed down. Stirring was discontinued at this point and the reaction mixture filtered through Celite. Anhydrous sodium acetate (0.5 g) was then added and the mixture concentrated to 7 ml. The mixture was diluted to 40 ml with water and let stand at ice temperature. The white crystals that formed were collected and weighed 720 mg: m.p. 196-200°. Recrystallization once from methanol gave 590 mg (64 %) of oxime: m.p. 198-200°. A sample was recrystallized once more from methanol: m.p. 200-202°. Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 65.13; H, 10.42; N, 7.75 %. The oxime was examined by 60 MHz n.m.r. as a solution in D_4-acetic acid since it was nearly insoluble in deuteriochloroform. The spectrum (Fig. 19) showed a 9-proton singlet at τ9.17 for the hydrogens of the t-butyl group. A one-proton multiplet (half-band width 7 Hz) at τ5.56 is assigned to the hydrogen at the 2-position of the cyclohexane ring.

E. Sodium Borohydride Reduction of 4-t-Butylcyclohexanone and 2-substituted 4-t-Butylcyclohexanones

1. General

A ratio of 1.9 mmoles of ketone to 2.65 mmoles of sodium borohydride to one ml of ethyl acetate to 5 ml of tetrahydrofuran was maintained for all reactions. All reductions were carried out at 0°. The work-up of the reaction mixtures was essentially the same in all cases and is presented in detail for only one reduction.

2. Reduction of 4-t-butylcyclohexanone (23)

A solution of 200 mg of sodium borohydride in 2 ml of cold (0°) water was added in one portion to a cold (0°), stirred solution of 0.5 g (3.83 mmoles) of 4-t-butylcyclohexanone (23) in a mixture of 2 ml of ethyl acetate and 10 ml of tetrahydrofuran. The solution was stirred for 20 min at 0°. T.l.c. analysis (solvent system A) indicated that no starting material remained after 7 min. After the 20 min, glacial acetic acid was added, dropwise and with stirring, until the reaction mixture remained acid to pH paper. Water (20 ml) was added and the reaction mixture extracted with Skelly B (3 x 10 ml). The Skelly B extracts were combined and washed with 2.5 N hydrochloric acid (7 ml), saturated sodium bicarbonate solution (7 ml) and then water (10 ml). The Skelly B solution was dried followed by concentration to give a syrup, (580 mg, 97 % yield) which rapidly crystallized. The solid was taken up in deuteriochloroform and was examined by n.m.r. (60 MHz). There was present a narrow multiplet at τ6.0 (half-band width 7 Hz) and a broad multiplet at τ6.51 (half-band width 25 Hz) in the ratio 1:10.5, respectively. The broad multiplet was attributed to the hydrogen geminal to the hydroxyl group in *trans*-4-*t*-butylcyclohexanol (equatorial isomer) and the narrow multiplet to the hydrogen geminal to the hydroxyl group in *cis*-4-*t*-butylcyclohexanol (axial isomer). Acetylation of the crude alcohol mixture (procedure B) yielded a mixture of acetates showing a poorly resolved multiplet at τ5.02 (half-band width 12 Hz) and at τ5.38 (half-band width 25 Hz) in the ratio 1:6.8, respectively. Gas chromatographic analysis of the mixture of acetates (column B, 140°) gave two peaks with retention times of 14.2 min and 18.1 min in the ratio 1:16.2, respectively.

3. Reduction of *cis*-2-acetoxy-4-*t*-butylcyclohexanone (*1*)

Cis-2-acetoxy-4-*t*-butylcyclohexanone (203 mg, 0.96 mmole) was reduced in the indicated manner and after work-up yielded 200 mg (98 %) of a liquid that did not crystallize. The n.m.r. spectrum (Fig. 2) showed a broad one-proton multiplet at τ5.37 (half-band width 25 Hz), a narrow multiplet at τ5.98 (half-band width 7 Hz), a broad multiplet at τ6.50 (half-band width 27 Hz), a one-proton singlet at τ7.08 that disappeared on treatment with deuterium oxide, a singlet at τ7.93 (integration 3.2 hydrogens) plus complex signals between τ7.8 and τ9.0 (integration 7 hydrogens) and the *t*-butyl signal at τ9.16. The signal at τ5.37 was assigned to the axial hydrogens, geminal to the acetoxy groups in *cis*-2-acetoxy-*cis*-4-*t*-butylcyclohexanol and *trans*-2-acetoxy-*trans*-4-*t*-butylcyclohexanol.

The singlet at τ7.08 was assigned to the hydrogens of the hydroxyl groups, and the singlet at τ7.93 to hydrogens of the acetoxy groups. The signals at τ5.98 and τ6.5 were in a ratio of 1:5 and were assigned to the hydrogens geminal to the hydroxy groups in the axial and equatorial alcohols, respectively.

A sample of the alcohol mixture was trifluoroacetylated. Analysis by g.l.p.c. on column B at 140° gave two peaks with retention times of 11.7 min and 14.3 min in the ratio 1:5.9, respectively. Impurities amounted to less than 1 % of the total. The trifluoroacetyl derivative of *cis*-2-acetoxy-*cis*-4-*t*-butylcyclohexanol had a retention time of 11.7 min under these conditions.

4. Reduction of *trans*-2-acetoxy-4-*t*-butylcyclohexanone (**16**)

Trans-2-acetoxy-4-*t*-butylcyclohexanone (203 mg, 0.96 mmole) was reduced as before and, after work up, a quantitative yield of a colorless liquid was obtained. The product was examined by n.m.r. (Fig. 22) and showed a narrow multiplet at τ4.82 (half-band width 8 Hz), a narrow multiplet at τ5.07 (half-band width 8 Hz), a broad one-proton multiplet at τ6.30 (half-band width 20 Hz), a one-proton singlet at τ7.37 that disappeared on exchange with deuterium oxide, a 3-proton singlet at τ7.90 plus complex signals between τ8.0 and 8.8 and the *t*-butyl signal at τ9.14. The signals at τ4.82 and τ5.07 were in the ratio 5.7:1 and integrated as one hydrogen. These signals were assigned to the equatorial hydrogens geminal to the acetoxy groups in *cis*-2-acetoxy-*trans*-4-*t*-butylcyclohexanol and in *trans*-2-acetoxy-*cis*-4-*t*-butylcyclohexanol, respectively. The broad multiplet at τ6.3 was assigned to the hydrogens geminal to the hydroxyl groups in the axial and equatorial alcohols. The singlet at τ7.37 was assigned to the hydrogens of the hydroxyl groups and the singlet at τ7.90 to the hydrogens of the acetoxy groups.

A sample of the reduction product was trifluoroacetylated and examined by g.l.p.c. using column B at 140°. After the solvent peak, two well resolved peaks appeared with retention times of 12.0 min and 14.9 min in the ratio 1:6.15, respectively. The trifluoroacetyl derivative of trans-2-acetoxy-cis-4-t-butylcyclohexanol has a retention time of 12.0 min under the same conditions. A sample of the reduction product (130 mg) was fractionated by passage through a column (15 x 2.5 cm) of Silica Gel G (28 g). Solvent system C was used and 4 ml fractions were collected. Fractions 14-21 contained the minor component and fractions 27-35 contained the major component. Fractions 27-35 were pooled and the solvent removed in vacuo. The residue was distilled (70°/0.05 mm) and yielded 40 mg of an oil. The n.m.r. spectrum (Fig. 20) of this indicated that it was cis-2-acetoxy-trans-4-t-butylcyclohexanol. Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.55; H, 10.40 %.

5. Reduction of trans-4-t-butyl-2-methoxycyclohexanone (13)

Trans-4-t-butyl-2-methoxycyclohexanone (100 mg, 0.54 mmole) was reduced in the usual manner and yielded 99 mg of a liquid alcohol mixture. A sample was acetylated (procedure B) and the product was examined by n.m.r. (Fig. 27) which revealed a multiplet at τ5.29 (half-band width 20 Hz) and a partly overlapping narrow multiplet at

τ5.01 (half-band width 7 Hz). There was also present a one-proton multiplet at τ6.33 (half-band width 8 Hz), a 3-proton singlet at τ6.61, a 3-proton singlet at τ7.93, complex signals in the region τ7.9-8.8 and a 9-proton singlet at τ9.13. The signals were assigned as follows: τ5.29 and 6.33, the hydrogens geminal to the acetoxy and methoxy groups, respectively, in *cis*-2-acetoxy-*trans*-5-*t*-butyl-methoxycyclohexane: τ6.61, hydrogens of the methoxyl groups; τ7.93, hydrogens of the acetoxy groups; τ9.13 the hydrogens of the *t*-butyl groups in *cis*-4-*t*-butyl-*trans*-2-methoxycyclohexanol and *trans*-4-*t*-butyl-*cis*-2-methoxycyclohexanol.

A sample of the alcohol mixture was trifluoroacetylated and examined by g.l.p.c. using column C at 140°. There were two peaks in the chromatogram with retention times of 5.9 min and 7.8 min and in the ratio 1:9, respectively. The trifluoroacetyl derivative of authentic *cis*-4-*t*-butyl-*trans*-2-methoxycyclohexanol had a retention time of 5.9 min under these same conditions.

6. Reduction of *trans*-2-benzyloxy-4-*t*-butylcyclohexanone (**22**)

Trans-2-benzyloxy-4-*t*-butylcyclohexanone (1.0 g, 3.8 mmoles) was reduced as described above and yielded 990 mg (98 %) of a white solid. The sample was dissolved in methylene chloride and an aliquot acetylated (procedure B). The mixture of acetates was examined by n.m.r. which revealed a 5-proton singlet at τ2.68, a weak and narrow multiplet at τ5.00, a singlet superimposed on a broad multiplet at τ5.20 to 5.50, a multiplet at τ6.16 (half-band width 12 Hz), a multiplet at τ6.40 (half-band width 12 Hz), a sharp 3-proton singlet at $\tau 8.03$, complex signals between $\tau 8$ and 9 and the signal for the t-butyl groups at $\tau 9.18$. The signal at $\tau 2.68$ was assigned to the hydrogens of the phenyl groups, the signals in the region $\tau 5.00$ to 5.50 to the hydrogens of the methylene groups of the benzyl groups and the hydrogens geminal to the acetoxy groups in the axial and equatorial acetates. The multiplets at $\tau 6.16$ and $\tau 6.40$ were in the ratio 6.6:1 and were assigned to the equatorial hydrogens geminal to the benzyloxy groups in trans-4-acetoxy-trans-3-benzyloxy-t-butylcyclohexane and cis-4-acetoxy-trans-3-benzyloxy-t-butylcyclohexane, respectively.

A sample of the reduction product was trifluoroacetylated and examined by g.l.p.c. on column B at 205°. After the solvent peak, two peaks appeared with retention times of 10.3 min and 14 min in the ratio 1:5.9, respectively. The trifluoroacetyl derivative of authentic trans-2-benzyloxy-cis-4-t-butylcyclohexanol had a retention time of 10.3 min under these same conditions.

F. Catalytic Hydrogenation of 4-t-Butylcyclohexanone Acetylhydrazone, Azine and Benzyloxycarbonylhydrazone

1. General

A Parr hydrogenation apparatus was used for the reductions. Hydrogenations were carried out at 60 p.s.i. and at room temperature for 18 hr. In all cases 5 % palladium on carbon was used as the catalyst.

2. Reduction of 4-t-butylcyclohexanone acetyhydrazone (36)

a. In glacial acetic acid containing 1.1 equivalents of hydrochloric acid.

A solution of 3.75 g (17.7 mmoles) of 36 in 45 ml of glacial acetic acid, containing 1.63 ml (19.9 mmoles) of concentrated hydrochloric acid and one g of catalyst, was hydrogenated. After hydrogenation the catalyst was removed by filtration through Celite. Anhydrous sodium acetate (1.6 g, 20 mmoles) was added and the solution concentrated.

The residue was dissolved in methylene chloride (15 ml) and washed with water (7 ml). The solution was dried and concentrated. A white solid remained and this was recrystallized from ethanol-water to give 2.42 g (65 %) of white crystals: m.p. 141-143°. A sample for analysis was recrystallized three times from ethanol-water: m.p. 149-150.5°. Anal. Calcd. for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39; N, 13.19. Found: C, 67.96; H, 11.44; N, 13.31 %. The n.m.r. spectrum of the pure material (Fig. 28) was nearly identical with

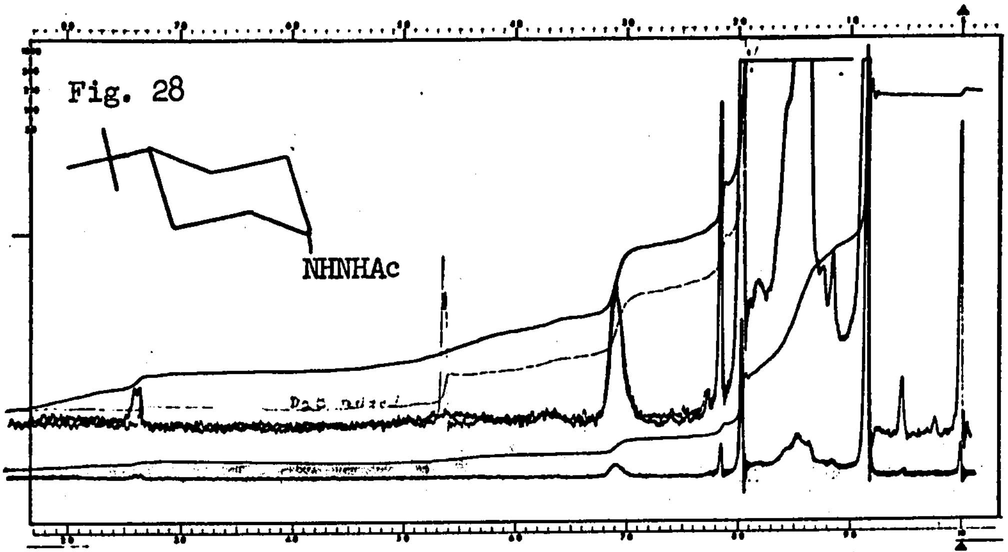


Fig. 28

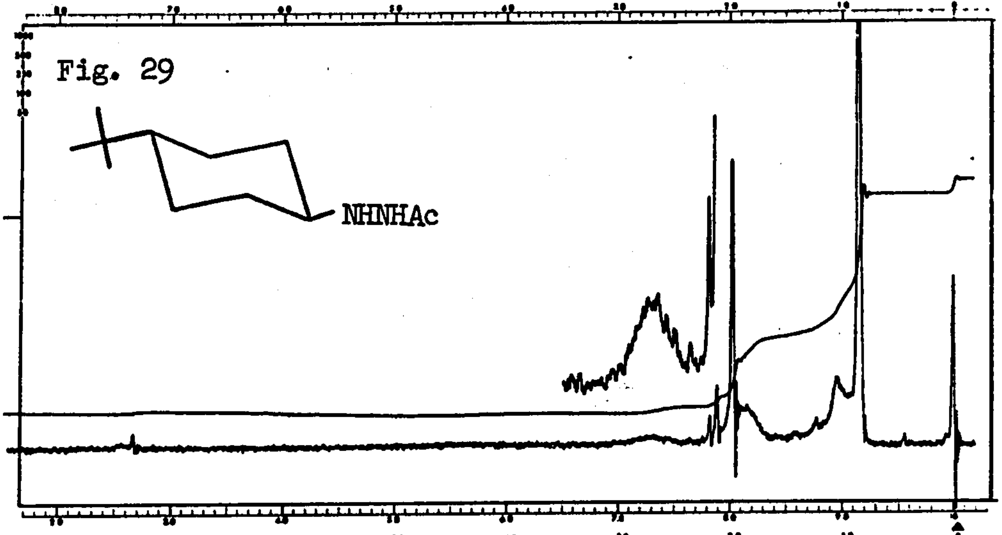


Fig. 29

Fig. 30

Figure 28. 60 MHz N.M.R. Spectrum of 1-Acetyl-2-(<u>cis</u>-4′-<u>t</u>-butylcyclohexyl)hydrazine (37) in $CDCl_3$. Figure 29. 60 MHz N.M.R. Spectrum of 1-Acetyl-2-(<u>trans</u>-4′-<u>t</u>-butylcyclohexy)hydrazine (38) in $CDCl_3$. Figure 30. 60 MHz N.M.R. Spectrum of Azo-<u>cis</u>-4-<u>t</u>-butylcyclohexane (34) in $CDCl_3$.

that of the crude product. There was present in the spectrum a 3-proton singlet at τ 8.08 for the hydrogens of an acetyl group and a 9-proton singlet at τ 9.18 for the hydrogens of a t-butyl group. There was also present a one-proton multiplet at τ 6.91 (half-band width 7 Hz) which is assigned to the hydrogen geminal to the N-acetylhydrazino group in 1-acetyl-2-(cis-4'-t-butylcyclohexyl) hydrazine (37).

b. In 90 % ethanol.

A solution of 2 g (9.53 mmoles) of 36 in 90 % ethanol (20 ml) containing 0.5 g of 5 % palladium on carbon was hydrogenated. After hydrogenation the catalyst was removed by filtration through Celite. The filtrate was concentrated to yield a residue that was examined by n.m.r. There was present in the spectrum signals for the hydrogens of an acetyl group and a t-butyl group as well as multiplets at τ 6.92 (half-band width 8 Hz) and τ 7.32 (half-band width 25 Hz) in the ratio 1.8:1, respectively. The signal at τ 6.92 was attributed to the hydrogen geminal to the N-acetylhydrazino group in 1-acetyl-2-(cis-4'-t-butylcyclohexyl) hydrazine (37) and the signal at τ 7.32 to the hydrogen geminal to the N-acetylhydrazino group in 1-acetyl-2-(trans-4'-t-butylcyclohexyl) hydrazine (38).

Material (5.7 g) from a similar experiment was separated into its components by column chromatography. Chromatography was carried out using 490 g of silicic acid in a column 4 x 78 cm. Elution was with acetone-Skelly B (1:1, v/v) and 8 ml fractions were collected. Thin layer chromatographic analysis indicated that fractions 48-60 contained a single component. These fractions were pooled and the solvent removed in vacuo. The residue was recrystallized from acetone to yield 1.83 g (32 %) of material m.p. 143-145°. The n.m.r. spectrum of this material was identical to that of axial compound 37. Fractions 61-66 contained a mixture of isomers and fractions 67-90 contained one component. Fractions 67-90 were pooled and the solvent removed in vacuo. The residue was recrystallized from acetone to give 1.45 g (25 %) of white crystals: m.p. 125.2°-128°. Anal. Calcd. for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39; N, 13.19. Found: C, 67.90; H, 11.29; N, 13.43 %. The n.m.r. spectrum (Fig. 29) of this material confirmed that it was 1-acetyl-2-(trans-4'-t-butylcyclohexyl) hydrazine (38). The spectrum showed the presence of a signal for the hydrogens of an acetyl group (τ 8.07) and a t-butyl group (τ 9.17). Also present was a one-proton multiplet at τ 7.32 (half-band width 25 Hz) which is assigned to the hydrogen geminal to the N-acetylhydrazino group in 38.

3. Reduction of 4-t-butylcyclohexanone azine (33)

A solution of one g (3.3 mmoles) of 33 in 30 ml of glacial acetic acid, containing 0.3 ml of concentrated hydrochloric acid and 0.5 g of 5 % palladium on carbon, was hydrogenated. After hydrogenation the reduction mixture was examined by t.l.c. (solvent system A) which indicated that starting material was present along with at least 3 other components. One spot in the chromatogram moved with the solvent front. The mixture was concentrated and the residue dissolved in chloroform (15 ml). The solution was washed with water (10 ml), saturated sodium bicarbonate solution and again water (10 ml). After drying, the solution was concentrated. A yellow solid remained weighing 0.48 g. Recrystallization of this material twice from acetone gave 140 mg of light yellow, hexagonal crystals: m.p. 117-119°. The crystals were insoluble in dilute acid. Thin layer chromatographic analysis (solvent system A) showed a single spot moving with the solvent front. The n.m.r. spectrum (Fig. 30) showed the presence of a single down field signal at τ 6.45 (half-band width 7 Hz) indicating the presence of two deshielded equatorial hydrogens. The absence of an i.r. absorption in the region 1640-1670 cm^{-1} indicated that no carbon-nitrogen double bond was present. This indicated that this material might be the diaxial azo compound 34 (see p-51 for structure). Anal. Calcd. for $C_{20}H_{38}N_2$: C, 78.38; H, 12.43; N, 9.14. Found: C, 78.22; H, 12.40; N, 8.90 %.

4. Reduction of 4-t-butylcyclohexanone N-benzyloxycarbonylhydrazone (35)

A solution of one g (3.3 mmoles) of 4-t-butylcyclohexanone N-benzyloxycarbonylhydrazone (35) in 40 ml of 90 % ethanol, containing 0.5 g of catalyst, was hydrogenated. T.l.c. (solvent system A) indicated that no starting material remained. A component was present that moved with the solvent front and there was a spot at the origin.

The reduction mixture was filtered through Celite and then concentrated. The residue was dissolved in ethanol (3 ml) and hexagonal crystals formed that were collected by filtration. After recrystallization from 95 % ethanol the material (50 mg) had a m.p. of 114-116.5°. The n.m.r. spectrum of this material was identical with the azo compound (33) obtained in the preceding experiment. The mother liquors were combined and concentrated and the residue dissolved in methylene chloride (10 ml). The solution was extracted with 3 ml of 2.5 N aqueous hydrochloric acid and the extract concentrated. The residue was acetylated (Procedure A). After work-up, 35 mg (5.4 %) of material was obtained that was examined by n.m.r. The general appearance of the spectrum and the presence of multiplets at τ5.90 (half-band width 15 Hz) and τ6.34 (half-band width 25 Hz) in the ratio 1.3:1, respectively, indicated that the material was a 1.3: mixture of cis-4-acetamido-t-butylcyclohexane (42) and trans-4-acetamido-t-butylcyclohexane (40).

G. Catalytic Hydrogenation 4-t-Butylcyclohexanone Oxime

1. Apparatus

A sloping manifold, atmospheric pressure hydrogenator (63) was used for the reductions. The reaction vessel consisted of a 100 ml round bottomed flask fitted with hooks for attachment to the hydrogenator with springs.

2. General reduction procedure

Catalyst (169 mg), oxime (338 mg, 2 mmoles) and a Teflon coated, magnetic stirring bar were placed in the reaction vessel which was flushed with nitrogen before the solvent (20 ml) was added. After the flask had been attached to the hydrogenation apparatus, the system was evacuated and then filled with hydrogen. This process was repeated twice more and the volume recorded. Stirring was started and the progress of the reductions followed by plotting hydrogen uptake against elapsed time. The one third reduction times recorded in Table IV represent the times required for absorption of one third of the theoretical amount of hydrogen. In all cases stirring was continued until hydrogen uptake had ceased.

a. Preparation of the sample for the determination of the percentage conversion of oxime to amine.

(i) Reductions carried out using glacial acetic acid as solvent.

The reduction mixture was filtered through Celite and the filter cake washed with glacial acetic acid. The filtrate was made up to 50 ml in a volumetric flask. A 20 ml aliquot was removed and 96.6 uml (79.2 mg, 0.8 mmole) of cyclohexylamine added as internal standard. The solution was then concentrated to a few ml. The concentrate was transferred to a separatory funnel with 10 ml of water. The aqueous solution was extracted with methylene chloride (3 x 5 ml) to remove nonbasic materials. Basic materials were set free by the addition of 10 ml of 10 N aqueous sodium hydroxide solution followed by extraction with methylene chloride (3 x 7 ml). The methylene chloride extracts were combined and dried. The methylene chloride solution was then concentrated to 5 ml volumne. Trifluoroacetic anhydride (0.5 ml, 3.5 mmoles) was added and the solution let stand for 0.5 hr. The solution was then concentrated to a sirup, methylene chloride (4 ml) added and the solution used for g.l.p.c. analysis.

(ii) Reductions carried out in the absence of acid.

Concentrated hydrochloric acid (0.3 ml, 3.6 mmoles) was added to the reduction mixture before filtration through Celite. The rest of the work up procedure was identical to that used when the reduction mixture contained glacial acetic as solvent.

b. Preparation of the sample for the determination of the percentage yield of amine.

The samples were prepared for analysis in the same manner as described above except that the internal standard was added after the work up and before the trifluoroacetylation step.

3. Analysis of the reduction products by g.l.p.c.

The solutions of *N*-trifluoroacetates obtained from the above work up were analyzed by g.l.p.c. on column A at 145°. Under these conditions the retention times of the *N*-trifluoroacetates of cyclohexylamine, *cis*-4-*t*-butylcyclohexylamine and *trans*-4-*t*-butylcyclohexylamine were 4, 8.3 and 16.2 min, respectively. The precentages of *cis*-4-trifluoroacetamido-*t*-butylcyclohexanes were obtained by comparison of the area under their respective peaks in the g.l.p.c. The analysis by g.l.p.c. of mixtures (of known composition) of trifluoroacetamidocyclohexane and the *N*-trifluoroacetate of *cis*-(or *trans*) 4-*t*-butylcyclohexylamine indicated that a correction factor was necessary for direct comparison of the areas under the g.l.p.c. peaks. Analysis, by g.l.p.c., of a mixture of one mmole of the *N*-trifluoroacetate of cyclohexylamine and one mmole of the *N*-trifluoroacetate of *cis*- (or *trans*) 4-*t*-butylcyclohexylamine, produced peaks in the ratio 1:1.25, respectively. The percentage conversion (or yield) was obtained by use of the following equation:

$$\%\ \text{Conversion (or yield)} = \frac{C + T}{S} \times 0.8 \times 100$$

where C, T and S represent the areas under the curves corresponding to the N-trifluoroacetates of *cis*-4-*t*-butylcyclohexylamine, *trans*-4-*t*-butylcyclohexylamine and cyclohexylamine, respectively.

The one third reduction times, percentage conversion and percentage yields for the various reductions are listed in Table IV.

H. Catalytic Hydrogenation of 2-Substituted 4-t-Butylcyclohexanone Oximes

1. General

The reductions were carried out at atmospheric pressure and at 25 ± 1°, using the same apparatus as described for the reduction of 4-t-butylcyclohexanone oxime. A ratio of one mmole of oxime to 183 mg of catalyst to 10 ml of solvent was used for all reductions. Stirring was continued until hydrogen uptake had ceased. One third reduction times were obtained as before and are recorded in Tables VI, VII, and VIII with total yields of the amine mixtures and the composition of the mixtures.

G.l.p.c. was carried out on column C at 160° for the trifluoroacetyl derivatives of the 2-methoxy-4-t-butylcyclohexylamines and on column C at 150° for the trifluoroacetyl derivatives of the 2-hydroxy-4-t-butylcyclohexylamines.

2. Reduction of cis-4-t-butyl-2-methoxycyclohexanone oxime (25)

a. In 90 % ethanol, containing 1.1 mmoles of hydrochloric acid, using 5 % palladium on carbon as catalyst.

Cis-4-t-butyl-2-methoxycyclohexanone oxime (199 mg, 1 mmole) in 10 ml of 90 % ethanol containing 0.0916 ml (1.1 mmoles) of concentrated hydrochloric acid and 183 mg of 5 % palladium on carbon was stirred under an atmosphere of hydrogen until absorption ceased. The one third reduction time was 8.6 min and 43.4 ml of hydrogen was absorbed during 96 min. After hydrogenation, the catalyst was removed by filtration through Celite. The filtrate was concentrated and the residue dissolved in water (10 ml). The solution was extracted with methylene chloride (3 x 7 ml) to remove nonbasic materials. Sodium hydroxide (3 ml of 10 M aqueous solution) was added and the amine set free was extracted into methylene chloride (3 x 7 ml). The methylene chloride extracts were combined and dried followed by concentration to yield a liquid residue that weighed 140 mg (75 %). A sample was trifluoroacetylated and examined by g.l.p.c. After the solvent peak, there appeared two peaks with retention times of 7.9 min and 10.1 min in the ratio 22:1, respectively.

The remaining free amine was acetylated (procedure B) and the product examined by n.m.r. The spectrum contained signals for the hydrogens of an acetyl group and a methoxy group as well as a low field signal at $\tau 5.62$ that was assigned to the hydrogen geminal to the N-acetyl group. This signal became narrower when the solution was treated with sodium deuterio oxide which indicated that it was coupled with the hydrogen on the nitrogen of the acetamido group. The half-band width of the signal (8 Hz) indicated that the acetamido group was axial. The signal for the hydrogen geminal to the methoxy group appeared at about $\tau 6.7$ as a broad multiplet superimposed on the signal for the hydrogens of the methoxy group.

The N-acetate was recovered from the n.m.r. tube and recrystallized once from Skelly B and then twice from methanol-water to give crystals with a m.p. of 118-120°. Anal. Calcd. for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.63; H, 11.08; N, 6.02 %. The 100 MHz n.m.r. spectrum (Fig. 31) of the pure

Fig. 31

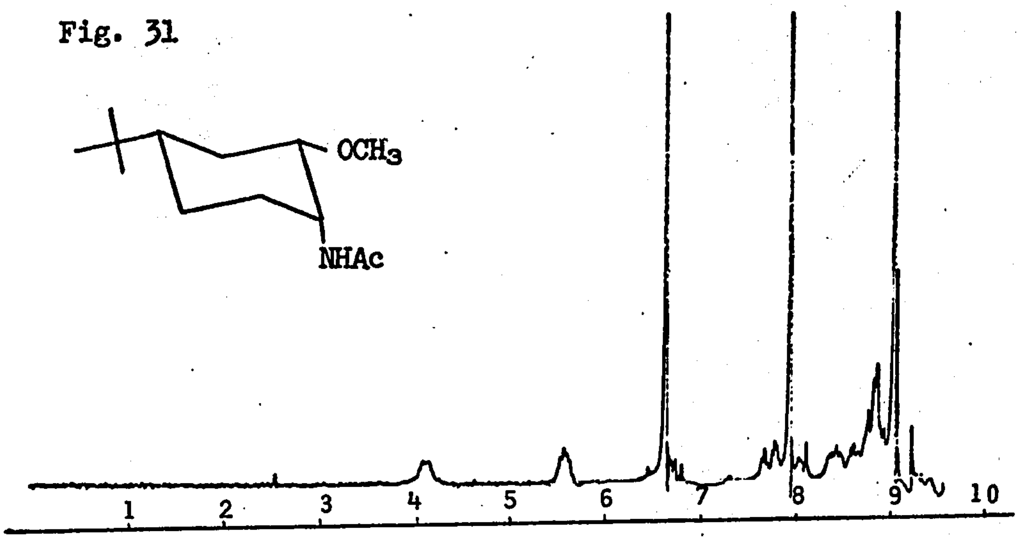


Fig. 32

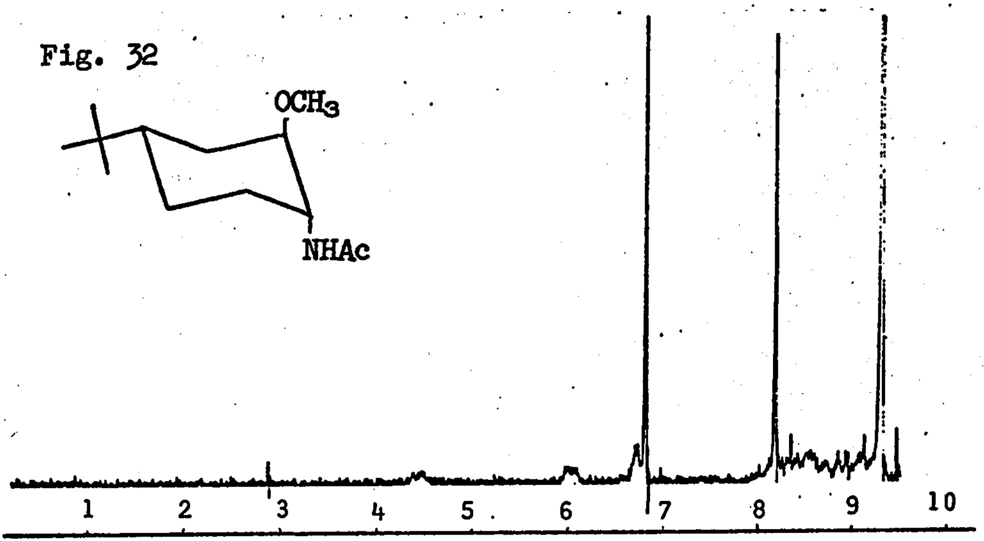


Fig. 33

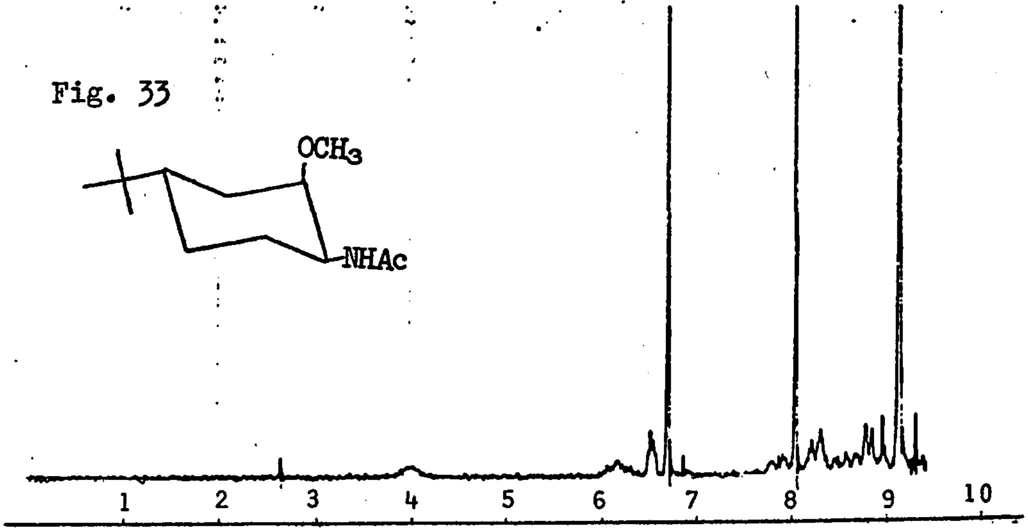


Figure 31. 100 MHz N.M.R. Spectrum of cis-2-Acetamido-cis-5-t-butyl-methoxycyclohexane (46) in CDCl$_3$ (Sweep width 1000 Hz). Figure 32. 100 MHz N.M.R. Spectrum of trans-2-Acetamido-trans-5-t-butyl-methoxy-cyclohexane (47) in CDCl$_3$ (Sweep width 1000 Hz). Figure 33. 100 MHz N.M.R. Spectrum of cis-2-Acetamido-trans-5-t-butyl-methoxycyclohexane (48) in CDCl$_3$ (Sweep width 1000 Hz).

material was nearly identical with that of the crude acetylation product and indicated that the material was cis-2-acetamido-cis-5-t-butyl-methoxycyclohexane (46) and therefore the hydrogenation had yielded nearly pure cis-4-t-butyl-cis-2-methoxy cyclohexylamine (51)

b. In 90 % ethanol, using 5 % rhodium on carbon as catalyst.

The reduction was carried out in the usual manner. The one third reduction time was 62.4 min and 40.8 ml of hydrogen was absorbed during 491 min.

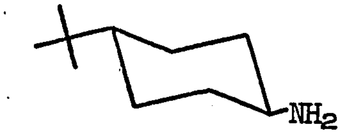
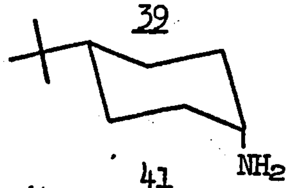
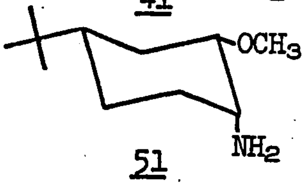
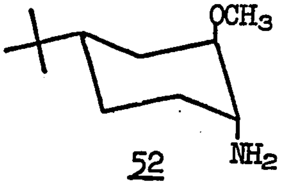
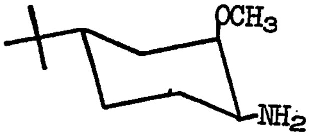
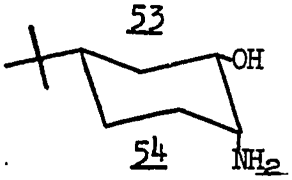
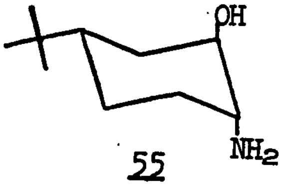
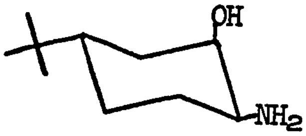
After hydrogenation 1.1 mmoles of hydrochloric acid was added and the mixture worked up as before. A yield of 118 mg (64 %) of free amine was obtained. A sample was trifluoroacetylated and examined by g.l.p.c. Peaks appeared with retention times of 7.2 min, 7.9 min, 9 min, and 10.1 min in the ratio 1:37:2.5:6.3, respectively.

Table X lists the retention times given by the trifluoroacetyl derivatives of the pure 2-methoxy-4-t-butylcyclohexylamines. On the basis of retention times the mixture was composed of: 51 (80 %), 52 (5 %), 53 (2 %), which meant that cis-4-t-butyl-cis-2-methoxy-cyclohexylamine (51) accounted for at least 86 % of the 4-t-butyl-2-methoxycyclohexylamines in which the 2-methoxy substituent was equatorial.

c. In 90 % ethanol, containing 4.1 mmoles of 85 % hydrazine hydrate, using 5 % palladium on carbon as catalyst.

The oxime was dissolved in 10 ml of 90 % ethanol containing 0.235 ml of 85 % hydrazine hydrate (4.1 mmoles) and let stand 1 hr

TABLE X
G.L.P.C. Retention Times of Trifluoroacetylated, 2-Substituted 4-t-Butylcyclohexylamines

Amine	Retention Time[a] in min. (Column[b] temp.)
 39	9.9 (140°) 8.5 (150°)
 41	7.9 (140°) 6.7 (150°)
 51	7.9 (160°)
 52	7.2 (160°)
 53	8.9 (160°)
 54	9.2 (150°)
 55	7.9 (150°)
 (c)	8.7 (150°)

---

a. Of trifluoroacetylated amine. b. A 6 ft. x 0.25 in. (O.D.) copper tube packed with 20 % silicone gum rubber (SE 30) on acid washed Chromosorb P (40-60 mesh). c. Compound not isolated.

after which catalyst was added and hydrogenation started. A total of 40 ml of hydrogen was absorbed during 20 hr.

After hydrogenation, the catalyst was removed by filtration through Celite. The filtrate was concentrated and the residue dissolved in methylene chloride (10 ml). The methylene chloride solution was washed with water (3 x 5 ml) to remove any hydrazine present. The methylene chloride solution was extracted with 2.5 N aqueous hydrochloric acid (5 ml) and the aqueous layer separated and washed with methylene chloride (3 x 5 ml) to remove nonbasic materials. The acid solution was concentrated to give a residue of amine hydrochloride weighing 135 mg (62 %). The residue was dissolved in water (5 ml) and 10 M sodium hydroxide solution (3 ml) added. The solution was extracted with methylene chloride (3 x 5 ml). The extracts were combined, dried and then concentrated. The liquid amine obtained was trifluoroacetylated for gas chromatographic analysis. Two peaks were present with retention times of 7.9 min and 9.9 min in the ratio 8.1:1 which indicated that 88 % of the product was cis-4-t-butyl-cis-2-methoxycyclohexylamine (51).

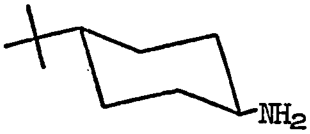
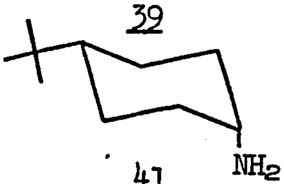
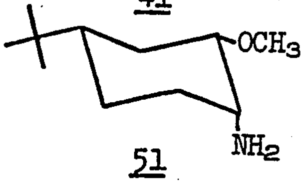
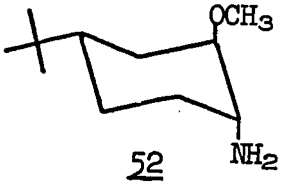
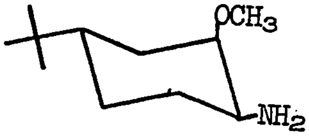
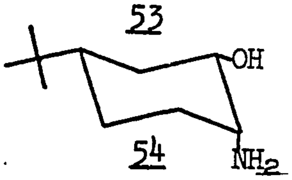
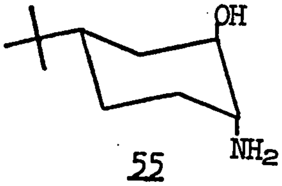
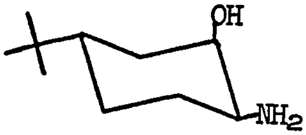
3. Reduction of trans-4-t-butyl-2-methoxycyclohexanone oxime (26)

a. In 90 % ethanol, containing 1.1 mmoles of hydrochloric acid, using 5 % palladium on carbon as catalyst.

This reduction was carried out in the same manner as the reduction in H-2-a except that trans-4-t-butyl-2-methoxyclohexanone oxime (26) was used as the substrate. The one third reduction time

TABLE X

G.L.P.C. Retention Times of Trifluoroacetylated, 2-Substituted 4-t-Butylcyclohexylamines

Amine	Retention Time[a] in min. (Column[b] temp.)
 39	9.9 (140°) 8.5 (150°)
 41	7.9 (140°) 6.7 (150°)
 51	7.9 (160°)
 52	7.2 (160°)
 53	8.9 (160°)
 54	9.2 (150°)
 55	7.9 (150°)
 (c)	8.7 (150°)

---

a. Of trifluoroacetylated amine. b. A 6 ft. x 0.25 in. (O.D.) copper tube packed with 20 % silicone gum rubber (SE 30) on acid washed Chromosorb P (40-60 mesh). c. Compound not isolated.

indicating that this signal was due to the hydrogen geminal to the acetamido group. The half-band width of this signal (8 Hz) required that the acetamido group be axial. The signal at $\tau 6.57$ was assigned to the hydrogen geminal to the methoxy group. The half-band width (8 Hz) of this signal indicated that the methoxy group was axial. Thus, this compound was trans-2-acetamido-trans-5-t-butyl-methoxycyclohexane (47). The elemental analysis was consistant with the structure. Anal. Calcd. for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.51; H, 11.12; N, 6.15 %. M.p. and n.m.r. data for this compound are listed in Table V.

The slower moving isomer (most abundant) had a m.p. of 121.7° after one recrystallization from Skelly B followed by sublimation. Anal. Calcd. for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.81; H, 11.16; N, 6.28%. The 100 MHz n.m.r. spectrum (Fig. 33) of this compound was similar to that for 47 except that the signal for the hydrogen geminal to the acetamido group appeared at $\tau 6.18$. The half-band width of this signal was 25 Hz indicating that the acetamido group was equatorial and, therefore, that this compound was cis-2-acetamido-trans-5-t-butyl-methoxycyclohexane (48).

It was concluded from the above that this reduction produced a 1:2.2 mixture of cis-4-t-butyl-trans-2-methoxycyclohexylamine (52) and trans-4-t-butyl-cis-2-methoxycyclohexylamine (53). On the basis of the g.l.p.c. retention time data (Table X) the minor compound must be cis-4-t-butyl-cis-2-methoxycyclohexylamine (51) indicating that some epimerization of the 2-methoxy group occurred during the hydrogenation.

b. In 90 % ethanol, using 5 % rhodium on carbon as catalyst.

This reduction was carried out in the same manner as the reduction in H-2-b except that trans-4-t-butyl-2-methoxycyclohexanone oxime (26) was used as the substrate. The one third reduction time was 62 min and 52.5 ml of hydrogen was absorbed during 660 min. Work up as before yielded 107 mg (58 %) of mixed amine. A sample of the amine mixture was trifluoroacetylated and examined by g.l.p.c. There were present peaks with retention times of 7.2 min, 7.9 min, 8.9 min and 10.1 min in the ratio 7.7:6.7:12:1, respectively. This indicated (see Table X for retention time data) that the mixture was composed of the N-trifluoroacetyl derivatives of: 52 (28 %), 51 (24 %), 53 (44 %) and an unidentified component (4 %).

A sample of the amine mixture was acetylated and examined by n.m.r. at 100 MHz (in deuteriochloroform) and revealed signals at τ5.66 (half-band width 11 Hz), τ 5.91 (half-band width 9 Hz) and τ6.23 (half-band width 21 Hz) in the ratio 1:1.1:2, respectively. These corresponded to the signals produced by the hydrogens geminal to the acetamido groups in the N- acetyl derivatives of 51, 52 and 53, respectively and confirmed the composition assignment made on the basis of retention times of the trifluoroacetylated amine mixture. This indicated that cis-4-t-butyl-trans-2-methoxycyclohexylamine (52) accounted for 39 % of the 4-t-butyl-2-methoxycyclohexylamines in which the 2-methoxy substituent was axial.

c. In 90 % ethanol, containing 4.1 mmoles of 85 % hydrazine hydrate, using 5 % palladium on carbon as catalyst.

This reduction was carried out in the same manner as the reduction in H-2-c except that trans-4-t-butyl-2-methoxycyclohexanone oxime (26) was used as the substrate. The one third reduction time was 115 min and 32 ml of hydrogen was absorbed during 21 hr. Work-up as before yielded 81 mg (37 %) of a mixture of amine hydrochlorides. A sample of free amine was trifluoroacetylated and examined by g.l.p.c. There were present peaks with retention times of 7.2 min, 7.9 min, 8.9 min, and 10.1 min in the ratio 4.6:4.2:8.8:1, respectively. On the basis of retention times, these peaks were assigned to the N-trifluoroacetyl derivatives of 52, 51, 53 and an unidentified component, respectively. Therefore cis-4-t-butyl-trans-2-methoxycyclohexylamine accounted for 32 % of the 4-t-butyl-2-methoxycyclohexylamines in which the 2-methoxy substituent was axial.

4. Reduction of trans-4-t-butyl-2-hydroxycyclohexanone oxime (32)

a. In 90 % ethanol, containing 1.1 mmoles of hydrochloric acid, using 5 % palladium on carbon as catalyst.

This reduction was carried out in the same manner as the reduction in H-2-a except that the substrate was trans-4-t-butyl-2-hydroxycyclohexanone oxime (32). The one third reduction time was 195 min and 38 ml of hydrogen was absorbed during 22 hr. Work-up in the usual manner yielded 100 mg (58 %) of solid amine. After dissolving the amine in methylene chloride an aliquot was removed and trifluoroacetylated for g.l.p.c. analysis. There was present, in the gas chromatogram, peaks with retention times of 5.6 min, 6.4 min, 7.6 min, 8.7 min and 10.7 min in the ratio 2.6:1:54:1.2:1, respectively. The remainder of the amine was acetylated for examination by n.m.r. at 60 MHz (in deuteriochloroform). The n.m.r. spectrum indicated that the material was mostly cis-4-acetamido-trans-3-acetoxy-t-butylcyclohexane (50) as shown by the presence of signals at τ5.10 (half-band width 8 Hz) and τ5.97 (half-band width 9 Hz) attributed to the hydrogens geminal to the O-acetyl and N-acetyl groups, respectively.

A sample of the acetylated material was recrystallized once from methylene chloride-Skelly B and once from methanol-water to give crystals with a m.p. of 157.5-158.5°. Anal. Calcd. for $C_{14}H_{25}NO_3$ C, 65.85; H, 9.87; N, 5.49. Found: C, 65.43, 65.72; H, 10.09, 10.11; N, 5.77 %. The n.m.r. spectrum of the pure product (Fig. 24) was nearly identical with the crude product obtained from acetylation. There was present in the spectrum signals for the hydrogens of two acetyl groups and one-proton multiplets at τ5.10 (half-band width 8 Hz) and τ5.95 (half-band width 16 Hz). When the solution was treated with sodium deuterio oxide the signal at τ5.95 became narrower (half-band width now 8 Hz) indicating that this was the signal for the hydrogen geminal to the acetamido group. The signal at τ5.10, therefore, was due to the hydrogen geminal to the acetoxy group. The half-band width of these multiplets indicated that the acetamido and acetoxy groups were axial and therefore this was the diacetyl derivative (50) of cis-4-t-butyl-trans-2-hydroxycyclohexylamine (55).

b. In 90 % ethanol, using 5 % rhodium on carbon as catalyst.

This reduction was carried out in the same manner as the reduction in H-2-b except that the substrate was trans-4-t-butyl-2-hydroxycyclohexanone oxime (32). The one third reduction time was 12.3 min and 48 ml of hydrogen was absorbed during 109 min. Work up in the usual manner yielded 66 mg (38 %) of solid amine. The free amine was trifluoroacetylated and examined by g.l.p.c. There were present peaks with retention times of 5.5 min, 6.4 min, 7.9 min and 8.8 min in the ratio 4.5:1:89:1.1, respectively. The peak with a retention time of 7.9 min was assigned to the trifluoroacetyl derivative of cis-4-t-butyl-trans-2-hydroxycyclohexylamine (55), on the basis of the results of the preceding experiment, which meant that 55 accounted for at least 96 % of the 4-t-butyl-2-hydroxycyclohexylamines in which the 2-hydroxy substituent was axial.

5. Reduction of cis-2-acetoxy-4-t-butylcyclohexanone oxime (27)

a. In 90 % ethanol, containing 1.1 mmoles of hydrochloric acid, using 5 % palladium on carbon as catalyst.

This reduction was carried out in the same manner as the reduction in H-2-a except that the substrate was cis-2-acetoxy-4-t-butylcyclohexanone oxime (27). The one third reduction time was 12 min and a total of 42.5 ml of hydrogen was absorbed during 41 min.

After hydrogenation, the catalyst was removed by filtration through Celite and the filtrate concentrated. The residue was hydrolyzed in 5 ml of concentrated hydrochloric acid-ethanol (1:1, v/v) for 18 hr. After work up in the usual manner a 46 % yield of solid amino alcohol was obtained. A sample was trifluoroacetylated and examined by g.l.p.c. There were peaks present in the chromatogram with retention times of 6.2 min, 9.1 min and 10.6 min in the ratio 1:29.4:1.8, respectively.

The material was acetylated and examined by n.m.r. at 60 MHz (in deuteriochloroform) and appeared to be nearly pure _cis_-4-acetamido-_cis_-3-acetoxy-_t_-butylcyclohexane (_49_). A sample recrystallized from methanol-water had a m.p. of 161-162°. Anal. Calcd. for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49. Found: C, 65.72; H, 9.98; N, 5.33 %. The n.m.r. spectrum (Fig. 34) of the pure material was nearly identical with that of the crude material obtained from acetylation. The spectrum showed one-proton multiplets centered at τ5.18 (half-band width 20 Hz) and τ5.60 (half-band width 17 Hz) and these were assigned to the hydrogens geminal to the acetoxy and acetamido groups, respectively. The signal at τ5.60 became narrower (half-band width now 8 Hz) when the deuteriochloroform solution was treated with sodium deuterio oxide solution, indicating that this hydrogen had been coupled with the hydrogen on the nitrogen of the acetamido group. The half-band width of the multiplets required that the acetoxy group be equatorial and the acetamido group axial and that this material was the diacetyl derivative (_49_) of _cis_-4-t-butyl-_cis_-2-hydroxycyclohexylamine (_54_). From the g.l.c.p. data it was apparent

Fig. 34

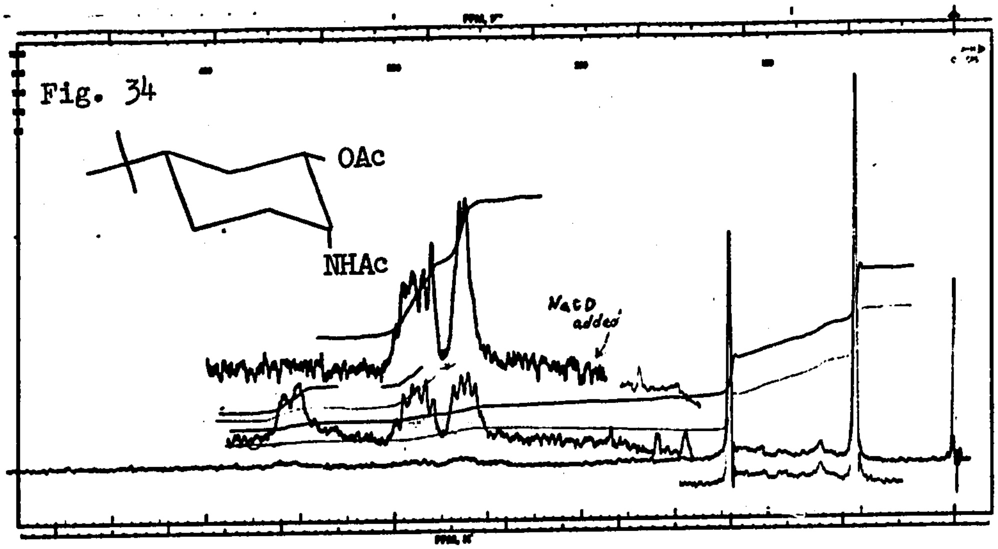


Fig. 35

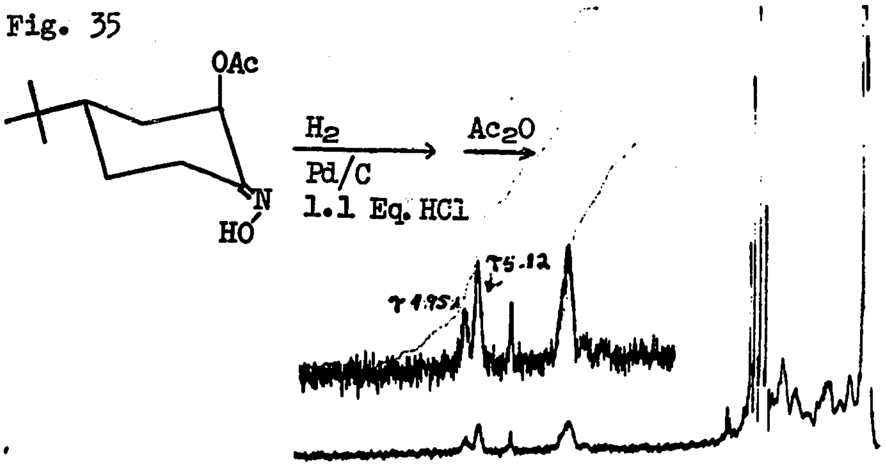


Figure 34. 60 MHz N.M.R. Spectrum of cis-4-acetamido-cis-3-acetoxy-t-butylcyclohexane (49) in $CDCl_3$. Figure 35. 100 MHz N.M.R. Spectrum of the Acetylated Product from Catalytic Hydrogenation of trans-2-Acetoxy-4-t-butylcyclohexanone Oxime (28) over 5 % Palladium on Carbon in 90 % Ethanol, containing 1.1 Equivalents of Hydrochloric Acid (In $CDCl_3$, Sweep width 1000 Hz).

that 54 accounted for at least 94 % of the 4-t-butyl-2-hydroxycyclohexylamines in which the 2-hydroxy substituent was equatorial.

b. In 90 % ethanol, using 5 % rhodium on carbon as catalyst

This reduction was carried out in the same manner as the reduction in H-2-b except that cis-2-acetoxy-4-t-butylcyclohexanone oxime (27) was used as the substrate. The one-third reduction time was 63 min and 49 ml of hydrogen was absorbed during 428 min. The crude product of hydrogenation was hydrolyzed in hydrochloric acid-ethanol. After work-up in the usual manner, 43 mg (24.6 %) of free amine was obtained. A sample was trifluoroacetylated and examined by g.l.p.c. which revealed components with retention times of 6.2 min, 9.2 min, 10.6 min and 11.6 min in the ratio 1:9.3:1.6:1.

A sample of the amine mixture was acetylated and examined by n.m.r. at 60 MHz. There were present multiplets at τ5.20 (half-band width 21 Hz), τ5.62 (half-band width 8 Hz) and two poorly resolved multiplets at τ5.9 (half-band width approximately 8 Hz) and τ6.3 (half-band width approximately 25 Hz). The multiplets at τ5.20 and τ5.62 were assigned to the hydrogens geminal to the acetoxy and acetamido groups, respectively, in cis-4-acetamido-cis-3-acetoxy-t-butylcyclohexane (49). It was apparent from the integration that at least 60 % of the product from acetylation was 49.

On the basis of the findings of the preceding experiment, the major peak in the gas chromatogram was assigned to the ditrifluoroacetyl derivative of cis-4-t-butyl-cis-2-hydroxycyclohexylamine (54) and this compound, therefore, accounted for at least 85 % of the 4-t-butyl-2-hydroxycyclohexylamines in which the 2-hydroxy group was equatorial.

5. Reduction of trans-2-acetoxy-4-t-butylcyclohexanone oxime (28)

a. In 90 % ethanol, containing 1.1 mmoles of hydrochloric acid, using 5 % palladium on carbon as catalyst.

This reduction was carried out in the same manner as the reduction in H-2-a except that the substrate was trans-2-acetoxy-4-t-butylcyclohexanone oxime (28). The one third reduction time was 46 min and a total of 40.2 ml of hydrogen was absorbed during 19 hr. After hydrogenation, the catalyst was removed by filtration through Celite and the solution concentrated. The residue was hydrolyzed in hydrochloric acid-ethanol as before. After work-up in the usual manner, 152 mg (89 %) of an amine mixture was obtained. A sample was trifluoroacetylated and examined by g.l.p.c. There was present, in the gas chromatogram, peaks with retention times of 6.7 min, 8 min, and 8.5 min in a ratio of 2:7.9:1, respectively. The presence of a peak with a retention time of 6.7 min indicated (see Table X for retention time data) that the trifluoroacetyl derivative of cis-4-t-butylcyclohexylamine (41) was present.

A sample of the mixed amines was acetylated and examined by n.m.r. at 100 MHz. The spectrum (Fig. 35) showed multiplets at $\tau 4.95$ (half-band width 8 Hz), $\tau 5.1$ (half-band width 8 Hz) and $\tau 6.02$ (half-band width 13 Hz) in the ratio 1:2.2:3.2. There were also weak signals at $\tau 6.2$ (half-band width about 18 Hz) and $\tau 6.40$

(half-band width about 20 Hz). By comparison of this spectrum with the n.m.r. spectrum (Fig. 24) of pure cis-4-acetamido-trans-3-acetoxy-t-butylcyclohexane (50) it was apparent that two of the signals (at τ5.1 and τ5.97) were due to the presence of 50 and that 50 constituted the bulk of the mixture. However, the signal at τ5.97 (spectrum of the mixture) was not symmetrical indicating the presence of another overlapping signal. The g.l.p.c. data had indicated the possible presence of cis-4-t-butylcyclohexylamine (41) in the reaction mixture and the presence of 41 would explain the distortion of the n.m.r. signal at τ5.97 since the n.m.r. spectrum of the N-acetyl derivative of cis-4-t-butylcyclohexylamine shows (Fig. 26) a multiplet centered at τ5.91 for the hydrogen geminal to the acetamido group.

The gas chromatographic peak with retention time 8.5 min could be due to the trifluoroacetyl derivative of trans-4-t-butylcyclohexylamine (see retention time data in Table X). The N-acetyl derivative of trans-4-t-butylcyclohexylamine shows a signal in the n.m.r. spectrum (Fig. 25) at τ6.35 and a similar signal is present in the spectrum of the acetylated amine mixture.

The signal in the n.m.r. spectrum (Fig. 35) of the mixture at τ4.95 is assigned to the hydrogen geminal to the acetoxy group in the diacetyl derivative of trans-4-t-butyl-cis-2-hydroxycyclohexylamine (57). The peaks at τ4.95 and τ5.1 were in the ratio 1:2.2, respectively, therefore cis-4-t-butyl-trans-2-hydroxycyclohexylamine accounted for at least 70 % of the 4-t-butyl-2-hydroxycyclohexylamines present in the hydrolyzed reduction mixture.

b. In 90 % ethanol, using 5 % rhodium on carbon as catalyst.

This reduction was carried out in the same manner as in H-2-b except that the substrate was trans-2-acetoxy-4-t-butylcyclohexanone oxime (28). The one third reduction time was 52 min and 57 ml of hydrogen was absorbed during 348 min. After hydrogenation the catalyst was removed by filtration through Celite. The filtrate was concentrated and the residue hydrolyzed in hydrochloric acid-ethanol as before. After work up in the usual manner 61 mg (36 %) of an amine mixture was obtained. A sample was trifluoroacetylated and examined by g.l.p.c. There was present in the gas chromatogram peaks with retention times of 6.7 min, 8.0 min, and 8.5 min in the ratio 1.55:1.25:1, respectively. A sample was acetylated and examined by n.m.r. at 100 MHz. The spectrum (Fig. 23) showed the presence of multiplets at τ4.9 (half-band width 8 Hz), τ5.12 (half-band width 8 Hz), τ 5.97 (half-band width 14 Hz) and two overlapping multiplets in the region τ6.1-6.6. The integration of the signals for the hydrogens of N-acetyl groups (in the region τ5.8-6.6) was about 3 times that for the signals due to the hydrogens of O-acetyl groups (in the region τ4.8-5.2). The large peak (retention time 6.8 min) in the gas chromatogram indicated that a considerable amount of cis-4-t-butylcyclohexylamine was formed during the reduction. The multiplets at τ4.9 and 5.1 were assigned, as before (preceding experiment) to the hydrogens geminal to the acetoxy group in the diacetyl derivatives of trans-4-t-butyl-cis-2-hydroxycyclohexylamine (57) and cis-4-t-butyl-trans-2-hydroxycyclohexylamine (55), respectively. The ratio of these signals indicated that 55 accounted for 60 % of the 4-t-butyl-2-hydroxycyclohexylamines present in the hydrolyzed reaction product.

I. Catalytic Hydrogenation of Isopropyl 2-oximino-α-D-*arabino*-hexopyranoside (56) and Isopropyl 3,4,6-tri-O-acetyl-2-oximino-α-D-*arabino*-hexopyranoxide (29)

1. General

The reductions were carried out at atmospheric pressure and at 25 ± 1°, using the same apparatus as described for the reduction of 4-*t*-butylcyclohexanone oxime. A ratio of 1 mmole of substrate to 183 mg of catalyst to 10 ml of solvent was used in all cases. Table IX summarizes the results of the reductions.

2. Reduction of isopropyl 3,4,6-tri-O-acetyl-2-oximino-α-D-*arabino*-hexopyranoside (29)

a. In methanol, containing 1.1 equivalents of hydrochloric acid, using 5 % rhodium on carbon as catalyst.

Isopropyl 3,4,6-tri-O-acetyl-2-oximino-α-D-*arabino*-hexopyranoside (29) (367 mg, one mmole) and 5 % rhodium on carbon (183 mg) were added to a solution of 0.0916 ml (1.1 mmoles) of concentrated hydrochloric acid in 10 ml of anhydrous methanol (flushed with nitrogen). The mixture was stirred under an atmosphere of hydrogen until absorption ceased. A total of 12 ml of hydrogen was absorbed during 21 hr. After hydrogenation the reaction mixture was filtered through Celite and the filter cake washed with solvent (3 x 4 ml). The filtrate was concentrated and the residue partitioned between water (10 ml) and methylene chloride (10 ml). The aqueous layer was separated and filtered through a filter paper moistened with water.

Removal of the solvent in vacuo left a crystalline solid (90 mg) which was acetylated using procedure B. The acetylated material was dissolved in 12 ml of methanol-water (1:1) containing 0.7 ml of triethylamine and let stand for 14 hr. The triethylamine was removed by swirling the solution with 5 ml of a slurry of washed (methanol) Amberlite IR-120 ion exchange resin (H^+ form) until slightly acid to pH paper. The resin was removed by vacuum filtration and washed with methanol (3 x 3 ml). The filtrate was concentrated. The hydroxylic hydrogens were exchanged for deuterium by dissolved the residue in 2 ml of deuterium oxide followed by freeze drying. This was repeated once more and the residue from this dissolved in deuterium oxide for n.m.r. analysis (using pyrazine as internal standard). Analysis of the spectrum (100 MHz) revealed the presence of two doublets, one at $\tau 5.33$ with a spacing of 3.5 Hz and one centered at $\tau 5.49$ with a spacing of 1.5 Hz. The doublets, which were attributed to the H_1 hydrogens of the α-D-glucosaminyl and the α-D-mannosaminyl glycosides, respectively, had relative intensities of 1.3:1.0, respectively.

b. In 95 % ethanol, containing 20 mmoles of hydrazine, using 5 % rhodium on carbon as catalyst.

One mmole of isopropyl 3,4,6-tri-O-acetyl-2-oximino-α-D-arabino-hexopyranoside (29) was dissolved in 10 ml of 95 % ethanol, flushed with nitrogen and 183 mg of 5 % rhodium on carbon added. The reaction mixture was stirred under a hydrogen atmosphere for one hr during which no uptake occured. The reaction flask was removed from the hydrogenator, flushed with nitrogen and 20 mmoles (0.64 ml) of 98 % hydrazine added. The solution was kept under nitrogen for 80 min and checked periodically by t.l.c. (Silica Gel G, acetone-Skelly B, 1:1,v/v). That de-O-acetylation was probably completed in 80 min was indicated by the slow formation of a spot at the origin and by the disappearance of starting material and intermediate spots. The mixture was replaced on the hydrogenator and stirred under an atmosphere of hydrogen. Hydrogenation was slow; a total of 64 ml of hydrogen being absorbed during 48 hr. After hydrogenation the crude product was acetylated (procedure A). Excess acetic anhydride was destroyed by the addition of 5 ml of methanol followed by the evaporation of solvents in vacuo. The acetylated material was taken up in 10 ml of methylene chloride and washed with water (3 x 7 ml), 2.5 N aqueous hydrochloric acid (10 ml), saturated sodium bicarbonate solution and then water (10 ml). The methylene chloride solution was dried and then concentrated. The residue was de-O-acetylated with triethylamine-methanol and yielded a syrup that soon crystallized. After treatment with deuterium oxide, the crude N-acetylated product was dissolved in deuterium oxide and examined by n.m.r. (100 MHz). The ratio of α-gluco to α-manno isomers was 4:1.

3. Reduction of isopropyl 2-oximino-α-D-arabino-hexopyranoside (56)

a. In water, using 5 % palladium on carbon as catalyst.

Isopropyl 3,4,6-tri-O-acetyl-2-oximino-α-D-arabino-hexopyranoside (29) (367 mg, one mmole) was dissolved in 12 ml of methanol-water (1:1) containing 0.7 ml of triethylamine and let stand for 5 hr, after which it was stirred with 5 ml of washed IR-120 resin (H^+ form) until slightly acidic to pH paper. The resin was removed by vacuum filtration and washed with methanol (3 x 7 ml). The filtrate and washings were combined and concentrated to a syrup which crystallized when placed under vacuum at the pump. The crystalline isopropyl 2-oximino-α-D-arabino-hexopyranoside (56), thus obtained, was transferred with 10 ml of 90 % ethanol to a reaction vessel containing 183 mg of 5 % palladium on carbon under a nitrogen atmosphere. The reaction vessel was placed on the hydrogenator and the contents stirred under a hydrogen atmosphere until hydrogen was no longer absorbed. Uptake was rapid; the one third reduction time was 20 min. A total of 55.8 ml of hydrogen was absorbed during 15.8 hr. After hydrogenation the catalyst was removed by filtration through Celite, the filter cake washed with ethanol (3 x 3 ml) and the filtrate divided into two equal portions. One portion was concentrated *in vacuo* to a syrup. The syrup was treated with deuterium oxide and then analyzed by n.m.r. (100 MHz) as a deuterium oxide solution. Two sets of doublets were present centered at τ5.11 and τ5.23 with spacings of 3.5 Hz and 1.5 Hz, respectively. These were attributed to the H_1 hydrogens of the α-D-glucosaminyl and α-D-mannosaminyl glycosides and had relative intensities of 2:1. At a later date a 10 mg sample of the mixture of 2-amino glycosides was dissolved in 1 ml of trifluoroacetic anhydride-acetonitrile (1:1, v/v). After 10 min the mixture was examined by g.l.p.c. using column D at 250°. After the solvent peaks, two major peaks appeared with retention times of 10.7 min and 11.7 min in the ratio 1:4, respectively.

The second portion of filtrate was acetylated (procedure B) followed by de-O-acetylation with triethylamine in methanol-water. After work-up in the usual manner the N-acetylated residue was treated with deuterium oxide. Examination of the material, as a deuterium oxide solution, by n.m.r. (100 MHz) indicated that the relative amounts of α-gluco to α-manno isomers was 1:4.

b. In 90 % ethanol, containing 4 mmoles of hydrazine, using 5 % palladium on carbon as catalyst.

Isopropyl 3,4,6-tri-O-acetyl-2-oximino-α-D-arabino-hexopyranoside (29) (367 mg, one mmole) was de-O-acetylated as previously described. The de-O-acetylated oximinosugar was transferred to the hydrogenation flask with 10 ml of 90 % ethanol, flushed with nitrogen and 0.235 ml (4 mmoles) of 85 % hydrazine hydrate solution added. After standing for one hr, the reaction flask was placed on the hydrogenator and the solution stirred under an atmosphere of hydrogen until uptake ceased. Uptake was rapid; the one third reduction time was 14 min. A total of 50.3 ml of hydrogen was absorbed during 18 hr. After hydrogenation the catalyst was removed by filtration through Celite and the filter cake washed with ethanol (3 x 3 ml). Concentration of the filtrate yielded 230 mg (88 %) of a syrup that was treated with deuterium oxide and examined by n.m.r. (60 MHz, external TMS). The anomeric signal of the α-D-gluco isomer was observed as a doublet at τ 4.97 with a spacing of 3.7 Hz, but no doublet corresponding to the α-D-manno isomer was present. A sample from a similar run, using only 2 mmoles of hydrazine, was trifluoroacetylated and examined by g.l.p.c. The gas chromatographic analysis indicated that the gluco to manno isomer ratio was 20:1 with less than 7 % of unidentified impurities.

The reduction product was recovered from the n.m.r. tube and acetylated (procedure B) followed by de-O-acetylation as previously described. The crude N-acetate was dissolved in 3 ml of 95 % ethanol and 7 ml of ethyl acetate added. After seeding with authentic isopropyl 2-deoxy-2-acetamido-α-D-glucopyranoside (56) white, silky crystals formed which were collected by vacuum filtration and washed with ethyl acetate to yield 150 mg (58 %) of 56; m.p. 196-197.5°, $[\alpha]_D^{25}$ + 157° (c, 1.3 in water). Lit (28) $[\alpha]_D^{25}$ + 150° (c, 1.3 in water). A mixture m.p. with authentic isopropyl 2-deoxy-2-acetamido-α-D-glucopyranoside (56) of m.p. 194.8-196.2° was undepressed.

c. In water, containing 4 mmoles of hydrazine, using 5 % palladium on carbon as catalyst.

One mmole of isopropyl 2-oximino-α-D-arabino-hexopyranoside (56) was reduced as in the preceding experiment except that 10 ml of water was used as the solvent. The crude product obtained was examined by n.m.r. (100 MHz) which indicated an α-gluco to α-manno isomer ratio of 6.1:1. A sample was trifluoroacetylated and examined by g.l.p.c. The gas chromatographic analysis indicated a gluco to manno isomer ratio that was identical to that found by the n.m.r. analysis.

d. In 90 % ethanol, containing 4 mmoles of triethylamine, using 5 % palladium on carbon as catalyst.

One mmole of isopropyl 2-oximino-α-D-*arabino*-hexopyranoside (56), was dissolved in 10 ml of 90 % ethanol (flushed with nitrogen) containing 0.4 ml (4.0 mmoles) of redistilled triethylamine and 184 mg of 5 % palladium on carbon. The solution was placed under an atmosphere of hydrogen and stirring started immediately. The one third reduction time was 21 min and a total of 35.5 ml of hydrogen was absorbed during 25 hr. After hydrogenation the catalyst was removed by filtration through Celite. The filtrate was concentrated and the residue analyzed by n.m.r. (100 MHz). The α-*gluco* to α-*manno* isomer ratio was 10:1. A sample of the amine mixture was trifluoroacetylated for analysis by g.l.p.c. The gas chromatogram indicated a ratio of α-*gluco* to α-*manno* isomers of 6.15:1 with virtually no impurities.

e. In water, using 5 % rhodium on carbon as catalyst.

One mmole of isopropyl 2-oximino-α-D-*arabino*-hexopyranoside (56) in 10 ml of water containing 184 mg of 5 % rhodium on carbon was hydrogenated in the usual manner. The one third reduction time was 132 min and 49.3 ml of hydrogen was absorbed during 24.6 hr. The crude product, after work-up, was examined by n.m.r. (100 MHz) and an α-*gluco* to α-*manno* isomer ratio of 0.95:1 was indicated. The *N*-acetylated product had an α-*gluco* to α-*manno* isomer ratio of 1.6:1 by n.m.r. (100 MHz). A sample of crude reduction product was trifluoroacetylated and examined by g.l.p.c. which indicated an α-*gluco* to α-*manno* isomer ratio of 1.2:1. It also indicated the presence of impurities (with shorter retention times then the trifluoroacetylated amino glycosides) to the extent of 15 % of the total material present.

BIBLIOGRAPHY

1. P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, Inc., New York, N. Y., 1967, pp. 134-157.
2. W. H. Lycan, S. V. Puatambeker and C. S. Marvel, Org. Syn., Coll. Vol. 2, 318 (1943).
3. N. S. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 751-760.
4. E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., 1965, pp. 112-121.
5. W. Hückel, R. Danneel, A. Gross and H. Naab, Ann. Chem., 502, 99 (1933).
6. G. Drefahl and S. Huneck, Chem. Ber., 93, 1961 (1960).
7. W. Hückel and K. D. Thomas, Ann. Chem., 645, 177 (1961).
8. F. E. King, J. A. Barltrop and R. J. Walley, J. Chem. Soc., 277 (1945).
9. Mm. P. Anziani and R. Cornubert, Bull. Soc. Chim. Fr., 857 (1948).
10. A. Skita, Chem. Ber., 53, 1792 (1920).
11. D. V. Nightingale, J. D. Kerr, J. A. Gallagher and M. Maienthal, J. Org. Chem., 17, 1017 (1952).
12. D. Y. Curtin, R. D. Stolow and W. Maya, J. Amer. Chem. Soc., 81, 3330 (1959).
13. G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, ibid., 75, 422 (1953).
14. J. D. Albright and L. Goldman, ibid., 87, 4214 (1965).
15. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., 1967, pp. 986-989.
16. P. J. Beynon, P. M. Collins, P. T. Doganges and W. G. Overend, J. Chem. Soc., C, 1131 (1966).

17. E. J. Mcdonald, Carbohyd. Res., 5, 106 (1967).

18. W. Sowa and G. H. S. Thomas, Can. J. Chem., 44, 836 (1969).

19. R. U. Lemieux, T. L. Nagabhushan and S. W. Gunner, ibid., 46, 405 (1968).

20. L. Anderson and H. A. Lardy, J. Amer. Chem. Soc., 72, 3141 (1950).

21. T. Posternak, Helv. Chim. Acta, 33, 1597 (1950).

22. E. L. May and E. Mosettig, J. Org. Chem., 14, 1137 (1949).

23. H. Straube-Rieke, H. A. Lardy and L. Anderson, J. Amer. Chem. Soc, 75, 694 (1953).

24. J. S. Brimacombe and M. C. Cook, J. Chem. Soc., 2663 (1964).

25. B. Lindberg and O. Theander, Acta Chem. Scand., 13, 1226 (1959).

26. G. J. F. Chittenden and R. D. Guthrie, J. Chem. Soc., C, 1508 (1966).

27. P. M. Collins and W. G. Overend, ibid., 3448 (1965).

28. R. U. Lemieux and S. W. Gunner, Can. J. Chem., 46, 397 (1968).

29. R. U. Lemieux, S. W. Gunner, Y. Ito and M. E. Evans, Abstrasts, 154 th meeting of the American Chemical Society (Chicago), September 1967, D-18.

30. R. U. Lemieux and T. L. Nagabhushan, Can. J. Chem., 46, 401 (1968).

31. R. U. Lemieux, R. Suemitsu and S. W. Gunner, ibid., 46, 1040 (1968).

32. P. J. Newstaedter in "Steroid Reactions," C. D. Djerassi, Ed., Holden-Day, Inc., San Francisco, California, 1963, pp. 135-143.

33. O. R. Vail and D. M. S. Wheeler, J. Org. Chem., 27, 3803 (1962).

34. H. Kwart and T. Takeshita, J. Amer. Chem. Soc., 84, 2833 (1962).

35. H. O. House, H. Babad, R. B. Toothill and A. W. Noltes, J. Org. Chem., 27, 4141 (1962).

36. W. G. Dauben, G. J. Fonken and D. S. Noyce, J. Amer. Chem. Soc., 78, 2579 (1956).

37. M. G. Combe and H. B. Henbest, Tetrahedron Lett., 404 (1961).

38. N. A. LeBel and R. F. Czaja, J. Org, Chem., 26, 4768 (1961).

39. H. Haubenstock and E. L. Eliel, J. Amer. Chem. Soc., 84, 2368 (1962).

40. E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, Inc., New York, N. Y., 1962, pp.-237.

41. C. L. Stevens, R. F. Glinski and K. G. Taylor, J. Org. Chem., 33, 1586 (1968).

42. R. U. Lemieux and T. L. Nagabhushan, Unpublished observations.

43. See reference 40, P. 207.

44. R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, J. Amer. Chem. Soc., 80, 6098 (1958); R. U. Lemieux, R. K. Kullnig and R. Y. Moir, ibid., 80, 2237 (1958).

45. A. C. Huitric, J. B. Carr, W. F. Trager and B. J. Nist, Tetrahedron, 2145 (1963); M. Karplus, J. Amer. Chem. Soc., 85, 2870 (1963).

46. J. Allinger and N. L. Allinger, Tetrahedron, 2, 64 (1958).

47. For an excellent review see A. S. Kende in "Organic Reactions," A. C. Cope, Ed., 11 (1960), p. 261.

48. J. Favorskii, J. Russ, Phys. Chem. Soc., 26, 559 (1894); J. Prakt. Chem. 51, 533 (1895).

49. W. M. Jones, T. G. Squires and Merrill Lynn, J. Amer. Chem. Soc., 89. 318 (1967).

50. A. Bowers, E. Denot, R. Urquiza and L. M. Sanchez-Hidalgo, Tetrahedron, 8, 116 (1960).

51. A. Fürst and P. A. Plattner, Abstr. Papers, 12th Intern. Congress Pure and Appl. Chem., New York, N. Y., 1951, p. 409. See also E. L. Eliel in "Steric Effects in Organic Chemistry," M. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 130-134.

52. A. B. Devine and R. E. Lack, J. Chem., Soc., C, 1902 (1966).

53. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc., 39 (1946); P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch and G. W. Wood, ibid., 2402 (1951); A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, ibid., 2548 (1953).

54. C. Djerassi, E. J. Warawa, R. E. Wolff and E. J. Eisenbraun, J. Org. Chem., 25, 917 (1960).

55. L. Schmerling, J. Amer. Chem. Soc., 69, 1121 (1947).

56. E. D. M. Eades, D. H. Ball and L. Long, Jr., J. Org. Chem., 30, 3949 (1965).

57. A. Nickon, M. A. Castle, R. Harada, C. E. Berkoff and R. O. Williams, J. Amer. Chem. Soc., 85, 2185 (1963).

58. J. A. Pople, W. G. Schneider and H. J. Bernstein "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Company, Inc., New York, N. Y. 1959, pp. 176-183.

59. W. F. Trager and A. C. Huitaic, Tetrahedron Lett., 825 (1966).

60. G. Janzsó, F. Kállay and I. Koczor, Tetrahedron, 23, 3699 (1967).

61. A. Daniel and A. A. Pavia, Tetrahedron Lett., 1145 (1967).

62. R. U. Lemieux and J. D. Stevens, Can. J. Chem., 44, 249 (1966); 43, 2059 (1965).

63. R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, Inc., New York, N. Y., 1965, p. 12.

64. E. Breitner, E. Roginski and P. N. Rylander, J. Chem. Soc., 2918 (1959).

65. E. Baer, J. Maurukas and M. Russell, J. Amer. Chem. Soc., 74, 152 (1952); C. G. Overberger and M. Lapkin, ibid., 77, 4651 (1955); G. Wilbert and P. Sosis, U. S. Patent 3,028,429, Apr. 3, 1962; W. H. Hartung and Y. T. Chang, J. Amer. Chem. Soc., 74, 5927 (1952).

66. See reference 1, p. 9.

67. M. Freifelder, W. D. Smart and G. R. Stone, J. Org. Chem., 27, 2209 (1962).

68. D. H. R. Barton, R. E. O'Brien and S. Sternhell, J. Chem. Soc., 470 (1962).

69. J. H. Biel, A. E. Drukker, T. F. Mitchell, E. P. Sprengeler, P. A. Nuhfer, A. C. Conway and A. J. Horita, J. Amer. Chem. Soc., 81, 2805 (1959).

70. D. Y. Curtin and T. C. Miller, J. Org. Chem., 25, 885 (1960).

71. H. Metzger, Chem. Abst., 60, 14407 b, Ger. Patent 1,162,359, Feb. 6, 1964.

72. A. W. Burgstahler and I. C. Nordin, J. Amer. Chem. Soc., 83, 198 (1961).

73. C. H. DePuy and P. R. Story, ibid., 82, 627 (1960).

74. S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, J. Amer. Chem. Soc., 75, 147 (1953).

75. A. S. Hussey and R. H. Baker, J. Org. Chem., 25, 1434 (1960).

76. W. Hückel and K. Heyder, Chem. Ber., 96, 220 (1963).

77. E. J. Bourne, S. H. Henry, C. E. M. Tatlow and J. C. Tatlow, J. Chem. Soc., 4014 (1952).

78. K. Hofmann, A. Lindenmann, M. Z. Magee and N. H. Khan, J. Amer. Chem. Soc., 74, 470 (1952).

79. P. P. T. Sah, Rec. Trav. Chem., 59, 1036 (1940).

80. J. Sicher, F. Sipos and M. Tichy', Chem. Abstr., 55, 16446 (1961); Collect. Czech. Chem. Commun., 26, 845 (1961).

81. R. J. Bridgewater and C. W. Shoppee, J. Chem. Soc., 1709 (1953).

82. R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 60.

83. See reference 82, pp. 218-219.