

The PREPARATION and ATTEMPTED RESOLUTION
Of BENZOYL-MALIC ACID

Thesis

by

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PURPOSE OF The RESEARCH:

The final object of this research was to prepare m-nitrobenzoyl malic acid and to separate it, if possible, into the four stereoisomers predicted by the Huggins' theory of the benzene ring. Inasmuch as the quantity of m-nitrobenzoyl chloride available was limited it was thought better to first prepare i-benzoyl malic acid and then attempt to resolve it. The resolution of m-nitrobenzoyl malic acid could probably be accomplished by a similar method.

THEORY:

The Huggins' theory of the benzene predicts ortho and meta stereoisomers, e.g. the accompanying figures represent



compounds which are mirror images of each other and which should be stereoisomers. (I) If a chain contain-

ing an asymmetric carbon atom be joined to the benzene ring, as is the case in m-nitrobenzoyl malic acid, four stereoisomers of the resulting compound would be expected.

(I)

- a) M.L.Huggins, Science 55, 679-80- (1922)
- b) J.A.C.S. 44, 1607-17, (1922)
- c) Rolfe, Optical Activity. (MacMillan)

PREVIOUS WORK:

The above isomers have never been found although a number of chemists have done work on different compounds. (2)

The preparation of i-benzoyl malic acid is described by E.E.Shafer, Jr. (3) Its resolution was not attempted by him. (4)

The resolution of malic acid as described by Dakin was applied to i-benzoyl malic acid but it did not give satisfactory results. It was found that by the use of quinine there were obtained two substances of decidedly different habit of crystallization and possessing different degrees of rotation. Lack of time prevented further investigation.

A redetermination of the equivalent weight of i-benzoyl malic acid gave results which indicate that the acid crystallizes from water with $\frac{1}{2}H_2O$. This is lost when the compound is heated at 90° C. for 48 hours, the resulting substance being the anhydrous acid. These results do not agree with those obtained by Shafer.

(2)

- a) Le Bel, Bulletin Soc. Chem. 38, 98 (1882)
- b) Lewkowitsch, Trans. Chem. Soc. 53, 78 (1888)
- c) V. Meyer and Luhn Ber. 28, 2795 (1895)

(3)

- a) E.E.Shafer, Jr., Senior thesis, Calif. Inst. Tech. 1925.

(4)

- a) Dakin, Jour. Biol. Chem. 59, 7, (1924)

EXPERIMENTAL WORK:

21.1 g. (.15 mole) of redistilled benzoyl chloride B.P. 192.5°-193° C. and 20.1 g. (.15 mole) of i-malic acid (Eastman's) were placed in a 1 l. balloon flask. The mixture was refluxed over a water bath until the evolution of HCL became quite slow. Another molal portion of benzoyl chloride was then added and the mixture was heated until no more HCL was evolved. About 1½ hours were required for the completion of the reaction. The resultant liquid was poured off, cooled and the solid obtained was broken up. It was washed repeatedly with benzene to remove benzoyl chloride and benzoic acid. The solid was dissolved in hot water and the solution allowed to crystallize. 12.5 g. of a substance melting at 126°-128° was obtained. By recrystallization from hot water a product melting at 137.5° was obtained. Weight 11 g. Yield 30.8% on basis of malic acid. Shafer found that pure benzoyl malic acid crystallized from water melted at 110°-110.7° C. and the substance after drying in an oven at 90° for 48 hours melted at 137.5°-138.5°. This yield was rather small and difficulty was found in obtaining the pure substance so a second preparation was thought advisable.

2d Preparation:

The reaction was carried out as in the 1st preparation except a smaller excess of benzoyl chloride was used. The crude product melted at 132°-135° and after one crystallization from hot water, at 128°-130°. These results indicate, first that the reaction did not go to completion, and second

that hydrolysis takes place in hot water.

3d Preparation:

33.5 g. (.25 mole) of finely ground dry malic acid and 35.1 g. (.25 mole) of benzoyl chloride were mixed and refluxed for $\frac{1}{2}$ hour by which time the evolution of HCL had become slow. Another molal portion of benzoyl chloride was added and the mixture was heated until all the malic acid had disappeared. This required 45 minutes longer. The resultant liquid solidified on cooling. The solid was ground in a mortar with benzene, filtered, and washed with benzene.

Weight of solid 48 grams. On standing the mass became gummy but finally dried. This effect is due to the absorption of water by the benzoyl chloride which hydrolyzes to benzoic acid. The solid was mixed with 150 c.c. of benzene and refluxed for $\frac{1}{2}$ hour to free it from benzoic acid. The solid dissolved leaving a gummy solid on the flask. This gummy substance is malic acid that failed to react. The benzene was poured off and allowed to cool whereupon a solid substance separated. It was filtered and washed with benzene. Weight 16.5 g. M.P. 120-124 The mother liquor from the above crystallization was allowed to evaporate and more crystals separated. Weight 18 g. M.P. 130 Softened at 109-118. By recrystallization of the substances crystals were obtained that melted at 94-96° Weight 29.5 g. 49.5% yield. Investigation of the mother liquors showed that they consisted mainly of benzoic acid and small amounts of malic acid.

A better way of separating benzoyl malic acid from benzoic acid was desired so the following procedure was used:

Impure benzoyl malic acid was dissolved in cold water and lead acetate was added until the precipitate of lead benzoyl malate no longer formed. Lead benzoate is soluble in water. The precipitate was filtered and washed with hot water. It was then suspended in water and H_2S was bubbled through the solution. The precipitate of lead sulfide was filtered off and the filtrate was allowed to evaporate spontaneously. Crystals of benzoyl malic acid melting at 110° - 111° were obtained. It was found that solutions of the acid hydrolyzed appreciably even when heated at 70° - 80° . Consequently all solutions of it must be made cold and allowed to evaporate spontaneously.

TREATMENT OF BENZOYL MALIC ACID WITH CINCHONINE:

8.4 g. (.025 mole) of cinchonine and 6.0 g. (.025 mole) of benzoyl malic acid were dissolved in 65 cc of hot methyl alcohol. A brown solution resulted but no crystals formed on standing for several days. The solution was evaporated further and a brown glass-like substance remained, It showed no crystalline structure when dry. All attempts to crystallize it from other solvents failed. *heat (?)
of
liquid
-temp.*

Attempts to prepare the neutral cinchonine salt resulted in the formation of a similar non-crystalline gum.

TREATMENT OF BENZOYL MALIC ACID WITH BRUCINE:

2.3 g. (.005 mole) of brucine and 1.2 g. (.005 mole) of benzoyl malic acid were dissolved in 30 cc of hot 95% alcohol. The solution was allowed to stand overnight uncorked.

A few crystals formed but the liquid was too viscous for crystallization to continue. More alcohol was added and the mixture was stirred. The crystals formed by this treatment were dissolved in 50 cc of hot water and the solution was allowed to stand. Circular nodules formed. They consisted of exceedingly fine crystals which were arranged about a center. M.P. 173-175°. The habit of crystallization and the melting point indicate that the substance is mainly brucine.

2d TREATMENT OF BENZOYL MALIC ACID WITH BRUCINE:

2.3 g. of brucine and 1.2 g. of benzoyl malic acid were dissolved in 30 cc of hot 95% alcohol and stoppered. Nodular crystals formed after standing for several days. They were washed with alcohol. M.P. 171-172°. The mother liquor was allowed to stand longer. Fine crystals appeared which were separated and washed with alcohol. M.P. 138-143°. The mother liquor from the second crystallization was allowed to evaporate slowly. Plate like prisms resembling those of benzoyl malic acid crystallized out. M.P. 108-110°. The 1st two crops of crystals obtained were almost insoluble in water. Solutions made by filtering hot extracts of them were optically inactive.

TREATMENT OF BENZOYL MALIC ACID WITH QUININE:

1.89 g. (.005 mole) of quinine and 1.19 g. (.005 mole) of benzoyl malic acid were dissolved in about 30 cc of hot absolute alcohol. The solution was filtered and allowed to stand until compact nodules separated out. The solution was then poured off. The nodules were washed with alcohol and dissolved

in absolute alcohol. Small needle-like crystals appeared. The recrystallized product decomposed at 150°. This is called quinine benzoyl malate A. The mother liquor from the 1st crystallization was allowed to evaporate slowly. Nodules formed at first but a new type of crystal appeared. The liquid was poured off in order to separate the two kind of crystals. The 2d. type was needle like in structure. This is called quinine benzoyl malate B. Crystals of it turned brown at 125° and melted at 128-129°.

ROTATION OF QUININE BENZOYL MALATES A AND B:

Solution #1 was made by dissolving .1006 g. of quinine benzoyl malate A in 50 cc of butyl alcohol; solution #2 by dissolving .0516 g. Of quinine benzoyl malate B in 25 cc of butyl alcohol. Attempts to polarize the solutions using a sodium flame were unsuccessful because the intensity of the light was too small. The results below were obtained by using a mercury arc giving the line $\lambda = 5461 \text{ \AA}$.

Reading #	1	2	3	4	Avg.	Obs. Rot.	Spec. Rot. [α] _D ²⁵
Water	+ .93°	+ .93°	+ .92°	-	+ .926°	-	-
Butyl Alc.	+ .87°	+ .86°	+ .86°	-	+ .863°	-	-
Sol. #1	+ .23°	+ .24°	+ .23°	-	+ .233°	- .63°	- 128°
Sol. #2	+ .33°	+ .30°	+ .30°	+ .32°	+ .315°	- .545°	- 108°

Probable error 4.0%

Specific rotation of quinine (in 97% alcohol) - 145.2°
 Specific rotation of anhyd. quinine " - 170.5°

The results obtained in the treatment of benzoyl malic acid with cinchonine and brucine might indicate that the substance thought to be the acid was the anhydride. For this reason the following determinations were made:-

Standardization of $\text{Ba}(\text{OH})_2$

	Sample #1	Sample #2
Weight of Oxalic acid	.4040 g.	.4002 g.
Titration- Final Read.	48.88 cc	48.42 cc
Initial "	.06 cc	.03 cc
Volume used	48.82 cc	48.39 cc
Normality	.1313 N.	1313 N.

Titration of Benzoyl Malic Acid Crystallized from Water:-

	Sample #1	Sample #2
Weight of Acid	.7511 g.	.7508 g.
Titration- Final Read. $\text{Ba}(\text{OH})_2$	46.57 cc	46.43 cc
Initial " "	.10 cc	.02 cc
Volume used "	46.47 cc	46.41 cc
Equivalent Weight	123.1	123.2
Avg. Equiv. Weight	123.15	Shafer's value was 121.

Titration of the Substance obtained by Heating Benzoyl
Malic Acid for 48 Hours at 90° C.

Shafer's Prep.	-Sample #1	Sample #2	My Prep. #1	#2
Weight	.7317 g.	.4002 G.	.6005 g.	.6005 g.
Final Reading	47.40 cc	26.41 cc	38.70 cc	38.63 cc
Initial "	.02 cc	.55 cc	.13 cc	.03 cc
Volume used	47.38 cc	25.86 cc	38.57 cc	38.60 cc
Equiv. Weight	117.5	118.0	118.7	118.5
Average " "		117.75		118.6
Shafer's Value		116.5		

Check on the Normality of Ba(OH)₂ made at end of titrations:-

	Sample #1	Sample #2
Weight of Oxalic Acid	.3000 g.	.3003 g.
Final Reading Ba(OH) ₂	36.57 cc	36.44 cc
Initial " "	.04 cc	.05 cc
Volume used	36.53 cc	36.39 cc
Normality	.1303 N.	.1309 N.
Avg. " "	.1306 N.	
Avg. " -Ist. Deter.	.1313 N.	
Difference	.54%	

CONCLUSIONS:

The best method for the preparation of benzoyl malic acid is the following:-

Finely ground dry malic acid and benzoyl chloride are mixed in molal proportions and refluxed over a water bath until the evolution of HCL becomes slow; this requires about 45 minutes. Another molal portion of benzoyl chloride is then added and the mixture is heated until no more HCL is evolved; this requires about 30 minutes. The liquid obtained is then poured out into a mortar and the solid formed on cooling is ground up with benzene. The residue may be treated in the following ways:-

a) Dissolve the solid in water at 50° C. and filter off the crystals formed on cooling. They consist largely of benzoic acid. Allow the filtrate to evaporate spontaneously and recrystallize the product obtained from cold water. Another crystallization may be necessary to give a product melting at 110° - 111° C.

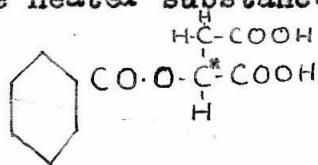
b) Dissolve the solid in water at 50° C. and add the quantity of lead acetate crystals necessary to precipitate the acid as lead benzoyl malate. Filter off the precipitate and wash it with hot water, Suspend it in water and pass in H_2S for a considerable time. Filter off the precipitate of PbS and allow the filtrate to evaporate spontaneously. This method furnishes very pure crystals of benzoyl malic acid but the reaction between lead benzoyl malate and H_2S takes considerable time and agitation to complete, especially if large quantities of the lead salt are involved.

Cinchonine failed to form a crystalline salt with benzoyl malic acid. Attempts were made to form both the acid and neutral salt.

Treatment of benzoyl malic acid with brucine failed to produce a salt.

The treatment of benzoyl malic acid with quinine seems to indicate that a compound is formed between the two substances. Shortage of time prevented the purification and further investigation of the salt.

The titration of benzoyl malic acid and the substance described by Shafer as the anhydride leads to some new conclusions, The difference in equivalent weight between the two substances is 4.5, This represents a difference of 9 in their molecular weights. The molecular weight obtained for the heated substance is 238 which is that of the compound;-



or benzoyl malic acid.

The conclusion reached is that the substance crystallizing from water is a hydrate containing $\frac{1}{2}\text{H}_2\text{O}$ per molecule of acid and that the compound obtained by heating the hydrate at 90 C. is the acid itself.

This research was carried out under the direction of Prof. H.J.Lucas whose kind assistance I wish to acknowledge here.

SUMMARY:

1) Benzoyl malic acid was prepared and then purified by two methods a) By treatment of the lead salt with H_2S .

b) By crystallization from water.

2) The resolution of benzoyl malic acid was attempted by the use of cinchonine, brucine and quinine. The first two alkaloids gave negative results but favorable evidence was obtained by the use of quinine.

3) A redetermination of the equivalent weight of the acid crystallizing from water and the compound obtained by heating leads to different results from those obtained by Shafer.