SOME INVESTIGATIONS OF THE PREPARATION OF

4-(4-CARBOXYPHENYL)SEMICARBAZIDE

AND ITS CAMPHOR DERIVATIVE


A SENIOR THESIS

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of Washington and Lee University

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BY

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## VITA

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## ACKNOWLEDGEMENT

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## INTRODUCTION

At present the series of reagents available for the resolution of optically active carbonyl compounds shows some definite inadequacies. The investigations discussed in this thesis were undertaken to fill these gaps.

Before dealing with specific compounds, it is necessary to review the general requirements which a satisfactory reagent must meet. Perhaps the most important requirement is that the reagent must react with as wide a variety of carbonyl compounds as possible and that it must be stable before and after reaction. A second important requirement is that the reagent must be of sufficient molecular weight that the product will be a solid. Finally, as a matter of convenience, the solid product should not melt above 250° since high temperatures require additional apparatus and frequently lead to inaccuracies. A common reagent which meets these requirements is 2,4-dinitrophenylhydrazine.

Although the majority of the common reagents for carbonyl compounds are monofunctional, bifunctional reagents have been synthesized and, in spite of their instability, these reagents were found to possess certain advantageous properties. Reagents such as p-hydrazinobenzoic acid[1] and hydrazinoacetic acid[1] could be extracted with dilute base solutions and, in addition, the molecular weight of their products could be readily obtained through a neutral equivalent. Bifunctional reagents had long been used in the resolution of optically active alcohols and it was hoped to apply the same principle to the resolution of

optically active carbonyl compounds.

In the past it has been common practice to attempt resolution of optically active carbonyl compounds through the use of reagents which were themselves optically active. In the case of camphor and 3-methylcyclohexanone such methods proved successful. Separation depended upon coupling a d or l reagent with a d,l carbonyl compound and hoping that the diastereoisomers would have physical properties sufficiently different to permit separation by fractional recrystallization or extraction. If the particular reagent proved unsatisfactory it was necessary to hydrolyze off the reagent and react the carbonyl compound with a new optically active reagent. This hydrolysis resulted in the loss of both compound and reagent and hence was not very satisfactory.

In an attempt to solve this problem Shillington et. al.[2] began a series of studies to develop bifunctional reagents, one of which involved the synthesis of the carboxymethoxime[1] of the carbonyl compound. By forming a salt with such naturally occurring optically active bases as brucine, the resulting d,l or ll pairs may be separated. If physical properties are not sufficiently different, all that is necessary is to acidify, recover the solid acid by filtration, and react with a new optically active base. This process should result in no significant losses. The only major disadvantage is the loss which occurs in the two step synthesis of the carboxymethoxime of the carbonyl compound and in the single, final hydrolysis.

This method stimulated the search for other reagents containing a free carboxy group and possessing the properties desired

in a carbonyl reagent.  It now remained to select a satisfac-
tory group to react with the carbonyl compound and to find a
satisfactory moiety on which to attach these groups.  After
some consideration it became obvious that a phenyl ring would
be the most practical foundation.  The following were among the
reasons for this choice: **1.**The phenyl ring is more readily sub-
stituted than most aliphatic groups; **2.**The distance between the
carboxy group and the other functional groups, particularly in
the para position, would tend to prevent cyclization; **3.**Since
the acidity of phenyl carboxy groups is slightly greater than
that of aliphatic carboxy groups, ~~the Brucini carboxy groups~~,
the Brucine salts should form more readily. **4.**Finally the phenyl
carboxy salts should be less soluble than aliphatic carboxy
salts.

It remained now to select a satisfactory group to react
with the carbonyl compound.  In the search, hydrazines, such as
a p-substituted phenyl hydrazine, were considered but rejected
because of instability.  Hydrazides were rejected because of
lower reactivity.  Half acid hydrazides and semioxamides were
considered but rejected.  Factors began to point to the semi-
carbazide as the satisfactory group.  It was reactive, stable
and usually gave good crystals.  The addition the ketone could
be readily recovered by adding phthalic anhydride to a solution
of the compound and steam distilling or by displacement of the
carbonyl compound by pyruvic acid.

Having decided on the desired reagent there remained the
problem of synthesizing it from low-cost, readily available

materials.  Considering that phenyl ring with a carboxy group
attached was readily available the problem centered on a means
of substituting a semi-carbazide group on the ring.  Three possi-
ble methods of synthesis seemed to be available.  The transamina-
tion of a semi-carbazone by an amine  had  been attempted but
had not been successful[3] when a negative group such as a carboxy
was present on the ring.  Greenough[4] attempted to synthesize the
semi-carbazide by treating a substituted carbonic acid ester
with hydrazine but was unsuccessful.  The remaining possibility
involved the reaction of a mono substituted  urea with hydrazine.
The study of this process is the basis for this thesis.

## HISTORICAL

### Resolution of Carbonyl Compounds

The history of the resolution of racemic carbonyl compounds is surprisingly brief since success has been achieved only during the past twenty-five years. Each method of resolving optically active carbonyl compounds, to date, has involved the use of an optically active-reagent. The earliest successful resolution of a racemic carbonyl compound was reported in 1930[5] using $\alpha$-($\alpha$-benzylamino) naphthol. A ketone was first successfully resolved by Crawford & Wilson[6] in 1934 using l-menthylsemicarbazide. In 1940[7], d-4-(d-phenylpropyl) semicarbazide was used and in 1941, l-menthylhydrazide[8] was synthesized and found to be satisfactory. Finally in 1950, 5-(1-phenylethyl) semioxamiazide[9] was used in resolving 3-methylcyclohexanone. An attempt in 1949[10] to resolve optically active aldehydes through the use of optically active bisulfites was not successful yet it was felt to be promising. It can be seen from these references that the field of resolving optically active carbonyl compounds is open to improvement.

### 4-(4-Carboxyphenyl)semicarbazide

The primary interest of this thesis is in the synthesis of 4-(4 carboxyshenyl)semicarbazide, a reagent for carbonyl compounds that introduces a new principle into the resolution of optically active carbonyl compounds. This reagent follows a principle used successfully in the resolution of optically active
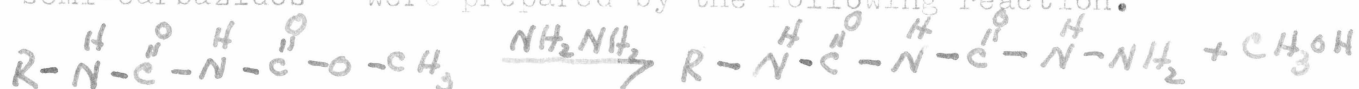
alcohols - that of forming a salt with a naturally occuring;
optically active base such as brucine.  Having decided to use
compound consisting of a phenyl ring substituted with a carboxy
group and a semi-carbazide group, a literature search was made
to determine if such a compound had been synthesized previously.
The search revealed that no compound containing a free carboxy
group and a free semi-carbazide group had been built but it re-
vealed three possible methods for its synthesis.

The first possible method was developed in 1925 by Wilson
and Crawford[11] in synthesizing 4(3-carbethoxyphenyl)semi-car-
bazide[(I)].
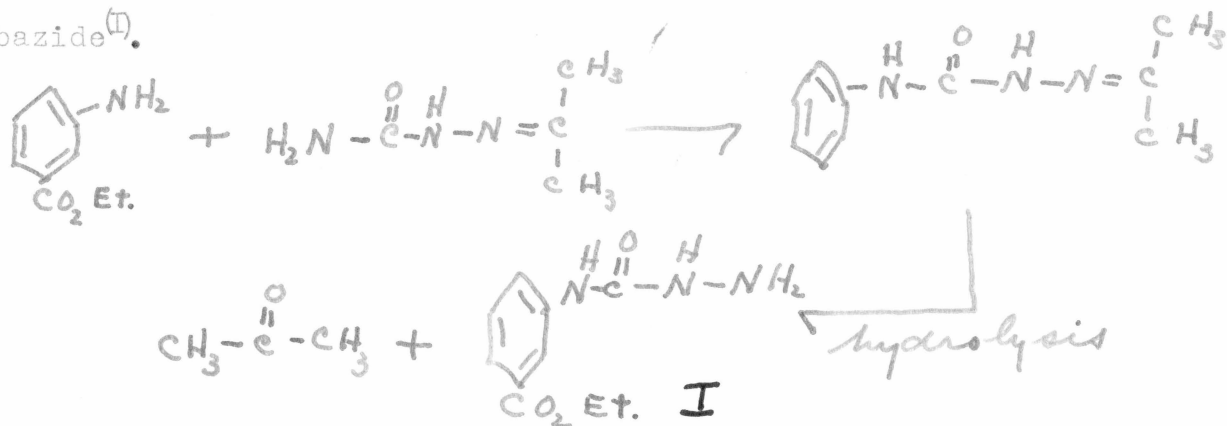
The hydrolysis to give the free semi-carbazide group (I)
was successful in the case of the meta isomer but the para decom-
posed.  The transamination of the ortho form did not occur.
Attempts to hydrolyse the ester to give a free carboxy group were
unsuccessful due to decomposition of the molecule.

The second possible method involved the hydrazination of
a urethan or a closely related compound.  In 1940, 4-carb**anyl**
semi-carbazides[12] were prepared by the following reaction.

and in 1951[13] the following synthesis was completed.

$$O_2N-\text{(ring)}(OH)-N(H)-C(O)-O-CH_2CH_3 \xrightarrow{NH_2NH_2} O_2N-\text{(ring)}(OH)-N(H)-C(O)-N(H)-NH_2 + CH_3CH_2OH$$
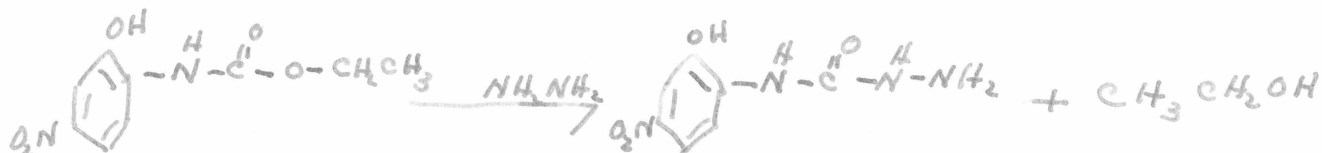
In 1953 Greenough[4] attempted the synthesis of 4-(4-carboxy-phenyl) semicarbazide (II) by the hydrazination of p-carboxyphen-ylurethan.

$$HO_2C-\text{(ring)}-N(H)-C(O)-O-CH_2CH_3 \xrightarrow{NH_2NH_2} HO_2C-\text{(ring)}-N(H)-C(O)-N(H)-NH_2 + CH_3CH_2OH$$

II

After several attempts under various conditions and concentra-tions he was unable to report any success.

The final possibility involved the transhydrazination of a substituted urea. Barré and Piché[14] in 1941 synthesized 4-(4-introphenyl) semicarbazide from p-ureidonitrobenzene by the following reaction.

$$O_2N-\text{(ring)}-N(H)-C(O)-NH_2 \xrightarrow{NH_2NH_2} O_2N-\text{(ring)}-N(H)-C(O)-N(H)-NH_2 + NH_3$$

Paralleling this synthesis Shillington[2] attempted the hydrazination of p-ureidobenzoic acid with some apparent suc-cess and prepared, in addition, the acetone derivative.

## DISCUSSION

It was decided to attempt the synthesis of 4-(4 carboxy-phenyl)semi/carbazide by way of the hydrazination of para-urei-dobenzoic acid. This necessitated initially a study of the preparation of para-ureidobenzoic acid. Through previous studies of Greenough[4] and Shillington[2] a synthesis was devised based on the work of Blanchard and Davis.[15,16]

### Urea Nitrate

Having no available directions for the synthesis of the starting material, urea nitrate, it was easily prepared by adding concentrated nitric acid to a water solution of urea. The resulting white crystals were dried in preparation for the synthesis of nitrourea.

### Nitrourea

Following a procedure given in Organic Synthesis[17], urea nitrate was added to an ice cold solution of concentrated sulfuric acid in a 2-l. beaker fitted with a mechanical stirrer. A beaker was found to be more convenient than an erlenmeyer flask. During this preparation it was essential to keep the temperature below 3° to prevent the decomposition of nitrourea in acid solution. The final step involved pouring the solution over 1 Kg. of ice to precipitate the nitrourea. It was found to be important to surround the beaker containing the ice with an ice-salt mixture to prevent excessive warming. After the product was filtered off, cooling the mother liquor produced a sizeable

amount of product (27.4 g).  During the first run the mother liquor was discarded thus lowering the average yield of the two runs.  The product was difficult to filter and had to be pressed dry on the filter using a glass bottle top.  In addition, the acidity of nitrourea made it necessary to use nichrome spatulas instead of the standard variety.

## Para-Ureidobenzoic Acid

Para-Ureidobenzoic acid was prepared using a proceedure found satisfactory by Shillington[2].  The substitution of 95% ethanol for 100% ethanol did not seem to affect the yield.  The use, however, of technical grade p-aminobenzoic acid may have affected the yield and the color and purity of the product.  It is recommended that Eastman White Label or a similar grade of p-aminobenzoic acid be used.

Experience showed that the separation of the product from any unreacted p-aminobenzoic acid could be accomplished by first evaporating the reaction mixture to dryness and then triturating with 100 ml.. of 95% ethanol to remove the p-aminobenzoic acid. p-Ureidobenzoic acid is 1.2 parts/100 soluble in ethanol at room temperature while p-aminobenzoic acid is 11.3 parts/100 soluble in alcohol at 10°.  When this proceedure was followed in the second run and the resulting alcohol solution evaporated to dryness, triturated with water, filtered and dried, the product was a solid which melted over a range from 180° to 190°. P-Aminobenzoic acid melts at 187-8°.[18]

It was found to be difficult to get the p-ureidobenzoic acid to melt over a short temperature range. Even after two recrystallizations the sample melted over as much as a 10° range. It might be better, in fact, to consider it as a decomposition rather than melting, for softening was accompanied by darkening and in most cases the end product was a dark brown, shrunken solid.

The neutral equivalent of a sample which had been recrystallized twice from a dimethylformamide-water pair was 181.42. This differed by 0.7% from a value calculated for $C_8H_8O_3N_2$ - 180.16. This error may have been due in part to the fact that the burette used for the titration of the sample was not the one used in standardizing the base.

## 4-(4-Carboxyphenyl)semicarbazide

The synthesis of 4-(4-carboxyphenyl)semicarbazide was attempted following a procedure which Shillington[2] had used with success. The isolation of the product seemed to be a routine proposition following a very simple synthesis. It first became apparent that the synthesis was not going well when the product failed to melt in the 215-25° range where the products of previous successful runs had melted. At first it was believed that only purification was needed to obtain a melting point in the desired range. A mixed melting point[2] had been run on a rough 50/50 mixture of p-ureidobenzoic acid to 4-(4-carboxyphenyl) semicarbazide. This mixture had not melted at 275°. A rough 75/25 4-(4-carboxyphenyl)semicarbazide/p-ureidobenzoic acid mix-

ture melted at 256-57°. These results tended to indicate that the presence of as much as 25% of the p-ureidobenzoic acid would raise the melting point into the range of the sample isolated from run I. When recrystallization from a dimethylformamide-water pair failed to lower the melting point, it was decided to make a complete investigation of the synthesis and isolation as compared with previous successful runs to determine any possible sources of error.

Before the investigation had proceeded very far, a second run was made. When the product of this second run melted at 212-15° it aroused hope that the synthesis had been successful. Recrystallization of this product from a dimethylformamide-water pair resulted in a melting point as follows: Shrinking and darkening at 263° and melting at 266-67°. At this point, it was decided to investigate the possibility that the dimethyl-formamide might be responsible for the raised melting point. A nickel chloride-carbon, disulfide test for secondary anines was run on the dimethylformamide to test for decomposition and showed only traces of secondary anine to be present. A sample of the product from run II was dissolved in 5% sodium hydroxide and reacidified with glacial acetic acid to a pH of 5 where a precipitate formed, was filtered off and set to dry. This solid began shrinking at 247° and was completely melted at 263°. This seemed to indicate that the dimethylformamide was not at fault.

A clean-up of the mother liquor from run II gave a tan solid which melted between 220° and 230° and gave a neutral equivalent

of 179.7 compared with a calculated value of 180.1 for p-ureido-
benzoic acid and 195.2 for 4(4-carboxyphenyl)semicarbazide. It
was felt that this tan solid was p-ureidobenzoic acid with some
impurity of hydrazine dihydrochloride ( M.P.-198°) being respon-
sible for the lowered melting point.

Having been unable to isolate any satisfactory product
from the first two runs even after careful recrystallization,
it was decided to consult the reference[14] which had formed the
basis for the original synthesis followed by Shillington. It
was discovered that both Shillington's successful run and the
synthesis which he had paralleled the mixture had been refluxed
for 48 hours or longer. This was in sharp contrast to the 24
hours which the unsuccessful runs had been refluxed. This mis-
take was probably due to misreading the recorded data on the
successful preparation. Investigation is now underway to deter-
mine the effect of refluxing the mixture for an additional 24
hours.

The results of the recrystallization of the product from
run II have more meaning in view of the effect of time on the
completeness of the reaction. It was found that after two
recrystallizations the product from run II gave a neutral equiva-
lent of 183.87. The difference between this value and that
calculated for p-ureidobenzoic acid is 3.77. The difference be-
tween the calculated neutral equivalent of 4-(4-carboxyphenyl)
semicarbazide and p-ureidobenzoic acid is 15. $\frac{3.77}{15} \times 100 \doteq 25\%$
This would seem to indicate that after 24 hours of refluxing
approximately 25% of the p-ureidobenzoic acid had reacted to

form 4-(4-carboxyphenyl)semicarbazide.  With so small a percent-age of product formed, recrystallization would tend to result in purified p-ureidobenzoic acid since it is the larger component of the mixture.

## Camphor 4-(4-carboxyphenyl)semicarbazone

The attempted synthesis of camphor 4-(4-carboxyphenyl)semi-carbazone resulted in failure.  It became apparent after three trials that the material used as reagent was p-ureidobenzoic acid rather than 4-(4-carboxyphenyl)semicarbazide.  The discovery of this led to renewed efforts to perfect the synthesis of the reagent.

## EXPERIMENTAL*

Urea Nitrate. - In 300 ml. of distilled water, 200 g. of urea were dissolved and the resulting solution was cooled in an ice salt bath. To this solution, 220 ml. of concentrated nitric acid were added and the resulting mixture was placed in the refrigerator and cooled to 2-3°. The white crystals were filtered off and set to dry. The average yield of two runs was 367 g., 90%.

Nitrourea. - The procedure followed was essentially that of Organic Syntheses[17] with one change. A 2-1. beaker was substituted for the 2-1. Erlenmeyer flask to facilitate addition of urea nitrate. It is also recommended that the 2-1. beaker containing the kilogram of ice used in diluting the sulfuric acid mixture be surrounded by an ice-salt mixture to maintain the low temperature necessary to prevent the decomposition of the nitrourea in an acid solution. Cooling the mother liquor produced an additional 27 g. The average yield of 2 recrystallizations was 110.4 g., 65%.

para-Ureidobenzoic Acid. - The procedure followed was essentially that of Shillington[2]. To 800 ml. of 95% ethanol in a 2-1. beaker, 85 g. (0.62 moles) of p-aminobenzoic acid (Eastman White Label) and 75 g. (0.71 moles) of nitrourea were added. This mixture was warmed on a steam bath for 6 hours. The mixture

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* All melting points are uncorrected and taken in sealed tubes.
# The dimethylformamide was furnished through the courtesy of the Grasselli division of the du Pont Company, and Rohm and Haas.

was then placed in an evaporating dish with one liter of distilled water and this slurry evaporated almost to dryness, triturated with 100 ml. of 95% ethanol, filtered and set to dry. The crude yield was 91.9 g., 82%.

After 2 recrystallizations from dimethylformamide[*] water pair, the melting point[2] was as follows: Shrinking began at 258°, followed by darkening with a change to a semi-liquid waxy state in the range of 262-4°. Bubbling began at 265° and continued with darkening until the substance became honey-like at 271°. Above this temperature the substance darkened without change in physical state. The N. E. 181.42; the N.E. calcd. for $C_8H_8O_3N_2$, 180.16.

The N.E. of a sample of crude material dissolved in 5% NaOH, reacidified with glacial acetic acid to pH 4-5, filtered off and dried, was 176.73.

The Attempted Synthesis of 4-(4-Carboxyphenyl)semicarbazide. The preparation followed was esentially that of Shillington[2]. In a 500 ml. r.b. g.g. flask fitted with a condenser, 300 ml. of 95% ethanol, 50 ml. (1 mole) of 100% hydrazine hydrate and 36 g. (0.2 moles) of p-ureidobenzoic acid were added and set to reflux for 24 hours. The procedure up to this point was identical for all trial runs. For the remainder of the procedure, details will be given under individual headings.

A. Run I. - The resulting liquid was filtered and placed in a beaker cooled in an ice-salt bath and 162 ml. of a solution of concentrated hydrochloric acid/water(1:1) were gradually added

[*] SEE PREVIOUS PAGE.

with stirring to an estimated pH of 4-5 at which point a cloudiness appeared followed by a coagulation which seemed to require time. On further standing a heavy precipitate was formed. This mixture was placed in a refrigerator to cool, then filtered and the solid set to dry.

Five grams of this crude material were recrystallized from a dimethylformamide-water pair. The yield from this recrystallization was 3.71 g. The melting point was as follows: Shrinking began at 264°, darkening with some liquid at 265° and all liquid at 267°. By adding water to the mother liquor, an additional 0.44 g. were forced out.

The melting point of this forced out material was: shrinking at 241° with darkening at 243-6°. Above this temperature some liquid was formed with bubbling. The 3.71 g. were again recrystallized from a dimethylformamide-water pair. This yielded 1.94 grams which melted as follows: Shrinking at 267°, at 268-9° brown spots appeared and at 270-5° and above the sample became honey-like with some liquid spots and bubbling. Adding water to this mother liquor produced an additional 1.08 g. This sample melted as follows: Shrinking at 246°, darkening at 250°, honey-like with bubbling at 252-3° and at 258-9° complete melting giving a tan liquid.

During the filtration of the original preparation some long white needle-like crystalls were isolated. These were recrystallized from concentrated hydrochloric acid giving fine white crystalline needles which gave a positive permanganate and dichromate tests and melted sharply at 206-7°.

B. Run II. - The procedure of the second run was essentially that of the first run with the following exceptions. In Run II, seven more milliliters of concentrated hydrochloric acid-water (1:1) solution were added lowering the pH to 2-3. The solid resulting form this acidification, was filtered off and dried giving 20.14 g. of product. This melted as follows: Shrinking at 210° and melting at 212-5°. The mother liquor was evaporated to dryness and the resulting solid triturated with 100 ml. of water and filtered, yielding 11.57 g. of a tannish solid which melted as follows: Shrinking began at the bottom of the melting point tube at 220° and continued tó rise through the sample until at 227° the solid had become honey-like. Above 230° the sample bubbled and began to rise up the tube. It gave an N.E. of 179.7; the N.E. calcd. for $C_8H_8O_3N_2$, 180.16, for $C_8H_9O_3N_3$, 195.1.

A small sample of the 20.14 g. was recrystallized from a dimethylformamide-water pair. The check the effect of oven-drying, part was dried in an oven at 80° and part was air dried. The oven dried sample melted as follows: Shrinking at 257-8° and became honey-like at 260° and above. The air dried sample melted as follows: Shrinking and darkening began at 263° and melted with bubbling at 265-6°. Adding water to the mother liquor from this recrystallization forced out a small amount of solid which melted as follows: Shrinking at 241°, gradually darkening and honey-like with bubbling at 242-6° and became liquid at 255°.

A small sample of the 11.57 g. resulting from the evapora-
tion and trituration was recrystallized with difficulty from a
dimethylformamide-water pair and the resulting product was sep-
arated into an air dried and an oven dried sample as before. The
oven dried sample melted as follows: Shrinking at 230°, became
honey-like with bubbling at 234-8° and remained unchanged when
heated to 244°. The air dried sample melted as follows: Shrink-
ing at 232° and between 240° and 245° it gradually darkened with
the formation of some liquid and bubbling.

To check the effect of redistilling the dimethylformamide,
a sample of the 20.14 g. from the second run was recrystallized
from a dimethylformamide-water pair, using redistilled dimethyl-
formamide. The product melted as follows: brown spots at 245°,
shrinking at 257°, more darkening and shrinking occured as it
became deep brown at 261°, at 262-3° bubbling began and at
268-9°, the sample was entirely liquid. This material was recrys-
tallized a second time from a dimethylformamide-water pair. The
resulting product melted as follows: brown spots at 253°, shrink-
ing at 258-9°, and 260° bubbling began and by 268° the sample
had all turned to liquid. The N.E. of this sample was 183.87.

A sample of the 20.14 g. was dissolved in 5% sodium hydroxide
and reacidified with glacial acetic acid to a pH of 4-5, gave a
N.E. of 181.98. The N.E. calcd. for $C_8H_8O_3N_2$, 180.16, for
$C_8H_9O_3N_3$, 195.1

The crude yields from 2 runs were 18.5 g., 46% and 20.14 g.,
50%; the melting points were as follows: Shrinking at 242°, melt-

ing at 246-51° and shrinking at 210° and melting at 212-15°,
respectively.

### The Attempted Synthesis of Camphor 4-(4-Carboxyphenyl)semicarbazone.

A. Run I. - In a 50 ml. erlenmeyer fitted with a reflux con-
denser, 0.5 g (o.00256 moles) of 4-(4-carboxyphenyl)semicarbazide
and 0.9 g. (0.0059 moles) of sodium acetate were dissolved in
5 ml. of dimethylformamide and 5 ml. of methyl alcohol and set
to reflux for 6 hours. This resulted in a yellow liquid to which
5% sodium hydroxide was added until the solution became basic
to litmus. An ether extraction was attempted at this point but
ether proved to be readily soluble in the dimethylformamide-
methanol-water mixture. At this point, it was decided to return
the mixture to neutrality and boil off the ether. After this
was done, 25 ml. of distilled water were added to produce a
cream colored precipitate which was filtered off and placed in
a stoppered erlenmeyer to prevent possible sublimation. The
yield was 0.35 g., 41%, of a cream solid which melted as follows:
Gradual softening above 169° with no sharp melting point. The
solid was only partly soluble in 5% sodium bicarbonate and 5%
sodium hydroxide, so the mixture was extracted with ether and
reacidified to congo red using glacial acetic acid. The result-
ing cream colored precipitate was filtered off and set to dry.
This solid melted as follows: Turned brown and melted at 268-9°
with bubbling. After being recrystallized from a dimethylforma-
mide-water pair it melted as follows: Some liquid at 269°, turn-
ing to a dark liquid with bubbling at 272-3°. A mixed melting

point was taken with recrystallized para-ureidobenzoic acid.
It was as follows: Shrinking began at 274°, some dark liquid
formed at 275° and bubbling began at 276°.

B. Run II. - Run II was essentially the same as Run I except
that it was proportionately increased 5 times and a different
means of separation was used. In this run a tan solid was left
after the refluxing and was filtered off. The mother liquor
was placed in an evaporating dish on a steam bath and evaporated
until a tan precipitate formed. This was filtered off and set
to dry. An excess of water was added to the mother liquor forc-
ing out a white solid. The yields were respectively 0.6, 1.06,
and 4.3 g.

A portion of the 0.6 g. sample was triturated with ether
three times and the remaining solid dried. This solid was soluble
in water to give an approximately neutral solution and an acid-
ification with dilute acetic acid, a tan precipitate formed.
The precipitate was dried and a sample was heated on a platinum
crucible cover until all traces of black had disappeared. A
drop of water on the cover gave a pH 10 with pHydrion paper.
The solid melted as follows: Heated to 344° without change.

C. Run III. - To check the effect of sodium acetate on the
reaction, run III was made using the same amount of all components
except replacing the solvent of 5 ml. of methanol and 5 ml. of
dimethylformamide with 10 ml. of dimethylformamide alone. Water
was added to precipitate the product which was filtered and set
to dry.

## SUMMARY

Improvements have been made in the preparation of nitrourea, p-ureidobenzoic acid and 4-(4-carboxyphenyl)semicarbazide. In the future investigations will be made to determine the effect of time on the synthesis of 4-(4-carboxyphenyl) semicarbazide from p-ureidobenzoic acid. An attempt will also be made to see if recrystallization of the p-ureidobenzoic acid is necessary prior to the hydrazination step. It is believed that examination will show that previous runs failed because improper time was allowed for refluxing.

The attempts to prepare the camphor derivative were unsuccessful.

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