

A STUDY OF CHEMICAL METHODS FOR THE RESOLUTION
OF dl-TARTARIC ACID

by

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INTRODUCTION

The investigations which are recorded in this thesis deal with the study of the resolution of dl-tartaric acid. This work was undertaken (1) to obtain some l-tartaric acid, which was needed for investigations in another field, (2) to review the work of resolution which had been done by Pasteur and other investigators, and (3) to develop a more detailed procedure for the process of resolution of this compound than is given anywhere in the literature.

HISTORICAL

The study of optical activity grew out of the discovery of and the investigations with polarized light. Malus (8) in 1808, by using double refracting prisms, found that sunlight reflected from the windows of the Luxembourg Palace was broken up into two rays which alternately disappeared and reappeared as the prism was rotated through successive right angles. The name polarization was given to the change which the light underwent in the process of reflection. Polarized light is now designated as that light in which all the vibrations lie in one plane.

Arago (7) in 1811, noticed that the plane of polarization was turned through a certain angle if a ray of polarized light was passed through a second rhomboid of Iceland spar.

Blot (2) in 1813, announced that a number of organic substances, such as oil of turpentine, sugar solutions, and solutions of tartaric acid, turned the plane of polarized light to a marked degree.

In 1844 two forms of tartaric acid were known. One was the ordinary commercial acid, the other was a very rare form which had been found by Kestner (1) in 1820. In 1844, Mitscherlich (5) discovered that the ordinary commercial

tartaric acid rotated the plane of polarized light to the right while the "rare form" of Kestner's did not rotate the light either to the right or to the left. The "rare form" is now called dl-tartaric acid, or sometimes less correctly, racemic acid.

The first attempts to explain these observations were made by Pasteur. In 1848, while attempting to form the sodium ammonium salt of the "rare form", he observed that two kinds of crystals were obtained if the solution were evaporated below a temperature of 28° . By means of tweezers he was able to separate the crystals mechanically. He observed that these crystals had faces that were non-superimposable. The face of one type of crystal appeared as the mirror image of the face of the other type of crystal. After these two forms were mechanically separated Pasteur dissolved them separately in water and made the solutions of the same concentration. The solution of the crystals with the "right-handed faces" was found to rotate the plane of polarized light to the right, whereas the solution of the crystals with the "left-handed faces" rotated polarized light an equal amount to the left. In this manner, Pasteur was able to separate the optically inactive mixture of sodium ammonium tartrate into two optically active forms. The process of separating a dl-mixture into its active forms is called resolution and this particular method of

resolution is spoken of as a "physical method". Hitherto, no optically active substance (one whose solution has the property of rotating the plane of polarized light) had been obtained in the laboratory from inactive substances. On mixing equal quantities of the sodium ammonium tartrate crystals, Pasteur observed that he obtained an optically inactive mixture.

In addition to the "physical method" for the resolution of an optically inactive substance into its optically active modifications, Pasteur later discovered and used two other methods: (a) resolution by means of biological organisms; and (b) resolution by means of optically active compounds. In the "biological method" a solution of an optically inactive mixture is subjected to the action of lower plant organisms, such as moulds, yeasts, and bacteria, which destroy one of the antipodes. Pasteur found, for example, that if *Penicillium glaucum* is grown in a solution of ammonium dl-tartrate, the salt of the d-acid is destroyed and a solution of the salt of the l-acid remains.

The "chemical method" depends upon the formation of a pair of optically active compounds, called diastereoisomers. When an optically active compound reacts with a dl-mixture optically active derivatives are formed which have different physical properties. Since these optically active compounds have different solubilities they may be separated by

fractional crystallization and each original antipode or enantiomorph regenerated and purified later. "Chemical methods" for resolving mixtures of d- and l-tartaric acids were used rather successfully by Pasteur. He combined optically inactive mixtures of dl-tartaric acid with such alkaloids as cinchonine, cinchonidine, cinchonine, quinine, strychnine, and brucine, and separated by fractional crystallization the resulting d- and l-salts. From these d- and l-salts the original d- and l-acids were regenerated. In a lecture which Pasteur gave before the Societe Chimique of Paris he said, "Here are ten or twelve grams of perfectly pure left tartaric acid, which have been obtained in this manner. Their preparation has cost me much trouble" (7).

A satisfactory explanation of the phenomenon of optical isomerism which had been observed by these early investigations did not appear until about a quarter of a century later. Pasteur believed that differences in the optical activity of d- and l-tartaric acid were physical and due to causes outside the molecule.

LeBel (3) and Van't Hoff (2) in 1874, formulated quite independently of each other and almost simultaneously an hypothesis to explain optical activity. LeBel concluded that optical activity must exist within the molecule. This

optical activity was explained by him as due to the presence of an asymmetric carbon atom; viz., a carbon atom holding four different atoms or groups of atoms. In such compounds the attached atoms or groups of atoms may occupy two different positions in space and are related to each other as an object is related to its mirror image. Van't Hoff reached similar conclusions and proposed to represent the asymmetric carbon atom with a tetrahedron, assuming the asymmetric carbon atom to occupy the center and its four valences to be directed toward the four corners.

During the next few years numerous investigations were undertaken in the field of stereochemistry and particularly optical activity. These investigations were carefully reviewed and criticized by Wislicenus (1887) in a paper (9) which has become a classic in this field of chemistry.

EXPERIMENTAL PART

The "chemical method" for the resolution of dl-mixtures appears to be the best procedure to obtain appreciable quantities of both isomers. There seems to be also many opportunities for improving the general procedures which are commonly used in "chemical methods" of resolution. Accordingly, the resolution of dl-tartaric acid into its optically active forms was made in the laboratory by means of this method using the natural alkaloid d-cinchonine.

In the following discussion especial care has been taken to give a detailed account of the exact procedure which was followed and an explanation of the results.

Preparation of d-Cinchonine Hydrogen l- and d-Tartrates

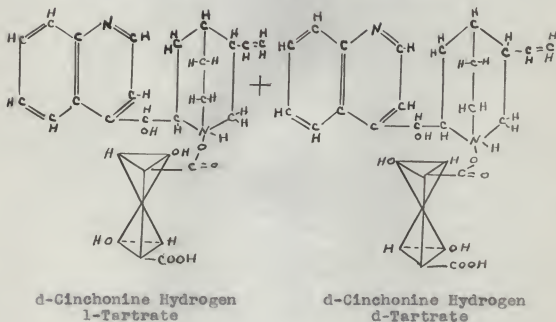
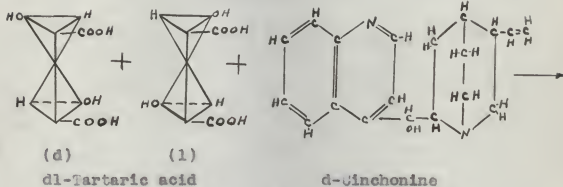
The d-cinchonine hydrogen l- and d-tartrates were prepared as follows: 27.508 grams (.16 moles)¹ of dl-tartaric acid crystals (racemic acid) were placed in a three neck flask, a reflux condenser was attached to one mouth, an electric stirrer to another, and the third mouth was kept stoppered and used to add new material as it was needed. 100 cc. of methyl alcohol (pure, free from water) were added and the mixture brought to boiling over a water bath. Then 49.03 grams of d-cinchonine (alkaloid) (.16 moles) were added to the boiling methyl alcohol-dl-tartaric acid mixture. The d-cinchonine was added in small portions, and the solution was kept boiling under the reflux condenser and constantly stirred. More methyl alcohol was added until a clear solution was obtained. This made the volume up to about 500 cc. The solution was stirred and kept boiling for about three hours, then filtered hot from small

1. Markwald (4) used an aqueous solution and used two molecular portions of dl-tartaric acid to one of d-cinchonine. In this study, it was found that the acid salt was the more soluble and easier to get into solution.

amounts of insoluble impurities into a 500 cc. Erlenmeyer flask. The flask was stoppered and the mixture allowed to stand for two or three days. In warm weather it was necessary to cool the solution by using a mixture of salt and ice to hasten the crystallization. Upon cooling the d-cinchonine hydrogen l-tartrate precipitated out slowly. In the salts of d-cinchonine hydrogen l-tartrate and d-cinchonine hydrogen d-tartrate the cinchonine parts of both molecules are the same whereas the tartrate parts are not the same. The two salts are not enantiomorphously related for their molecules are not in the relationship of an object to its mirror image. The two salts have different solubilities and may be separated by fractional crystallization. Since there was a wide difference in the solubility of the two salts, the precipitate of d-cinchonine hydrogen l-tartrate was found to be relatively pure. The precipitate was filtered off with suction upon a Buchner funnel. A second crop of crystals of the same purity was obtained by distilling off about 50 cc. of the solvent.

Precipitate: d-Cinchonine Hydrogen l-Tartrate.

Filtrate: d-Cinchonine Hydrogen d-Tartrate.



Precipitate: d-Cinchonine Hydrogen l-Tartrate. Purification:

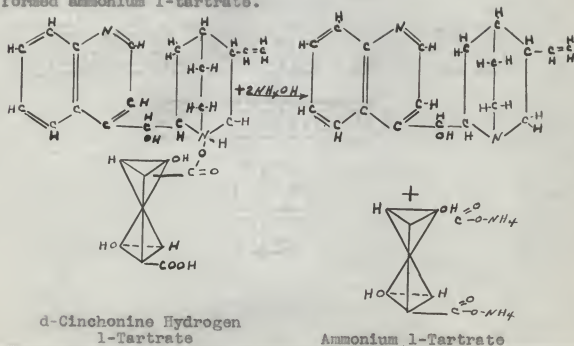
The precipitate containing d-cinchonine hydrogen l-tartrate was recrystallized from water. Several solvents were tried. A mixture of acetone and methyl alcohol (equal

volumes) gave the best results. However, recrystallization from water, since it proved almost as satisfactory, was used.

Yield: 26.6 grams d-cinchonine hydrogen 1-tartrate.
Melting point 187 - 190°. $[\alpha]_D^{22} = + 112$ (in water).

Decomposition of the d-Cinchonine Hydrogen 1-Tartrate With Ammonium Hydroxide

The crystals of d-cinchonine hydrogen 1-tartrate were placed in a 600 cc. beaker and 200 cc. of distilled water were added. Due to the insolubility of the salt all the crystals do not go entirely into solution. Then, concentrated ammonium hydroxide was added until a portion of the filtrate no longer gave a white precipitate of d-cinchonine. The ammonium hydroxide precipitated the cinchonine and formed ammonium 1-tartrate.



The d-cinchonine was filtered off with suction upon a Buchner funnel.

Precipitate: d-Cinchonine.

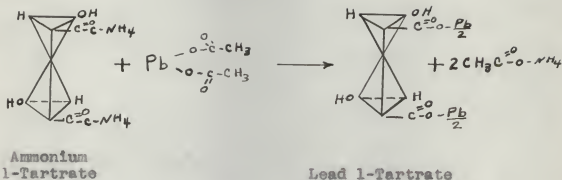
Filtrate: Ammonium l-tartrate.

Precipitate: The precipitate of d-cinchonine was washed with distilled water. It was then dissolved in dilute sulfuric acid and reprecipitated with ammonium hydroxide. The reprecipitated alkaloid was then washed with water and dried.

Filtrate: The filtrate of ammonium l-tartrate was poured into a large evaporating dish and the solution set aside in order to allow the excess ammonia to evaporate. Evaporation was hastened by placing the solution in front of an electric fan. The filtrate was evaporated down to approximately two-fifths of its original volume. The solution was then filtered to remove any impurities.

The Precipitation of Lead l-Tartrate

The filtrate containing ammonium l-tartrate was treated with a 40 per cent solution of lead acetate until a portion of the filtrate no longer gave a precipitate of lead l-tartrate. Lead l-tartrate was precipitated and ammonium acetate formed in solution.



The lead 1-tartrate was filtered off with suction upon a Buchner funnel.

Precipitate: Lead 1-tartrate.

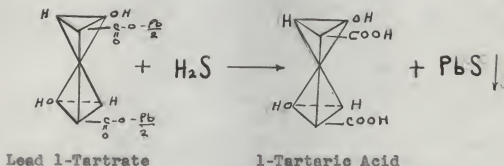
Filtrate: Ammonium acetate.

The Decomposition of Lead 1-Tartrate With Hydrogen Sulfide

The lead 1-tartrate was washed with distilled water to remove any ammonium acetate. The crystals were placed in a 500 cc. Erlenmeyer flask and 100 cc. of distilled water were added. Hydrogen sulfide was led into the solution, precipitating lead sulfide and leaving 1-tartaric acid in solution.¹ The hydrogen sulfide for this precipitation was

1. Pasteur decomposed the lead salt with sulfuric acid. However, by using hydrogen sulfide the difficulty of having excess sulfuric acid is avoided.

thoroughly washed by bubbling it through distilled water. If the hydrogen sulfide is not washed, colloidal particles which cannot be removed remain in the solution of l-tartaric acid.



The lead sulfide was filtered off with suction upon a Buchner funnel.

Precipitate: Lead Sulfide.

Filtrate: l-Tartaric Acid.

Recovery and Purification of l-Tartaric Acid

The filtrate was poured into a large evaporating dish and evaporated almost to dryness in a vacuum desiccator. The crystals which separate were filtered off with suction upon a Buchner funnel. The l-tartaric acid was further purified by recrystallization from amyl alcohol.

Yield: 4 grams l-tartaric acid. Melting point $169-172^\circ$. $[\alpha]_D^{22} = -13.24$. (In water).

Precipitation of d-Cinchonine Hydrogen d-Tartrate

The filtrate, obtained from the first precipitation of d-cinchonine hydrogen l-tartrate, was placed in a 500 cc. distilling flask with a condenser attached, and the solution concentrated under a vacuum to a volume of about 250 cc. The solution was transferred to an Erlenmeyer flask. The flask was corked and set aside for at least 24 hours. A heavy precipitate of d-cinchonine hydrogen d-tartrate usually forms. On warm days it was necessary to produce crystallization by cooling the solution in a freezing mixture and by scratching the inside walls of the containing vessel. If no crystals formed, the solution was further concentrated by distilling off 50 cc. portions and repeating the chilling process after each concentration. This process of crystallization was continued until the solution was concentrated almost to a gummy mass. The successive crops of crystals of the d-salt were relatively free from the l-salt because they are very much more soluble in methyl alcohol. Each crop of crystals was filtered off with suction upon a Buchner funnel.

Precipitate: d-Cinchonine hydrogen d-tartrate.

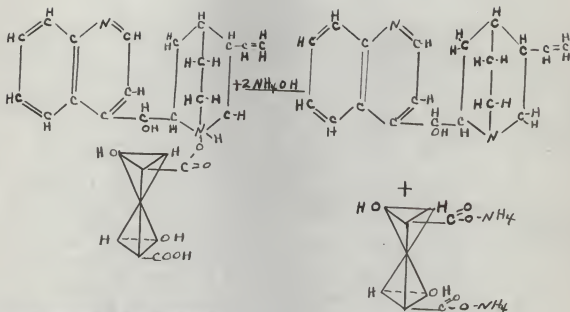
Filtrate: Impurities, discard.

Purification of d-Cinchonine Hydrogen d-Tartrate: The precipitates containing d-cinchonine hydrogen d-tartrate were washed with a small amount of distilled water. This removed a large amount of the impurities which had given the precipitate a dark brown color. The d-cinchonine hydrogen d-tartrate was placed in a 600 cc. beaker and a small amount of acetone was added. The mixture was brought to boiling over a water bath and more acetone was added to bring all of the salt into solution. The solution was filtered while hot and set aside for the d-cinchonine hydrogen d-tartrate to crystallize out. The crystals were filtered off with suction upon a Buchner funnel.

Yield: 15.2 grams d-cinchonine hydrogen d-tartrate.
Melting point 183-189°. $[\alpha]_D^{22} = +169$.

Decomposition of the d-Cinchonine Hydrogen d-Tartrate With Ammonium Hydroxide

The crystals of d-cinchonine hydrogen d-tartrate were placed in a 600 cc. beaker and 200 cc. of distilled water were added. Concentrated ammonium hydroxide was then added until a portion of the filtrate did not give a white precipitate. The ammonia precipitated the d-cinchonine and formed ammonium d-tartrate.



d-Cinchonine Hydrogen
d-Tartrate

Ammonium d-Tartrate

The precipitate was filtered off with suction upon a Buchner funnel.

Precipitate: d-Cinchonine.

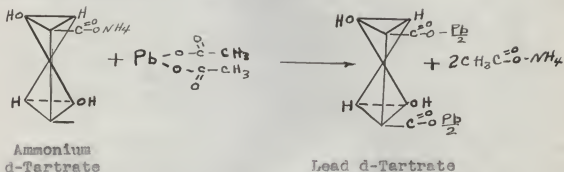
Filtrate: Ammonium d-Tartrate.

Precipitate: The precipitate was washed with distilled water and the d-cinchonine recovered as previously described.

Filtrate: The filtrate was poured into a large evaporating dish and set aside in order to allow the excess ammonia to evaporate. The evaporation was hastened by means of a fan.

The Precipitation of Lead d-Tartrate

The filtrate containing ammonium d-tartrate was now treated with a 40 per cent solution of lead acetate, until a portion of the filtrate no longer gave a precipitate of lead d-tartrate. Lead d-tartrate was precipitated and ammonium acetate formed in solution.



The lead d-tartrate was filtered off with suction upon a Buchner funnel.

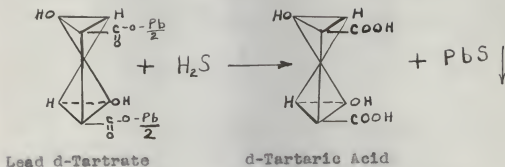
Precipitate: Lead d-Tartrate.

Filtrate: Ammonium Acetate.

The Decomposition of Lead d-Tartrate With Hydrogen Sulfide

The lead d-tartrate was washed with distilled water to remove ammonium acetate. The crystals were placed in a 500 cc. Erlenmeyer flask and 200 cc. of distilled water were added. Hydrogen sulfide was led into the solution (under pressure) and lead sulfide precipitated leaving

d-tartaric acid in solution.



The lead sulfide was filtered off with suction upon a Duchner funnel.

Precipitate: Lead Sulfide.

Filtrate: d-Tartaric Acid.

Recovery and Purification of d-Tartaric Acid

The filtrate was poured into a large evaporating dish and evaporated almost to dryness in a vacuum desiccator. The crystals which separate were filtered off with suction upon a Duchner funnel. The d-tartaric acid was further purified by recrystallization from amyl alcohol.

Yield: 5 grams d-tartaric acid. Melting point $169-172^{\circ}$. $[\alpha]_D^{22} = + 13.27$. (In water).

Resolution of dl-Tartaric Acid with Other Alkaloids

In a similar procedure, attempts to resolve dl-tartaric acid by means of 1-cinechonidine proved unsuccessful.

When l-cinchonidine was added to the boiling methyl alcohol-dl-tartaric acid mixture and refluxed for several hours, the alkaloid did not react with the dl-tartaric acid to any appreciable extent.

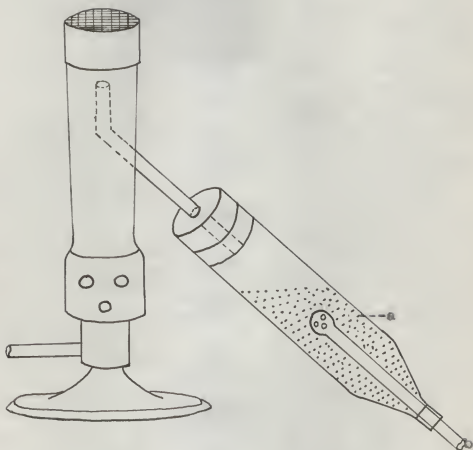
DISCUSSION

All the specific rotation readings which have been recorded were made with a solution containing .25 gram of solid dissolved in 25 cc. of distilled water.

A twenty decimeter tube was used in all cases. The rear of the polariscope was at a distance of 22 centimeters from the sodium light.

A three per cent solution of sodium dichromate was placed in the short glass tube attached to the rear end of the polariscope. This serves as a filter to remove foreign rays especially the blue rays.

The sodium light was obtained by blowing finely pulverized dry sodium chloride into the flame of a Meeker burner. The accompanying diagram describes the apparatus which was used. A very excellent sodium flame of an exceptionally high intensity was obtained with this apparatus.



- a - Pulverized sodium chloride
b - Compressed air intake

Diagram of Burner for Giving Sodium Light

SUMMARY

The successful resolution of dl-tartaric acid into its optically active modifications, d- and l-tartaric acid, by means of cinchonine has been described.

Attempts to resolve dl-tartaric acid with l-cinchonidine proved unsatisfactory.

ACKNOWLEDGMENT

The writer desires to express his sincere appreciation to Professor C. W. Colver, of the Department of Chemistry, Kansas State College, under whose direction the study of this problem has been made. The kindly assistance and many helpful suggestions given by him have been invaluable.

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