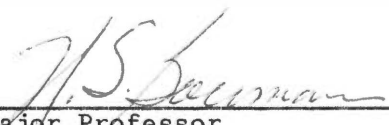


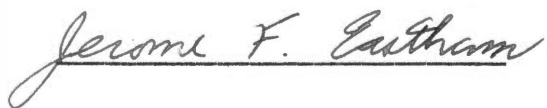
November 27, 1964

To the Graduate Council:

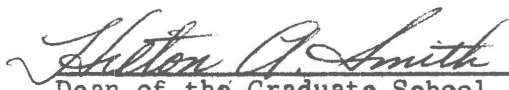
I am submitting a thesis written by George Truett McCloud entitled "Separation of Optical Isomers by Solvent Extraction." I recommend that it be accepted for eighteen quarter hours credit in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.


Major Professor

We have read this thesis and
recommend its acceptance:

Accepted for the Council:


Dean of the Graduate School

SEPARATION OF OPTICAL ISOMERS
BY SOLVENT EXTRACTION

A Thesis
Presented to
the Graduate Council of
The University of Tennessee

In Partial Fulfillment
of the Requirements for the Degree
Master of Science

by
George Truett McCloud
December 1964

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TABLE OF CONTENTS

CHAPTER	PAGE
I. INTRODUCTION.	1
A. General	1
B. Methods of Resolution	5
1. Mechanical.	5
2. Diastereoisomers.	5
3. Complexes	5
4. Biological.	6
5. Chromatography.	7
6. Crystallization	7
7. Solvent Extraction.	8
C. Other Methods of Obtaining Optically Active Compounds . .	9
1. Asymmetric Transformations.	9
2. Preferred Transition States	11
3. Synthesis	12
II. DISCUSSION.	13
A. Theory of Resolution.	13
B. Results	16
1. D-Diisopropyl Tartrate.	16
2. dl-Bis-4-pyridylglycol.	19
3. dl-Camphoric Acid	23
4. dl-2,3-Dibromobutane-1,4-diol	30
5. dl-Phenylephrine.	37

CHAPTER	PAGE
III. EXPERIMENTAL.	41
A. Method for Preequilibrating the Solvent System.	41
B. Instruments Used to Obtain Analytical Data.	41
1. Infrared.	41
2. Melting Points.	42
3. Optical Rotation Values	42
4. Nuclear Magnetic Resonance.	42
5. Gas Chromatography.	42
C. Preparation of D-Diisopropyl Tartrate	42
D. Preparation of dl-Bis-4-pyridylglycol	45
E. Partial Resolution of dl-Bis-4-Pyridylglycol.	47
1. Experiment No. 1.	47
2. Experiment No. 2.	47
3. Experiment No. 3.	48
F. Partial Resolution of dl-Camphoric Acid	49
1. Experiment No. 1.	49
2. Experiment No. 2.	50
3. Experiment No. 3.	51
G. Preparation of dl-2,3-Dibromobutane-1,4-diol.	52
H. Partial Resolution of dl-2,3-Dibromobutane-1,4-diol . . .	52
1. Experiment No. 1.	52
2. Experiment No. 2.	54
I. Partial Resolution of dl-Phenylephrine.	55
1. Experiment No. 1.	55

CHAPTER	PAGE
III. (CONTINUED)	
2. Experiment No. 2.	55
3. Experiment No. 3.	55
J. Attempted Preparation of Isohydrobenzoin.	56
IV. SUMMARY	58
BIBLIOGRAPHY.	60

LIST OF TABLES

TABLE	PAGE
I. Summary of D-(+)-Diisopropyl Tartrate Runs Made	18
II. Data on dl-Camphoric Acid Extractions	29
III. Data on dl-2,3-Dibromobutane-1,4-diol	38
IV. Analytical Data Obtained on dl-Bis-4-Pyridylglycol Runs . . .	46
V. Analytical Data Obtained on dl-2,3-Dibromobutane-1,4-diol . .	53

CHAPTER I

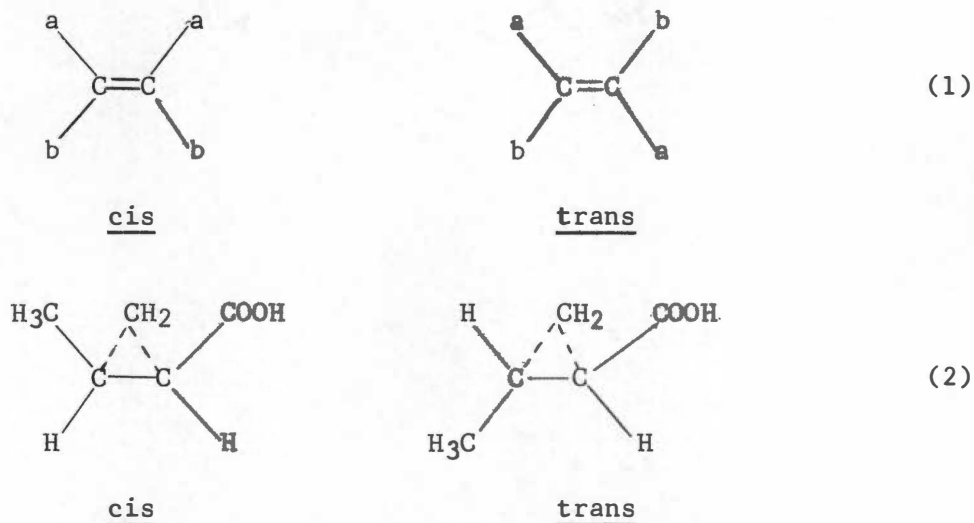
INTRODUCTION

A. General

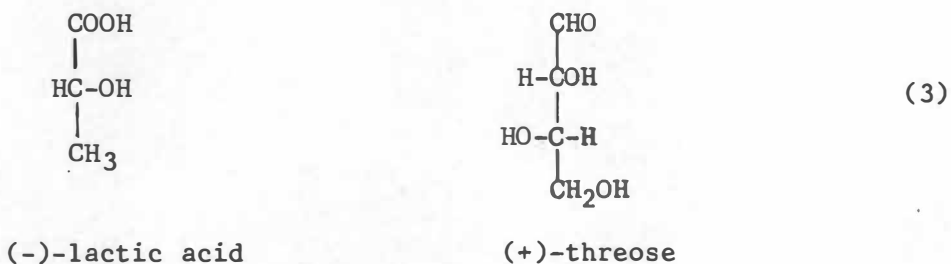
The purpose of this research was to develop a solvent extraction method to resolve optical isomers. Earlier work²⁵ done in this laboratory has indicated that partial resolution had been obtained by using D(+)-diisopropyl tartrate and water as the immiscible solvent system. Further work done by the author indicates that this method can be used to partially resolve racemic modifications. Before this method is discussed in detail, a summary of the known methods of resolution should be presented.

Many different methods have been used in the resolution of optically active compounds. Before any of these methods are described, it would be advantageous to consider the nature of racemic modifications. In 1815 Biot¹ found that certain organic compounds rotated the plane of polarized light. In 1858 Kekule² originated the fundamentals of modern structural organic chemistry. LeBel³ and van't Hoff⁴ conceived the concept of the tetrahedral carbon simultaneously. They also recognized that two types of isomerism, optical and geometrical, could result from this arrangement. Optical isomerism is usually caused by the attachment of four different atoms or groups to one of the carbon atoms in the molecule. Geometrical isomerism may be described as

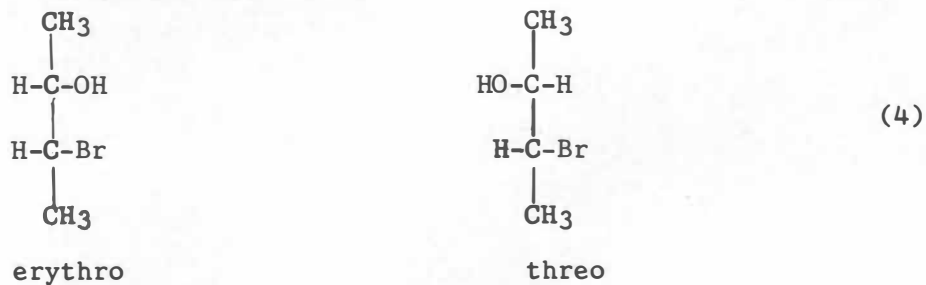
different arrangement of groups around double bonds or in ring compounds. Usually the ring compounds are the only type of geometrical isomers which show optical activity. Geometrical isomerism may be illustrated as follows:



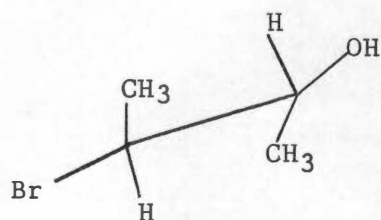
Optical isomerism is often found in very complex structures, however examples of some simple molecules are as follows:



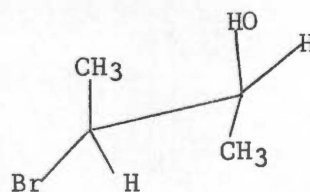
A number of different formulae are used to depict the orientation of the asymmetric atoms. The most common ones are as follows:



Fisher projection formulae



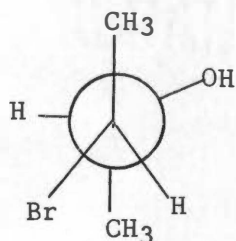
erythro



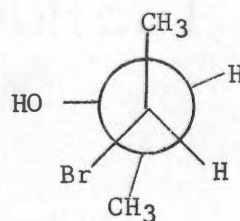
threo

(5)

Sawhorse formulae



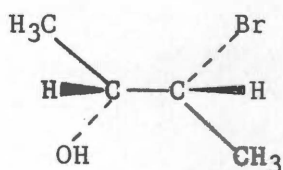
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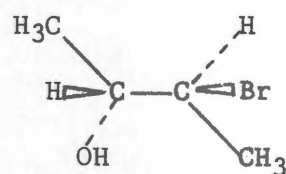
threo

(6)

Newman projection formulae



threo



erythro

(7)

Flying-wedge formulae

Molecules of most substances are optically active if they are dissymmetric. However, the substance in bulk may not be optically active because it may be constituted of equal numbers of dextrorotatory (+) and levorotatory (-) molecules so that the average rotation is zero. An assembly such as this is called a racemic modification.

Eliel⁵ gives a complete summary of formation of racemic modifications. The most important methods are by synthesis, racemization, epimerization, mutarotation, and asymmetric transformations.

The difficulties encountered in the resolution of racemic modifications may be envisioned by considering their physical and chemical properties. In the gaseous and liquid state, an ideal mixture is most often obtained. Thole⁶ showed that significant deviations from ideality could occur in liquids capable of hydrogen bonding. The solid state is not subject to ideality.⁷ Intercrystalline forces between molecules are highly specific and sensitive to even minor changes in geometry. The following three cases may arise for the solid state:

a. Racemic mixtures. If the unit cell or the macroscopic crystal consists of either the (+) or (-) form alone, this arrangement is called a racemic mixture. Thus equal numbers of (+) and (-) crystals are formed. The X-ray and infrared spectra are similar to the pure enantiomers; however the melting point is lower.

b. Racemic compounds. If the unit cell contains equal numbers of the (+) and (-) forms, this arrangement is referred to as a racemic compound. Again the physical properties differ from that of the pure enantiomers.

c. Racemic solid solutions. If a random arrangement of molecules occur, the resulting compound shows near ideal behavior. This arrangement is referred to as a racemic solid solution. The physical properties of the solution are the same as those of the pure enantiomers.

Affinity for like or unlike molecules is believed to be the cause for the formation of the three different type crystals.

B. Methods of Resolution

1. Mechanical

The first resolution of a racemic modification was achieved by Louis Pasteur in 1848⁸ in his famed experiment whereby he picked apart the two kinds of crystals of the sodium ammonium salt of racemic tartaric acid. It is fortunate that this salt is a racemic mixture, for racemic compounds or racemic solid solutions cannot be resolved by this method.

2. Diastereoisomers

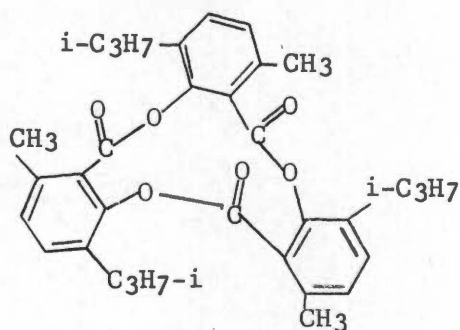
A more useful method which was also developed by Pasteur is that of formation of diastereoisomers. An example would be a dl-acid neutralized with a dextrorotatory (d) base. The two salts formed are diastereoisomers which have different physical properties. The salts are usually purified by fractional crystallization. This method is limited by the fact that racemic modifications readily form reaction products with only a limited number of available resolving agents. Moreover, only one of the pure enantiomers can be obtained by this method as the other one is left in the mother liquor.

3. Complexes

Complexes formed by treating a dl-pair with dissymmetric reagent often offers a method for resolution. The complex may be thought of as being a mixture of two diastereoisomers. One form of the diastereoisomer can usually be made to precipitate. A pure enantiomer of the

original dl-pair can be obtained by decomposition, chromatography, or chemical treatment of the complex.

The clathrate or inclusion complexes are similar. The complex is formed by crystallizing a compound that forms a hole which another component can occupy if it is of suitable shape. Desoxycholic acid has been used to resolve camphor.⁹ Another example is that of tri-o-thymotide crystallized from 2-bromobutane.¹⁰ Tri-o-thymotide exists as the dl-form. After crystallizing from the solvent, it is found that one enantiomer of 2-bromobutane is present in one form of the thymotide.



Tri-o-thymotide

Urea is not an asymmetric molecule; however it crystallizes in spiral-shaped asymmetric crystals. As a result, 2-chlorooctane has been resolved by preferentially fitting into the lattice of urea.¹¹ The hemihedric urea crystal must be induced by inoculating with the preferred seed.

4. Biological

Pasteur discovered that when the microorganism *penicillium glaucum* is grown in a dilute solution of nutrient salts containing racemic tartaric acid, the originally optically inactive solution

slowly acquired a levorotatory character. Natural d-tartaric acid is consumed by the microorganism faster than the l-form. Many other instances are known where microorganisms show a preference for one form of a dl-pair.

5. Chromatography

Chromatography has been used as a method of resolution. Diastereoisomeric adsorbates are formed. If column chromatography is employed, one technique involves the use of optically active substrates. The resolution of p-phenylene-bis-iminocamphor has been reported to have been resolved on a lactose column. This method is sometimes used to determine whether a compound is a dl-pair or an inactive species. After chromatographing, if the eluent shows activity, the material is a dl-pair. However, this method fails for some species. Sometimes an inactive substrate can be treated with an active compound to induce resolution. Paper chromatography has also been used.¹³ Both types of resolution are effected by the difference in solubilities of the two diastereoisomers in the optically active substrate. In more recent years gas-liquid chromatography has been used. Partial resolution of 2-butanol has been obtained on a stationary phase of (-) ethyl tartrate.¹⁴

Dialysis through an optically active membrane has been used to resolve the dl-pair of tartaric acid.¹⁵

6. Crystallization

Crystallization from an optically active solvent has been used to resolve 2,3-dibromobutane-1,4-diol;²⁰ (+)-diisopropyl tartrate was used as the solvent.

A theoretical discussion of this method is given by Secor.²⁴ The author employs the physical approach, and derives phase diagrams indicating that resolutions can be obtained from both binary and ternary systems. He also suggests that resolution by crystallization from a binary system may be the most convenient and practical method of separation. A supersaturated solution is needed; however the crystallization may be carried out isothermally or by cooling. A seed crystal of the desired isomer is used to induce crystallization. Ternary systems involve essentially the same technique. The solvent is saturated with the racemic modification at an elevated temperature. The solution is then cooled, and a seed crystal of the desired isomer is added.

The crystallization procedure for resolution is easy to apply; however the separation for a single crystallization is usually far from complete. Repeated crystallizations, usually by alternating the removal of the d and l isomers, may give complete separation.

No general theory has been fully developed, and as a result it is not yet possible to predict whether the resolution of a given racemic modification can be achieved by this method.

7. Solvent Extraction

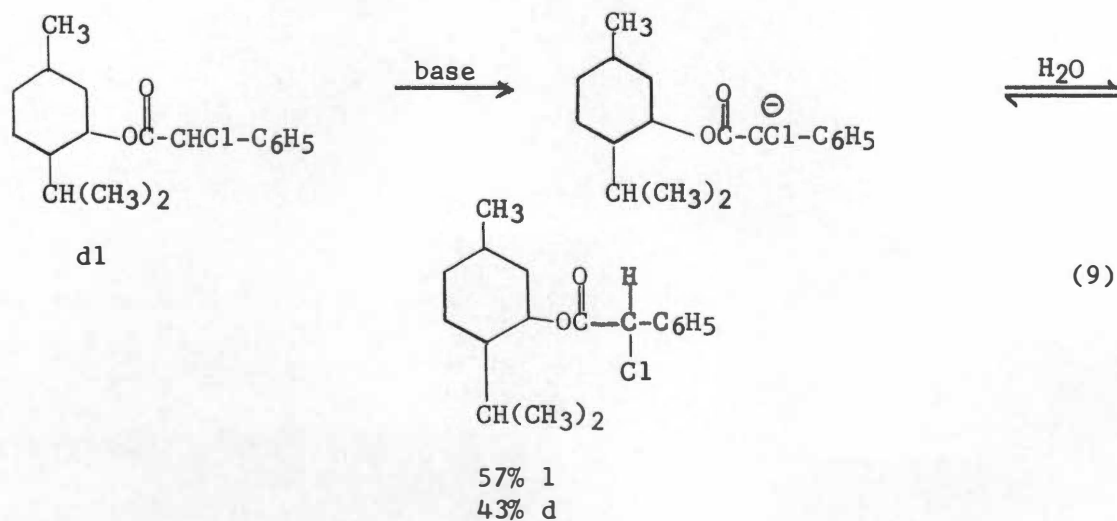
Preliminary data from this investigation indicate that dl-pairs may be partially resolved by solvent extraction. An optically active solvent, D(+)-diisopropyl tartrate, and water have been used to partially resolve dl-2,3-dibromobutane-1,4-diol, dl-phenylephrine, dl-camphoric acid, and dl-bis-4-pyridylglycol. This thesis elucidates the techniques used.

C. Other Methods of Obtaining Optically Active Compounds

1. Asymmetric Transformations

A number of asymmetric transformations are known. Mutarotating sugars illustrate a good example of this technique. In solution glucose is present in an equilibrium mixture of the α and β forms. The position of equilibrium depends on the solvent. Crystallization of the least soluble form will occur from a concentrated solution. The concentration of the sugar remaining in solution is changed from its equilibrium value, which results in formation of more of the least soluble species, which in turn continues to crystallize. Essentially a pure sample of either form may be obtained, depending on the solvent.

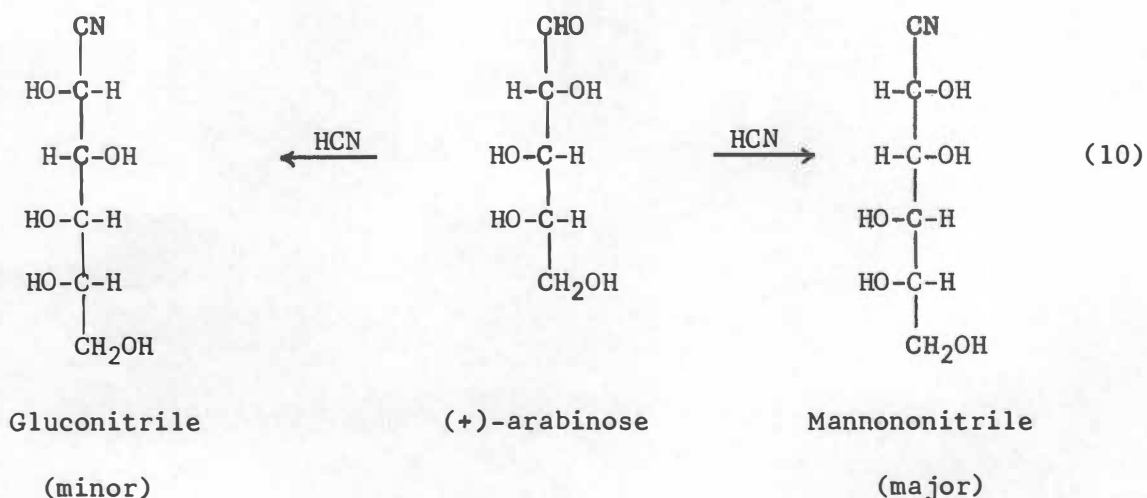
Epimerization may be induced by controlling the pH. Phenylchloroacetic acid may be partially resolved in a basic medium.



The equilibrium mixture contains 57 per cent ester of the (-) acid and 43 per cent ester of the (+) acid.¹⁶

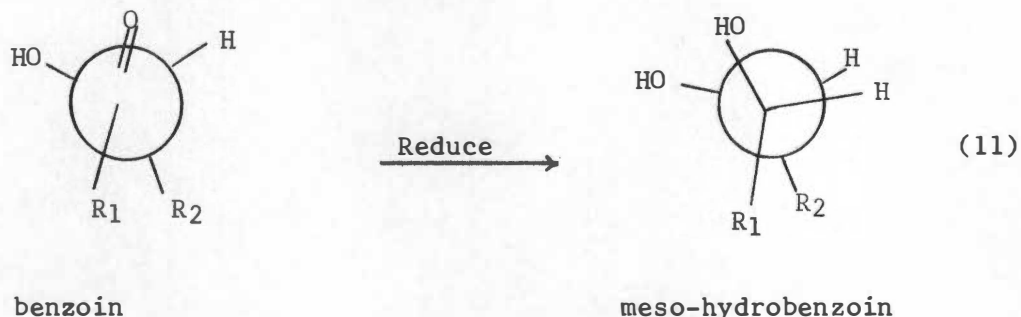
Kinetic asymmetric transformation may be explained by differences in the transition state since diastereoisomers usually differ in free energy of the transition state. The reaction of cis and trans-1,2-cyclopentanediol with lead tetraacetate illustrates this point.¹⁷ The cis isomer reacts 3000 times as fast as the trans compound. An application using this principle is the reaction between (±)-menthol and (±)-mandelic acid. If only one form of the racemic alcohol is used, resolution can be obtained. Thus (-)-menthol can form only two diastereoisomers with racemic acid, and data indicate that the (+) (-) isomer predominates. Separation of the resulting mixture yields a material enriched in (+)-mandelic acid.

Asymmetric synthesis may also be used to advantage. The syntheses of sugars offer good illustrations. Gluconitrile and mannnonitrile synthesized from (+)-arabinose may be illustrated as follows:

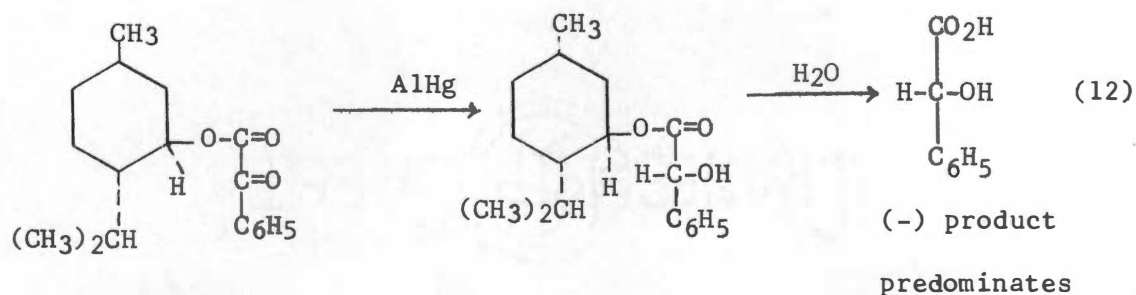


A consideration of what happens in an asymmetric synthesis shows that an asymmetric center introduced in a molecule containing one or more asymmetric centers may form a pair of diastereoisomers.

In the reduction of ($\pm$)-benzoin, the major product at low temperatures is the meso form and even at higher temperatures the product is still a 60:40 mixture in favor of the inactive compound. Cram's¹⁸ rule predicts this product.



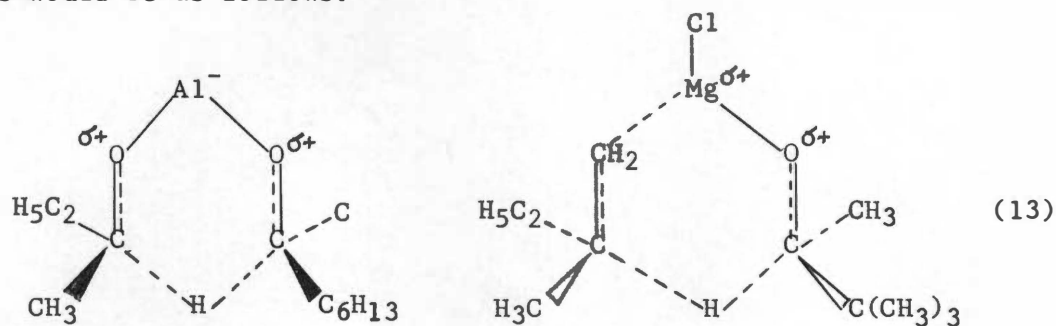
Optically active compounds can be made from inactive starting materials by the kinetic induction method. Using this technique, (-)-mandelic acid was prepared by the reduction of (-)-menthyl phenylglyoxylate.¹⁹



2. Preferred Transition States

Preferred transition states often lead to asymmetric synthesis. In the Meerwein-Ponndorf reductions, the preferred transition state is that in which the two largest groups are on opposite sides of the plane of the ring. Asymmetric Grignard reductions may be rationalized on

similar reasoning. Preferred Meerwein-Ponndorf and Grignard transition states would be as follows:



3. Synthesis

Compounds having weakly reactive functional groups usually cannot be resolved. Synthesis using optically active starting materials are generally the methods used to obtain the desired compounds.

CHAPTER II

DISCUSSION

A. Theory of Resolution

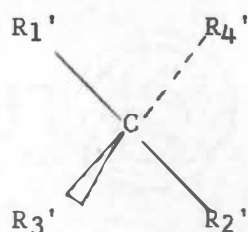
Since Pasteur⁸ demonstrated that dl-transformations can be resolved, much research has been done to perfect the methods used. Many techniques that yield partial to complete separation have been developed. This thesis essentially describes another method of resolution.

For many years after Pasteur's work, many workers believed that the concentration of the d and l form were the same in any solvent. Work done in recent years indicate that this is not true for all dl-transformations. Luttringhaus²⁰ has clearly shown that the d and l forms of 2,3-dibromobutane-1,4-diol are not equally soluble in an optically active solvent. Secor²⁴ gives illustrations whereby the solubility of the two forms of certain dl-transformations can be made to differ in supersaturated solutions.

Work done in this laboratory indicates that the d and l forms of some dl-transformations indeed differ in their solubilities in an optically active solvent. The technique used by the author differs considerably from any method reported in the literature. Crystallization from supersaturated solutions induced by seeding is the general method which has previously been used. Luttringhaus²⁰ was the first to report resolution by crystallization from an optically active solvent without seeding.

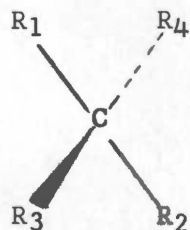
Solvent extraction was used by the author.

To explain the difference in solubility of the d and l form, one can visualize a number of rationalizations. One method may be that of a three point attachment between the solute and solvent.²⁶ Consider a simple optically active solvent molecule. Now consider a simple dl-transformation dissolved in the solvent.

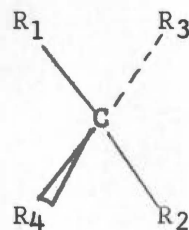


(14)

(Solvent) D-diisopropyl tartrate



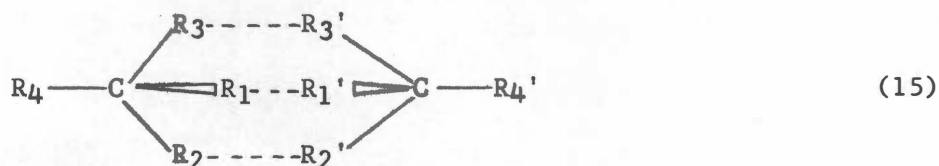
d-solute



l-solute

Let us now assume that the groups on the solute molecule (R_1 , R_2 , and R_3) are in some manner (ionic, hydrogen bonding, dipole-dipole, etc.) preferentially attracted to the corresponding groups (R_1' , R_2' , R_3' in that order) on the solvent molecule. Now there is only one spacial orientation whereby the three groups of the solvent molecule can come in contact with the corresponding three groups of the solute. Only one form of the solute will have the right configuration for this attachment.

Structure 15 shows one way that a solute molecule and a solvent molecule



can interact if the two molecules have the required orientation with respect to each other.

One can carry this approach further by assuming that only two sites on each molecule are necessary for interaction. The third pair of sites will then have no interaction if there is no repulsion between the groups or if no steric effects are encountered.

Thus one can see that interaction between solute and solvent molecules may effect the solubility of a dl-pair in an optically active solvent. If the interaction is strong enough, this investigation indicates that partial resolution of the dl-pair can be effected by using solvent extraction methods.

For simple dl-transformations, where the actual conformations may be known, it might be possible to predict which form of the dl-pair would be the most soluble in the solvent. However, in more complex systems where the actual spacial arrangement is unknown, no predictions can be made. To elucidate this point, in the four systems studied by the author, three of the l-isomers were the more soluble in the optically active solvent; the d-isomer was more soluble in the other system.

D-Diisopropyl tartrate would appear to be a good solvent where hydrogen bonding between solute and solvent may occur. Preferential

interaction between the solute form having the more favorable three point orientation as a result of hydrogen bonding with the tartrate molecule would result in a difference in solubilities of the enantiomers in the ester. If an initial quantity of the optically active solvent is saturated with a dl-pair, and then an equal volume of water is added, two phases will result. If the mixture is shaken until equilibrium is attained and then the phases separated, the ester phase will be more concentrated in one form of the dl-solute. That form of the solute having the least attraction for the solvent molecules will be concentrated in the water phase. If a suitable method is available for isolating the material from each phase, one may obtain samples enriched in the respective isomers.

B. Results

1. D-Diisopropyl Tartrate

The solvent used for all the resolutions attempted was D-diisopropyl tartrate. The material was synthesized as needed. Ten runs were made during the course of this investigation. The procedure given in the literature was found to be inadequate. Knowing that the formation of the ester from the acid is reversible in presence of water, an increased yield was obtained on each run by distilling the water formed in the initial reaction. Additional pure isopropanol was then added to the mixture, and the reaction was allowed to continue. This method increased the yield from 80 per cent to above 90 per cent.

Erratic yields (or none at all) were obtained until it was found that the ester decomposed in the presence of atmospheric oxygen at temperatures required for distillation. Complete decomposition was found to occur if the distillation was carried out at temperatures greater than 150°. The results from experiments shown in Table I illustrate the effects of oxygen on distillation. As further proof that oxygen has a detrimental effect on yield, one reaction mixture was divided into two equal portions after the excess isopropanol and water was distilled from the final reaction mixture. The distillation of the product was carried out using atmospheric oxygen as the ebulliting gas with one sample and dry nitrogen with the other. A 43 per cent increase in product yield was obtained from the nitrogen distillation compared to the one where oxygen was used. See Table I.

Steam bath temperature was found not to be high enough to effect the ester formation from the acid in good yield. A heating mantle was used to obtain satisfactory refluxing temperature. Yields from the reaction heated by a steam bath was only 30 per cent of those obtained by using a heating mantle. See Table I. Preparations reported in the literature were made by using a steam bath to effect the ester formation.

Physical constants reported in the literature are as follows:

$$[\alpha]_D = 16.50^\circ$$

Refractive index = 1.4368.

The physical constants on the material made using the above described modifications are as follows:

TABLE I

SUMMARY OF D-(+)-DIISOPROPYL TARTRATE RUNS MADE

Date Run Made	Tartaric Acid Used (g.)	Yield (g.)	Ebulliting Gas	Heating Method Used	$[\alpha]_D$	Refractive Index	Infrared
1/29/64	900	760	None	Heating Mantle	18.00	1.4368	Checked authentic sample
2/18/64	1000	0.0	Air	Heating Mantle	--	--	--
2/26/64	600	0.0	Air	Heating Mantle	--	--	--
3/3/64	1200	105	Air	Heating Mantle	18.00	1.4368	Checked authentic sample
4/1/64	700	130	Air	Heating Mantle	18.00	1.4364	Checked authentic sample
4/24/64	800						
After distilling off water		175	Air	Heating Mantle	18.00	1.4370	Checked authentic sample
Split into 2 equal parts		250	Nitrogen	Heating Mantle	20.00	1.4372	Checked authentic sample
5/25/64	700	200	Nitrogen	Steam Bath	20.00	1.4368	Checked authentic sample
6/26/64	700	650	Nitrogen	Heating Mantle	20.00	1.4370	Checked authentic sample
8/8/64	700	650	Nitrogen	Heating Mantle	20.00	1.4372	Checked authentic sample
9/2/64	700	600	Nitrogen	Heating Mantle	20.00	1.4372	Checked authentic sample

$$[\alpha]_D = 20.00^\circ$$

Refractive index = 1.4372.

In summary it can be said that this modified procedure gives a greater yield and better quality product.

2. dl-Bis-4-pyridylglycol

The preparation of dl-bis-pyridylglycol was carried out as described in the experimental section. The synthesis of the compound was found to be fairly easy, however two runs were made to obtain enough material for the desired experiments. The higher melting meso-isomer was separated from the dl-pair by repeated recrystallizations from a water-methanol mixture (50:50) until a product having a constant melting point of 169° was obtained. Three recrystallizations were done on each run, the products obtained from the two runs were combined, and recrystallized again.

The best method found for the partial resolution of the dl-pair was that of dissolving 4.2 g. of the glycol in 90 ml. of preequilibrated diisopropyl tartrate followed by adding the same quantity of preequilibrated water and then shaking the mixture for 5 hours. The phases were separated, and the bis-4-pyridylglycol obtained from each phase by removal of the ester under vacuum.

It was found that the glycol was not readily soluble in the initial preequilibrated ester. Heating the ester to 40° and then saturating with glycol proved to be satisfactory. If the ester was heated above 40° and then saturated with the sample, precipitation occurred upon cooling.

Freeing the dl-bis-4-pyridylglycol from the diisopropyl tartrate proved to be harder than anticipated. Extensive decomposition of the glycol occurred if the distillation temperature was greater than 150°. At normal operating conditions, very little ester could be removed at this temperature. However, by obtaining a vacuum of 0.25 mm., the ester could be slowly distilled. Wrapping all the exposed surface of the distillation flask with a heating tape and applying just enough voltage to maintain distillation temperature throughout the flask also helped.

After obtaining the crude glycol from both phases in this manner, purification was carried out by repeated recrystallizations from a water-methanol mixture (50:50) until a product having a constant melting point of 169° was obtained. Infrared data was then obtained to be certain no ester remained in the sample. The strong carbonyl absorption at 5.9 μ is capable of indicating concentrations of less than 0.5 per cent ester. All analytical data showed that samples purified by using this procedure were free from ester contamination; however the sample obtained from the ester phase at this point was highly colored.

Optical rotations were obtained on portions of samples collected from the ester and water phases. The material obtained from the ester phase gave such a highly colored solution that the rotation values were questionable.

The remainder of the samples were recrystallized. Charcoal was added to the sample obtained from the ester phase to remove the color.

Optical rotations were then obtained again on the samples. It was demonstrated that the values were in close agreement with the first set.

The procedure used to obtain rotations was that of zeroing the polarimeter with a blank of dl-racemate. The unknown was then analyzed using the same sample size as was used for the blank. Ten readings were taken on each sample and these values averaged. The rotations in glacial acetic acid were as follows:

$[\alpha]_D = +6.17^\circ$ for the material isolated from ester phase

$[\alpha]_D = -34.75^\circ$ for the material isolated from the water phase.

The resolutions were calculated as follows:

$$[\alpha]_D = \frac{\alpha}{l \times \frac{g}{v}}$$

$[\alpha]_D$ = specific rotation = 88.50° in acetic acid

α = observed rotation

l = length of cell in decimeters

g = grams of sample

v = volume of solvent.

After obtaining α from the optical readings, the observed rotation was calculated for the same size sample of the pure isomer. It follows that

$$\frac{\text{Observed rotation of unknown sample}}{\text{Calculated rotation of pure isomer}} \times 100 = \% \text{ resolution .}$$

The calculations for the experiments were as follows:

a. Sample isolated from water phase:

$\alpha = -1.385^\circ$ from measurement by dissolving 0.100 g. in 5.0 ml.

acetic acid using a 2.0 decimeter cell.

Calculated α for an equivalent concentration of the pure isomer:

$$88.50^\circ = \frac{\alpha}{2 \times \frac{0.100}{5.0}} \quad \alpha = -3.540.$$

Per cent resolution obtained from one extraction for water phase:

$$\frac{-1.38}{-3.540} \times 100 = 39.10\% .$$

b. Sample isolated from ester phase:

$\alpha = +0.212^\circ$ from measurement by dissolving 0.085 g. in 5.0 ml.

acetic acid and using a 2.0 decimeter cell.

Calculated α for the pure isomer:

$$88.50^\circ = \frac{\alpha}{2 \times \frac{0.085}{5.0}} \quad \alpha = +3.01.$$

Per cent resolution obtained from one extraction for ester phase:

$$\frac{0.212}{3.01} = 7.05\% .$$

The solubility of dl-bis-4-pyridylglycol was found to be 6.5 per cent by weight in the preequilibrated ester and 2.2 per cent by weight in preequilibrated water. From these data one would expect that the resolution obtained from the material recovered from the water phase would be three times that obtained from the ester phase. From the above data, the ratio is 5.54:1, which is fairly close to the estimated value. Only if the mixture behaved as an ideal solution would the calculated ratios be obtained.

3. dl-Camphoric Acid

This compound was obtained from K and K Laboratories, Inc.

The best procedure found for the partial resolution of the dl-pair was that of dissolving 6 g. of the acid in 100 ml. of preequilibrated diisopropyl tartrate followed by addition of the same quantity of pre-equilibrated water, and then shaking the mixture for 5 hours. The phases were separated, and most of the water distilled from the water phase sample. (The volumes of water in both samples was held constant to 10 ml. throughout the purification step to avoid excessive loss of the dl-camphoric acid.) Sodium bicarbonate was then added to each sample to form the salt. The salt was freed from the ester by extracting with chloroform. The salt was then converted to the free acid by the addition of dilute sulfuric acid. The free acid from both samples was collected by vacuum filtration. Each sample was washed with distilled water. Infrared data and a melting point of 202° indicated that both samples were pure. Since it was impossible to tolerate even a few milligrams of the diisopropyl tartrate in the material, the sodium salts of the two acid samples were again prepared and the method repeated.

This method of obtaining the camphoric acid from each phase was found to be superior to that of removal of the ester contaminant by distillation.

Optical rotations were taken in acetone using a 2.0 decimeter cell. The solubility of the dl-camphoric acid was so much greater in the ester phase that extreme difficulties were encountered in obtaining enough

purified sample for analysis from the water phase from a single extraction. For this reason three extractions were carried out on the ester phase using fresh preequilibrated water for each extraction. Sufficient sample was obtained by combining the three water extracts.

The rotations in acetone were as follows:

$$[\alpha]_D = -0.209^\circ \text{ for the ester phase sample}$$

$$[\alpha]_D = +0.209^\circ \text{ for the combined water phases.}$$

These values were smaller than expected, based on previously studied systems. However two additional experiments gave essentially the same results.

It was decided to do a multiple extraction experiment in hopes of obtaining larger rotation values. Two experiments were carried out; the first involved 12 extractions of the ester phase by changing the preequilibrated water phase each time, and the second involved 33 extractions by again using fresh preequilibrated water for each extraction.

The samples were collected and purified as described above. The specific rotations were calculated along with the per cent resolution. The discussion section of dl-bis-4-pyridylglycol outlines the method used to calculate these values. Since a number of extractions was carried out with this system, it was decided to calculate a separation factor. This factor was derived as follows:

C_D = Concentration of D form

W_D = Weight of D form

K = Partition coefficient

V = Volume

MW = Molecular weight .

$$\frac{C_D \text{ (org.)}}{C_D \text{ (aq.)}} = K_D$$

$$\frac{\frac{W_D \text{ (org.)}}{MW \times V \text{ (org.)}}}{\frac{W_D \text{ (aq.)}}{MW \times V \text{ (aq.)}}} = K_D$$

$$V \text{ (org.)} = V \text{ (aq.)}$$

$$\frac{W_D \text{ (org.)}}{W_D \text{ (aq.)}} = K_D .$$

Let

W_D = Original total weight of D form

W_{D1} = Weight of D form remaining in ester phase after first extraction

$W_D - W_{D1}$ = Weight of D form extracted into aqueous phase.

Then

$$\frac{W_{D1}}{W_D - W_{D1}} = K_D$$

$$W_{D1} = K_D W_D - K_D W_{D1}$$

$$W_{D1} (1 + K_D) = K_D W_D$$

$$W_{D1} = \frac{K_D}{1 + K_D} W_D$$

for two extractions

$$\frac{W_{D2}}{W_{D1} - W_{D2}} = K_D$$

$$W_{D2} = K_D W_{D1} - K_D W_{D2}$$

$$W_{D2} (1 + K_D) = K_D W_{D1}$$

$$w_{D2} = \frac{K_D w_{D1}}{1 + K_D}$$

and from the above

$$w_{D1} = \frac{K_D w_D}{1 + K_D}$$

$$\therefore w_{D2} = \left(\frac{K_D}{1 + K_D} \right)^2 w_D$$

for n extractions

$$w_{Dn} = \left(\frac{K_D}{1 + K_D} \right)^n w_D$$

Similarly for the L-form:

$$w_{Ln} = \left(\frac{K_L}{1 + K_L} \right)^n w_L$$

$$\frac{w_{Dn}}{w_{Ln}} = \frac{\left(\frac{K_D}{1 + K_D} \right)^n}{\left(\frac{K_L}{1 + K_L} \right)^n} = S^n$$

since

$$w_D = w_L$$

Now the separation factor (S) can be related to the resolution as follows:

In a partially resolved sample of mass m let g be the excess of one form.

$$m - g = \text{mass racemic}$$

$$\frac{m - g}{2} = \text{mass L (rac.)} = \text{mass D (rac.)}$$

$$\frac{m - g}{2} + g = \text{total mass of the form in excess}$$

$$\frac{m - g + 2g}{2} = \frac{m + g}{2}$$

$$\frac{m - g}{2} = \text{total mass of the other form.}$$

Now solving for g and m from the equation

$$[\alpha]_D = \frac{\alpha \text{ (observed)}}{\frac{g}{v} \times 1}$$

$$g = \frac{\alpha \text{ (observed)} \times v}{1 [\alpha]_D}$$

$$[\alpha]_D = \frac{\alpha \text{ (calculated)}}{\frac{m}{v} \times 1}$$

$$m = \frac{\alpha \text{ (calculated)} \times v}{1 \alpha_D}$$

From above

$$S = \frac{C_D}{C_L}$$

$$S = \frac{\frac{m + g}{2v}}{\frac{m - g}{2v}} = \frac{m + g}{m - g}$$

$$= \frac{\frac{\alpha \text{ (calculated)} \times v}{1 [\alpha]_D} + \frac{\alpha \text{ (observed)} \times v}{1 [\alpha]_D}}{\frac{\alpha \text{ (calculated)} \times v}{1 [\alpha]} - \frac{\alpha \text{ (observed)} \times v}{1 [\alpha]_D}}$$

$$= \frac{\alpha \text{ (calculated)} + \alpha \text{ (observed)}}{\alpha \text{ (calculated)} - \alpha \text{ (observed)}}$$

$$= \frac{1 + \frac{\alpha \text{ (observed)}}{\alpha \text{ (calculated)}}}{1 - \frac{\alpha \text{ (observed)}}{\alpha \text{ (calculated)}}} = S$$

$$S = \frac{100 + \frac{\alpha \text{ (observed)}}{\alpha \text{ (calculated)}} \times 100}{100 - \frac{\alpha \text{ (observed)}}{\alpha \text{ (calculated)}} \times 100}$$

$$S = \frac{100 + \% \text{ resolution}}{100 - \% \text{ resolution}}$$

The separation factor (S) for the camphoric acid system was calculated from the experiment involving 33 extractions.

$$S^{33} = \frac{100 + 1.66}{100 - 1.66}$$

$$S^{33} = \frac{101.66}{98.34} \quad S = 1.001.$$

Calculating the per cent resolution for 3 extractions:

$$\frac{100 + X}{100 - X} = (1.001)^3 = 1.003$$

$$100 + X = 100.3 - 1.003X$$

$$2.003X = 0.3$$

$X = 0.15$ per cent calculated resolution .

Calculating the per cent resolution for 12 extractions:

$$\frac{100 + X}{100 - X} = 1.012$$

$$100 + X = 101.2 - 1.012 X$$

$$2.012X = 1.2$$

$X = 0.60$ per cent calculated resolution .

Table II lists the data obtained from the extractions carried out on this system. Although the values are small, these data indicate that there is a steady increase in resolution as the extractions increase.

During the time these experiments were being carried out, the procedure for obtaining the optical values was changed. Earlier rotations were obtained by using a J. and J. Fric-Praha polarimeter with a 2.0 decimeter cell. Extreme difficulties were encountered in reproducing small readings until a generalized procedure was developed. It was found that small readings could be reproduced if the following procedure was followed:

TABLE II
DATA ON DL-CAMPHORIC ACID EXTRACTIONS

Phase from Which Sample Obtained	$[\alpha]_D^{27}$ in Acetone	No. of Extractions	Observed Resolution	Resolution Calculated from Separation Factor
Ester	-0.209°	3	0.42%	0.15%
Combined water	+0.209°	3	0.42%	--
Ester	-0.418°	12	0.84%	0.60%
Combined water	+0.209°	12	0.42%	--
Ester	-0.836°	33	1.66%	1.66% ^a
Combined water	+0.209°	33	0.42%	--

^aAssumed correct.

The zero point was established by filling the cell with the same concentration of the dl-racemate as was to be used for the unknown samples. After the zero point was established, the cell was washed clean without removing the two end caps. The unknown samples were then analyzed. Ten readings were obtained on each sample and their average value was taken as the true rotation. The blank reading was never taken as the zero point after the elapse of one day. The caps were not removed from the cell for it was learned from a series of readings involving removing the caps to fill the cell that slightly different rotations were obtained from the same solutions. It was found that the cell could be cleaned and filled from the center opening. Reproducible results could always be obtained if these precautions were followed.

Later rotations were obtained by using a Bendix Automatic Model 143A polarimeter. No difficulties were encountered in reproducing small readings to $\pm 0.01^\circ$ of the observed reading over a significant period of time. For readings taken over a shorter period of time, the reproducibility was 0.002° . This unit was a major improvement over the other polarimeter in terms of reproducibility and time.

4. dl-2,3-Dibromobutane-1,4-diol

The preparation of this compound was carried out by bromination of 2-butene-1,4-diol in methylene chloride at $0-10^\circ$. The product is insoluble in the solvent at low temperatures, and this allowed the methylene chloride to be decanted at the completion of the reaction.

The product was purified by repeated recrystallizations from benzene until a material having a melting point of 87° was obtained.

The most satisfactory method found for the partial resolution of the dl-pair was that of dissolving 15 g. of dl-2,3-dibromobutane-1,4-diol in 20 ml. of doubly preequilibrated ester followed by addition of the same volume of doubly preequilibrated water and shaking the mixture for 5 hours. Doubly preequilibrated ester and water are materials obtained by discarding the water from the first preequilibration and adding an equal volume of distilled water to the remaining ester phase and repeating the preequilibration procedure. See the Experimental section for a complete discussion.

The phases were then separated, and the complete removal of the water in both samples was effected at steam bath temperature under aspirator vacuum. Benzene was then added to each sample and crystallization induced by placing the samples in an ice bath. The first part of the precipitate was discarded by decanting the benzene solution after precipitation had begun to occur. The residual diol in the decanted benzene was then allowed to precipitate and the material was collected. Recrystallizations were repeated in this manner until a product having a melting point of 87° and showing no carbonyl absorption in the infrared spectrum was obtained.

Optical readings were taken in methanol using a 2.0 decimeter cell. Similar to the dl-camphoric acid system, the readings from the first experiments were taken on a J. and J. Fric-Praha polarimeter while the latter readings were taken on a Bendix Model 143A.

The optical rotations obtained from the first series of experiments were discouraging. The purified samples isolated from both phases gave negative rotation values. These results were confirmed in three subsequent experiments. A number of explanations were postulated and the most logical at that time was that the D-diisopropyl tartrate was reacting with the dl-2,3-dibromobutane-1,4-diol. Diastereoisomers, at least one of which was levorotatory, could have been formed and through the purification a negatively rotatory impurity could thus have been coprecipitated with the diol. It was also possible that the rate constant for the formation of one of the diastereoisomers was greater than the other. This would leave an excess of one form of the unreacted dl-dibromobutane-1,4-diol. An impurity could also have been present in the original ester.

A series of experiments were undertaken to determine the cause. It was noted that during the purification of the isolated material from both phases that an impurity was present in both samples. The lowering of the melting point and spurious infrared bands both indicated an impurity.

An attempt was made to isolate the impurity. Infrared data showed that the impurity was more concentrated in the material obtained from the water phase than that of the ester. It was found that the impurity was more concentrated in those portions of the diol samples which first crystallized from the benzene solvent. A sample containing approximately 25 per cent of the impurity (as indicated by infrared)

was isolated by collecting the first part of the crystallizations from benzene. Data obtained from the infrared analyses of this impure sample indicated an ester formed by the reaction of dl-2,3-dibromobutane-1,4-diol with D-diisopropyl tartrate was one possibility. Infrared data indicated that the impurity had strong absorption bands at 5.9 μ , 8.6 μ , and 8.8 μ . Nuclear magnetic resonance was not of much value, for the spectrum was very similar to that of the dl-2,3-dibromobutane-1,4-diol. Other possibilities that the infrared spectra suggested was that of tartaric acid.

The possibility that the impurity could be residual D-diisopropyl tartrate was not ruled out. However, considering the method of purification and also that the ester should give a positive rotation, this was thought to be unlikely.

An experiment was devised to determine if any acidic impurities were in the isolated material obtained from the two phases. A concentrated sample of the impurity was dissolved in hot benzene. The material was then extracted with dilute sodium hydroxide. The aqueous layer was separated and neutralized with dilute acid. The water was then evaporated from the material and the infrared spectra obtained. A lack of a carbonyl band indicated that the material probably contained no organic acid.

Another possibility was that the impurity was in the original D-diisopropyl tartrate and that it was more soluble in water than in ester. To determine if an impurity was in the original ester, 30 ml. of water

was added to 30 ml. of D-diisopropyl tartrate and the mixture shaken for 5 hours. The phases were separated. The aqueous phase was extracted 10 times with chloroform to remove the ester. The rotation value was then obtained on the residual aqueous solution. No rotation was observed. It was concluded that this experiment offered very little since no definite conclusions could be drawn from the data and the impurity, if present, was equally soluble in chloroform.

Another experiment was designed to determine if a reaction was occurring between the D-diisopropyl tartrate and the dl-2,3-dibromobutane-1,4-diol. Four grams of 2,3-dibromobutane-1,4-diol was dissolved in 8 ml. of preequilibrated ester and the rotation with respect to time was determined. The initial rotation of the solution did not change over a period of 3 days. Nuclear magnetic resonance spectra indicated no change also. It was concluded that if a reaction was occurring these data did not show it.

Another experiment carried out which indicated further evidence that no reaction was occurring was that of dissolving 2 ml. of L-diisopropyl tartrate in 20 ml. of water. Two grams of dl-2,3-dibromobutane-1,4-diol was added and the mixture was shaken overnight. The dl-2,3-dibromobutane-1,4-diol was recovered from the solution by using the standard procedure. The rotation of the diol sample was taken and found to be zero. If a reaction had occurred in this solution, the diol should have given a positive rotation, assuming that the cause of both samples being negative was due to a reaction between the diol and the ester. Again, the data indicated that no reaction was occurring between the diol and the ester solvent.

The possibility of an impurity being in the original ester was reconsidered. The negative rotations could be explained by an impurity being in the original D-diisopropyl tartrate which gave a negative rotation and was highly water soluble. An experiment was carried out by preequilibrating an ester sample the usual way. After this initial step the phases were separated and 2.0 g. of diol was added to 3.0 ml. of the preequilibrated ester and 2.0 g. of diol added to 20 ml. of the preequilibrated water. The samples were allowed to stand overnight. The diol from each sample was isolated and purified by the usual procedure. The rotations in methanol were as follows:

$[\alpha]_D = -0.790^\circ$ for sample obtained from the preequilibrated ester

$[\alpha]_D = -24.24^\circ$ for sample obtained from the preequilibrated water.

These data indicated that an impurity could be in the original ester. Another experiment was carried out to see if this compound could be extracted from the D-diisopropyl tartrate. A preequilibrated ester sample was prepared in the same manner. After this initial step the preequilibrated water was discarded. Fresh distilled water in equal volumes was added to the preequilibrated ester and after shaking the phases were separated. Materials obtained by this method will be referred to as doubly preequilibrated.

A series of three experiments were carried out by adding 2.0 g. diol to 3.0 ml. of pure ester, 2.0 g. of diol to 20 ml. of the doubly preequilibrated water and 2.0 g. of diol to 3.0 ml. of doubly preequilibrated ester. The three samples were left to stand overnight.

The diol was recovered from each sample by the standard procedure. Optical rotations were zero on the materials isolated from the doubly preequilibrated water and ester, and $[\alpha]_D = -0.790$ for the diol obtained from the pure ester. These data indicate that an impurity was in the original ester and was highly soluble in the water. The impurity could, for example, be the result of chloride ion replacing a hydroxyl group in the esterification of the tartaric acid.

As further proof that an impurity was in the original ester an experiment carried out before most of the data was accumulated was reconsidered and found to be informative. An early experiment had been carried out to determine if the D-diisopropyl tartrate after being used as the solvent for one extraction could be reused without distillation. A normal extraction of the diol was carried out employing previously used ester. The material isolated from the water phase gave a positive rotation while that from the ester phase gave a negative rotation. The data were discounted at that time for in the initial phase of this work it was believed that the rotation of material from the water phase was negative, and that from the ester phase was positive. It was concluded from these data that the impurity had been extracted into the water in the previous experiment and that the D-diisopropyl tartrate was now pure. These later data showed this to be true and that the experiment was valid.

It was also suggested earlier that the negative rotations obtained from both phases were the result of recrystallizing from a solution containing an optically active compound. The experiment using doubly pre-

equilibrated materials indicated that this preferential recrystallization was not occurring for the rotations obtained from the doubly pre-equilibrated system would also have been negative.

Now that it had been determined how to obtain an authentic sample from each phase, another series of experiments were carried out. Extractions ranging from one to 12 times were carried out on the doubly pre-equilibrated ester phase by using fresh doubly preequilibrated water for each extraction.

Four experiments were performed. Two involved one extraction each, one involved 6, and the other 12.

The solubility of the dl-2,3-dibromobutane-1,4 diol was found to be 9.0 per cent by weight in preequilibrated water and 50 per cent by weight in preequilibrated ester.

Data obtained from these experiments indicated that separation steadily increased with the number of extractions. The per cent observed resolution, $[\alpha]_D$, the calculated resolution as obtained from the separation factor, and other data are given in Table III.

The calculations derived from the separation factor were done as described in the dl-camphoric acid system.

5. dl-Phenylephrine

The best method found for the partial resolution of dl-phenylephrine was to dissolve 4.0 g. of the amine in 40 ml. of doubly pre-equilibrated ester followed by the same volume of doubly preequilibrated

TABLE III
DATA ON DL-2,3-DIBROMOBUTANE-1,4-DIOL

Phase from Which Sample Obtained	$[\alpha]_D^{27}$ in Methanol	No. of Extractions	Observed Resolution	Resolution Calculated from Separation Factor
Ester	-0.562°	1	0.75%	0.50%
Combined water	+0.374°	1	0.29%	--
Ester	-1.690°	6	3.40%	2.91%
Combined water	+0.374°	6	0.29%	--
Ester	-2.430°	10	4.90%	4.90% ^a
Combined water	+0.560°	10	0.42%	--

^aAssumed correct.

water and shaking for 5 hours. The phases were then separated and the complete removal of water from each phase was accomplished by using aspirator vacuum at 70°. Butanol was added to each sample and the chloride salts were then made by bubbling dry hydrogen chloride through each sample. The phenylephrine hydrochloride salts were then separated from the ester by the addition of ether. The oily precipitates were then dissolved in butanol and ether added again to effect separation. This procedure was repeated until a solid precipitate was obtained upon the addition of ether. The precipitates were then recrystallized three times from butanol. The purity of the isolated material was established by infrared. Optical readings were obtained on a Bendix polarimeter.

Two experiments were carried to completion. The sample isolated from the ester phase was lost through contamination in the first experiment. The following data were obtained from the two experiments:

1st experiment: $[\alpha]_D = -0.90^\circ$ for the water phase sample

2nd experiment: $[\alpha]_D = -0.75^\circ$ for the water phase sample

$[\alpha]_D = +0.60^\circ$ for the ester phase sample.

From these data the resolution is calculated as 1.33 per cent for a one time extraction. Additional recrystallizations of portions of the samples gave no change in rotation values.

The solubility of the free amine in both doubly preequilibrated water and ester was not definitely established. Approximately 15 per cent of the amine by weight was soluble in the doubly preequilibrated ester. Exact values could not be determined for the water phase for as

it was later pointed out that this value was highly dependent on pH. However, approximately equal amounts of sample were isolated from each phase which is in qualitative agreement with the rotations observed. The pH of the aqueous phase after equilibrium had been established was 8.3. No multiple extractions were carried out because of this equal solubility ratio.

These data indicate that the D-isomer is more soluble in the ester. Data obtained from the study of the other three systems indicated that the L-isomers were more soluble in the D-diisopropyl tartrate.

The dl-phenylephrine was obtained from Chemetron Corporation, Newport, Tennessee.

CHAPTER III

EXPERIMENTAL

A. Method for Preequilibrating the Solvent System

Data obtained in the past indicated that the solvent system must be thoroughly preequilibrated to obtain reproducible results.²³

Water and D-diisopropyl tartrate were the immiscible solvent system used in the resolution of all dl-pairs attempted. Equal volumes of the pure ester and distilled water were mixed and shaken for 5 hours on an automatic shaker. The material was then poured into a separatory funnel and the two phases separated. Materials obtained by this method will be referred to as preequilibrated ester and preequilibrated water. Doubly preequilibrated ester is that which the water from the first equilibration has been discarded, fresh distilled water added, and the equilibration procedure repeated. This precaution was taken after data indicated that a highly water soluble impurity was present in some batches of diisopropyl tartrate.

B. Instruments Used to Obtain Analytical Data

1. Infrared

A Beckman IR-5A and a Perkin Elmer Infracord Model 137 were used. The potassium chloride disc procedure was used for all solids. All

liquids were analyzed as such sandwiched between two sodium chloride plates. Figures 1 and 2 show infrared curves of the compounds studied.

2. Melting Points

All melting points were taken using a Mel-Temp electrical heating apparatus.

3. Optical Rotation Values

Optical readings were obtained by using a J. and J. Fric-Praha unit. Later readings were obtained by using a Bendix Automatic Polarimeter Model-143A.

4. Nuclear Magnetic Resonance

Limited data were obtained using the Varian A-60 unit.

5. Gas Chromatography

Limited data were obtained using a Perkin Elmer Model 154 Vapor Fractometer in verifying the purity of 2-butene-1,4-diol.

C. Preparation of D-Diisopropyl Tartrate

Seven hundred grams of d-tartaric acid and 500 ml. of isopropanol were placed in a 3-liter, round-bottomed flask equipped with a mechanical stirrer. The mixture was brought to reflux and hydrogen chloride gas slowly bubbled through the mixture for a period of 12 hours. The excess isopropanol and water were stripped from the material under aspirator vacuum, 500 ml. of pure isopropanol added, and the resulting mixture

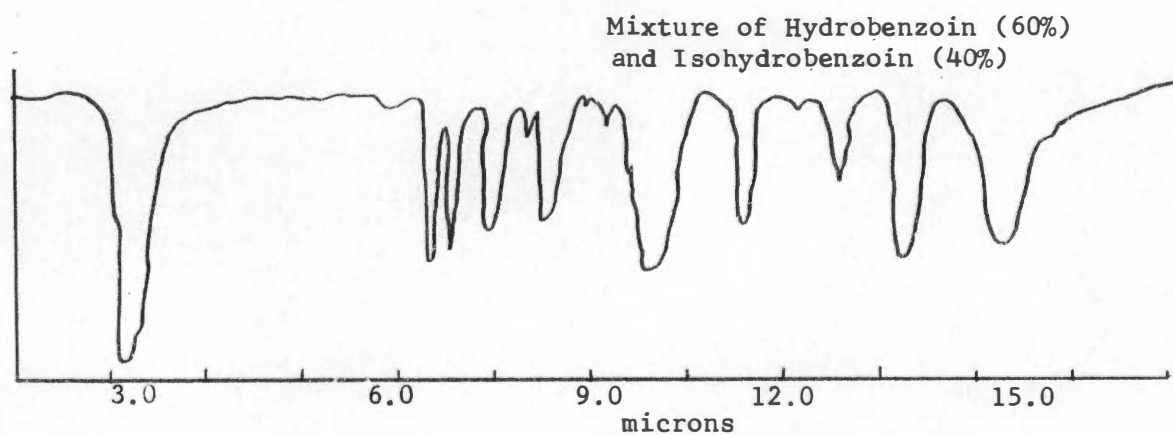
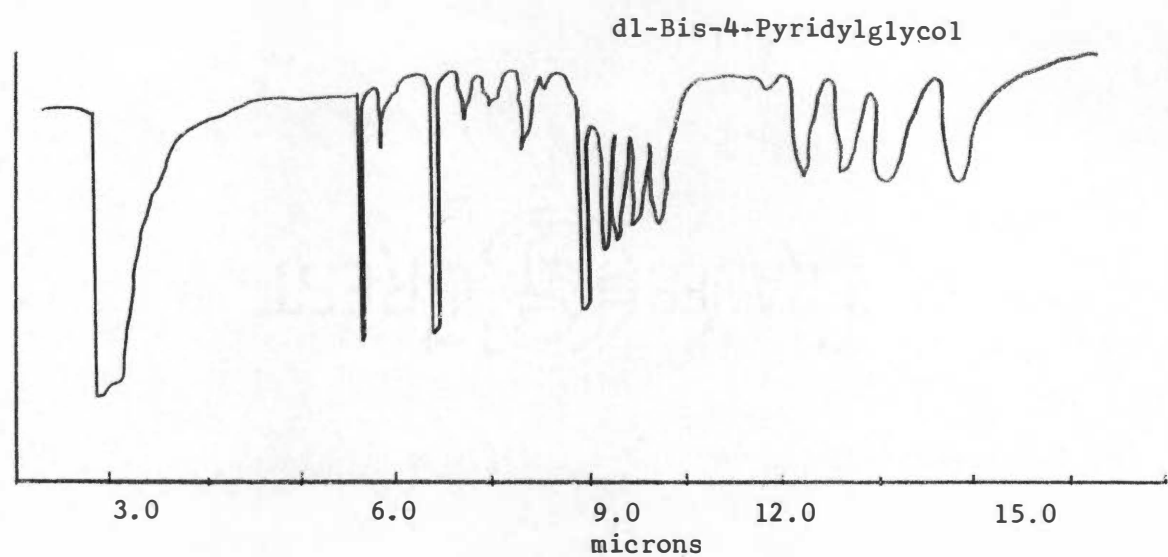
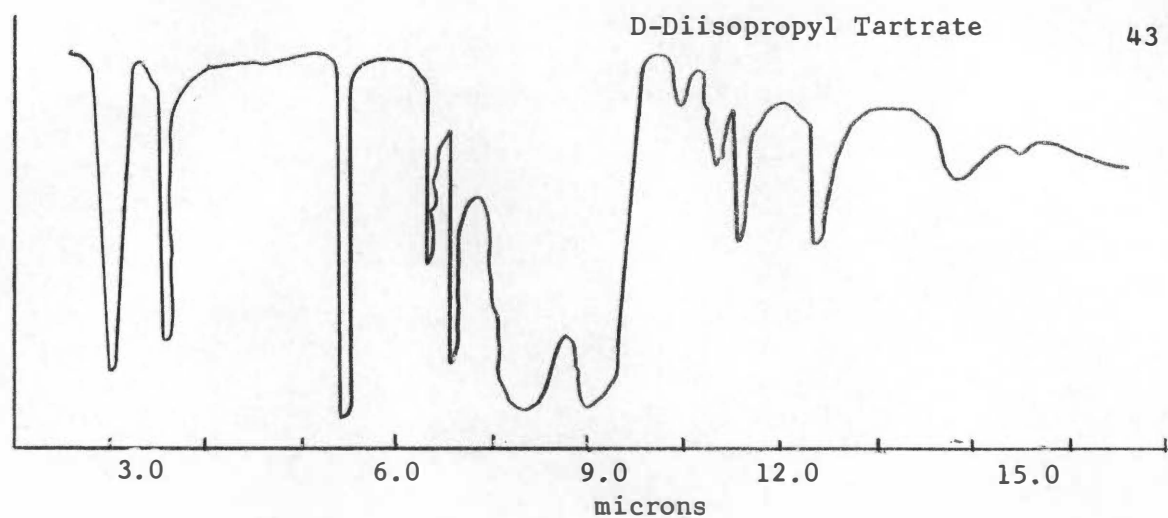


Figure 1. Infrared spectra on compounds studied.

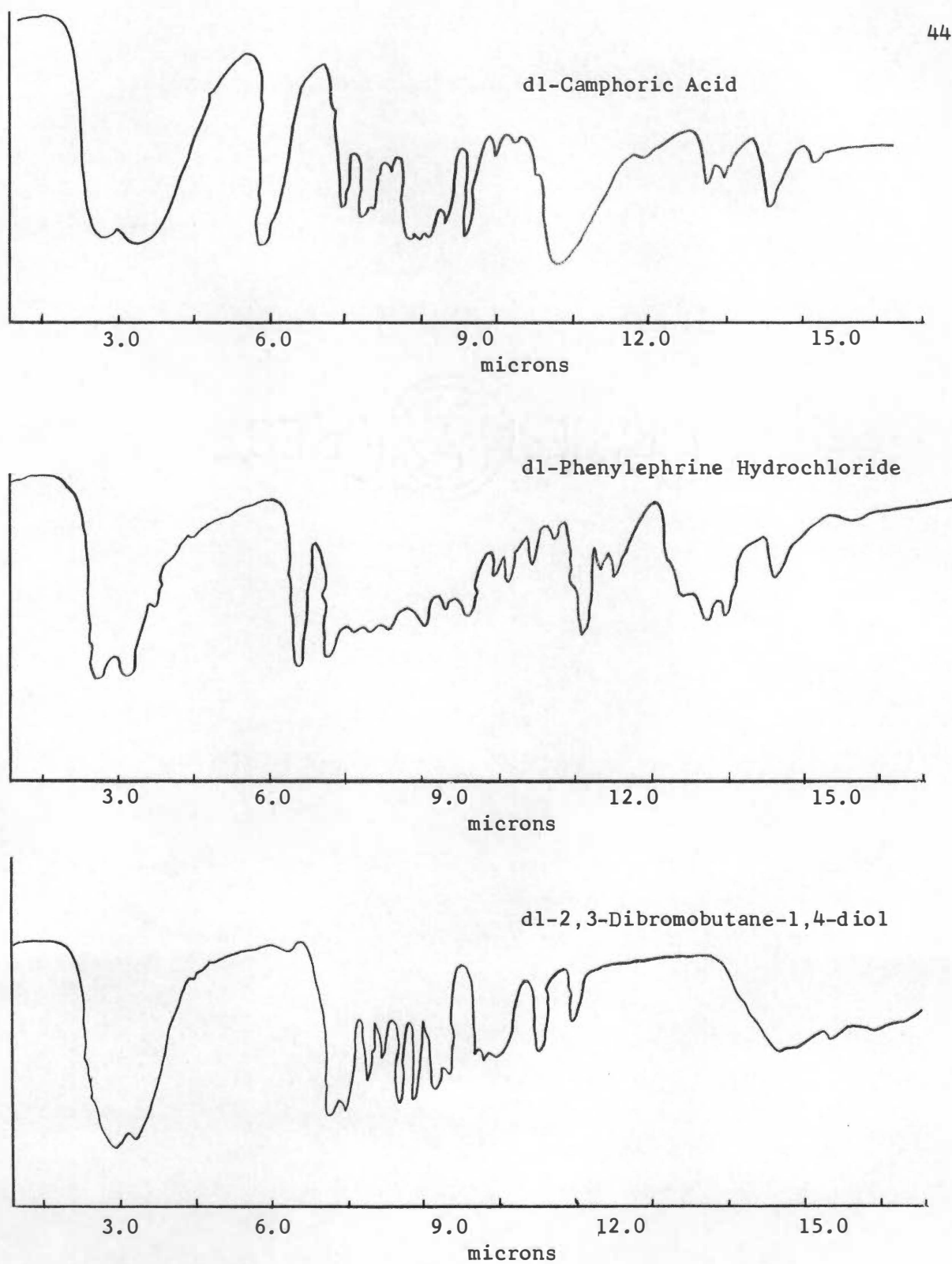


Figure 2. Infrared spectra on compounds studied.

refluxed for another 12 hours with the slow addition of dry, gaseous hydrogen chloride. The water and excess isopropanol were then distilled from the reaction mixture under aspirator vacuum. A vacuum pump was then connected to the system. Since oxygen had been found to cause decomposition of the product, nitrogen was bubbled through the ebulliting tube. Seven hundred twenty-five grams of crude product was collected boiling at 140-150°/1.5 mm. This material was redistilled under the same conditions using a 30 cm. Vigreux fractionating column.

During distillation of the ester, a heating tape was used along with the mantle to maintain an adiabatic distillation. The distillation apparatus was insulated with glass wool. The product (650 g.) obtained had a refractive index of 1.4370 and an optical rotation of $[\alpha]_D = +20.00$. Infrared data was obtained on each batch as a check that the material was comparable to that made in the past.

D. Preparation of dl-Bis-4-pyridylglycol

A detailed procedure for making this compound is given in the literature.²¹ Essentially the procedure involves the reduction of 4-pyridyl aldehyde with zinc dust. After complete reduction, the meso compound is separated from the dl-racemate by repeated recrystallizations from boiling methanol to a constant melting point of 169°. Table IV describes the runs made.

TABLE IV
ANALYTICAL DATA OBTAINED ON DL-BIS-4-PYRIDYLGLYCOL RUNS

Date Batch Made	Starting Material (g.)	Yield (g.)	Melting Point (°C.)	Infrared
2/4/64	25	10	169°	Checked authentic sample
2/7/64	50	16	169°	Checked authentic sample

E. Partial Resolution of dl-Bis-4-Pyridylglycol

1. Experiment No. 1

The first experiment was carried out by dissolving 4.0 g. of the glycol in 80 ml. of preequilibrated ester. An equal volume of preequilibrated water was added and the material was allowed to shake overnight. Inspection of the sample the next day showed that some of the glycol had precipitated. The sample was discarded.

2. Experiment No. 2

Another system was prepared by dissolving 2.5 g. of glycol in 95 ml. of preequilibrated ester. The same volume of preequilibrated water was added and the material was shaken for 5 hours. An attempt was then made to isolate the glycol in the ester phase by distillation of the ester using a heated oil bath to control the temperature. (Past experience had shown that diisopropyl tartrate could be distilled at head temperatures between 120-150° (depending on the pressure).) The bath temperature was taken to 170° before any appreciable quantity of ester was collected. The residue began to decolorize rapidly and the distillation was stopped for fear of decomposing the glycol. It was known that the glycol decomposed at temperatures slightly greater than 170°.

When stripping was continued, a heating tape was wrapped around all the exposed surface. The oil bath temperature was taken to 150°. The manometer indicated 1.5 mm. pressure. Only approximately one-half of the ester could be removed under these conditions. The distillation

was stopped and the material transferred to a beaker. Benzene (200 ml.) was added, and the beaker placed in an ice bath. Since precipitation of the glycol could not be induced, the sample was discarded.

The water layer was then freed of water by use of aspirator vacuum and moderate heating. Most of the ester was left undistilled for fear of decomposing the glycol. The glycol-ester mixture was transferred to a baker and 200 ml. of benzene added. The glycol precipitated after placing the beaker in an ice bath. After recrystallizing the material from water, very little product was obtained and it was discarded.

3. Experiment No. 3

In a third experiment, 4.2 g. of glycol was added to 90 ml. of preequilibrated ester. The same volume of preequilibrated water was added and the mixture shaken for 5 hours. The phases were separated, and, under a vacuum of 0.25 mm., both phases were distilled at an oil bath temperature of 150°. The distillation was aided by using a heating tape.

A crude yield of 1.5 g. was obtained from the water phase and 1.0 g. from the ester phase by recrystallizing both from benzene. Two additional recrystallizations of each sample from a 50:50 mixture of water and methanol yielded pure bis-4-pyridylglycol. Infrared and melting point (m.p. = 169°) data indicated that the samples were free of the ester.

Optical rotation values were then obtained on the two samples. A 2.0 decimeter cell was used which was filled with a solution containing

0.100 g./5.0 ml. acetic acid. The solution from the ester phase was so highly colored that the readings were questionable. Ten readings were obtained on each sample and also on the blank. The average values were as follows:

$$[\alpha]_D = -34.75^\circ \text{ for the water phase}$$

$$[\alpha]_D = +6.17^\circ \text{ for the ester phase.}$$

The remainder of each sample was recrystallized and the optical readings were repeated as a check to be sure the samples were free of ester. The sample from the ester phase was recrystallized from a solution containing charcoal to obtain a colorless product. From this second recrystallization, 0.085 g. of product was obtained from the ester phase and 0.080 g. from the water phase. The optical values checked the above results.

F. Partial Resolution of dl-Camphoric Acid

1. Experiment No. 1

Six grams of dl-camphoric acid was dissolved in 60 ml. of pre-equilibrated ester, and then the same volume of preequilibrated water was added. The mixture was shaken for 10 hours and the phases were then separated.

The camphoric acid in the water phase was freed from water and ester by vacuum distillation. The water was removed using an aspirator and an oil bath at 70° . After removal of the water, a vacuum pump was connected to the system and the oil bath taken to 150° . The ester was

distilled at this temperature under a vacuum of 0.25 mm. The distillation residue was recrystallized from 30 per cent aqueous methanol. Infrared data and a melting point above 250° indicated that the material was inorganic.

The same distillation technique was used to obtain the desired material from the ester phase. The residue was recrystallized from a 30 per cent aqueous methanol mixture. Three recrystallizations gave a product with a melting point of 202°. The optical rotation value $[\alpha]_D = -0.90^\circ$ was obtained by using a 2.0 decimeter tube filled with a solution containing 0.500 g./5.0 ml. acetone.

2. Experiment No. 2

The next experiment was carried out by adding 6.0 g. of dl-camphoric acid to 150 ml. of preequilibrated ester. The same volume of preequilibrated water was added and the mixture was shaken for 5 hours. Again the camphoric acid from each phase was isolated by removal of the water and ester under reduced pressure; the technique used was that as described in Experiment No. 1.

The isolated material from the ester phase was recrystallized 3 times from a 30 per cent aqueous methanol mixture. A purified sample (as indicated by infrared and m.p. = 202°) of 0.460 g. was obtained. The optical rotation in acetone was $[\alpha]_D = -0.90^\circ$.

The material obtained from the water phase again appeared to be inorganic.

3. Experiment No. 3

A third experiment was carried out in order to obtain a sample from the water phase. Six grams of dl-camphoric acid was added to 100 ml. of preequilibrated ester. The same volume of preequilibrated water was added and the mixture was shaken 5 hours. The two phases were separated, a fresh 100 ml. portion of preequilibrated water was added to the ester phase and the procedure repeated. Three extractions of the ester phase were done in this manner. The three water phase samples thus obtained were combined and most of the water was removed under aspirator vacuum. Five grams of sodium bicarbonate was added and the solution was extracted three times with 50 ml. portions of chloroform. The salt was then neutralized with 5 per cent sulfuric acid. The precipitated camphoric acid was extracted into ether. The ether was evaporated and the isolated solid was washed with benzene. Infrared and m.p. = 202° indicated that the material was pure; however the sodium salt was again made and the purification step repeated. The rotation in acetone was $[\alpha]_D = +0.40$.

The camphoric acid in the ester phase was collected by using the same procedure. The rotation in acetone was $[\alpha]_D = -0.40$.

After this method was developed five more experiment were carried out, ranging from one to 33 extractions of the ester phase with fresh preequilibrated water each time.

G. Preparation of dl-2,3-Dibromobutane-1,4-diol

The literature²⁰ gives the reaction procedure in detail. Essentially this method involves bromination of 2-butene-1,4-diol in methylene chloride at 0-10°. The literature recommends removing the solvent from the reaction mixture under reduced pressure; however it was found that the product is essentially insoluble in this solvent below 5°. This step was eliminated by decanting the solvent at the completion of the reaction. Purification of the product was obtained by leaching the residual mixture with boiling benzene. After all the soluble portions had gone into solution, the product was allowed to crystallize in an ice bath. Using 200 ml. of 2-butene-1,4-diol, it was found that three benzene leachings of 600 ml. each were sufficient. After the first recrystallization, the crude product was repeatedly recrystallized until a constant melting point of 87° was obtained. Usually, three or four recrystallizations were necessary. Three runs were made using the above procedure. The yields and other data are listed in Table V.

H. Partial Resolution of dl-2,3-Dibromobutane-1,4-diol

1. Experiment No. 1

Six grams of diol were dissolved in 20 ml. of preequilibrated ester. The same volume of preequilibrated water was added and the mixture was shaken for 5 hours. The two phases were separated and complete removal of water obtained by vacuum distillation at a maximum bath

TABLE V
ANALYTICAL DATA OBTAINED ON DL-2,3-DIBROMOBUTANE-1,4-DIOL

Date of Preparation	2-Butene-1,4-diol Used (g.)	Yield After 3 Recrystallizations	Melting Point (°C.)
7/4/64	200	80	87
8/9/64	200	75	87
9/3/64	200	70	87

temperature of 70°. The distillation residues were transferred to beakers and 200 ml. of benzene added to each. Crystallization of the diol was induced by placing the beakers in an ice bath. It is important that the material be free of water for experiments indicate that precipitation will not occur if significant water is present. The material was recrystallized from boiling benzene until a compound having a melting point of 87° was obtained and showed no carbonyl in the infrared spectrum. Three recrystallizations gave the desired quality.

The optical readings were taken by using a 2.0 decimeter tube filled with a solution containing 0.700 g. sample/5.0 ml. methanol. (See the Discussion section for interpretation of the optical values.)

2. Experiment No. 2

In order to obtain more sample from the water phase, 15 g. of diol was dissolved in 20 ml. of preequilibrated ester. The same volume of preequilibrated water was added and the mixture shaken for 5 hours. The two phases were then separated, and the sample from each phase was collected and purified as described in the first experiment.

This procedure was used for all other experiments carried out at a later date. The experiments varied from one to 12 extractions of the ester phase. For the multiple extractions, the water phase was changed each time with fresh portions of doubly preequilibrated water. All later experiments were carried out by using doubly preequilibrated solvents.

The optical readings from the latter experiments were obtained by using a Bendix polarimeter. The rotations in methanol were $[\alpha]_D = -1.13^\circ$

for the ester phase sample and $[\alpha]_D = +0.750$ for the water phase sample.

I. Partial Resolution of dl-Phenylephrine

1. Experiment No. 1

The first experiment was carried out by dissolving 3.0 g. of the amine in 50 ml. of preequilibrated ester followed by the addition of the same volume of preequilibrated water. The mixture was shaken for 5 hours and the phases separated. Dilute 10 per cent hydrochloric acid was added to each phase to form the amine salt. Each sample was extracted six times with chloroform. Infrared data indicated that ester was still present in the samples. Attempts to recrystallize the amine salt from butanol were unsuccessful.

2. Experiment No. 2

Another experiment was done using essentially the same technique. After the material was extracted with chloroform, the water was removed from the samples from a steam bath using aspirator vacuum. The samples were then placed in a steam bath drying oven (70°) overnight. Attempts to recrystallize the samples from butanol resulted in failure.

3. Experiment No. 3

In a third experiment, 4.0 g. of the amine was added to 40 ml. of twice preequilibrated ester followed by the addition of 40 ml. of twice preequilibrated water. The mixture was shaken for 5 hours. The phases were separated and complete removal of water was obtained by vacuum

distillation using a water aspirator with a maximum bath temperature of 70°. One hundred milliliters of butanol were added to the residual material. The solution was transferred to a beaker and dry hydrogen chloride gas was bubbled through the solution for 10 minutes. The material was allowed to cool and the phenylephrine hydrochloride was separated by the addition of ether. This oily product was redissolved in hot butanol and again caused to precipitate by the addition of ether. This procedure was repeated until a grainy precipitate was obtained. As long as any appreciable quantities of ester remain in the solution, the amine hydrochloride salt will not precipitate from butanol. The sample was recrystallized three times from boiling butanol. Infrared data indicated that the material contained no carbonyl and that it was comparable to an authentic sample of phenylephrine hydrochloride. Optical readings were obtained on a Bendix polarimeter using a 0.4 decimeter cell filled with a solution containing 0.500 g./6.0 ml. water. This procedure was found to be satisfactory and another experiment was done using this method.

The optical values for the one time extraction were:

$[\alpha]_D = +0.60^\circ$ for the ester phase

$[\alpha]_D = -0.75^\circ$ for the water phase.

J. Attempted Preparation of Isohydrobenzoin

Fifty grams of benzoin were added slowly to a one liter refluxing mixture of dioxane containing 15 g. of lithium aluminum hydride. After

all the benzoin was added (about one hour), the mixture was allowed to reflux for 20 hours. (Lithium aluminum hydride decomposes at 125° and care was taken with the reaction.)

After complete reduction, 25 per cent phosphoric acid was added to decompose the complex. The solution was kept in an ice bath during this step to prevent excessive heating. The mixture was then extracted three times using 300 ml. portions of ether. The extractions were combined and the ether evaporated on a steam bath.

The product made using this procedure was 60 per cent hydrobenzoin (the meso form) and 40 per cent of the dl-pair.²²

Two runs of the material were made in this manner to obtain enough sample. Five recrystallizations from water gave a compound melting at 132°. The same number of recrystallizations from isopropanol gave a product melting at 138°. Additional recrystallizations from either solvent showed no change in the melting point. Infrared data indicated that no benzoin was present in either sample. As the desired melting point is 121°, it was concluded that it would be difficult to separate the dl-pair from the mixture. The project was discontinued for this reason.

CHAPTER IV

SUMMARY

Preliminary studies involving the resolution of optically active compounds by solvent extraction have been completed. Four optically active compounds have been partially resolved using the methods developed. Multiple extractions were carried out on two of the dl-racemates, and single extractions for the other two.

The four optically active compounds studied were as follows:

- (1) dl-bis-4-pyridylglycol
- (2) dl-camphoric acid
- (3) dl-2,3-dibromobutane-1,4-diol
- (4) dl-phenylephrine.

The resolution per extraction varied from 0.15 per cent for the dl-camphoric acid to 7.0 per cent for the dl-bis-4-pyridylglycol systems.

Multiple extractions carried out on the dl-camphoric acid and the dl-2,3-dibromobutane-1,4-diol systems indicated that the resolutions increased in a manner related to their respective separation factors.

The method of resolution for all the compounds studied was to saturate a portion of preequilibrated D-diisopropyl tartrate with the desired dl-racemate. The same volume of preequilibrated water was then added and the resulting mixture was shaken for 5 hours. The two phases were then separated and the desired material was isolated from each

phase and the optical rotation taken. The multiple extractions were carried out by changing the water phase after each extraction with pre-equilibrated water.

A hypothesis was suggested to explain the resolutions. This essentially entailed the ability of the solvent and solute molecules to be preferentially attached to each other through the greatest number of active sites. One form of the dl-modification will have a more suitable configuration to interact with the solvent (D-diisopropyl tartrate) molecule than the other.

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