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SYNTHESIS AND ATTEMPTED RESOLUTION
OF
4-HYDROXYMETHYLCYCLOHEXANONE OXIME

BY

CANAN AVUNDUK BONNICE

B. S., American College for Girls
Istanbul, Turkey, 1962

A THESIS

Submitted to the University of New Hampshire
In Partial Fulfillment of
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Doctor of Philosophy

Graduate School
Department of Chemistry
June, 1967

This thesis has been examined and approved.

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May 22, 1967

Date

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She wishes to dedicate this thesis to her husband and to her parents.

Carolee Ann Bonaire

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INTRODUCTION

To show optical activity a molecule should be able to exist in two isomeric forms related as non-superimposable mirror images. This fundamental criterion has subsequently been delineated by three stereochemical symmetry conditions.^{1,2} To have optical rotatory power the molecule must be devoid of a center of inversion, a plane of symmetry, and an alternating rotation-reflection axis of symmetry.

Compounds exhibiting optical activity may be divided into two classes,³ those having at least one asymmetric atom and those in which asymmetry is due to the special arrangement of the atoms in the molecule as a whole. In the latter case, the lack of symmetry and three dimensional structure are caused by the restricted rotation about single bonds as in appropriately substituted biphenyls⁴ and arylamines,⁵ to fixing of a configuration by small rings as in allenes^{6,7} and cyclohexylidene⁸ derivatives and spiranes.^{9,10} All of these compounds possess a rotatory power because they satisfy the fundamental stereochemical requirement for optical activity, namely they are devoid of the above mentioned symmetry elements.

The two benzene rings of biphenyls are free to rotate about the single pivot bond. However, when this rotation is obstructed by steric hindrance between bulky ortho substituents, the two benzene rings cannot be coplanar. Dipole moment and X-ray diffraction data have shown that these benzene rings are coaxial¹¹ as shown in Figure 1.

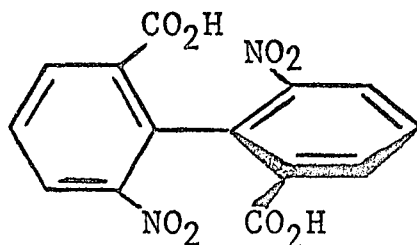


Fig. 1. o,o'-dinitrodiphenic acid

In this shape the molecule does not possess any symmetry elements; it is not superimposable on its mirror image and is therefore optically active.

Similarly, in a molecule of allene (Figure 2) the two planes that contain the terminal methylene (CH_2) groups are mutually perpendicular because of the rigidity and directional character of the two cumulative double bonds as seen in Figure 2.

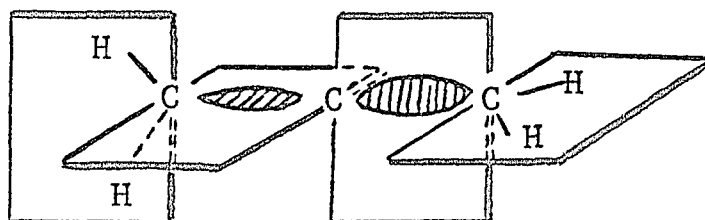
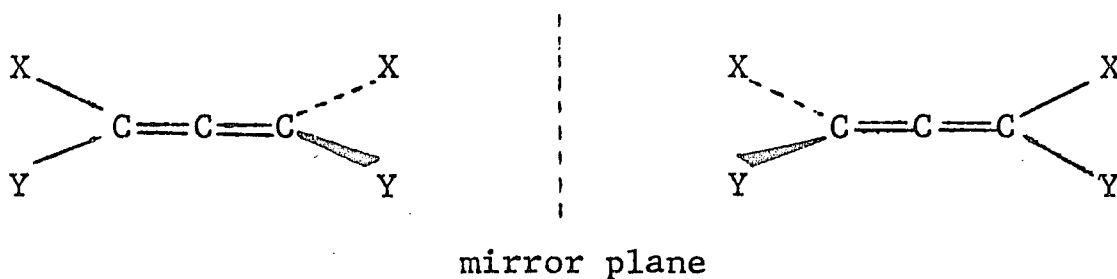


Fig. 2. Geometry of an allene

Consequently, an allene of the type $\text{XYC}=\text{C}=\text{CXY}$, in which X and Y are different, is asymmetric and can exist in two, non-superimposable, optically active forms.



Molecules not far different from allenes in their general structure may be illustrated by 4-methylcyclohexylidene acetic acid (Figure 3). In this molecule one of the double bonds of the allene structure has been replaced by a six-membered ring. The methyl and the hydrogen on carbon atom 4 lie in a plane perpendicular to the plane containing the carboxyl group and the adjacent hydrogen. The molecule has none of the elements of symmetry and is non-superimposable on its mirror image.

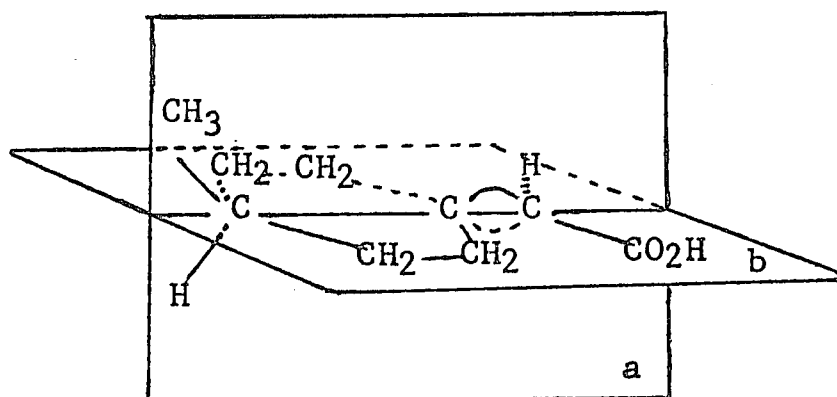


Fig. 3. 4-Methylcyclohexylidene acetic acid

When both of the double bonds of an allene are replaced by rings, a bicyclic ring system is obtained in which the two rings have one atom in common. The two rings of the spiranes cannot lie in a common plane; hence, provided that each ring is substituted so that it has no plane of symmetry, the substance can exist as one or the other of a pair of optically active enantiomers (Figure 4).

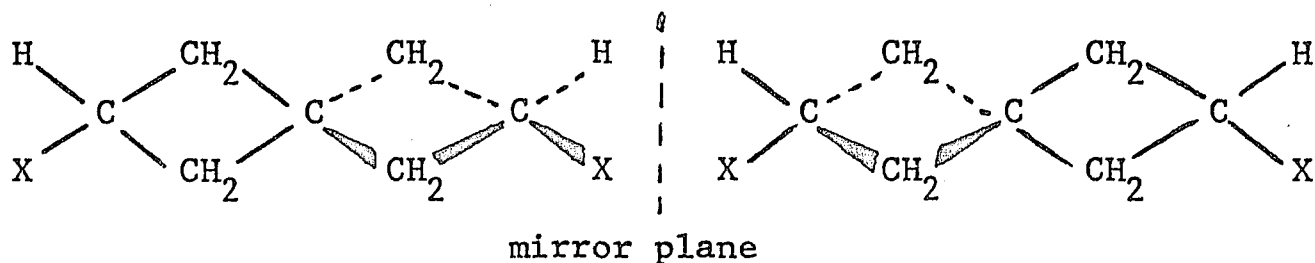


Fig. 4. An optically active spirane

A large number of molecularly asymmetric, optically active compounds such as biphenyls have been resolved into their enantiomers. Such resolution in the case of allenes^{6,7} and alkylidenecycloalkanes⁸ has been more difficult. Mills and co-workers resolved a number of doubly bonded nitrogen derivatives: oxime, semicarbazone and phenylbenzoylhydrazone of 1-cyclohexanone-4-carboxylic acid^{12,13,14,15} shown in Figure 5. Although ordinarily the syn and anti-isomers of oximes are not readily interconvertible, the above compounds showed low optical stability and racemized on standing due to the presence of the carboxyl group in the molecules.¹⁶

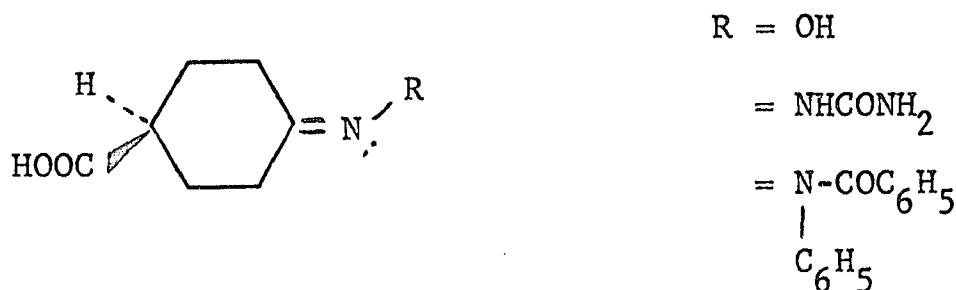


Fig. 5. Oxime, semicarbazone and phenylbenzoylhydrazone of 4-carboxycyclohexanone

In this dissertation, the study of a compound, 4-hydroxymethylcyclohexanone oxime, similar to those prepared by Mills and co-workers,¹⁰ is described. Geometrically, this molecularly asymmetric molecule is analogous to 4-methylcyclohexylidene acetic acid and hence it should also be

optically active. That the free pair of electrons on nitrogen is capable of holding the configuration sufficiently long to permit resolution has been shown for a number of oximes which shows that plane a is not a symmetry plane (Figure 6).

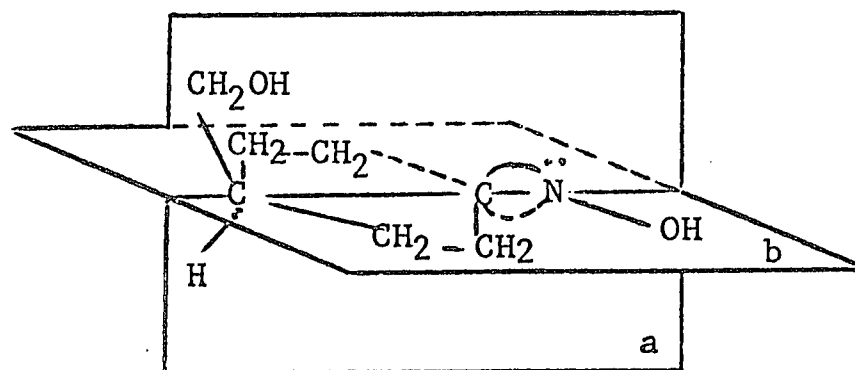
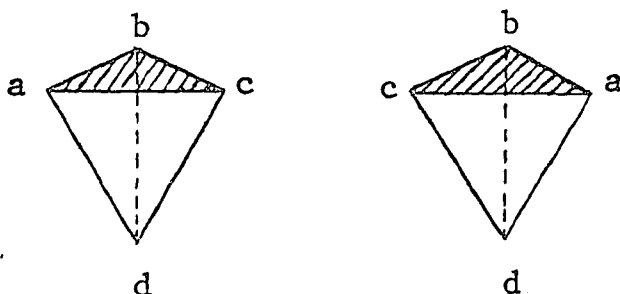


Fig. 6. 4-Hydroxymethylcyclohexanone Oxime

Lacking the acidic properties and the ease of enolization of the carboxyl group in the 4-carboxycyclohexanone oxime, 4-hydroxymethylcyclohexanone oxime is expected to possess a higher optical stability. Thus it was expected to be a better system for the study of the resolution and optical stability as well as for the determination of the absolute configuration of one of these molecularly asymmetric molecules.

HISTORICAL BACKGROUND

The concept of the tetrahedral carbon atom was deduced independently by van't Hoff and Le Bel, in 1874.¹⁷ Le Bel impressed by the correlation suggested by Pasteur¹⁷ between the rotatory power of the tartrates and the hemihedral character of the crystals, saw that molecular asymmetry could exist if four different groups are joined to a non-planar carbon atom. van't Hoff proposed the tetrahedral arrangement as an explanation for the existence of optical isomers of the formula C_{abcd} . The two forms, which are optical opposites or mirror image isomers, are not superimposable on each other.



As studies on optical activity developed, it was noticed that other molecules which did not bear an asymmetric carbon atom also rotated the plane of polarized light. In these molecules the optical activity was found to be a function of their peculiar dissymmetric geometry as in the case of biphenyls with bulky ortho substituents that could not exist in planar form due to restriction of rotation about single bonds.

Another prediction made by van't Hoff^{16,18} in 1874 was that unsymmetrically substituted allenes should exist in two enantiomeric forms and thus should be resolvable. The reason for the dissymmetry is that the groups a and b at one end of the system lie in a plane at right angles to those at the other end.

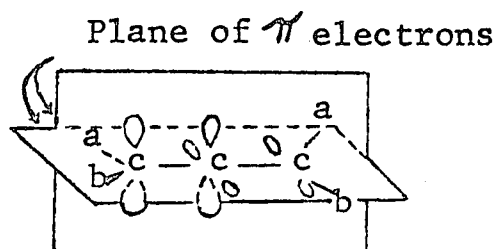
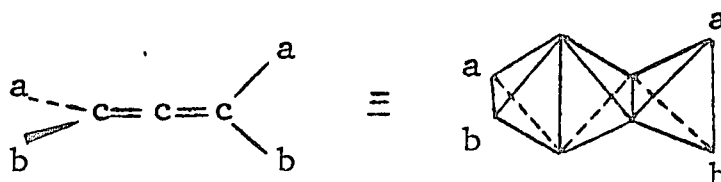


Fig. 7. Geometrical representations of a dissymmetric allene.

If the double bonded carbon atoms are viewed as tetrahedra joined edge to edge, a view originally proposed by van't Hoff and reaffirmed in slightly modified form by Pauling,¹⁹ the non-coplanarity of the two sets of groups follows from the geometry of the system. Alternatively, if the double bond is viewed as being made up of pairs of sigma and pi electrons, quantum-mechanical considerations indicate that the two planes of the pi bonds attached to the central carbon atom must be orthogonal and since the a and b groups attached to the trigonal carbon lie in a plane at right angles to the plane of the adjacent pi bond, their planes are orthogonal to each other, as shown in Figure 7.

Examination of models in Figure 8 where the doubly bonded carbon atoms are viewed as tetrahedra joined edge to edge shows that these molecules do not possess a plane of symmetry and they are non-superimposable mirror images.

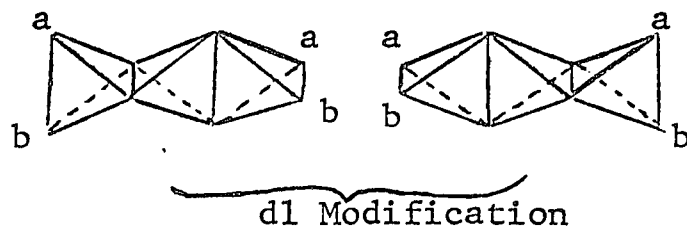
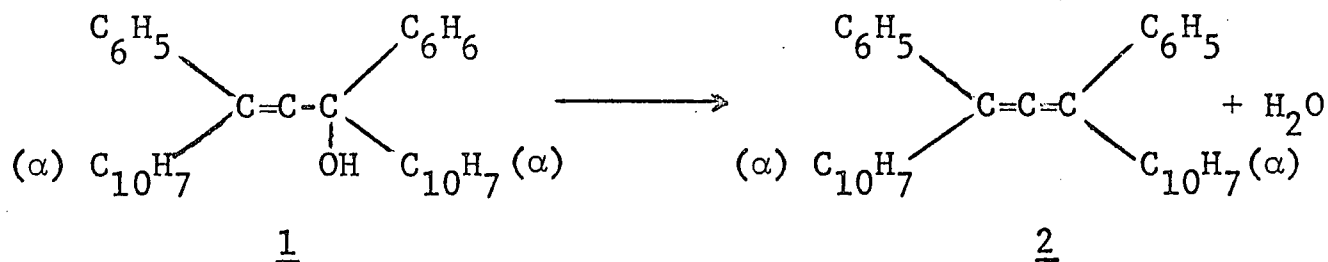
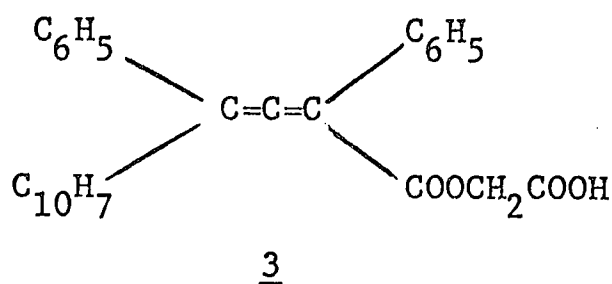


Fig. 8. Mirror image forms of an allene

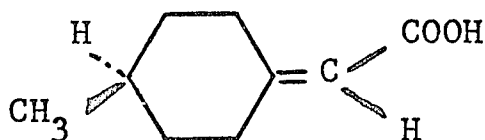
van't Hoff's prediction was experimentally realized sixty years later. In 1935 Mills and Maitland⁶ accomplished a catalytic asymmetric dehydration of the alcohol 1 by means of the optically active camphorsulfonic acids. In this way, 1,3-diphenyl-1,3-di- α -naphthylallene 2 was obtained in both levo- and dextrorotatory forms.



Kohler, Walker and Tishler⁷ completed the first actual resolution of the racemic form of an allene, namely the glycolic ester of diphenylnaphthylallene-carboxylic acid 3 by crystallization of the brucine salt.



In 1909, Perkin, Pope and Wallach⁸ resolved an alkylidenecycloalkane, 4-methylcyclohexylidene acetic acid 4. This was the first molecule to be resolved which did not contain an asymmetric atom.

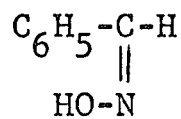


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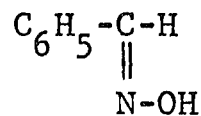
Its optical activity is due to the same cause as that of allenes. The groups attached to the double bond extend in a plane at right angles to that defined by the groups attached at the 4-position of the ring. As a result, even when the ring is considered for stereochemical purposes in its average planar form, the molecule does not contain any elements of symmetry and thus it is asymmetric.

In this respect it is different from the simplest dissymmetric compounds of the allene type, e.g. Figure 7, which are relatively symmetrical since they possess an axis of two-fold symmetry similar to that of a two-bladed propeller in which the forward edges of the blades are unlike the backward edges. These allenes are therefore dissymmetric without being asymmetric.

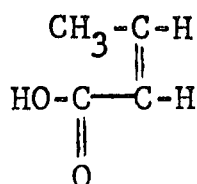
In 1890, Hantzsch and Werner²⁰ proposed that the three bonds of double linked nitrogen do not lie in a plane and can therefore give rise to isomerism just as in the case of ethylenes.



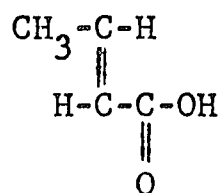
and



Benzaldoxime

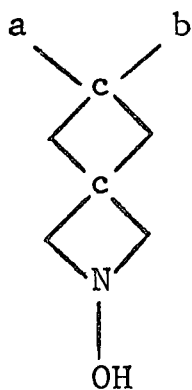
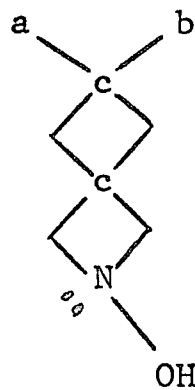


and



Crotonic acid

To test this idea, Mills and Bain¹² decided to synthesize a compound which could have either configuration 5 or 6.

56

A molecule of configuration 5 is superimposable on its mirror image, while one of configuration 6 is not. As shown in Figure 9, a substance of configuration 6 is closely analogous to allene derivatives of the type:

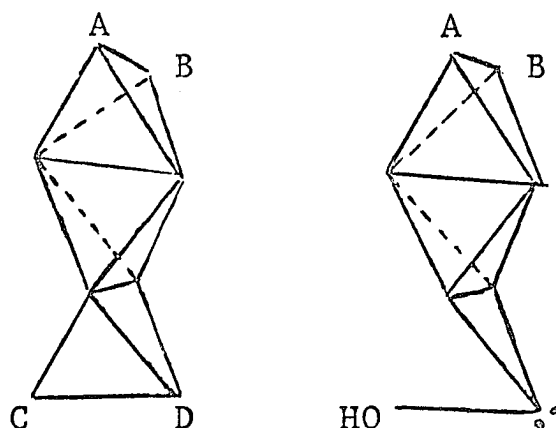
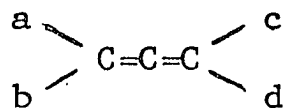


Fig. 9. Geometric relationship of an allene to a keteneoxime.

Since the preparation and manipulation of a compound of this type would be more difficult than that of allenes which had resisted resolution due to isomerization to the symmetrical alkyne derivatives, Mills and Bain¹² expanded the "two membered" ethylene ring into the hexamethylene ring. An oxime of a 4-substituted cyclohexanone bears the same relationship to ketene oxime (6) as the 4-methylcyclohexylideneacetic acid (4) bears to the corresponding allene.¹²

Mills and Bain¹² proposed that if the "valencies" of the nitrogen atom in the oximino group are not in one plane, the oxime of such a ketone must consist of an equimolecular mixture of two enantiomorphous forms as seen in Figure 10.

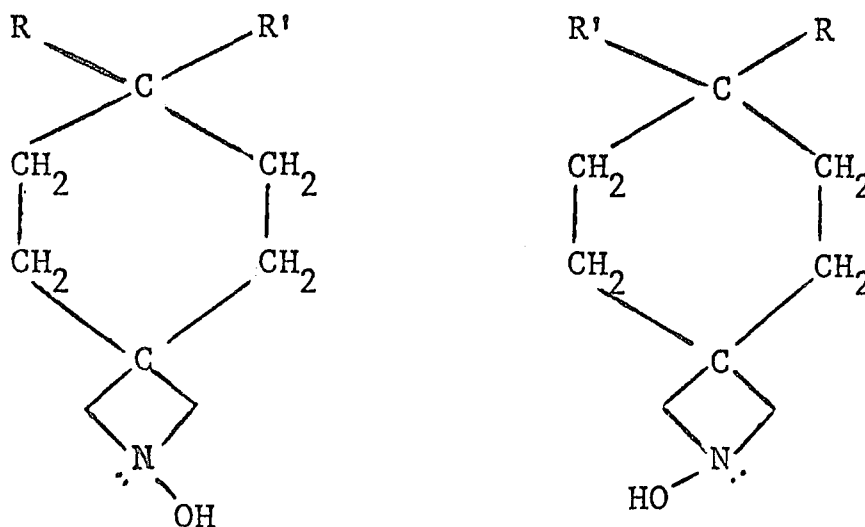
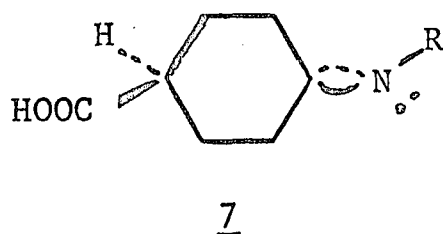


Fig. 10. Enantiomeric forms of 4,4-disubstituted cyclohexanone oxime.

For this study they employed the oxime 7a and succeeded in separating it into its two enantiomers. Mills and Bain¹³ further resolved the semicarbazone 7b and the phenylbenzoylhydrazone 7c of the same acid.



R = OH (a)

= NHCONH₂ (b)

= N-COC₆H₅
|
C₆H₅ (c)

The ketones from which these compounds are derived possess a plane of symmetry, perpendicular to the plane of the ring as in Figure 11. This plane of symmetry is destroyed by the non-planar configuration of the =N-R group where R may be -OH, -NH·CO·NH₂, -NRR', etc.

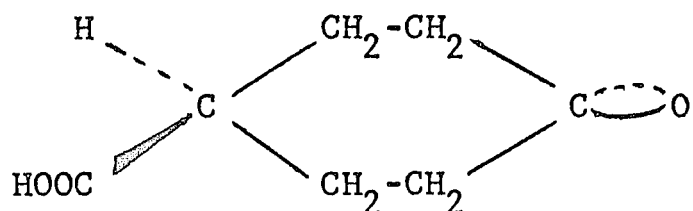
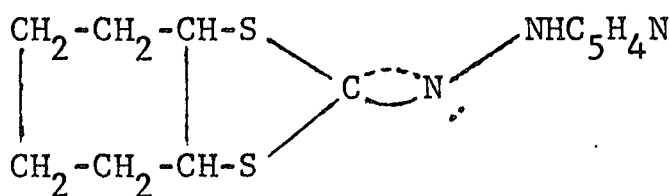
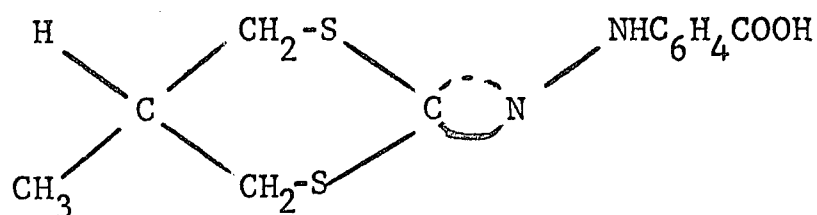


Fig. 11. 4-Carboxycyclohexanone

The compound 8 was prepared by Mills and Schindler¹⁴ in order to avoid the risk that the double bond in 7a, b, c might have migrated into the ring $[-\overset{|}{\text{C}}\text{H}-\overset{|}{\text{C}}=\text{NR} \rightarrow -\overset{|}{\text{C}}=\overset{|}{\text{C}}-\text{NHR}]$, in which case the carbon atom carrying the carboxyl group would become asymmetric. The compound 9 was prepared¹⁵ in order to eliminate the risk that the dissymmetry of 8 might depend on the buckling of the ring, giving rise to a possible cis-trans isomerism comparable to that of decalones. This latter concept was borne out by the establishment of the mechanistic pathway leading to 8 which showed that the compound actually resolved possessed the trans ring geometry rather than the cis fusion necessary for this special type of molecular dissymmetry.

8

Pyridylhydrazone of cyclohexylidenedithiocarbonate

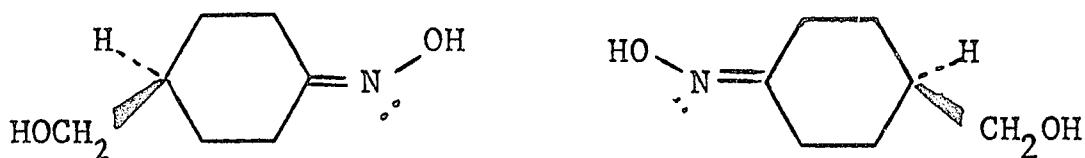
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o-Carboxyphenylhydrazone of methyltrimethylene
dithiocarbonate 9

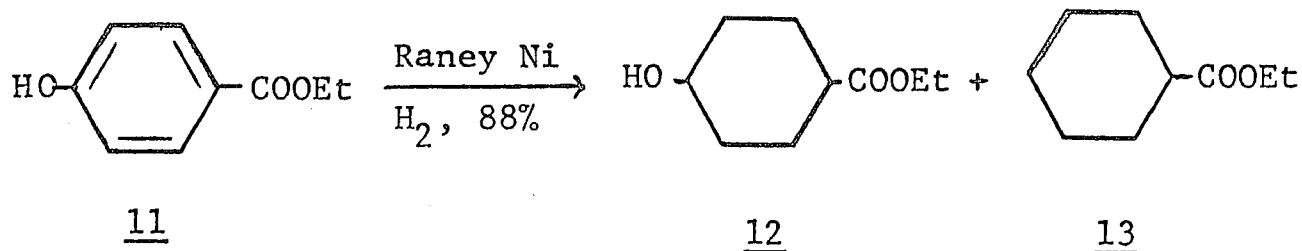
The optical activity of the oxime 7a was not very stable, and only one salt was obtained when it was resolved with an alkaloid but both enantiomers could be prepared by using different alkaloids. The ammonium salt of the acid 7a racemized to the extent of 50 per cent in 13 minutes, but in the presence of half equivalent of ammonia this half life occupied 8.5 hours. The same trend was observed with the sodium salt in the presence of excess sodium hydroxide. The racemization was, therefore, checked by the addition of alkalis and perhaps proceeded through the enolization of the free acid.

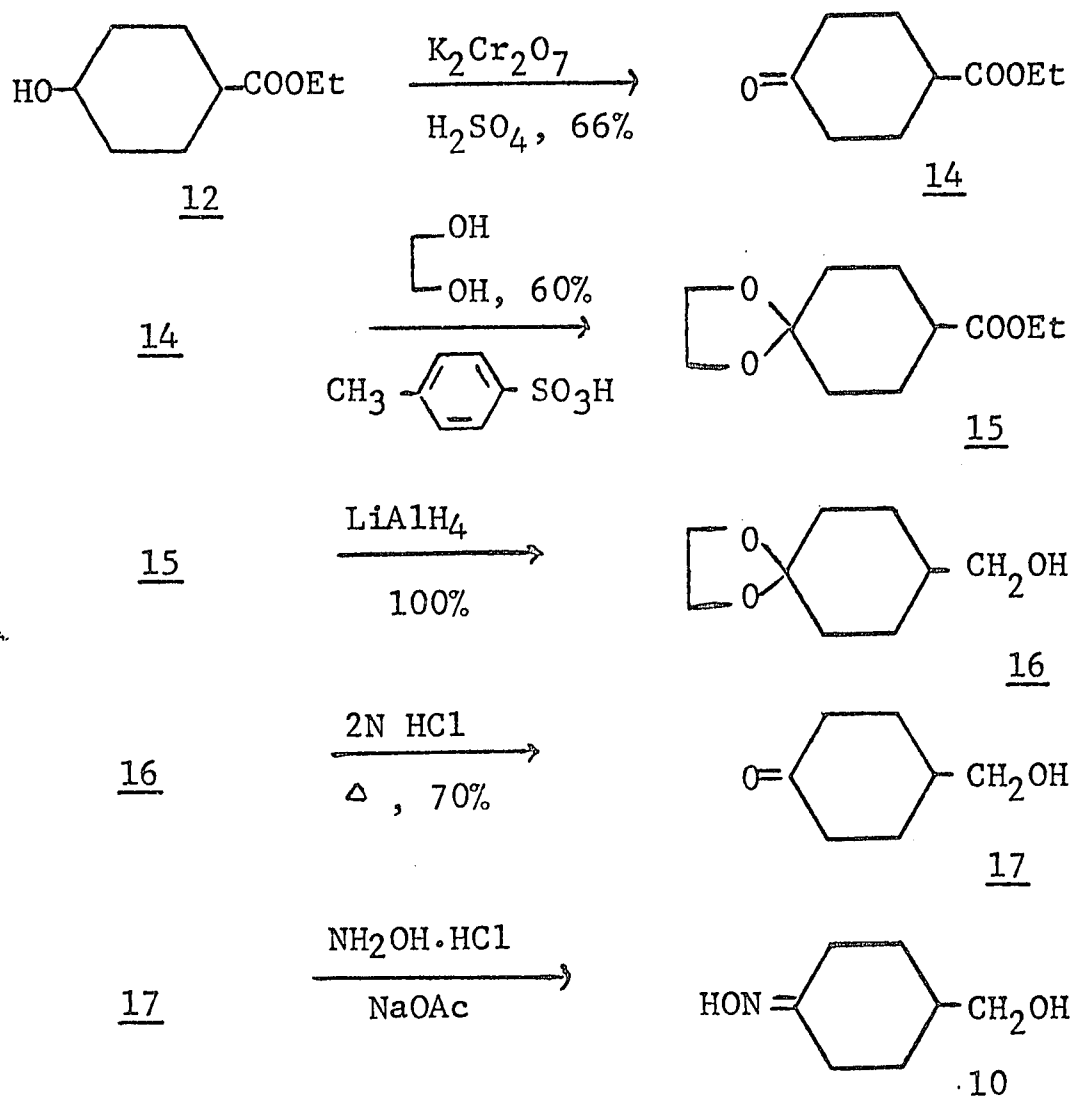
DISCUSSION

The purpose of this project has been the synthesis and resolution of a cyclic oxime which possesses no asymmetric carbon atom and is of the type reported by Mills and Bain.¹² The compound of choice was 4-hydroxymethylcyclohexanone oxime (10) a very similarly constituted molecule to 4-carboxycyclohexanone oxime (7a) studied previously.¹² Since the presence of the carboxyl group in 7a decreased its optical stability, it was replaced by the hydroxymethyl group which would not permit enolization but would serve as a handle for resolution.

10Synthesis of 4-Hydroxymethylcyclohexanone Oxime

The synthesis of 4-hydroxymethylcyclohexanone oxime has been attempted previously by Lyle and Barrera²² using the following scheme:





This pathway was abandoned mainly due to the persistent, extremely disagreeable smell of ethyl cyclohexane carboxylate (13) which results from hydrogenolysis during the reduction of ethyl *p*-hydroxybenzoate with Raney nickel. Other methods of reduction were less favorable. Catalytic hydrogenation with PtO_2 in acetic acid yielded 50% of ethyl cyclohexanecarboxylate along with 35% of the desired ester and no reduction was observed using Li with ethylene diamine.

Another unattractive aspect of this route was the resistance of the ketal 14 to hydrolysis. Various attempts using acetic acid met with failure. However, boiling with 2N HCl regenerated the desired ketone.

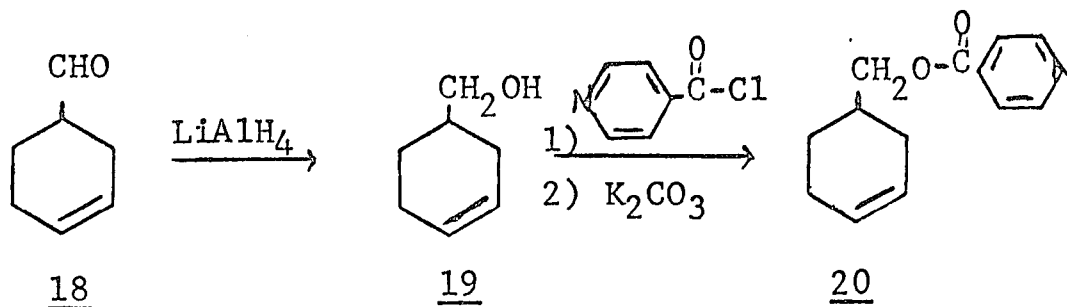
The yield of the oxime 10 from the ketone 17 was also low. The presence of two functional groups, namely the carbonyl and the hydroxyl in the ketone 17, the oximino and the hydroxyl group in the oxime 10, made these molecules of relatively low molecular weight extremely water soluble. This complicated their isolation from aqueous reaction mixtures. The problem was encountered also in the following schemes in the current investigation and constituted one of the main factors for low yields and difficulty in purification of reaction products.

Protecting the hydroxyl group in the 4-hydroxymethyl cyclohexanone 17 with an ester function would decrease the reaction of this functional group and increase the molecular weight of this small molecule. The resulting larger molecule should then be less water soluble and by virtue of its larger molecular weight its oxime derivative should be more crystalline, thus easier to purify.

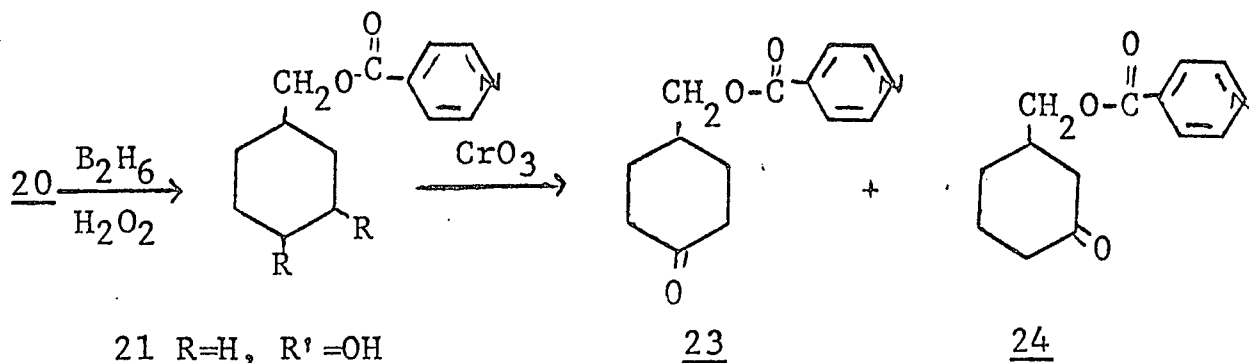
An ester function with a basic nitrogen in its structure was most desirable. Besides protecting the hydroxyl group, this group could form quaternary ammonium salts with acids. This would provide a powerful tool in the isolation of the desired products as solids from the reaction mixtures and would assist in the resolution of the molecularly dissymmetric oxime 10 by the formation of diastereomeric salts with an optically active acid.

Synthesis of 4-Hydroxymethylcyclohexanone oxime (10)
via 3-Cyclohexenylmethyl isonicotinate

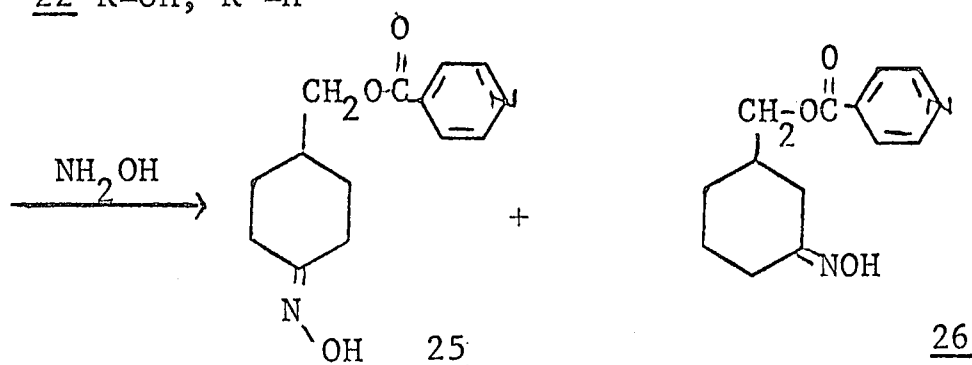
The synthesis outlined below involves the preparation of the isonicotinyl ester of 3-cyclohexenemethanol (19) from which the isonicotinate of 4-hydroxymethylcyclohexene (20) could be prepared.



Hydroboration of 20 followed by oxidation of the borate complex with hydrogen peroxide in basic medium was expected to lead to a mixture of alcohols 21 and 22 which on chromic acid oxidation should give the corresponding ketones 23 and 24.



22 R=OH, R' =H



The corresponding oximes (25 and 26) would then be prepared upon reaction with hydroxyl amine and separated with fractional crystallization or chromatography. With the basic nitrogen on the isonicotinyl group the (\pm)-isonicotinyl ester of 4-hydroxymethylcyclohexanone oxime will form a salt which should be separable into diastereomers by an optically pure acid such as (-)-methoxytartaric acid by fractional crystallization. Hydrolysis would then yield the desired optically pure 4-hydroxymethylcyclohexanone oxime (10).

The reduction of 3-cyclohexenecarboxaldehyde was carried out using a modification of Wilcox's procedure.²³ When a 27.5 g sample of I was subjected to lithium aluminum hydride reduction using anhydrous ether as solvent, a 75.5% yield of 19 was obtained. The infrared spectrum of 19 was superimposable with that of a previous preparation of 19.²⁴ The melting point of the p-nitrobenzoate of the previous preparation of 19 was compared with the melting point of p-nitrobenzoate of 3-cyclohexene-1-methanol obtained by Wilcox and Chibber²³ from lithium aluminum hydride reduction of ethyl 3-cyclohexenecarboxylate. The comparison was favorable and an attempt was made to prepare the isonicotinyl ester.

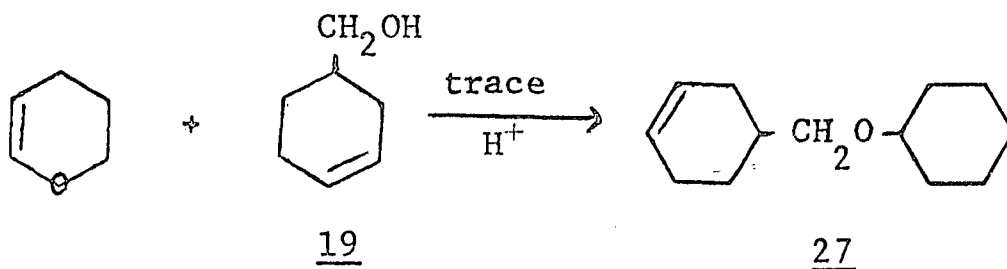
The isonicotinyl chloride was prepared using a procedure suggested by Dr. R. E. Lyle. Since the acid chloride is easily hydrolyzable it was not taken out of the reaction flask for further purification and calculation of its percentage yield. The excess thionyl chloride was removed by reduced pressure distillation over a steam bath.

The reaction of the alcohol 19 with the isonicotinyl chloride with subsequent vacuum distillation did not give a very good yield of ester. After removal of the pyridine

which was present in the esterification reaction mixture to neutralize the hydrogen chloride evolved, the ester was converted to the hydrochloride salt.

The double bond in the cyclohexene ring of 20 was then subjected to hydroboration. Oxidation with hydrogen peroxide in alkaline medium of the alkylborane should produce the two alcohols 21 and 22. Previous experiments, however, had shown that isonicotinyl esters were readily hydrolyzed during this reaction producing no identifiable products.^{24,25} This protecting group was, therefore, considered to be impractical and an alternative group was sought.

Attempted Synthesis of Oxime 10 via the Tetrahydropyranyl ether of 3-cyclohexene-1-methanol. The ester group being prone to hydrolysis was shown above to be unfavorable as a protecting group on the alcoholic function of 3-cyclohexene-1-methanol. A more stable protecting group that would withstand the alkaline hydrogen peroxide oxidation of the alkylborane produced in the hydroboration was necessary. Formation of an ether with the alcohol group in 3-cyclohexene-1-methanol appeared attractive. 2,3-Dihydropyran was chosen for this purpose due to the stability of the tetrahydropyranyl ethers to base and oxidation.²⁶ The ether was easy to make but its purification was complicated with excessive foaming during distillation. Anti-foaming agents were found to be of little assistance.

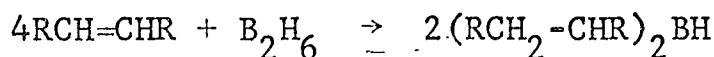


The ether 27 was subjected to hydroboration followed by oxidation with alkaline hydrogen peroxide following Brown's procedure.²⁷ After the removal of the solvent, the reaction mixture was subjected to fractional distillation which was not very successful due to excessive foaming, an unavoidable use of high temperatures even under reduced pressure, the solid or glassy-like state of the liquid, and the presence of many products with very close boiling points. The distillation was repeated three times.

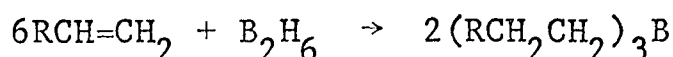
The infrared spectra of various fractions from the distillation contained strong $-OH$ bands. On comparison of the I. R. spectra of the lower boiling fractions with the spectrum of 19, it was concluded that cleavage had occurred at the ether linkage during the course of the hydroboration yielding the starting alcohol 19. The proportion of this product in relation to the total yield was quite high. The higher boiling fractions were analyzed with vapor phase chromatography. The presence of ten substances was indicated and the peaks could not be separated distinctly from each other with the available columns.

An explanation for these results can be offered by a closer look at the reaction conditions and the stereochemistry of the substances involved.

The procedure used for the hydroboration was taken from a reaction involving 1-decene as the olefin which is unhindered and thus relatively reactive. Cyclohexenes are less reactive and usually go only to the dialkyl boron stage unlike unhindered olefins which proceed to the trialkylborane stage.²⁸



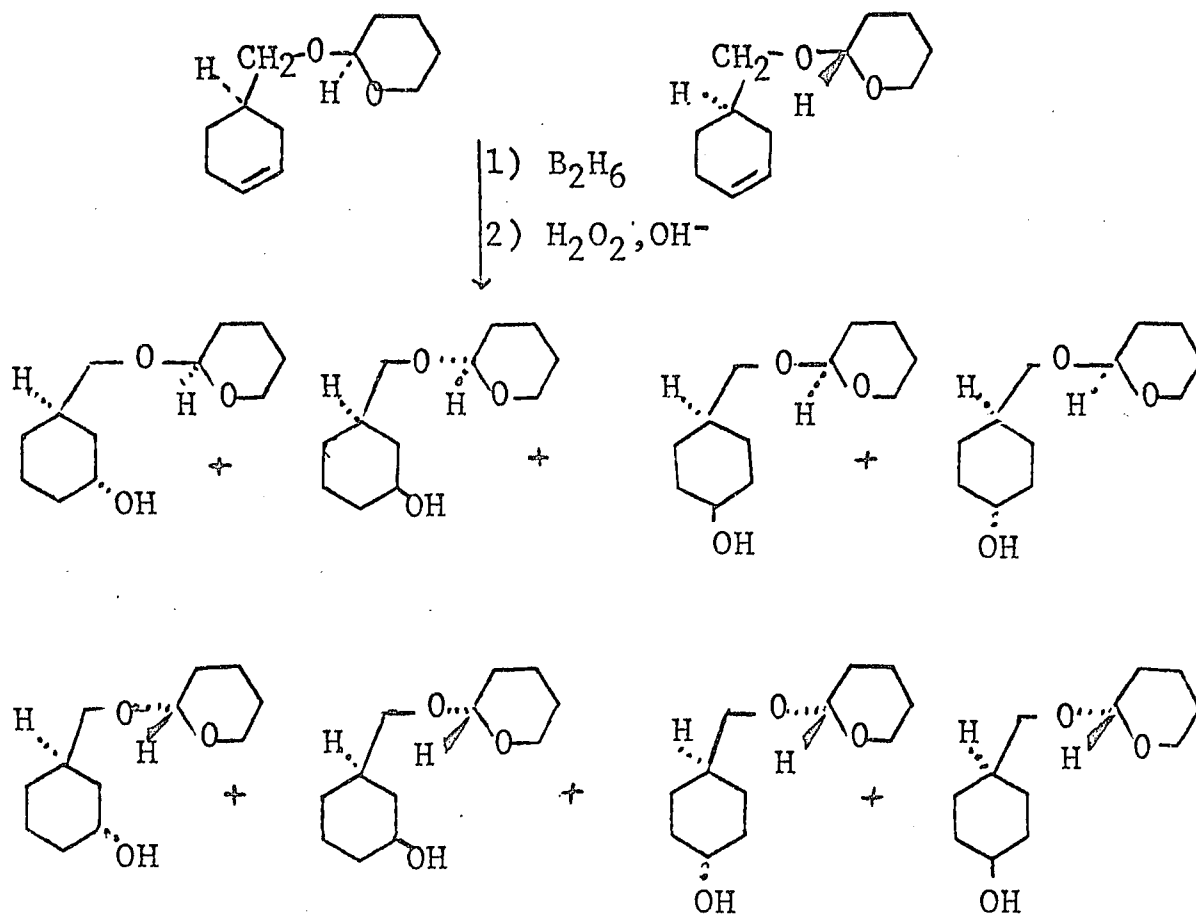
versus



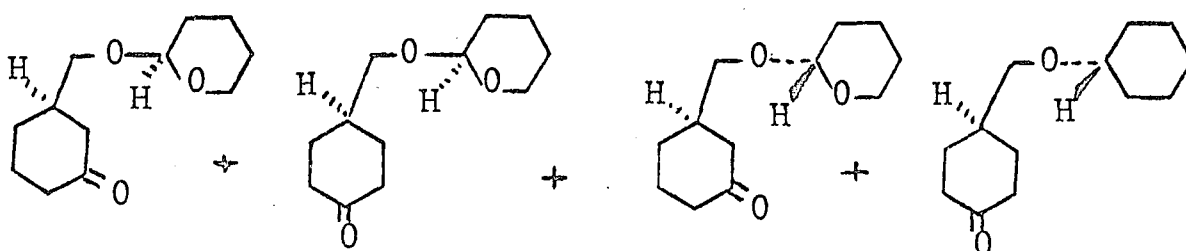
When the olefin used is hindered, 4 moles of the olefin react with a mole of diborane producing two moles of dialkylborane. However, when the olefin is unhindered, six moles of the olefin take up one mole of diborane giving two moles of the trialkylborane. On this basis it is possible that the diborane generated in our reaction may not have been sufficient to react with all of the olefin present.

Tetrahydropyranyl ethers are stable to base, oxidation and Grignard reagents but they can be easily removed by acid hydrolysis or reduction. Since no acid was used in this hydroboration, diborane must have also caused the reduction of this sensitive ether linkage.

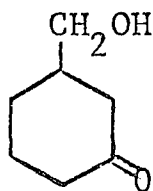
Because the presence of the ten products indicated by gas chromatography could not be explained by the data present, the purity of the starting materials was questioned. The vapor phase chromatogram of the tetrahydropyranyl ether showed two peaks of equal intensity. When the starting alcohol 19, which was used in the esterification, was introduced into the sample tested by gas chromatography, the



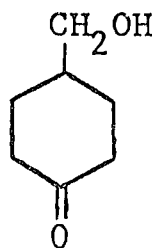
Since the structures of these isomers are similar, their physical properties will also be similar, thus making their separation almost impossible with the available techniques. Simplification of this problem, after obtaining the high boiling fraction from the distillation of the hydroboration mixture, may be effected by oxidizing the mixture under mild conditions which will not cause the cleavage of the ether group. Oppenauer conditions for oxidation should be mild and lead to a mixture of four ketones:



These then could be hydrolyzed to the two corresponding hydroxy ketones.

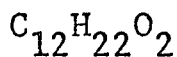
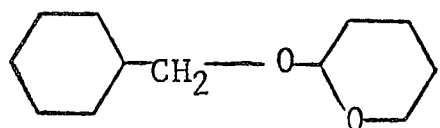


28

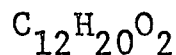
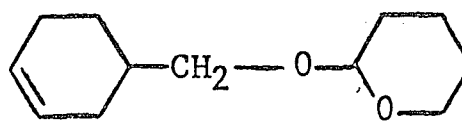


17

However, the extensive cleavage of the tetrahydropyranyl group and the low yield, the hard to handle very viscous almost glassy state of the higher boiling portion which could contain the desired products made this route undesirable. At this point elemental analysis of the dihydropyranyl ether (27) of 3-cyclohexenemethanol (19) suggested the possibility of the absence of the double bond in the cyclohexyl ring. A negative test was also obtained when 27 was treated with bromine.



Calc. 72.68% C
11.18% H

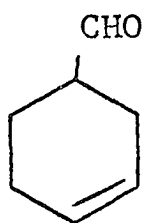
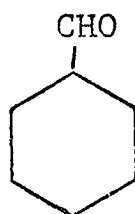
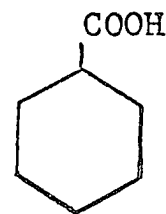


Calc. 73.43% C
10.27% H

Found: 72.31% C
72.46% C
11.30% H
11.10% H

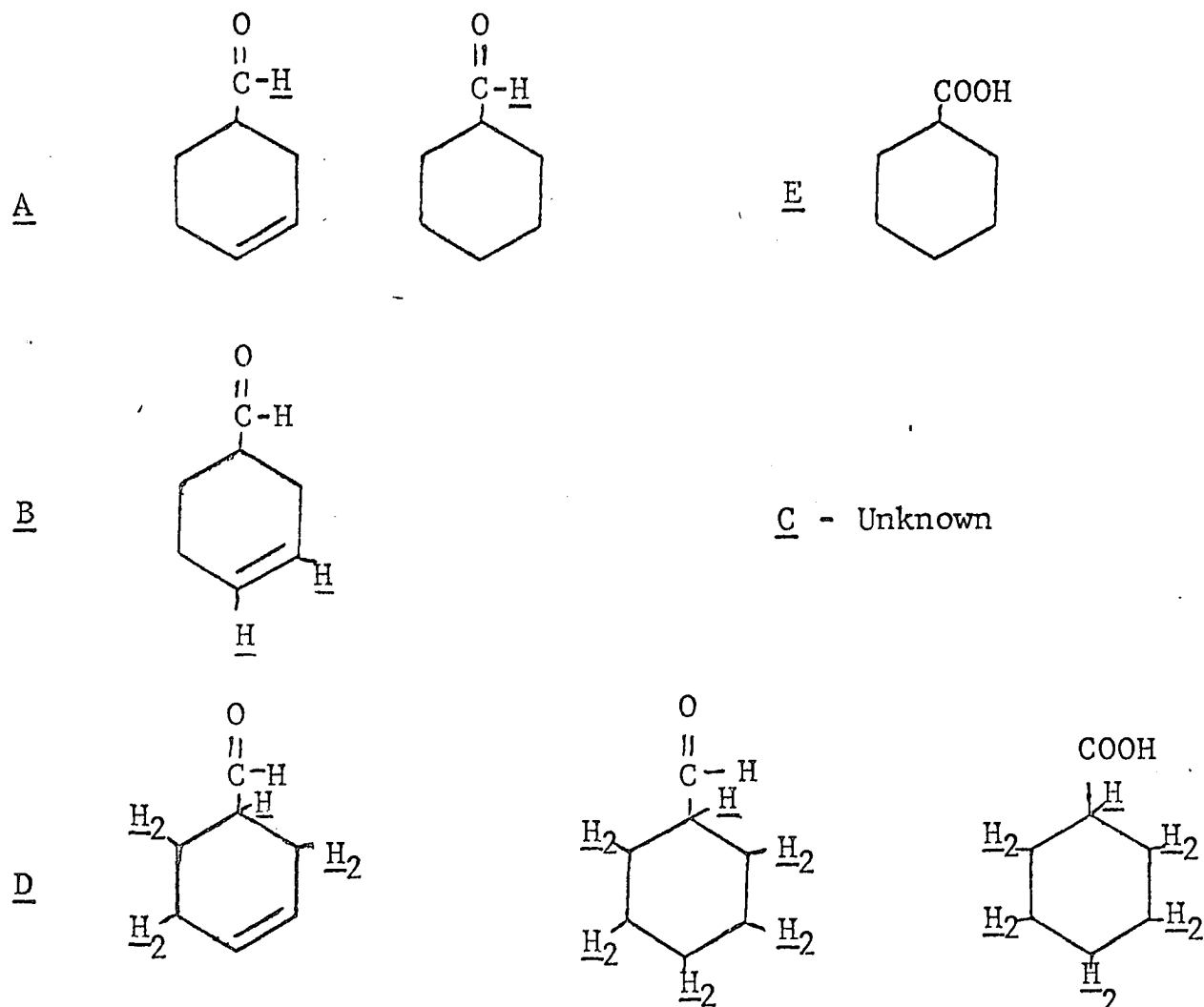
To find out in which step in the synthesis scheme the double bond in the cyclohexane moiety in 18, 19 and 27 disappeared, NMR spectra of these three compounds were taken. The NMR spectrum of the aldehyde 18 showed a multiplet at τ 8.3 with an area of 13.6 for the ring protons, a broad undefined multiplet at τ 6.8 with an area of 0.5, a singlet at τ 4.3 with an area of 0.6 for the vinyl protons, a broad, undefined multiplet at τ 3.4 with an area of 0.4 for the carboxylic proton of the acid 18b, and a doublet at τ 0.4 and τ 0.2 for the aldehydic proton in 18. (Fig. 18).

When to a CCl_4 solution of this sample some D_2O was introduced, the peak at τ 3.4 disappeared. These data indicate that the aldehyde sample was a mixture of 18, 18a, and 18b.

1818a18b

This conclusion can be explained by the following analysis:

Assignment of Protons



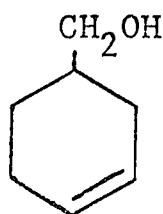
	<u>A</u>	<u>E</u>	<u>B</u>	<u>C</u>	<u>D</u>
Observed areas	.9	.4	.6	.5	13.6
No. of protons in <u>18</u>	1Hu		2Hu		7Hu
Areas for protons in <u>18</u>	.3		.6		2.1
Remaining areas	.6	.4	0	.5	11.5
No. of protons in <u>18a</u>	1Hs				11Hs
Areas for protons in <u>18a</u>	.6		0		6.6
Remaining areas	0		0		4.9
No. of protons in <u>18b</u>		1Hu			11Hu
Areas for protons in <u>18b</u>		.4			4.4
Remainder	0	0		.5	.5

The remaining area of 1.0 is in the experimental error range considering the possibility of unknown compounds in the mixture.

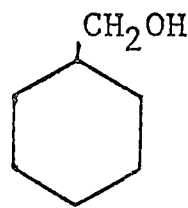
Relative amounts: 1Hu: 1Hs : 1Ha
 .3: .6 : .4
 1 : 2 : 1 1/3

Percentage of 18 found in the sample of starting aldehyde:

$$100 \times \frac{u}{s+u+a} = 100 \times \frac{.3}{.6+.3+.4} = 23\%$$



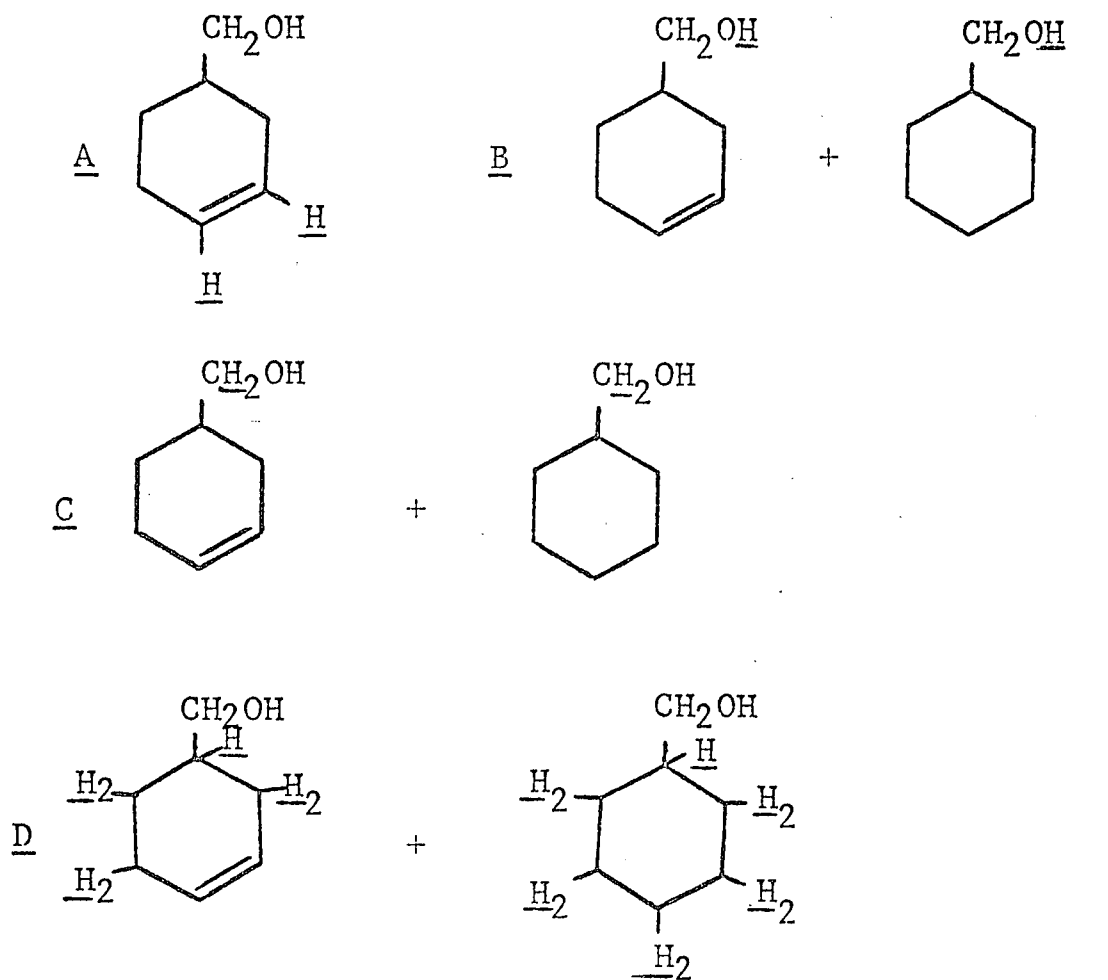
19



19a

For alcohol 19 four peaks were observed: a multiplet at τ 8.6 with an area of 16.1 for the ring protons; a doublet at τ 6.6 and τ 6.7 with an area of 3.2 for the protons on the carbon bearing the hydroxyl group; a singlet at τ 5.1 with an area of 1.6 for the hydroxyl proton, and a singlet at τ 4.3 with an area of 0.8 for the vinyl protons. From these data it is obvious that this alcohol sample was a mixture consisting of 19 and 19a in a 1:4 ratio. This conclusion can be clarified by the following explanation.

Assignment of Protons

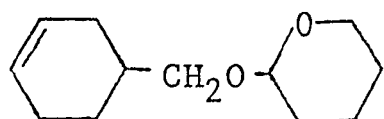
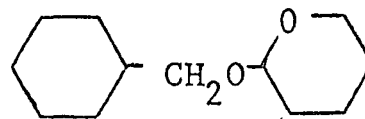


	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>
Observed areas	.8	1.6	3.2	16.1
No. of protons in <u>19</u>	2Hu	1Hu	2Hu	7Hu
Areas for protons in <u>19</u>	.8	.4	.8	2.8
Remaining areas	0	1.2	2.4	13.3
No. of protons in <u>19a</u>		1Hs	2Hs	11Hs
Areas for protons in <u>19a</u>		1.2	2.4	13.2
Remaining areas	0	0	0	.1
Relative amts:	$\frac{S(17a)}{u(17)} = \frac{Hs}{Hu} = \frac{1.2}{.4} = \frac{3}{1}$			

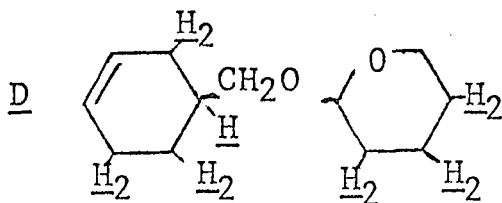
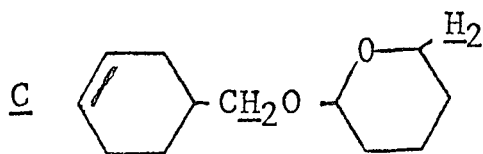
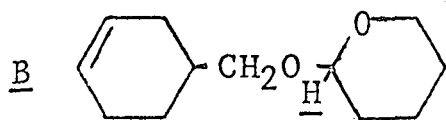
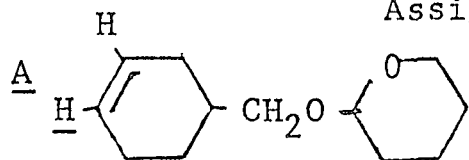
Percentage of 19 found in the sample of the alcohol obtained on reduction of the aldehyde:

$$100 \times \frac{u}{s+u} = \frac{.4}{1.2+.4} \times 100 = .25(100) = 25\%$$

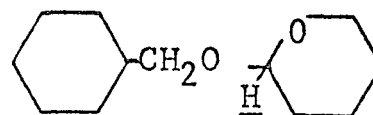
The NMR spectrum of the ether 27 showed a multiplet at τ 8.4 with an area of 15.3 for the ring protons, a multiplet at τ 6.5 with an area of 4 for the four protons on the carbon attached to the cyclohexene ring bearing the oxygen of the ether linkage and the carbon attached to the oxygen in the pyranyl ring, a singlet at τ 5.5 with an area of 1 for the bridgehead proton, and a singlet at τ 4.3 with an area of 0.2 for the vinyl protons in the cyclohexene moiety. These data suggest that the ether 27 is a mixture of 27 and 27c with a ratio of 1 to 9.

2727c

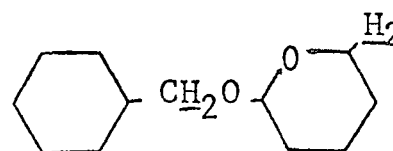
Assignment of Protons



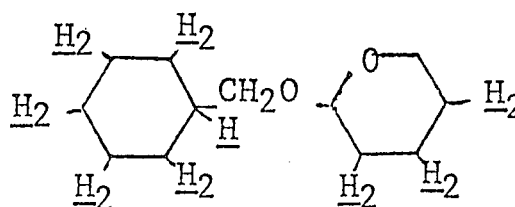
+



+



+



	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>
Observed areas	.2	1.0	4.0	15.9
No. of protons in <u>27</u>	2Hu	1Hu	4Hu	13Hu
Areas for protons in <u>27</u>	.2	.1	.4	1.3
Remaining areas	0	.9	3.6	14.6
No. of protons in <u>27c</u>		1Hs	4Hs	17Hs
Areas for protons in <u>27c</u>		.9	3.6	15.3
Remaining areas	0	0	0	.7

$$\text{Relative amounts: } \frac{s}{u} = \frac{1\text{Hs}}{1\text{Hu}} = \frac{.1}{.9} = \frac{1}{9}$$

Percentage of 27 found in the sample of the pyranyl ether:

$$= 100 \times \frac{u}{s+u} = \frac{1}{10} \times 100 = 10\%$$

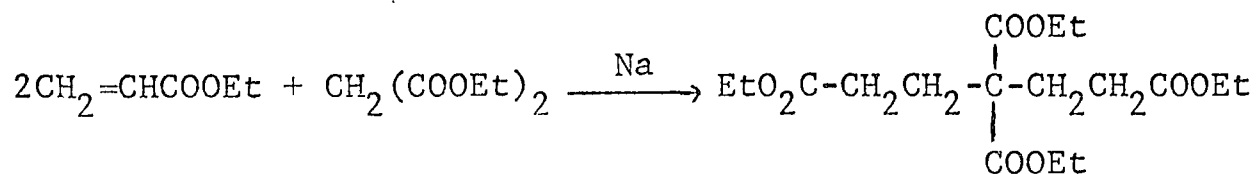
The NMR data explained the reason why the hydroboration reaction had failed. The products which were present in the gas chromatographic analysis included stereoisomers of both saturated and unsaturated derivatives. Since a large amount of the saturated aldehyde 18a was present along with the unsaturated aldehyde in 18, the final product contained an appreciable quantity of saturated materials thus complicating the purification of the desired products. This route was therefore abandoned.

Attempted Synthesis of Ethyl 4-Oxocyclohexane Carboxylate via Condensation Reactions

Singh and Saksena²⁹ reported a new synthesis of 4-oxocyclohexane carboxylate with an overall yield of 36.4%.

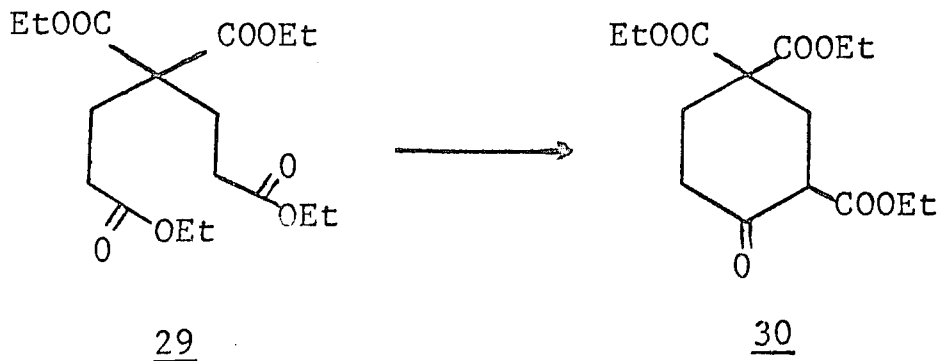
Using this compound in the procedure followed by Lyle and Barrera²² reported above, a plausible pathway to the desired 4-hydroxymethylcyclohexanone oxime could be envisioned.

The synthesis of Singh and Saksena²⁹ involved a Michael addition of diethylmalonate to two moles of ethyl acrylate using traces of sodium as catalyst to yield 65% of tetraethyl-1,3,3,5-tetracarboxylate.

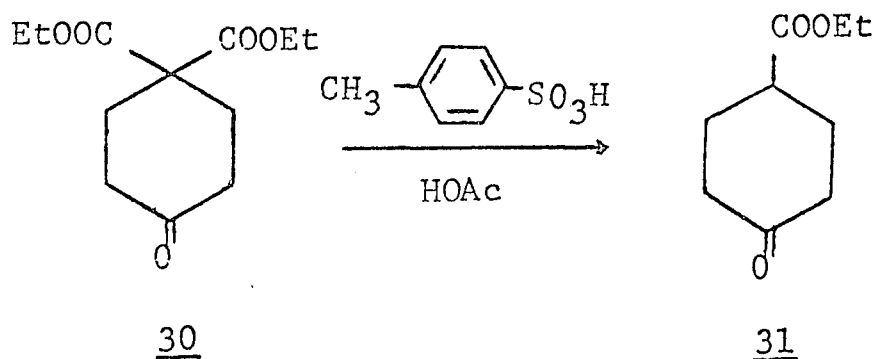


29

29 Was subjected to a Dieckman cyclization with NaH to form triethyl 1-oxocyclohexane-2,4,4-tricarboxylate (30) in 80% yield.



Treatment of 30 with p-toluenesulphonic acid gave ethyl 4-oxocyclohexanecarboxylate (31) with a yield of 70%.



The tetraester 29 obtained in the first step of the synthesis is reported to be a solid, melting at 38°C. The compound corresponding to compound 29 that we obtained did not crystallize. However, it also failed as expected to give a positive ferric chloride test, and its infrared spectrum showed a strong ester carbonyl stretching band at 1735 cm^{-1} as reported.

The infrared spectrum of 29 is very similar to that of diethylmalonate except for bands at 1040 vs. 1020 cm^{-1} and a strong band at 950 cm^{-1} vs. one peak at 870 cm^{-1} . 29, however, differed from diethyl malonate by crystallizing in a Dry-Ice-acetone bath whereas diethyl malonate did not.

The Dieckman cyclization using NaH can be dangerous if time is not allowed for its induction period. This reaction was carried out to give an oil which gave a positive 2,4-dinitrophenylhydrazine test indicating the presence of a carbonyl group. Its infrared spectrum also contained the reported ester carbonyl at 1736-1730 cm^{-1} and the chelated carbonyl at 1661-1668 cm^{-1} .

The decarboxylation step did not yield the reported ethyl 4-oxocyclohexanecarboxylate. A low yield of a viscous oil was obtained which resisted crystallization. It gave a positive 2,4-dinitrophenylhydrazine test indicating the presence of a carbonyl group. It was soluble in a 5% solution of sodium bicarbonate. This suggested that a carboxylic acid group was present. Its infrared spectrum also had a broad band between 3300-2800 cm^{-1} and about 1730-1690 cm^{-1} indicative of a carboxyl group. Following various attempts at purification and crystallization, the gummy liquid solidified after being dried in a vacuum desiccator for several days and melted at 148-155°. It could not be recrystallized.

The above reactions were repeated several times with the same results. The product from the decarboxylation could not be identified due to its impure state. Upon not being able to obtain the desired ethyl 4-oxocyclohexanecarboxylate, this pathway was also abandoned.

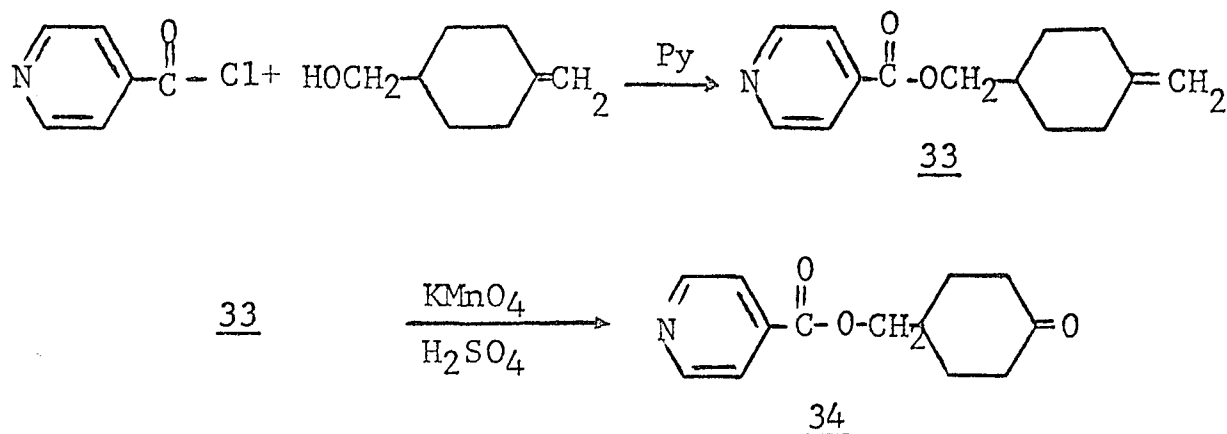
Synthesis of 4-Hydroxymethylcyclohexanone oxime via
4-Methylenecyclohexanemethanol

a. Isonicotinyl Ester of 4-Methylenecyclohexanemethanol. A new approach to the synthesis of 4-hydroxymethylcyclohexanone oxime involved 4-methylenecyclohexanemethanol* as the basic starting compound. It was desirable to protect the alcohol group with an appropriate group to prevent side reactions from taking place at that center during various stages of the synthesis. Since the alcohol function would provide the linkage for the resolution of the molecularly dissymmetric oxime, this protective group had to lend itself to reaction with an optically pure compound capable of forming diastereomers with the racemic oxime.

These qualifications seemed to be met by the isonicotinyl ester function. With its free electrons on the nitrogen in the pyridine ring it should be able to form a salt with an optically pure acid.

The sequence of the synthesis involved the reaction of isonicotinyl chloride with 4-methylene cyclohexanemethanol (32) forming the ester 33 which, in turn, would be oxidized with acidic potassium permanganate to yield the ketone 34.

*The author would like to thank the Tennessee Eastman Company Research Laboratories for the generous complementary supply of this compound.



Conversion of this ketone to the oxime, resolution via formation of diastereomeric salts with an optically pure acid and subsequent liberation from the isonicotinyl group would give the desired, resolved 4-hydroxymethylcyclohexanone oxime.

Of the following sequence only the first two steps could be followed. The ester 33 was very sensitive to acid and heat and was decomposed and/or polymerized if the esterification was carried out in larger quantities than about 12 grams due to the presence of greater amounts of HCl formed during the reaction of the alcohol with the isonicotinyl chloride. The pyridine added to the reaction mixture to neutralize the hydrogen chloride evolved formed pyridine hydrochloride, a white precipitate which interfered with the stirring, and the heat applied to the system did not get evenly dispersed.

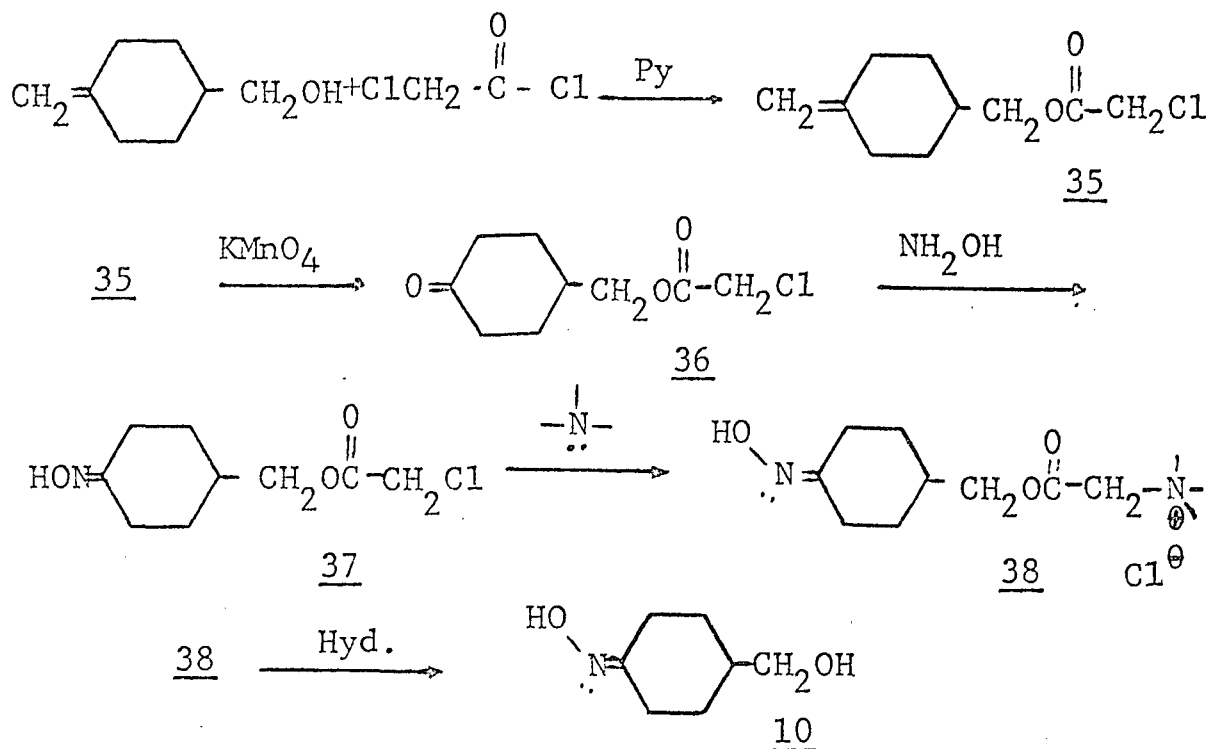
The purification of the ester was attempted by vacuum distillation and some pure ester was obtained. However, as the temperature rose above 115°, a white gel-like solid formed in the condenser and eventually poisoned the system. This solid has a very disturbing, pungent smell and is also a lacrymator. Upon standing at room temperature, it turns reddish and melts. Each sample obtained from differ-

ent esterification reactions gave a different infrared spectrum which was not informative.

The potassium permanganate oxidation of the above ester led to viscous oils which resisted distillation and crystallization. The crude product, however, responded positively to 2,4-dinitrophenylhydrazine indicating the presence of a carbonyl group. Its infrared spectrum showed a shoulder on the 1735 cm^{-1} band at 1720 cm^{-1} indicating the ketone carbonyl. The carbon-carbon double bond stretching frequency at 1650 cm^{-1} was diminished to a mere shoulder at the end of the strong carbonyl absorption band. The presence of a band at 3400 cm^{-1} indicated the presence of a hydroxyl group, suggesting that some hydrolysis had accompanied the oxidation.

The combination of the above reasons made the isonicotinyl ester group unsuitable as a protective unit for this particular sequence of reactions. Therefore, a new protecting group was chosen.

b. α -Chloroacetyl Ester of 4-Methylenecyclohexanemethanol. The presence of the α -chlorine in α -chloroacetyl chloride made it attractive as a dual function protecting group. Besides protecting the primary alcohol in the later steps of the synthesis, after the formation of the racemic oxime it can be reacted with an optically pure base to effect the desired resolution by forming diastereomers. The synthesis comprised of treating 4-methylenecyclohexanemethanol (32) with α -chloroacetyl chloride to form the ester 35 which upon oxidation with acidic potassium permanganate would yield the ketone 36. Reaction with hydroxylamine would give the desired racemic oxime 37.



An optically pure amine such as (+)-amphetamine would then give the corresponding two diastereomeric salts 38 which would be separated by fractional crystallization. The resolved 4-hydroxymethylcyclohexanone oxime (10) could then be liberated from the protecting group.

The esterification reaction of 4-methylenecyclohexanemethanol with commercial α -chloroacetyl chloride gave a quantitative yield of 4-methylenecyclohexanemethyl α -chloroacetate (35). Distillation under reduced pressure yielded 75.3% of a sweet smelling ester whose infrared spectrum did not contain the OH-stretching frequency at $3600\text{--}3450\text{ cm}^{-1}$ but showed a carbonyl band for the ester at 1750 cm^{-1} . The compound gave a positive Beilstein test indicating the presence of chlorine. A sodium fusion test also confirmed this evidence.

The oxidation step has also been carried out successfully using a 10% acidic, aqueous solution of potassium permanganate. The product gave a (+)-Beilstein test for halogen and a yellow precipitate with 2,4-dinitrophenylhydrazine.

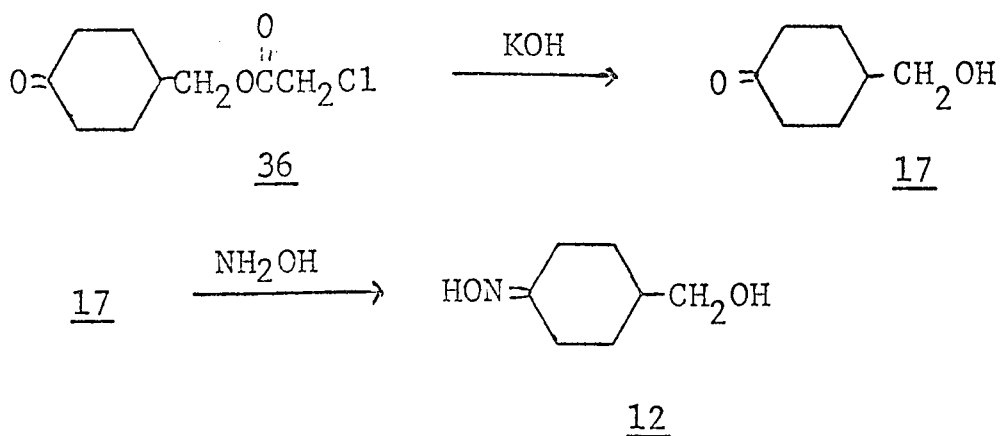
The infrared spectrum showed the absence of the carbon-carbon double bond stretching band at 1650 cm^{-1} and the presence of a ketone carbonyl stretching band at 1710 cm^{-1} as well as a band for the ester carbonyl at 1740 cm^{-1} . The ketoester 36, however, decomposes with the application of heat and thus attempts toward its distillation under reduced pressure failed. Optimum results were obtained when 10 g samples were oxidized with potassium permanganate in a 1:2 ratio of the olefin and permanganate.

The important step of the synthesis involved the formation of the oxime from the above keto-ester. This had to be carried out under relatively mild reaction conditions to avoid the hydrolysis of the ester group. When the keto-ester 36 was treated with hydroxylamine hydrochloride and the reaction mixture neutralized with sodium bicarbonate, a thick oil was obtained, the infrared spectrum of which indicated the oxidation reaction had not been completed. Along with an oxygen-hydrogen stretching band at 3300 cm^{-1} and a carbon-nitrogen double bond stretching band at 1650 cm^{-1} (shoulder), the spectrum also contained the 1720 cm^{-1} band for the ketone carbonyl along with the 1740 cm^{-1} band for the ester. Lengthening of the reaction time did not change these results.

Reaction of the keto-ester with hydroxylamine hydrochloride neutralized with sodium acetate yielded the same results. In both cases if the oximation procedure was repeated on the oxime-ketone mixture, hydrolysis seemed to take place as indicated by the similarity of the infrared spectra of these mixtures with infrared spectra of the mixtures obtained from reactions of 4-hydroxymethylcyclohexanone with hydroxylamine.

The separation of the oxime 37 from the keto-ester 36 in these mixtures was not successful. Crystallization could not be induced and distillation under reduced pressure was not possible.

The alternative was the saponification of the keto-ester 36 to 4-hydroxymethylcyclohexanone (17) and conversion of 17 to the desired oxime 10.



The saponification was accomplished by boiling the keto-ester 36 with a methanolic solution of potassium hydroxide. The keto alcohol 17, thus obtained, formed a very viscous glassy mass in the condenser, probably due to dehydration and subsequent polymerization during an attempted vacuum distillation. However, enough pure 4-hydroxymethylcyclohexanone (17) was obtained to take a good infrared spectrum. This infrared spectrum was identical to the one obtained by Lyle and Barrera¹⁶ from a sample of the 4-hydroxymethylcyclohexanone they prepared starting with ethyl *p*-hydroxybenzoate.

Since the keto-ester 36 could not be used in the formation of the ester-oxime 37 directly, the α -chlorine on the α -chloroacetyl group was no longer useful. An acetate ester without the α -chlorine would also undergo saponification and yield 4-hydroxymethylcyclohexanone. Therefore, in

the subsequent esterification reactions acetyl chloride was used in place of the α -chloroacetylchloride. The acetyl ester was then employed later in the oxidation and saponification steps. This ester, however, having a lower molecular weight than the α -chloro derivative, was more water soluble and, therefore, the yields in these reactions were somewhat lower.

Various methods were tried for the conversion of 4-hydroxymethylcyclohexanone (17) to the corresponding oxime 10. When the ketone IV was treated with hydroxylamine hydrochloride neutralized with sodium acetate using the procedure of Huckel and Sachs,³⁰ a thick oil was obtained, the infrared spectrum of which indicated that most of the ketone had been left unreacted. Further treatment of this mixture with hydroxylamine did not fully convert the ketone to the oxime.

The same mixture, but richer in the ketone counterpart, was obtained from the reaction of ketone 17 with hydroxylamine hydrochloride neutralized with pyridine in absolute ethanol.³¹

The separation of the ketone 17 from oxime 10 in these mixtures has not been successful. An attempted vacuum distillation failed due to decomposition and polymerization upon application of heat. Trituration with petroleum ether with subsequent attempts at crystallization in various solvents was unsuccessful. Another attempt at the separation involved dissolving the mixture in base. The more acidic oxime should be soluble in this alkaline medium whereas the ketone should remain undissolved. Extraction of the aqueous mixture with ether should remove the ketone leaving the oxime in solution. Acidification should regenerate the oxime freed of the ketone. This method did not

give any separation, chiefly due to the fact of the great solubility of 4-hydroxymethylcyclohexanone (17) in water.

The keto-alcohol 17 and the oxime 10 are very similar in polarity and solubility. This fact has been the main reason for the difficulties encountered in the separation of the oxime from the ketone in the mixtures obtained from the above oximation reactions.

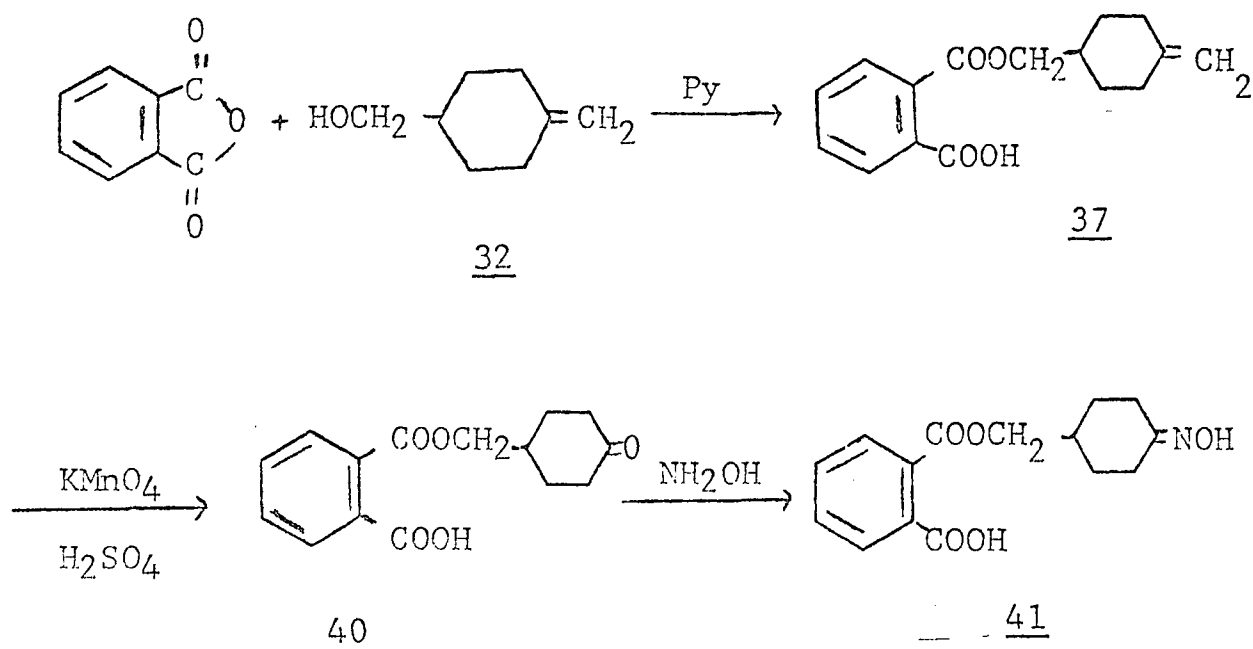
Since the above milder reactions did not completely convert the keto-alcohol to the oxime, more stringent reaction conditions were employed. When 4-hydroxymethylcyclohexanone (17) was refluxed with hydroxylamine hydrochloride dissolved in an ethanolic solution of potassium hydroxide²⁵ a viscous oil was obtained, the infrared spectrum of which did not contain any carbonyl stretching band for the ketone carbonyl at 1720 cm^{-1} . The oxygen-hydrogen stretching band at $3400\text{-}3300\text{ cm}^{-1}$ and the carbon-nitrogen double bond at 1650 cm^{-1} were indicative of the 4-hydroxymethylcyclohexanone oxime (10). This infrared spectrum was identical to the one obtained by Lyle and Barrera in their synthesis of the same oxime.²²

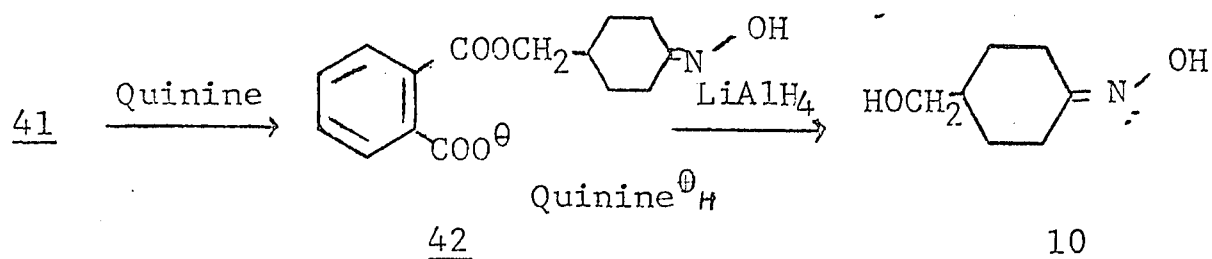
The stringent conditions used in this last procedure for the formation of the oximes would be also strong enough to cause the hydrolysis of the ester function protecting the alcohol group in the keto-ester 36. If the keto-ester 36 is treated with an alcoholic solution of potassium hydroxide containing hydroxylamine hydrochloride, the two reactions would take place in one manipulative step and the desired oxime 10 would be obtained with less handling.

This reasoning was shown to be true by our experiments. When 14.8 g of the keto-ester was treated as described above, a 46.2% yield of 4-hydroxymethylcyclohexanone

oxime (10) was obtained. Its infrared spectrum was identical to the infrared spectrum of the oxime obtained from 4-hydroxymethylcyclohexanone (17) itself. Both of these oxime samples, however, were thick oils which could not be crystallized.

c. Hydrogenphthalate ester of 4-Methylenecyclohexane-methanol. Increasing the molecular weight of the 4-hydroxymethylcyclohexanone oxime by means of a suitable ester derivative of the primary alcohol group using a high molecular weight acid should increase the probability of obtaining this desired oxime in crystalline form. Such an ester could be formed using phthalic anhydride. This ester, besides adding to the molecular weight, would also have a free carboxyl group which can be used as a handle during resolution. Reaction of this monophthalate with an optically active base, such as quinine or brucine, should give diastereomeric salts that could be separated by fractional crystallization. A scheme for this synthesis can be outlined as follows:





Following a modification of the procedure by Kenyon,³² ester 39 was obtained in quantitative yield from the reaction of phthalic anhydride with 4-methylenecyclohexanemethanol in the presence of pyridine. The ester is a solid which melts at 102-103°C.

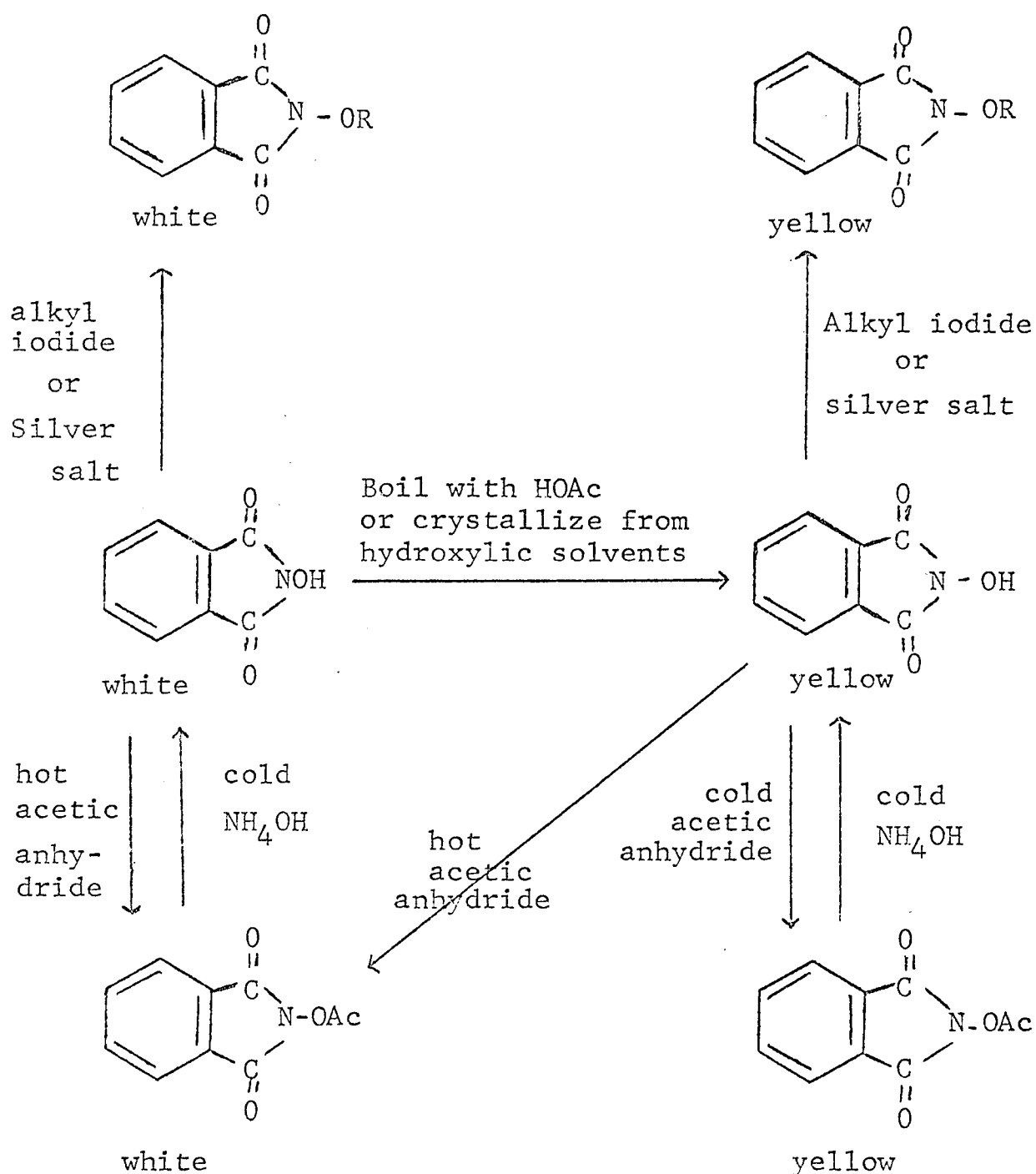
Reaction of 39 with acidic potassium permanganate oxidized the methylene group attached to the cyclohexane ring in 92.2% yield. The resulting ketone 40 had a carbonyl stretching band for the ketone function at 1720 cm^{-1} along with a carbonyl stretching band for the ester group at 1740 cm^{-1} . It also gave a positive test with 2,4-dinitrophenylhydrazine.

This ketone, however, was not crystalline. Attempts to crystallize it using the same method that was used in converting the viscous oily ester 39 to its crystalline form by dissolving it in acetone and adding crushed ice failed. Crystallization using dioxane-ice water, ether-petroleum ether solvent combinations, benzene, carbon tetrachloride solutions or trituration with petroleum ether was not possible. Only once, when to the keto-ester 40 anhydrous ether was added, a precipitate formed. Precipitation was encouraged by cooling in the refrigerator. Upon filtration a white, fluffy solid was obtained. It melted at 120-122°C and give an infrared spectrum which was superimposable with that obtained from the keto-ester in its oily forms. The

oily ester did not make mulls with either nujol or halocarbon and its infrared spectrum was taken using a chloroform solution. When this method of crystallization was tried again, the solid obtained oiled on the filter paper after filtration.

The keto-ester 40 was converted to the oxime 41 using a modification of the procedure used by Hückel and Sachs,³⁰ but dioxane was used as the solvent for dissolving the water-insoluble keto-ester in the aqueous solution of sodium acetate and hydroxylamine hydrochloride. The viscous oil obtained was separated into two solids, mp 220-225° and 150-155°, and a brownish oil. Both solids gave positive tests for nitrogen in sodium fusion tests. From various different oximation preparations using the same procedure, however, two forms of this high melting solid were obtained. In one form this substance was a white powder while in the other it had shiny, fluffy long yellow needles. Both forms had the same melting point and gave identical infrared and nuclear magnetic resonance spectra. The physical properties of this solid corresponded to those of phthaloxime³³ 43.

Baker and Baker³⁴ have investigated the two forms of phthaloxime and found that both forms melt and decompose at the same temperature. Both yield a series of derivatives in which characteristic difference in color persists. Analogous derivatives of both melt at the same temperature. Mixed melting points show no depression.

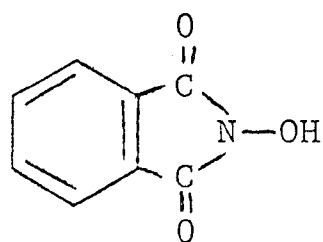


An authentic sample of phthaloxime was prepared by the reaction of phthalic anhydride in dioxane with an aqueous solution of hydroxylamine hydrochloride and sodium acetate. The sample obtained was a white solid. Its infrared spectrum was found to be superimposable with that of the high melting solid obtained from the oximation reaction of the keto-ester 40. It also had the same melting

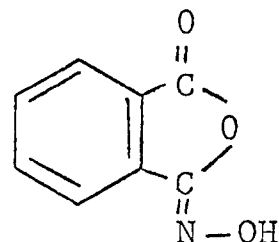
point range (220-225°).

The white solid was converted to the white acetyl derivative 44 with hot acetic anhydride. The yellow phthaloxime obtained from the oximation of keto-ester 40 was also treated with hot and cold acetic anhydride, but only a white acetyl derivative was obtained in both instances. All three acetyl derivatives had superimposable infrared spectra and identical melting points.

The formula for phthaloxime is written in two forms:



43a

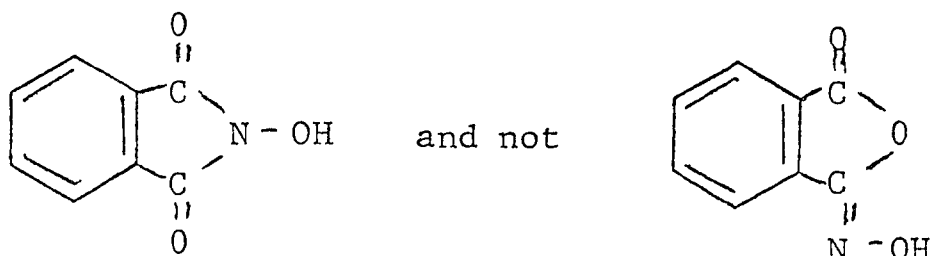


43b

If the structure is 43a, the NMR spectrum of phthaloxime should be very similar to that of phthalic anhydride. There are only two different kinds of aromatic protons giving an A_2B_2 system. If 43b is the structure, all of the aromatic protons are different and one should obtain a multiplet in the NMR spectrum.

If the two different forms of phthaloxime correspond to these two different structures, these two forms should give two different NMR spectra. However, both forms gave identical NMR spectra consisting of a singlet at 7.86 ppm for the 4 aromatic protons. Phthalic anhydride also gave a singlet at 8.1 ppm. Since the chemical shifts of H_a and H_b are very similar, they were not resolved by the A-60 instrument. The oxime proton could not be located in the spectrum.

It was most likely hidden under the methyl proton absorption of dimethyl sulfoxide which was used as the solvent. These spectra show that the structure of phthaloxime is:



The lower melting solid from the oximation of the keto-ester 40 was shown to be the desired oxime 41. The elemental analysis corresponded to the calculated values and the infrared spectrum had an oxygen-hydrogen stretching band at 3250 cm^{-1} for the oxime oxygen and a stretching band for the carbon-nitrogen double bond at 1640 cm^{-1} .

The yield of the crystalline oxime was low (10.3%) but was slightly improved by carrying out the reaction using the procedure suggested by Smith, Mainthal and Tipton.³⁵ Purification of the resulting oil left over after crystallization was not possible. Only unidentifiable oils were obtained from column chromatography. Application of heat caused decomposition.

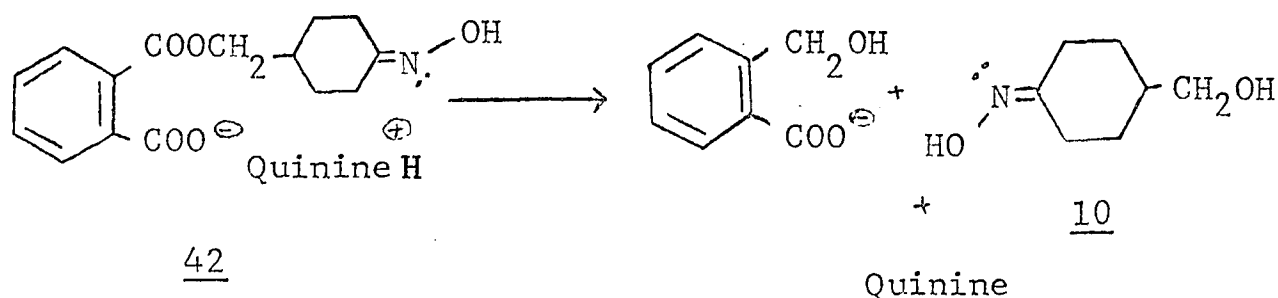
Attempted Resolution of Oxime 10

To carry out the resolution of this molecularly dissymmetric oxime, formation of a crystalline salt with an optically active base was necessary. A variety of optically active bases was used for reaction with oxime 41 and of these the salts of brucine and ephedrine were oils that resisted crystallization. The salts obtained from cinchonine, quinine and (+)-amphetamine were crystalline. The cinchonine salt,

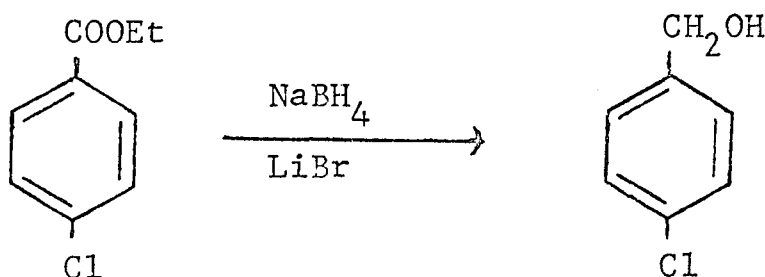
however, was difficult to crystallize and the more amenable quinine was selected as the resolving agent.

Quinine readily formed a crystalline salt 42 on treatment with the hydrogen phthalate ester 41 of 4-hydroxymethylcyclohexanone oxime in acetone solution. The resulting salt, however, was quite insoluble in acetone and the subsequent recrystallizations were carried out in absolute ethanol. The salt yielded one of the diastereomers on recrystallization. The levorotatory isomer was the less soluble and could be isolated with maximum rotation after five recrystallizations.

The regeneration of 4-hydroxymethylcyclohexanone oxime (10) from the salt presented problems. Since the oxime is very water soluble and readily racemized with acids, the usual procedure used in regenerating optically active alcohols from phthalate alkaloid salts by reaction with concentrated hydrochloric acid to remove the alkaloid followed by saponification of the ester function with sodium hydroxide was not desirable. However, if the ester function could be reduced with complex metal hydride without reducing the oximino function, the optically active oxime could be obtained without racemization.



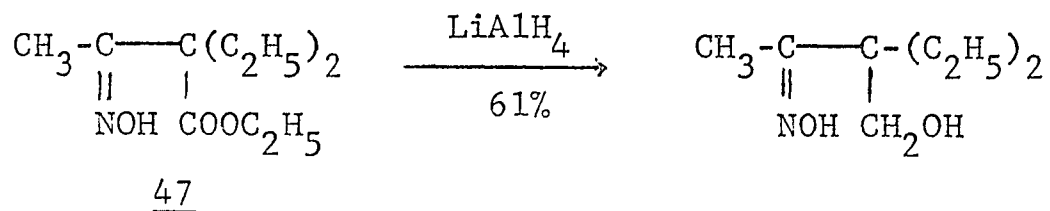
H. C. Brown³⁶ reported that lithium borohydride prepared in situ from lithium bromide and sodium borohydride in diglyme solution reduced esters readily but did not react with nitriles. Brown³⁷ reported the reduction of ethyl *p*-chlorobenzoate to *p*-chlorobenzyl alcohol in 91% yield.



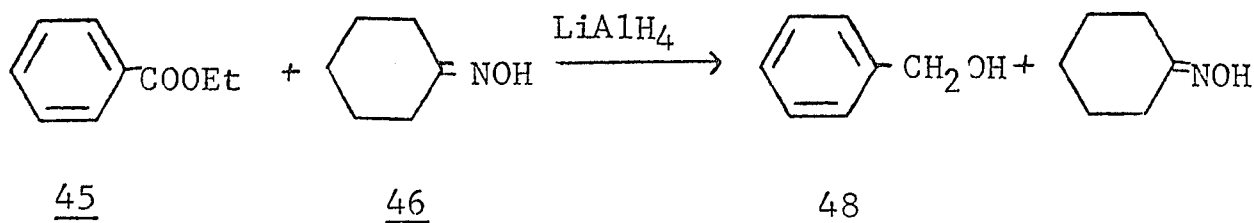
Since the quinine salt of the phthalate ester (42) of 4-hydroxymethylcyclohexanone oxime was not available in large quantity, the reduction was first tested with a 1:1 ratio of ethyl benzoate (45) and cyclohexanone oxime (46). No reduction of ethyl benzoate took place when the reaction was carried out using Brown's procedure or when the reaction time was extended to six hours. The cyclohexanone oxime could not be isolated or detected in the reduction products. When the aqueous layer from the reduction mixture was highly basified and extracted with ether, the infrared spectrum of the product approximately resembled that of cyclohexylamine but the similarity was not conclusive. Without further investigation this procedure was abandoned.

Felkin³⁸ found that by the addition of an ethereal lithium aluminum hydride solution containing the theoretical quantity of reducing agent to a solution of 3-carboethoxy-3-

ethyl-2-pentanone oxime (47) at room temperature, it was possible to selectively reduce the carboxyl function without affecting the oximino grouping. However, no reduction was obtained under these conditions using a three hour reaction time or when the reaction time was increased to six hours.

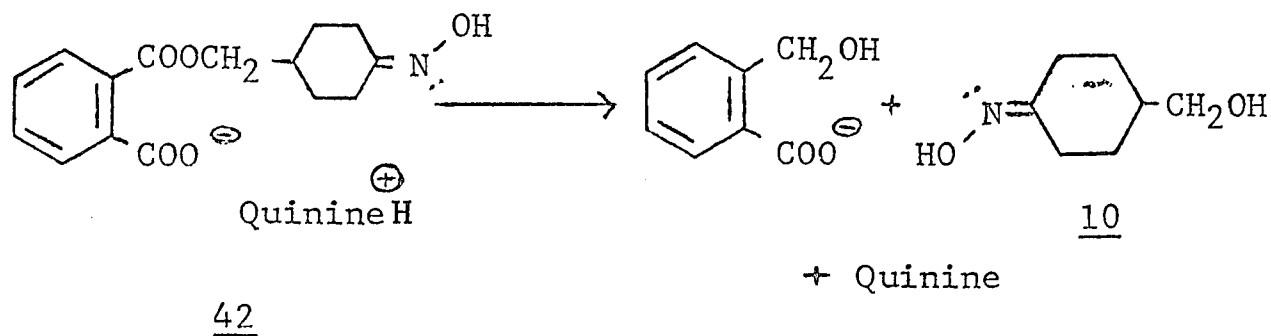


When an ethereal solution of cyclohexanone oxime 46 and ethylbenzoate was treated at room temperature with a 100% excess amount of lithium aluminum hydride above the theoretical quantity, ethylbenzoate was selectively reduced in about 90% yield. The infrared spectrum of the product was superimposable on that obtained from an authentic sample of benzyl alcohol (48) and cyclohexanone oxime. The same results were obtained when the reduction was carried out in tetrahydrofuran. Care was taken not to allow an increase in the reaction temperature since the oximino function also reduces at reflux temperature of ethyl ether.³⁵



Using the above conditions the quinine salt of the hydrogenphthalate ester (42) of 4-hydroxymethylcyclohexanone oxime was subjected to lithium aluminum hydride reduction using ether as the solvent. The salt 42 was insoluble in ether, and the course of the reaction could not be conven-

iently followed. The reaction was allowed to go three hours longer than the reduction of ethylbenzoate and the cyclohexanone oxime mixture.



The infrared spectrum of the product obtained did not contain any carbonyl stretching bands, indicating that the reduction had been successful. However, the spectrum was very similar to the infrared spectrum of quinine suggesting that it consisted chiefly of quinine. Recrystallization and melting point comparison substantiated the fact that only quinine was present. Any 10 produced in the reaction was undoubtedly lost because of its water solubility. Subsequent experiments indicated that no reduction had taken place.

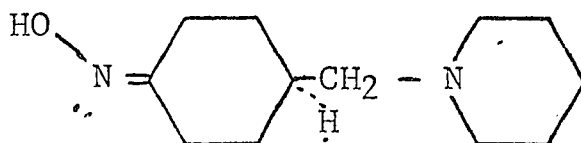
The lithium aluminum hydride reduction of the salt 42 was repeated using tetrahydrofuran as the solvent. A solid product was obtained which, on trituration with petroleum ether, yielded an oil which was unreduced ester 41. The remaining solid consisted only of quinine.

To see whether or not the reduction of the ester linkage in the salt 42 was really successful, a sample of ester 41 was subjected to lithium aluminum hydride reduction using the same procedure. The infrared spectrum of the product obtained was very similar to that of oxime 10

except for the presence of a very weak carbonyl band at about 1700 cm^{-1} indicating the presence of some of the ester 41 and that the reduction was not quantitative. The oily product could not be crystallized.

The difficulty in effecting the reduction of the salt 42 apparently results from the lack of solubility of the reagent. Although it is much more soluble in tetrahydrofuran than in ether, the fact that the oximino ester 41 could be successfully reduced but the quinine salt 42 failed to reduce suggests that a solubility complication is the underlying cause of the difficulties.

It is apparent from the study described herein that 4-hydroxymethylcyclohexanone oxime (10) may be prepared in an optically active form but that the complications resulting from solubility and lability problems preclude success in the determination of its absolute configuration. In view of these problems, it seems plausible to suggest that the choice of a higher molecular weight, less polar molecule would lead to the successful completion of this problem. A logical related compound which could be synthesized utilizing some of the reactions described herein and which would meet the restrictions mentioned above would have the hydroxyl group replaced by a dialkylamino moiety. Basicity would be incorporated in the molecule allowing formation of diastereomeric salts directly with an optically active acid. Further investigation of the problem of Mills oxime should be extended to 4-piperidinomethylcyclohexanone oxime (50).

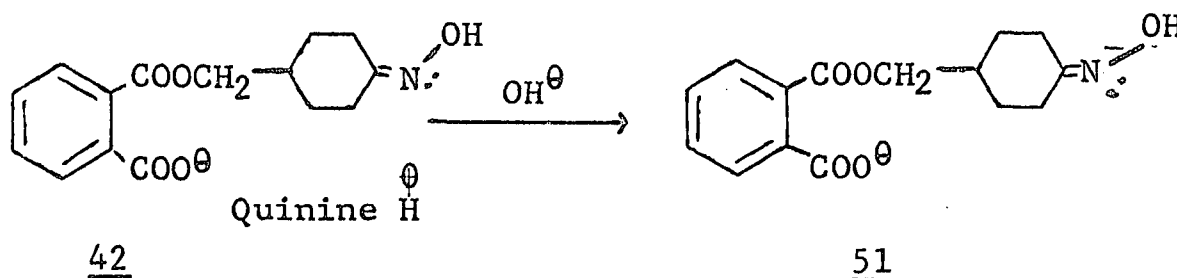


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May 24, 1967

ADDENDUM

To get some information as to the possible rotatory power of 4-hydroxymethylcyclohexanone (10), the resolved quinine salt 42 was subjected to a mild basic hydrolysis. The precipitated quinine was removed by filtration and the water solution containing 51 was studied by ORD.



A negative plain curve was obtained with relatively small rotational magnitudes. The small rotation at the sodium D-line had led us previously to assume that 10 had racemized.

To prove that the plain negative curve was not the result of left over quinine dissolved in the basic solution containing 51, the ORD curve of a saturated solution of quinine was obtained in 2.7% NaOH. The negative plain curve obtained had much lower rotational values than the curve obtained from 51.

These data strongly suggest that 51 retained some of its optical activity during the hydrolysis. Since the ORD study was made on 51 one week after its hydrolysis, the oxime moiety in 10 seems to hold its configuration in basic media.

EXPERIMENTAL

Melting Points: Melting points were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected.

Infrared Absorption Spectra: The infrared absorption spectra were determined using a Perkin-Elmer Model 137B infrared spectrophotometer ("Infracord") equipped with sodium chloride optics and a Perkin-Elmer Model 337 grating infrared spectrophotometer. Those spectra determined on the Model 137 are indicated by No., while those determined on the model 337 are indicated by No. 337.

The spectra of liquids were determined as films and the spectra of solids were determined as mulls in halocarbon oil from 4000 to 1300 cm^{-1} and in Nujol from 1300 to 650 cm^{-1} . All of the bands were strong except otherwise indicated and the location of the bands is given in frequency units, cm^{-1} .

Optical Rotation Data: The rotations of optically active compounds were determined using a Rudolph recording spectropolarimeter Model 260/658/850/810-609 with a 1.0 cm tube length. The solvent and concentration (g per 100 ml of solution) are indicated for each determination.

Analytical Data: Microanalysis for compound 41 was determined by Schwarzkopf Microanalytical Laboratory, Woodside, New York, and all of the others at the University of New Hampshire, using an F & M Model 180 carbon, hydrogen, nitrogen analyzer.

Nuclear Magnetic Resonance Spectra: The nuclear magnetic resonance spectra were determined using a Varian Model A-60 proton resonance spectrometer. Unless otherwise indicated, the spectra were obtained neat and the chemical shifts are given in p.p.m. relative to tetramethylsilane, an internal standard.

Gas Liquid Chromatography Data: Gas liquid chromatography data were determined using a Varian Aerograph Model A90-P3. The column packings were D-C Silicone Grease and Apiezon L, and the carrier gas was helium.

Attempted Synthesis of 10 via Hydroboration

3-Cyclohexene-1-Methanol 19. A solution of 27.5 g (0.25 mole) of 3-cyclohexenecarboxaldehyde in 20 ml of anhydrous ether was added dropwise to a stirred slurry of 5.0 g (0.12 mole) of lithium aluminum hydride in 300 ml of anhydrous ether. Stirring was continued for 4 hr after which time the excess hydride was destroyed first with wet ether, then water (20 ml) and 15 ml of 5% hydrochloric acid were added dropwise to the stirring reaction mixture. Stirring was continued until the reaction mixture turned white and the aluminum hydroxide coagulated. The ether layer was then separated and the residue washed with ether. The ethereal solutions were combined and dried over magnesium sulfate. The solvent was removed by distillation leaving an oily residue which upon distillation under reduced pressure yielded 21.00 g (0.172 mole) (75.5%) of 3-cyclohexene-1-methanol 19; bp 90-93° at 2.0 mm; lit.²³, bp 102° at 19 mm, NMR Spectrum Fig. 19.

I. R. Spectrum (No. 3962, film): 3400, 2998, 2900, 1650 (VW), 1440, 1370, 1335, 1260, 1205, 1175, 1135, 1090, 1080, 1055, 1030, 985, 955, 918, 897, 870, 843 cm^{-1} .

Isonicotinyl Chloride Hydrochloride. To 18 g (0.147 mole) of isonicotinic acid in a 250 ml round bottom flask fitted with a condenser 75 ml of thionyl chloride was added dropwise. When the initial vigorous reaction had subsided, the reaction mixture was heated with a heating mantle for 4.5 hr. From time to time the evolution of hydrogen chloride was tested with NH_4OH at the open end of the condenser. The excess thionyl chloride was removed by distillation under reduced pressure and remaining traces of thionyl chloride were removed by heating on the steam bath under reduced pressure for an additional 0.5 hr. The product has a light tan color and was used without further purification.

3-Cyclohexenylmethyl Isonicotinate (20). To the above freshly prepared isonicotinyl chloride hydrochloride in 150 ml of anhydrous benzene, 11.0 g (0.10 mole of 3-cyclohexene-1-methanol in benzene was added followed by 10 ml of pyridine. Upon addition of the pyridine to the reaction mixture a white precipitate pyridine hydrochloride appeared in the solution. The reaction mixture was magnetically stirred and heated with a heating mantle under a reflux condenser fitted with a calcium chloride drying tube for 3 hr. Water was added and stirring continued until solution was completed. Neutralization of the reaction mixture with a saturated solution of potassium carbonate followed by separation of the organic layer and drying over potassium carbonate with subsequent evaporation of the solvent and the pyridine under reduced pressure left a brown oil which after distillation under reduced pressure yielded 12.52 g (50.9%) of 3-cyclohexenylmethyl isonicotinate (20), bp 100-103° at 2.0 mm.

I. R. Spectrum (No. 2035, film). 3075, 2998, 2870, 1705, 1600, 1555, 1495, 1440, 1390, 1385, 1318, 1270, 1210, 1120, 992, 975, 955, 945, 922, 902, 757, 705, 675 cm^{-1} .

Tetrahydropyranyl ether of 3-Cyclohexene-1-Methanol (27). 3-Cyclohexene-1-methanol (19), (35.0 g, 0.312 mole) was mixed with 26.3g(0.312 mole) of 2,3-dihydropyran. Concentrated hydrochloric acid (10-12 drops) was added slowly to the stirred mixture. The reaction vessel was cooled with ice for 1 hr and the mixture was stirred for 2 hr. A few sodium hydroxide pellets were added to the reaction mixture to destroy the acid, and the product (42.7 g, 70.0%) was purified directly by distillation under reduced pressure using a Todd-spiral column with anti-foaming agents to yield the fractions, bp 103-110° at 25 mm and bp 142-145° at 22 mm. The second fraction was redistilled giving a sample boiling at 117-118° at 16 mm, N.M.R. spectrum, Fig. 20.

I. R. Spectrum (No. 414, film). 2924, 2850, 1475, 1420, 1375, 1325, 1260, 1200, 1135, 1120, 1075, 1060, 1040, 980, 904, 870, 820 cm^{-1} .

Hydroboration of Tetrahydropyranyl ether of 3-cyclohexene-1-methanol (27). Boron trifluoride dietherate was shaken with dry ether, let stand for some time, and distilled under water pump pressure. A portion boiling at 68° at 55 mm was used. Diglyme was distilled over lithium aluminum hydride under reduced pressure.

In a 500 ml three-necked round bottom flask fitted with a mechanical (mercury sealed) stirrer, a pressure equilized dropping funnel, and nitrogen inlet and outlet was placed 0.05 mole (9.8 g) of tetrahydropyranyl ether of 3-cyclohexene-1-methanol, 10 ml of diglyme and 0.015 mole (0.6 g) of NaBH_4 in 15 ml of diglyme (15 ml of 1.00 M solution in diglyme). In the dropping funnel was placed .02 mole (2.85 g) of boron trifluoride dietherate in 5 ml of

diglyme. The apparatus was flushed out with nitrogen and then a slightly static pressure of the gas was maintained as boron trifluoride dietherate solution was added to the stirred solution over a period of 0.5 hr. During this time the flask was cooled in a water-ice bath. The reaction mixture was permitted to stand at room temperature for a second hour, the nitrogen inlet replaced by a reflux condenser and the reaction mixture hydrolyzed with 4 ml of water. When hydrogen was no longer evolved, 6.7 ml of 3N NaOH was added and oxidation carried out by adding 6.7 ml of 30% hydrogen peroxide in small batches at such a rate that a gentle reflux was maintained. The reaction mixture was allowed to cool, treated with ice water and the product taken up in ether. The ether extracts were washed with ice water to remove the diglyme and the product recovered by distillation under reduced pressure. The three fractions boiling at 99°-106°, 110°-128° and 159° under 24 mm were redistilled and analyzed with gas liquid chromatography. The data obtained from NMR examination of the product are discussed on pp. 30-31.

I.R. Spectrum (No. 4092, film). 3600, 3000, 2900, 1460, 1370, 1350, 1260, 1210, 1200, 1140, 1090, 1070, 1050, 990, 910, 880, 875, 850, 825 cm^{-1} .

Attempted Synthesis of 10 via Condensation Reactions:

Tetraethylpentane-1,3,3,5-tetracarboxylate (29). Ethyl acrylate (130 g, 1.3 mole) was added slowly to diethyl malonate (80 g, 0.5 mole), sodium (2 g) and dry benzene (200 ml) at 40°. The contents were stirred and heated under reflux for 6 hr. Water (50 ml) and dilute hydrochloric acid (20 ml) were added. The mixture was extracted three times with 100 ml portions of benzene and the combined benzene extracts dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure left a heavy yellow liquid, which could not be distilled.

I. R. Spectrum (No.: 5384, film): 3000, 1735, 1460, 1370, 1300, 1250-1170, 1100, 1125, 940, 860 cm^{-1} .

Triethyl-1-oxocyclohexane-2,4,4-tricarboxylate (30).

In a 500 ml three-necked round bottom flask fitted with a mechanical stirrer, an addition funnel, and a reflux condenser fitted with a CaCl_2 drying tube, 6 g of NaH in 100 ml dry benzene was heated and stirred for 0.5 hr. A small portion of 19 g (0.053 mole) of tetraethylpentane-1,3,3,5-tetracarboxylate (29) in 100 ml dry benzene was added dropwise to the warm, stirred slurry of NaH in benzene and the reaction mixture was brought to reflux. Slowly the remaining benzene solution of tetraethylpentane-1,3,3,5-tetracarboxylate (29) was added and the reaction mixture stirred and heated under reflux for 12 hr. Hydrochloric acid (50 ml, 5% w/v) and 50 ml of water were slowly added and the mixture extracted three times with benzene. The combined benzene extracts were dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure left a yellow oil (9.2 g, 55.3%), whose IR spectrum agreed with that reported.²⁹

I. R. Spectrum (No. 5225, film): 3010, 2990, 1735, 1665, 1610, 1450, 1370, 1300, 1150, 1100, 1035, 870, 830 cm^{-1} .

Synthesis of 10 from 4-Methylenecyclohexanemethanol

4-Methylenecyclohexylmethyl Isonicotinate (33). To freshly prepared isonicotinyl chloride using 15 g (0.112 mole) of isonicotinic acid with 20 ml of thionyl chloride 12.6 g (1.0 mole) of 4-methylenecyclohexanemethanol (32) was added slowly, followed by 10 ml of dry pyridine. The mixture was stirred and refluxed for four hours.

The reaction mixture was transferred to a 500 ml Erlenmeyer flask and stirred magnetically while water was slowly and cautiously added until solution was completed. The solution was neutralized with a saturated solution of potassium carbonate while keeping the mixture cooled in an ice bath. The reaction mixture was extracted several times with ether and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure left 18 g of orange colored liquid residue which after distillation yielded 15.0 g (66.5%) 4-methylenecyclohexylmethyl isonicotinate, bp 110-117° at 0.05 mm.

I. R. Spectrum (No. 5476, film). 3050, 2950, 1735, 1650, 1600, 1550, 1450, 1270, 1150, 1050, 970, 890, 800, 760, 710, 650 cm^{-1} .

4-Methylenecyclohexylmethyl Isonicotinate (34). Methyl-
cyclohexylmethyl isonicotinate (3 g) in 100 ml of acetone was placed in a 250 ml round bottomed flask fitted with a reflux condenser and an addition funnel containing 3 g of KMnO_4 in 30 ml of water and 3 ml H_2SO_4 .

Potassium permanganate was added slowly to the magnetically stirred solution of the olefin in acetone. Since the purple color of the permanganate did not disappear readily, the reaction mixture was heated to reflux. The reaction then proceeded rapidly and was allowed to go for 15 additional minutes at room temperature. The brown-black precipitate of manganese dioxide was removed with suction filtration and washed several times with acetone and pressed on the filter.

The acetone from the acetone-water solution of the oxidation product was evaporated under reduced pressure. The remaining aqueous layer was neutralized with a 5% solution of sodium hydroxide and extracted with ether several times. The combined ether extracts were dried over anhydrous magnesium sulfate. Upon removal of the solvent under reduced pressure, a dark tan viscous oil was obtained (1.7 g). As described in the discussion (p.35), the product decomposed on distillation and no further experiments were carried out.

4-Methylenecyclohexylmethyl α -chloroacetate (35).

4-Methylenecyclohexanemethanol (12.6 g, 0.1 mole) was dissolved in 80 ml of dry benzene in a three necked 200 ml round bottom flask fitted with an addition funnel and a reflux condenser equipped with a calcium chloride drying tube. Dry pyridine (8 g) was added and the mixture was stirred magnetically. α -Chloroacetyl chloride (11.3 g, 0.1 mole) was added slowly. The heat evolved brought the reaction to reflux and a white precipitate separated as the reaction proceeded. The addition was continued for 0.5 hr. and the mixture was stirred for an additional 1.5 hr.

The reaction mixture was separated with suction filtration to remove the white solid shown to be pyridine hydrochloride. To the mother liquor, water was added slowly and the mixture was extracted several times with ether. The ethereal solution was dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure left 20.1 g (99.2%) of a sweet smelling, colorless oil which upon distillation under reduced pressure yielded 15.2 g (75.2%) of 4-methylenecyclohexylmethyl α -chloroacetate, bp 62-71° at 1-2 mm, n_D^{26} 1.4830.

I. R. Spectrum (No. 7599, film). 2980, 1770, 1650, 1450, 1420, 1320, 1180, 990, 900, 780 cm^{-1} .

4-Oxocyclohexylmethyl α -chloroacetate (36). 4-Methyl-enecyclohexylmethyl α -chloroacetate (7.5 g) in 100 ml of acetone was placed in a 500 ml three necked round bottom flask fitted with a reflux condenser and an addition funnel. The reaction mixture was cooled and stirred magnetically as a solution of 12 g KMnO_4 and 3 ml of concentrated sulfuric acid in 120 ml of water was added dropwise. The reaction was fast and exothermic. After all of the potassium permanganate was added, the reaction was allowed to go for 15 minutes longer. The mixture was filtered twice with suction to remove the dark brown precipitate of manganese dioxide.

Acetone was evaporated from the solution and the remaining aqueous layer after neutralization was extracted several times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure left 6.1 g of an oil which could not be distilled without decomposition and was not further investigated.

I. R. Spectrum (No. 7672, film). 2980, 1750, 1740-1710, 1450, 1420, 1320, 1180, 1000, 780 cm^{-1} .

Saponification of 4-oxocyclohexyl α -chloroacetate (36). A solution of 3 g (0.075 mole) of sodium hydroxide in 100 ml of water was added to a solution of 12.3 g (0.0612 mole) of 4-oxocyclohexylmethyl α -chloroacetate (36) in 75 ml of methanol. The mixture was refluxed for 2 hr, cooled and extracted four times with ether. The remaining water layer was saturated with sodium chloride and extracted

again with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the ether under reduced pressure left a tan colored oil, which on distillation yielded 4.2 g (58.0%) of 4-hydroxymethylcyclohexanone (17); bp 110-120° at 1.5 mm. The IR spectrum was identical with that obtained previously.²²

I. R. Spectrum (No. 337 6805, film): 3400, 2980, 1715, 1450, 1375, 1335, 1250, 1160, 1100, 1050, 1000, 970, 950, 890, 825 cm^{-1} . Fig. 12.

Oximation of 4-Hydroxymethylcyclohexanone (17).

(a) Pyridine method. 4-Hydroxymethylcyclohexanone (17) (1 g), 5 ml of pyridine, 1 g of hydroxylamine hydrochloride, and 5 ml of absolute alcohol were combined and refluxed for 2.5 hr. The mixture was allowed to cool. The solvents were removed under reduced pressure leaving behind a solid-like oil to which 5 ml of water was added. The mixture was extracted five times with ether and the combined ether extracts were dried over anhydrous magnesium sulfate. Upon removal of the solvent, a yellow oil was obtained which was contaminated with unreacted ketone.

I. R. Spectrum (No. 6987, film): 3400, 2980, 1720, 1650, 1450, 1380, 1275, 1100, 1050, 1000, 950, 900, 850 cm^{-1} .

(b) Sodium Acetate Method. 4-Hydroxymethylcyclohexanone (17), 1.3 g (0.01 mole), 1.3 g hydroxylamine hydrochloride and 1.6 g of sodium acetate were dissolved in 10 ml of water. Enough methanol was added to give a clear solution. The reaction mixture was stirred and refluxed for 8 hr. After removal of methanol under reduced pressure, the water layer was extracted several times with ether and the ether extracts were combined and dried over anhydrous magnesium sulfate. Upon evaporation of the ether under reduced pressure, 0.7 g of a yellow oil was obtained.

I. R. Spectrum (No. 6891, film) is identical to the I. R. Spectrum of the product obtained using the pyridine method and was also a mixture of products.

(c) Potassium hydroxide method. 4-Hydroxymethylcyclohexanemethanol (17) (1 g), and 1 g of hydroxylamine hydrochloride were added to a solution of 4 g of potassium hydroxide in 20 ml of 95% ethanol. The mixture was refluxed for 2 hr, cooled and poured into 100 ml of water. It was neutralized with hydrochloric acid, and extracted several times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure left a heavy yellow oil, 4-hydroxymethylcyclohexanone oxime (10). The infrared spectrum was identical with that of the previously prepared oxime.²²

I. R. Spectrum (No. ³³⁷ 6806, film): 3400, 2980, 1650, 1450, 1375, 1350, 1260, 1090, 1050, 1000, 950, 875 cm^{-1} . Fig. 13.

(d) Reaction of 4-Oxocyclohexylmethyl α -chloroacetate (36) with hydroxylamine in Ethanolic Potassium Hydroxide. 4-Oxocyclohexylmethyl α -chloroacetate (36) 12.8 g (0.073 mole) and 9.09 g (0.13 mole) of hydroxylamine hydrochloride were added to a solution of 36 g potassium hydroxide in 180 ml of 95% ethanol. The mixture was stirred and refluxed for 19 hr. It was cooled, poured into 250 ml of water and neutralized with concentrated hydrochloric acid. The solution was extracted five times with ether and the ether extracts were combined and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure left 6.6 g of a viscous yellow oil.

I. R. Spectrum (No. 7007, film) is superimposable with that of the oxime prepared from 4-hydroxymethylcyclohexanone except for a small band at 1710 cm^{-1} .

Purification of Phthalic Anhydride. To commercial phthalic anhydride placed in an Erlenmeyer flask, enough cold chloroform was added to dissolve almost all of the solid. The mixture was stirred for 0.5 hr at room temperature and filtered. Upon evaporation of the chloroform white long needles of pure phthalic anhydride were obtained; mp $131\text{-}132^\circ$, lit.³³ 131.6° .

4-Methylenecyclohexylmethyl Hydrogenphthalate (39).
A mixture of 75.6 g (0.6 mole) of 4-methylenecyclohexanemethanol, 88.8 g (0.6 mole) of pure phthalic anhydride and 48 g (0.6 mole) of dry pyridine was placed in a 300 ml round bottomed flask fitted with a condenser. It was magnetically stirred and heated in a water bath for 3-4 hr. The resulting viscous mass was dissolved in an equal volume of acetone. Slowly, with stirring, 66 ml of concentrated hydrochloric acid diluted with approximately an equal volume of crushed ice was added. More ice was added until the oil completely precipitated. The solid was separated by filtration, washed several times with ice water and ground thoroughly in a mortar with ice water, filtered and washed again. It was dried in air, yielding 162 g (98.5%), mp $102\text{-}103^\circ\text{C}$.

I. R. Spectrum (No. 337 6798, mull). 2900, 2500, 1730, 1690, 1660, 1600, 1480, 1450, 1400, 1300, 1250, 1140, 1130, 1080, 1050, 960, 890, 800, 750, 690 cm^{-1} . Fig. 14.

Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{O}_4$: C, 70.05; H, 6.61.
Found: C, 69.82; H, 6.69.

4-Oxocyclohexylmethyl Hydrogenphthalate (40). To 27.4 g (0.1 mole) of 4-methylenecyclohexylmethyl hydrogenphthalate (39) dissolved in 250 ml of acetone in a three necked 300 ml round bottomed flask fitted with a condenser and an addition funnel, a 300 ml aqueous solution of 32 g (0.2 mole) of potassium permanganate containing 10 ml of concentrated sulfuric acid was added slowly. During the reaction the mixture was cooled in an ice-salt bath and stirred magnetically. The addition lasted 45-60 min. As the oxidation proceeded, a brown-black precipitate of manganese dioxide accumulated. This mixture was then filtered with suction and the manganese dioxide washed several times with acetone. The acetone was removed from the filtrate under reduced pressure and the water layer was neutralized with sodium bicarbonate to pH 6, and it was extracted five times with chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate. Upon evaporation of the solvent under reduced pressure a light yellow viscous oil (25.4 g) was obtained. The oil decomposes upon application of heat. Crystallization was successful once with one sample in dry ether, mp 120-122°.

I. R. Spectrum (No. 337 6799, mull): 3100, 2900, 1710, 1600, 1580, 1475, 1450, 1400, 1300, 1130, 1080, 950, 910, 750 cm^{-1} . Fig. 15.

Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{O}_5$: C, 65.21; H, 5.48.
Found: C, 63.38; H, 5.86.

4-Oximinocyclohexylmethyl Hydrogenphthalate (41).

(a) Preparation using Dioxane as Solvent. To 37.2 g (0.133 mole) of 4-oxocyclohexylmethyl hydrogenphthalate (40) a solution of 17.5 g (0.2 mole) of hydroxylamine hydrochloride in 40 ml of water, followed by a solution of 28.7 g (0.35 mole) of sodium acetate in 50 ml of water and 35 ml of dioxane was added and the mixture magnetically stirred and refluxed for 30 hr. The stirring was continued for 3 days. The orange mixture was transferred to a beaker and basified with potassium carbonate keeping the total volume down to about 300 ml. The deep red solution was extracted three times with ether to remove any traces of insoluble oils. The water layer was reacidified with concentrated hydrochloric acid and extracted five times with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate. Upon evaporation of the solvent under reduced pressure, 26.6 g of a yellow, gummy, opaque oil was obtained. To this mass, after addition of hot dry benzene, stirring and allowing to cool, yellow crystals of phthaloxime separated. The mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The residual oil was dissolved in hot ethyl acetate; enough petroleum ether was added to cause a slight turbidity, and the solution was allowed to cool. Upon standing in the refrigerator, the oxime crystallized. Recrystallization gave 4.0 g (10.3%) of 41, mp 157°.

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.87; H, 5.84; N, 4.81. Found: C, 62.06; H, 5.37; N, 4.77.

I. R. Spectrum (No. 337 6800, mull): 3250-2950, 2500, 1850, 1730, 1695, 1660, 1600, 1450, 1250, 1200, 1140, 1130, 1070, 1035, 1000, 960, 910, 800, 750, 700, 650 cm^{-1} .

Fig. 16.

(b) Using Ethanol as Solvent. To 4-oxocyclohexylmethyl hydrogenphthalate (40) (21.5 g, 0.074 mole) dissolved in 100 ml of 95% ethanol, a solution of 7.5 g (0.087 mole) of hydroxylamine hydrochloride and 12.5 g (0.153 mole) of sodium acetate in 50 ml of water was added. The clear solution was refluxed for two hr on the steam bath, and stirred magnetically for two more days at room temperature. The ethanol was removed under reduced pressure and the resulting mixture was extracted with chloroform seven times. The combined chloroform extracts were dried over anhydrous magnesium sulfate. To the gummy yellow oil that was obtained after the removal of the solvent under reduced pressure was added 100 ml of benzene and the mixture heated over the steam bath to cause solution, a small amount of a thick oil separated which was filtered and washed again with more hot benzene. The combined filtrates were evaporated to dryness yielding a clear, viscous oil. This oil was dissolved in 25-30 ml of ethyl acetate with least amount of heat possible, and the excess solvent removed under a cold stream of air. Crystals began to appear as the volume of the solution decreased. The total volume was reduced to 15 ml, the mixture cooled in the ice box for several days and the crystals filtered with suction and washed with cold ethyl acetate giving 2.9 g (13.5%) of 41, mp 157°.

The infrared spectrum is superimposable with that of the oxime prepared using dioxane as the solvent.

Phthaloxime (43). Phthalic anhydride (3 g, 0.02 mole) in 15 ml of dioxane was treated with a solution of 2.1 g (0.03 mole) hydroxylamine hydrochloride and 3.3 g (0.04 mole) of sodium acetate in 30 ml water. The solution was refluxed for 24 hr and allowed to stir at room temperature for an additional two days. It was brought to pH 3 with concentrated hydrochloric acid. The white precipitate that

separated was removed, washed with water and dried in a vacuum desiccator giving 2.1 g (64.4%) of 43, mp 220-225°; lit.³³ 220-226°.

I. R. Spectrum: (No. ³³⁷4590, mull): 3130, 1850, 1780, 1710, 1600, 1455, 1375, 1280, 1180, 1135, 1075, 1018, 970, 880, 780, 690 cm^{-1} .

Acetyl Phthaloxime (44). Phthaloxime (0.1 g) was dissolved in excess hot acetic anhydride, allowed to stir for 2-3 hr. at room temperature and poured into a beaker of crushed ice. Stirring was continued. In 2 hr a white fluffy solid separated which was removed and washed several times with water and allowed to dry in a vacuum desiccator. The product 44 (0.75 g, 60%) melted at 183-185°; lit.³³, mp 183-185°.

I. R. Spectrum (No. 8109, mull): 1850, 1815, 1790, 1750, 1620, 1475, 1375, 1290, 1170, 1085, 1030, 1020, 970, 890, 790, 760, 700 cm^{-1} .

Resolution of 4-hydroxymethylcyclohexanone oxime (10)

Quinine Salt of Hydrogenphthalate Ester of 4-Hydroxymethylcyclohexanone Oxime (42). A solution of 9.45 g (0.029 mole) quinine in acetone was added to an acetone solution containing 8.48 g (0.029 mole) of the oxime 41. The salt crystallized as a fine powder, 11.3 g, mp 157-160°, $[\alpha]^{25}_D$ -93.5° (absolute ethanol, c = 2.0). Fractional recrystallization of this salt from absolute ethanol gave a first crop (8.1 g) of the salt, mp 187-188°C, $[\alpha]^{25}_D$ -98.2° (absolute ethanol, c = 2.0). Fractional recrystallizations were repeated until the D-line rotation of the salt remained constant. The mp's and $[\alpha]$'s of the subsequent recrystalliza-

tions were as follows: second recrystallization, 5.1 g, mp 188-189°, $[\alpha]^{25}_D$ -102.5 (absolute ethanol, c = 2.0); third recrystallization, 4.3 g, mp 188-189°, $[\alpha]^{25}_D$ -104.4°; (absolute ethanol, c = 2.0); fourth recrystallization, 2.7 g, mp 188-189°, $[\alpha]^{25}_D$ -112.0° (absolute ethanol, c = 2.0).

I. R. Spectrum (No. ³³⁷ 6801, mull) Figure 17: 3500, 3300 (m), 2900 (m), 2400 (2), 1700, 1670 (sh), 1610, 1590, 1500, 1460, 1420, 1395, 1350, 1290, 1260, 1250, 1245, 1200, 1170, 1095, 1090, 1040, 1000, 970, 955, 935, 860, 840, 815, 775, 730, 690 cm^{-1} . Fig. 17.

Anal. Calcd. for $\text{C}_{35}\text{H}_{41}\text{N}_3\text{O}_7$: C, 68.27; H, 6.71; N, 6.82. Found: C, 68.49; H, 6.81; N, 6.84.

Lithium Aluminum Hydride Reduction of a Mixture of Ethylbenzoate (45) and Cyclohexanone Oxime (46). (a) Using Ether as Solvent. Finely powdered lithium aluminum hydride (0.7967 g, 0.021 mole, 100% excess) was added to 50 ml anhydrous ether in a three necked 200 ml round bottomed flask fitted with an addition funnel and a reflux condenser fitted with a calcium chloride drying tube. To the magnetically stirred slurry a solution of 2.2632 g (0.02 mole) of cyclohexanone oxime and 3.0034 g (0.02 mole) of ethylbenzoate in 20 ml anhydrous ether was added dropwise while maintaining a gentle reflux. The stirring was continued for 3 hr and excess hydride was decomposed by addition of a few ml of wet ether followed by water. The ether layer was separated, the residue washed several times with more ether and the ether solutions combined and dried over anhydrous magnesium sulfate. Upon removal of the ether under reduced pressure, 4.5 g of a product which consisted of a mixture of benzylalcohol and cyclohexanone oxime was obtained. The IR spectrum of this mixture is identical with the IR of a 1:1 mole mixture of benzylalcohol and cyclohexanone oxime.

I. R. Spectrum (No. 8508, film): 3400, 2980, 1660, 1490, 1450, 1340, 1250, 1220, 1150, 1110, 1085, 1030, 1000, 960, 930, 900, 845, 740, 700 cm^{-1} .

(b) Using tetrahydrofuran as a solvent. A solution of 1.4145 g (0.0125 mole) of cyclohexanone oxime and 1.8771 g (0.0125 mole) of ethyl benzoate in anhydrous tetrahydrofuran was added slowly to a stirred slurry of 0.4980 g (0.0125 mole) of lithium aluminum hydride in THF. The reaction flask was cooled in an ice bath, and the stirring was continued for 3 hr. Excess hydride was destroyed with a saturated solution of 10 ml ammonium chloride. Stirring was continued until the aluminum hydroxide coagulated. The tetrahydrofuran layer was separated and the residue washed with ether several times. The ethereal solutions were combined and dried over anhydrous magnesium sulfate. Upon removal of the solvents under reduced pressure, an oil with a suspended solid was obtained. No evidence of unreduced ester was present.

The infrared spectrum was found to be superimposable with that of the mixture prepared using ether as solvent.

Reduction of Quinine 4-oximinocyclohexylmethyl Hydrogenphthalate (42). (a) Using ether as solvent. A slurry of 3.28 g (0.0053 moles) of quinine salt 42 in anhydrous ether was added slowly to a stirred slurry of 0.2130 g (0.0053 mole) of lithium aluminum hydride. The reaction flask was cooled in an ice-bath. The stirring was continued for 6 hr after which time the excess hydride was destroyed with a few ml of wet ether, water and concentrated ammonium chloride solution. The amount of water was kept at a minimum. The ether layer was decanted. More ether was added and the reaction mixture was stirred for 10 minutes, and the ether

layer decanted. This was repeated several times. The combined ether solutions were dried over anhydrous magnesium sulfate. Upon the evaporation of the ether under reduced pressure, 2.4 g of a thick oil was obtained. A solid resulted when the remaining traces of water in this oil were removed by azeotroping with benzene.

The theoretical amount of quinine present in the reaction mixture was 1.73 g, and the product weighed 2.4 g. The difference of 0.7 g was due to something other than quinine, most likely the oxime 10. Since the relative amount of quinine with respect to the oxime 10 in the product obtained was so large, the infrared spectrum of the product would be expected to be very similar to that of quinine. The product was recrystallized from benzene and the solid obtained was dried in an oven at 125-130° for a day. The melting point of this solid (167-169°) compared favorably with that of quinine (mp 169-172°).

I. R. Spectrum (No. 8546, mull): 3100, 2850, 1610, 1590, 1500, 1450, 1420, 1250, 1240, 1200, 1100, 1040, 910, 890, 860, 830, 765, 720 cm^{-1} .

(b) Using tetrahydrofuran as solvent. To a stirred slurry of 0.35 g (0.0087 mole) of lithium aluminum hydride in tetrahydrofuran, a tetrahydrofuran solution of the quinine salt 42 (4.3 g) was added slowly. The reaction flask was occasionally cooled in ice. The stirring was continued for 3 hr after which time the excess hydride was destroyed with 5-10 ml of a saturated solution of ammonium chloride. The stirring was continued until the aluminum salts formed a paste that stuck on the walls of the reaction flask. The liquid layer was decanted and the inorganic paste in the flask was washed ten times with ether. The ethereal solu-

tions were combined and dried over anhydrous magnesium sulfate. Upon removal of the solvents under reduced pressure and azeotroping the remaining traces of water with benzene from the resulting oil, 3.5 g of a solid product, mp 160-170° was obtained. Trituration of the solid with petroleum ether yielded 0.2 g of a red oil whose IR spectrum indicated it was unreduced ester 41. The solid remaining was quinine.

I. R. Spectrum (No. 8738, film): 3200, 2900, 1750, 1620, 1600, 1500, 1465, 1380, 1240, 1050, 800, 760 cm^{-1} .

Reduction of 4-Oximinocyclohexylmethyl Hydrogen-phthalate (41). A solution of 4.8 g (0.0165 mole) of oxime 41 in tetrahydrofuran was added slowly to a stirred slurry of 1.0 g (0.026 mole) of lithium aluminum hydride in tetrahydrofuran. The reaction flask was cooled in an ice bath. The stirring was continued for 3 hr, and the excess hydride was destroyed with 5-10 ml of a saturated solution of ammonium chloride. The slurry was stirred until the aluminum salts formed a thick paste. The liquid layer was decanted and the remaining paste was washed several times with ether. The combined ether solutions were dried over anhydrous magnesium sulfate. Upon removal of the solvents under reduced pressure and azeotroping the remaining traces of water in the residue with benzene, a thick, dark oil was obtained which appeared to be chiefly the oxime 10 but contaminated with some unreduced ester.

I. R. Spectrum (No. 8125, mull): 3300, 2900, 1700, 1650, 1600, 1585, 1450, 1375, 1310, 1260, 1200, 1090, 1040, 950, 900, 800, 750 cm^{-1} .

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ADDENDUM

Hydrolysis of Salt 42

Quinine salt 42 (2.50 g, 0.0041 mole) was added to a solution of 0.42 g of NaOH in 20 ml of water. The mixture was warmed and stirred for several hours and the precipitated quinine was removed as carefully as possible with suction filtration. The quinine was dried in a vacuum desiccator to give 1.5 g which appeared to be only quinine. The remaining solution containing 51 was concentrated to 15 ml.

ORD Curve (No. 742, 2.7% NaOH in H₂O, l = 1 dm):

$$\begin{aligned} \alpha_{610} &= -.042, \alpha_{600} = -.044, \alpha_{575} = -.046, \alpha_{550} = -.048, \\ \alpha_{525} &= -.050, \alpha_{500} = -.056, \alpha_{475} = -.060, \alpha_{450} = -.076, \\ \alpha_{425} &= -.090, \alpha_{400} = -.116, \alpha_{390} = -.126. \end{aligned}$$

Assuming that there is at most 1.0 g of 41 in solution, $c \leq 6.67$: $[\phi]_{610} = -1.8$, $[\phi]_{600} = -1.9$, $[\phi]_{575} = -2.0$, $[\phi]_{550} = -2.1$, $[\phi]_{525} = -2.2$, $[\phi]_{500} = -2.4$, $[\phi]_{475} = -2.6$, $[\phi]_{450} = -3.3$, $[\phi]_{425} = 3.9$, $[\phi]_{400} = -5.1$, $[\phi]_{390} = -5.5$.

A saturated solution of quinine was prepared using 0.016 g of quinine in 100 ml of 2.7% NaOH. The mixture was heated to assist solution, but not all of the quinine dissolved.

ORD Curve (No. 742, 2.7% NaOH, $c < 1.6$): $\alpha_{610} = -.008$,

$$\begin{aligned} \alpha_{600} &= -.008, \alpha_{575} = -.010, \alpha_{550} = -.010, \alpha_{525} = -.010, \alpha_{500} = \\ &-.010, \alpha_{475} = -.010, \alpha_{450} = -.012, \alpha_{425} = -.016, \alpha_{400} = -.020, \\ \alpha_{375} &= -.022, \alpha_{350} = -.028. \end{aligned}$$

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ADDENDUM

At each of ten points the proportionality factor, α for solution of 51 / α for solution of quinine in 2.7% NaOH, was computed for increasing the concentration of quinine such that the resulting quinine solution would give the same rotations as the solution containing 51. The proportionality constants were proportional to 5.25, 5.5, 4.6, 4.8, 5.0, 5.6, 6.0, 6.3, 5.6, 5.8. The variations in these constants indicated that the curves would not be superimposable which was verified by drawing a curve calculated from these data.

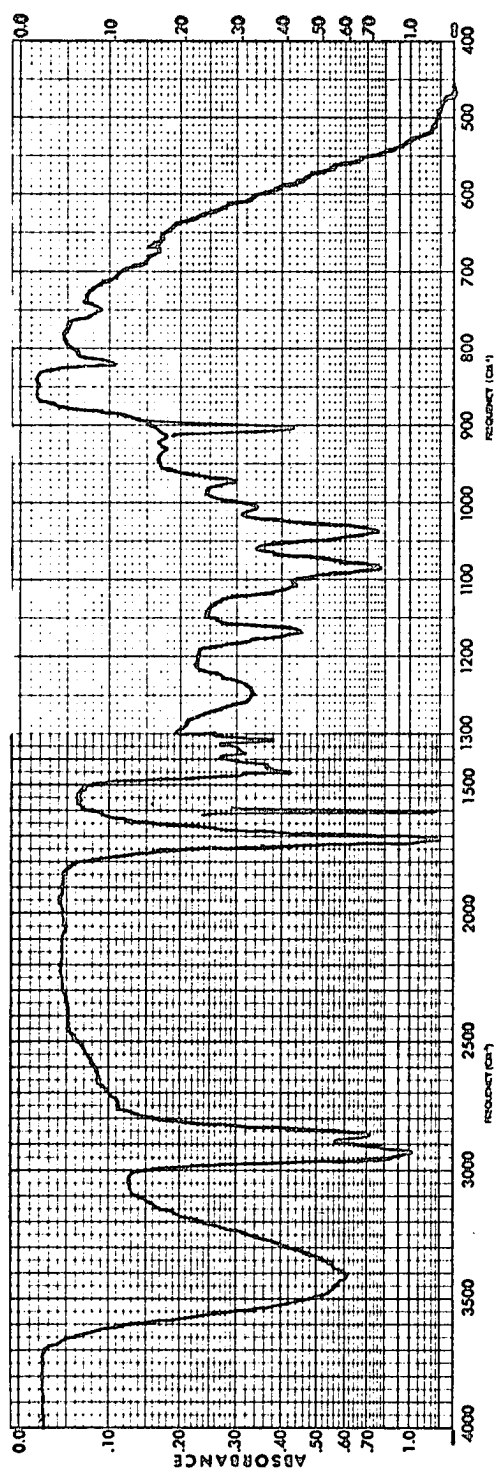


Fig. 12. I. r. Spectrum of 4-Hydroxymethylcyclohexanone

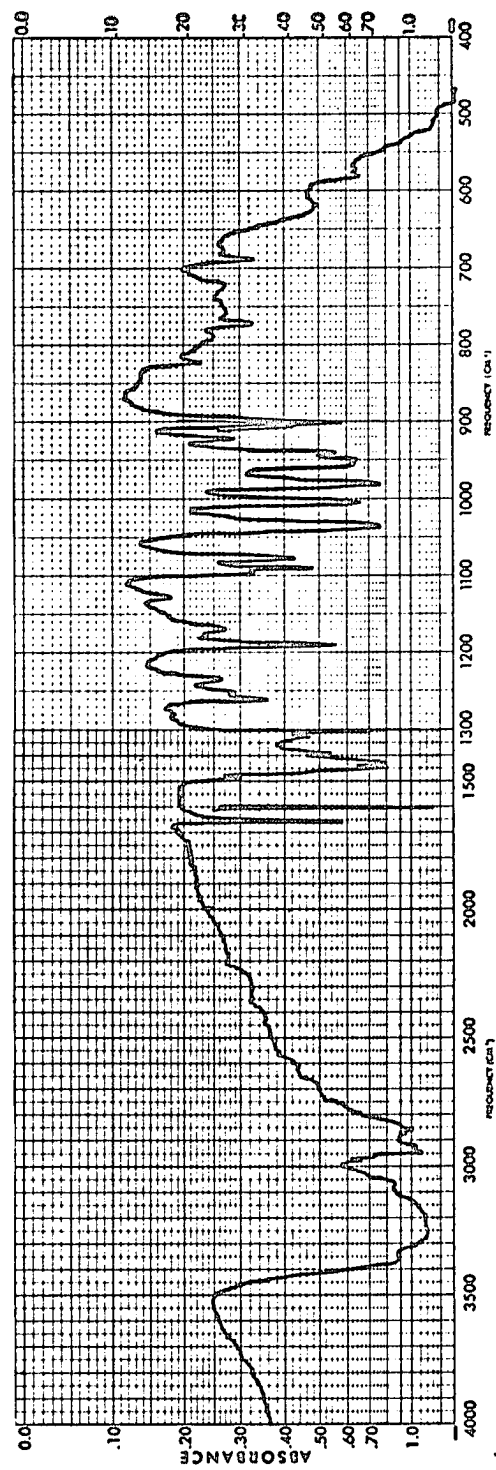


Fig. 13. I. r. Spectrum of 4-Hydroxymethylcyclohexanone Oxime

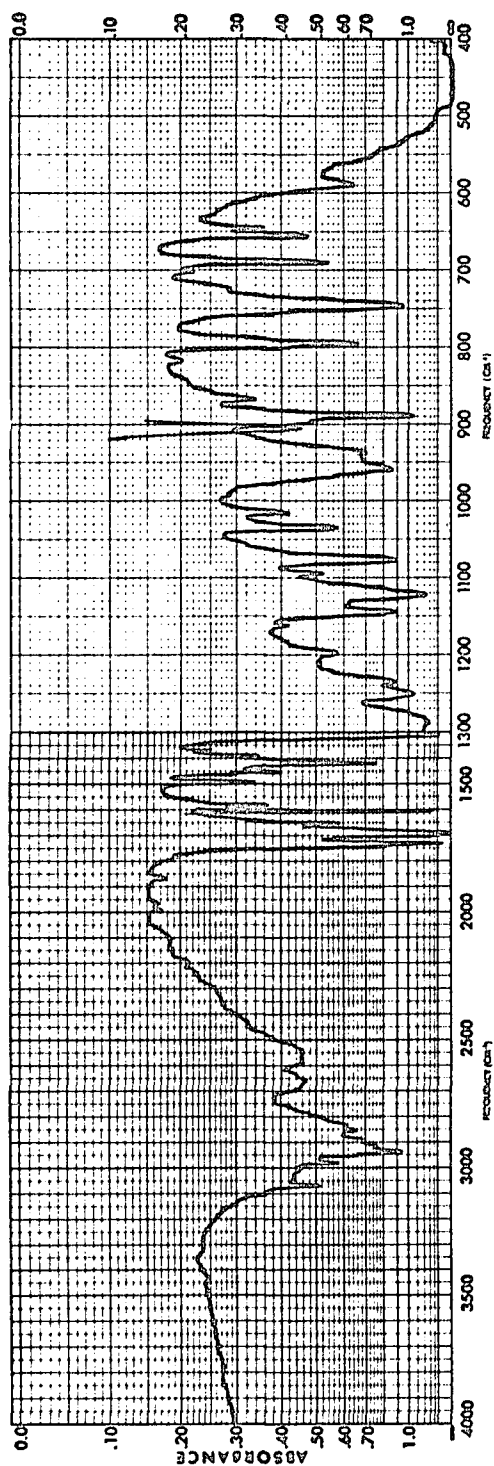


Fig. 14. I. r. Spectrum of 4-Methylenecyclohexylmethyl Hydrogenphthalate

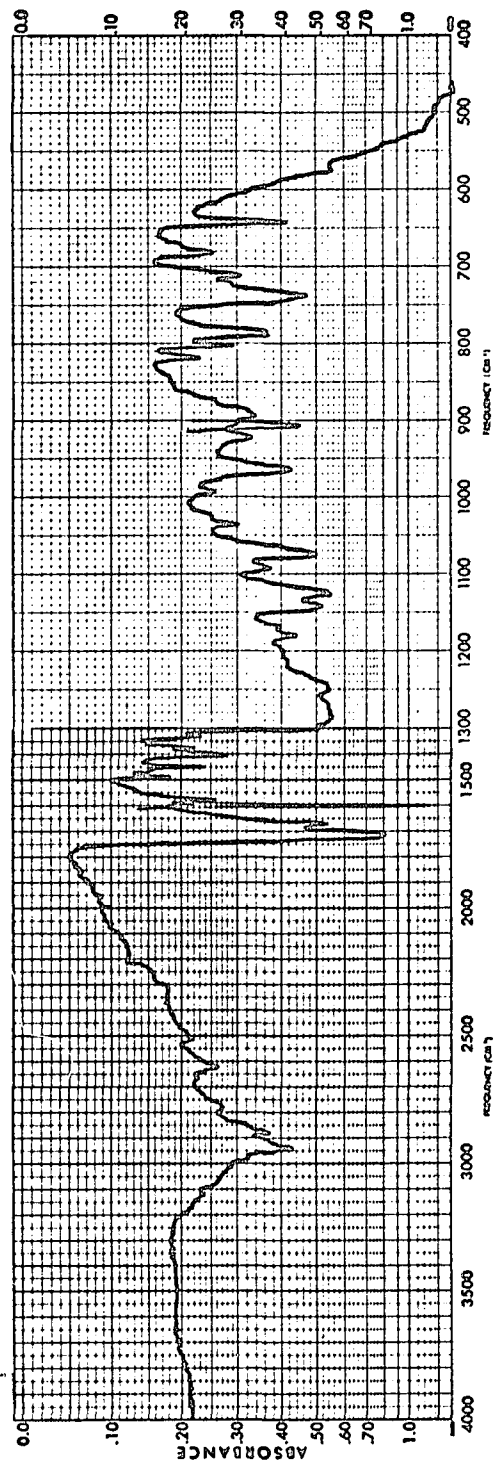


Fig. 15. I. r. Spectrum of 4-Oxocyclohexylmethyl Hydrogenphthalate

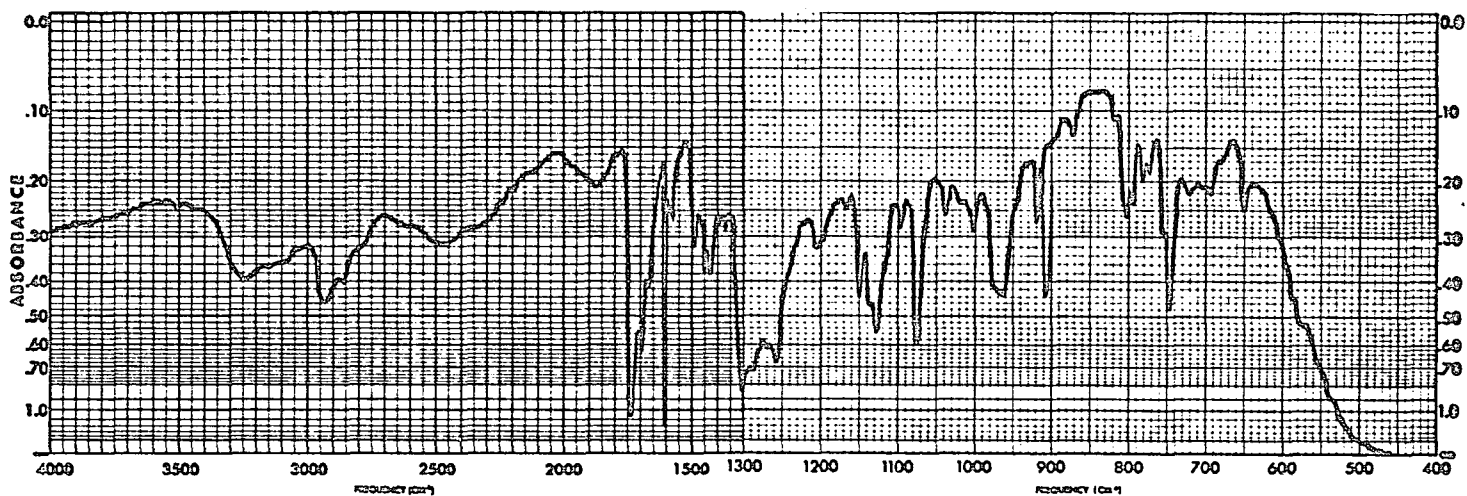


Fig. 16. I. r. Spectrum of 4-Oximinocyclohexylmethyl Hydrogenphthalate

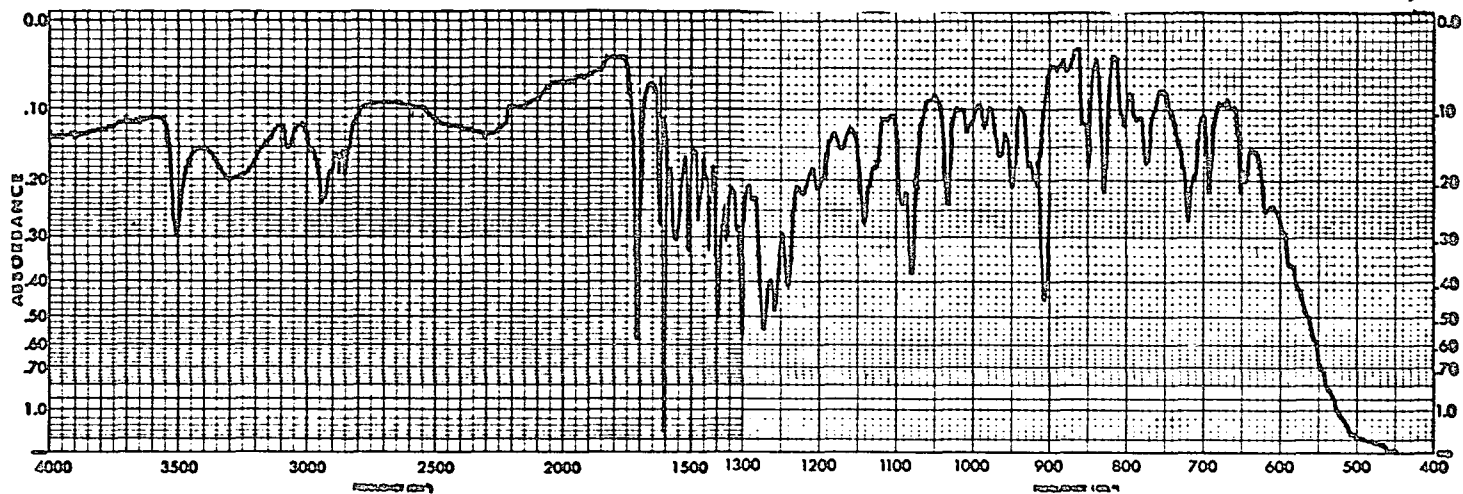


Fig. 17. I. r. Spectrum of Quinine 4-Oximinomethylcyclohexylmethyl Hydrogenphthalate

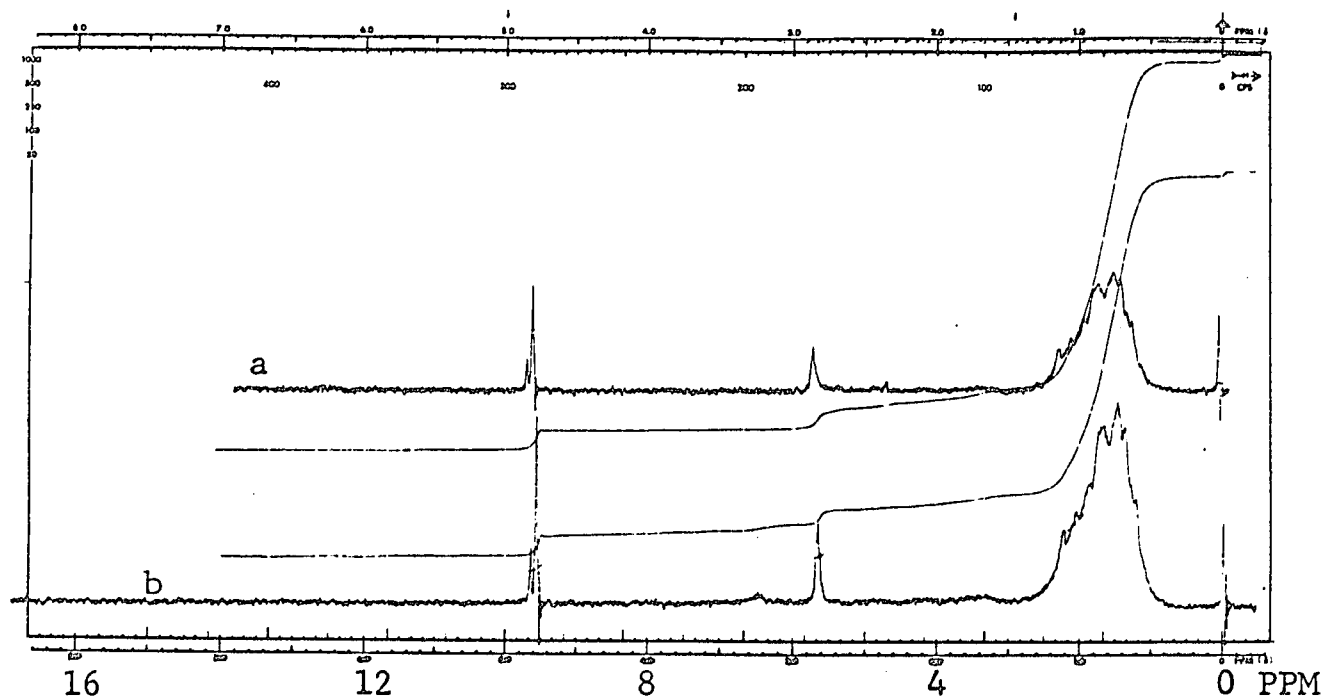


Fig. 18. N.m.r. Spectrum of 3-Cyclohexene carboxaldehyde
 a) in $\text{CCl}_4/\text{D}_2\text{O}$
 b) neat

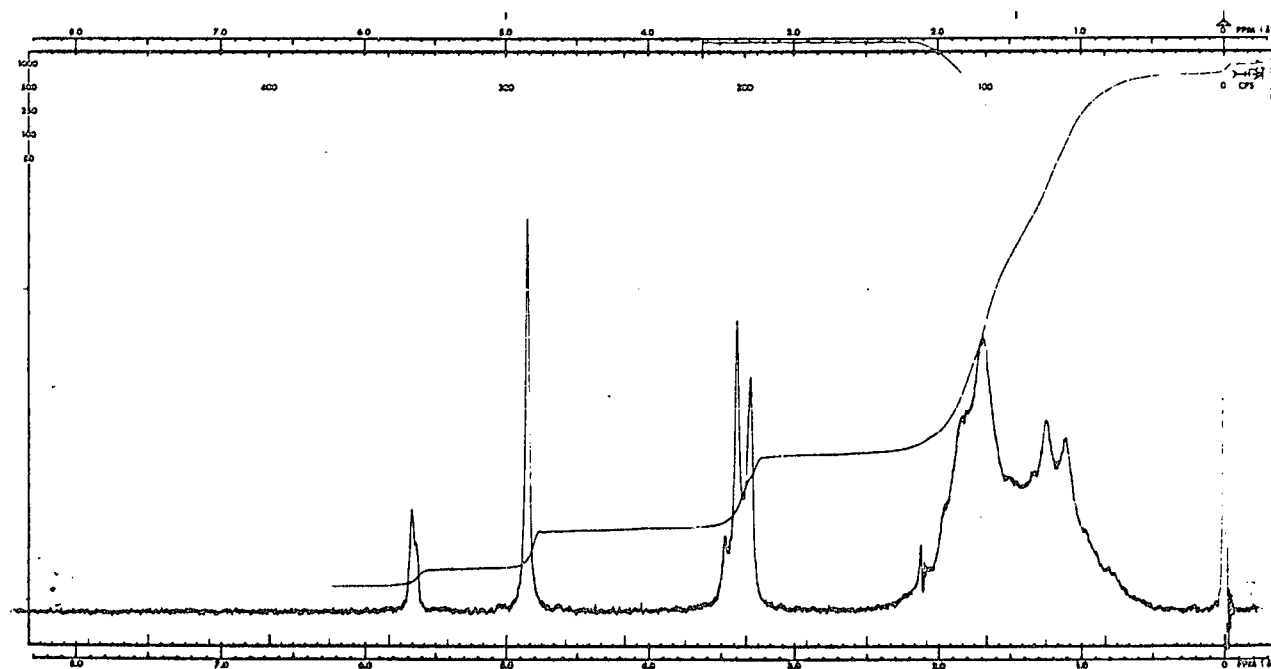


Fig. 19. N.m.r. Spectrum of 3-Cyclohexene-1-methanol

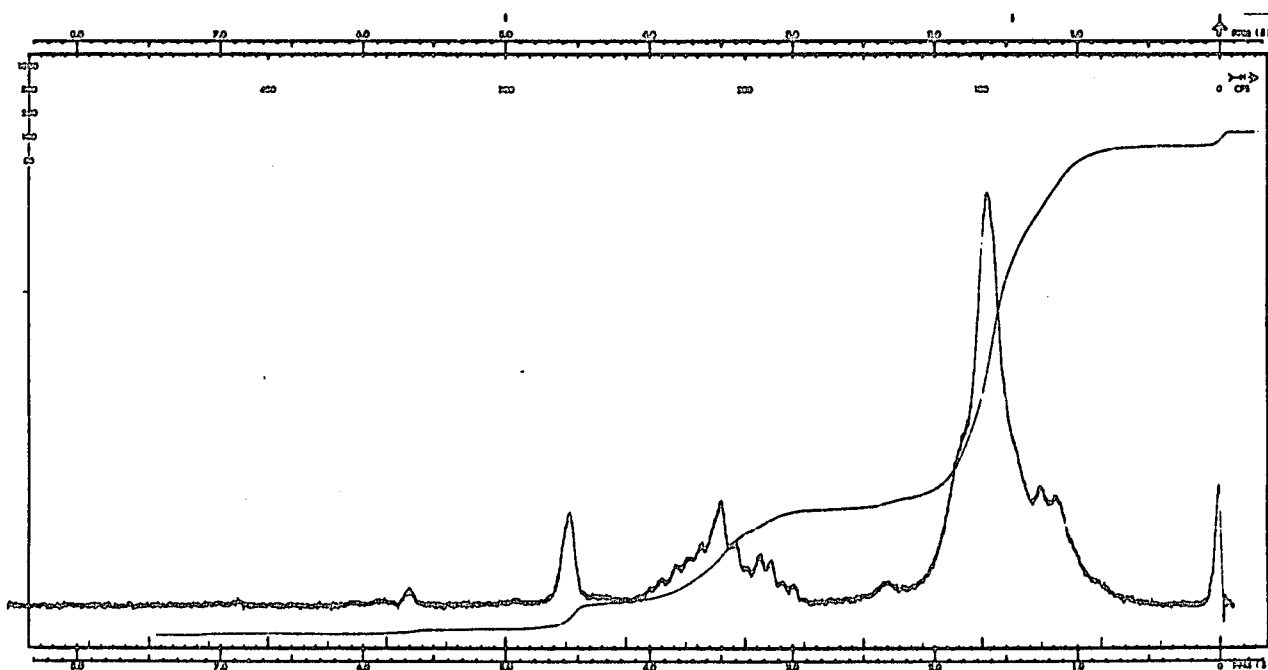


Fig. 20. N.m.r. Spectrum of Tetrahydro-pyranyl ether
of 3-cyclohexene-1-methanol

SUMMARY

The purpose of the research described in this dissertation was to synthesize the molecularly dissymmetric compound, 4-hydroxymethylcyclohexanone oxime (10) and resolve it into its enantiomers. Various routes for its synthesis have been investigated. The first route involved the reduction of 3-cyclohexenylcarboxaldehyde with lithium aluminum hydride to 3-cyclohexenylmethanol (19). The pyranyl ether derivative 27 was synthesized from 19 and subjected to hydroboration. The mixture of products resulted from the impurities in the commercial product used as starting material, 3-cyclohexenylcarboxaldehyde, as established by NMR and GLC.

The synthesis of ethyl 4-oxocyclohexanecarboxylate by the method of Singh and Saksena²⁹ was not successful.

Isonicotinyl, α -chloroacetyl, acetyl and phthalate ester derivatives of 4-methylene cyclohexanemethanol were prepared and oxidized to the 4-oxocyclohexanemethanol esters. The phthalate ester 37 yielded a ketone 40 which produced a crystalline oxime derivative 41. Hydrolysis of 41 gave the racemic oxime 10 of established structure.

For the resolution of the oxime 41, diastereomeric salts were prepared using various optically active bases as resolving agents including amphetamine, cinchonine and quinine. The quinine salt 42 yielded on fractional crystallization a salt which appeared to be optically pure. The insolubility of the salt and the lability of the oximino function complicated the hydrolysis of the ester and removal of the basic quinine.

Lithium aluminum hydride reduction of ester groups in the presence of oxime functions was developed into a satisfactory procedure with readily soluble molecules, but the method failed with the complex, insoluble quinine salt 42 of the phthalate ester. Mild basic hydrolysis of the ester gave a water solution which was optically active to a slight extent but from which the oxime could not be recovered in active form.

The results indicated that the hydroxymethyl substituent on the cyclohexanone oxime structure was perhaps less satisfactory than the carboxylic acid function in the analogous structure investigated by Mills.¹² The recommended alternative route for the investigation of molecular asymmetry in this type of molecule would be to use a basic moiety of sufficiently large molecular weight to minimize the water solubility. Such an approach should lead to a successful study of dissymmetric molecules.

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