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## The Reaction of Ketosemicarbazones with Lead Tetraacetate

Thomas M. Davies

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THE REACTION OF  
KETOSEMICARBAZONES  
WITH  
LEAD TETRAACETATE

by

Thomas M. Davies

A thesis presented to the Faculty of the  
School of Graduate Studies in partial fulfillment  
of the  
Degree of Master of Arts

Western Michigan University  
Kalamazoo, Michigan  
January 1964

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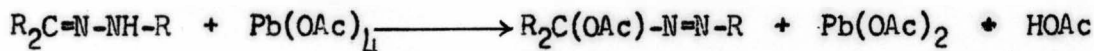
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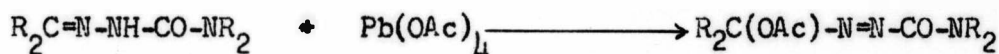
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## INTRODUCTION

It has been demonstrated that lead tetraacetate will oxidize ketohydrazones to azoacetates in good yields (11).



Since ketosemicarbazones are structurally equivalent to ketohydrazones, it was thought that the reaction of ketosemicarbazones with lead tetraacetate would proceed in a similar manner. Originally the object of this research was to prepare a series of new azo compounds related to semicarbazones by lead tetraacetate oxidation.



The 4,4-disubstituted ketosemicarbazones were chosen for the research in order to avoid possible complications that may arise from the reaction of lead tetraacetate and amide hydrogen atoms.

This series of compounds was of interest because of the potential biological activity as a result of the azo function in the molecule. Aromatic azo compounds have shown anti-tumor activity (15) and activity against tubercle bacilli (14). Derivatives of ketosemicarbazones have also proven effective as pesticides (5, 19, 20, 21). Aromatic azo dyes have shown carcinogenic properties (1).

Apparently no previous work has been directed toward the preparation of these compounds. A literature search reveals no references to the azo oxidation products of ketosemicarbazones.

## EXPERIMENTAL

In the following section, all boiling and melting points are in degrees Centigrade and are uncorrected. The micro-analytical data were obtained from the Galbraith Laboratories, Knoxville, Tennessee.

## Preparations of 4,4-Disubstituted Ketosemicarbazones

A. Attempt via Carbamyl Chlorides and Hydrazine.- A solution of 23.2 g. (0.1 mole) of diphenyl carbamyl chloride dissolved in 250 ml. of ethanol was added slowly to 13.5 g. (0.4 mole) of 95% hydrazine solution precooled to 5°. This temperature was maintained throughout the addition and for 15 min. afterward. Mixing during the reaction was accomplished with a magnetic stirrer. A white solid formed in the reaction vessel and dissolved when the mixture was warmed on a steam bath. After one recrystallization from ethanol, 21.9 g. (76%) of white crystalline 4,4-diphenylsemicarbazide was isolated; m.p. 156-157°. Lit.: m.p. 154° (18).

Five and seven tenths grams (0.025 mole) of 4,4-diphenylsemicarbazide prepared in the preceding manner, 8.7 g. (0.15 mole) acetone, 1.5 g. sodium acetate and 25 ml. of water were mixed and refluxed for 10 hrs. The reaction was cooled and extracted 3 times with chloroform, dried with sodium sulfate and concentrated on a vacuum evaporator. Upon refrigeration the yellow viscous oil solidified. After recrystallization from an ethanol-water mixture



3.0 g. of white product was obtained; m.p.  $53-54^{\circ}$ . Examination of the infrared spectrum later identified this material as diphenylamine and the amount isolated corresponds to a 71% conversion.

A similar reaction of 4,4-diphenylsemicarbazide with 3-pentanone also yielded diphenylamine as the major product.

B. Attempt via Ethyl Chlorocarbonate.- Forty grams (1.0 mole) of sodium hydroxide was dissolved in 200 ml. of water. After cooling to  $0^{\circ}$ , this solution was added to a second solution of 45 g. (1.0 mole) of dimethylamine in 100 ml. of water. To this solution there was added 108.0 g. (1.0 mole) of ethyl chlorocarbonate with the temperature maintained between 0 and  $10^{\circ}$ . During the addition the mixture was stirred on a magnetic stirrer. Upon completion of the addition of the ethyl chlorocarbonate the reaction was warmed to room temperature and extracted 3 times with ethyl ether. The ether solution was dried over sodium sulfate and concentrated on a vacuum evaporator. The residue was distilled under reduced pressure. Fractions were collected having properties indicated in table I. Combination of fractions 4-6 provided 77.9 g. (67%) of pure N,N-dimethyl urethane. Lit.: b.p.  $147^{\circ}$  (4).

A mixture of 23.4 g. (0.2 mole) of N,N-dimethyl urethane and 10.1 g. (0.2 mole) of 95% hydrazine solution was refluxed for 20 hrs. At the end of this time no visible change was evident. The reaction was repeated using n-butanol as solvent. The resultant solution was added to dilute hydrochloric acid. The acid solution

was extracted 3 times with ethyl ether, neutralized with sodium hydroxide and extracted with chloroform. This was dried with sodium sulfate and concentrated on a vacuum evaporator. The urethane was recovered in 96% yield, indicating essentially no reaction.

TABLE I

## Distillation of N,N-Dimethyl Urethane

Fraction	Boiling Range	Pressure	Weight	$n_D^{26^\circ}$
1	41-55°	80 mm.	3.3 g.	1.3902
2	55-73°	"	3.9 g.	1.3978
3	73-80°	"	6.3 g.	1.4093
4	80-81°	"	37.6 g.	1.4129
5	81-81°	"	31.6 g.	1.4129
6	81-81°	"	8.7 g.	1.4130

C. Attempt via Ketohydrazone and Carbamyl Chloride.— A solution of 13.5 g. (0.1 mole) of diethyl carbamyl chloride in 50 ml. of benzene was slowly added to a second solution containing 19.6 g. (0.1 mole) benzophenone hydrazone and 7.7 g. (0.1 mole) pyridine in benzene. This was stirred at room temperature for 48 hrs. The mixture was then refluxed for 2 hrs. After cooling, the solution was extracted twice with water, dried with sodium sulfate and concentrated by vacuum evaporation of the benzene. The residue solidified into a tan solid which was recrystallized from ethanol. The white crystalline solid obtained weighed 12.2 g. and melted at

162-163°. By comparison of infrared spectra this was later identified as benzophenone azine. Lit.: m.p. 162° (3). The reaction was repeated using twice the molar requirement of carbamyl chloride and five times the required amount of pyridine. The reaction product was again benzophenone azine.

D. Preparation via Secondary Amine Exchange with Ketosemicarbazones.-

1. Preparation of acetone semicarbazone.- A solution of 22.4 g. (0.2 mole) semicarbazide hydrochloride, 14.4 g. (0.25 mole) acetone and 25 g. sodium acetate was mixed with 100 ml. of water. This was warmed in a boiling water bath and after cooling to room temperature, crystals formed. The white solid was isolated and recrystallized from dilute ethanol to yield 18.9 g. (82%) of acetone semicarbazone; m.p. 186-187°. Lit.: m.p. 187° (8).

2. Preparation of benzophenone semicarbazone.- A solution of 36.5 g. (0.2 mole) of benzophenone in hot ethanol was prepared. Water was added to this to bring the solution to the saturation point. A mixture of 22.4 g. (0.2 mole) semicarbazide hydrochloride and 25 g. sodium acetate was added to this. All solid components were dissolved by heating the mixture, which crystallized when cooled. The benzophenone semicarbazone was recrystallized from ethanol to yield 20.5 g. (86%) of white product; m.p. 164-165°. Lit.: m.p. 164-165° (8).

3. Preparation of acetophenone semicarbazone.- This compound was prepared in 89% yield following the above procedure for benzophenone semicarbazone. The pure acetophenone semicarbazone melted

at 200-201°. Lit.: m.p. 198-199° (8).

#### 4. Reaction of ketosemicarbazones with secondary amines.-

According to the procedure of Stratton and Wilson (17), piperidine was dried over potassium hydroxide pellets and distilled to provide anhydrous amine. Acetone semicarbazone was dried over calcium chloride in a vacuum dessicator. Anhydrous toluene was obtained by distillation and storing over sodium cuttings.

Seventeen grams (0.2 mole) piperidine and 23 g. (0.2 mole) acetone semicarbazone were mixed with 200 ml. of anhydrous toluene. The acetone semicarbazone did not completely dissolve. The reaction was refluxed for 24 hrs. at which time no undissolved semicarbazone remained. The hot solution was filtered and concentrated by vacuum evaporation of the toluene. A viscous brown semi-solid residue remained. This was redissolved in benzene and crystallized to yield 11.4 g. of white acetonepiperidinoformylhydrazone.

Other 4,4-disubstituted ketosemicarbazones were prepared in an analogous manner. The properties and the analyses (if not previously reported) are summarized in table II.

Reactions of 4,4-Disubstituted Ketosemicarbazones with Lead Tetraacetate.

A. Reaction with 4,4-Diethyl Benzophenonesemicarbazone.- A solution containing 13.9 g. (0.032 mole) of lead tetraacetate dissolved in methylene chloride was added slowly to a cooled solution of 8.85 g.

TABLE II

## Properties and Analyses of 4,4-Disubstituted Ketosemicarbazones

Compound	M.p.	Yield	Nitrogen Calc.	Anal. Found
$(\text{CH}_3)_2\text{C}=\text{N}-\text{NH}-\text{CO}-\text{N}(\text{CH}_2-)_5$	100-101°*	66%	-	-
$(\text{CH}_3)_2\text{C}=\text{N}-\text{NH}-\text{CO}-\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$	95-95°	92	22.68%	22.34%
$\phi_2\text{C}=\text{N}-\text{NH}-\text{CO}-\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$	104-105°	84	13.58	13.65
$\phi_2\text{C}=\text{N}-\text{NH}-\text{CO}-\text{N}(\text{CH}_2\text{CH}_3)_2$	100-101°	85	14.27	14.32
$\begin{array}{c} \text{CH}_3 \\ \diagdown \\ \phi \end{array} \text{C}=\text{N}-\text{NH}-\text{CO}-\text{N}(\text{CH}_2\text{CH}_3)_2$	88-89°	96	18.01	18.13

\*Lit.: m.p. 100-101° (17).

(0.03 mole) of benzophenone 4,4-diethylsemicarbazone dissolved in 50 ml. of methylene chloride. The solution was stirred by a magnetic stirrer and was cooled to -5° in an ice salt bath. The temperature was maintained between 5 and -5° throughout the addition. After the addition was completed the mixture was stirred an additional 15 min. at room temperature. After mixing with 100 ml. of water the methylene chloride solution was filtered through Celite, washed with water, sodium bicarbonate solution, and again with water. The methylene chloride solution was dried with anhydrous sodium sulfate and concentrated by vacuum evaporation to leave a red-orange viscous liquid. This residue evolved a gas presumed to be nitrogen and was

refrigerated. After 20 hrs. at  $0-5^{\circ}$  the liquid was passed through a basic alumina column using benzene as an eluent. Nine fractions of 10 to 20 ml. were collected and after concentration the residues in the first six solidified and were combined. This solid was recrystallized from pentane to yield 6.15 g. (63%) of 2-oxo-1,1-diphenylpropyldiethyl carbamate; m.p.  $70-71^{\circ}$ .

Anal. Calc'd. for  $C_{20}H_{23}NO_4$ : C, 73.82; H, 7.12; N, 4.31.  
Found: C, 74.00; H, 7.22; N, 4.15.

The mother liquor from the above recrystallization was concentrated and combined with the chromatography fractions that did not solidify and stirred at reflux with 50 ml. of 20% phosphoric acid for 20 hrs. The reflux condenser was connected to a trap containing lime water. The evolution of carbon dioxide in the hydrolysis was indicated by the formation of a dense white precipitate of calcium carbonate in the trap.

After the reaction mixture had cooled it was extracted 3 times with 50 ml. portions of pentane. The acid solution was neutralized and reacted in the conventional Schotten-Baumann manner with p-toluene sulfonyl chloride. A solid product was isolated and recrystallized from a small amount of dilute ethanol to yield N,N-diethyl p-toluene-sulfonamide; m.p.  $59^{\circ}$ . The reported value for this amide is  $60^{\circ}$  (8). The pentane extract of the acid hydrolysis mixture was washed with dilute sodium hydroxide. From this pentane solution 2.1 g. (0.0093 mole) of 1-hydroxy-1,1-diphenylpropanone was isolated; m.p.  $70-71^{\circ}$ . Lit.: m.p.  $66-67^{\circ}$  (16).

Anal. Calc'd. for  $C_{15}H_{14}O_2$ : C, 79.62; H, 6.24. Found: C, 79.43; H, 6.05.

The sodium hydroxide wash solution was neutralized with dilute hydrochloric acid and extracted with pentane. The pentane was dried with sodium sulfate and concentrated by vacuum evaporation. The residue weighed 0.3 g. and melted at  $150^{\circ}$  indicating that this substance was benzoic acid (0.0013 mole). Lit.: m.p.  $150^{\circ}$  (8).

The 1-hydroxy-1,1-diphenylpropanone was treated with alkaline iodine solution. A positive haloform test was indicated by the isolation of iodoform; m.p.  $117-118^{\circ}$ , and benzoic acid; m.p.  $150^{\circ}$ . Lit.:  $CHI_3$ , m.p.  $119^{\circ}$ ; benzoic acid, m.p.  $150^{\circ}$  (8). A mixed melting point determination with authentic benzoic acid showed no depression.

B. Reaction with Benzophenone-morpholinoformylhydrazone.— This morpholine derivative of benzophenone-semicarbazone (0.025 mole) was reacted with lead tetraacetate (0.027 mole) in the above manner. After the reaction and subsequent recrystallization from a benzene-pentane mixed solvent 4.6 g. (52%) of 2-oxo-1,1-diphenylpropyl 4'-morpholine carboxylate was isolated; m.p.  $160-161^{\circ}$ .

Anal. Calc'd. for  $C_{20}H_{21}NO_5$ : C, 70.78 ; H, 6.24; N, 4.13. Found: C, 70.92; H, 6.20; N, 3.96.

A 3.31 g. portion of this compound was subjected to hydrolysis in 50 ml. of 20% phosphoric acid. Distillate from this hydrolysis was neutral indicating the absence of an acetate ester in the original compound. From this hydrolysis mixture 1.55 g. of 1-hydroxy-1,1-

diphenylpropanone was isolated; m.p. 70-71°.

C. Reaction with 4,4-Diethyl Benzophenonesemicarbazone in Acetic

Acid.- A solution containing 18.2 g. (0.042 mole) of lead tetraacetate dissolved in 30 ml. of glacial acetic acid was added slowly to a second solution of 11.8 g. (0.04 mole) of 4,4-diethyl benzophenone-semicarbazone dissolved in 20 ml. of glacial acetic acid. The reaction was run in much the same manner as described above, with the exception that the temperature was maintained at 15-20°. The reaction mixture evolved a gas as before. After removal of the solvent by dilution with water, the reaction product was extracted with methylene chloride. This solution was washed with water and sodium bicarbonate solution. After drying with sodium sulfate and removal of the methylene chloride by vacuum evaporation, a semi-solid residue remained. This was washed with pentane. After concentration of the pentane solution, 1.1 g. (8.5%) of 2-oxo-1,1-diphenylpropyl-diethyl carbamate was isolated. The pentane insoluble portion was dissolved in 50 ml. of benzene. This was passed through an alumina column and collected in six 10 ml. fractions. Recrystallization from benzene pentane mixed solvent yielded 5.1 g. (57%) of benzhydrol acetate; m.p. 40-41°. Lit.: m.p. 39-41° (7). A mixed melting point with authentic benzhydrol acetate showed no depression.

D. Reaction with Acetonepiperidinoformylhydrazone.- A solution of 26.8 g. (0.062 mole) of lead tetraacetate dissolved in methylene chloride was slowly added to a stirred solution of 10.2 g. (0.06 mole)



of acetonepiperidinoformylhydrazone in 50 ml. of methylene chloride. The reaction proceeded in the usual manner described above. One of the anticipated reaction products was quite water soluble, so in the isolation of products only small amounts of ice cold water were used in the washing operations. The methylene chloride solution was distilled through a 30 cm. column packed with stainless steel helices. The methylene chloride solvent was collected first. The residue was distilled at atmospheric pressure and the fractions and properties are summarized in table III.

TABLE III

Distillation of Product from Reaction of Lead Tetraacetate with  
Acetonepiperidinoformylhydrazone

Fraction	Boiling Range	Weight	$n_D^{25^\circ}$
1	56-80°	1.13 g.	1.3599
2	80-86°	0.97	1.3661
3	86-88°	0.60	1.3708
4	88-89°	1.41	1.3748
5	89-89°	1.89	1.3751
6	89-105°	0.22	1.4094

The properties of fractions 4 and 5 correspond to those of isopropyl acetate and represent a minimum yield of 57% for this ester produced in this oxidation. Examination of the original reaction mixture by vapor phase chromatography indicated a major component having the same retention time as isopropyl acetate. The

reported properties for isopropyl acetate are; b.p.  $88.4^{\circ}$ ,  $n_D^{20}$  1.3770 (12).

E. Reaction with 4,4-Diethyl Acetophenonesemicarbazone.- A solution containing 13.9 g. (0.032 mole) of lead tetraacetate was reacted with 8.85 g. (0.03 mole) of 4,4-diethyl acetophenonesemicarbazone in the previously described manner. A workup of the reaction mixture as before provided material which on distillation through the 30 cm. column described above gave the following fractions and properties.

TABLE IV

Distillation of Product from Reaction of Lead Tetraacetate with  
4,4-Diethyl Acetophenonesemicarbazone

Fraction	Boiling Range	Pressure	$n_D^{25}$
1	$48-50^{\circ}$	1 mm.	1.4851
2	$50-51^{\circ}$	"	1.4972
3	$51-53^{\circ}$	"	1.4975
4	$53-55^{\circ}$	"	1.4991
5	$55-60^{\circ}$	"	1.5009
6	$60-110^{\circ}$	"	1.5717

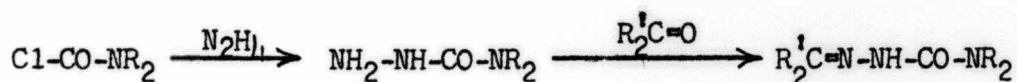
The combined weight of fractions 1-5 was 3.86 grams. The infra-red spectrum of each of these fractions was obtained and compared with the spectrum of pure  $\alpha$ -phenylethyl acetate. The spectrum of each fraction exhibited all of the bands of the authentic ester as well as some additional bands ( $3400$ ,  $1725$ ,  $1625$ , and  $1435$   $\text{cm}^{-1}$ ) indicating

impurities. Vapor phase chromatography of each fraction indicated the ester to be the major constituent. The reported properties for  $\alpha$ -phenylethyl acetate are; b.p.  $215^{\circ}$  and  $n_D^{18^{\circ}}$  1.5003 (13).

## DISCUSSION AND CONCLUSION

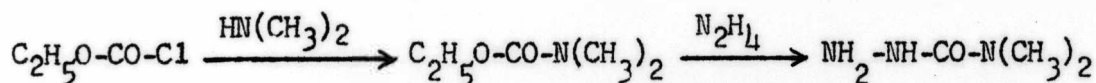
This research divides into two main parts; the preparation of the 4,4-disubstituted ketosemicarbazones and, secondly, the reaction of these semicarbazones with lead tetraacetate.

Four routes to the 4,4-disubstituted ketosemicarbazones were investigated in the course of the study. The first attempt was one based upon a method reported by Vogelesang (22) and shown schematically as follows:



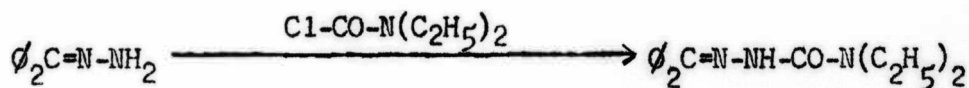
The 4,4-disubstituted semicarbazides necessary for the preparation of the keto derivatives were prepared by the reaction of N,N-disubstituted carbamyl chlorides with hydrazine. This reaction was successfully carried out on commercially available N,N-diphenyl carbamyl chloride to yield the 4,4-diphenylsemicarbazide. The next step was to be the conversion of the semicarbazide to the semicarbazone by reaction with a ketone in the conventional manner. With both acetone and 3-pentanone this reaction failed to produce the semicarbazone. Instead and quite unexpectedly, diphenyl amine was the only isolated product. This reaction was conducted in the presence of aqueous sodium acetate as is the customary procedure in the preparation of other hydrazine derivatives. Evidently hydrolysis of this amide occurs unusually fast. The reaction was not attempted under non-aqueous conditions.

A second attempt was made starting from ethyl chlorocarbonate as shown in the following sequence:



The first reaction readily yielded N,N-dimethyl urethane. The second step in the synthesis, which is the reaction of the urethane with hydrazine, may be considered analogous to the ammonolysis of an ester. This reaction also failed in two attempts. The reactants were quantitatively recovered after a reaction time of twenty hours. In one instance refluxing n-butanol solvent was employed to attain a higher reaction temperature.

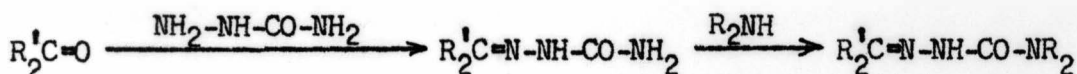
Benzophenone hydrazone was reacted with N,N-diethyl carbamyl chloride in a third attempt to obtain the desired 4,4-disubstituted ketosemicarbazones:



Excess pyridine was introduced as a base to make this reaction similar to the conventional Schotten-Baumann acylation of amines. Even with excess carbamyl chloride, benzophenone azine was produced and no semicarbazone was isolated.

The fourth and successful reaction considered involved the reaction of an unsubstituted ketosemicarbazone with a secondary amine after the method used by Stratton and Wilson (17) in the preparation of acetone-piperidinoformylhydrazone. This reaction appears to provide a general route to these substituted semicarbazones and is summarized in the

following steps:



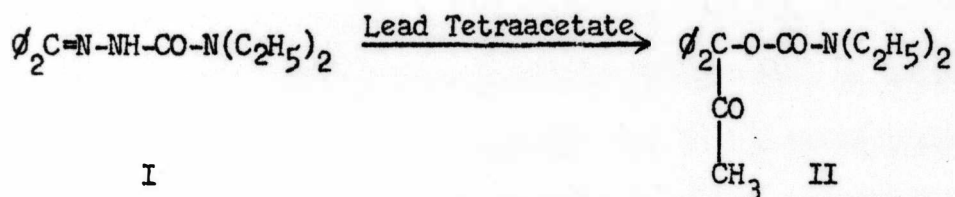
The first step in this synthesis was the preparation of unsubstituted semicarbazones. This was accomplished in the usual manner by reaction of semicarbazide hydrochloride with a ketone. Secondly, the semicarbazone was refluxed under strictly anhydrous conditions with a secondary amine. This amine was exchanged with the unsubstituted  $NH_2$  group. The evolution of ammonia evidently assists in the completion of the reaction. The isolation of products was quite easily accomplished. Apparently few impurities were produced in the reactions. Many of the compounds prepared in this manner crystallized immediately upon evaporation of the reaction solvent.

The yields obtained in this series of reactions of secondary amines with ketosemicarbazones ranged from a low of 66% for the previously reported acetonepiperidinoformylhydrazone (17) to 96% in the reaction of diethyl amine with acetophenone semicarbazone.

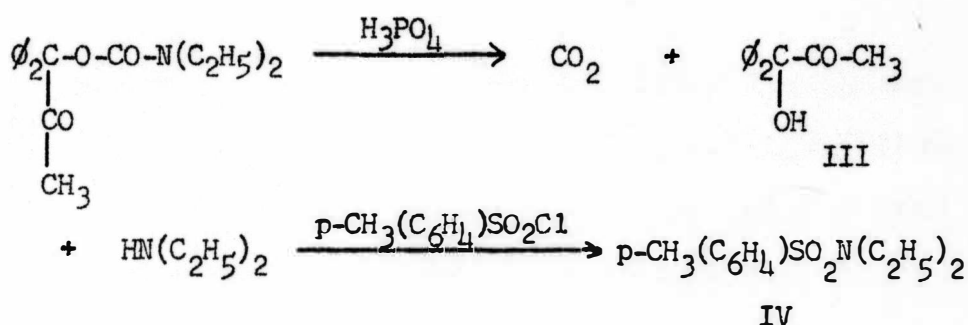
The reaction of lead tetraacetate with 4,4-diethyl benzophenone-semicarbazone, I, presented an unexpected complication. It was first thought that an azoacetate would be obtained from this reaction which would parallel the oxidation of ketohydrazone by lead tetraacetate as reported by Iffland and coworkers (11). However, the product isolated was not an azoacetate as expected, but was 2-oxo-1,1-diphenyl-propyldiethyl carbamate, II.

After reaction of the ketosemicarbazone with lead tetraacetate in

the manner described for ketohydrazones (11), the mixture was noted to evolve a gas, presumably nitrogen. After refrigeration for twenty



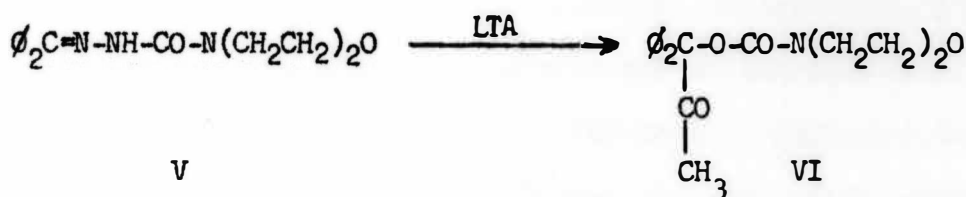
hours, the product, II, was isolated in 63% yield. The structure of the product was established from the following observations: A portion of II was subjected to acid hydrolysis in boiling 20% phosphoric acid. From this hydrolysis mixture a neutral substance, 1-hydroxy-1,1-diphenylpropanone, III, and a base were separated. The base, with p-toluene sulfonyl chloride, formed an amide identified as N,N-diethyl p-toluenesulfonamide, IV. Carbon dioxide was also shown to be evolved in this hydrolysis. A positive iodoform test was achieved on both II and III. From the solution resulting from this test on III, benzoic acid was also identified.



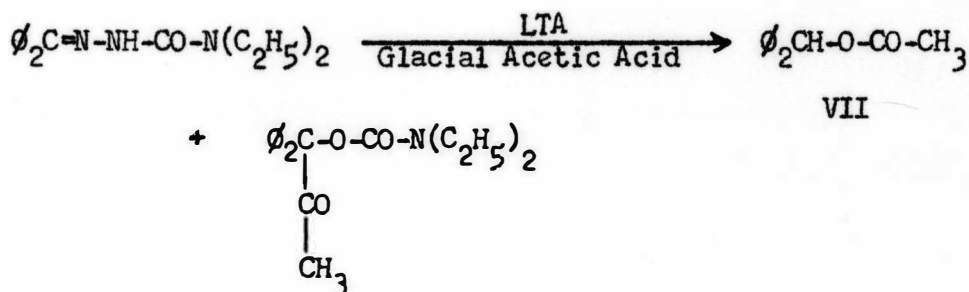
The infrared spectrum of II showed strong bands at  $1708 \text{ cm}^{-1}$  for the carbamate carbonyl group and at  $1720 \text{ cm}^{-1}$  for the saturated ketone carbonyl group (2). These observations leave no alternate

choice for the structure of II.

Benzophenonemorpholinoformylhydrazone, V, was also reacted with lead tetraacetate. The reaction product in this case was identified as 2-oxo-1,1-diphenylpropyl 4'-morpholine carboxylate, VI, and was formed in 52% yield. This product was hydrolyzed in boiling 20% phosphoric acid as before and yielded the same neutral product; 1-hydroxy-1,1-diphenylpropanone, III.



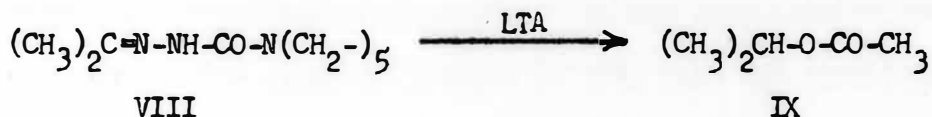
The reaction of 4,4-diethyl benzophenonesemicarbazone with lead tetraacetate was next conducted in glacial acetic acid solvent. (Methylene chloride was used in all previous reactions.) The reaction mixture again evolved a gas. This time II was isolated as before, but in only 8.5% yield. The major product was identified as benzhydrol acetate, VII, and was collected in 57% yield.



Acetonepiperidinoformylhydrazone, VIII, when reacted with lead tetraacetate in methylene chloride with no added acetic acid, gave

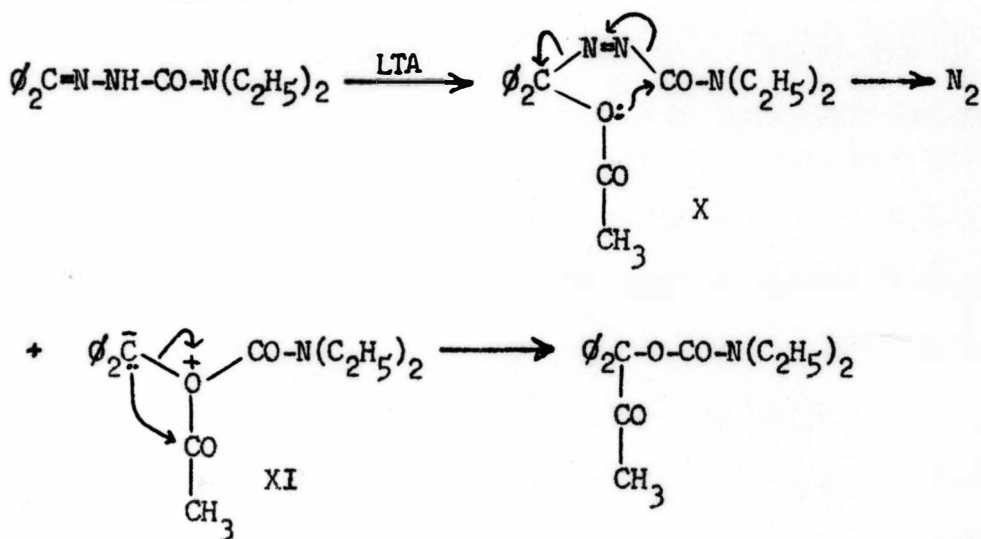


isopropyl acetate in a minimum yield of 57%.



Finally, in similar fashion, the reaction of 4,4-diethyl acetophenonesemicarbazone with lead tetraacetate was shown qualitatively to form  $\alpha$ -phenylethyl acetate. The esters from these reactions of acetonepiperidinoformylhydrazone and 4,4-diethyl acetophenonesemicarbazone were initially identified using vapor phase chromatography. The minimum yield of isopropyl acetate was based on isolation of pure ester from the reaction mixture, however the distillation of the crude  $\alpha$ -phenylethyl acetate yielded no pure product.

A mechanism has been proposed to account for the results obtained in these reactions (10).

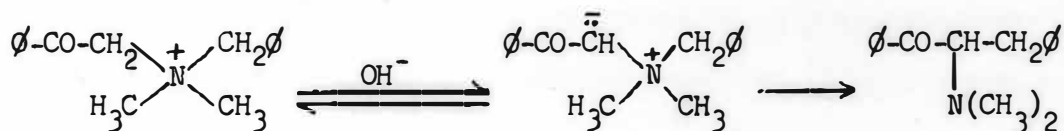


This mechanism proposes the formation of the azoacetate, X, which was the anticipated product of the reaction. As noted above, this is

comparable to the compounds which result from the reaction of lead tetraacetate with ketohydrazones. This formation of the intermediate azoacetate is followed by an intramolecular nucleophilic displacement at the amide carbonyl and the elimination of nitrogen.

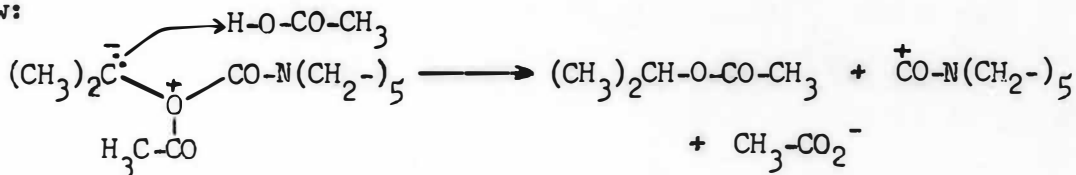
The intermediate zwitterion, XI, is then converted into II by a 1,2 shift. This shift is similar to the shift observed in the Stevens' rearrangement. This is apparently the first rearrangement of this type which involves an oxonium ion intermediate.

An example of a Stevens' rearrangement (6) appears below:



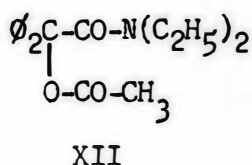
In this example, the carbanion portion of the intermediate is stabilized by the benzoyl group. If this is replaced by a phenyl group the rearrangement no longer occurs. The phenyl group does not provide sufficient stabilization for the intermediate to form.

In the decomposition of the azoacetates under consideration the principal driving force for the reaction is the formation of molecular nitrogen rather than the stabilization of the zwitterion. Nevertheless the basicity of the carbanion portion of the intermediate will increase as the phenyl groups are successively replaced by alkyl groups. The increased basicity may explain the preferential reaction of the zwitterion from the acetonepiperidinoformylhydrazone with acetic acid as shown below:



Following protonation of the zwitterion it is expected that the resulting oxonium ion would decompose by elimination of the most stable group attached to the oxygen atom. The amide acyl carbonium ion may reasonably be the most stable departing positive ion in this case.\* The acetic acid is necessarily present as a by-product in the initial reaction with lead tetraacetate. Consequently this reaction may be forced to be the main course in acetic acid solvent even with the zwitterion derived from benzophenone semicarbazone.

The mechanism proposed would also be expected to give another product by an alternate rearrangement of the zwitterion XI. This would lead to the ester, XII, by attack of the carbanion portion on the amide carbonyl carbon atom.




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\*In all crude reaction mixtures obtained from the 4,4-disubstituted ketosemicarbazones with lead tetraacetate, an infrared band at  $1820\text{ cm}^{-1}$  was observed suggesting an acid anhydride impurity (the lower frequency anhydride carbonyl band would be masked by other carbonyl absorptions). The anhydride may arise in this process following the elimination of an acetyl carbonium ion. With the benzophenone derivatives the benzhydryl carbonium ion may be the more stable leaving group. In the presence of acetic acid, the reaction products will be the same regardless whether the benzhydryl ion or the amide acyl ion departs. Another carbonium ion acceptor must be used in order to distinguish between these possibilities.

This product has been shown to be present in the reaction mixture of 4,4-diethyl benzophenonesemicarbazone with lead tetraacetate. The infrared spectrum of fractions purified by an alumina column chromatography process showed an acetate carbonyl stretching band at 1750  $\text{cm}^{-1}$  in addition to the already mentioned bands at 1708  $\text{cm}^{-1}$  and 1720  $\text{cm}^{-1}$ .

In the hydrolysis with 20% phosphoric acid of the mother liquor from recrystallization of II, there was isolated 0.0013 mole of benzoic acid and 0.0093 mole of III. Benzoic acid would result from acid hydrolysis of the ester XII. From this information and the original yield of III, the ratio of yields of the rearrangement products (II to XII) may be about 20 to 1.

It should be re-emphasized that the expected azoacetate was not isolated in any of these experiments. However, the products actually isolated can be rationalized most easily on the assumption that the azoacetate was present as an intermediate. Consequently interest is focused on structural changes in the molecule which will stabilize this azoacetate intermediate and allow its isolation. The following modifications have been considered but not yet explored. Atoms or groups attached to the semicarbazone carbonyl carbon having less electron withdrawal effect than the oxygen or amide nitrogen should be relatively less favorable for the first step in the proposed rearrangement process. The substitution of sulfur for the carbonyl oxygen and an alkyl group for the amide nitrogen may accomplish this. Qualitatively 4,4-disubstituted thiosemicarbazones with lead tetraacetate produced a

mixture which evolved nitrogen (9) suggesting that this modification was insufficient to achieve stability. The reaction of acyl hydrazones is currently under investigation (23).

Alternately the zwitterion intermediate may be destabilized by electron release to the carbanion center. The reaction of  $p,p'$ -dimethoxybenzophenone derivatives has been considered in this respect. Finally, the formation of esters with large partial positive charges on the ester carbonyl carbon atom may result in destabilization by forcing large positive charges on adjacent atoms. The use of lead tetratrifluoroacetate instead of lead tetraacetate as an oxidizing agent may accomplish this.

## SUMMARY

Unexpected reaction products have been isolated from a series of reactions of lead tetraacetate with 4,4-disubstituted keto-semicarbazones. A mechanism has been proposed to account for the course of the reactions. All the reactions studied so far indicate that the proposed mechanism is reasonable and the most probable explanation for the products that were isolated.

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