

THE SYNTHESIS OF 4-CARBOXYBENZENESULFHYDRAZIDE AND
AN INVESTIGATION OF ITS USE IN THE RESOLUTION
OF 3-METHYLCYCLOHEXANONE

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by
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VITA

George Ashley Allen was born in Chester, South Carolina on April 26, 1943, the son of Anne Lathan Allen and Augustus Theodore Allen. He attended elementary school in Chester and graduated from Episcopal High School in Alexandria, Virginia in June of 1961. He entered Washington and Lee University in the fall of 1961 and is working toward a Bachelor of Science degree with special attainments in Chemistry.

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TABLE OF CONTENTS

	<u>Page</u>
INTRODUCTION	1
DISCUSSION	7
EXPERIMENTAL	14
SUMMARY	18
FOOTNOTES	19

The present problem was undertaken to provide an intermediate for the resolution of racemic carbonyl compounds. But before continuing, a short discussion of the different types of reagents and a brief explanation of the method of resolving used seems appropriate.

In dealing with functional groups there are three general types of reagents (although there is some overlap,) which are used in the laboratory. These three types of reagents are identification reagents, separation reagents, and resolution reagents. In the case of the carbonyl group, there are many useful identification and separation reagents, but very few elegant resolution reagents. This paper concerns the problem of the lack of resolution reagents for racemic carbonyl compounds, but not only the problem of a resolution reagent but a single reagent that could be used for all three of the necessary reagents. To understand what will be required of just such a reagent, let us examine the three types of reagents.

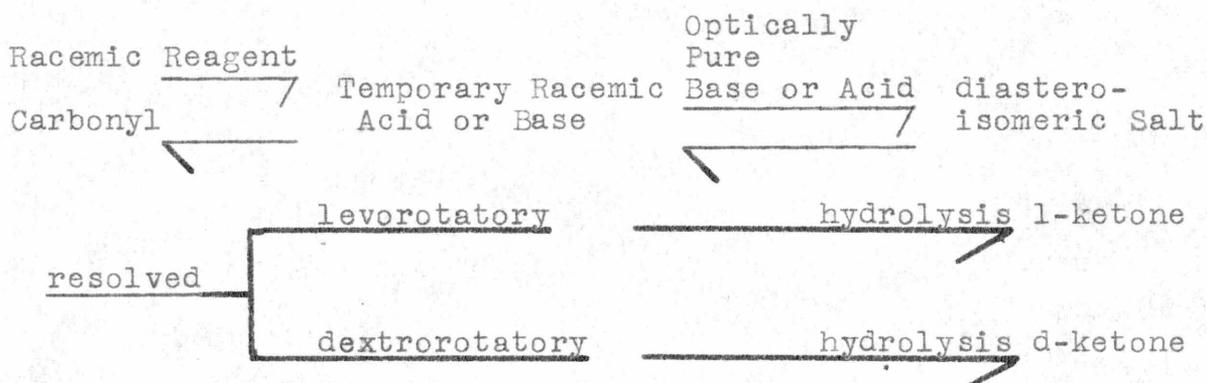
The characteristics of a reagent used for identification of carbonyls are that it should react with most aldehydes and ketones to form stable compounds, that the reagent should also be of such molecular weight that when reacted with carbonyls it will form solids that melt between 50 and 250°C, and that it should provide proper separation of compounds. Examples of carbonyl identification reagents

are phenyl hydrazine, oxime, semicarbazide, and 2,4-dinitrophenyl hydrazine.

Most of the identification reagents for the carbonyl group are also used as separation reagents, but recently a different type of separation reagent has been developed--a bifunctional reagent. Hydrazinoacetic acid, carboxymethoxime, and p-hydrazinobenzoic acid¹ are examples of this type and are quite valuable in that they can be used for molecular weight determination by use of the Neutral Equivalent.

The final type of reagent consists of first making an optically active carbonyl reagent, resolving it, and then reacting it with a carbonyl compound and then resolving the diastereoisomers by fractional recrystallization. The carbonyl compounds were usually obtained by hydrolysis of their respective crystalline fractions. The first resolution of a carbonyl compound was accomplished in 1903 by Carl Neuberg who resolved dl-arabinose. Between 1903 and 1950 there were only ten resolutions of carbonyl compounds. For a complete list of resolutions, the reader is referred to the thesis of J. P. Freeman.² There are good reasons for so few. First the resolved reagent must be reactive with the carbonyl compound. Next the resulting diastereoisomers must have physical properties which have enough differences that they may be separated. If these two conditions are not met then an entirely new enantiomeric reagent must be made to resolve the carbonyl compound.

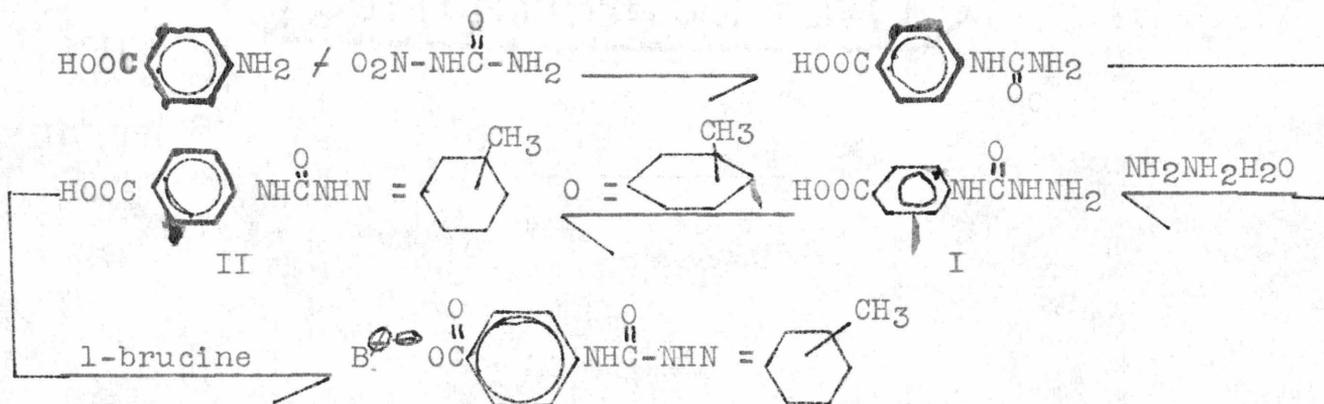
In 1953, however, a novel method was introduced by Dr. James K. Shillington. The essence of this method is that a racemic carbonyl is reacted with some reagent to form a racemic temporary intermediate which is either an acid or base. This intermediate is in turn reacted with an optically pure base or acid to form a diastereoisomeric salt. The salt is resolved by fractional recrystallization and the optically pure form of the carbonyl compound is recovered by hydrolysis



What are the advantages of this new method? The tedious process of making an optically active reagent without knowing if it will resolve the carbonyl compound is not present in this method. The ketone, however, cannot be easily hydrolyzed nor can good yields be obtained from hydrolysis. By using this method, if we find, however, that the racemic acid once reacted with an alkaloid cannot be resolved because of little difference in solubilities of the two isomers, then the alkaloid group may be stripped off by

simple ionic hydrolysis and another alkaloid added. This is caused by the strength of a covalent bond versus the strength of an ionic bond. Although the new method may take more time, the versatility of it far outdoes its faults.

In August of 1957, the first resolution of a ketone by this method was reported by James K. Shillington, et al.³ The following is a short resume of that resolution:



The brucine salt was resolved by recrystallization from methyl alcohol, and when hydrolyzed the levototatory ketone form was obtained.

Since 1957 the results of this method have not been as gratifying. Several possible intermediates have been made, but as of yet no other resolutions have been completed. For a complete survey of the research done on this method the reader should consult the work of the following men:

William B. Guenough, III, "The Synthesis of a Bifunctional Reagent for Carbonyl Compounds," Amherst College, 1953.

- Alexander Choate, "The Resolution of dl-Benzoin via the Carboxymethoxime," Amherst College, 1953.
- David M. Lemal, Summer Report, Washington and Lee University, September, 1955.
- O. B. Ramsey, Summer Report, Washington and Lee University, September, 1956.
- Thomas P. Foley, Jr., Summer Report, Washington and Lee University, September, 1958.
- David D. Reys, Summer Report, Washington and Lee University, September, 1959.
- Rardon Bevill, "The Synthesis and Investigation of Hydrazido-malonic Acid," May, 1960.
- Thomas C. Imeson, II., "The Synthesis and Investigation of Hydrazidoterephthalic Acid," May, 1960.
- Henry C. Hawthorne, Jr., Summer Report, Washington and Lee University, September, 1961.
- George B. Fozzard, Summer Report, Washington and Lee University, September, 1961.
- Robert M. Auburn, Summer Report, Washington and Lee University, September, 1962.
- John Mack Roper, "An Investigation of the use of N-(3-Carboxyhydrazidopropanyl)-4-Aminobenzoic Acid as a Resolving Agent for Racemic Carbonyl Compounds," Washington and Lee University, May, 1963.
- Edward B. Eadie, Jr., Research Report, Washington and Lee University, May, 1963.
- George S. Denning, Jr., "Some Investigations of the Preparation of 4-(4-Carboxyphenyl) Semicarbazide and its Camphor Derivative," Washington and Lee University, June, 1954.
- George S. Denning, Jr., Summer Report, Washington and Lee University, September, 1955.
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Rardon Bevill, Summer Report, Washington and Lee University, September, 1960.

O. B. Ramsey, "The Use of 4-(4-Carboxyphenyl)-Semicarbazide in the Resolution of 3-methyl cyclohexanone," Washington and Lee University, June, 1955.

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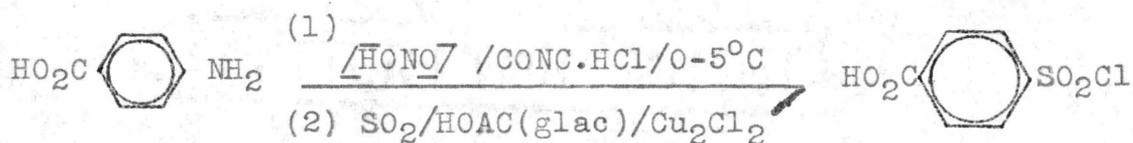
John Paul Freeman, "The Use of Potassium Hydrazidooxalate in the Resolution of Racemic Ketones," Washington and Lee University, June, 1959.

DISCUSSION

The intermediate worked with was p-carboxyphenyl-sulfhydrazone. The project was begun in the fall of 1962 by Edward B. Eadie, Jr. Little progress was made, however, in the synthesis of this intermediate until the spring of 1963. Since then the preparation of the intermediate has been found to be very satisfactory.

4-Chlorosulfonylbenzoic Acid (4-CSBA).

This starting material, which was received extremely impure⁴, was first recrystallized from benzene but we had very little luck with this procedure. The trash and color of this material was believed to have given a cream tan color to all of the compounds. During the summer of 1964, the 4-CSBA was made in the laboratory and was obtained quite pure.⁵



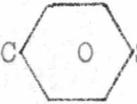
The derivatives made from this material were of a very white nature, but upon standing tended to slowly change to tan. Larger quantities of the 4-CSBA can be made, but one must be careful to add a sufficient amount of catalyst.

p-Toluenesulfonylhydrazine

This experiment, which paralleled a preparation taken

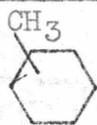
from the literature^{6,7} was run to gain experience in working with this type of compound. The experiment was straightforward and no difficulty was encountered.

p-Carboxybenzenesulfhydrazide.

In the preparation of HO_2C  SO_2NHNH_2 as little heat as possible should be used. Through experience and also from the literature, it was found that hydrazines decomposed with heat. The gradual change in color with time was probably caused by decomposition. One is thus advised to keep the material out of light of any type and in a cool place. When filtering, filter-aid should be used. It appears not only to filter faster but also clears up the solution. Do not use charcoal; it was found to do little good and has a history of being detrimental to hydrazides. Different pH's were used in an effort to find the "isoelectric point," but because of limited equipment this was impossible. A pH of 3 does seem to be quite adequate, giving yields in the 80-85% range. If this pH is overshot, base can be used for the return with no ill effects. A major problem was to dry the intermediate with very little heat. It was left at room temperature for several days (very slow process), dried in vacuum pistol with P_2O_5 at 64°C . under reduced pressure. The best method for quickness and lack of heat was to pull dry for one day at approximately 0.5mm pressure. A very white fluffy powder was thus ob-

tained. The melting point depended upon the rate at which it was taken, but by setting the rate reproducible MP's were obtained.

3-Methylcyclohexylidene-4-Carboxybenzenesulphydrazone.

In making dl  = NNSO_2  CO_2H , the major problem again was to overcome the heat. At first it was impossible to run quantities larger than 1/g., but upon practice runs of 10 and even 25 gs were made with little trouble. Metal beakers were used in an effort to cool the solution more quickly, but little was accomplished. (Do not scrape the inside of copper beakers because part of metal will also scrape off. Might use plastic scraper.) If the heat is not reduced quickly after adding the ketone small yellow balls form. This is believed to be the precipitate partially dissolved in excess ketone. When dried in the pistol the ketone is either boiled off under the reduced pressure or is taken up by the P_2O_5 . This theory is without proof except for the fact that after drying the yellow balls were no longer present. Because of the heat factor it was decided that it was best to dry at room temperature and about 0.5mm pressure. A white fluffy powder was obtained in this way with no sign of yellow balls. It is best to prepare the compound just before using for it decomposes with time.

Brucine Salt of 3-Methylcyclohexylidene-4-Carboxybenzene-sulfhydrazone.

In the resolution of the brucine salt many different solvents (and mixtures of solvents) were tried. The general procedure was to find a solvent that the derivative and brucine were soluble in and in which the brucine salt was insoluble. The solubility of ^{the} salt was tested by making the salt by heating to dryness a mixture of brucine and derivative in ethanol. The salt was found to be too soluble in most solvents tried. Among the ones tried for resolution were MeOH, EtOAc, DMSO, and benzene. None of these seemed to work very well. A mixture of benzene and hexane was also tried. For further particular information on this part of resolution one should see Allen: Summer Research Notebook - 1964. This line of resolution was abandoned because an apparently more desirable one had developed.

The new method used, was reacting brucine and the derivative in a mole ratio of 1/2. The solvent used was an excess of benzene. Brucine is soluble in benzene; the salt is soluble in benzene; but the derivative is not. Therefore the residue (solid) left unreacted was the derivative. It was believed (and hoped) that one form of the salt would be more soluble than the other. A run was made in this fashion and a polarimeter reading was taken, and rotation was found. Variations of amount, temperature, length of refluxing, and

amounts and times of washing were tried. A derivative was made from the 1-3-methylcyclohexanone. A reading was taken on this and the $[\alpha]_{\text{DMF}} = -11.55^{\circ}$. This compared to a $[\alpha]_{\text{DMF}} = -13.99^{\circ}$ in DMF for the derivative we had been working with. Apparently the resolution had been accomplished. The more minus rotation was believed to be caused by brucine that had not been or could not be washed off.

Hydrolysis of Brucine Salt

The hydrolysis of the apparently resolved salt was accomplished by mixing the derivative with an excess of 9N H_2SO_4 and refluxed the mixture while it was being stirred mechanically. A steam distillation was then carried out; the distillate was extracted with ethyl ether several times. (Note saturated salt water had to be added for good separation between layer). The ether was stripped off and the apparently resolved ketone thus obtained.

3-Methylcyclohexanone Semicarbazone

A derivative of this apparently resolved ketone was made and its rotation checked against that in the literature. The semicarbazone derivative was used. By following the directions found in literature, the derivative was made and a $[\alpha]_{\text{EtOH}}$ of -8.05° was found for the ketone derivative. In Heilbron, Dictionary of Organic Compounds, Vol. III the $[\alpha]_{\text{EtOH}}$ for 1-3-methylcyclohexanone semicarbazone was

given as -20.8° thus it was believed that a partial resolution of 3-methylcyclohexanone had been accomplished. Upon further runs of the 1/2 ratio it became apparent that a complete resolution could not be accomplished by this method.

Ephedrine Salt of 3-methylcyclohexylidene-4-carboxybenzene-sulphhydrazone

The Ephedrine Salt was made in a similar manner to the brucine salt but in a 1/1 ratio. The salt, however, was found to be too soluble in all solvents used to be practical for resolution. Some of the solvents used were DMSO, DMF, nitromethane, acetonitrile, benzene, H_2O , and methyl alcohol.

Cinchonidine Salt of 3-methylcyclohexylidene-4-carboxybenzene-sulphhydrazone

It was found that the salt could be recrystallized from MeOH. The salt required a very large amount of MeOH to dissolve after which the volume could be reduced considerably and upon standing crystals would form. A typical reduction in volume would be from 75 mls to 10 mls. The melting point and rotation varied directly. After about ten recrystallizations, each requiring a larger amount of MeOH to dissolve the salt, a melting point of $245-46^{\circ}C$ and a $[\alpha]_{DMSO}$ of -67.7° was reached. At all times the salt had a distinct ketone smell. The crystals grew in the form

of igloos and reached the size of 1/2 inch in diameter. The crystals were very white but upon long standing formed a cream tan outer coating.

Hydrolysis of Cinchonidene Salt

A hydrolysis was carried out of some of the salt with a melting point of 245-46°C in the same manner as that used on the brucine salt, but no ketone was obtained. Trial runs were then made on the old salt by the previous hydrolysis method and also by refluxing salt in a saturated solution of oxalic acid and then extracting with methylene chloride. In both of these cases ketone was obtained. Then the salt melting at 245-46° and $[\alpha]_{\text{DMSO}}^{-67^\circ}$ was refluxed in saturated solution of oxalic acid. No ketone was obtained. It thus appeared that during the many recrystallizations the ketone had been hydrolyzed off and permanently lost.

Cinchonidene Salt of p-carboxybenzenesulphidrazone

The salt was made to determine if the ketone was being hydrolyzed off during the resolution. The crystals obtained, however, were a very pure form of 4-carboxybenzenesulphidrazide. Due to lack of time no further experimentation was done along this line.

EXPERIMENTALp-Toluenesulfonylhydrazide

To p-toluenesulfonyl chloride (9.32 g) in 25 ml benzene, 10 gs. hydrazine hydrate was added and shaken by hand till no more heat evolved. It was filtered, dried, and recrystallized from CHCl_3 .

Wt. = 6.0 gms

MP = 109-110°C

p-Carboxybenzenesulphhydrazide

To 10.0 gms 4-chlorosulfonylbenzoic acid, 300 ml Benzene was added and stirred mechanically for ten (10) minutes to form a slurry. Then 10.4 ml of 100% hydrazine hydrate and 350 ml of H_2O were added and stirring was continued for one or two minutes. To this mixture three large scoops of filter-aid were added and this was filtered under suction. The two layers of filtrate were separated and to the water layer, 20 ml of 20% HCl was added (pH3). The white precipitate was filtered off and dried at 0.5mm pressure and at room temperature.

MP - 198-200°C (explosion with white smoke at rate of ten (10))

% Yield = 82%

NE = 217

3-Methylcyclohexylidene-4-carboxybenzenesulphydrazone

To 1.0 gs of p-carboxyphenylsulphydrazide, 50 ml H₂O was added and the mixture was heated to 95-98°C or where became almost clear solution. It was then hot filtered directly into an ice-cold filter flask containing 0.5 ml of 3-methylcyclohexanone which was being stirred by a magnetic stirrer. The white crystals were dried at room temperature and under a pressure of 0.5mm.

MP = 161-61.5°C (Rate of 4)

NE = 154-55

% Yield = 81%

Hydrolysis and isolation of 3-methylcyclohexanone from
3-methylcyclohexylidene-4-carboxybenzenesulphydrazone

In a 1000 ml round bottom flask was placed 5.67 gs of 3-methylcyclohexylidene-4-carboxybenzenesulphydrazone and 11.0 ml 9N H₂SO₄, and the mixture refluxed for ten minutes. The flask was then assembled in a steam distillation set up and the steam distillation carried out. Ten ml of saturated NaCl solution was added and the mixture was extracted five times with ten ml portions of ethyl ether. The ethyl ether extract was dried over anhydrous Mg₂SO₄. The ether was stripped off and the ketone distilled.

BP = 162-168°C

Yield = .56 ml

3-Methylcyclohexanone Semicarbazone

In 4-5 ml of H₂O was dissolved 1.3 gs of semicarbazide hydrochloride and 1.95 gs sodium acetate. This was filtered under suction and the filtrate added to 0.5 ml of 3-methylcyclohexanone dissolved in 2 ml of MeOH (acetone free). White crystals were filtered off and dried in oven at 110°C. Recrystallized from methyl alcohol-water mixture.

MP = 180-182°C; Lit. MP = 181°C⁸

Ephedrine Salt of 3-methylcyclohexylidene-4-carboxybenzenesulfhydrazone

Into 75 ml of MeOH was placed 2.0 gs of 3-methylcyclohexylidene-4-carboxybenzenesulfhydrazone and 1.2 gs Ephedrine. The mixture was taken to dryness over steam. Crystals were formed from the resultant glue by scratching.

MP = 57-93°C

Cinchonidine Salt of 3-methylcyclohexylidene-4-carboxybenzenesulfhydrazone

Into 2 l of MeOH was placed 24.05 gs of 3-methylcyclohexylidene-4-carboxybenzenesulfhydrazone and 26.0 gs cinchonidine. The volume was reduced 1300 ml. The crystals were recrystallized from MeOH.

MP = 246-47°C

$[\alpha]_{\text{D}}^{\text{DMSO}} = -66^{\circ}$

Cinchonidene Salt of 4-carboxybenzenesulphydrazide

To 150 ml MeOH was added 2.0 gs 4-carboxybenzenesulphydrazide and 1.9 gs of cinchonidene. The volume was reduced to approximately 25 ml. On standing crystals formed. These were filtered off and dried. Crystals were very pure 4-carboxybenzenesulphydrazide.

MP = 197°C (explosion)

NE = 217

Hydrolysis of Cinchonidene Salt

Reflux 3.0 gs of salt and 25 ml of saturated solution of oxalic acid for ten minutes. Extract the mixture with five 10 ml portions of methylene chloride and then strip off methylene chloride.

Yield = 0.0

NOTE: This method is the best method for the hydrolysis of the salts. Do not use the other.

SUMMARY

The reagent has been made and it seems to be stable. There is doubt, however, as to the purity of the ketone derivative. Further investigation of this derivative should be carried out especially as to the ease of hydrolysis.

A combination of some type using the two methods of resolution (spoken of in this thesis) should be done. Also one should run a study of infrared on the different compounds. This study could be useful for the determination of the presence of the ketone.

In conclusion it appears that theory is still ahead of reality, but this may well be from the inexperience of the researcher with resolutions.

FOOTNOTES

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