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# A study of stereoselective attacks on enantiotopic faces of carbonium ions by chiral nucleophile.

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A STUDY OF STEREOSELECTIVE ATTACKS ON ENANTIOTOPIC FACES  
OF CARBONIUM IONS BY CHIRAL NUCLEOPHILE.

BY

JANET P. POTTER

A Thesis

Submitted to the Faculty of Graduate Studies through the  
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Windsor, Ontario

1973

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## ABSTRACT

A study of stereoselective attack by the chiral nucleophiles 2-butanol and 2-octanol on the enantiotopic faces of substituted benzhydryl carbonium ions is presented. An attempt to separate the diastereomeric ether products thus formed was attempted by gas chromatography in order that the diastereomeric ratio might be determined and hence whether attack by chiral nucleophile did indeed occur stereoselectively.

In one case, some evidence for the separation was obtained, but in general, this method was unsuccessful.

One trityl system was examined similarly, but again attempts to separate the diastereomeric ethers were unsuccessful.

## ACKNOWLEDGEMENTS

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## CHAPTER I

### INTRODUCTION

#### I. 1. Historical Introduction

The first outline of asymmetric synthesis was drawn up by Emil Fischer<sup>1,2</sup> in 1894, based on his experiments on the conversion of a sugar to its next higher homolog. Since that time there has been much work and discussion on the subject. Kuhn<sup>3</sup>, for example, in his work on the directing influence of circularly polarized light in the asymmetric decomposition of racemic mixtures, has shown that naturally occurring optically active substances may be formed in a similar manner, due to the right circularly polarized light which is found at the earth's surface in reflected sunlight.

An asymmetric synthesis has been defined as "a reaction in which an achiral unit, in an ensemble of substrate molecules (which must have either enantiotopic or diastereotopic groups or faces), is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts."<sup>4</sup> Reactant, in this definition includes chemical reagents, solvents, catalysts and physical



forces such as circularly polarized light. The stereoisomeric products may be enantiomeric or diastereomeric, and they will be chiral and non-racemic with rare exceptions.

There are two types of relationship between groups residing in stereoisomeric environments, which are not equivalent. If the environments of the groups are enantiomeric, then they are termed 'enantiotopic'<sup>5</sup>, if they are diastereomeric then they are called diastereotopic.(fig.1).

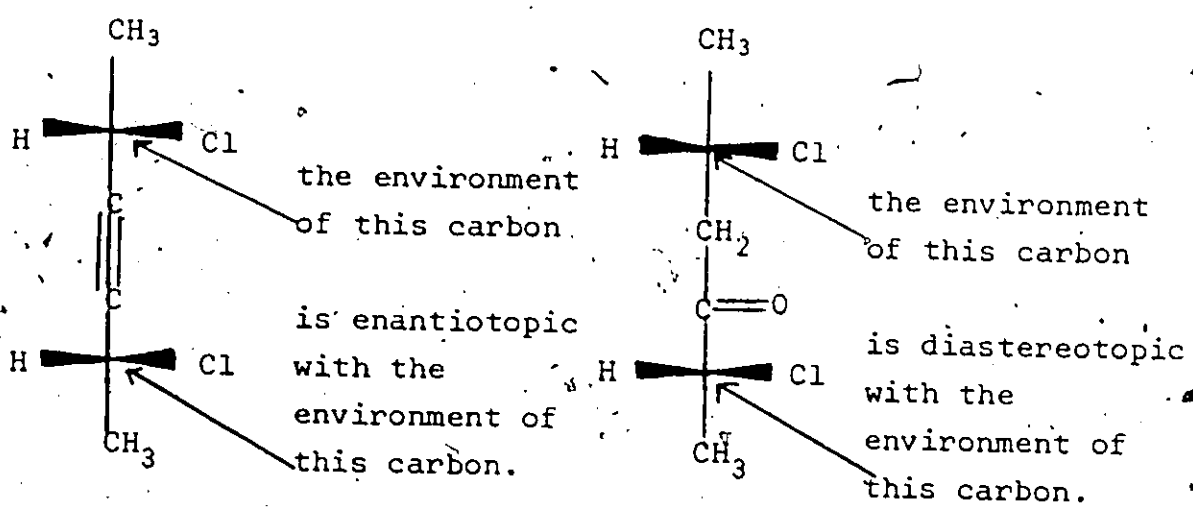


Fig.1.enantiotopic and diastereotopic groups.

Those molecules which are chiral cannot contain enantiotopic groups, thus any molecule possessing such groups must be achiral. As asymmetric molecules are chiral and non-axial, then they must not contain equivalent or enantiotopic groups.

Many molecules with enantiotopic faces have been used as reagents in asymmetric syntheses<sup>6,7</sup>. For example, if acetaldehyde (a prochiral reagent, i.e. a reagent

containing one or more carbon atoms, which can be converted to asymmetric centres by reaction) was considered to react with an achiral substrate A, the following results may be seen: (Fig.2).

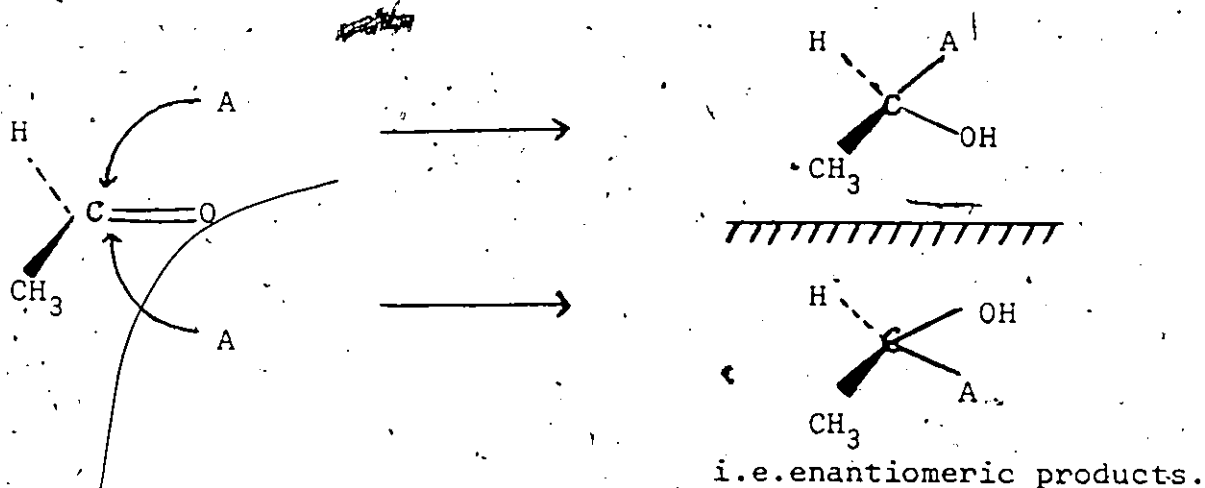


Fig.2.

If, however, a chiral reagent, with no other disymmetric influence was used, a different result may be predicted: (Fig.3)

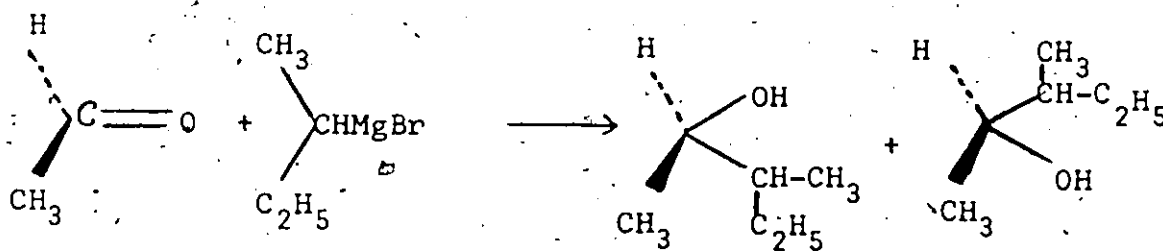
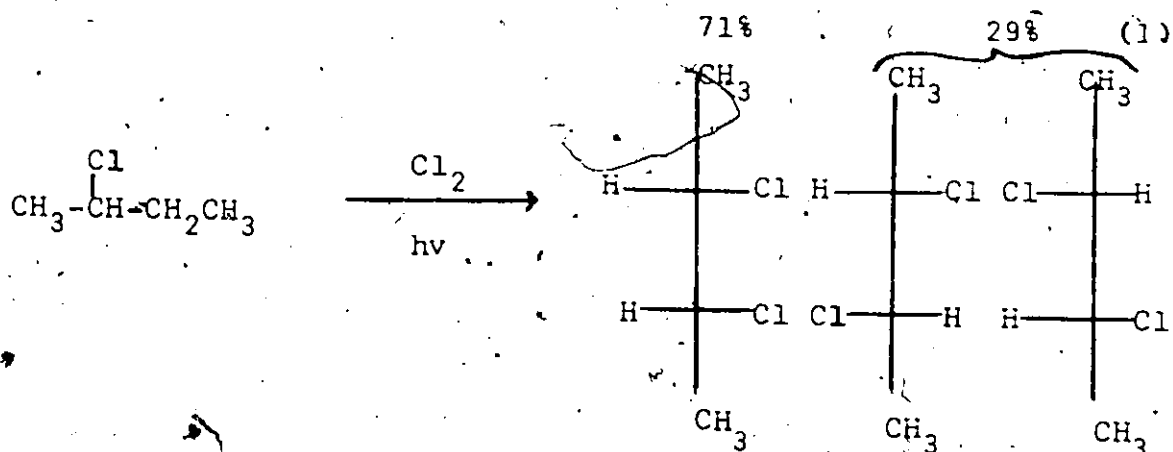


Fig.3.

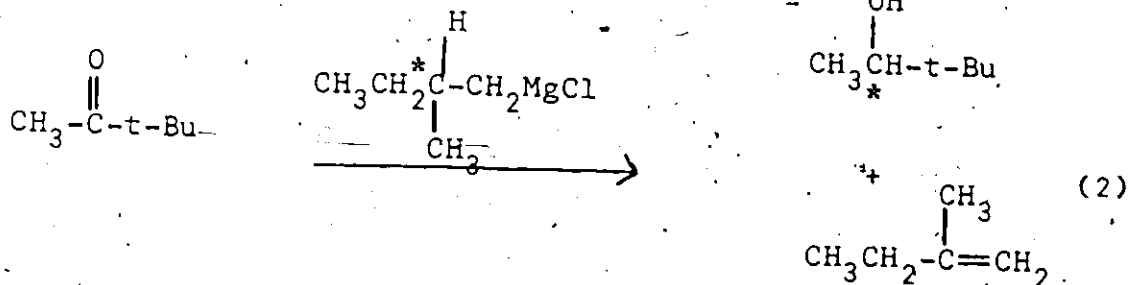
Mislow has classified asymmetric synthesis into two main types<sup>8</sup>. Those in which a new asymmetric carbon is produced in the presence of the old, without destruction of the latter, he has designated "conservative". Those in which the inducing asymmetric centre is destroyed during the course of the reaction, he has termed "self-immolative". An example of a conservative asymmetric synthesis may be given by the radical chlorination of dl-2-chlorobutane (Eqn.1).



The major product of the reaction is the meso compound (71%), 29% being the dl-2,3-dichlorobutane. The new asymmetric centre is created under the influence of the old, which is conserved during the course of the reaction.

An example of a self-immolative asymmetric synthesis can be given by the reduction of methyl t-butyl ketone by optically pure 7-methylbutylmagnesium chloride<sup>9</sup>. The product, methyl t-butyl carbinol is formed (Eqn.2) by a  $\beta$ -hydride transfer process which destroys the asymmetric centre of the Grignard reagent<sup>10</sup>. Thus, a new asymmetric centre is created in this reaction, at the expense of the old. Therefore the

term self-immolative is used.

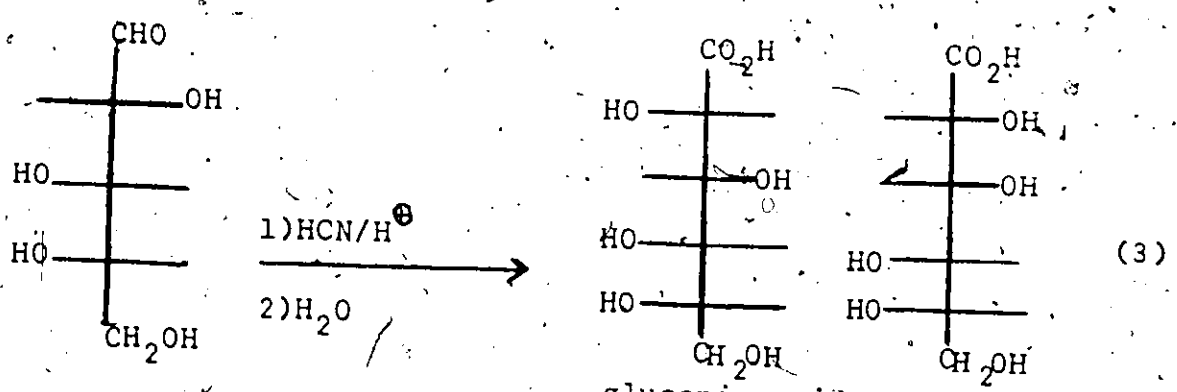


There are several methods of asymmetric synthesis known at present. These include both chemical and physical means:-

1. Reaction of an achiral (but prochiral) substrate with a chiral reagent, or, of an achiral (but prochiral) group within a chiral substrate with an achiral reagent to give a chiral product. This type of reaction may be called an asymmetric synthesis.
2. The reaction of one reagent with enantiotopic faces (i.e. prochiral) and an achiral (may or may not be prochiral) substance, in an optically active environment. This may be considered as asymmetric catalysis.
3. Reactions in which an achiral substrate and achiral reagent are used, together with a chiral physical force such as circularly polarized light, to give a chiral product. Such processes can be classified as absolute asymmetric syntheses.
4. Reactions in which one enantiomer of a racemic substrate, reacts preferentially with a chiral reagent. This type of

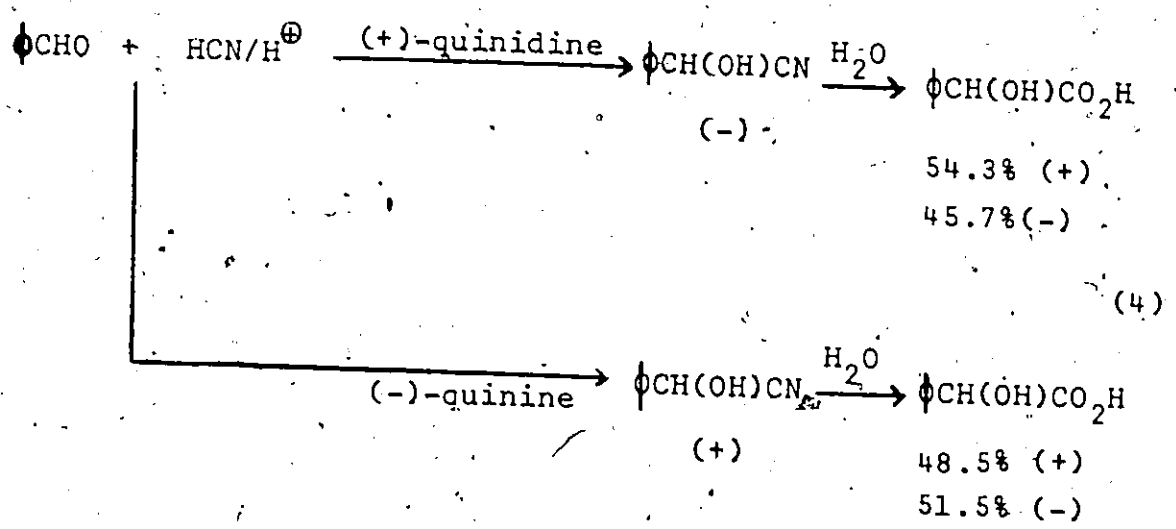
synthesis includes enzyme reactions. The energies of activation for the formation of diastereomers is obviously important, and for this reason this class of reaction is generally known as kinetic resolution. There is some similarity here to syntheses of type (1), except that in the latter it is not necessary for the substrate to be racemic.

The first two methods are examples of partial asymmetric synthesis<sup>11</sup>, in which a new asymmetric centre is created in a molecule which is usually, but not always, already dissymmetric. An example of type (1) can be given by the Kiliani synthesis, used to ascend the aldose series: (Eqn.3)



After hydrolysis the ratio of mannonic acid to gluconic acid was found to be 3:1, and this must be due to the cyanohydrins being formed at different rates, since the energy of activations will be unequal for the formation of the diastereomers. An example of type (2) was given by Bredig and Fiske<sup>12</sup>, who studied the addition of hydrogen cyanide to benzaldehyde in the presence of (+)-quinidine and (-)-quinine, as asymmetric catalysts (Eqn.4).

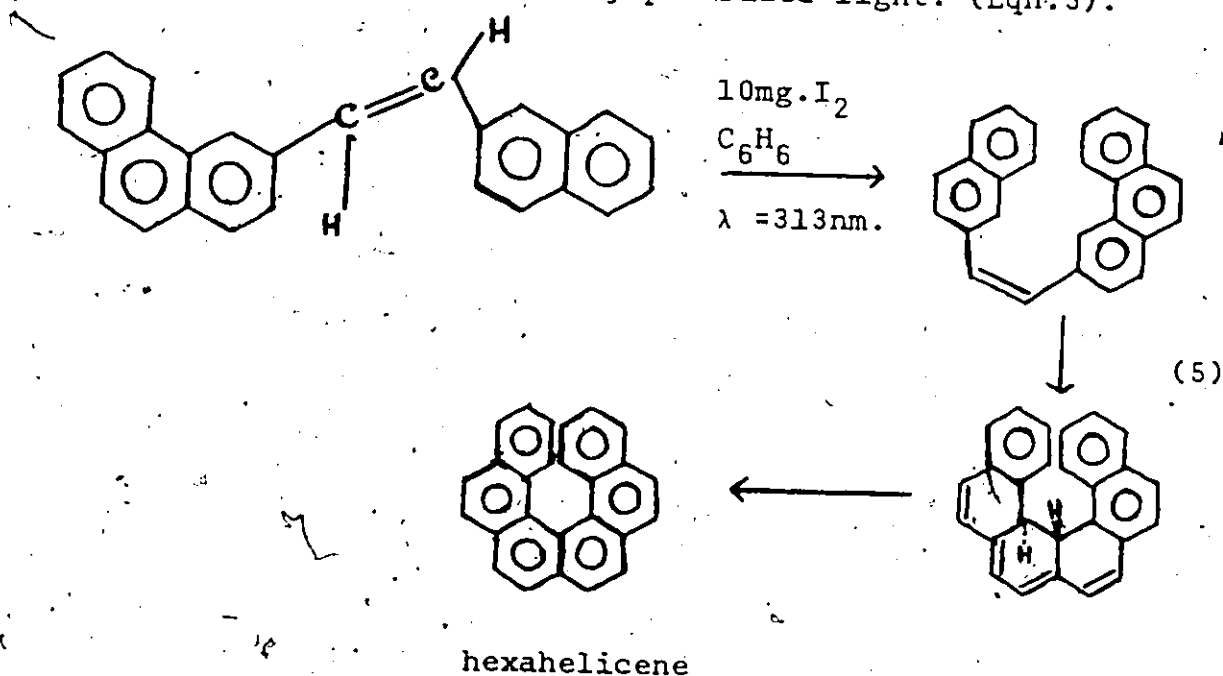
There are also a number of examples of reactions of



type (3)<sup>13-18</sup>. Interest in this type of synthesis was generated by the hypothesis that naturally occurring optically active compounds may be formed in this way, work in the early part of this century strengthening this argument<sup>19</sup>. For example, Davis and Ackerman<sup>17</sup> worked on a total asymmetric synthesis of tartaric acid using diethyl fumarate and anhydrous hydrogen peroxide in the presence of both right and later left, circularly polarized ultraviolet radiation of wavelength 2535Å. From the experiments using right circularly polarized radiation, the maximum rotations of the diethyl tartrate formed was found to be 0.073° and 0.030° in two separate experiments, readings which were larger than the maximum experimental error of ±0.02°.

Recently Moradpour et al.<sup>13</sup> have studied the photocyclisation of 1,2-diarylethylenes to the dihydrohelicenes and hence to hexahelicene in the presence of oxidants, such as iodine or oxygen, and circularly polarized light at 313nm.

Optically active hexahelicenes of opposite sign were produced with right and left circularly polarized light. (Eqn. 5).



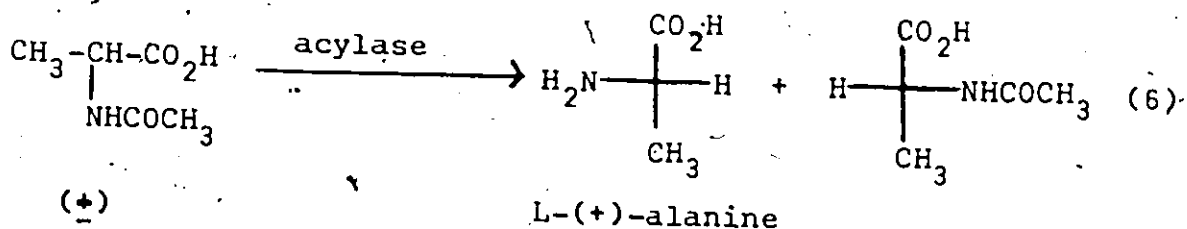
with right circularly polarized light  $[\alpha]_{436}^{23} = -30.0 \pm 0.3^\circ$   
( $c=2.08, \text{CHCl}_3$ )

with left circularly polarized light  $[\alpha]_{436}^{23} = +30.5 \pm 0.9^\circ$   
( $c=0.77$ ).

To confirm that the experiment was a method of asymmetric synthesis, rather than a partial asymmetric destruction, the racemic hexahelicene was subjected to irradiation under the same experimental conditions. After 110 hours of photolysis, 25% of the starting material had been destroyed by slow photodestruction. However, the specific rotations given by the remaining material were smaller, and of an opposite sign to the photocyclizations. Calvin, Bernstein and Buchardt<sup>14</sup> obtained similar results using circularly polarized light of varying wavelengths (290-410nm.).

There are examples of asymmetric synthesis using circularly polarized light in other types of reactions, such as free radical chlorination<sup>20</sup>, halogenation of double bonds<sup>15,16</sup>, and photoresolution of organochromium(III) complexes<sup>21</sup>.

The fourth type of asymmetric synthesis, kinetic resolution, is best exemplified by an enzyme system, these being highly stereoselective. For instance Greenstein<sup>22,22a</sup> has worked on the enzymatic resolution of acetylated racemic  $\alpha$ -amino-acids, for example dl-alanine. The l-isomer, which is naturally occurring, undergoes hydrolysis with swine-kidney acylase at least 10,000 times faster than the d-isomer which is therefore left in solution as the acetylated form. (Eqn. 6).



Several partial separations of enantiomers have been carried out by column chromatography. Snyder and co-workers<sup>23</sup> have achieved partial resolution of amino acids on a polystyrene resin which contained an optically active copper(II) complex, (N-carboxymethyl-L-valine) copper II. The complex has been found to co-ordinate more strongly with the L-amino acids, therefore on elution, the D-enantiomers concentrated toward the front of the amino acid band, and



were collected first by ligand displacement chromatography with ethylenediamine. The first fractions collected for valine were found to contain 80% D- and 20% L-valine under the optimum conditions, although the amount of resolution did of course vary with different amino acids. Snyder et al found that the extent of resolution decreased as the bulkiness of the alkyl group in the amino acid,  $^+NH_3CH(R)CO_2^-$  decreased, and therefore suggested that there may be some steric repulsion between this group and the isopropyl side chain of the N-carboxymethyl-L-valine. (Fig.4).

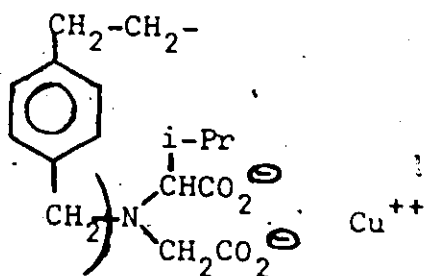
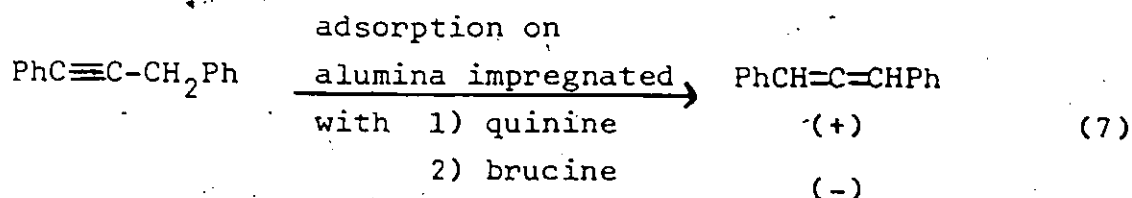


Fig.4.

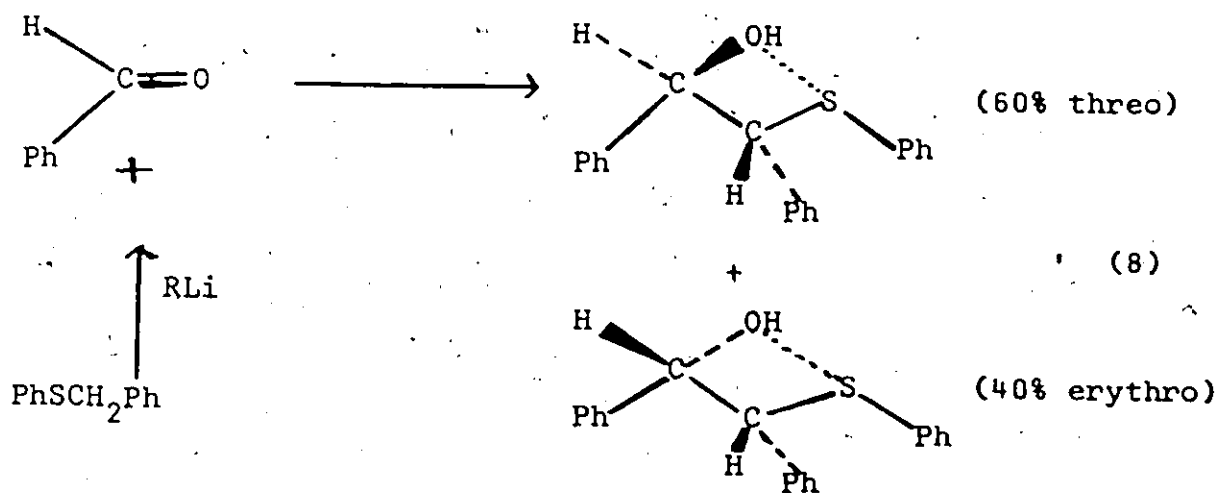
Similar studies by Rogozhin and Davankov<sup>24, 24a</sup> have shown that D,L-proline can be completely resolved by elution through an L-proline copper(II) complex which has been bound to a styrene-divinyl benzene copolymer. The results of these studies suggest that the resin and copper/valine complex may well be used for absolute configuration assignments. This type of resolution may be considered as kinetic resolution.

Jacobs and Dankner<sup>25</sup> were able to synthesize partially asymmetric allenes by a similar method. 1,3-diphenyl propyne and 1-(p-biphenyl)-3-phenyl-1-propyne rearranged

to the corresponding allenes by adsorbing the acetylinic compounds on columns of neutral activated alumina, impregnated with brucine or quinine. Brucine gave laevo products, and quinine dextrorotatory products. (Eqn.7).

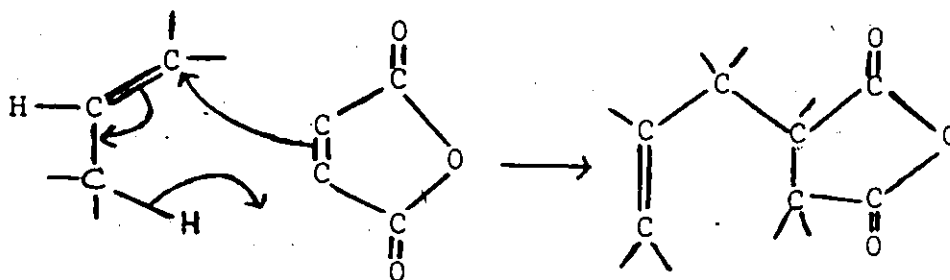


Kingsbury<sup>26</sup> has accomplished the asymmetric synthesis of diastereomeric hydroxy sulfides, sulfoxides and sulfones by condensation and oxidation reactions. It was found that the condensation of the lithium salt of phenyl benzyl sulfide with benzaldehyde proceeded to give 40% erythro and 60% threo 2-thiophenoxy-1,2-diphenyl-1-ethanol (Eqn.8).



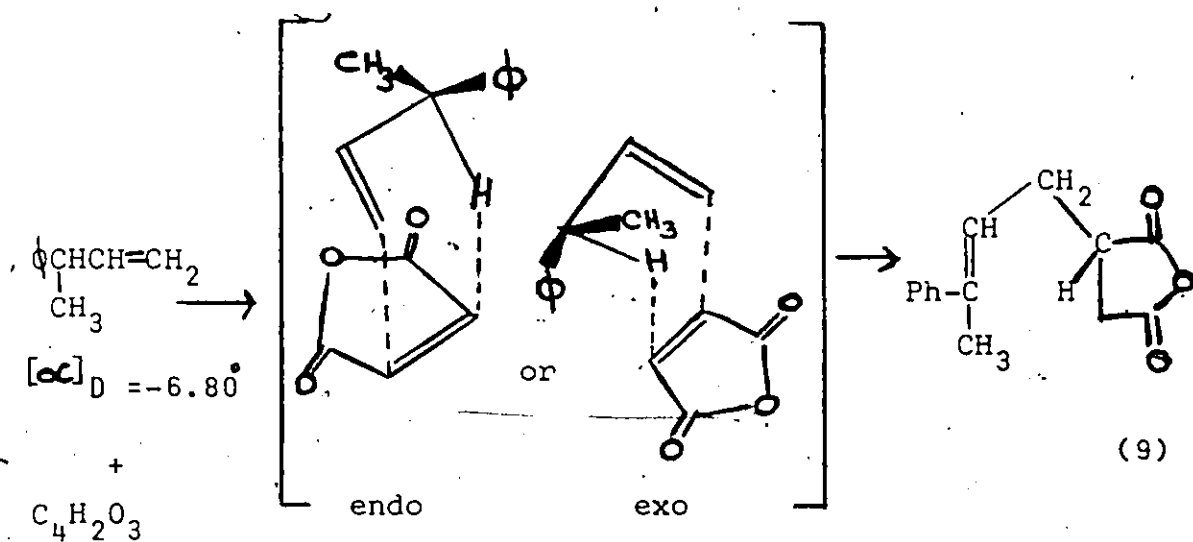
Similarly, for the condensation of the lithium salt of phenyl benzyl sulfone ( $\text{PhSCH}_2\text{Ph}$ ) with benzaldehyde, there was a predominance of the threo product. Condensation with the lithium salt of the phenyl benzyl sulfoxide reflected the same trend of producing more of the threo products.

In some reactions in which certain conformations of the transition state are preferred to others the products have been found to be optically active. For example in the "ene" reaction, which bears a similarity to the Diels-Alder reaction, e.g.

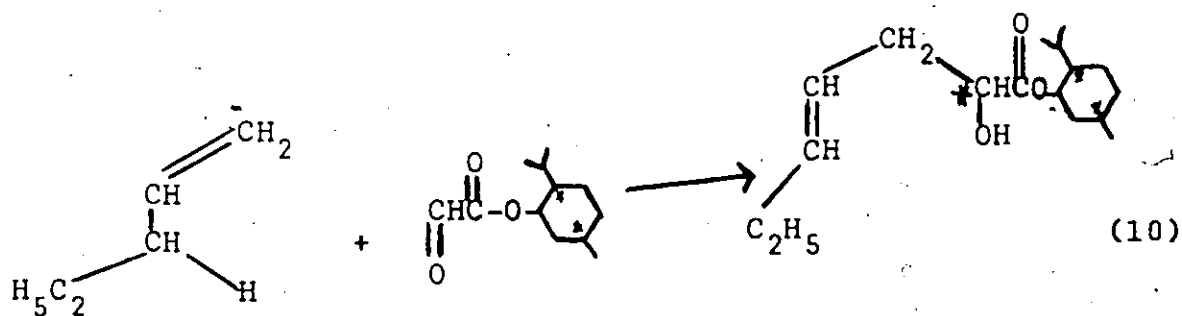


Hill and Rabinowitz<sup>27</sup> demonstrated that in the reaction of optically active (R)(-)-3-phenylbut-1-ene with maleic anhydride the preferred conformations of the six-membered cyclic transition states, as shown below (Eqn.9), would lead to the formation of the same enantiomer of 3-phenylbuten-2-yl succinic anhydride. That is, the orientation of the product appears to be governed by steric considerations.

Further studies by Achmatowicz and Szechner<sup>28</sup> on the ene condensation of pent-1-ene and (-)-menthylglyoxylate in the presence of a Lewis acid catalyst showed that the optical yield



of the reaction was dependant on temperature, solvent and catalyst. For instance, the configuration of the product, (-)-menthyl-2-hydroxy-4-heptenoate, was found to be R when aluminum chloride was used as catalyst, but S when stannic chloride, boron trifluoride or titanium tetrachloride were used. (Eqn.10). Without a catalyst the configuration was R,

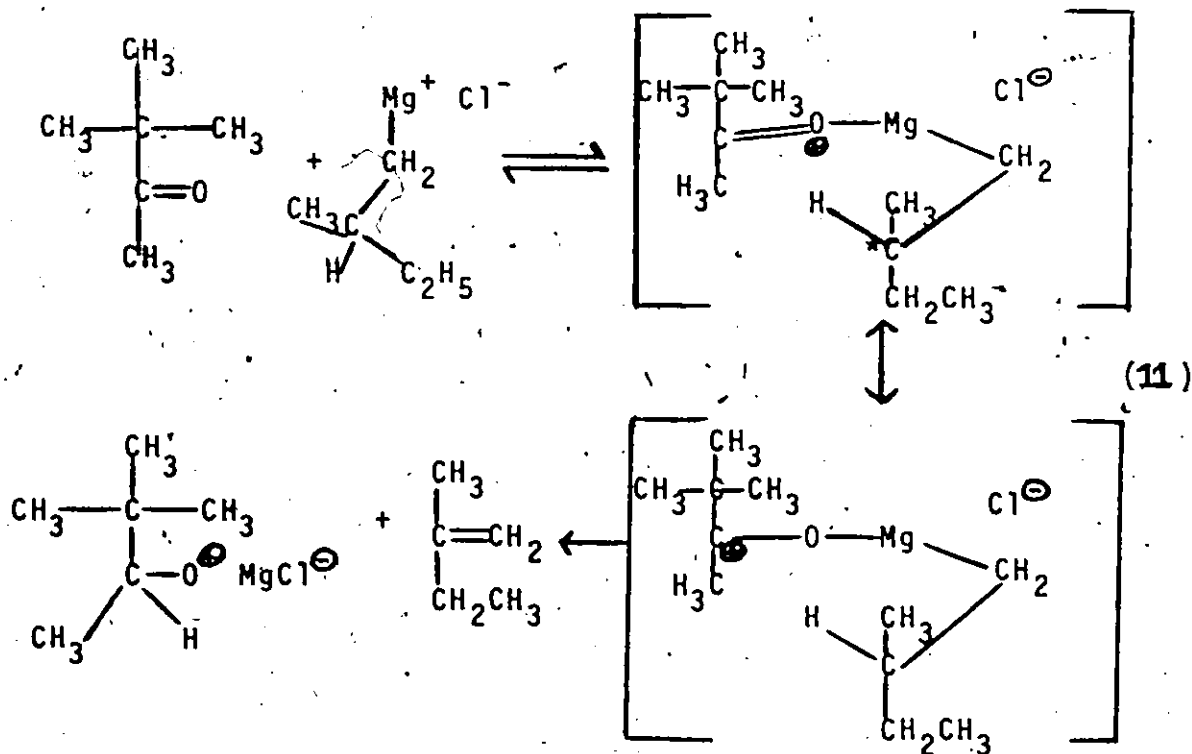


but the optical yield was very much lower than those preparations carried out using a catalyst. The authors believe that the Lewis acids govern the equilibrium between the four

possible transition states, owing to their ability to form complexes with carbonyl groups.

Asymmetric reductions of prochiral carbonyl compounds by various methods are of considerable interest. Some examples are described here:

Mosher et al<sup>9,29-35</sup> have studied a series of partial asymmetric reductions using optically active Grignard reagents. For example, Mosher and La Combe<sup>9</sup> showed that (+)-2-methylbutyl magnesium chloride reduced methyl t-butyl ketone to give the carbinol with a rotation of 13.0-13.7% of the rotation for the pure dextro isomer. The results support the mechanism proposed earlier by Whitmore<sup>36</sup>, as proceeding via a six-membered ring complex. In this case the mechanism was proposed as in equation 11.



The transition state shown, in which the t-butyl and methyl groups are on the same side of the ring, would have less steric hindrance than a transition state in which the ethyl and t-butyl groups were on the same side. Hence the activation energy required to give the former transition state should be less. It was thought that the position of the asymmetric carbon atom in the Grignard reagent was critical, Mosher expecting that if the asymmetric centre was delta or gamma to the magnesium atom, and therefore out of the six-membered ring, then there would be no noticeable effect on the stereochemistry of the reaction. To this end Mosher and La Combe<sup>29</sup> later worked on the reduction of methyl t-butyl ketone with (+)-3-methylpentylmagnesium chloride. Assuming the same type of transition state, the following may be written: (Fig. 5).

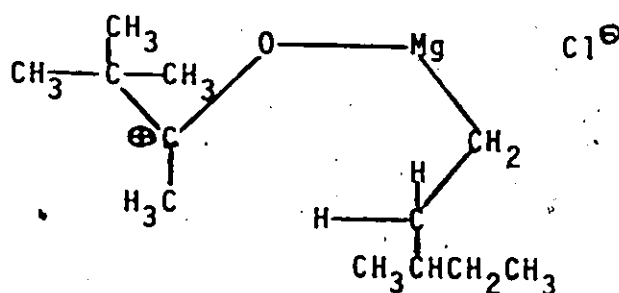


Fig. 5.

However, in this transition state there are two hydrogen atoms on the beta carbon atom; both have an equal chance to attack the carbonyl carbon atom, the attack therefore taking place both above and below the plane of the ring. Thus equal amounts of the two enantiomorphs would be

expected, and they were indeed found.

Similarly, Doering and Young<sup>37</sup> have carried out a partially asymmetric Meerwein-Ponndorf-Verley reduction using (+)-2-butanol, 6-methyl-2-heptanone and racemic aluminum-2-butoxide, to afford (+)-6-methyl-2-heptanol, corresponding to 5.9% asymmetric reduction. The reaction is believed to go through a 6-membered ring transition state akin to that for the Grignard reductions. (Fig. 6).

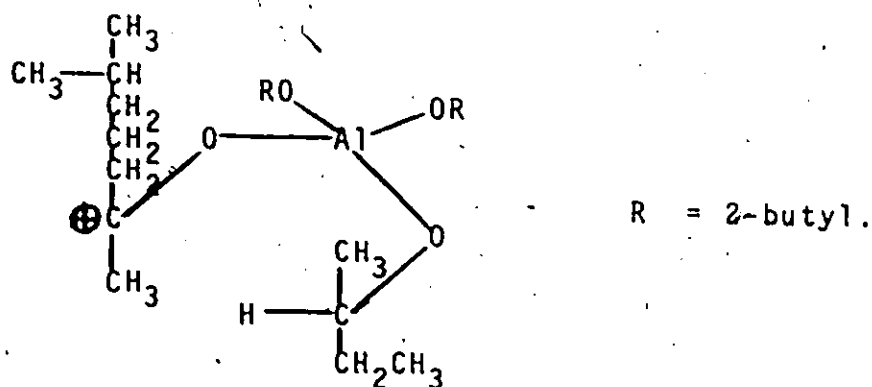


Fig. 6.

Again, when the asymmetric centre was not beta to the aluminum atom, as in Baker and Linn's work<sup>38</sup> the product did not show any observable activity. This can again be explained by the structure of the transition state, as above.

Mosher et al, in their series of papers, continued to study the asymmetric reductions of alkyl t-butyl ketones<sup>33</sup>, alkyl phenyl ketones<sup>34</sup> and cyclohexyl alkyl ketones<sup>35</sup> with (+)-1-chloro-2-methylbutane. For a series of alkyl t-butyl ketones, the absolute configurations of the products were deduced, and found to be related. In the case

of the alkyl phenyl ketones the latter was also found to be true, but in addition, it was found that the extent of asymmetric reduction increased as the steric bulk of the alkyl group increased. These findings are opposite to those for the alkyl t-butyl carbinol series, where, as the bulk of the alkyl group increased, the percent asymmetric reduction decreased.

In their studies on the benzophenone systems, Mosher and Parker<sup>30</sup> found that for the para-substituted systems, the products of the reduction with (+)-2-methylbutylmagnesium chloride, were optically inactive as expected, since a para group would be too far from the reducing centre to exert a steric effect. Ortho-substituted chlorobenzophenones, however, were reduced to give an active product corresponding to 10% asymmetric reduction.

Another type of asymmetric reduction was carried out by Klabunovskii et al<sup>39</sup>, who carried out the reduction of the carbonyl group in ethyl acetoacetate in the presence of a modified ruthenium catalyst. The catalyst was formed by using silica, as a support, which had been treated with 2% D-tartaric acid at pH 4.2-5.9, and 5% ruthenium. The reduction was carried out at 75°C and 80 atmospheres to give three percent optical activity in the resulting ethylhydroxybutyrate.

A Grignard synthesis of a tertiary alcohol was done by Allentoff and Wright<sup>40</sup> in the presence of optically

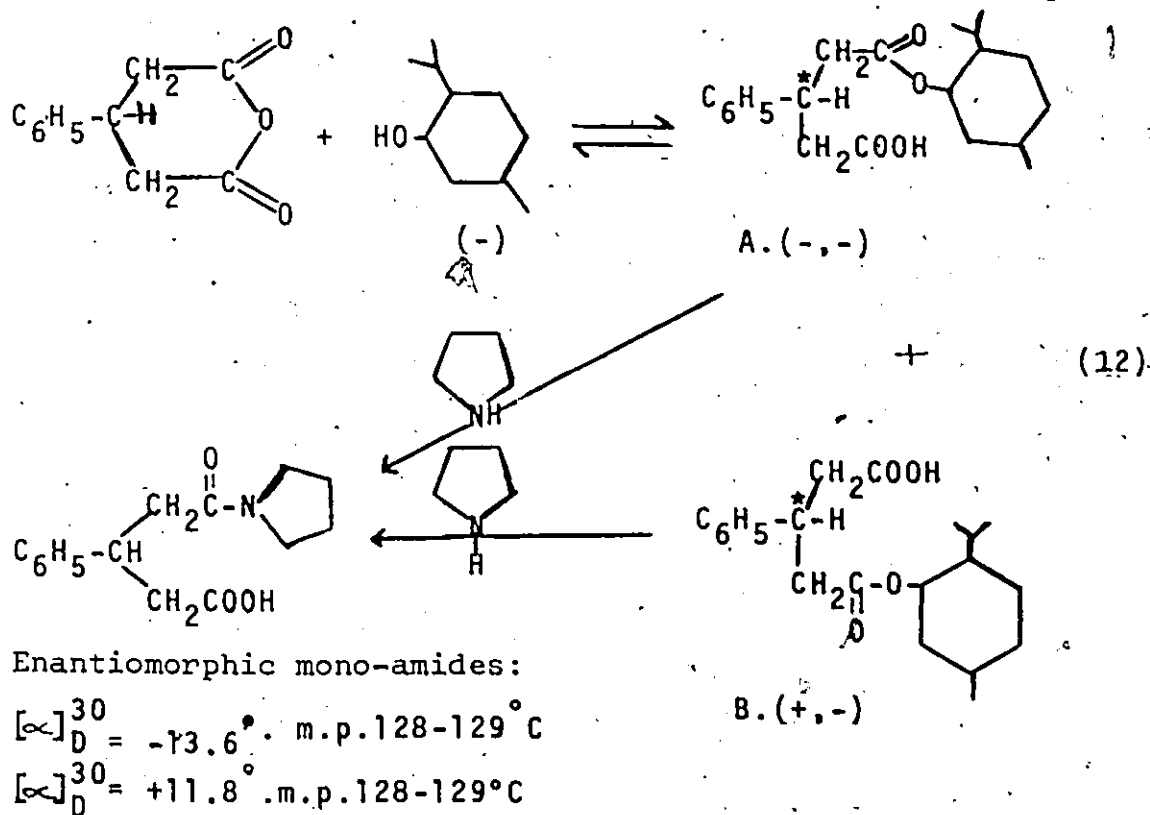


active solvents. Two different methods were used to prepare 2-phenyl-2-butanol; addition of 2-butanone to the bromobenzene Grignard reagent, and acetophenone addition to the ethyl bromide Grignard reagent. Three different optically active ethers were used as solvents, these being (+)-2,3-dimethoxybutane, D-(+)-mannitol-hexamethyl ether and D(-)-arabitol-pentamethyl ether. Monoethers were found not to induce asymmetry. The optical activity of the product was found to be five times as great when 2-butanone was used than when acetophenone was taken, and the sign of rotation of the product was different when dimethoxybutane was employed, than when using the other two ethers. Yields were also greater in dimethoxybutane. The greatest asymmetry produced by these authors was a 17.4% preponderance of one enantiomer, when 2-butanone and phenyl magnesium bromide were reacted in the presence of benzene-dimethoxybutane solvent. This result was comparable to that of Mosher and La Combe<sup>9</sup> using an optically active Grignard reagent, and thus if one equivalent of dimethoxybutane can be made to induce such an amount of activity, then the ether solvent must play a considerable part in the mechanism of the reaction.

Another example of asymmetric hydrogenation has been given by Ohgo et al<sup>41</sup>, using cyanocobalt-optically active diamine complexes on atropate. The hydrogenation of atropate using R(-)-1,2-propanediamine as a ligand with

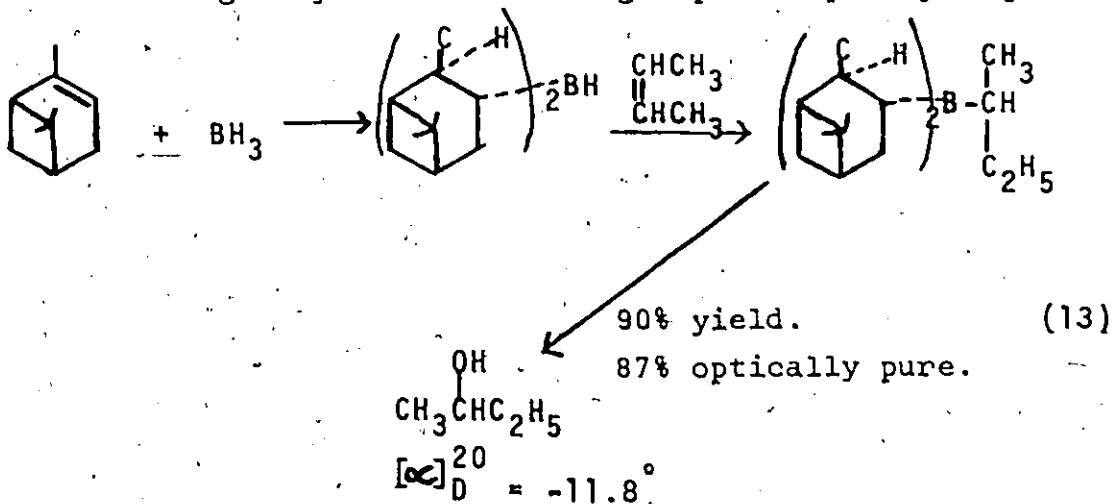
the cyanocobalt, gave a one percent optical yield of S(+)-hydratropic acid, with a rotation for the purified product  $[\alpha]_D = +1.1^\circ$ . When N,N'-dimethyl-1,2-propanediamine was used as the ligand, the optical yield of product rose to seven percent, a trend which was expected owing to the induction of asymmetry on the nitrogen atom, and therefore a more selective asymmetric co-ordination to the substrate.

A partial asymmetric synthesis has been carried out by Altschul et al<sup>42</sup> using  $\beta$ -phenylglutaric anhydride and l-menthol. Both possible diastereomers were formed, and those were converted by reaction with inactive pyrrolidine (tetrahydropyrrole) into enantiomeric mono-amides (Eqn.12).



The yields of diastereomers A and B were found to be in the ratio 54:46. By altering the reaction conditions, Altschul was able to ascertain that there was some degree of reversibility in the initial reaction to form diastereomers; however, it was not clear whether the major product was given by kinetic control or thermodynamic control. It could also be, as is thought for many enzyme systems, that a three point contact between enzyme and compound controls the unequal rates of reaction at two similar groups in a molecule.

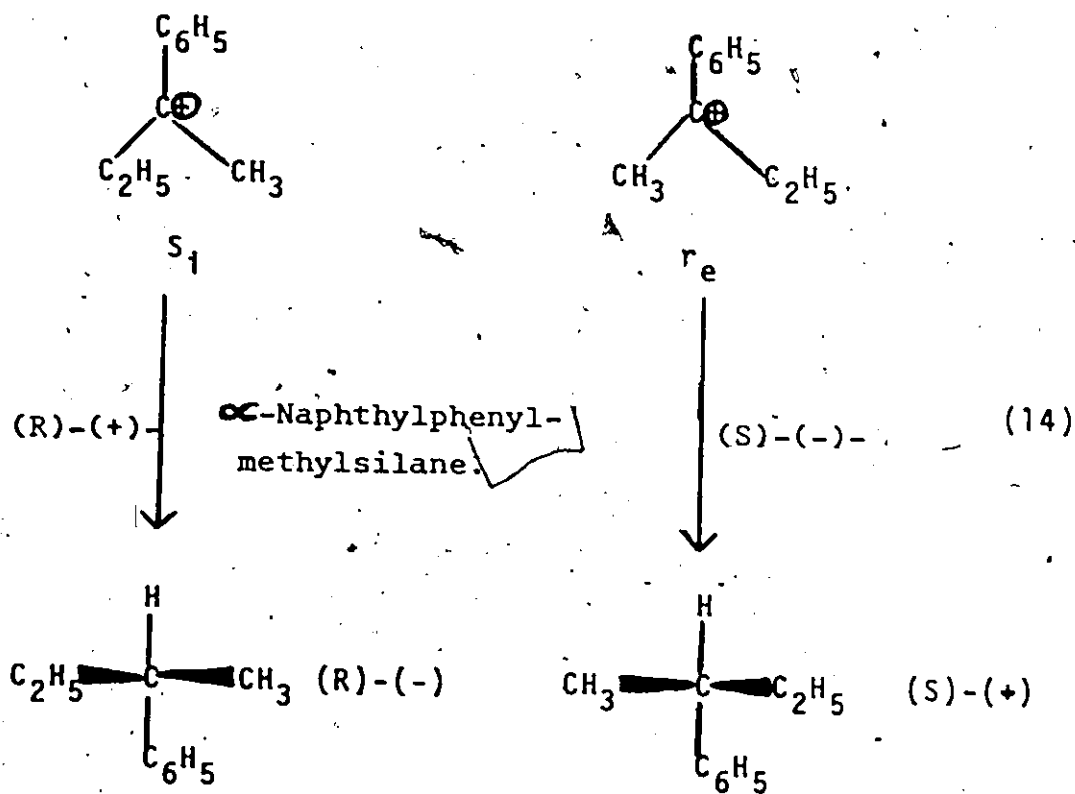
Brown and Zweifel<sup>43</sup>, in 1960, found that hydroboration reactions could be used conveniently and easily for the asymmetric synthesis of alcohols. Using  $\alpha$ -pinene and boron trihydride as the effective reagents, a complex of di-isopinocampheylborane was formed. To this a number of cis-olefins were added, and after work up, oxidation with sodium hydroxide and hydrogen peroxide, gave the alcohols in good yields with a high optical purity (Eqn.13).



Highly hindered and trans olefins react slowly with the di-isopinocampheylborane so that this reaction is of no real value for them.

## I.2. Nature of the Present Investigation.

Recently Fry<sup>7</sup> has worked on the stereoselective attack of a carbonium ion by chiral nucleophile, at one enantiotopic face. It was thought that the high reactivity of carbonium ions may preclude the formation of optically active products, since the necessary discrimination between the two faces of the carbonium ion may be too small to detect experimentally. However, Fry was able to obtain optically active 2-phenylbutane by the capture of the 2-phenyl-2-butyl cation with a chiral organosilicon hydride. The latter are known to reduce carbonium ions with a certain degree of sensitivity to stereochemical factors<sup>44</sup>. To this end, Fry used (R)-(+)- and (S)-(-)-1-naphthylphenylmethylsilane on the carbonium ion generated from 2-phenyl-2-butanol and found an enantiomeric excess of (R)-(-)- or (S)-(+)-2-phenylbutane, in the region of two to three percent (Eqn. 14). The data was interpreted as a preferential attack of (R)-(+)-silane on the *si* face of the cation, while the (S)-(-)-silane attacked the *re* face<sup>45</sup>. At the present time it is still uncertain whether the only important factor governing the magnitude and direction of stereoselectivity is steric

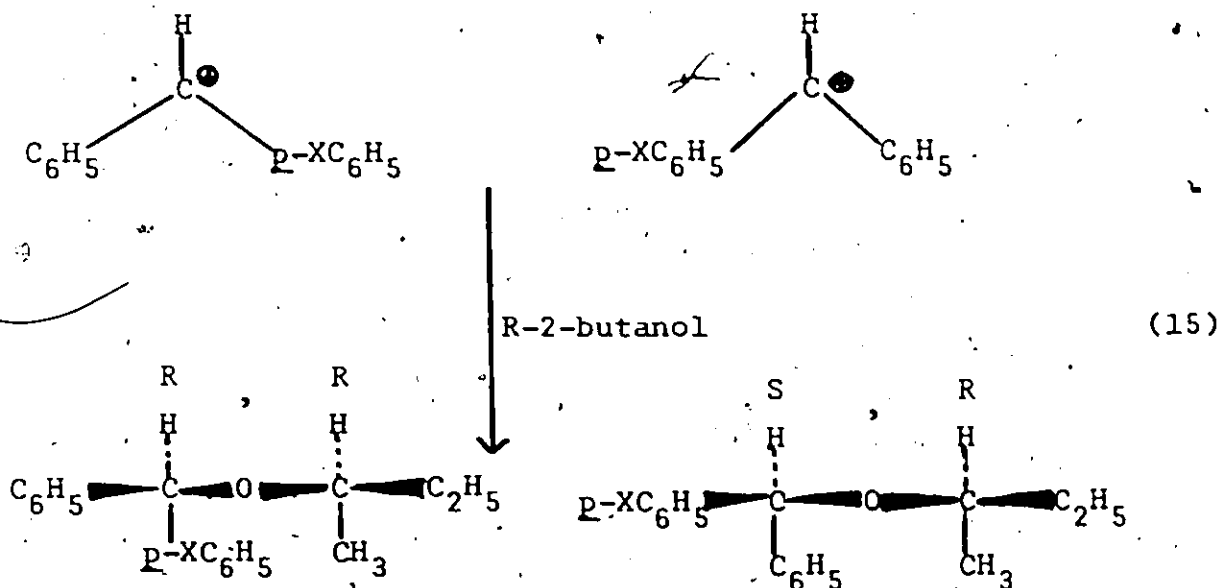


bulk, but further work, should help clarify matters.

In 1966, Murr<sup>46</sup> demonstrated that the solvolysis of 1-phenylbiphenyl- $\alpha$ -naphthyl methyl benzoate, and some of its derivatives, in acetone, ethanol and dioxane, proceeded with net retention of configuration. This was envisaged as a solvent capture of a free, asymmetric carbonium ion, a large mass-law effect supporting the idea of dissociated, ionic species. Since triaryl and diaryl carbonium ions are known to be non-planar<sup>47</sup>, it follows that a free carbonium ion may exhibit enantiomeric faces. The fact that in Murr's work net retention of configuration was found, then the rate of product formation must proceed faster than the rate of conversion of the enantiomeric forms. Also, it is more than

probable that the initial ionisation-dissociation of the parent benzoate gives unequal amounts of the enantiomeric carbonium ions.

In a similar manner to Fry, we have taken certain benzhydryl systems and trityl systems and generated the carbonium ions, which are known to be relatively stable. These carbonium ions have enantiomeric faces which would be expected to react at different rates with a chiral nucleophile. Considering attack of a substituted benzhydryl cation by R-(-)-2-butanol, one may obtain the following results: (Eqn.15).



That is, (R,R) ether or (S,R) ether will be obtained and their yields should not be equal. Likewise, using (S)-(+)-2-butanol, we would expect different amounts of (S,S) and (R,S) ethers to form. Although the theory on  $S_N1$  reactions would allow us to predict equal amounts of [(R,R) + (S,S)]

and [(R,S)+(S,R) ] ethers if racemic 2-butanol was used, we have proposed that the former theory be extended. That is one could postulate that since one diastereomer predominates in the reaction with chiral nucleophile, an unequal amount should also be produced with racemic nucleophile. e.g. If for (R)-(-)-2-butanol we have:

$$(R,R) = x\% \quad (S,R) = y\%$$

$$\text{and for (S)-(+), } (S,S) = x\% \quad (R,S) = y\%$$

then for the dl-alcohol we would expect:

$$(R,R) + (S,S) = 2x \text{ and } (R,S) + (S,R) = 2y$$

or, the relative amounts of the products will remain the same.

As can be seen, if racemic 2-butanol was used, the (R,R) ether and (S,S) ether will be an enantiomeric pair. Likewise, the (S,R) and (R,S) ethers will also be an enantiomeric pair. But the (R,R) and (S,S) ethers bear diastereomeric relationships to the other two products, and it is reasonable to assume that one may be able to separate diastereomeric products, for example by gas-liquid chromatography, followed by a determination of the stereochemistry of the products.

A further aim was to study both systems containing electron-donating and electron withdrawing substituents, and hence ascertain whether electronic effects are an important factor. Gas-liquid chromatographic analysis would also show easily any differences in the amount of each diastereomer obtained, for each type of substituent. This method is relatively quick and accurate compared to that of

Fry, in which the product was first purified by vapour phase chromatography and then its optical activity measured. Where there is only slight enantiomeric excess, the observed rotation will probably be also small, thus the error introduced by the polarimeter measurement would be relatively large, so making the method rather inaccurate for small amounts.

It has been known for several years that enantiomers exhibit differences in their physical properties when in optically active solvents<sup>48,49</sup>. An alternative analysis by N.M.R. spectroscopy may therefore be feasible if a suitable solvent could be found, since two enantiomeric pairs of ethers should form. On the other hand, the chemical shifts may overlap or be rather complex. However, the enantiomeric pairs are diastereomeric and one would expect the methyne proton of the benzhydryl group to exhibit a different chemical shift in suitable solvents. On integration of these proton values, one should be able to find the ratio of one form to the other.



## CHAPTER II

### EXPERIMENTAL

#### II. 1. Introduction

The benzhydryl cations were generated from the related benzhydryl chlorides, which in turn were prepared from the alcohols. The latter were obtained, by several methods of reduction, from the substituted benzophenones. Similarly, the trityl cations were obtained from the trityl chlorides which had been prepared from the alcohols. The trityl alcohols were made by Grignard synthesis with the appropriate substituted benzophenones.

Once the required chlorides had been obtained in a pure form, they were reacted immediately with previously purified dl-2-butanol or dl-2-octanol. The alcohols were purified by drying over anhydrous sodium sulphate, and then redistilling, collecting the fractions with the appropriate boiling points, and then analysing by NMR and gas-liquid chromatography. The extent of the reaction to form the ethers was followed by NMR spectroscopy, and after some purification the products analysed by gas-liquid chromatography.

All melting points were recorded on a Fisher-Johns melting point apparatus, and are uncorrected. Infra-red spectra were obtained on a Beckman I.R.12, and I.R.10. N.M.R. spectra were obtained on a Jeo; C-60H.L. (60MHz). The gas chromatography analyses were done on a Varian aerograph model 700.

The yields of the solvolysis products are tabulated in Table I (page 44).

## II.2. Preparation of Substituted Benzhydrols.

1. 4-Methylbenzhydrol. - This compound was prepared by three different methods of reduction, method ii being preferred:

i). 4-methylbenzophenone (27.1g., 0.139mole) was placed in a 500ml three-necked round-bottomed flask, together with sodium hydroxide (25g., 0.62mole), zinc powder (25g., 0.38mole), and 95% ethanol (250ml). The flask was equipped with a magnetic stirrer and a condenser, and the reaction mixture stirred until the temperature slowly rose to 70°C. After three hours, when the temperature had begun to fall, the mixture was filtered by suction, the residue being washed twice with 25ml portions of hot ethanol. The filtrate was then acidified by pouring it into one litre of ice-water containing 50ml of concentrated hydrochloric acid. The 4-methylbenzhydrol separated as a yellow-white solid at about pH=6, the latter being obtained by the addition of ammonium hydroxide. Recrystallisation from carbon tetrachloride yielded 14.5g. (0.073mole, 53%) of white crystals, melting point 50 - 52°C. ( reported <sup>50</sup> ,<sup>51</sup> 52°C).

ii). A solution of 4-methylbenzophenone (29.4g., 0.35mole), and tetrahydrofuran (400ml) was placed in an Erlenmeyer flask and stirred magnetically. Addition of excess sodium borohydride (3.03g., 0.08mole) was carried out by dissolving 0.25g. portions of the reducing agent in 2.5ml of slightly basic ice-cold water, each successive portion being added at such a rate as to maintain the reaction temperature below 35°C. After the last addition, the mixture was stirred for a further three hours, then poured onto a slurry of ice (500g.) and concentrated hydrochloric acid (25.5ml). The tetrahydrofuran was removed overnight by air oxidation<sup>52</sup>. The crystals formed were filtered off, dried and recrystallised from ether, yielding 21.9g. (74.4%) of white crystals, melting point, 52°.

iii). 4-methylbenzophenone (19.6g., 0.1mole) was added in portions to a solution of excess lithium aluminum hydride (1.92g., 0.05mole) in ether (300ml), in a round-bottomed flask fitted with a reflux condenser. After the addition was complete the mixture was refluxed overnight. The resulting solution was then acidified with water and hydrochloric acid, the excess hydride first being destroyed with ethyl acetate. Solvent was removed on the rotary evaporator, leaving 16.8g. (85%) of pure crystals after recrystallisation from ether, melting point 51-52°C.

The infra-red spectrum of each sample was run in carbon tetrachloride, and showed free OH stretching at  $3610\text{cm}^{-1}$

aromatic skeletal vibrations at  $1610\text{cm}^{-1}$  and  $1490\text{cm}^{-1}$  and  $\text{C}=\text{O}$  stretching at  $1025\text{cm}^{-1}$ . The N.M.R. spectrum also confirmed the structure of the expected product with the OH proton appearing at 4.25ppm and the methine proton at 5.8ppm.

2. 4-Methoxybenzhydrol. - The sodium borohydride method was used to prepare this compound, the following proportions being used: 21g. (0.1mole) 4-methoxybenzophenone in 300ml of tetrahydrofuran, 3g. (0.08mole) sodium borohydride. After hydrolysis with ice and hydrochloric acid, and evaporation of the solvent, the crude product was recrystallised from carbon tetrachloride to yield 15g. (70%) of pure crystals, melting point  $62-64^{\circ}\text{C}$ , (reported<sup>53</sup>,  $62-65^{\circ}\text{C}$ ). The infra-red spectrum showed free OH stretching at  $3280-3570\text{cm}^{-1}$ ,  $\text{C}=\text{O}$  stretching at  $1250\text{cm}^{-1}$  and  $1035\text{cm}^{-1}$ , aromatic CH stretchings at  $3005-3080\text{cm}^{-1}$ , and aliphatic CH stretching at  $2900-2960\text{cm}^{-1}$ . The N.M.R. spectrum agreed with the structure of the product, with the methine proton appearing at 5.48ppm.

3. 4-Nitrobenzhydrol. - A similar reduction of 4-nitrobenzophenone (22.7g., 0.10mole) was carried out using sodium borohydride (3.03g., 0.08mole). The crude product was recrystallised from methanol, yielding 16g. (69%) of pure product, melting point  $74^{\circ}\text{C}$  (reported<sup>54</sup>,  $74.5-75^{\circ}\text{C}$ ). An infra-red spectrum in chloroform showed OH stretching at  $3605\text{cm}^{-1}$ , and aromatic CH stretchings at  $3010-3090\text{cm}^{-1}$ , asymmetric

and symmetric  $\text{NO}_2$  stretching at  $1530$  and  $1350\text{cm}^{-1}$  respectively, and C-N stretching at  $870\text{cm}^{-1}$ . The N.M.R. spectrum showed the methine proton at  $5.95\text{ppm}$ .

4. 4-Chlorobenzhydrol. - Similarly  $21.6\text{g.}$  ( $0.1\text{mole}$ ) of 4-chlorobenzophenone was reduced with sodium borohydride ( $3.03\text{g.}$ ,  $0.08\text{mole}$ ), and the crude product recrystallised from ether. After two recrystallisations the yield was  $16.5\text{g.}$  ( $76.3\%$ ) of 4-chlorobenzhydrol, melting point  $59.5-60.5^\circ\text{C}$  (reported<sup>55</sup>,  $60-61^\circ\text{C}$ ). The infra-red spectrum showed OH stretching at  $3200-3600\text{cm}^{-1}$ , and aromatic CH stretchings at  $3040-3100\text{cm}^{-1}$  and  $1600\text{cm}^{-1}$ . The N.M.R. spectrum showed the methine resonance at  $5.5\text{ppm}$ .

5. 4-Bromobenzhydrol. - Using the same method, 4-bromobenzophenone ( $26.1\text{g.}$ ,  $0.1\text{mole}$ ), and sodium borohydride ( $3.03\text{g.}$ ,  $0.08\text{mole}$ ) were reacted to yield, after recrystallisation from ether,  $25\text{g.}$  ( $88.9\%$ ) of 4-bromobenzhydrol, melting point  $60.5-62^\circ\text{C}$ , (reported<sup>56</sup>,  $62-63^\circ\text{C}$ ). The infra-red spectrum was similar to that of 4-chlorobenzhydrol, but in the N.M.R., the methine proton appeared at  $4.47\text{ppm}$ .

6. 4-Hydroxybenzhydrol. - Similarly, sodium borohydride ( $3.03\text{g.}$ ,  $0.08\text{mole}$ ) was added to 4-hydroxybenzophenone ( $19.8\text{g.}$ ,  $0.1\text{mole}$ ). After recrystallisation of the crude product from ethanol, the yield was  $16.5\text{g.}$  ( $82.5\%$ ), melting point  $164^\circ\text{C}$ , (reported<sup>57</sup>,  $130^\circ\text{C}$ ).

In the infra-red spectrum the OH absorption was at  $3600-2900\text{cm}^{-1}$  with aromatic CH stretchings at  $1600\text{cm}^{-1}$ . The N.M.R. spectrum in  $\text{CDCl}_3$  showed deuterium exchange with both OH protons, which appeared at 9.4-9.9ppm and 4.5-5ppm. The methine singlet absorbed at 5.7ppm, with the aromatic multiplet appearing at 7.5-6.7ppm.

7. 2-Hydroxybenzhydrol. - Similarly, a 0.1mole quantity (19.8g) of 2-hydroxybenzophenone, melting point  $35-37^\circ\text{C}$  was taken. The dark yellow liquid became paler during reaction with sodium borohydride (3.03g., 0.08mole), until finally it was colourless. On standing the product became yellow again. Attempted recrystallisation from ethanol gave a light brown powder, melting point  $137^\circ\text{C}$ . No literature value was found, and no infra-red spectrum could be obtained. An N.M.R. run in  $\text{CD}_3\text{COCD}_3$  showed a broad OH absorption at 12ppm, the aromatic multiplet at 7.6-7.9ppm, the methine singlet at 6ppm and another broad OH absorption at 4.5-5.2ppm. Both OH peaks can be shown to exchange with  $\text{D}_2\text{O}$ . Yield 4g. (20%).

8. Benzhydrol. - Benzhydrol was produced by the reaction of benzophenone (27.3g., 0.15mole) with sodium borohydride (4.5g. 0.12mole) in 400ml of tetrahydrofuran. Similar precautions as in the previous reactions were taken. The crude yield was 27.6g., melting point  $65^\circ\text{C}$ , compared to  $68^\circ\text{C}$  for the pure compound. However, the infra-red spectrum of the prepared

benzhydrol and an authentic sample were identical. It showed OH stretching at  $3100-3640\text{cm}^{-1}$ , aromatic CH stretching at  $3000-3080\text{cm}^{-1}$ , and at  $1600\text{cm}^{-1}$ .

### II.3. Preparation of Benzhydryl Halides.

Benzhydryl bromide: Acetyl bromide (18.6g., 0.15mole) was added slowly to a warmed solution of benzhydrol (27g., 0.15mole) in benzene, over a period of an hour. After the addition was complete, the reaction was refluxed for thirty minutes, then cooled in ice-water. Petroleum ether (bp.  $30-60^{\circ}\text{C}$ ) was added to force out the crystals. As only a few formed, the benzene was stripped off on the rotary evaporator to give brownish crystals of melting point  $37^{\circ}\text{C}$ . Both infra-red and N.M.R. spectra showed good agreement with those of an authentic sample (mp.  $40-42^{\circ}\text{C}$ ). Yield 20g. (66%).

4-Methylbenzhydryl chloride. - The 4-methylbenzhydryl chloride was prepared by the method of Norris and Blake<sup>59</sup>. 7g. (0.03mole) of 4-methylbenzhydrol was dissolved in a minimum amount of carbon tetrachloride, and anhydrous calcium chloride added to the flask, which was also equipped with a magnetic stirrer. Anhydrous hydrogen chloride gas was passed into this solution via a drying tube containing calcium chloride and drierite, and a trap. The flow rate was controlled by a "bubbler" containing oil, at the end of the apparatus. After about

15 minutes the addition was completed, and the flask opened to dried air. However some hydrolysis still occurred. The solvent and excess hydrogen chloride gas were stripped off on the rotary evaporator, the resulting solution being vacuum distilled. 4-Methylbenzhydryl chloride distilled over at 135-140°C at 0.95mm. (reported<sup>59</sup>, bp. 147-148°C/2mm) as a yellow oily liquid. A small amount of product was then removed for an N.M.R. spectrum, which gave the proton ratio as expected. The methine proton in the chloride appeared at 5.9ppm, the methyl protons at 2.05ppm, and the aromatic multiplet at 6.7-7.5ppm. Yield 7g. (91%).

4-Bromobenzhydryl chloride .- 4-Bromobenzhydryl (13.3g., 0.05mole) was dissolved in a minimum amount of carbon tetrachloride as previously described. Upon passage of dry hydrogen chloride gas, the solution turned pink and finally dark red. When the reaction was complete, the mixture was transferred under nitrogen, to a one-necked flask and the solvent stripped off at the rotary evaporator. The flask was opened to nitrogen again, and the chloride vacuum distilled, having a boiling point of 170-172°C/3.75mm., (reported<sup>59</sup>, 188-191°C/10mm = 168-170°C/3.75mm). A small amount of the chloride was removed for spectral analysis, and the majority of the oil was used immediately for the solvolysis reaction. The N.M.R. spectrum of the chloride showed the aromatic multiplet at 7.1-7.6ppm, and the methine CH at 6ppm. The yield was 11.3g. (79%).



4-Chlorobenzhydryl chloride. - Again the method of Norris and Blake was used. The reaction was done in the presence of drierite, and at the completion of the reaction the solution was blue. The crude product was vacuum distilled and a yellow oil was obtained, boiling point  $121^{\circ}\text{C}/0.3\text{mm.}$  compared to the literature value of  $172-173^{\circ}\text{C}/6\text{mm.}$ <sup>59</sup>. The N.M.R. spectrum gave the aromatic multiplet at 6.8-7.25ppm and the singlet methine proton at 5.75ppm. From 10.9g. (0.05mole) of alcohol, 8.5g. (75%) of the chloride was obtained.

4-Nitrobenzhydryl chloride. - 4-Nitrobenzhydrol (13.5g., 0.058mole) was reacted with excess thionyl chloride (10g., 0.075mole), in the presence of pyridine, at room temperature for 28 hours in a reflux apparatus. Precipitate and solvent were removed by filtration and with a rotary evaporator. The chloride was then vacuum distilled, b.p.  $170^{\circ}\text{C}/2.25\text{mm.}$  It was used for solvolysis immediately. An N.M.R. spectrum of the chloride in carbon tetrachloride, gave an aromatic multiplet of 9 protons at 7-8.25ppm and a CH singlet at 6.03ppm. Approximately 8.7g. (60%) yield was obtained.

4-Hydroxybenzhydryl chloride. - The method of Norris and Blake was again used. The 4-hydroxybenzhydrol in the presence of drierite yielded a red solution. After completion of the reaction, the excess solvent was removed on the rotary evaporator, leaving a red semi-solid. An attempt to

recrystallise this product from acetone failed. An N.M.R. spectrum of the crude material in  $\text{CD}_3\text{COCD}_3$  was not conclusive. It was decided to use this impure chloride for the preparation of the ether in 2-butanol.

#### II.4. Solvolysis of Substituted Benzhydryl Halides.

Immediately after the pure substituted benzhydryl halides had been isolated, they were treated with an excess of previously purified dl-2-octanol or dl-2-butanol. Several of the solvolysis preparations were repeated, in order to find the optimum conditions for this type of reaction. The extent of reaction was followed by N.M.R. spectroscopy, the chemical shift of the benzhydryl methine proton being different for the chlorides and ethers. It was found that the maximum yield of ether could be obtained by initial heating and stirring of the solvolysis mixture for 24 hours followed by addition of 2-5ml of pyridine and refluxing for 72 hours. In this way a maximum yield of 85% was obtained for 4-methylbenzhydryl 2-butyl ether, for example, (judged on the ratio of the benzhydryl methine N.M.R. peaks). In order to remove any last traces of benzhydryl halide, the reaction mixture was then washed with water, followed by washing with sodium bicarbonate to remove any last acidic traces. In most cases, the resulting solution was extracted with ether, the ether evaporated, and the reaction mixture

was vacuum distilled. For some reactions, product purification by vacuum distillation was unsatisfactory. In these cases, purification by column chromatography was attempted. In all cases as pure a product as possible was obtained before subjecting the reaction mixture to gas-liquid chromatographic analysis. An initial trial run was carried out for benzhydryl 2-octyl and 2-butyl ethers, to find the best separation method for the pure products.

Solvolysis of Benzhydryl Bromide in dl-2-Octanol. - 10g. (0.049 mole) of benzhydryl bromide was treated with excess pure, dry dl-2-octanol as above. After refluxing and extraction, one half of the reaction mixture was vacuum distilled in order to remove the remaining excess of alcohol. Two fractions were obtained; at 61-63°C/2.7mm, due to a mixture of 2-octanol and 2-octanone, and at 180-185°C/3.25mm. An N.M.R. spectrum of the second cut still showed a slight excess of aliphatic protons, but appeared to be the ether fraction.

The other half of the reaction mixture was separated by column chromatography on an alumina column, using benzene as eluent. The fractions obtained were traced by means of their refractive index changes. After the solvent was evaporated off, the fraction corresponding to the desired ether product still showed a very slight excess of aliphatic protons in the N.M.R.. When this fraction was further purified by vacuum distillation the result was not improved by much.

Both fractions were then subjected to gas-liquid chromatography on various columns:

1. 5½' x 1/4" LAC 728. (Diethylene Glycol Succinate).

Varying column temperatures and carrier gas flow rates were tried, but even at the highest operating temperature possible (190°C), only two peaks were seen. The first peak was found to be 2-octanol, and the second, which was very unsymmetrical, indicated that the sample did not remain in the vapour state, and the column was therefore of little use.

2. 6' x 1/4" Carbowax 20 m. on chromosorb W. A/W. DMCS 60/70 mesh. Up to the maximum operating temperature of 250°C for this column, the results were similar to those for the LAC 728 column, and therefore of no practical use.

3. 6' x 1/4" SE 30, (10% silicone rubber on 60-80 W 720 U.P.). The optimum conditions for this column were found to be 280°C (column max. 375°C), with a helium flow rate of 60 ml/minute, at which temperature three peaks were obtained. The first peak was identified as a mixture of 2-octanol and 2-octanone; the second as diphenylmethane, both by N.M.R. and by an authentic sample; the final peak, after collection, was identified by N.M.R. spectroscopy as the desired ether. The analysis was repeated using a 2' x 1/4" SE-30 column and similar results were obtained. G.L.C. traces of the undistilled mixture showed a greater proportion of the second peak (diphenylmethane).

Infra-red spectrum (in  $\text{CCl}_4$ ):

Aromatic CH stretch at 3100, 3070, and 3040  $\text{cm}^{-1}$  (medium);  
 Aliphatic CH stretch at 2990, 2890 and 2860  $\text{cm}^{-1}$  (strong);  
 Aromatic overtones at 1660  $\text{cm}^{-1}$ ; Methylene CH bends at 1455  
 $\text{cm}^{-1}$ ; C-O-C stretch at 1090, 1080 and 1050  $\text{cm}^{-1}$  (strong, broad).

N.M.R. spectrum (in  $\text{CCl}_4$ ):

Aromatic resonance, 7.4-6.85 ppm. (9H);  $\text{Ar}_2\text{CH}-\text{O}-\text{CH}(\text{CH}_3)\text{C}_6\text{H}_{13}$ -  
 singlet at 5.3 ppm (1H);  $\text{Ar}_2\text{CH}-\text{O}-\text{CH}(\text{CH}_3)\text{C}_6\text{H}_{13}$ -multiplet at  
 3.6-3.0 ppm (1H); Aliphatic multiplet at 1.7-0.7 ppm (16H).

Solvolysis of benzhydryl Bromide in dl-2-Butanol.- 15 g

(0.068 mole) of benzhydryl bromide was dissolved in previously purified dl-2-butanol. After stirring for 24 hours at room temperature, the reaction mixture was washed with sodium bicarbonate and by water, as before. The dark brown reaction mixture was vacuum distilled to remove the excess dl-2-butanol. (bp 99.5°C/760 mm) and any 2-butanone (bp 80°C/760 mm) formed. The remaining fraction was put through a 2' x 1/4" SE 30 column on the G.C., the two peaks which were observed being collected. The second peak was found to be the desired ether (the first being remaining 2-butanol). In later trials, it was found that the benzhydryl 2-butyl ether could also be isolated on a 6' x 1/4" XF 1150 column.

Infra-red spectrum (in  $\text{CCl}_4$ ):-

Aromatic CH stretch at 3100, 3080 and 3040  $\text{cm}^{-1}$  (med-weak);  
 Aliphatic CH stretch at 2980(s), 2940(m), 2880  $\text{cm}^{-1}$  (m);

C-O-C absorption at  $1065\text{cm}^{-1}$  (strong).

N.M.R. spectrum (in  $\text{CCl}_4$ ):

Aromatic resonance at 7.5-7.0ppm. (9H);  $\text{Ar}_2\text{CH-O-CH}(\text{CH}_3)\text{C}_2\text{H}_5$ -singlet at 5.28ppm. (1H);  $\text{Ar}_2\text{CH-O-CH}(\text{CH}_3)\text{C}_2\text{H}_5$ -sextet at 3.55-3.0ppm. (1H);  $\text{Ar}_2\text{CH-O-CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ -quintet at 1.5ppm. (2H);  $\text{Ar}_2\text{CH-O-CH}(\text{CH}_3)\text{C}_2\text{H}_5$ -doublet at 1.1ppm. (3H);  $\text{Ar}_2\text{CHOCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ -triplet at 0.8ppm. (3H).

At this point, as the separation of the unsubstituted ethers had not proved difficult, it was decided to solvolyse a series of substituted benzhydryl chlorides, and carry out their G.L.C. analysis simultaneously.

Solvolysis of 4-Methylbenzhydryl Chloride in dl-2-Octanol.-

8g. (0.034mole) of 4-methylbenzhydryl chloride was dissolved in 50ml of dl-2-octanol and stirred at room temperature for 96 hours. After this time, the excess 2-octanol was distilled off at  $50^\circ\text{C}/1.25\text{mm}$ . An infra-red spectrum of the recovered solvent showed a greater proportion of carbonyl absorption at  $1720\text{cm}^{-1}$  than in the original dl-2-octanol used. This was confirmed by a G.L.C. trace on a 6' x  $\frac{1}{4}$ " SE30 column, of the original and recovered solvents. The residue, containing 4-methylbenzhydryl 2-octyl ether was set aside for G.L.C. analysis. An infra-red spectrum of the residue showed the presence of strong COC stretching bands at 1085 and  $1065\text{cm}^{-1}$ . Elemental analysis for  $\text{C}_{10}\text{H}_{14}\text{O}$ , on the collected G.L.C. fraction, gave C-84.77%, H-9.31%, (calculated C-85.11%, H-9.73%), for the 4-methylbenzhydryl 2-octyl ether.

Solvolysis of 4-Methylbenzhydryl Chloride in dl-2-Butanol.

10.5g. (0.043mole) of 4-methylbenzhydryl chloride was dissolved in an excess (50ml) of redistilled and dried dl-2-butanol. The solution was stirred at room temperature for 39 hours, after which time the N.M.R. spectrum showed approximately 40% of the desired ether (judged on the benzhydryl methine proton ratio). Therefore, 3ml of pyridine was added and the reaction mixture refluxed for 72 hours. An N.M.R. spectrum of the solution then showed approximately 85% of the 4-methylbenzhydryl 2-butyl ether to be present. The excess dl-2-butanol was removed by distillation; on cooling, a white salt separated out in the residue (mp. 250°C), probably the pyridinium salt. The remaining residue was washed several times with water to destroy any unreacted 4-methylbenzhydryl chloride, and then taken into ether and dried. Distillation gave a fraction, bp. 123-126°C/2.25mm, whose N.M.R. spectrum indicated it to be largely 4-methyl-diphenylmethane. It was assumed that the 4-methylbenzhydryl 2-butyl ether had remained in the dark brown residue from the distillation and this was therefore set aside for G.L.C. analysis.

N.M.R. of the residue (in  $\text{CCl}_4$ ):

Aromatic multiplet at 7.5-6.8ppm. (integrated to more than 9H's); singlet at 5.36ppm. (due to  $\text{Ar}_2\text{CH}-\text{O}-\text{CH}(\text{CH}_3)\text{C}_2\text{H}_5$ ); sextet at 3.7-3.1ppm. ( $\text{Ar}_2\text{CHOCH}(\text{CH}_3)\text{C}_2\text{H}_5$ ); singlet at 2.2ppm. (due to the aromatic methyl substituent); multiplet at

1.9-1.2ppm. (due to  $\text{Ar}_2\text{CHOCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ ); doublet at 1.2-1.0ppm. (due to  $\text{Ar}_2\text{CHOCH}(\text{CH}_3)\text{C}_2\text{H}_5$ ); triplet at 1.0-0.65ppm. ( $\text{Ar}_2\text{CHOCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ ). The protons of the aromatic group and the methyl group at 2.2ppm., were in the expected ratio of 9:3, indicating that the major impurities in the residue were 4-methylbenzhydryl chloride and 4-methyldiphenylmethane.

Similar results were found for all solvolysis reactions carried out (3g., 7g., and 9g.; in 50ml of alcohol)..

Elemental analysis for CHO, carried out on the ether fraction collected by G.L.C. gave C-84.61%, H-8.22% (calculated C-84.99%, H-8.7%).

#### Solvolysis of 4-Bromobenzhydryl Chloride in dl-2-Octanol.-

The solvolysis step was carried out as previously reported, and the excess dl-2-octanol was distilled off at the end of the reaction. The residue showed an excess of aromatic protons in its N.M.R. spectrum (probably due to 4-bromodiphenylmethane). It was purified by column chromatography on a silica gel column (ratio of 1g. residue : 60g. of silica gel), using benzene and benzene/ethyl acetate as eluents. Samples were collected by following the refractive index changes of the eluents collected. From the N.M.R.'s of the coloured fractions obtained, it became apparent that a good separation was not possible, the aromatic proton ratios still being too large. The residue was therefore set aside for G.L.C. analysis.

In subsequent preparations the solvolysis mixture



was vacuum distilled to yield two fractions, one at 162-170°C/2.25mm and the other at 175-77°C/2.1mm. Both of these were set aside for G.L.C. analysis.

N.M.R. of fractions (in  $\text{CCl}_4$ ):

Aromatic multiplet at 7.4-6.8ppm; singlet at 5.3ppm. ( $\text{Ar}_2\text{CHOR}$ ); broad absorption at 3.7-3.2ppm. ( $\text{Ar}_2\text{CHOCHRR}'$ ); multiplet at 1.6-0.6ppm. due to protons of the octyl group. The major impurities were 4-bromobenzhydryl chloride and 4-bromodiphenylmethane.

Solvolysis of 4-Bromobenzhydryl Chloride in dl-2-Butanol. -

Similarly, the solvolysis mixture was treated as described previously. An N.M.R. of the residue showed the presence of the desired ether, along with 4-bromodiphenylmethane. This residue was set aside for G.L.C. analysis.

N.M.R. of the residue (in  $\text{CCl}_4$ ):

Aromatic multiplet at 7.5-6.9ppm; singlet at 5.95ppm. ( $\text{Ar}_2\text{CHOR}$ ); multiplet at 3.9-3.2ppm. ( $\text{Ar}_2\text{CHOCHRR}'$ ); multiplet at 1.8-0.7ppm. (aliphatic butyl protons).

The proton ratios showed a slight excess of aliphatic protons.

Solvolysis of 4-Chlorobenzhydryl Chloride in dl-2-Butanol. -

After the solvolysis step had been carried out, the reaction mixture was extracted into acetone and ether, and dried over anhydrous sodium sulphate. Vacuum distillation removed the excess solvent, and a fraction of bp. 175-77°C/0.55mm was

collected. An N.M.R. spectrum of this distillate showed a large excess of aromatic protons due to the presence of 4-chlorobenzhydryl chloride and 4-chlorodiphenylmethane. Both the distillate and the residue were analysed by G.L.C.

N.M.R. (in  $\text{CCl}_4$ ):

Aromatic multiplet at 7.35-7.1ppm.; singlet at 5.35ppm. ( $\text{Ar}_2\text{CHOR}$ ); sextet at 3.6-3.1ppm. ( $\text{Ar}_2\text{CHOCH}(\text{CH}_3)\text{C}_2\text{H}_5$ ); multiplet at 1.8-1.2ppm. ( $\text{Ar}_2\text{CHOCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ ); doublet at 1.2ppm. ( $\text{Ar}_2\text{CHOCH}(\text{CH}_3)\text{C}_2\text{H}_5$ ); triplet at 0.9ppm. ( $\text{Ar}_2\text{CHOCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ ).

Solvolysis of 4-Nitrobenzhydryl Chloride in dl-2-Butanol. -

The solvolysis step was carried out as previously reported and the excess dl-2-butanol removed by distillation. However, N.M.R. and I.R. spectra of the resulting residue showed a large excess of aliphatic protons. Further purification by distillation did not improve the quality of the residue. It was set aside for G.L.C. analysis.

N.M.R. of residue (in  $\text{CCl}_4$ ):

Aromatic multiplet at 8.3-7.0ppm; singlet at 6.1ppm. ( $\text{Ar}_2\text{CHOR}$ ); multiplet at 3.8-3.3ppm. ( $\text{Ar}_2\text{CHOCHRR}$ ); aliphatic multiplet at 2.0-0.5ppm. (indistinguishable because of a large excess).

Infra-red of residue (in  $\text{CCl}_4$ ):

Aromatic CH stretch at  $3000\text{cm}^{-1}$ ; aliphatic CH stretch at 2960, 2900 and  $2860\text{cm}^{-1}$ ; asymmetric and symmetric  $\text{NO}_2$  stretch at 1455 and  $1360\text{cm}^{-1}$  respectively; COC stretch at  $1220\text{cm}^{-1}$ , and

C-N stretch at  $865\text{cm}^{-1}$ .

Solvolysis of 4-Hydroxybenzhydryl Chloride in dl-2-Butanol. -

After solvolysis and removal of the excess dl-2-butanol, an N.M.R. spectrum of the residue did not indicate the presence of any ether; similarly for the infra-red spectrum.

Yields from the solvolyses mixtures were judged on the traces from the gas chromatograph and were as given in Table I.

Table I

Halide	Alcohol	Yield
Benzhydryl	2-Butanol	85%
Benzhydryl	2-Octanol	70%
4-Methylbenzhydryl	2-Butanol	85%
4-Methylbenzhydryl	2-Octanol	60%
4-Bromobenzhydryl	2-Butanol	70%
4-Bromobenzhydryl	2-Octanol	30%
4-Chlorobenzhydryl	2-Butanol	85%
4-Nitrobenzhydryl	2-Butanol	70%

## II.5. Gas Chromatographic Analysis of Solvolysis Products.

All the prepared ethers were analysed by gas-liquid chromatography with the following columns. Due to the differing natures of the substituents on the benzhydryl ethers, it is difficult to predict what type of column material, would give the best separation.

1. 2' x  $\frac{1}{8}$ " SE 30 (10% silicone gum rubber on 60-80W 720UP). For each ether analysed four peaks were obtained; the first was identified as the unreacted dl-alcohol, the second as the substituted diphenylmethane compound, the third as the substituted benzophenone, and the final peak, in each case was found to be predominantly the required ether. Separation of the ether peak into its diastereomeric components was not possible on this short column.

2. 6' x  $\frac{1}{8}$ " SE 30. - Similar results were obtained with this column as to the two foot column. However, it was noticed that as the column temperature was lowered, the peaks for the 2-octyl series of ethers began to tail, probably owing to the fact that they were no longer remaining in the vapour state. No change was seen in the 2-butyl ethers.

3. 10' x  $\frac{1}{8}$ " SE 30. - When all conditions, such as injector and detector and column temperature, and helium flow rate

had been altered to their optimum values, (175-210°C depending on substituent), the ether peak began to show some asymmetry in all cases. It was possible that the ethers were beginning to separate, but the evidence was minute. An N.M.R. spectrum of the collected peak, with its shoulder, was no different from the previous ones which had shown no asymmetry, and therefore, was a hopeful indication of separation of the diastereomeric pairs being possible.

4. 6' x  $\frac{1}{8}$ " Carbowax 20M. (10% on chromosorb W A/W DMCS 60/80 mesh). - The best recorded trace on this column was for the 4-methylbenzhydryl 2-butyl ether (at 180°C), where the third of the four peaks showed the presence of two overlapping components. When this peak was collected, however, it was found to be a mixture of the diphenylmethane derivative and possibly the related benzophenone. None of the peaks collected were the purified ether, so it was apparent that decomposition was taking place either on the injector or the column, such that diphenylmethane derivatives were being formed. Altering the injector temperature made little difference, however.

5. 5 $\frac{1}{2}$ ' x  $\frac{1}{8}$ " LAC 728. (Diethylene glycol succinate). - As in the case of the unsubstituted ethers, this column was found to be of little use. At its maximum temperature of operation (190°C) the ether peak trailed over a period of thirty

minutes, yielding no information about its components.

6. 6' x  $\frac{1}{8}$ " Viton 2A. (synthetic rubber, soluble in 2-butanone). - This column (at 185°C), gave similar traces to those of an SE 30 column of comparable length. However, at no time did the ether containing peak (identified by collection and N.M.R.'s) become non-symmetrical, whatever conditions were altered. Owing to the possibility also, of 2-butanone being formed and reacting with some of the column material, the column was abandoned.

7. 6' x  $\frac{1}{8}$ " XF 1150. (silicon fluid containing 5% nitrile). - As this column had previously been used to collect the unsubstituted ethers, it was hoped that it might yield the required results. For those ethers having electron-donating substituents, such as methyl, the ether peak was seen in a short time (at 180-190°C) as a fairly sharp, symmetrical peak. Altering carrier gas flow rate and the like, made no difference to the peak; it could not be resolved into its components, nor was any indication given that the peak represented anything but one pure compound. For those ethers containing electron-withdrawing groups, such as bromo-, chloro-, and nitro-, the ether peak took twice as long to begin emerging, and trailed over a thirty minute period. In neither case could column conditions be found which gave the hoped for results.

8. 6' x  $\frac{1}{4}$ " Tris (2-cyanoethoxy) propane. - Similar work carried out in this laboratory<sup>†</sup> with  $\alpha$ -phenethyl 2-butyl ethers had shown that the two sets of diastereomers could be partially separated on this column. When the benzhydryl systems were injected onto the column, however, no resolution could be achieved. With the column at 120°C, the ether was the third fraction to emerge, in the case of 4-methylbenzhydryl 2-butyl ether. A slight shoulder could be seen on the leading edge of the peak, but altering the operating conditions did not improve the situation.

9. 6' x  $\frac{1}{4}$ " QF 1. on chromosorb W. - The peak due to the ether component again showed some evidence of overlapping of peaks, but, as the column temperature was lowered, the peak began to show trailing. Altering the carrier gas flow rate did not improve the results.

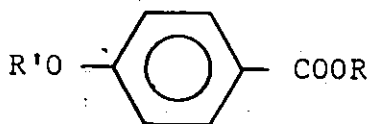
10. 10' x  $\frac{1}{4}$ " Di-isodecyl phthalate. - Even at its maximum operating temperature of 175°C, the ether peak had not appeared after two hours, and therefore further work was judged impractical.

11. 6' x  $\frac{1}{4}$ " XE 60. (10% on chromosorb W). - Again at the highest operating temperature for the column, the ether peak took a long time to emerge, and was somewhat trailing, yielding no practical information.

<sup>†</sup>Private communication from S. Walker

12. 8' x 1/4" 5% Versamid. - The ether emerged as a rounded, rather than sharp peak at 190°C. Raising the column temperature resulted in a shorter emergence time, and a slightly sharper peak, but no resolution could be achieved.

13. 10' x 1/4" Apiezon L. (10% on chromosorb W). - Wilcox<sup>60</sup>, has studied the separation of a series of alkyl ether derivatives of para-hydroxy benzoate esters by gas-liquid



R = Me, Et, n-Pr, n-Bu.

R' = Me, Et, n-Pr, i-Pr,  
n-Bu

chromatography. In addition to a 4metre (x4mm i.d.) 1.5% SE 30 column, he found that a 50metre (x 0.25mm i.d.) Apiezon L column effected a separation. Even though the ethers used in this work were not related in the same way, it was felt that an Apiezon L column may yield some positive results. In each case, three symmetrical peaks were obtained, which were not further resolved by altering the column temperature or the carrier gas flow rate. It was decided, at this point, to return to the most hopeful column material, SE 30, and use the longest column available.

14. 50' x 1/8" SE 30. (2% High Pak silicone gum rubber). - At 230°C, the ether peak showed a certain amount of resolution,



being split into two minor peaks for one-tenth of its height. As the column temperature was lowered, the components tended to show a greater resolution; however, at the same time, the individual component peaks began to trail. It was, therefore, rather difficult to decide with certainty, whether the assumed component peaks were, for instance, the pure diastereomers needed, collection on an eighth of an inch column being impossible. Also, because of the large amount of overlap, an accurate determination of the ratios of the peaks was not possible, especially since the peaks themselves had begun to trail so much. A rough estimate gave 47%:53% for the two component peaks, but this cannot be regarded as a precise figure.

## II.6. Preparation and Solvolysis of Substituted Trityl Chlorides.

1. Preparation of Triphenylmethanol. - Into a dry three-neck flask, fitted with reflux condenser, and stirrer, were placed magnesium turnings (6.1g., 0.25mole), and bromobenzene (4g.) in 20ml of anhydrous ether. After the reaction was initiated, a further 35.5g. of bromobenzene (total amount 0.25mole) in ether was added dropwise, in order to maintain gentle boiling. After the addition was complete, the reaction mixture was stirred and refluxed gently for 45 minutes, and then allowed to cool. To the prepared Grignard reagent,

benzophenone (45.5g., 0.25mole) in ether, was added slowly and with rapid stirring. The reaction mixture was heated for a further 30 minutes after the addition, a bright pink solution remaining, a solid appearing on cooling. The salt produced was hydrolysed with ice and sulphuric acid, and the ether layer separated. After concentration, this layer yielded 39g. of yellow crystals. These were recrystallised from benzene/carbon tetrachloride, giving 35g. of white crystals, melting point  $162^{\circ}\text{C}$ . (literature value<sup>61</sup>,  $164^{\circ}\text{C}$ ).

Preparation of 2-Octyl Triphenylmethyl Ether. - Triphenylmethanol was dissolved in 8ml of concentrated  $\text{H}_2\text{SO}_4$ , to generate the carbonium ion. Separately, 100ml of dl-2-octanol was prepared in an ice-cold bath, and the acid solution added dropwise with stirring, keeping the temperature at  $0^{\circ}\text{C}$ . Upon completion, the solution was poured onto 200g. of ice and neutralised with sodium bicarbonate. A white solid appeared, which was removed and found to have a melting point of  $300^{\circ}\text{C}$ , which indicated an inorganic compound, probably sodium sulphate. The organic layer was cooled and gave an off-white solid, melting point  $155-160^{\circ}\text{C}$ . An N.M.R. spectrum could not be carried out on this product, due to the fact that no solvent could be found. An I.R. spectrum was carried out as a KBr pellet, giving the following peaks: OH stretch,  $3470-3500\text{cm}^{-1}$ , probably from octanol; aromatic  $\text{CH}$  stretch at  $3040$ -and  $3070\text{cm}^{-1}$ ; aliphatic CH stretch at  $2920-2940\text{cm}^{-1}$ ;

C=C or C=O absorption at  $1660-1675\text{cm}^{-1}$ , due either to elimination from 2-octanol, or from the formation of benzophenone; aromatic overtones at  $1600\text{cm}^{-1}$ ; methylene CH bend at  $1450\text{cm}^{-1}$ ; COC asymmetric stretch at  $1160\text{cm}^{-1}$ ; COC symmetric stretch at  $1020$  and  $1035\text{cm}^{-1}$ ; CH out of plane bending  $800\text{cm}^{-1}$ .

Owing to the strong COC stretching peaks, the spectrum does indicate the presence of the required ether, but obviously impure with one or both alcohols.

2. Preparation of Phenyl; 4-methoxyphenyl,  $\alpha$ -naphthyl methanol (Thakers alcohol). - A Grignard preparation was carried out using magnesium (3.6g., 0.152mole), and  $\alpha$ -bromonaphthalene (31.1g., 0.15mole, in total), in anhydrous ether. A light brown powdery solid was produced. To this Grignard reagent, was added 4-methoxybenzophenone (29.8g., 0.152mole) in ether. After refluxing was complete, a yellow solid separated out ( $\text{ArC-O}^-\text{MgBr}^+$ ). This was filtered off and washed with cold, anhydrous ether until white. The solid was then redissolved and hydrolysed with ammonium chloride in water (pH=5). The dark yellow ether layer was separated and cooled, followed by concentration and the addition of heptane to force the crystals out. Total yield was 35g. (72%), melting point  $109-112^\circ\text{C}$  (literature value<sup>62</sup>,  $109^\circ\text{C}$ ). The N.M.R. spectrum showed the aromatic protons at 8.8-8.5ppm. and 7.9-6.8ppm. The methyl group absorption appeared at 2ppm. After correction for the  $\text{C}_6\text{D}_6$  peak at 7.4-7.2ppm. the proton ratios were as expected.

The I.R. spectrum showed free OH stretching at  $3570\text{cm}^{-1}$  (med. and sharp); aromatic CH stretch at  $3090, 3060, \text{ and } 3040\text{cm}^{-1}$ ; aliphatic CH stretch at  $2950 \text{ and } 2920\text{cm}^{-1}$  (weak); aromatic overtones at  $1600\text{cm}^{-1}$ ;  $\text{CH}_3$  (CH) bend at  $1390\text{cm}^{-1}$ ; COC asymmetric and symmetric stretches at  $1170-1160, \text{ and } 1125-1115\text{cm}^{-1}$ ; and polynuclear CH out of plane bends at less than  $850\text{cm}^{-1}$ .

Preparation of Thakers Chloride. - Bachmann's method<sup>64</sup> was used for this preparation. Thakers alcohol (26g., 0.08mole) was heated in benzene, in a dry three-necked flask equipped with condenser and dropping funnel. All apparatus and reactants were kept dry. Over a period of thirty minutes, 15ml of acetyl chloride was added, and the mixture stirred until clear. The contents were then refluxed for thirty minutes, and allowed to cool. Petroleum ether was added to force out the yellow-green crystals, and these were filtered off quickly to minimise any hydrolysis which may have taken place. Petroleum ether was also used to wash the crystals, which were then dried over soda lime. A small amount of the solid, mp.  $140^\circ\text{C}$  (lit. value<sup>64</sup>,  $140^\circ\text{C}$ ) was kept aside for spectra, the remaining chloride being dissolved in excess, previously dried and distilled, dl-2-octanol and the solution heated<sup>65</sup>. Upon cooling, a small amount of solid formed.

Spectra of the prepared chloride showed that hydrolysis had already occurred to the alcohol. Spectra of

the Thakers chloride dissolved in dl-2-octanol, also indicated that a mixture of the alcohols now existed.

Resolution of dl-2-Octanol. - dl-2-Octanol was resolved using the method of Kenyon<sup>66,67</sup>. Many preparations were carried out, the volumes being limited by the amount of brucine available.

Equimolar amounts of phthalic anhydride, dl-2-octanol and pyridine were refluxed together for two hours, and allowed to cool, so that the hydrogen phthalate ester of dl-2-octanol separated out (dl-A). This product was filtered off, washed with acetone and allowed to dry.

l-(-)-Brucine.4H<sub>2</sub>O (1B), was added in equimolar amounts to a warm solution of sec-octyl hydrogen phthalate in acetone, and the mixture warmed until everything was in solution. Upon cooling, crystals of (dA,1B) separated out and were filtered off and washed with acetone several times. The filtrate and mother liquor, containing (1A,1B), were then combined, and concentrated to approximately half the volume, at which point it was poured into dilute hydrochloric acid, (acid to congo red). Initially an oil separated, which quickly became a cream coloured solid, and was filtered off and washed with cold water. (This solid was the 1A salt). The crystals (dA,1B) were treated with 1:1 HCl after covering with acetone, until the solution was acid to congo red. Brucine hydrochloride would therefore be in the

remaining solutions, and the solids left were the l-ester and the d-ester respectively. The melting point of each of the pure esters was found to be  $75^{\circ}\text{C}$  after several recrystallisations (on average 3 times, sometimes as many as 6), from 90% acetic acid. As the purity of the ester determined that of the resolved alcohol, directly, it was decided to check the rotations of the resolved esters. A 5% solution (w/v) of each ester in ethanol gave  $[\alpha]_{\text{D}}^{23} = \pm 46^{\circ}$  before recrystallisation increasing to  $58^{\circ}$  at mp.  $74-75^{\circ}\text{C}$ .

After purification of the esters, each was hydrolysed separately by steam distillation with 30% NaOH, using 1mole ester:2mole NaOH. The alcohol obtained was dried over anhydrous potassium carbonate and distilled at  $179^{\circ}\text{C}$  at atmospheric pressure. Rotations on the resolved alcohols were then taken, in 5% ethanol solutions. In the first few runs, the product was 90% pure, having rotations of  $[\alpha]_{\text{D}}^{23} = +9.26^{\circ}$  (c2.1g/100ml EtOH), and the l-product about 60% optically pure,  $[\alpha]_{\text{D}}^{28} = -6.1^{\circ}$  (1.78g./EtOH). (lit. values<sup>66,67</sup>  $[\alpha]_{\text{D}}^{17} = +9.9^{\circ}$  and  $-9.9^{\circ}$ ).

Brucine was recovered from solution, for further use, by addition of excess dilute ammonium hydroxide. However, after several preparations, it was found that the resolution became inefficient and later non-existent. When the rotation of the brucine itself was checked it was found to vary from  $[\alpha]_{\text{D}}^{22} = -6.24^{\circ}$  to  $71^{\circ}$ , although the Aldrich catalogue gives a value of  $-85^{\circ}$ .

## CHAPTER III

### RESULTS AND DISCUSSION

Until recently it was thought that formation of optically active products from unsymmetrically substituted carbonium ions would be highly improbable since the diastereomeric transition states arising from attack by a chiral reagent on either face of the carbonium ion would differ little in energy, due to the reactivity of the ions. However, Fry<sup>7</sup> was able to produce a 2-3% enantiomeric excess of one form of 2-phenylbutane by capture of the 2-phenyl-2-butyl cation by a chiral organosilicon hydride. This was thought to be due to a preferential attack at one enantiotopic face of the carbonium ion. Murr<sup>46</sup> in his studies on the solvolysis of an optically active benzoate (1-phenylbiphenyl- $\alpha$ -naphthyl benzoate) in aqueous acetone, dioxane and ethanol, found that the solvolysis proceeded with net retention of configuration, from which he concluded that an asymmetric carbonium ion was formed. The enantiomeric forms of the carbonium ion are shown below: (Fig. 7)

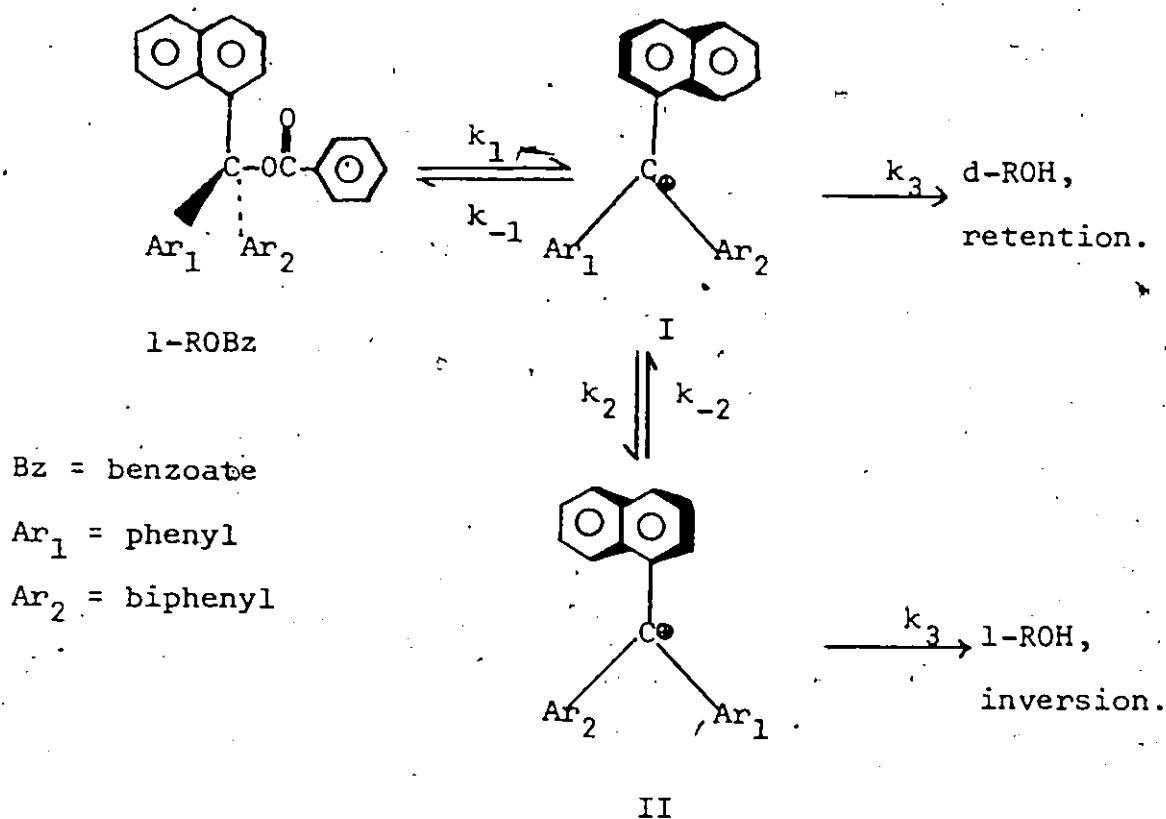


Fig.7.

The results of Murr's studies showed that the rate of conversion of I to II was slower than the rate of product formation, probably due to a torsional energy barrier in going from cation I to II. In other words, the rate of attack on the two faces of cation I differ and the nucleophile attacks that face which is furthest from the unsubstituted naphthalene ring, and this attack is faster than the rate of conversion of the two carbonium ions.

The carbonium ions from benzhydryl and trityl systems



are known to be relatively stable. If one considers a mono-substituted benzhydryl system, for example, then the carbonium ion which is generated will exhibit enantiotopic faces. Reaction with a chiral nucleophile would be expected to give unequal amounts of diastereomeric products, since the free energies of activation and thus the two rates of formation for the two products should be different. For example, for a benzhydryl carbonium ion which exhibits (re) and (si) faces toward (R)-2-butanol, the products obtained will be (R,R) and (S,R) in the ratio  $x:y$ , where  $x \neq y$ . (Fig.8)

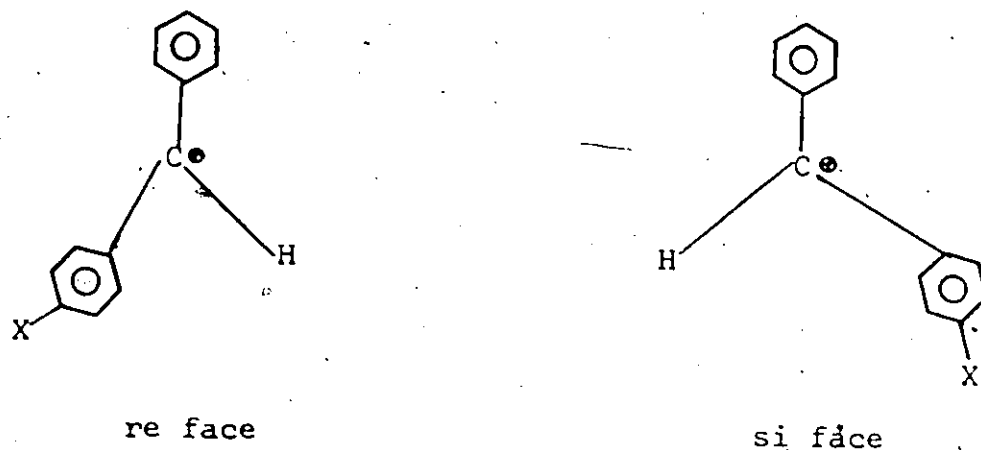


Fig.8.

Similarly, with (S)-2-butanol, one would expect (S,S) and (R,S) products in the same ratio of  $x:y$ . There seems to be no reason that one cannot assume the same results with attack by racemic (R,S)-alcohol. Here, the expected results would be [(R,R) + (S,S)] and [(R,S) + (S,R)], in the same ratio of  $x:y$  for the diastereomeric forms. Our initial aim was to find the

numerical value of x:y for the diastereomeric pairs, and to see if this ratio was altered with change in the substituent on one of the benzene rings. To do this required the complete separation of the enantiomeric pairs from their diastereomeric pair (but we would not know, at this point, which components represented which pair of diastereomers). After this had been accomplished for the products of reaction with racemic alcohol, it was hoped that it could be repeated easily with the ethers obtained from the reaction with optically active alcohol; for example, with (S)-alcohol the produced (S,S) and (R,S) ethers could be separated and analysed by optical rotatory dispersion, in order to determine which component had which absolute configuration. Once this had been accomplished, it was hoped that a mechanism could be proposed to rationalize the results.

The solvolysis reactions to produce the benzhydryl ethers were carried out with substituted benzhydryl halides and an excess of either 2-butanol or 2-octanol. Substituted benzophenones were reduced to the substituted benzhydrol compounds which were previously known, and whose spectra after recrystallisation were consistent with those expected. The benzhydryl halides were then obtained from the benzhydrols by reaction with dry hydrogen chloride gas, thionyl chloride or acetyl bromide, and purification by distillation under reduced pressure. (Fig.9). The alcohols used in the solvolysis reactions were purified by distillation and drying just prior

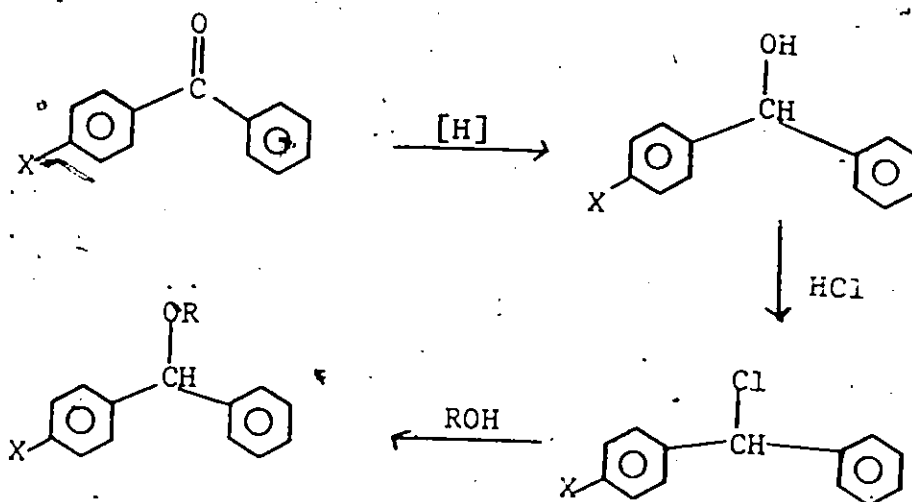
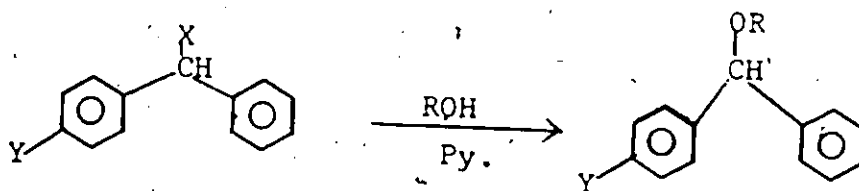


Fig. 9.

to use. Optimum conditions for the solvolysis reactions were found to require initial stirring of the halide in the alcohol for 24 hours, followed by addition of pyridine and refluxing for 72 hours. After this time the excess alcohol was removed, followed by distillation under reduced pressure which removed any residual alcohol and the more volatile by-products of the solvolysis reaction. The desired ether product was assumed to remain in the residue of this distillation (from their N.M.R. spectra), which was then set aside for separation of the diastereomeric pairs. In this way, solutions of the following ethers were successfully obtained for the separation step:



Y = H                    R = 2-butyl

Y = H                    R = 2-octyl

Y = methyl              R = 2-butyl

~~Y = methyl~~          R = 2-octyl

Y = bromo-              R = 2-butyl

Y = bromo-              R = 2-octyl

Y = chloro-             R = 2-butyl

Y = nitro-               R = 2-butyl

The 4-hydroxybenzhydryl ethers could not be obtained in this way. N.M.R. spectra of the solvolysis products from 4-methylbenzhydryl chloride and 4-chlorobenzhydryl chloride may be seen in Appendix I, and are typical of those obtained in other solvolysis reactions.

Analysis of the substituted benzhydryl ethers was carried out in sequence as samples of pure unsubstituted benzhydryl 2-butyl and 2-octyl ethers were readily obtained by preparative G.L.C.

Fry, in his work<sup>7</sup>, had produced an enantiomeric pair of 2-phenylbutanes, and chose to purify them initially by distillation, followed by preparative scale vapour phase chromatography on a di-isodecyl phthallate column. After their purification, he subjected the neat solution to polarimetry measurements. This requires a knowledge of the sign and specific rotation for at least one of the enantiomers of the given compound in order that the optical purity of the reaction product can be calculated. Since the specific

rotation of a compound could be small and the enantiomeric excess in the reaction product is also usually very small, the observed rotations would be difficult to determine accurately. Indeed, for an excess of 2-3% of one enantiomer in the 2-phenylbutane system, the observed rotation of a 1 dm. neat sample was about  $0.5^\circ$  which is close to the error limit of most instruments.

Since there are no references in the literature for the ethers prepared, the specific rotation for any given optical isomer is not known. Enantiomers have the same physical and chemical properties, except for the direction in which they rotate plane polarised light, and the way in which they react with other optically active compounds, and we would not be able to isolate any of the pure optical isomers from the reaction with racemic alcohol. Pirkle et al<sup>48,49</sup> have shown the nonequivalence of proton magnetic spectra of enantiomers in optically active solvents, but this method would be of little use in this work since two enantiomeric pairs form, which cannot be resolved. However, diastereomers do exhibit different properties and one should be able to separate them by physical methods.

Corey and Mitra<sup>49a</sup> have previously attempted the separation of diastereomeric dithioketals by vapour phase chromatography, and it was thought that this method may be of value in our work. Therefore exhaustive efforts were undertaken to determine whether the G.L.C. method could be

employed for the separation. A total of eleven different liquid phases were tried, which varied in polarity from non-polar through to very polar, as follows:

Column length	Liquid phase	Support	Polarity <sup>49b</sup>
2', 6', 10'	SE 30	Chromosorb W	N
50'	SE 30	2% High Pak	N
10'	Apiezon L	Chromosorb W	N
6'	Viton 2A	Chromosorb W	N
6'	XF 1150 nitrile	Chromosorb G	I
6'	QF 1	Chromosorb W	I
10'	Diisodecyl phthallate	Chromosorb G	I
6'	XE 60	Chromosorb W	I
6'	Carbowax 20M	Chromosorb W (DMCS)	P
5½'	LAC 728	Chromosorb G	P
6'	1,2,3 Tris(2cyanoethoxy) propane		P
8'	Versamid	Chromosorb G	P

N = non-polar

I = intermediate

P = polar

Column lengths were also varied from a 2' x ¼" SE 30 (on Chromosorb W 60/80 mesh) upto 50' x 1/8" SE 30 (2% High

Pak). Problems encountered on the various columns included very long retention times, decomposition either in the injector or on the column (e.g. Carbowax 20M). In the case of Viton 2A, since 2-butanone is known to be able to dissolve the liquid phase material it was possible that the impurity in the reaction products would affect this column. On these columns, therefore attempts were made to separate the eight pairs of diastereomers arising from all the previously mentioned solvolysis solutions. In spite of these prolonged efforts with this variety of ethers, varying flow rates, injector and column temperatures, no satisfactory separation of the diastereomers could be effected on any one of the fourteen previously mentioned columns. The only exception to this and the most promising of the columns was a 50' x 1/8" SE 30 (2% High Pak) on which some separation was achieved, though incomplete. In the case of 4-methylbenzhydryl 2-butyl ether, the peak maxima of the still overlapping diastereomers were only separated by 7.5 seconds. A rough estimate of the ratio of the two diastereomeric components was carried out both by calculating the areas under the peaks and by weighing the chart paper. Both methods assume that the peaks have a similar shape. The ratio of the two diastereomers found was 47:53 in both the weighing method (errors in this method are generally in the order of 1-2%, although the proximity of the peaks could introduce a much larger error<sup>49b</sup>), and in the method of comparing peak areas (error quoted<sup>49b</sup> as

generally less than 3%). However, since the separation was so incomplete, making collection of the individual diastereomers impossible, further work with this column did not appear promising.

Up until the present time the following points are known about the stereochemistry of the ether linkage; from electron diffraction data on diethyl ether<sup>69</sup>, the C-O-C bond angle has been determined as  $108^\circ \pm 3^\circ$ ; microwave studies on dimethyl ether show that the most stable conformation is the one having a carbon-hydrogen bond of one methyl group staggered with respect to the carbon-oxygen bond of the other<sup>70</sup>. (Fig. 11).

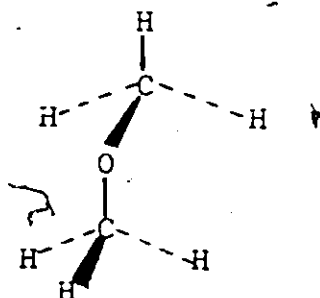


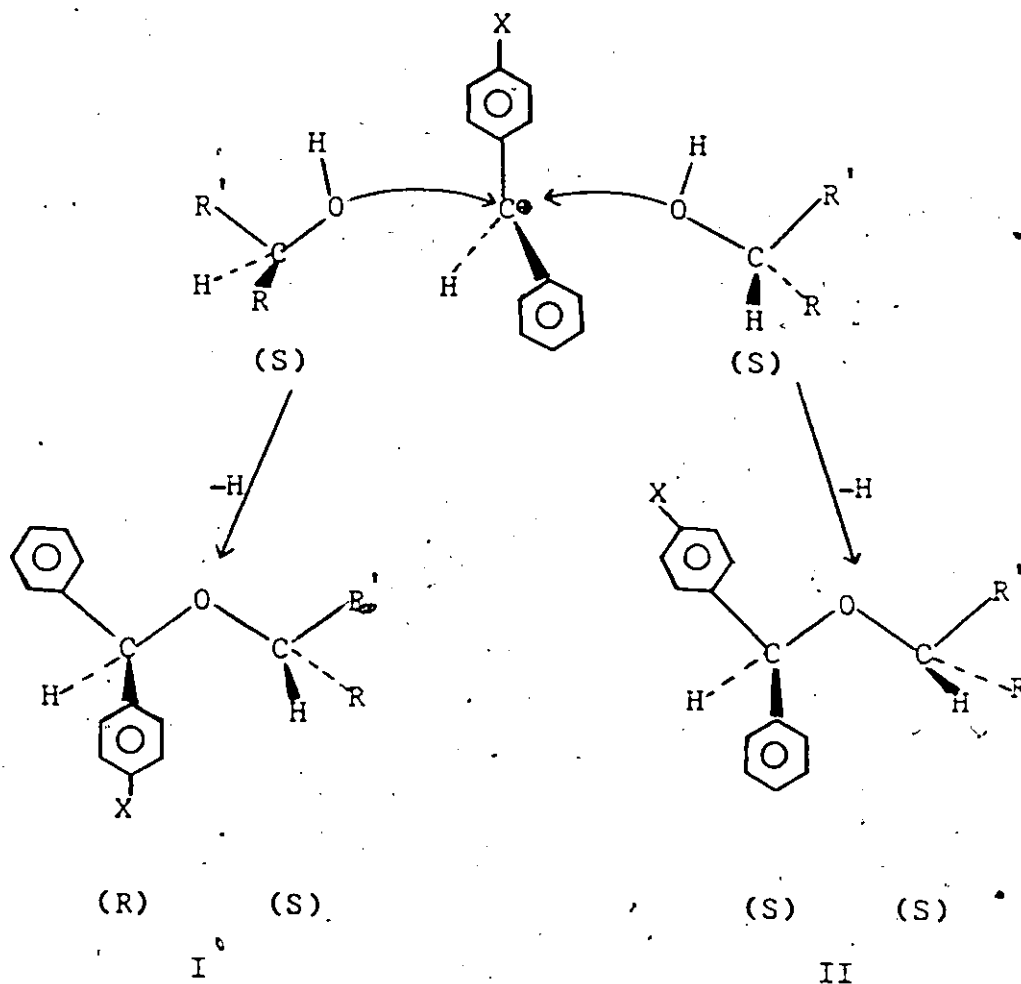
Fig. 11.

Roberts et al<sup>71,72</sup>, have used this latter information as a model for the stereochemistry about the ether oxygen atom of 1-phenylethyl benzyl ether and a series of compounds related to it.

In the reaction of optically active alcohol with benzhydryl carbonium ions one may propose the following



reactions (Fig.12).



When R = methyl

I = (R)(S)

R' = ethyl

II = (S)(S)

and, when

R = ethyl

I = (R)(R)

R' = methyl

II = (S)(R)

Fig.12.

Although the carbon bearing the positive charge and the three atoms attached to it should lie in the same plane, the aromatic rings may not lie in the same plane<sup>47</sup>. Thus the substituted benzhydryl cation possesses enantiotopic faces. If there was any preference in the direction of attack by a nucleophile, one would expect this preference to be altered by change in the para-substituent. Those carbonium ions with electron-releasing substituents (e.g. methyl) would be expected to have a longer life-time, allowing them to be more selective with regards to the stereochemical outcome of their reaction. When the para-substituent is electron-withdrawing, the carbonium ion would be relatively destabilised, and therefore one would expect less selectivity in its reaction with nucleophile. However, the basis of the electronic effect in this case, can be considered as a competitive overlap of the aromatic groups with the carbonium ion centre. Thus if the para-substituent is electron-donating, one may envisage the following, providing that one ring stays in the plane of the carbonium ion in preference to the other. (Fig.13).

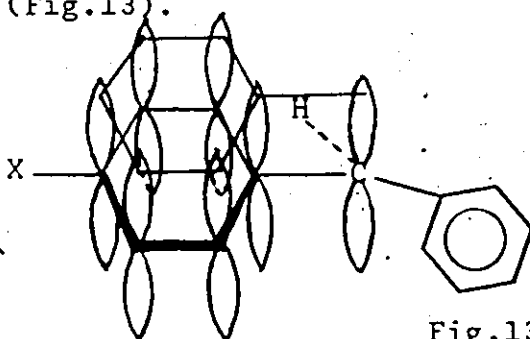


Fig.13.

If the substituent is electron-withdrawing, then the unsubstituted ring should prefer overlap with the carbonium ion centre.

If one uses Cram's rule, then one may predict that one enantiotopic face will be preferred by an attacking chiral nucleophile, as shown below. (Fig.14).

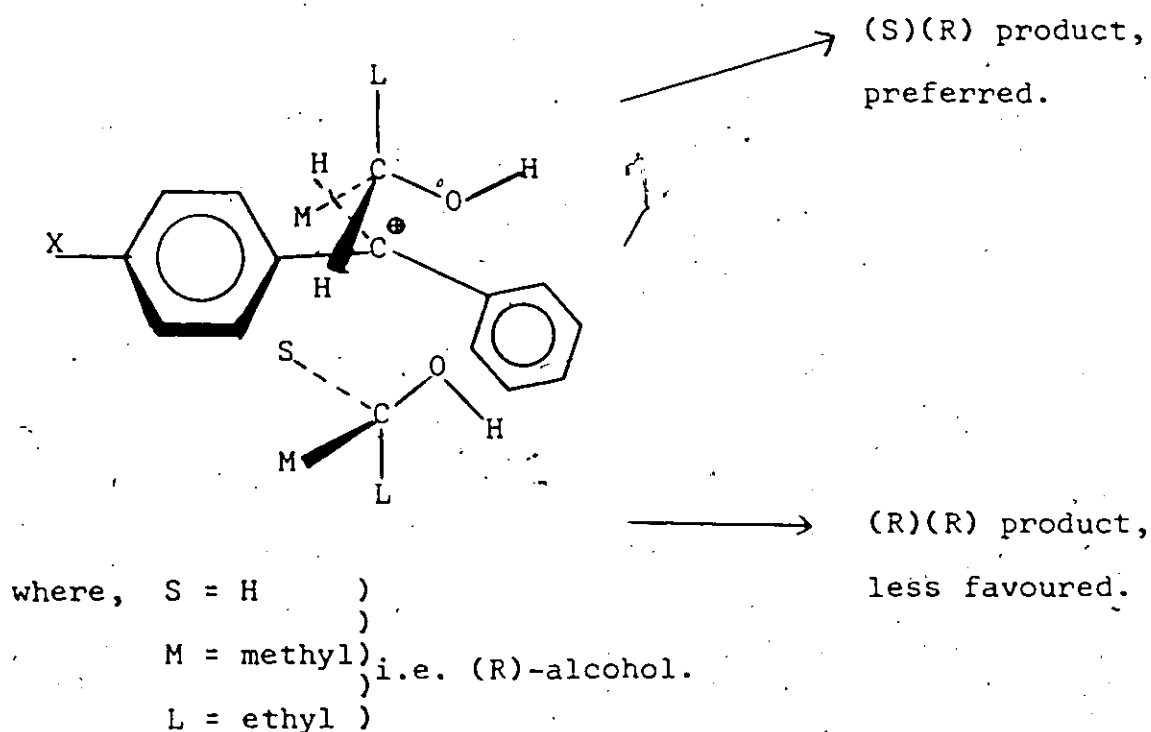


Fig.14

Thus for a benzhydryl system with an electron-donating substituent, attack by (R)-alcohol should give the (S,R)-ether as the preferred product, and attack by the (S)-alcohol the (R,S)-ether. Similar transition states may be drawn for

those benzhydryl systems containing electron-withdrawing para-substituents, and in these cases it is found that the (R,R)- and (S,S)-ethers will be the preferred products in the solvolysis reaction. Since the substituents are in the para-position, any complications arising from the steric effect will be minimised.

Spectra of the collected fractions from chromatography and from recovered solvent from solvolysis reactions, yielded interesting information. Firstly, the recovered solvent, both in the case of 2-octanol and 2-butanol, contained a greater proportion of the related ketone as compared to the starting alcohol, as was seen from the infra-red and N.M.R. spectra. The residues from the distillation of the benzhydryl chloride solvolyses products also contained some substituted benzophenone as a side-product, being detected in the infra-red spectrum by the carbonyl absorption band at  $1660\text{cm}^{-1}$ . Also, the fractions collected from the G.L.C. peaks included some 2-butanone (or 2-octanone), substituted diphenylmethane, and a small amount of the related benzophenone in some cases. It was noticed both from the G.L.C. traces and the N.M.R. spectra, that standing in light and prolonged contact with the metal of a syringe, gave more of the above side-products, probably due to the decomposition of the initially formed ether. However, decomposition occurred even in mixtures which had not been used for analysis, and therefore it seems probable

that the decomposition may be produced by heat or light. If there were any acidic traces in the solvolysis mixtures, this could also initiate decomposition, but since the solvolyses were carried out in the presence of pyridine and washed with sodium bicarbonate, this seems unlikely. Another possibility is that the diphenylmethane was formed in the initial reduction of the substituted benzophenones by transfer of a second hydride ion, but this was not detected in the N.M.R. spectra of either the benzhydrols or the benzhydryl chlorides at any time. Therefore, one possible explanation might involve homolytic cleavage of the initially formed ether, followed by disproportionation to the side-products. (Fig.15).

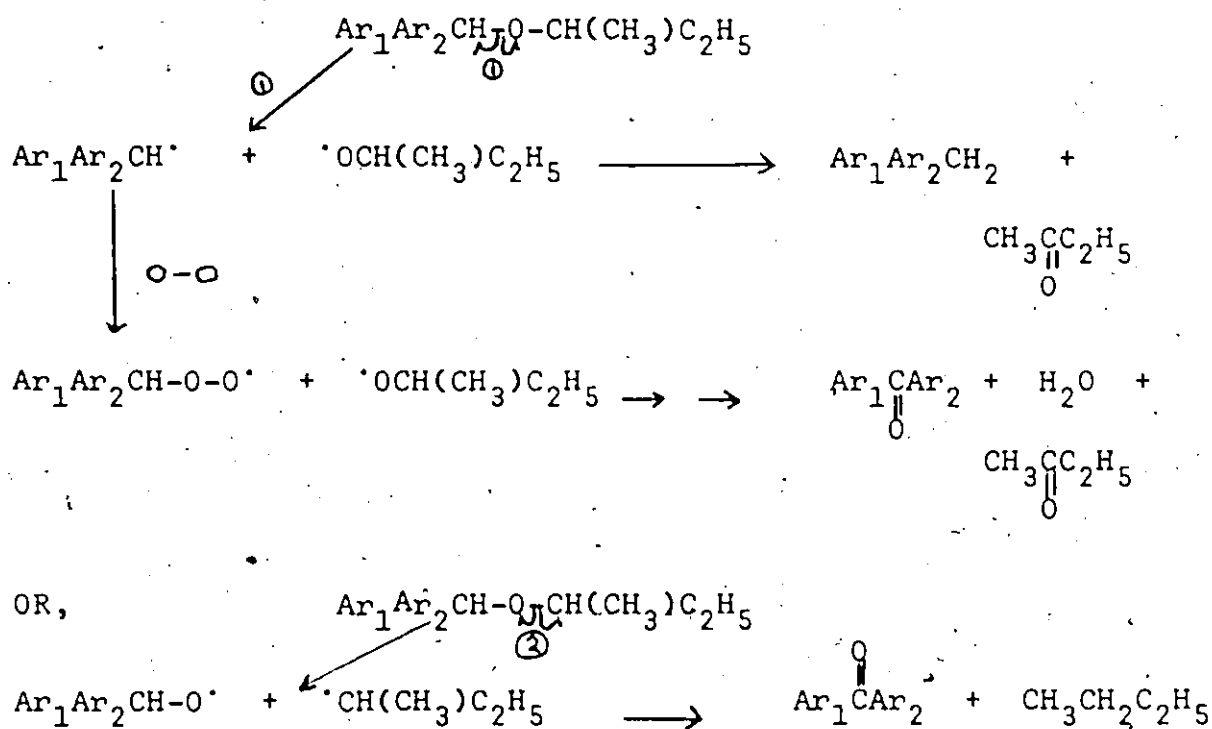


Fig. 15..

Cleavage 1 has advantages owing to the formation of a resonance stabilised radical, whereas cleavage 2 forms an aliphatic radical with no relative stabilisation. In the majority of cases larger amounts of substituted diphenylmethane and 2-butanone (or 2-octanone) were observed in the spectra of solvolysis mixtures which had been set aside for some time for later work.

The trityl systems were not investigated by the G.L.C. method, as the solvolysis products were difficult to isolate in the quantity required, and also, it would be expected that they would be more difficult to analyse by G.L.C. owing to their higher boiling points. It was decided that they should be investigated after the work on the benzhydryl systems had been completed.

Our main objective in this work was to determine the isomer ratio obtained from the solvolysis mixtures. However, much longer chromatographic columns seem to be needed than those anticipated. Similar work carried out in our laboratory on the  $\alpha$ -phenethyl system<sup>73</sup>, has been more fruitful, leading to the separation of the diastereomeric pairs of  $\alpha$ -phenethyl 2-butyl ether on a 12' x  $\frac{1}{4}$ " Tris (2-cyanoethoxy) propane column. The G.L.C. traces of this system may be seen in Appendix I, and also the N.M.R. spectra (in  $\text{CCl}_4$ ) of the products, both before and after their separation. The chemical shift values for the separated diastereomers are seen to differ, although even in the

N.M.R. of the unseparated mixture the majority of peaks are seen as doublets owing to the differences in the chemical shifts of the diastereomers. In the benzhydryl systems, the benzhydryl methine proton appeared constantly as a single peak, so that the N.M.R. spectra did not even indicate the presence of diastereomers, although one would normally expect to observe them.

In the  $\alpha$ -phenethyl 2-butyl ether case, the diastereomeric ratio was found to be 52.7:47.3. It is not known at the present time which ratio represents which absolute configuration, as it has been impossible up to this time to obtain the optical rotatory dispersion traces which are necessary to determine absolute configurations. Once these have been determined it should be very interesting to see whether the theoretical predictions are upheld experimentally. Similar studies would also be required on the separated diastereomers from the benzhydryl systems once their separation has been achieved.



## APPENDIX I.

All of the spectra obtained from the purified substituted benzhydryl halide mixtures showed similar characteristics, as can be seen from Fig. 1. (4-methylbenzhydryl 2-butyl ether) and Fig. 2 (4-chlorobenzhydryl 2-butyl ether).

The trace of the gas-liquid chromatographic separation of the diastereomers of  $\alpha$ -phenethyl 2-butyl ether on a 12' x  $\frac{1}{8}$ " 1,2,3Tris(2cyanoethoxy) propane column <sup>73</sup> may be seen in Fig. 3. N.M.R. spectra of the unseparated mixture (Fig. 4), compared favourably with those of the separated diastereomers (Fig. 5 and 6); which showed obvious differences in the chemical shift values of the groups.



8

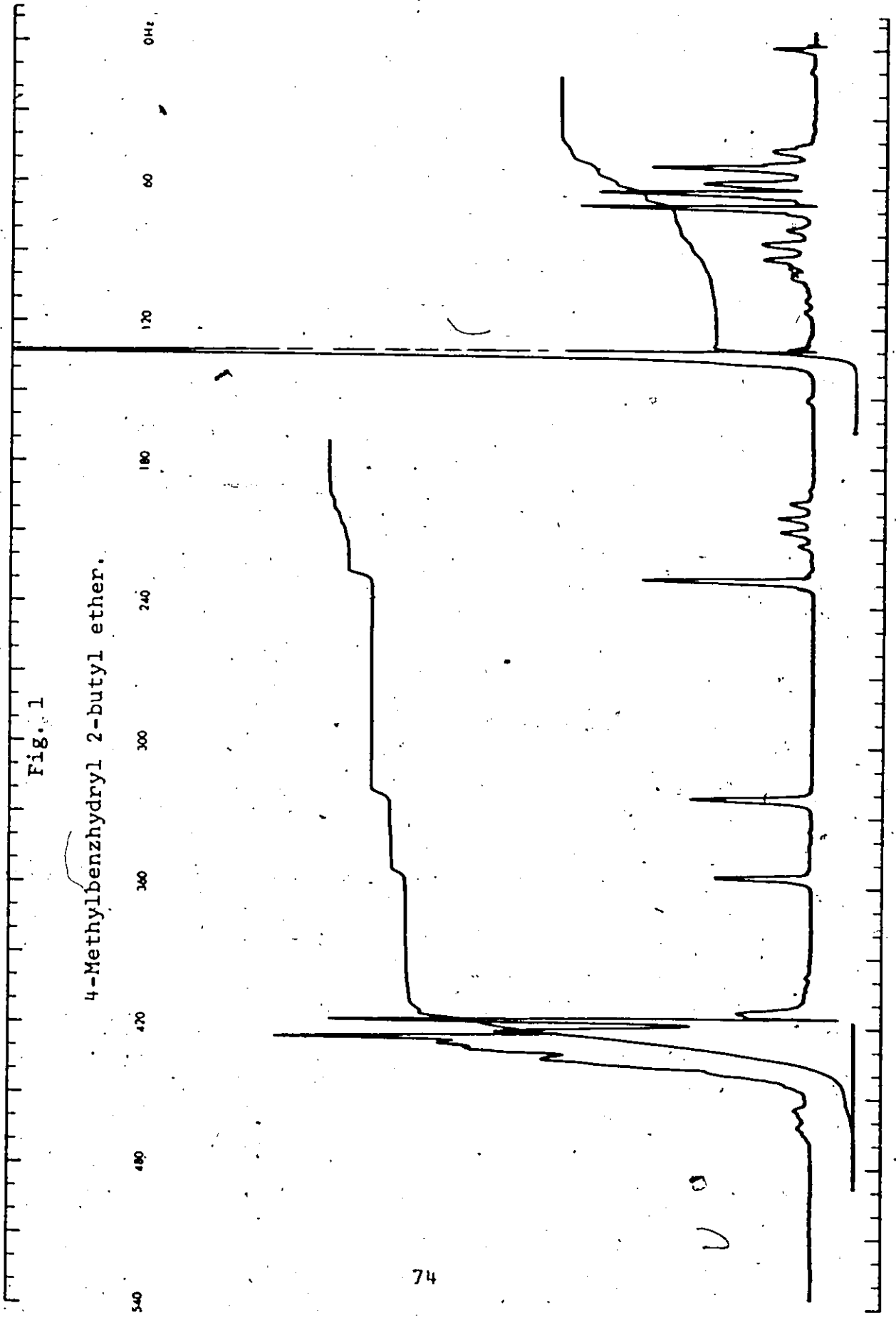


Fig. 1

4-Methylbenzhydryl 2-butyl ether.

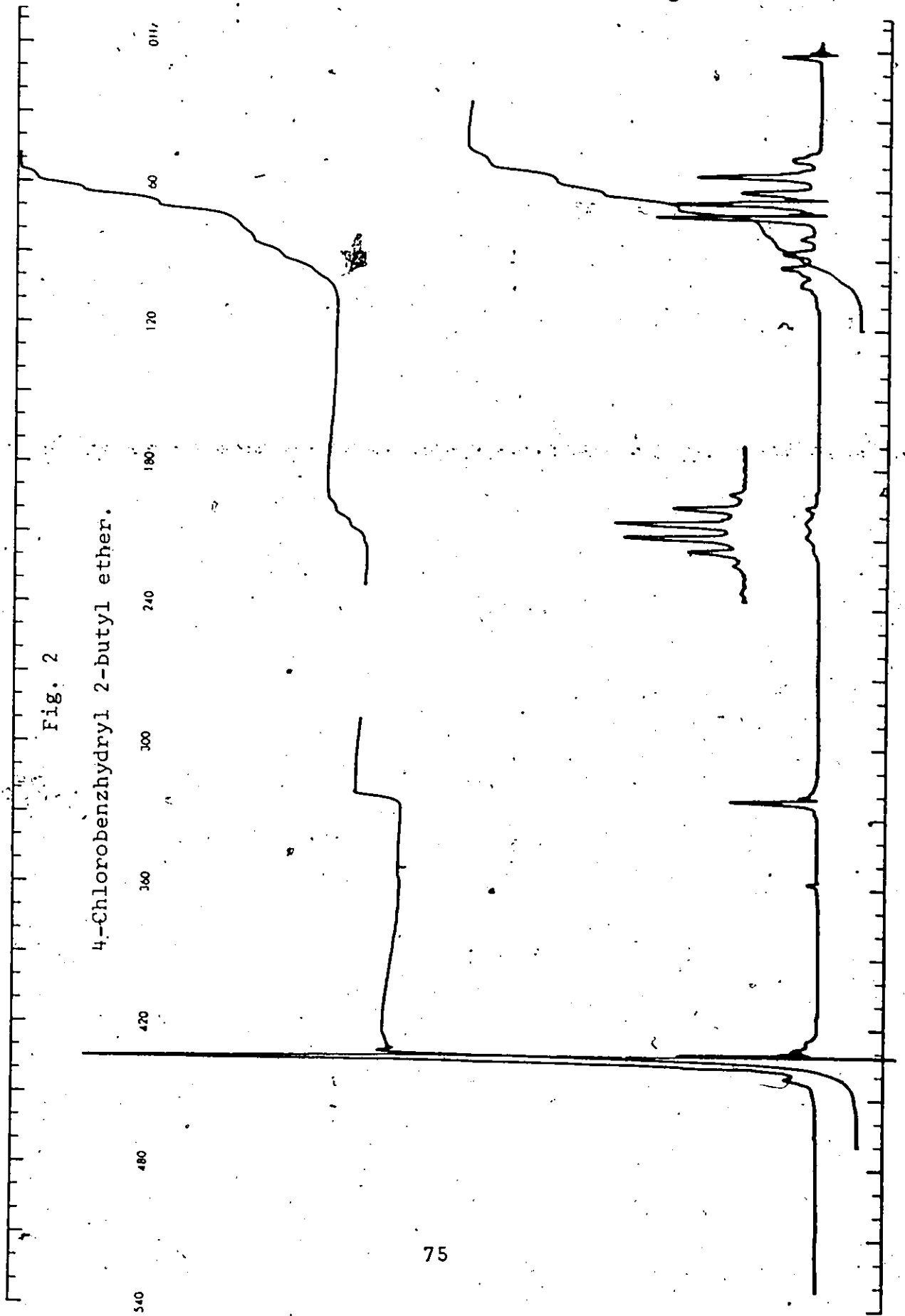
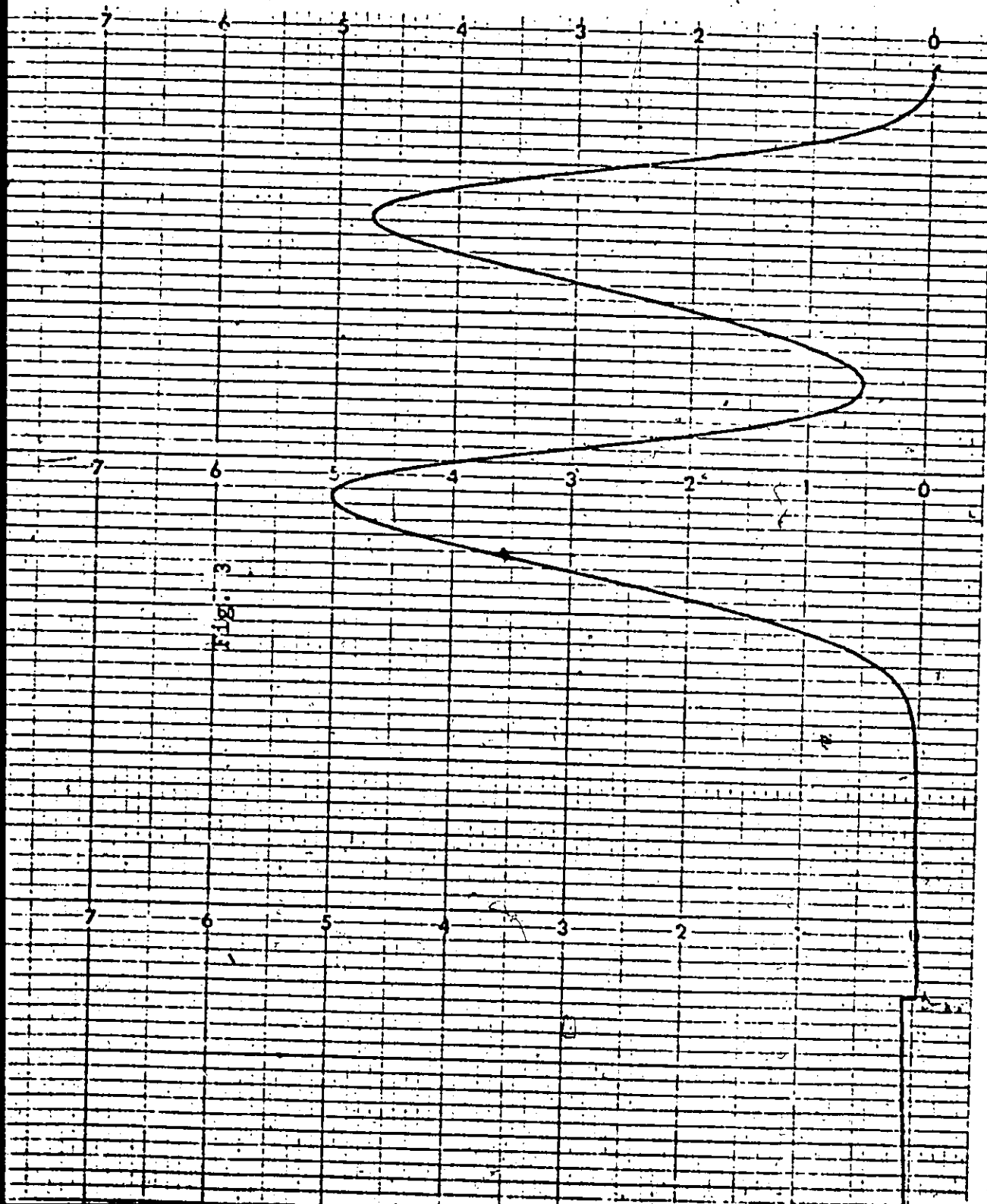


Fig. 2

4-Chlorobenzhydryl 2-butyl ether.

Separation of the diastereomers of  $\alpha$ -phenethyl 2-butyl ether  
on a 12' x  $\frac{1}{4}$ " Tris (2-cyanoethoxy) propane column.

Fig. 3



47.3

52.7

Fig. 4

$\alpha$ -Phenethyl 2-butyl ether (unseparated mixture).

splitting due to  
diastereomers.

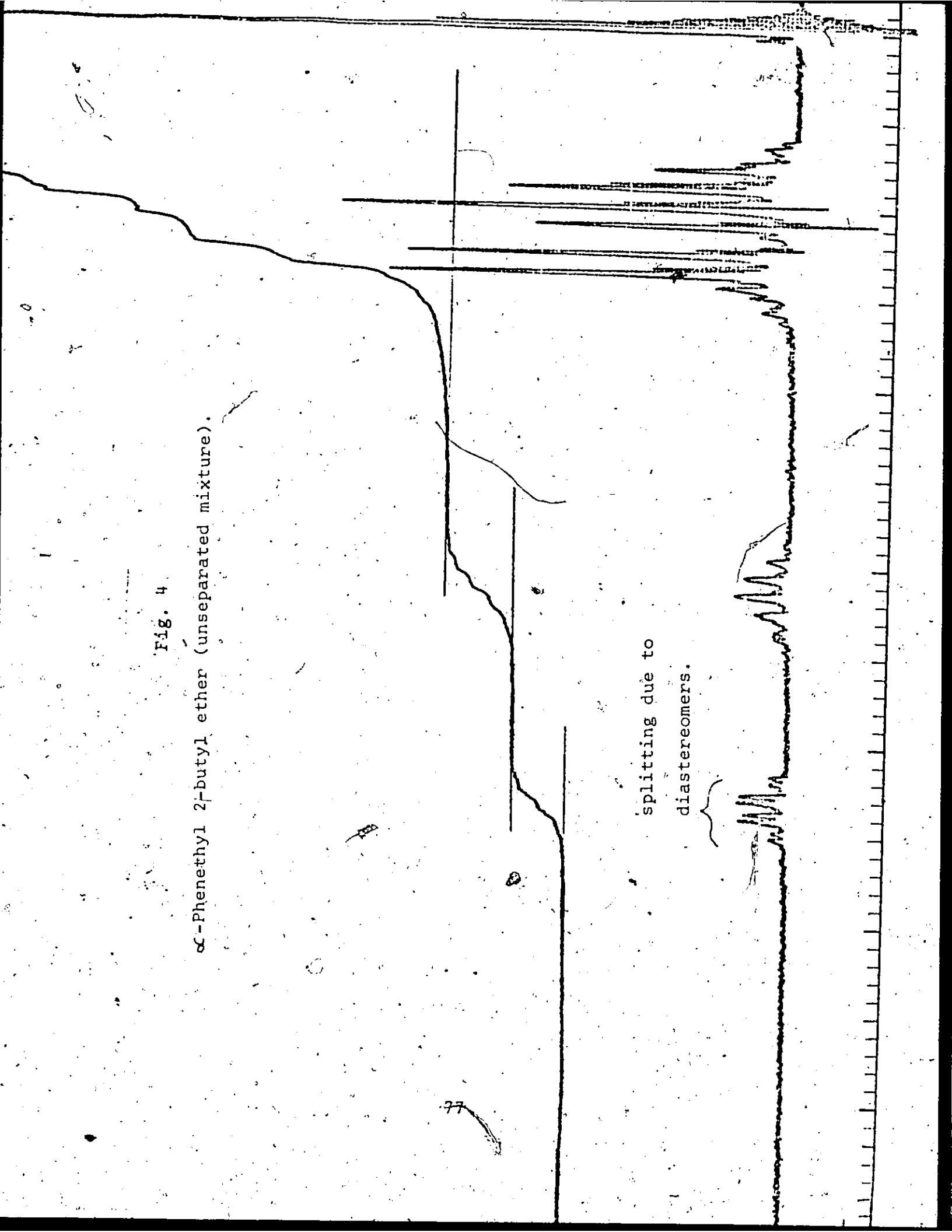
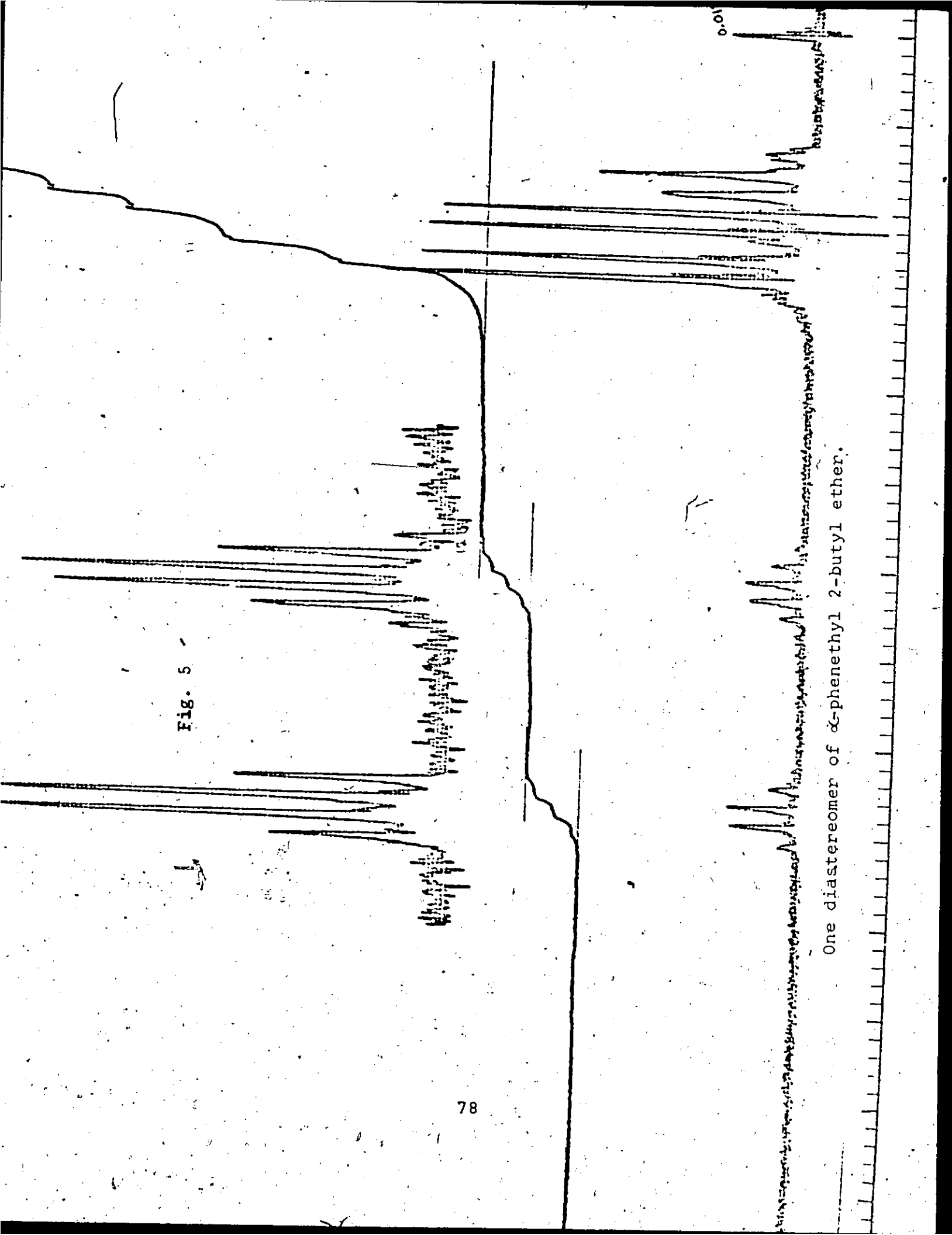
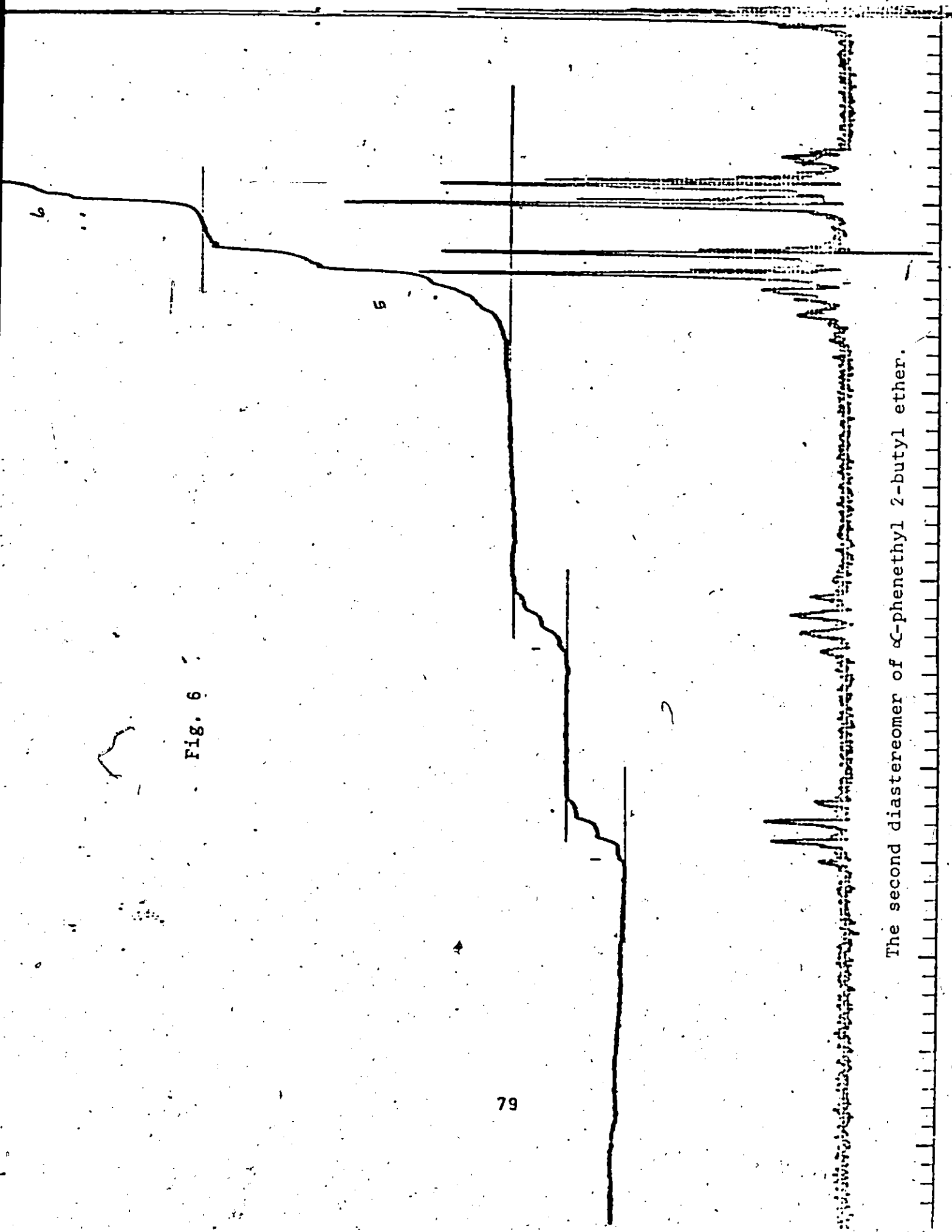


Fig. 5



One diastereomer of  $\alpha$ -phenethyl 2-butyl ether.

Fig. 6



The second diastereomer of  $\alpha$ -phenethyl 2-butyl ether.

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