

THE USE OF POTASSIUM HYDRAZIDOOXALATE  
IN THE RESOLUTION OF RACEMIC KETONES

A THESIS

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BY

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VITA

John Paul Freeman was born in Washington, D. C. on August 30, 1937, the first son of Mary Paul Barclift Freeman and John Elmer Freeman, Jr. He attended elementary schools in Hartselle, Alabama, Washington, D. C., and Atlanta, Georgia and high school in Atlanta at North Fulton High School. Having graduated from North Fulton in May, 1955, he entered Washington and Lee University the following September.

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## INTRODUCTION AND HISTORICAL REVIEW

This paper deals with a reasonably simple problem in laboratory technique which has long been crying for an answer: how does one resolve a racemic compound whose only principle function is a carbonyl group?

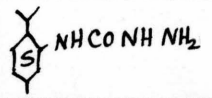
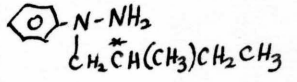
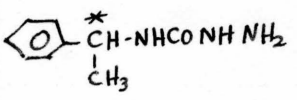
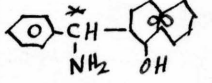
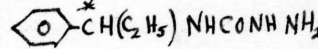
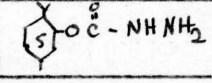
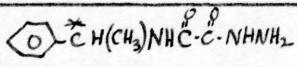
The problem is very similar to that of the separation and identification of carbonyl compounds; this problem has been solved for all practical purposes by the discovery of several selective reagents which, when condensed with a wide range of carbonyl-containing compounds, give a characteristic melting point below 250° for each. In addition, these reagents are so constructed such as to allow separation of the carbonyl compound from mixture or solution on the basis of differentiating solubility properties of the condensate. Bifunctional reagents (containing at least one carboxy group) provide a means of ascertaining molecular weights by the method of Neutral Equivalents.

The same general method has been applied to the resolution of carbonyl compounds. For about fifty years, beginning in 1903, a few aldehydes and ketones were resolved by a method of condensing the racemic carbonyl with the optically pure form of a substituted semicarbazide, semioxamazine, hydrazide, or hydrazine and separating the resulting diastereoisomers by fractional crystallization. The pure optical antipodes were then each recovered from their corresponding crystallization fractions by hydrolysis. Table I following summarizes the work up to 1953. For a detailed discussion on the difficulties of this approach to resolution, the reader is referred to the thesis of W. B. Greenough, III.<sup>1</sup>

In 1953, work was begun by J. K. Shillington and W. B. Greenough, III on a new approach to the problem of carbonyl resolution. Their idea was to synthesize a non-optically active intermediate which would give, upon reacting with the carbonyl group, a stable, solid condensate, easily

TABLE I

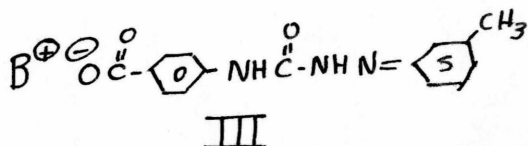
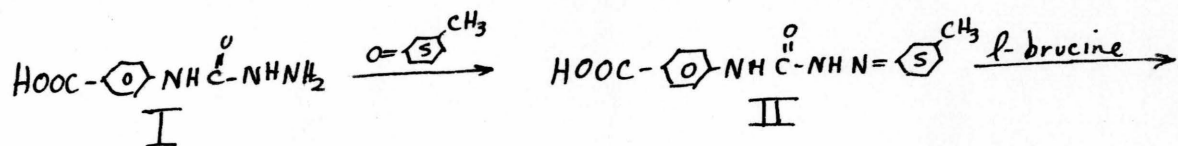
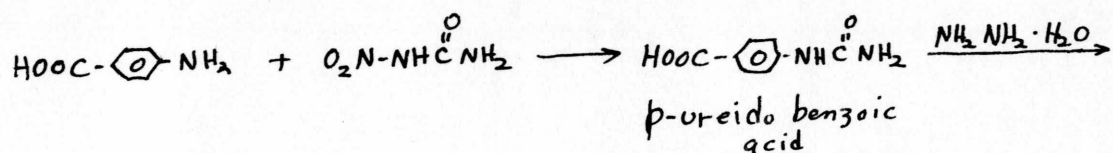
History of resolution via carbonyl group by use of optically active carbonyl reagents

|     | DATE | BY                         | LIT. REFERENCE                                   | REAGENT'S NAME                                  | REAGENT'S STRUCTURE   | CARBONYL COMP. RESOLVED        |
|-----|------|----------------------------|--|---|---|--------------------------------|
| 1.  | 1903 | Carl Neuberg               | <u>Ber.</u> , <u>36</u> , 1192 (1903).           | l-menthyl semicarbazide                         |    | dl-arabinose                   |
| 2.  | 1905 | Neuberg & Federer          | <u>Ber.</u> , <u>38</u> , 868 (1905).            | d-amyl phenylhydrazine                          |    | dl-arabinose<br>dl-galactose   |
| 3.  | 1928 | Hopper & Wilson            | <u>J.Chem.Soc.</u> , <u>1928</u> , 2483.         | d & l 4-(1-phenylethyl semicarbazide            |    | dl-benzoin                     |
| 4.  | 1930 | Betti & Pratesi            | <u>Ber.</u> , <u>63B</u> , 874 (1930).           | (2-naphthol-1)phenylamino methane               |    | dl-p-methoxy-hydratropaldehyde |
| 5.  | 1934 | Crawford & Wilson          | <u>J.Chem.Soc.</u> , <u>1934</u> , 1122.         | l-menthyl semicarbazide                         | See #1  | dl-benzoin                     |
| 6.  | 1934 | Betti & Pratesi            | <u>Biochem.Z.</u> , <u>274</u> , 1-3 (1934).     | (2-naphthol-1)phenyl-amino methane              | See #4  | dl-glycer-aldehyde             |
| 7.  | 1940 | A.J.Little, <u>et al</u>   | <u>J.Chem.Soc.</u> , <u>1940</u> , 336.          | d-4-(1-phenylpropyl) semicarbazide              |  | dl-benzoin                     |
| 8.  | 1941 | R.B.Woodward, <u>et al</u> | <u>J.Am.Chem.Soc.</u> , <u>63</u> , 120 (1941).  | l-menthylhydrazide (1-menthyl N-aminocarbamate) |  | dl-camphor                     |
| 9.  | 1943 | H.Sabotka, <u>et al</u>    | <u>J.Am.Chem.Soc.</u> , <u>65</u> , 1916 (1943). | l-menthyl hydrazide                             | See #8  | dl- $\alpha$ -ionone           |
| 10. | 1950 | Leonard & Boyer            | <u>J.Org.Chem.</u> , <u>15</u> , 42 (1950).      | 5-(1-phenylethyl)semioxam-azide                 |  | dl-3-methylcyclo-hexanone      |

hydrolyzable for regeneration of the aldehyde or ketone and which would, by means of a carboxy function, be able to form resolvable salts with commercially obtainable, optically active bases. By this method, the laborious task of synthesizing an optically active carbonyl reagent was eliminated. Furthermore, once a satisfactory intermediate was found and condensed with some racemic aldehyde or ketone, salts of different optically active bases could be tried successively with a minimum of effort until one was found which permitted resolution.

It should be noted at this point that the requirements for a suitable resolving agent are compounded over the requirements for a mere identification reagent; the resolving agent must not only condense with a wide range of carbonyl compounds, but its optical antipodes for each condensate must have solubility properties sufficiently different to allow separation. Past research as summarized in Table I indicates that this is almost too much to ask of a single reagent; thus, the new approach to resolution is, if anything, an effort to face reality, realizing that although the eventual resolution procedure achieved by using a non-optically active intermediate may be longer than that when an optically active reagent is used directly, nonetheless, we will probably in the long run discover resolution methods for more compounds more rapidly with this new method.

At the present time there is a wide gap between the above theory and laboratory application. In real life and practice, only a single resolution of a single racemic ketone by a single intermediary has so far been successful. In August of 1957, J. K. Shillington, et al<sup>2</sup>, reported the successful synthesis and use of 4-(4-carboxyphenyl)-semicarbazide (I) in the resolution of 3-methylcyclohexanone with l-brucine alkaloid as the active base. The total reagent synthesis and resolution are given below:

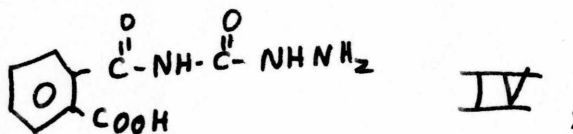


where  $\text{B}^{\oplus} = (\text{l-brucinium})^{\oplus}$  ion

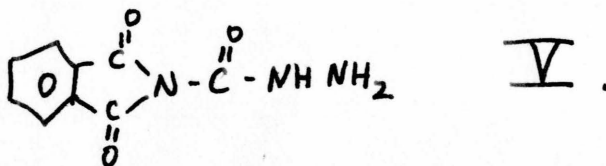
The racemic salt (III) was resolved using methanol as a solvent. The optically pure levorotary salt obtained was acidified to give the free acid (II) which was then hydrolyzed to give pure 1-3-methylcyclohexanone.

The difficult synthesis of the reagent (I) as well as the expense of the starting reagents has prompted the search for a new reagent.

In 1953, Greenough<sup>1</sup> explored the possibilities of building the mono-semicarbazide of phthalic acid,

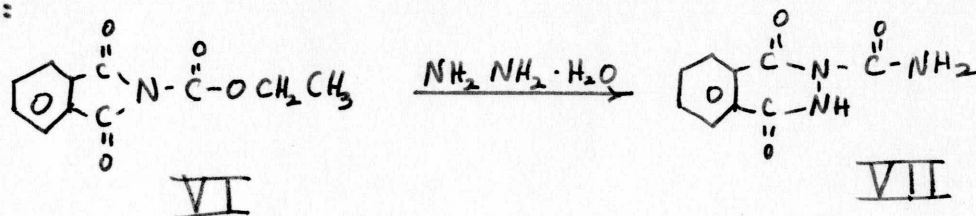


by way of the 4-phthalylimide of semicarbazide,

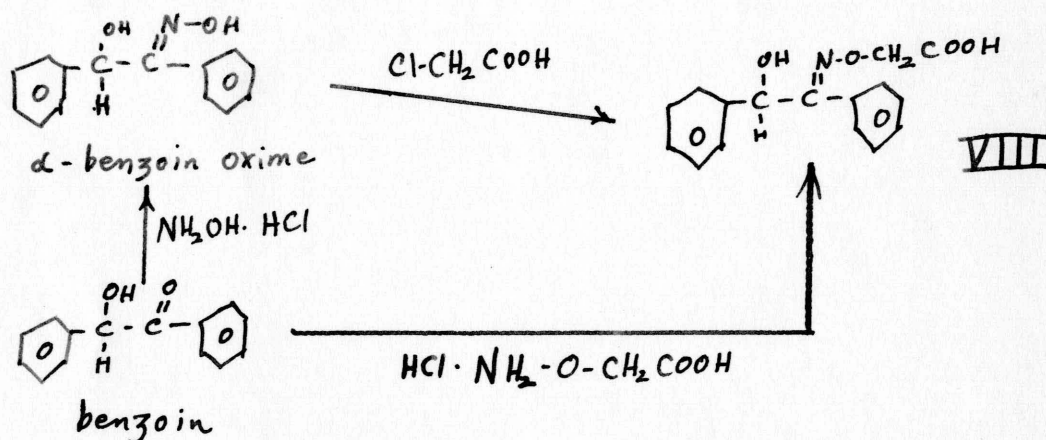


He found, however, that attempted conversion of ethyl 1,3-diketo-2-isoin-

dolinecarboxylate to V probably gave instead a binitrogen phthalazine ring:

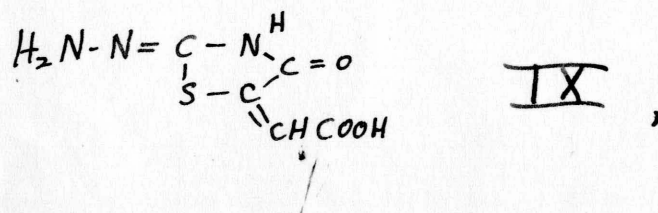


The resolution of dl-benzoin was attempted in 1953 by Alexander Choate<sup>3</sup> by two methods which involved the synthesis of benzoin's carboxymethoxime (VIII).



Compound VIII was not prepared by either route in high enough yields to attempt resolution. Two years later, David Lemal<sup>4</sup> succeeding in preparing enough of the carboxymethoxime of dl-camphor (8.4 gm) by the oxime route (supra vide) to achieve about 50% resolution of l-camphor using l-brucine as the resolving base. This work has never been followed up.

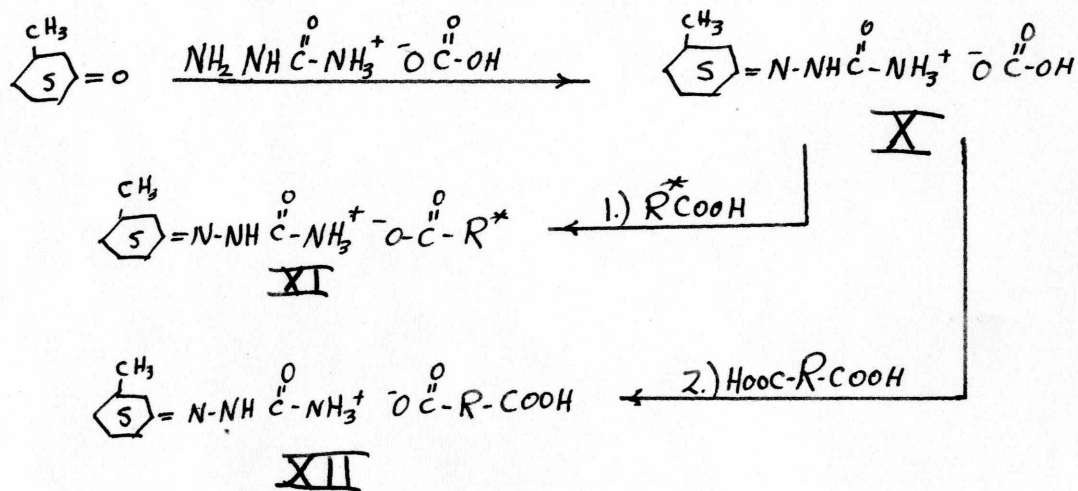
Concurrently with the work of Greenough and Choate, J. K. Shillington<sup>5</sup> was investigating the use of 2-azino-4- $\Delta^{5\alpha}$ -thiazalidene-acetic acid,





as a resolution intermediate. He succeeded in preliminary work in synthesizing the benzaldehyde and benzophenone derivatives of IX. However, due to the great insolubility of this group of compounds in almost any solvent, purification by recrystallization was made extremely difficult, and the project was abandoned as impractical.

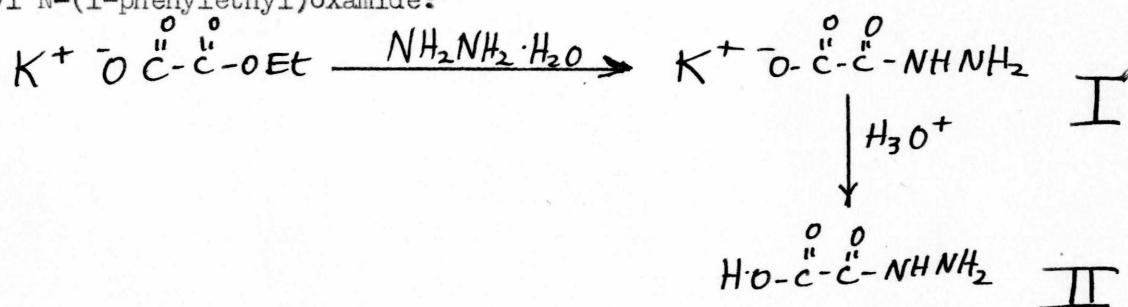
In the summer of 1958, J. K. Shillington and T. P. Foley, Jr.<sup>6</sup> explored the use of amino guanidine as a resolution intermediate. First, amino guanidinium bicarbonate was condensed with dl-3-methylcyclohexanone and the condensate (X) then reacted either with (1) an optically active acid or (2) a dicarboxy acid whose second carboxy group could be used in turn to form a salt with an optically active base:



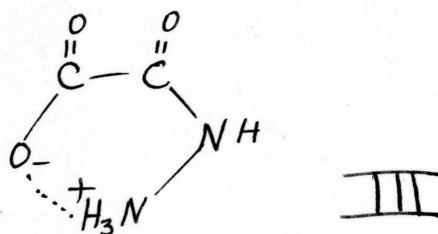
Acids of type (1) included l-mandelic, d-mandelic, d-tartaric, d-dibenzoyltartaric, d-diacetyltartaric, and l-malic. Type (2) acids tried were oxalic and succinic. In every case, an impasse was reached in finding a suitable recrystallization solvent for the condensate salts XI and XII. Most salts gave only amorphous solids or honeys upon recrystallization.

DISCUSSION

This paper is concerned with the use of potassium hydrazidoöxalate (I) as an intermediate reagent for resolving racemic ketones. The original plan was to use the free acid (II) for this resolution. It was easily obtained from the potassium salt by acidification. Potassium hydrazidoöxalate (I) was obtained in turn by the hydrazination of potassium ethyl oxalate in a manner analogous to Leonard and Boyer's hydrazination of ethyl N-(1-phenylethyl)oxamide:<sup>7</sup>



However, efforts to condense the free acid (II) with cyclohexanone failed. It is proposed that the free hydrazidoöxalic acid exists not as II, but as the zwitterion,

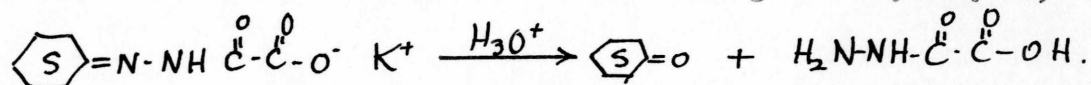


due to five-membered drive.

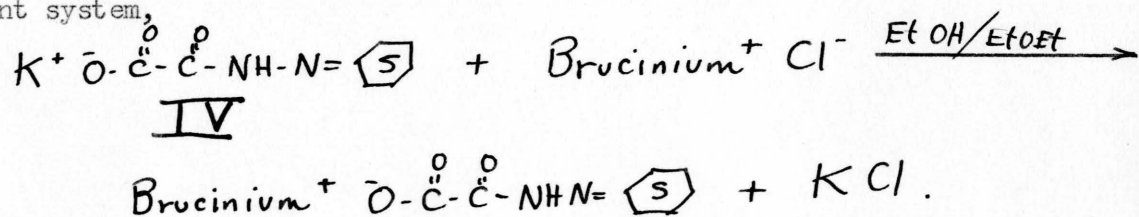
As a result of the foregoing failure, efforts were channeled to condensing cyclohexanone with potassium hydrazidoöxalate (I). Having succeeded in this, condensation was also achieved with dl-3-methylcyclohexanone. Condensations had to be run in strictly anhydrous conditions, for the condensates are all very susceptible to hydrolysis. The reaction is carried out using anhydrous benzene as a solvent which removes water of condensation as it forms. A small crystal of iodine is a neces-

sary catalyst.

The next step was to secure salts of these condensates with some optically active base. 1-Brucine was chosen due to its successful performance with 4-(4-carboxyphenyl) semicarbazide<sup>2</sup> and its (then) ready availability.<sup>8</sup> Here was encountered a new problem for, in our hands, the conversion of the potassium salts to the free acids invariably resulted in liberation of the attached ketone through acid hydrolysis,

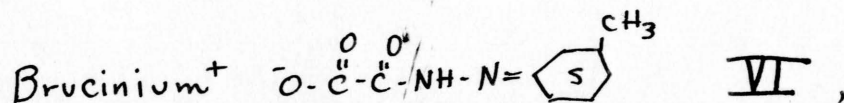


It appeared, then, that the potassium salts would have to be converted to brucinium salts directly. This could conceivably be done by reacting a potassium condensate salt such as IV with brucinium chloride, and, using the proper solvent system, precipitate out the brucinium hydrazono-oxalate condensate while retaining potassium chloride or vice versa in solution. This scheme was first performed successfully with potassium cyclohexylidenehydrazono-oxalate (IV) using an anhydrous ether-ethanol solvent system,



Solid V gave a positive brucine test,<sup>9</sup> and a negative silver nitrate test for chloride.

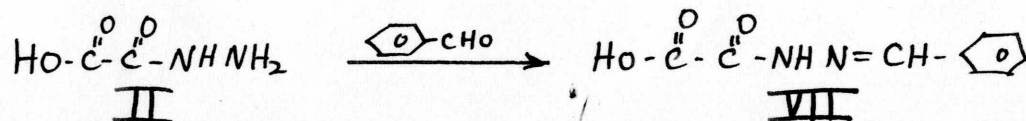
On the basis of the above results with the cyclohexanone derivative, it was decided to go ahead with the analogous synthesis using the optically active reagent, 3-methylcyclohexanone. The white, igloo-shaped crystals of brucinium dl-3-methylcyclohexylidenehydrazono-oxalate,



also gave a good positive test for brucine,<sup>9</sup> a negligible  $\text{AgNO}_3$  test for chloride, and a good test for the presence of the 3-methylcyclohexylidene function. (Acid hydrolysis produced a characteristic ketone odor, and a liquid which was identified successfully as 3-methylcyclohexanone by the preparation of the semicarbazone derivative.)

Since only a small portion of VI was prepared in this pilot run, it was impossible to proceed directly to the resolution. However, some trial recrystallizations of VI from methanol showed a good solubility relationship between solvent and solute. A portion of VI recrystallized nicely from a methanol-ether pair.

In addition to this main line of experimentation, it seemed desirable to make some correlation between our work and the literature. To this end we sought to convert some of our hydrazidoöxalic acid (II) into hydrazidoöxalic acid hydrochloride for which Curtius, et al<sup>10</sup>, gave a melting point of 128-9°C. Direct conversion proved impossible: mixing solid II with hydrochloric acid solution gave only the original reagent back; solid II was then suspended in dimethylformamide and gaseous HCl bubbled through until solution was completed, but then the salt, if present, could not be removed from solution; gaseous hydrogen chloride bubbled through anhydrous ethyl ether in which II was suspended gave only II back. At this point it was decided to try the round-about procedure described by Curtius.<sup>10</sup> Hydrazidoöxalic acid (II) was converted directly to benzylidenehydrazonoöxalic acid (VII) by reaction with benzaldehyde ~~in~~ in anhydrous conditions,



Compound VII melted at 172-3 (corr.) (Lit: 179-180<sup>10</sup>) after recrystalliza-

tion from hot water. This condensate was then hydrolyzed with conc. HCl and the resulting solid dried in a vacuum desiccator over potassium hydroxide. This melted at  $126.5^{\circ}$  (corr.) with decomposition and gave a Volhard chloride determination <sup>11</sup> of 23.40% (theoretical: 25.23%). These measurements, although at some variance with standards, do tend to validify our work.

EXPERIMENTAL

NOTE: All melting points are corrected.

POTASSIUM ETHYL OXALATE.<sup>12</sup> - A mixture of 143 gm. (132.5 ml., 0.98 mole) diethyloxalate<sup>13</sup>, 100 gm. (1.02 mole) potassium acetate,<sup>14</sup> and 100 ml. water were mechanically stirred and heated on a steam-bath until homogeneous, about 1 1/2 hrs. Mixture evaporated under vacuum to 100 ml., cooled, and 200 ml. 95% ethanol and 600 ml. ethyl ether added. Highly hygroscopic precipitate filtered and dried in vacuum desiccator over conc. H<sub>2</sub>SO<sub>4</sub>; yield 139.3 gm. (100%).

POTASSIUM HYDRAZIDOOXALATE. - A slurry was made of 31.2 gm. (0.2 mole) potassium ethyl oxalate in 100 ml. absolute ethanol and 3 ml. water, to which 16 ml. (0.204 mole) hydrazine hydrate was added at once. The thickened mass was diluted with 80 ml. absolute ethanol, warmed briefly on a steam-bath, cooled, filtered, and washed with 25 ml. absolute ethanol. Product was dried in an oven at 105°, found to be stable and non-hygroscopic; yield 27.0 gm. (95%), contracting and browning but no m.p.

HYDRAZIDOOXALIC ACID. - 7.2 gm., (0.051 mole) potassium hydrazidooxalate was dissolved in 20 ml. water and acidified to pH2 with about 26 ml. of 5% hydrochloric acid. Flask chilled and precipitate filtered, washed with cold water, and set to dry; yield 3.96 gm. (76%), m.p: contraction 242°, m.p. 246.8-248.9° with decomposition (sealed). In open m.p. tube, steady decomposition was observed from 235° to 295° with no sharp m.p.; this corresponds to Curtius'<sup>10</sup> observation of no m.p. up to 300°. A silver nitrate test for chloride did not give even a milky solution. Recrystallization accomplished from hot water in return yields of 10-37%; best m.p: contraction 244°, m.p. 247.9-248.8 with decomposition (sealed).

BENZYLIDENEHYDRAZONOÖXALIC ACID. - A mixture of 0.5 gm. (.0048 mole) hydrazidoöxalic acid, 0.522 gm. (.5 ml., 0.0049 mole) benzaldehyde, 110 ml. absolute ethanol, and a small crystal of iodine were heated to boiling on a hot plate. Mixture was transferred to a distilling flask and all but 10-20 ml. distilled off; 40 ml. water added; mixture cooled in refrigerator and filtered. Resulting crystals recrystallized from hot water, filtered, and dried; yield 0.3 gm. (33%), m.p. 172-3° (Literature<sup>10</sup> gives 179-180°), pH=1 in water. Heating on crucible lid gives noticeable benzaldehyde odor.

HYDRAZIDOÖXALIC ACID HYDRACHLORIDE.<sup>10</sup> - A mixture of 0.3 gm. (.00156 mole) benzylidenehydrazonoöxalic acid and 1.2 ml. concentrated hydrochloric acid were stirred together in a platinum crucible with a glass stirring rod. Resultant pasty solid washed in the crucible 6 times with benzene (decanting washings off) to remove the cleaved benzaldehyde, then dried thoroughly by leaving it in vacuum desiccator for two days over potassium hydroxide; m.p: contraction and softening 120.5°, decomposition 126.5° (Literature<sup>10</sup> gives 128-129°), Volhart chloride determination<sup>11</sup> 23.40% (Theoretical: 25.23%).

POTASSIUM CYCLOHEXYLIDENEHYDRAZONOÖXALATE. - Benzene made anhydrous by distilling off several ml. of cloudy forerun. To approx. 15 ml. left in distilling flask was added 4.91 gm. (5.18 ml., 0.05 moles) freshly distilled cyclohexanone and 3.55 gm. (0.025 mole) potassium hydrazidoöxalate. Distilling arm was corked and inclined just above horizontal, a crystal of iodine added as catalyst, and mixture refluxed gently for one hour after which setup <sup>was</sup> ~~is~~ rearranged for distillation and most of the benzene removed; bath not taken over 140° due to fear of decomposition of product. Flask cooled; solid removed, washed with benzene, filtered,

dried, and weighed; yield 4.85 gm. (96%), good potassium flame test,  $\text{pH}=5$ , browning, but no m.p. up to  $300^\circ$ . A 0.75 gm sample refluxed for fifteen min. with 5 ml. 3 M sulfuric acid. Resulting cooled liquid extracted thrice with 10 ml. portions of ether and etherial solution dried for three hours over anhydrous magnesium sulfate, filtered, and distilled with a Vigreux column and a water bath whose temperature was kept below  $90^\circ$ . Residual yellow oil dissolved in 35 drops methanol and a mixture of 1 gm. semicarbazide, 1.8 gm sodium acetate trihydrate, and 10 ml. water added with cooling. Resulting crystals of cyclohexylidene semicarbazone filtered, recrystallized from hot water, and dried five min. in  $105^\circ$  oven; m.p.  $162-165^\circ$  (Literature gives  $166^\circ$ ).

POTASSIUM dl-3-METHYLCYCLOHEXYLIDENEHYDRAZONOÖXALATE. - Benzene distillation forerun discarded. To approx. 15 ml. left in distilling flask was added 4.74 gm. (5.18 ml., 0.042 moles) dl-3-methylcyclohexanone<sup>13</sup>, 3.55 gm. (0.025 mole) potassium hydrazidoöxalate and a crystal of iodine. Mixture refluxed one hour, benzene distilled off, product filtered, washed thrice with benzene, dried, and weighed exactly as had been done when preparing cyclohexane's derivative; yield 5.2 gm. (88.2%).

EIGHT ATTEMPTED SYNTHESSES OF CYCLOHEXYLIDENEHYDRAZONOÖXALIC ACID. - 1.) A mixture of 5.18 ml. (0.05 moles) cyclohexanone, 2.61 gm. (0.025 moles) hydrazidoöxalic acid, 15 ml. anhydrous benzene, and a crystal of iodine were refluxed for an hour in the manner described for potassium cyclohexylidenehydrazonoöxalate, but no condensate product was obtained.

2.) To a mixture of 0.5 gm. potassium cyclohexylidenehydrazonoöxalate and 10 ml. absolute ethanol was added 0.5 ml. glacial acetic acid. Mixture was heated on steam-bath with solid completely dissolved. In an effort to get acid product out of solution, 20 ml. anhydrous ether added, but only



a sol forms. Gelatinous mass finally precipitated as a solid after addition of 20. ml. absolute ethanol and a few drops of saturated sodium chloride solution. Recrystallization from an absolute ethanol-water pair produced a small amount of white solid with no m.p. up to 250°, pH=4, and a good potassium flame test.

3.) Dissolving 0.5 gm. potassium cyclohexylidenehydrazonoöxalate in 3 ml. of sodium bisulfate solution produced the strong ketone odor of hydrolysis.

4.) Same treatment with 85% phosphoric acid gave strong ketone odor of hydrolysis, heat, and a yellow color.

5.) Same treatment with 10% phosphoric acid again gave hydrolysis and strong ketone odor.

6.) About 0.2 gm. potassium cyclohexylidenehydrazonoöxalate and 0.3 gm. ammonium chloride dissolved in 2 ml. water. Test tube shaken until solids dissolved and absolute ethanol added to get out acid. White solid precipitate gave good potassium flame test and silver nitrate test for chloride ion. It was probably potassium chloride.

7.) 0.3 gm. ammonium chloride dissolved in 5 ml. water and cooled to 0° in an ice-salt bath; 0.5 gm. potassium cyclohexylidenehydrazonoöxalate then dissolved in the solution which was subsequently extracted thrice with 6 ml. portions of ether. Ether distilled off, but no residue remained. Only potassium chloride could be isolated from the water layer.

8.) Small remaining amount of potassium cyclohexylidenehydrazonoöxalate dissolved in minimum water to which was then added a small amount of oxalic acid. Upon cooling in refrigerator, a small amount of brownish sand recovered which had no m.p.

1-BRUCINIUM HYDROCHLORIDE. - A mixture of 22.4 gm. (.048 mole) 1-brucine. $4H_2O$ , 3 ml. (.048 mole) hydrochloric acid, and 40 ml. water in a 150 ml. beaker was heated on a steam-bath until solid dissolved. Solution cooled in refrigerator. Igloo-shaped geods filtered off and recrystallized from hot water. Almost-dry crystals set in a tared beaker in an oil bath at 130° to drive off the water of crystallization and cooled in a vacuum desiccator; yield 20.7 gm(74.9%).

1-BRUCINIUM CYCLOHEXYLIDENEHYDRAZONOÖXALATE. - A mixture of 4.31 gm. (0.1 mole) anhydrous 1-brucinium hydrochloride, 2.22 gm.(0.1 mole) potassium cyclohexylidenehydrazonoöxalate, and 50 ml. absolute ethanol shaken vigorously cold, then heated on a steam bath to boiling, and quickly filtered. Temperature was adjusted to 30° and 70 ml. anhydrous ether and 2 ml. absolute ethanol added to adjust for crystallization. Sample set in a cold room; crystals filtered off, recrystallized from methanol, dried, and tested thus: In a test for brucine by Warren<sup>9</sup>, a small amount placed on a watch glass turned concentrated nitric acid blood red, color changed to violet with stannous chloride addition, then back to red when more concentrated  $HNO_3$  was added. Only a very slight cloudiness produced by a silver nitrate test for chloride. Melting point is very uncertain; sample decomposed over a wide range.

1-BRUCINIUM dl-3-METHYLCYCLOHEXYLIDENEHYDRAZONOÖXALATE. - A mixture of 4.31 gm (0.01 mole) anhydrous 1-brucinium hydrochloride, 2.22 gm (0.0094 mole) potassium dl-3-methylcyclohexylidenehydrazonoöxalate, and 50 ml. absolute ethanol shaken vigorously cold, then heated to boiling on a steam-bath and quickly filtered. Temperature adjusted to 30°, and 50 ml. anhydrous ether added to adjust solubility. Solution cooled under tap water and igloo crystals collected in a Buchner funnel. Experimentation

with recrystallization solvents showed a methanol-ether pair to be best; yield 1.4 gm (25.2%). A good Warren test<sup>9</sup> for brucine was obtained, and the presence of the 3-methylcyclohexylidene function was proved by hydrolyzing off 3-methylcyclohexanone and forming the semicarbazone (see procedure discussion under "potassium cyclohexylidenehydrazono~~o~~oxalate"); semicarbazone's m.p. 169-170.5° (Literature gives 179°). A one decimeter polarimeter tube filled with a saturated solution of the product gave a net rotation of +0.07°. The m.p. was characterized by slow decomposition and no sharp point.

SUMMARY

Results to date look very favorable for the use of potassium hydrazidoöxalate in the resolution of racemic ketones. Condensates have been made with several carbonyls, including optically active 3-methylcyclohexanone, and the l-brucinium salt of this condensate has been prepared. All that now remains is to prepare sufficient l-brucinium dl-3-methylcyclohexylidenehydrazonoöxalate to resolve by fractional crystallization. This procedure is discussed in David Lemal's summer report<sup>4</sup> and in O. B. Ramsay's 1956 summer report<sup>15</sup>. The latter reference discusses the fractional crystallization plan use for the successful resolution of 3-methylcyclohexanone by the use of 4-(4-carboxyphenyl) semicarbazide.

In conclusion, we would be reminded that in this project, as in all risky or experimental undertakings, the rewards are often plenteous, but the gamblers are few.

#### FOOTNOTES

1. William B. Greenough, III, "The Synthesis of a Bifunctional Reagent for Carbonyl Compounds," Amherst College, 1953.
2. J. K. Shillington, G. S. Denning, Jr., W. B. Greenough, III, Trafford Hill, Jr., and O. B. Ramsay, *J. Am. Chem. Soc.*, 80, 6551 (1958).
3. Alexander Choate, "The Resolution of dl-Benzoin via the Carboxymethoxime," Amherst College, 1953.
4. David M. Lemal, Summer Report, Washington and Lee University, September, 1955.
5. James K. Shillington, Laboratory Notebook #2, pp. 164-182, May-July, 1953.
6. Thomas P. Foley, Jr., Summer Report, Washington and Lee University, September, 1958.
7. N. J. Leonard and J. H. Boyer, *J. Org. Chem.*, 15, 42 (1950).
8. Domestic firms have suddenly stopped producing brucine and by May, 1959, have virtually exhausted their supply.
9. W. H. Warren, Detection of Poisons, 6th ed., Philadelphia: P. Blakiston's Son & Co., 1928, p. 173.
10. T. Curtius, A. Darapsky, E. Müller, *Ber.*, 40, 1176 (1907).
11. W. Pierce and H. Haenisch, Quantitative Analysis, 3rd. ed., New York: John Wiley & Sons, Inc., 1956, pp. 300-302.
12. D. A. Shirley, Preparation of Organic Intermediates, New York: John Wiley & Sons, Inc., 1951, pp. 160-161. From F. Adickes, W. Brunnert, and O. Lückner, *J. Prakt. Chem.*, 130, 169 (1931).
13. Eastman Kodak white label.
14. NF grade, used as is.
15. O. B. Ramsay, Summer Report, Washington and Lee University, September, 1956.