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PREPARATION AND RESOLUTION OF AN OPTICALLY ACTIVE KETIMINE

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PREPARATION AND RESOLUTION OF AN OPTICALLY ACTIVE KETIMINE

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To Birddean, Mother and Dad

for their love and self sacrifice

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TABLE OF CONTENTS

	Page
LIST OF TABLES	vi
LIST OF ILLUSTRATIONS	vii
Chapter	
I. INTRODUCTION	1
II. EXPERIMENTAL	11
III. RELATED EXPERIMENTAL	24
IV. DISCUSSION OF RESULTS	34
V. SUMMARY	37
BIBLIOGRAPHY	39

LIST OF TABLES

Table		Page
1.	Ketimines and Ketisoketimine	15
2.	Optical Activity of d-CSA, s-Butyl o-Tolyl Ketimine and Their Mixtures	19
3.	Optical Activity of s-Butyl o-Tolyl Ketimine d-CSA Salts and of s-Butyl o-Tolyl Ketimine	23

LIST OF ILLUSTRATIONS

Figure Page

1. Titration Curves for s-Butyl Phenyl Ketimine . . 16

PREPARATION AND RESOLUTION OF AN OPTICALLY ACTIVE KETIMINE

CHAPTER I

INTRODUCTION

In 1891 Hantzch and Kraft[1] reported the preparation of ketimine hydrochlorides and various N-substituted ketimines. These were obtained while attempting the preparation of a different compound by the reaction of the gem-dichloride of benzophenone with urethane. Since that time there has been a considerable amount of work directed toward the preparation and study of this type of compound.

Moureu and Mignonac[2-8] reported the first systematic study of ketimines prepared by the reaction of various alkyl and aryl Grignard reagents on aromatic nitriles. Two methods were used to decompose the ketiminemagnesium halide obtained, depending upon whether an aliphatic or aromatic Grignard reagent had been used.

When an alkyl Grignard reagent was used an anhydrous method of decomposition was necessary to prevent rapid hydrolysis of the ketimine to the ketone. The ether in the initial reaction mixture was distilled until the addition

product precipitated. The solid material was separated by filtration, washed with anhydrous ether, suspended in dry ether and decomposed either by passing anhydrous hydrogen chloride through the suspension or by refluxing with glacial acetic acid. Ammonia was then bubbled through the suspension, liberating the ketimine which was recovered from the inorganic salts by filtration. The ketimine was recovered by distillation of the filtrate.

In the case where an aromatic Grignard was used, the complex could be decomposed by pouring it into a mixture of ice and solid ammonium chloride. The ketimine and magnesium halide were produced by this treatment. Some hydrolysis of the ketimines to the ketones occurred, but in the aromatic series this is not a rapid reaction in cold solution and the yields of ketimines were not greatly decreased if the hydrolysis mixture was worked up rapidly. The ether layer was quickly separated, calcium chloride added and the solution kept cold during the drying period. Anhydrous hydrogen chloride was passed through the dried solution and the ketimine hydrochloride precipitate was separated from the ketone by filtration. The ketimine was recovered by suspending the ketimine hydrochloride in ether, passing anhydrous ammonia through the suspension, filtering the solution to remove ammonium chloride and then distilling the ether from the filtrate.

Additional ketimines were prepared and a method of

decomposing the Grignard complex to yield N-acyl ketimines was developed. This method of decomposition involved treating the Grignard complex with an acid chloride or an acid anhydride.

Mignonac[5] developed two additional methods of ketimine synthesis. In the first procedure aryl ketone vapors mixed with ammonia were passed over a hot (400°C) Thoria catalyst and then the vapors were chilled to prevent reversal of the reaction:

$$R_1 - \overset{\overset{O}{\|}}{C} - R_2 + NH_3 \rightleftharpoons R_1 - \overset{\overset{NH}{\|}}{C} - R_2 + H_2O$$

The ketimine was separated from the ketone in ether solution by precipitating the ketimine as the hydrochloride. The second method[6] was the low pressure catalytic reduction of ketoximes over nickel. Diaryl ketoximes gave excellent yields of ketimines in a very short time. Arylalkyl ketoximes gave some ketimines plus varying amounts of unreacted ketoxime, primary amine and alkylated ketimine.

The Hoesch reaction has been used to prepare ketimine hydrochlorides as intermediates in ketone syntheses as reported by Hoesch and co-workers[9,10] and Houben and Fischer.[11-15] The method consisted of dissolving a nitrile and a phenol, or phenolic ether, in a solvent such as ethyl ether or benzene. A catalyst such as ferric, aluminum or zinc chloride was added and the solution was saturated with

dry hydrogen chloride. The ketimine hydrochloride separated out after a period of time and it could be recovered and converted to the ketimine.

In 1950, Pickard and Vaughan[16] reported two new methods for non-hydrolytic decomposition of the Grignard complex.

The first method involved removing the reaction solvent and replacing it with anhydrous chloroform. The Grignard complex was then decomposed with anhydrous hydrogen chloride. The ketimine hydrochloride formed was soluble in the chloroform and the inorganic residue was removed by filtration. The hydrochloride was then precipitated, washed, suspended in anhydrous ether and converted into the ketimine by passing in anhydrous ammonia. While this method offered advantages over previous ones, the second procedure developed by Pickard and Vaughan was simpler and led to increased yields.

In the second procedure the Grignard-nitrile complex was decomposed by passing anhydrous ammonia through the cold solution. This reaction was sufficiently exothermic to reflux the toluene, which was used as the solvent, during the decomposition period. Decomposition was said to be complete when the solution had returned to room temperature. The ketimine solution was filtered to remove the inorganic solids and the solvent was removed by distillation. The residue was fractionated to obtain the ketimine. This method

was used extensively by Pickard and his co-workers[17-22] for the preparation of a large number of ketimines of aryl-aryl, aryl-alkyl, alkyl-alkyl, and heterocyclic-alkyl types. The individual compounds were selected to offer varying possibilities of imine-enamine tautomerism and of steric hindrance.

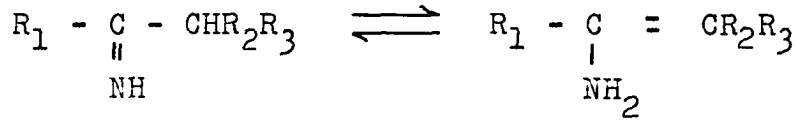
Tolbert[23] reported a new method for the decomposition of the Grignard-nitrile complex in which absolute methanol was used. He reported that the magnesium methoxide halide formed was much easier to filter than was the magnesium amide halide formed in the method used by Pickard and Vaughan. This is true when the solvent is ethyl ether, but no marked advantage was noted when the ethyl ether had been replaced as the solvent by toluene.

Moureu and Mignonac pointed out that diaryl ketimines were more stable to hydrolysis than were the alkyl-aryl ketimines. They were unable to prepare dialkyl ketimines because they hydrolyzed so readily with the procedures they used. Work by Hoesch showed that the polyhydroxy ketimines were more stable to hydrolysis than the unsubstituted diphenylketimine.

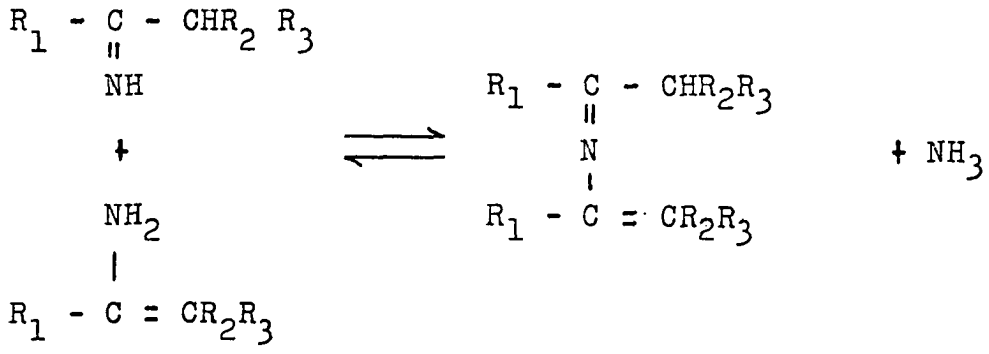
Two factors appear to play a role in affecting the sensitivity of ketimines toward hydrolysis: (1) a ketimine-enamine tautomerism and/or resonance, (2) steric hinderance.

The imine-enamine tautomerism was suggested by the work of Collie[24] and of Best and Thorpe.[25] Moureu and Mignonac[3,4] supported such tautomerism by their observation

that a ketimine containing an alpha hydrogen, such as ethyl phenylketimine, could be converted into a ketisoketimine and ammonia. Such a reaction they explained as a condensation between a molecule of ketimine and a molecule of isoketimine (an enamine tautomer) with the elimination of ammonia.



ketimine Isoketimine



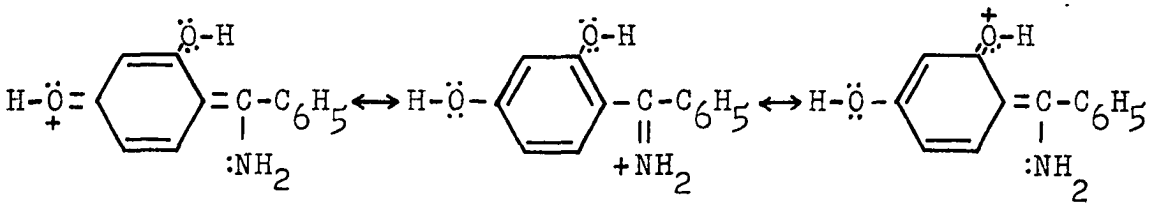
These ketisoketimines were hydrolyzed with hydrochloric acid to yield the ketones expected from the simple ketimines and ammonium chloride in a 2:1 molar ratio.

These products could also be formed by the hydrolysis of a compound of the type which could be formed by the elimination of a molecule of ammonia between two ketimine molecules in the enamine form.

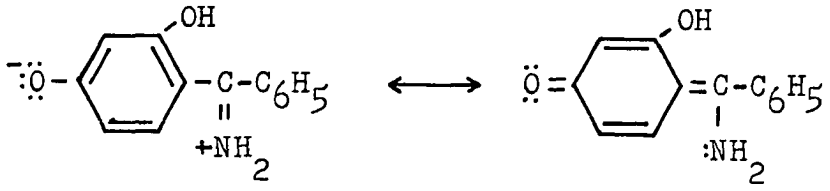
$$R_1 - CH = C - R_2$$
$$\quad\quad\quad

Shift of the phenolic "H" either from the para or the ortho position to produce the quinoid-amine forms (1) or (2) may be considered possible although (1) is more probable. The quinoid-amine forms should not be subject to hydrolysis; therefore, existence in these forms might account for the slow speed of hydrolysis of the phenolic ketimines prepared by Hoesch.

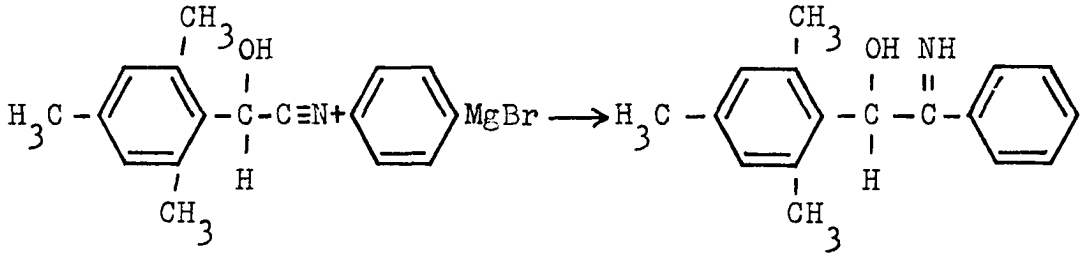
Resonance between imine and amine forms may be a concurrent stabilizing factor.

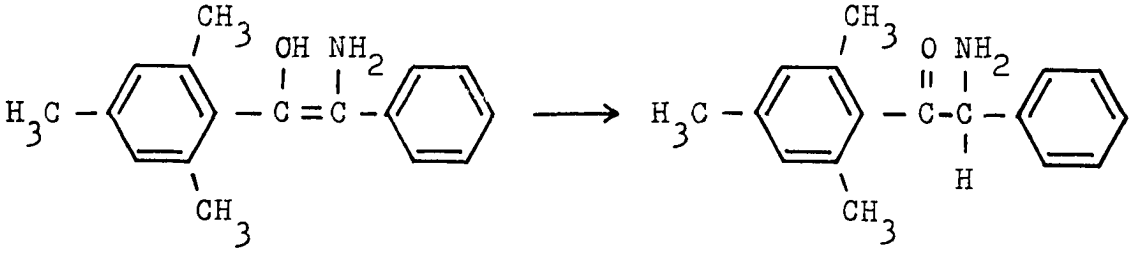


However it may be expected that this shift of electron density from oxygen toward nitrogen should lead to the dropping of a proton by oxygen and the gain of one by nitrogen. The net result would be tautomerism. A similar outcome could be realized from resonance of a phenolate ion:



Further support of the probability of the imine-enamine tautomerism is found in the work of Weissberger and Glass.[28] The cyanohydrin of 2,4,6-trimethylbenzaldehyde was reacted with phenylmagnesium bromide and on hydrolysis they obtained an -aminoketone instead of the benzoin. They explained this reaction by the tautomerism of the ketimine first formed on decomposition of the Grignard complex:





Culbertson[27] made a study of the factors affecting the relative rates of hydrolysis of diphenylketimine and substituted diphenylketimines. His conclusions were that the substituent effects which appeared to be established were tautomerism and/or resonance and steric hindrance. In his studies he found evidence of ketimine-enamine tautomerism in ultraviolet absorption spectra data.

Infrared spectra of fifteen ketimines were determined and analyzed by Pickard and Polly.[29] They found it impossible to prove the existence of enaminization of ketimines by infrared spectroscopy. They suggested that the carbon to nitrogen double bond band might overlap the carbon to carbon double bond band making proof impossible. They also stated that the bands due to nitrogen to hydrogen bonding are the same for the ketimines and the corresponding amines.

One method for establishing the proof of ketimine-enamine tautomerism which has not been investigated to date is the resolution of an optically active ketimine where the asymmetric carbon is alpha to the imino carbon. If the asymmetric carbon has an attached hydrogen which can take part in the ketimine-enamine tautomerism then the resolved ketimine should racemize with time. It was the purpose of this investigation to prepare and resolve such an optically active ketimine.

CHAPTER II

EXPERIMENTAL

Preparation of s-butyl o-tolyl ketimine. (Method A)

The Grignard reagent was prepared in a 500 ml. three necked flask equipped with a Friedrichs condenser, dropping funnel and a mercury sealed stirrer. The openings in the condenser and dropping funnel were protected with calcium chloride drying tubes. One hundred ml. of anhydrous ether was placed in the flask with 6.05 g. (0.25 g. atom) of magnesium. The s-butyl bromide, 34.2 g. (0.25 moles), was dissolved in 50 ml. of anhydrous ether and slowly added from the dropping funnel. After the halide had been added, the mixture was refluxed for about twenty minutes. One hundred ml. of anhydrous toluene was added and at the same time ether and toluene were distilled until the overhead temperature reached 100°C. At that time the solution of 29.4 ml. (0.25 mole) of o-tolunitrile in 50 ml. of toluene was added over a period of one hour. The resultant mixture was refluxed for 22 hours, cooled and then anhydrous ammonia was bubbled in for six hours. The ammonia was dried by passing through a sodium hydroxide packed tower. The reaction

mixture was filtered through a Buchner funnel and then through a sintered glass funnel (M porosity). Toluene was distilled from the filtrate and then the material was fractionated on the spinning band column* at 73-73.5°C. and 2 mm. Twenty ml. or 18.89 g. of material was obtained for a yield of 43.3 per cent.

A second preparation of the s-butyl o-tolylketimine was carried out in a two liter three necked flask using molar quantities of the reagents. The yield for this reaction was 40 per cent based on 70.8 g. of product obtained. B.p. was 83°C. at 4 mm.

Preparation of s-butyl o-tolyl ketimine. (Method B)

One gram atom of magnesium, 24.32 g., was placed in a two liter three necked flask equipped as described above. A small piece of iodine was placed in the flask with the magnesium and then the flask was heated with a small flame until the iodine began to vaporize. This method of using iodine for activation of the magnesium in a Grignard reaction has been described by Whitmore and Badertsher.[30] After the flask had cooled, ten ml. of a mixture of 137 g. (one mole) s-butylbromide in 400 ml. of anhydrous ether was added. When the reaction started, 150 ml. of anhydrous ether was added, rapid agitation was started and the halide-ether

---

*The spinning band column used in this work was one made by Dr. P. L. Pickard. It had a 3/8 inch stainless steel band and the effective column length was about 16 inches.

mixture was added at a rate to maintain continuous ether reflux. One and a half hours were required for the addition of the halide and at that time all but a trace of the magnesium had disappeared. One hundred grams (0.85 mole) of o-tolunitrile in 300 ml. of anhydrous ether was added as rapidly as possible and then the mixture was heated to reflux with a Glas-Col mantle for 35 hours. The Grignard-nitrile complex was decomposed by the addition of 120 ml. of anhydrous methanol. The mixture was filtered through a sintered glass funnel and the precipitate was washed with anhydrous ether. The filtrate was filtered again, the ether distilled and the remaining material was fractionated in a spinning band column at 83°C. and 4 mm. The yield was 95.2 g. of ketimine or 64.0 per cent.

Preparation of s-butyl phenylketimine. This reaction was carried out in a one liter three necked flask equipped with Friedrichs condenser, dropping funnel, and mercury sealed stirrer. Openings to the funnel and condenser were protected from moisture by calcium chloride drying tubes. All equipment was dried in an oven at 105°C. before use. About 50 ml. of anhydrous ether was placed in the flask with 24.32 g. (one g. atom) of magnesium. One g. mole of s-butyl bromide, 137 g., was dissolved in 400 ml. of anhydrous ether and about 5-10 ml. of the solution was added to the flask. The mixture in the flask was warmed to start the reaction. After the reaction had started, 100 ml. of anhydrous ether

was added, at the same time rapid agitation was initiated and continued during the addition of the halide which took two hours. When all of the halide had been added, a heating mantle was placed under the flask and the mixture was refluxed. Not all of the magnesium had disappeared after 90 minutes refluxing, so about two ml. of the halide was dissolved in ether and added. The mixture was refluxed for a total of ten hours and then a solution of 82.4 ml. (0.8 mole) of benzonitrile in 300 ml. of anhydrous ether was added to the Grignard reagent. The resultant mixture was refluxed for 44 hours. At the end of this time the ether was distilled from the mixture and saved for use in other Grignard reactions. An equal volume of ether which contained some methanol was added to the mixture. This ether had been obtained by distillation after decomposition of a Grignard complex. Three gram moles of anhydrous methanol were added to decompose the Grignard-nitrile complex. The mixture was filtered through a sintered glass funnel. Ether and methanol in the filtrate were removed by distillation. A small amount of solid material separated out of the liquid remaining after the distillation and was removed by filtration. The filtrate was fractionated in the spinning band column at 95°C. and 6 mm. to give 61.0 g. of s-butyl phenylketimine for a yield of 47.5 per cent. In addition to this material, 43.4 g. of a light yellow oil was obtained at 160-2°C. and 3 mm. This material was thought to be the ketisoketimine.

The yield was 35.6 per cent.

A sample of the ketimine was weighed and titrated by the method developed by Iddings.[31] The first titration 15 minutes after the sample was made up in glacial acetic acid showed 90.8 per cent purity. Two more titrations were made forty minutes after the first one and these indicated 98.0 per cent purity. One ml. of a solution of 0.1464 g. of ketimine in 25 ml. of glacial acetic acid was used for each titration. Pertinent physical data are recorded in Table 1 and titration curves are shown in Figure 1.

TABLE 1

KETIMINES AND KETISOKETIMINE

R_1-C(=NH)R_2	BP °C/mm	d_4^{20}	n_D^{20}	Hydrochloride m.p.
R_1 - s-butyl R_2 - o-tolyl	82-3/4mm	0.9446	1.5235	143-4
R_1 - s-butyl R_2 - phenyl	95/6mm	0.9566	1.5285	
Ketisoketimine of s-butyl phenyl ketimine	160-2/3mm	0.9813	1.5577	

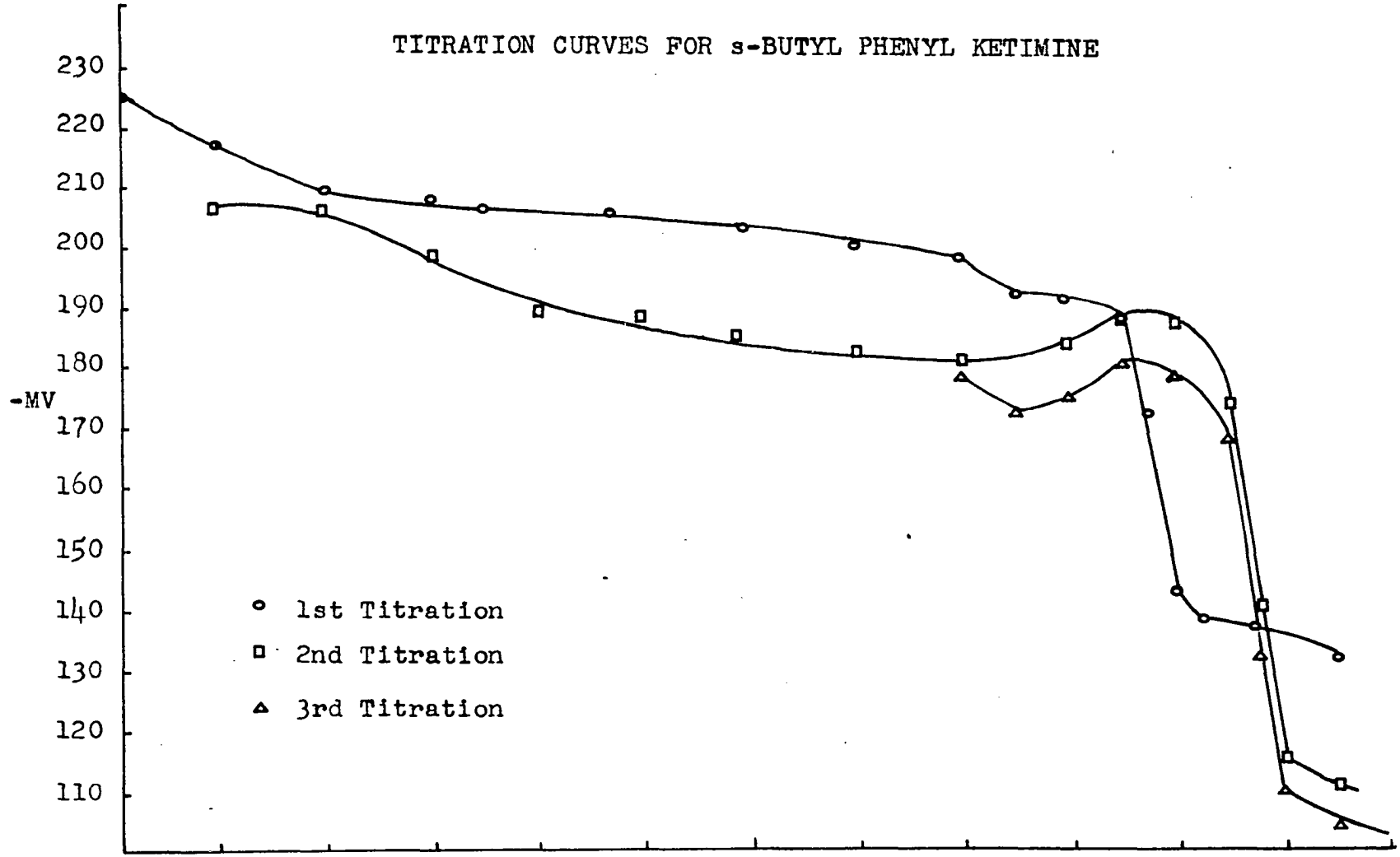

TITRATION CURVES FOR s-BUTYL PHENYL KETIMINE
230
220
210
200
190
180
-MV
170
160
150
140
130
120
110
1st Titration
2nd Titration
3rd Titration
0
1
2
3
4
5
6
7
8
9
10
11
Ml. of 0.01686 N HClO4

FIGURE 1

Studies of the reaction of d-10-camphorsulfonic acid with s-butyl o-tolyl ketimine. d-10-camphorsulfonic acid (hereafter called d-CSA) from Eastman Kodak Co. was used in these studies. In the first experiments, which were conducted in an attempt to prepare s-butyl o-tolyl ketimine d-CSA, the ketimine and d-CSA were dissolved in chloroform and the solutions mixed. A precipitate formed on standing, but tests established that it was ammonium d-CSA instead of the expected ketimine d-CSA salt. Apparently if there was any moisture present, the ketimine was readily hydrolyzed to the ketone. Renaude[32] in his polarographic studies of s-butyl o-tolyl ketimine showed that the ketimine itself was quite stable to hydrolysis but in the presence of a strong acid it was readily hydrolyzed to the ketone.

Pope and Gibson[33] reported that d-CSA crystallizes with $1\frac{1}{2}$ moles of water. The original d-CSA had been recrystallized from ethyl acetate but since the d-CSA was a possible source of moisture it was treated in the following manner: Benzene and d-CSA were placed in a flask which had a Stark-Dean type of distilling receiver and about four ml. of water was removed from 67 g. of d-CSA by refluxing the benzene. The d-CSA-benzene mixture was filtered and the d-CSA was placed in a vacuum desiccator to remove the benzene. Purity of this acid was 99.5 per cent as determined by titration with standard sodium hydroxide solution. A second sample, 100 g., was refluxed with benzene and 8 ml. of

water were removed. Purity of the acid was 99.8 per cent.

Samples of d-CSA and s-butyl o-tolyl ketimine were weighed and made up to volume with chloroform. The optical rotation of the individual solutions and various mixtures were determined on a Gaertner L-320 polarimeter, with a sodium vapor lamp as the illuminant and a four dcm. water jacketed tube. The results are shown in Table 2. It should be noted that the specific rotation for d-CSA in chloroform does not agree with the literature value of +39.5°.

A number of attempts were made to prepare the s-butyl o-tolyl ketimine d-CSA salt. The first successful procedure was to add a solution of d-CSA in chloroform to the ketimine. After about ten minutes the chloroform was distilled under reduced pressure. Anhydrous ether was added to the oil which remained and most of the oil went into solution. This solution was filtered. Shortly after filtration, a precipitate started to form. The precipitate, m.p. 108°C., was filtered and washed with ether. After the ether was distilled from the filtrate, an orange oil remained. Samples of both the crystals and the oil were weighed and made up to known volume with anhydrous methanol. The following data were obtained:

Orange oil 0.6139g/50ml rotation +0.84° $[\alpha]_D^{20}$ = +17.1

Crystals 0.5013g/25ml rotation +2.00 $[\alpha]_D^{20}$ = +25.0

TABLE 2

OPTICAL ACTIVITY OF d-CSA, s-BUTYL o-TOLYL KETIMINE AND THEIR MIXTURES

Sample No.	Sample	Wt. sample made up to 100 ml.	Solvent	Mole ratio d-CSA to Ketimine	Observed rotation-4dcm. Tube - 20°C Corrected for blank in degrees	$[\alpha]_D^{20}$
1	d-CSA	1.50	$CHCl_3$	-	+0.57	+ 9.5°
2	s-Butyl o-tolyl ketimine	1.13	$CHCl_3$	-	0	0
3	s-Butyl o-tolyl ketimine	0.57	$CHCl_3$	-	0	0
4	20 ml. #1 + 20 ml. # 3	-	$CHCl_3$	2/1	+1.36	+32.9°
5	10 ml. #1 + 20 ml. #3	-	$CHCl_3$	1/1	+1.24	+35.3°
6	10 ml. #1 + 20 ml. #2	-	$CHCl_3$	1/2	+1.25	+26.7°
7	20 ml. #1 + 10 ml. #3	-	$CHCl_3$	4/1	+1.18	+24.8°
8	d-CSA	4.00	H_2O	-	+3.46	+21.6°
9	d-CSA	4.00	CH_3OH	-	+6.30	+39.4°

Decomposition of the ketimine d-CSA salt. In the first attempt to isolate the active s-butyl o-tolyl ketimine from the salt, the reaction was carried out in a dry box. A weighed sample of the salt was dissolved in chloroform. The flask containing the solution was cooled in liquid ammonia. Dry ammonia gas was passed through the solution but no ammonium d-CSA formed. This was found to be due to the fact that the ammonium salt was soluble in the ammonia which condensed in the chloroform. When the chloroform solution was allowed to stand at room temperature for a time, ammonium d-CSA crystals precipitated. The ketimine which was obtained in this manner showed no optical activity.

In the second method sodium hydroxide solution was used for the decomposition of the ketimine d-CSA salt. A weighed sample of either the crystals or oil of the ketimine d-CSA salt was dissolved in chloroform in a separatory funnel. An aqueous solution of sodium hydroxide (ten per cent) was added to the funnel. After the layers had separated, the chloroform layer was drawn off, dried over anhydrous sodium sulfate, and made up to volume with chloroform. The results obtained from the decomposition of the crystals and the oil were:

Crystals 2.0g/50ml rotation +0.05° $[\alpha]_D^{20}$ = +0.73°

Orange oil 2.0g/50ml rotation -0.10 $[\alpha]_D^{20}$ = -1.45°

It should be noted that these readings changed to zero in about 30 minutes, resulting in complete racemization.

In a modification of the second method described above, ether was used as the organic solvent. After the solution had been dried, the ether was removed by distillation and the ketimine which remained was made up in chloroform for determination of its optical activity.

In another modification, n-hexane was used as the organic solvent. Results obtained using these last two procedures are discussed in a section which follows.

Fractional crystallization of s-butyl o-tolyl ketimine d-CSA. Sixteen grams of s-butyl o-tolyl ketimine was placed in a 250 ml. glass stoppered Erlenmeyer flask with anhydrous ether and 21.2 g. of d-CSA (one to one mole ratio) was added. Some of the ether boiled off as the ketimine and d-CSA reacted and it was replaced. No attempt was made to effect a separation of the diastereoisomers at that time. The material which precipitated was filtered on a sintered glass funnel, washed with ether and washings added to the filtrate. This precipitate weighed 33.16 g.

The ether was distilled from the filtrate. A dark oil remained in the flask. This material when decomposed in n-hexane had $[\alpha]_D^{20}$ = -0.73 1.0g/25ml rotation -0.05°

The precipitate was dissolved in a mixture of benzene and n-heptane and allowed to crystallize on

evaporation of the solvent. Although there was some evidence of separation in this procedure, it was not carried further for the formation of ammonium d-CSA was noted. Since the ammonium d-CSA is insoluble in chloroform, it was observed as insoluble material when samples of the ketimine d-CSA salt were made up in chloroform for determination of optical activity.

In another experiment, 8.75 g. of s-butyl o-tolyl ketimine was weighed into a 250 ml. glass stoppered flask containing about 125 ml. of anhydrous ether. To this solution 11.6 g. of d-CSA was added. After the ether had stopped boiling there was still a semi-solid material on the bottom of the flask which would not go into solution (Sample 1). The ether solution was poured into another flask where a small amount crystallized (Sample 2). The same procedure was carried out twice more to give samples 3 and 4. The ether solution which remained was concentrated to give sample 5 and the remaining ether was evaporated to give sample 6. Weighed portions of some of the samples were dissolved in chloroform filtered to remove insoluble ammonium d-CSA and rotatory values taken. Some of the samples also were decomposed to obtain rotatory values for the ketimine. These data are recorded in Table 3.

TABLE 3

OPTICAL ACTIVITY OF s-BUTYL o-TOLYL KETIMINE d-CSA SALTS AND OF s-BUTYL o-TOLYL KETIMINE

Sample No.	Wt. sample made up to 25 ml. in $CHCl_3$ corrected for NH_4 d-CSA	Wt. sample decomposed and made up to 25 ml. in $CHCl_3$	Corrected rotation 4dcm at 20°C	$[\alpha]_D^{20}$
1	-	1.2 g.	-0.10	-1.22
2	-	-	-	-
3	1.13 g.	-	+7.18	+39.7
3	-	2.0 g.	+0.05	+ 0.36
4	0.53 g.	-	+3.30	+38.9
5	0.426 g.	-	+1.56	+22.8

CHAPTER III

RELATED EXPERIMENTAL

A number of materials were investigated as possible compounds for use in this problem, but due to various reasons were not used in the final steps of preparation and resolution of the optically active ketimine.

Preparation of phenyl 3-(3- methyl hexyl) ketimine. The first step in the attempted preparation of this compound was the reaction of one g. mole of ethyl bromide with one g. atom of magnesium in 350 ml. of anhydrous ether. As soon as this reaction was completed, 0.88 g. mole of 2-pentanone was added. After the 2-pentanone had been added, the complex was decomposed by adding about 200 ml. of concentrated hydrochloric acid. The magnesium bromide chloride formed was removed by filtration and washed with ether. The filtrate was separated in a separatory funnel to recover the ether layer. Most of the ether was removed by distillation. The product remaining was returned to the separatory funnel where it was treated twice with about four times its volume of concentrated hydrochloric acid. After the hydrochloric acid treatment, the product was washed with sodium carbonate

solution, separated and dried over anhydrous sodium sulfate. The dried product was fractionated in the spinning band column. B.p. 35-37° at 13 mm. Yield overall from ketone to tertiary halide with 68.0 g. product obtained was 57.3 per cent. Whitmore and Badertscher[30] obtained 65.6 per cent yield of the carbinol and 90.0 per cent yield of the halide for an overall yield of 59.0 per cent.

Sixty seven grams (0.5 mole) of the halide reacted with 12.16 g. (0.5 g. atom) of magnesium in 150 ml. of anhydrous ether to give the Grignard reagent. A small amount of ethyl bromide was added to help start the reaction. Benzonitrile dissolved in toluene was added to the Grignard reagent and at the same time ether was removed by distillation. This mixture was refluxed for 18 hours. The Grignard-nitrile complex was decomposed by the addition of absolute methanol. Part of the magnesium salt was removed by filtration, but some remained in solution and precipitated as the toluene was distilled. The solution which remained after distillation was fractionated on the spinning band column but only toluene and benzonitrile were removed. A small amount of nitrile was left in the flask plus about 25 ml. of a dark-red gummy material. Part of this material was soluble in ether. The insoluble material was removed by filtration. Anhydrous ammonia was bubbled through the filtrate and a precipitate formed m.p. 235-236°C. The precipitate was removed by filtration. The red-brown oil which remained was soluble in

toluene or ether. Treatment of a solution of this oil in either toluene or ether with dry hydrogen chloride gas gave a gummy yellow precipitate, which in toluene turned red and settled out as an oil. A yellow precipitate settled out of the untreated red-brown oil on standing. These materials were not further investigated.

Preparation of phenyl p-tolyl methylcarbinol. This compound was prepared in a gram mole quantity by the reaction of p-tolylmagnesium bromide with acetophenone. After the reaction complex had been decomposed with hydrochloric acid, the ether was removed by distillation. Unreacted acetophenone was removed by distillation at 70°C. and 6 mm. Apparently the alcohol dehydrated at this time and on further distillation (b.p. 137°C. at 5 mm.) 72 per cent yield of the olefin was obtained. Tiffeneau[34] reported obtaining the olefin on distillation of the carbinol at atmospheric pressure. He reported the boiling point of the olefin as 145-146°C. at 6 mm.

An attempt was made to add hydrogen bromide to the olefin with no success.

Preparation of o-(p-toluyl)-benzoic acid. The method as given by Fieser[35] and Gilman and Blatt[36] was used for the preparation of this compound in 88.4 per cent yield after recrystallization. This material was of interest for two reasons. It was thought that it would be possible to prepare the nitrile from the acid. The reaction of the nitrile

with an aryl Grignard reagent should produce the imine and an asymmetric carbon atom at the same time. The second reason was that the acid could be decarboxylated and the ketone thus obtained used in the preparation of a triarylcarbinol. The triarylcarbinol could be converted to the halogen compound and this to the Grignard. From this point there were two routes to choose. The Grignard reagent if allowed to react with a nitrile might give the ketimine or the Grignard could be carbonated to yield the triarylacetic acid. The triaryl acetic acid could then be converted to the triaryl acetonitrile.

Preparation of o-(p-toluyl) benzamide. Limpricht and Wiegand[37] and Kippenberg[38] reported a method for preparing o-(p-toluyl) benzoyl chloride and o-(p-toluyl) benzamide. The method of preparation used here differed in that thionyl chloride was used to prepare the acid chloride. Excess thionyl chloride was removed under reduced pressure. Some benzene was added as a solvent before anhydrous ammonia was bubbled in. The solution was cooled with ice water when the benzene started to reflux. After the ammonia addition, the benzene was distilled, and the precipitate filtered and dissolved in 95 per cent ethanol. The ethanol solution was poured into boiling water which was filtered while hot. As the filtrate cooled, the desired product precipitated and was recovered by filtration. The yield of product was 45.6 per cent. The melting point of the product was 169-170°C.

while that given in the literature is 175-176°C.

Attempted preparation of o-(p-toluyl) benzonitrile. An attempt was made to dehydrate the amide by treatment with $POCl_3$ using a procedure such as that described by Reid and Hunter.[39] Benzene soluble and insoluble material was obtained. This material was not further characterized.

Preparation of diphenyl ketimine from benzamide. A few cases have been reported of the preparation of imines from the reaction of an amide with a Grignard reagent. Couturier[40,41] reported the reaction of 4-methoxybenzamide with ethylmagnesium bromide to give 70 per cent of the ethyl ester, some 4-methoxyphenyl ethyl ketimine and unreacted amide. He also reported the reaction of 90 g. of 3,4,5-trimethoxybenzamide with 144 g. of ethylmagnesium bromide to give 32 g. of the ethyl ester, 17 g. of the ketimine and 30 g. of unreacted amide. Bruzau[42] reported the reaction of α-phenylisobutryamide with 4-methoxyphenylmagnesium bromide to give α-methyl α-phenylethyl p-methoxyphenyl ketimine. These reactions suggested the possibility of preparing the imine from the amide instead of the nitrile. As a check on this, diphenyl ketimine was prepared from benzamide.

Phenylmagnesium bromide (0.4 mole) was prepared and reacted with 0.133 mole of benzamide dissolved in tetrahydrofuran. This mixture was refluxed for 17 hours. The Grignard complex was decomposed by the addition of methanol.

The magnesium salt was filtered and washed with ether. More magnesium salt precipitated on the addition of ether and it was also removed by filtration. Most of the solvent was removed by distillation. The remaining material was fractionated on the spinning band column at 125°C. and 3 mm. The yield of diphenyl ketimine was 25.0 per cent.

Reaction of o-(p-toluyl) benzamide with phenylmagnesium bromide. This reaction was carried out in the manner described above with a three to one mole ratio of Grignard reagent to o-(p-toluyl) benzamide. After the mixture had refluxed for 20 hours, the Grignard complex was decomposed with methanol. The precipitate was removed by filtration. The solvents in the filtrate was removed by distillation and solid material remained. The solid was extracted with ether and benzene. Both of the solids, obtained from the extract, left an ash when burned. This indicated that some magnesium salt was still present. It was difficult to remove all of the magnesium salts from the product remaining and no clean separation of the remaining material was accomplished.

Preparation of 2-(p- t-butylphenoxy)propionamide. The substituted propionic acid, which was obtained from Dow Chemical Co., was placed in a flask with thionyl chloride. The flask was fitted with a Friedrichs condenser whose outlet was protected with a calcium chloride drying tube. The acid-thionyl chloride mixture was heated to start the

reaction. A portion of the acid chloride formed was fractionated at 123°C. and 3-4 mm. n_D^{20} 1.5086

The acid chloride was poured into cold ammonium hydroxide whose temperature was kept below 15°C. The crude amide was filtered, washed with water and dried. The yield of crude material was 99 per cent.

Attempted preparation of 2-(p-t-butylphenoxy) propionitrile. The crude amide as prepared above was refluxed with excess thionyl chloride. Excess thionyl chloride was removed under reduced pressure. The remaining product was taken up in ether, washed with cold water, washed with 200 ml. of 10 per cent sodium hydroxide solution, and again washed with water. The ether solution was treated with Norite, filtered and the ether distilled. The resultant product was fractionated in the spinning band column at 121-123°C. and 1-2 mm. Yield based on crude amide was 76.6 per cent. In a second preparation the yield was 71.2 per cent. Molar refraction was calculated for the assumed nitrile from density 0.988g/ml and n_D^{20} 1.5023

Molecular refractivity experimental 59.46

Molecular refractivity theoretical[43] 60.02

Attempted preparation of α-(p-t-butylphenoxy)ethyl phenyl ketimine. Since the experimental and theoretical values for the molecular refractivity agreed so well, an attempt was made to prepare the ketimine by the reaction of the nitrile with phenylmagnesium bromide in anhydrous ether.

The Grignard-nitrile complex was decomposed with methanol. It was difficult to remove the magnesium salt even after the ether was distilled. It was thought that the magnesium salt might be held either as a chelate or as an etherate of the imine. Ether was added to the imine oil and anhydrous ammonia was passed through the solution. The precipitate which formed was removed by filtration. All of the precipitate which had been obtained was placed in a flask and anhydrous ammonia bubbled through the mixture. This was done three times, after which the ether was distilled and the oil obtained was combined with that mentioned above.

Extensive work with this oil led to the conclusion that a number of products were present. One method which seemed to offer some promise for separating the mixture was chromatography. Mallinckrodt's 100 mesh (powder) silicic acid was used to prepare the column. When ether was used as the solvent there was no separation, but with benzene as the solvent a number of bands were observed. Four bands were moved off of the column with benzene. Then a 90/10 benzene ether mixture was used, which moved the fifth band down the column. After the fifth band had been eluted, the silicic acid was extruded and the sixth and seventh bands cut out. The silicic acid which contained the bands was treated with ether to extract the organic material. The material from the third band when treated with n-pentane gave some white crystals m.p. 102-103°C.

Since such a large number of bands were found on the column, the question arose as to whether the product used in the attempted preparation of the ketimine was the nitrile as was indicated by molecular refraction. An infrared scanning of the supposed nitrile was made and there was no evidence of a nitrile band. This scanning indicated the presence of sulfur and chlorine which was confirmed by elemental analysis. It was assumed that instead of getting dehydration of the amide with thionyl chloride only an addition product was obtained. Treatment of this product with pyridine under reflux for eight hours did not change the infrared spectra. This product was distilled at 123-126°C. and 2 mm. n_D^{20} 1.5009

Preparation of phenyl p-tolyl o-tolyl carbinol and the bromo and chloro derivatives. The carbinol was prepared by the reaction of o-tolylmagnesium bromide (0.22 mole) with p-tolyl phenyl ketone (0.22 mole). The latter compound was prepared by the decarboxylation of o-(p-toluyl) benzoic acid with copper chromite catalyst as described by Fieser.[35] The copper catalyst used was that described by Adkins.[44] The ketone was distilled from the catalyst at 135°C. and 5 mm. and was recrystallized from ethanol.

The Grignard-ketone complex was decomposed by pouring onto 300 ml. of ten per cent sulfuric acid and some cracked ice. The mixture was separated in a separatory funnel, washed and then steam distilled. The material which

remained was dissolved in ether, separated from the water and the ether extract was dried over anhydrous sodium sulfate. The ether was distilled to give the carbinol. The carbinol did not crystallize. It was soluble in benzene and n-pentane, but separated from n-pentane as an oil when the solution was cooled. Small portions of the carbinol were allowed to react with acetyl chloride (as described by Marvel[45]) and acetyl bromide. The acetyl bromide was prepared from acetic acid and phosphorus tribromide by modification of the procedure given by Fieser[35] for the preparation of acetyl chloride. Both the triaryl chloromethane m.p. 72-73°C. and the triaryl bromomethane m.p. 100-101°C. crystallized from n-pentane on cooling.

Attempted preparation of triaryl acetonitrile. A 10.0 g. sample of the triaryl bromo compound was placed in a flask with 2.0 g. of potassium cyanide and 20 ml. of pyridine. When the pyridine was added, the mixture turned purple. The mixture was refluxed for 11 hours. At the end of this time, the mixture was poured into dilute ammonium hydroxide, extracted with ether, washed with dilute ammonium hydroxide, water, dilute hydrochloric acid, and water. The ether extract was dried over calcium chloride, filtered and ether distilled. The solid material obtained was resinous and it gave a negative nitrogen test after sodium fusion.

CHAPTER IV

DISCUSSION OF RESULTS

The s-butyl o-tolyl ketimine was prepared by two procedures with yields of 43.3 and 64.0 per cent. The ketimine was stored in sealed glass vials in the refrigerator until used.

It was pointed out in the chapter on experimental work that in the first attempts to obtain the ketimine d-CSA salt only ammonium d-CSA was obtained. This was due to the fact that s-butyl-o-tolyl ketimine hydrolyzes in the presence of moisture and a strong acid. The d-CSA was freed from water by refluxing with benzene and hydrolysis did not occur as readily. The dry d-CSA was found to be less soluble in chloroform than that before drying. Pope and Gibson[33] and Hilditch[46] reported a specific rotation for the d-CSA with the concentration of 5.0 g. d-CSA per 100 ml. chloroform. The dry d-CSA as used in this study was not soluble to this extent. It was found to have a solubility of 1.55 g./100 ml. of chloroform (Baker's analyzed). This is said to contain 0.2 per cent ethanol. The d-CSA was found to be more soluble in chloroform (USP) which contained a

larger amount of ethanol. Some qualitative experiments with the dry acid indicated that it was more soluble in wet chloroform. One other interesting fact noted was that the specific rotation for the dry d-CSA in chloroform differs from that reported for the d-CSA·$1\frac{1}{2}H_2O$.

When mixtures of solutions of d-CSA and o-tolyl ketimine in chloroform were made, a very marked increase in the specific rotation was noted. This was attributed to the formation of the diastereoisomers; however when the ketimine and d-CSA solutions in methanol were mixed the change was not as great.

One explanation for the fact that the specific rotation of d-CSA in water is lower than that in methanol is that the d-CSA is concentrated at the surface. Surface tension measurements showed that the surface tension of distilled water was greater than that of a d-CSA solution. The low value of the specific rotation in chloroform compared to that in methanol could be accounted for by the fact that the acid is probably ionized less in chloroform. Wet chloroform would cause the acid to ionize more and thus give a higher value for the specific rotation.

In decomposing the ketimine d-CSA salt it was hoped that this operation could be carried out at low temperature in non aqueous media in order to slow down the rate of racemization and hydrolysis. The method tested did not prove feasible and thus the decomposition was carried out in

aqueous media at room or ice temperature.

No attempt was made to determine the rate of racemization, for the observed values of rotation were so small that it would be difficult to follow in this manner. The best values obtained for the specific rotation of the ketimine were: $[\alpha]_D^{20}$ +0.73° and -1.45° (C. 1.72g/100ml). In about an hour the imine had racemized, for in both cases the observed rotation was zero. Although these values are low Cohen, Marshall and Woodman[46] reported a specific rotation for l-phenyl p-tolyl carbinol as:

$$[\alpha]_D^{20} \quad -1.4 \text{ (C. 2.226g./25ml.).}$$

A number of fruitless attempts were made to prepare a ketimine which had no hydrogens on the carbons alpha to the imino carbon. This material would have been of value for there would have been no possibility of tautomerism. In this work phenyl p-tolyl o-tolyl carbinol was prepared. Both the bromo and chloro derivatives were obtained, recrystallized and their m.p. taken. The acid chloride and amide of 2-(p-t-butyl phenoxy) propionic acid were prepared and physical data recorded.

CHAPTER V

SUMMARY

Moureu and Mignonac suggested that the formation of a ketisoketimine could be explained by the fact that ketimines which contain a hydrogen alpha to the imino group can undergo imine-enamine tautomerism. Thus a molecule of each tautomer would react, with the elimination of ammonia, to give the ketisoketimine. It has also been postulated that imine-enamine tautomerism could account, in part, for the more rapid hydrolysis of ketimines containing an alpha hydrogen. Culbertson found evidence of ketimine-enamine tautomerism in ultraviolet absorption spectra data. Pickard and Polly found it impossible to prove enaminization of ketimines by infrared spectroscopy.

The purpose of this research was to prepare and resolve an optically active ketimine whose asymmetric carbon atom was alpha to the imino group. Such a compound, when resolved, should racemize if it exhibits imine-enamine tautomerism.

The optically active compound, s-butyl o-tolyl ketimine, was prepared by a previously reported method. This

compound formed a salt with d-10-camphorsulfonic acid and the diastereoisomers were resolved by fractional crystallization from ether.

Anhydrous and aqueous procedures were developed for decomposing the s-butyl o-tolyl ketimine d-10-camphorsulfonate, but only the latter method was used with any success.

The optically active d- and l- forms of s-butyl o-tolyl ketimine were obtained but they racemized in about an hour at 20°C. This fact supports the original supposition that if enaminization occurs then the optically active ketimine should racemize.

The following compounds were prepared and physical data recorded in the attempted synthesis of other optically active ketimines: phenyl p-tolyl o-tolyl bromomethane, phenyl p-tolyl o-tolyl chloromethane, 2-(p-t-butylphenoxy) -propionyl chloride, 2-(p-t-butylphenoxy)-propionamide and s-butyl phenyl ketimine.

Diphenyl ketimine was prepared from benzamide and phenylmagnesium bromide.

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