

THE SYNTHESIS AND INVESTIGATION OF  
HYDRAZIDOMALONIC ACID

A THESIS

In partial fulfillment of requirements  
for the degree Bachelor of Science with  
special attainments in Chemistry at the

Department of Chemistry  
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BY

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VITA

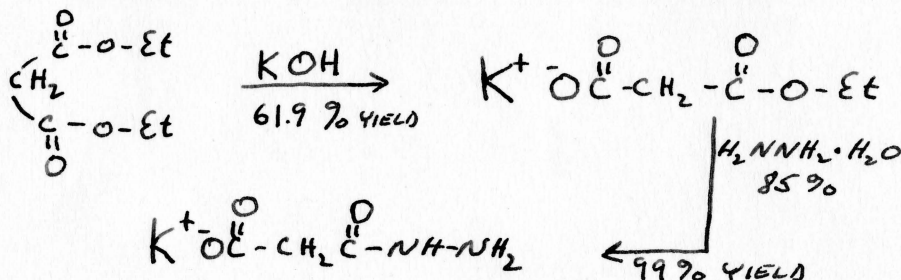
Rardon Dixon Bevill, III was born in Winnfield, Louisiana on February 23, 1938, the son of Susan Victoria Ballance Bevill and Rardon Dixon Bevill, Jr. He attended Winnfield Elementary School through the eighth grade, and in September, 1952, entered Sewanee Military Academy. Having graduated from Sewanee Military Academy in May, 1956, he entered Washington and Lee University.

### ACKNOWLEDGEMENT

The autor wishes to extend special thanks to Dr. James K. Shillington, without whose constant guidance and encouragement this work would have been impossible. Recognition is also due David N. Keys, whose work lay the foundation of this present work, and to Henry Hawthorne for his helpful assistance in the laboratory.

## HISTORICAL

The purpose of investigating hydrozidomalonic acid is its use as an intermediary compound in the resolution of optically active carbonyl compounds. D. N. Keys' in August, 1959, had synthesized potassium hydrazidomalonate as follows:



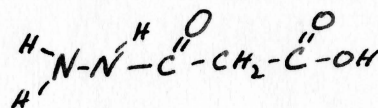
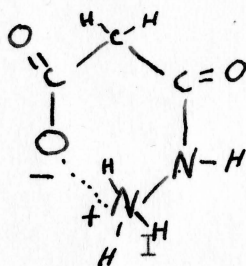
Acidification of potassium hydrazidomalonate by direct methods to produce hydrozidomalonate ~~acid~~ acid were all in vain. The free acid was never isolated. However, this did not hamper, but in fact helped the synthesis of hydrazone derivatives prepared from the potassium salt, since it was later discovered that the free acid will not condense with the carbonyl to form the hydrozone due to its existence as a zwitter-ion. The synthesis of the hydrazone derivatives was analogous to the method used by T. Curtius and co-workers<sup>2</sup> in the preparation of benzylidene hydrazonoöxalic acid, and the following derivatives were prepared: benzylidenehydrazonomalonic acid, cyclohexylidenehydrazonomalonic acid, and dl-3-methylcyclohexylidenehydrazonomalonic acid. The first two were isolated and purified by Mr. Keys, but the third one was never completely isolated.

2.

Hence there were two unfinished steps in a total investigation of hydrazidomalonic acid as an resolving reagent for optically active carbonyls, namely; the isolation and identification of hydrazidomalonic acid, and the complete isolation of dl-3-methylcyclohexylidenhydrazonomalonic acid. These steps must be accomplished before resolution can be attempted, and since our interest in hydrazidomalonic acid is its use in resolution, the isolation of these two compounds was undertaken.

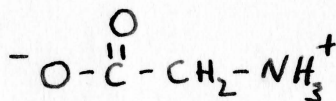
## DISCUSSION

The isolation and purification of hydrazidomalonic acid was never accomplished by D. N. Keys in August, 1959. The acidified potassium salt was water soluble which indicated either the existence of the acid as the zwitter-ion, or as the hydro-



II

chloride of the acid; or it indicated that the acid was polar enough to be water soluble. The zwitter-ion structure is shown in figure I, and the free acid structure in figure II. The first crystals isolated through a reduction in volume were found to be insoluble in methyl alcohol, and very soluble in water. These are the same solvent properties exhibited by glycine, which exists primarily in the zwitter-ion form. A parallel isolation scheme



III

was devised and the free acid (I) was forced out of solution with the addition of methanol. The

isolated acid was recrystallized from a water-methanol pair closely following the glycine recrystallization procedure. Two recrystallizations gave a product with a sharp melting point of  $133^{\circ}$  -  $135^{\circ}$  C. and a neutral equivalent of 118. (Molecular weight=118.05).

The condensation product of the potassium *SALT* of hydrazidomalonic acid with dl-3-methylcyclohexanone was acidified and the acid derivative precipitated in a water solution. After many attempts, it was purified through recrystallization from an ethanol-water pair. The acid derivative is stable to hydrolysis from the weakly acidic EtOH and ~~the~~ <sup>at</sup> moderate temperatures.

The malonic acid methylene group between the carbonyls acts as a sufficient electron shield to prevent the carbonyls from aiding each other in the weakening of the hydrazone double bond. The  $-\text{CH}_2-$  blocks electronically the hydrazide carbonyl from the carboxy group and this reduces the pull on the double-bond electrons. The stability of dl-3-methylcyclohexylidenehydrazonomalonic acid in gently heated, weakly acidic solutions against hydrolysis is evidence of this stronger hydrazone double bond.

## EXPERIMENTAL

POTASSIUM ETHYL MALONATE<sup>3</sup> To 75 grams of diethyl malonate in 300 ml of absolute alcohol was added 26.1 grams of potassium hydroxide in 300 ml of absolute alcohol; the mixture was stirred for two hours and a white precipitate came down. The salt was filtered and dried overnight in a vacuum desiccator. This preparation gave 47.6% yield.<sup>5</sup>

POTASSIUM HYDRAZIDOMALONATE<sup>4</sup>: 10 grams (.06 moles) of potassium ethyl malonate and 4 grams (.08 moles) of 85%hydrazine hydrate were mixed together and warmed over a steam bath until solution took place. Then they were quickly removed to a sulfuric acid vacuum desiccator for 20 minutes. Crystals came down immediately on cooling and were triturated twice with absolute ethyl alcohol and washed with ether. Salt was placed in 105° oven for six hours and then in vacuum desiccator overnight. Yield was 8.5 gramms (90.4%). Melting point was 173.5°-175° (corrected).

HYDRAZIDOMALONIC ACID: 3 grams of potassium hydrazidomalonate was dissolved in methyl alcohol and acidified to a pH of 2 with 5% hydrochloric acid. Ethyl alcohol and methyl alcohol were added to <sup>the</sup> acidified solution. White crystals came down very slowly for three days. Recrystallization from H<sub>2</sub>O-MeOH pair in the same way as glycine gave the pure acid in approximately 10-15% yield.



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Melting point was 131.4-133 C° with contraction and decomposition. N.E.=118 with second recrystallization.

POTASSIUM d,1-3-METHYLCYCLOHEXYLIDENEHYDRAZONOMALONATE: 5.6 grams (6.1 ml) of dl-3-methylcyclohexanone were mixed with 5.0 grams of potassium hydrazidomalonate in 15 ml of anhydrous benzene. Four drops of I<sub>2</sub> catalyst (1/2 crystal of I<sub>2</sub> dissolved in 20 ml of benzene) were added to the mixture. This was refluxed over an oil bath at 110° for two hours. The salt crystals were filtered and ~~crushed~~ <sup>WASHED</sup> with benzene and then dried in a vacuum desiccator overnight. The yield was 88% with a melting point of 178.5-179.8°C (corrected).

dl-3-METHYLCYCLOHEXYLIDENEHYDRAZONOMALONIC ACID: 5.0 grams of potassium dl-3-methylcyclohexylidenehydrazonomalonate were acidified with 5% HCL to a pH of 2. The crystals came down immediately, were filtered and washed with water and placed in a vacuum desiccator to dry overnight. Recrystallization was accomplished with an ethanol-water pair. (Note: the free acid is exceptionally soluble in hot EtOH and care should be taken to add only a minimum of EtOH ~~water~~ <sup>WITH</sup> heating to get sample into solution.) The per cent yield was 50% after recrystallization and the product had a melting point of 139-140°C (corrected). Lit. M.P.

POTASSIUM 2,6,8-TRIMETHYLNONYLIDENE-4-HYDRAZONO\*

MALONATE: 9.3 grams of 2,6,8-trimethyl-4-nona-  
none were mixed with 5.0 grams of potassium hydra-  
zidomalonite in 15 ml of anhydrous benzene. Four  
drops of I<sub>2</sub> catalyst were added to the mixture  
and it was refluxed over an oil bath at 110° for  
two hours. The salt was filtered and washed with  
benzene and then dried in a vacuum desiccator.

2,6,8-TRIMETHYL-4-NONYLIDENE HYDRAZONOMALONIC ACID:

3.0 grams of the potassium 2,6,8-trimethyl-4-  
nonylidenetrydrazonomalonate were acidified with  
5% HCl and volume reduced through vacuum distilla-  
tion. No precipitate came down. All attempts were  
in vain.

## SUMMARY

The complete isolation of dl-3-methylcyclohexylidenehydrazonomalonic acid is the final step before the formation of the diastereoisomers with l-brucine. The oxalic acid<sup>6</sup> route proved to be too unstable and the succinic acid<sup>6</sup> route produced compounds which could not be isolated in pure form. The malonic derivatives are stable and can now be obtained in pure form.

The attempted resolution through the procedure outlined in O. B. Ramsay's<sup>7</sup> 1956 summer report will be undertaken this summer by the author. The possibility for a successful resolution appears favorable in the light of the stability of the malonic series, and its ease of purification.

FOOTNOTES

1. David N. Keys, Summer Report, Washington and Lee University, September, 1959.
2. T. Curtius, A. Darapsky, E. Mueller, Ber., 40, 1176 (1907)
3. Ca., 47, 10501
4. T. Curtius and W. Sieber, Ber., 54, 1430 (1921)
5. For higher yields use: Ory, Syn., 37, 34 (1957)
6. Thomas C. Imeson, Summer Report, Washington and Lee University, September, 1959.
7. O. B. Ramsay, Summer Report, Washington and Lee university, September, 1956.