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Preparation and Lead Tetraacetate Oxidation of Aldehydic Hydrazones

Alan J. Quarfoot

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PREPARATION AND LEAD TETRAACETATE
OXIDATION OF ALDEHYDIC HYDRAZONES

by
Alan J. Quarfoot

A Thesis
Submitted to the
Faculty of the School of Graduate
Studies in partial fulfillment
of the
Degree of Master of Arts

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Alan J. Quarfoot

Your life, your achievement, your happiness, your person are of paramount importance. Live up to your highest vision of yourself no matter what the circumstances you might encounter. An exalted view of self-esteem is a man's most admirable quality.

Ayn Rand

MASTER'S THESIS

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QUARFOOT, Alan James

PREPARATION AND LEAD TETRAACETATE OXIDATION OF
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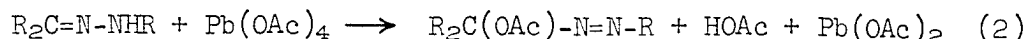
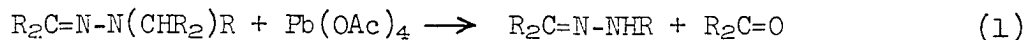
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INTRODUCTION

It is now well established that lead tetraacetate reacts with di-^{1a} and monosubstituted^{1b} ketohydrazones to form azoacetates in good yields:



The reaction has been extended to include the oxidation of pyrazolines,² semicarbazones,³ and ketazines⁴ but relatively little is known about the behavior, under similar conditions, of aldehydic hydrazones. In those cases which have been examined⁵⁻⁷ one or more of five different products were formed. All of the previous work however has involved benzaldehyde or substituted benzaldehyde hydrazones with the exception of Gillis⁸ who examined one vinylogous compound. In addition the hydrazones considered were prepared exclusively, again with the exception of Gillis,⁸ from mono- and disubstituted phenylhydrazines, from sulfonylhydrazines, and heterocyclic hydrazines. This wide range of diverse substituents combined with the use of different solvents and temperatures makes it very difficult to develop a product to substituent relationship. It therefore seemed of interest to study the oxidation of a series of simple and relatively similar aldehydic hydrazones, under the same conditions, in an attempt to better understand the course of the reaction and to examine its possible synthetic value.

EXPERIMENTAL

All melting points are corrected and boiling points uncorrected with both given in degrees Centigrade. The melting points were determined by the capillary method.

The infrared spectra were obtained with a Perkin Elmer Model 21 recording spectrophotometer and the assignment of bands made according to Bellamy.⁹

The nuclear magnetic resonance (nmr) spectra were recorded on a Varian Model A-60 spectrometer as approximately 10% solutions in deuteriochloroform except as noted. Chemical shifts are, in all cases, reported relative to tetramethylsilane as an internal standard. A Varian Model V-6040 temperature controller was used for the variable temperature work. The reduced temperatures were determined by measuring the separation between the methanol signals and using the Varian calibration chart.

The ultraviolet spectra were obtained with a Cary 14 recording spectrophotometer as solutions in 95% ethanol.

Elemental analyses were performed by Galbraith Microanalytical Laboratories of Knoxville, Tennessee.

The lead tetraacetate used in all of the oxidations was obtained from Alfa Inorganics, Inc. and was freed of excess acetic acid prior to use by successive washings with dry pentane. This pentane and the methylene chloride used as a solvent for the reactants were dried over calcium hydride prior to their use.

The benzaldehyde phenylhydrazone was obtained from Eastman Organic Chemicals, the Distillation Products Division and used without further purification. The methyl- and phenylhydrazine used in this study was similarly used without prior purification.

Preparation of Hydrazones

The hydrazones were prepared by dissolving the appropriate hydrazine in methanol containing a trace of acetic acid and then adding the aldehyde in small portions to this solution with external cooling. This order of addition was used to avoid possible condensation of the hydrazone with additional aldehyde.¹⁰ When the addition was complete the solution was heated on a steam bath for 15 minutes and then poured into a large volume of water. The hydrazone which separated was removed and washed with fresh portions of water. With one exception all of the hydrazones prepared were liquids and were dried over anhydrous magnesium sulfate without the use of a solvent and finally vacuum distilled just prior to use. In the case of acetaldehyde phenylhydrazone the crude crystals were dissolved in benzene and then dried as above.

1. Benzaldehyde methylhydrazone

Following the above procedure, 15.9 g (0.15 mol) of benzaldehyde was reacted with 7.6 g (0.16 mol) of methylhydrazine to give 12.7 g (63%) of the hydrazone: bp 112-115° (2 mm); n_D^{25} 1.6145 [lit.¹¹ bp 118-119° (8 mm), n_D^{25} 1.6053]; ir $\nu_{\text{max}}^{\text{neat}}$ (cm⁻¹) 3360 (m, NH), 2900 (m, br, CH), 753 and 693 (s, aromatic, monosubstituted); nmr (CCl₄) δ 2.80 (s, 3, NCH₃), 5.58 (s, 1, NH), and 7.37 ppm (m, 6, aromatic and benzoic).

2. Hydrocinnamaldehyde methylhydrazone

As in the above procedure, 33.5 g (0.25 mol) of hydrocinnamaldehyde

was reacted with 12.7 g (0.275 mol) of methylhydrazine to give 20.0 g (49%) of the hydrazone: bp 103-108° (about 2 mm); n_D^{25} 1.5217 [lit.¹² bp 118° (2 mm)].

3. Acetaldehyde methylhydrazone

Due to the solubility difficulties that would be expected in the isolation of acetaldehyde methylhydrazone, it was prepared and used in solution without isolation. To a solution of 2.3 g (0.05 mol) of methylhydrazine in 20 ml of methylene chloride, 2.6 g (0.06 mol) of acetaldehyde and one drop of acetic acid were added. The solution was heated on a steam bath for 15 minutes and dried over anhydrous magnesium sulfate.

4. Acetaldehyde phenylhydrazone

In the above manner, 25.8 g (0.59 mol) of acetaldehyde was reacted with 56.5 g (0.52 mol) of phenylhydrazine. Crystal formation occurred when the methanol solution was poured into water and cooled. The crude hydrazone was dissolved in benzene and dried. Most of the benzene was removed under vacuum and upon addition of pentane the hydrazone crystallized. Finally the hydrazone was recrystallized from 60-110° petroleum ether to give 35.5 g (51%) of acetaldehyde phenylhydrazone as red-orange crystals: mp 89-92° [lit.¹³ 63° and 99°]; * nmr δ 1.71 (d, 3, J = 5 Hz, CHCH₃ of anti isomer), 1.88 (d, 3, J = 5 Hz, CHCH₃ of syn isomer), 6.61 (quartet, 1, J = 5 Hz, N = CH of syn isomer), and 7.05 ppm (m, 13, aromatic, N=CH of anti isomer, and NH).¹⁵

*This melting point is dependent upon the relative amounts of the syn and anti isomers present¹⁴

5. Isobutyraldehyde phenylhydrazone

As in the above procedure, 18.0 g (0.25 mol) of isobutyraldehyde was reacted with 28.1 g (0.26 mol) of phenylhydrazine to yield 22.6 g (56%) of the hydrazone: bp 131-133° (12 mm); n_D^{25} 1.5625 [lit.¹⁶ bp 138° (12 mm)]; nmr δ 1.08 (d, 6, $J = 7$ Hz, CH_3CHCH_3), 2.47 (m, 1, $J = 7$ Hz, CH_3CHCH_3), and 7.00 ppm (m, 6, aromatic and $\text{N}=\text{CH}$).

It was necessary that the exposure of this hydrazone to air be minimized since it otherwise readily decomposes to a blood red oily material of undetermined nature.

6. Pivalaldehyde methylhydrazone

Using the above procedure, 43.1 g (0.50 mol) of pivalaldehyde was reacted with 25.4 g (0.55 mol) of methylhydrazine to give 39.7 g (58%) of the hydrazone: bp 40-44° (10 mm); n_D^{25} 1.4424; ir $\nu_{\text{max}}^{\text{neat}}$ (cm^{-1}) 3370 (s, NH), 3270 (m, NH), 2970 (vs, CH), 2880 (s, CH), 1630 (m, $\text{C}=\text{N}$), 1483 (s, br, CH_3), and 1115 (s, br, $\text{C}-\text{N}$); nmr (CCl_4) δ 1.07 (s, 9, t-Bu), 2.77 (s, 3, NCH_3), 4.91 (s, 1, NH), and 6.71 ppm (s, 1, $\text{N}=\text{CH}$).

Anal. Calcd for $\text{C}_6\text{H}_{12}\text{N}_2$: C, 63.11; H, 12.36; N, 24.53.

Found: C, 62.96; H, 12.28; N, 24.86. This hydrazone was also found to be very air sensitive.

7. Pivalaldehyde phenylhydrazone

Following the above procedure, 8.6 g (0.10 mol) of pivalaldehyde was reacted with 10.8 g (0.10 mol) of phenylhydrazine to give 14.0 g (79%) of the hydrazone: mp 36-38°; bp 83.5-85° (0.2 mm); n_D^{25} 1.5515;

ir $\nu_{\text{max}}^{\text{neat}}$ (cm^{-1}) 3320 (m, NH), 3055 and 3030 (w, aromatic CH), 2965 (s, aliphatic CH), 2870 (m, aliphatic CH), 1608 and 1515 (s, aromatic), 1258 (s, t-Bu), 743 and 685 (s, aromatic, monosubstituted); nmr δ 1.08 (s, 9, t-Bu) and 7.00 ppm (m, 7, aromatic, NH, and N=CH).

Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2$: C, 74.96; H, 9.15; N, 15.89.

Found: C, 74.84; H, 9.28; N, 15.98. This hydrazone was extremely sensitive to air and could only be handled in the open air for a few minutes before discoloration became obvious.

Oxidation of Hydrazones

In all cases the lead tetraacetate was washed with dry pentane and dried under vacuum just prior to use. The freshly distilled hydrazone was then dissolved in dry methylene chloride and cooled in an ice-water bath. The lead tetraacetate was similarly dissolved in dry methylene chloride and added dropwise with constant stirring to the hydrazone solution so as to maintain the temperature between 0 and 5°. The amount of solvent used in each case was simply that necessary to bring about solution of the lead tetraacetate and the amount used for the hydrazone solution was that which would give a convenient solution volume. As soon as the first drops of the lead tetraacetate solution were added to the hydrazone a yellow coloration developed and, depending on the nature of the hydrazone, this color would either only deepen slightly or would eventually turn to a deep red-brown. Associated with this color change was the formation of lead diacetate as a gummy, off-white precipitate. After the addition was complete the solution was allowed to stir for 20 to 30 minutes

without external cooling, at which time it was washed with successive portions of 5% aqueous sodium bicarbonate until there was little or no further evolution of carbon dioxide. It was observed, however, that even after this treatment bands attributable to acetic anhydride were present in the infrared. It was further noted that stirring with the sodium bicarbonate solution required approximately 24 hours to remove the last traces of the anhydride. Subsequently all reaction mixtures were treated with sodium bicarbonate as above and then allowed to stir for 15 minutes with a 5% solution of ammonium hydroxide. This combined treatment was found to remove all of the anhydride within the time indicated as evidenced by the lack of anhydride bands in the infrared. After washing with sodium bicarbonate the solution had to be filtered through a Celite mat to remove the lead carbonate which formed. Following the treatment with base the solution was dried at refrigeration temperatures with anhydrous magnesium sulfate and then most of the methylene chloride was removed under vacuum without external heating. The liquid or solid which remained at this point was worked up on an individual basis.

The mode of addition described above must be strictly adhered to or virtually no methylene chloride soluble material is isolated. Although this is not true for other systems¹ it appears to be inviolatable for the oxidation of aldehydic hydrazones.

1. Reaction of benzaldehyde methylhydrazone

As in the above procedure, 39.0 g (0.09 mol) of lead tetraacetate was reacted with 10.7 g (0.08 mol) of benzaldehyde methylhydrazone to

give 10.5 g (68%) of 1-acetyl-2-benzoylmethylhydrazine as white needles: mp 128-129° (n-Bu₂O); uv λ_{max} 224 m μ (log ϵ 4.10) and 265 m μ (log ϵ 3.52); ir $\nu_{\text{max}}^{\text{CCl}_4}$ (cm⁻¹) 3280 (m, NH), 3020 (w, br, CH), 1695 and 1660 (s, C=O); nmr δ 2.07 (s, 3, COCH₃), 3.23 (s, 3, NCH₃), 7.70 (m, 5, aromatic), and 10.43 ppm (s, 1, NH, exchanged slowly by D₂O).

Anal. Calcd for C₁₀H₁₂N₂O₂: C, 62.48; H, 6.29; N, 14.58.

Found: C, 62.53; H, 6.27; N, 14.59.

Only one other product could be isolated from this reaction and it was identified as benzaldehyde. The crude solid which remained after the methylene chloride was removed smelled strongly of benzaldehyde and was washed with pentane. On addition of phenylhydrazine to this pentane wash solution a yellow-orange precipitate of benzaldehyde phenylhydrazone formed: mp 158-159° (aq. ethanol) [lit.¹³ 158°].

2. Reaction of benzaldehyde phenylhydrazone

A solution of, 24.4 g (0.055 mol) of lead tetraacetate was reacted with 9.8 g (0.05 mol) of benzaldehyde phenylhydrazone following the above procedure to yield approximately 10 g of a blood red viscous oil. The vacuum distillation of this material, which proceeded with a great deal of gassing, yielded less than 2 g of distillate with the largest of the four fractions [bp 140-148° (0.6 mm), n_D^{25} 1.5789] being only 0.9 g. Approximately 8 g of nondistillable tarry material remained in the apparatus at the end of the distillation. Spectral data for this largest fraction seemed to indicate that it was a mixture of compounds: ir $\nu_{\text{max}}^{\text{neat}}$ (cm⁻¹) 3500, 3380, and 3225

(w, br, NH), 3075 (m, aromatic CH), 1750 with a shoulder at 1757 (s, C=O), 1717 with a shoulder at 1705 (s, br, C=O), and 1680 (m, br, C=O), 1232 (s, br, C-N?), 758, 709, and 681 (s, aromatic?); nmr δ 1.98 (s, 1, CH₃?), 2.30 (s, 3, CH₃CO?), and 7.97 ppm (m, 18, aromatic). There were also a series of small peaks between 1.8 and 2.6 ppm.

The apparent complexity and lack of this material precluded further serious examination. The other fractions were equally complex and represented only a few hundred milligrams.

3. Reaction of hydrocinnamaldehyde methylhydrazone

The reaction was carried out as above, by reacting 48.8 g (0.11 mol) of lead tetraacetate with 16.2 g (0.10 mol) of hydrocinnamaldehyde methylhydrazone to yield a blood red oil. Attempted vacuum distillation of this oil was accompanied by vigorous gassing but several small fractions were collected. The early fractions showed several NH and carbonyl bands as part of a generally complex infrared spectrum and the nmr data also indicated a complex mixture. The higher boiling fractions of the original oil consisted primarily of hydrocinnamaldehyde as evidenced by the equivalence of the nmr spectrum with that of an authentic sample. At the end of the distillation the vapor trap and the distillation flask smelled strongly of an ammonia-like substance indicating that ammonia or methylamine may have been formed as a decomposition product during the distillation.

4. Reaction of acetaldehyde methylhydrazone

Using the above procedure, 53.2 g (0.12 mol) of lead tetra-

acetate was reacted with the acetaldehyde methylhydrazone solution (theoretically 0.05 mol) previously prepared. After removing the solvent a small amount of a pale yellow oil remained and it was subjected to vacuum distillation. The largest fraction (1.6 g) also gave rise to the simplest spectra: bp 50-55° (40 mm); n_D^{25} 1.3780; ir ν_{\max}^{neat} (cm^{-1}) 3040 with shoulders at 3220 and 2950 (w, v br, NH or OH and CH_3), 1828 (s, C=O), 1757 (s, C=O), 1715 (vs, C=O), 1376 (s, CH_3), and 1127 (vs, C-N?); nmr δ 1.05 (s, 3, CH_3 ?), 1.18 (s, 3, CH_3), and 5.78 ppm (s, 1, NH or OH, exchanged by D_2O). Part or all of the carbonyl absorption may be due to anhydride. This fraction showed a very high solubility in water. Since this and the other fractions did not appear to be azo compounds or acylhydrazines it was assumed that they came from the reaction of the lead tetraacetate with free acetaldehyde and/or methylhydrazine and nothing further was done with this material.

5. Reaction of acetaldehyde phenylhydrazone

Using the above procedure, 53.2 g (0.12 mol) of lead tetraacetate was reacted with 13.4 g (0.10 mol) of the acetaldehyde phenylhydrazone to give a deep red-brown solution. After evaporation of the solvent, attempted vacuum distillation yielded only 2 g of distillate as three fractions. The largest fraction, almost 1 g, appeared to be a mixture: bp 59-69° (about 1 mm), ir ν_{\max}^{neat} (cm^{-1}) 3350 (w, NH), 3070 and 3040 (w, aromatic CH), 2960 (w, CH_3), 1765 (s, C=O), 1732 (vs, C=O), and 1700 (s, C=O), 1735 (s, CH_3), 1225 (vs, br, acetate?), 753 and 685 (m, aromatic); nmr (CCl_4) δ 1.95 (s, 1), 2.02 (s, 1), 2.08 (s, 2),

2.35 (s, 3), and 7.42 ppm (m, 5, aromatic). The other two fractions, of total weight 1 g, gave very similar spectra.

6. Reaction of isobutyraldehyde phenylhydrazone

A solution of 57.6 g (0.13 mol) of lead tetraacetate was reacted with 19.5 g (0.12 mol) of isobutyraldehyde phenylhydrazone following the above procedure to give a deep brown very viscous oil. This oil could not be caused to crystallize and several attempts at short path distillation failed as well. The spectral evidence, however, is consistent with the formation of 1-acetyl-2-isobutyrylphenylhydrazine: ir $\nu_{\text{max}}^{\text{neat}}$ (cm^{-1}) 3280 (m, br, NH), 2975 (m, CH), 1698 and 1673 but poorly resolved (s, C=O); nmr δ 1.09 (d, 6, $J = 7$ Hz, CH_3CHCH_3), 2.07 (s, 3, CH_3CO), 2.48 (m, 1, $J = 7$ Hz, CH_3CHCH_3), 7.60 (s, 5, aromatic), and 10.38 ppm (s, 1, NH).

7. Reaction of pivalaldehyde methylhydrazone

In the above manner, 119.7 g (0.27 mol) of lead tetraacetate was reacted with 28.6 g (0.25 mol) of pivalaldehyde methylhydrazone to give 25.9 g (60%) of 1-acetyl-2-pivalylmethylhydrazine as white crystals: mp 58-59° (60-110° petroleum ether); uv end absorption only; ir $\nu_{\text{max}}^{\text{CCl}_4}$ (cm^{-1}) 3300 (m, br, NH), 2970 (m, CH_3), 1700 and 1662 (s, C=O); nmr δ 1.25 (s, 9, t-Bu), 1.95 (s, 3, CH_3CO), 3.05 (s, 3, NCH_3), and 9.45 ppm (s, 1, NH, exchanged by D_2O).

Anal. Calcd for $\text{C}_8\text{H}_{16}\text{N}_2\text{O}_2$: C, 55.79; H, 9.36; N, 16.27.

Found: C, 55.68; H, 9.50; N, 16.36.

8. Reaction of pivalaldehyde phenylhydrazone

The reaction was carried out as above by reacting, 24.4 g (0.055 mol) of lead tetraacetate with 8.8 g (0.05 mol) of pivalaldehyde phenylhydrazone to yield a red-brown solution. After the methylene chloride was removed the resultant oil was vacuum distilled but very little distillate was obtained until finally 6.7 g (67%) of a red glass formed in the condenser. After this glass was removed it required several days before it began to crystallize. This material was first recrystallized from water, then 2:1 hexane:benzene, and finally from carbon tetrachloride to provide 1-acetyl-2-pivalyl-phenylhydrazine: ir $\nearrow_{\text{max}}^{\text{CCl}_4}$ (cm^{-1}) 3340 (m, br, NH), 2895 with a shoulder at 3080 (m, CH_3 and aromatic CH), 1692 and 1675 (s, C=O); nmr δ 1.23 (s, 9, t-Bu), 2.04 (s, 3, CH_3CO), 7.42 (s, 5, aromatic), and 9.55 ppm (s, 1, NH, exchanged by D_2O).

Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.49; H, 7.76; N, 11.88. The red impurity in the original material must have been present in low concentration because an nmr spectrum of the crude material showed no peaks not present in that of the pure sample and the integration of the peaks was very close to that of the pure sample. A thin layer chromatogram (silica gel, water eluent) of this crude material showed only two spots ($R_{\text{f}(1)}$ 0.62 and $R_{\text{f}(2)}$ 0.67).

Acylation of Methylhydrazine

A mixture of methylhydrazine (4.6 g, 0.10 mol) and pyridine (39.6 g, 0.50 mol) was dissolved in 50 ml of ethyl ether and cooled

in an ice-water bath with stirring. A solution of acetic anhydride (11.2 g, 0.11 mol) in 50 ml of ethyl ether was added dropwise over the course of 1 hour and then the solution was allowed to stir for an additional 1 hour without cooling. The majority of the ether was removed under vacuum to give a solution of mainly 1-methylacetylhydrazide¹⁷ in pyridine. A sample of this solution (4.0 g, theoretically containing 0.88 g of hydrazide, 0.01 mol) was reacted with a solution of p-nitrobenzaldehyde (1.5 g, 0.01 mol) in ethanol to yield a yellow precipitate of p-nitrobenzaldehyde acetylmethylhydrazone. This material was filtered and recrystallized from aqueous ethanol to give 1.1 g of the hydrazone: mp 186-188° [lit.¹⁸ mp 187-188° (aq. ethanol)]. The theoretical yield of the hydrazone, based on the 1-methylacetylhydrazide was 2.2 g. Thus the initial acylation reaction could not have produced the 1-methylacetylhydrazide in less than 50% yield.

The remainder of the crude hydrazide in pyridine from above was mixed with 100 ml of ethyl ether and cooled in an ice-water bath. A solution of benzoyl chloride (14.1 g, 0.10 mol), in 50 ml of ethyl ether was added dropwise with stirring to the hydrazide solution over the course of 1 hour. The solution was then allowed to stir for 4 hours without external cooling. The ether and pyridine were removed under vacuum and the remaining semi-solid material was dissolved in 50 ml of water. This solution was washed with six 25 ml portions of methylene chloride to extract the 1,2-diacylhydrazine. The methylene chloride washes were combined, washed with 20 ml of water, and dried over anhydrous magnesium sulfate. The dry solution was evaporated to yield an off-white solid which still smelled of pyridine. A

sample of this solid (117 mg) was mixed with iodoform (284 mg, 0.72 mmol), dissolved in dimethyl sulfoxide- d_6 , and an nmr spectrum was obtained for this solution. The iodoform, which resonates (δ 5.40 ppm) at a position different from any of the signals of the 1,2-diacylhydrazine, served as an internal standard to determine the purity of the hydrazine sample. Using this information the overall yield was calculated to be 55% based on methylhydrazine. Also, a sample of the crude product was recrystallized to give the 1-acetyl-2-benzoylmethylhydrazine: mp 126-128° (n-Bu₂O). The nmr and infrared spectra were identical to those of the product isolated from the lead tetraacetate reaction (p 9). A mixture of this material and the oxidation product showed an undepressed melting point.

Hydrolysis of 1-Acetyl-2-Benzoylmethylhydrazine

A sample of 1-acetyl-2-benzoylmethylhydrazine (267 mg, 1.39 mmol) obtained from the lead tetraacetate oxidation of benzaldehyde methylhydrazone was dissolved in 50 ml of 5% phosphoric acid (42.9 mmol), the system was purged with nitrogen, and then allowed to reflux for 2 hours still under nitrogen. After approximately 45 ml of liquid was distilled from the reflux apparatus under nitrogen the system was opened and 50 ml of water was added. The system was again purged with nitrogen and an additional 50 ml of distillate was collected. The distillate, approximately 95 ml total volume, was titrated with a standardized sodium hydroxide solution (0.1017N) to a pale pink end point (13.23 ml) using phenolphthalein as an indicator. This volume of base is equivalent to 1.35 meq of hydrogen

ion and that corresponds to 0.97 equivalents of hydrogen ion per mole of 1-acetyl-2-benzoylmethylhydrazine hydrolyzed.

A small portion of the neutralized solution gave no precipitate when added to a solution of barium chloride indicating the absence of phosphate ion. The remainder of the solution was concentrated to approximately 5 ml and converted to the S-benzylisothiuronium salt¹³ as was a known sample of sodium acetate. The precipitates were filtered, recrystallized from 1,4-dioxane, and dried under vacuum in the presence of anhydrous calcium chloride. For the known sodium acetate salt: mp 147-148°; for the hydrolysate salt: mp 146.5-148°; mixed melting point: undepressed [lit. 134°¹⁹ and 146-147°²⁰]. The melting point of 134° is that of the monohydrated salt^{20a} while the higher temperature corresponds to that of the anhydrous salt.^{20b} The number of equivalents of volatile hydrogen ion per mole, the absence of phosphate ion in the distillate, the undepressed melting point, and the agreement of the individual melting points strongly suggests that one and only one acetoxy group or acetate ion precursor is present in each molecule. This additionally rules out the possibility that the compound in question is an azodiacetate^{1b} which was initially considered a plausible structure.

There are, however, two basic precautions which must be observed in this procedure if meaningful results are to be obtained. If 5% sulfuric acid is substituted for the phosphoric acid and/or if the hydrolysis and distillation are carried out in such a manner that the system is open to the atmosphere then abnormally high and highly variable values are obtained for the number of equivalents of hydrogen

ion per mole of diacylhydrazine. When the above precautions were taken however three consecutive hydrolyses gave values of 0.99, 0.95, and 0.97 equivalents of volatile hydrogen ion per mole.

DISCUSSION

The lead tetraacetate oxidation of a series of aldehydic hydrazones was found to give rise to either 1,2-diacylhydrazines, in fairly good yields, or to complex mixtures of nitrogenous substances. At no time were azoacetates or azodiacetates¹ detected in the reaction mixtures.

The structures of the substituted hydrazines were established by elemental analysis, infrared, ultraviolet, and nuclear magnetic resonance spectra. The analyses for both the new hydrazones which were prepared and the oxidation products were well within acceptable experimental limits. The presence of NH absorption and two carbonyl bands in the infrared coupled with the lack of azo absorption in the ultraviolet ruled out the formation of azoacetates as major end products. However, certain limitations were found to exist which tend to restrict the scope of this reaction.

The hydrazones examined in this study may most easily be categorized on the basis of their behavior toward lead tetraacetate. The first group of hydrazones are those which yield 1,2-diacylhydrazines upon oxidation. The methylhydrazones of benzaldehyde and pivalaldehyde are good examples of this class of compounds since they both react smoothly to form the corresponding 1-acetyl-2-acylmethylhydrazines in 68 and 60% yields respectively. In addition no isolation problems were encountered with either of these compounds. It should be noted that both of these hydrazones were derived from an alkylhydrazine and an aldehyde which has no α -hydrogen atoms.

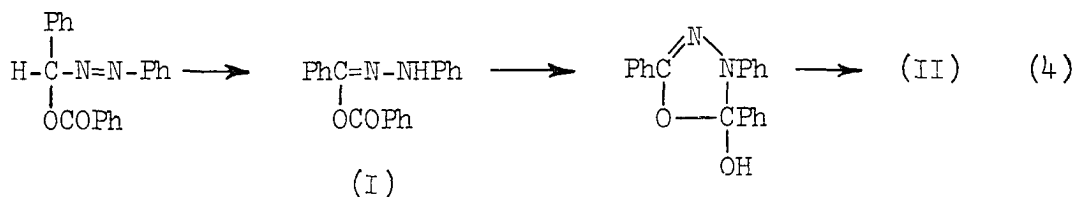
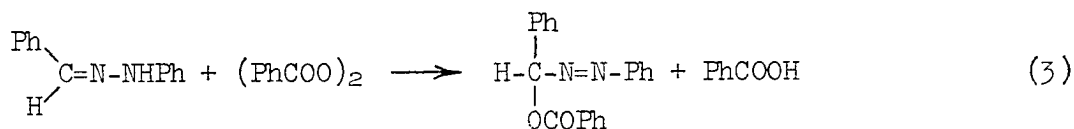
The reaction mixture from pivalaldehyde phenylhydrazone was much more difficult to work-up since it yielded a red glass which required several days before it began to crystallize and then it proved difficult to purify. In many solvents and solvent mixtures, attempted recrystallization led only to oils which would not crystallize. Finally, a series of different solvents were used to alternately remove the colored impurity and purify the hydrazine. Since an isolable diacylhydrazine was formed in the reaction this hydrazone must be included in this first group despite these purification problems. Isobutyraldehyde phenylhydrazone may also be considered to belong in this group, although its inclusion is somewhat tenuous. This hydrazone is different from pivalaldehyde phenylhydrazone only in the fact that one of the methyl groups has been replaced by a hydrogen atom in the starting aldehyde. Despite this small change the reaction gave only a dark brown viscous oil which would not crystallize and which could not be distilled at reduced pressures with short path apparatus. However, the spectral properties of this crude material were relatively simple and consistent with the expected 1-acetyl-2-isobutyrylmethylhydrazine. In spite of the spectral consistency it must be realized that the isolation problem is a major disadvantage in this last reaction.

The second group of hydrazones gave no isolable products but only red to brown viscous oils which could not be purified and appeared to be complex mixtures. The methyl and phenylhydrazones of acetaldehyde are excellent examples of this type of behavior. To some extent this might be unexpected since the isomeric benzaldehyde

methylhydrazone is smoothly converted to the corresponding diacylhydrazine and pivalaldehyde phenylhydrazone again leads to its corresponding hydrazine. Thus, it was felt that perhaps there was a causal relationship between the presence of α -hydrogen atoms in the "aldehyde" portion of the molecule and the formation of what appeared to be degradation products as opposed to diacylhydrazines. Gillis and LaMontagne have shown that cinnamaldehyde methylhydrazone is oxidized by lead tetraacetate in methylene chloride solution to form 1-acetyl-2-cinnamoylmethylhydrazine in 44% yield.⁸ This is neither surprising nor a test of the above α -hydrogen hypothesis, however, because the starting material is simply the vinylog of benzaldehyde methylhydrazone which is here shown to undergo oxidation to yield 68% of the corresponding diacylhydrazine. With this in mind, hydrocinnamaldehyde methylhydrazone was treated with lead tetraacetate; but all that was isolated was a small amount of hydrocinnamaldehyde and some unidentified degradation products.

There is one reference in the literature concerning the isolation of an azoacetate derived from the oxidation of an aldehyde. In this paper, Gladstone briefly reports that he isolated phenylazophenylcarbinol acetate from the reaction of lead tetraacetate and benzaldehyde phenylhydrazone.⁷ It is described as a stable yellow oil [bp 125° (0.05 mm)] prepared in " $\leq 27\%$ " yield. This is also the same system which Iffland, et al. referred to in their original azoacetate paper^{1b} and at that time they described only the formation of a red unstable oil. Therefore duplication of this azoacetate preparation was attempted but only a dark red viscous oil was obtained. This oil could not

be fractionated to obtain azoacetates or any other material which did not show NH absorption as part of a generally complex infrared spectrum. In his short communication Gladstone makes no mention of solvent, temperature, or general reaction conditions except that it was carried out in a nitrogen atmosphere. Although a nitrogen atmosphere was not employed here, Gladstone indicates his belief that the reaction proceeds by an ionic as opposed to a free radical mechanism as has been previously suggested^{1b,8} so that this seems to be an unnecessary precaution on his part. Perhaps of more relevance to this point is the hydrazone oxidation work by Edward and Samad.²¹ They have found that benzophenone phenylhydrazone reacts with benzoyl peroxide at room temperature in benzene solution to form an azobenzoate, phenylazodiphenylcarbinol benzoate. However they found that, under the same conditions, benzaldehyde phenylhydrazone reacted with benzoyl peroxide to form 1,2-dibenzoylphenylhydrazine with no azobenzoate being detected. They suggest that, by analogy, the azobenzoate is indeed initially formed but that it tautomerizes to the benzoxyhydrazone (I) which then further isomerizes to form the 1,2-dibenzoylphenylhydrazine (II):



The azo-hydrazone tautomerism is suggested from the work of O'Conner²² and the acyl group migration is also well supported.²³ This too, is

the mechanism invoked by Gillis in the cinnamaldehyde methylhydrazone work discussed above. In light of all of the above it at least seems questionable that azoacetates derived from aldehydes are capable of existing as such.

It is perhaps significant to note with respect to a substituent-product relationship that each of the hydrazones derived from aldehydes bearing α -hydrogen atoms gave no identifiable products except perhaps isobutyraldehyde phenylhydrazone although this last case may in part be due to steric factors. That is, if the reaction to form the degradation products proceeds by abstraction of an α -hydrogen atom the presence of the two methyl groups may sterically hinder this process. It should be noted also that the phenylhydrazones uniformly led to dark viscous residues from which no products could be isolated or which made isolation and purification a significant problem. This may have been the reason for the difficulty encountered with the benzaldehyde phenylhydrazone system despite the lack of α -hydrogen atoms in the precursor. Although, something more must be involved since in spite of the isolation problems a diacylhydrazine was obtained from the oxidation of pivalaldehyde phenylhydrazone. At this point there is not sufficient evidence to firmly establish this hypothesis but it is consistent with the experimental observations.

Initially it was felt that since the isolated products showed two carbonyl bands in the infrared that they might be azodiacetates. Therefore the hydrolysis was undertaken to quantitatively determine the number of acetoxy and acetyl groups present in the molecule. The finding of only one such group in the oxidation product of benzal-

dehyde methylhydrazone precludes the possibility of that product being an azodiacetate.

The low field signal in the nmr spectrum of the benzaldehyde methylhydrazone oxidation product was found to exchange only rather slowly with deuterium oxide so it was deemed necessary to determine if the chemical shift of that signal was temperature dependent. This information was needed to determine if the proton giving rise to that signal was bonded to a carbon atom or if it was bonded to a more electronegative element such as nitrogen. Table 1 shows that the shift is temperature dependent and in a regular manner (Figure I).

Table 1 Relationship between Temperature and Chemical Shift of the NH Resonance of 1-Acetyl-2-Benzoylmethylhydrazine

Temperature	-58°	-48.5°	-23°	-3.5°	16°	43°
Shift (Hz) *	680	679	666	658	643	624

* All shifts determined at 60 MHz on an approximately 10% solution in deuteriochloroform

In view of the temperature dependence of the chemical shift of this signal it may therefore be assumed that the proton responsible for this signal is bonded to a nitrogen atom.

As a final proof of structure an authentic sample of 1-acetyl-2-benzoylmethylhydrazine was prepared by the acylation of methylhydrazine. The infrared and nmr spectra of the material prepared in this manner proved to be identical to those of the oxidation product of benzaldehyde methylhydrazone. Also the melting points were the

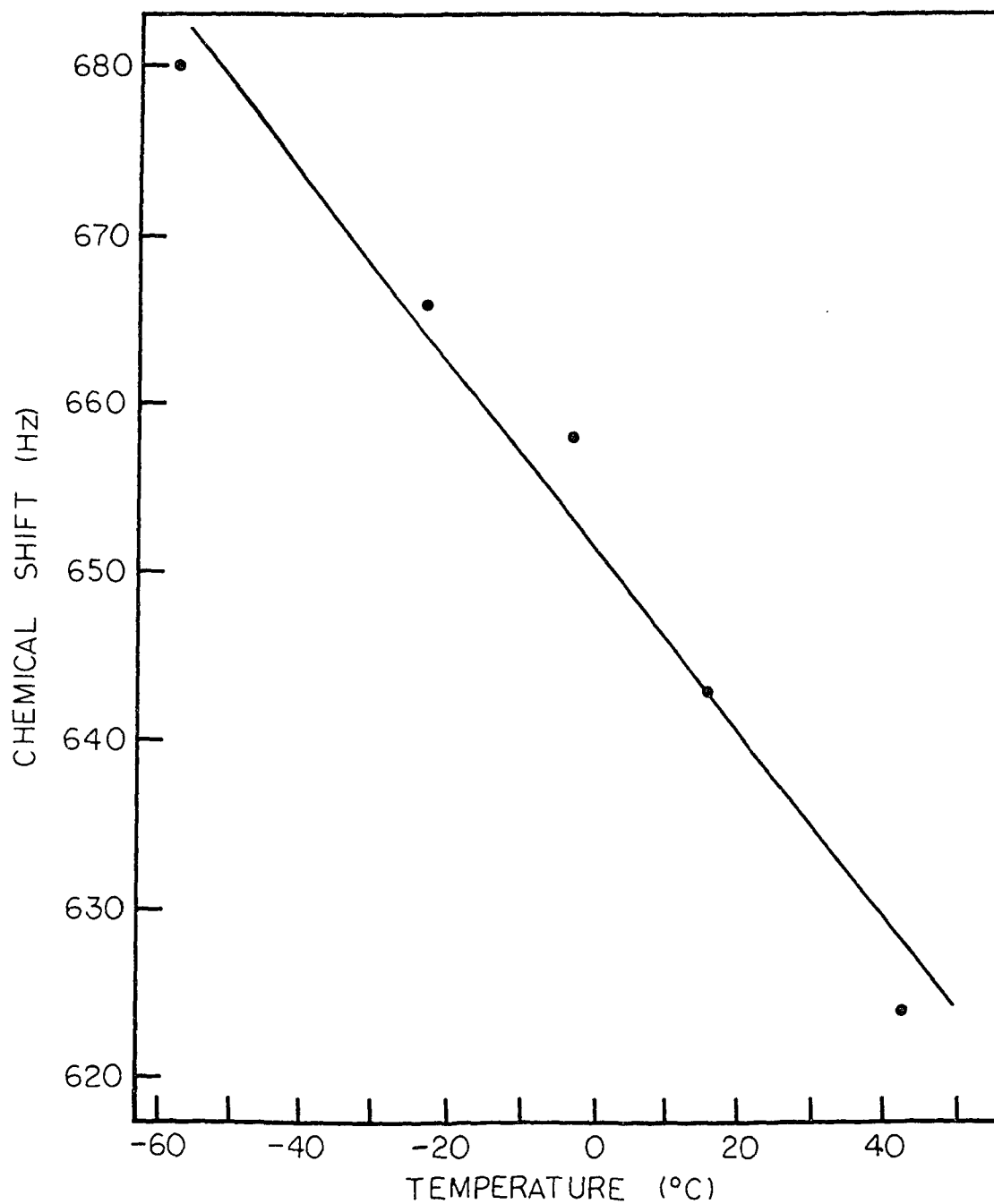


Figure I Relationship between temperature and chemical shift of the NH resonance of 1-acetyl-2-benzoylmethylhydrazine

same and the mixed melting point was not depressed.

No attempt has been made to study the effect of different solvents or reaction temperatures although it is known that lead tetraacetate can react to form different products from the same hydrazone depending on the nature of the solvent.⁸ In addition no attempt has been made to determine the mechanism of the reaction for the specific conditions used since there is already an abundance of evidence both for and against the free radical as well as the ionic mechanism^{8,24} and such a study is beyond the scope of this problem.

Although the lead tetraacetate oxidation of several hydrazones gave rise to red products, at no time could any of these be isolated in sufficient quantities to allow for a structural identification. It is possible that these were similar to the red oils formed from the reaction of some of the hydrazones with air. This might therefore represent one method of preparing material to further study this aspect of the problem.

SUMMARY

The lead tetraacetate oxidation of some simple aldehydic hydrazones was found to give either 1,2-diacylhydrazines or only degradation products. Three such new hydrazines were prepared in 60 to 70% yields and evidence for a fourth is presented. It is suggested that these could arise from the isomerization of azoacetates which may have been initially formed. A possible hydrazone substituent-product relationship is briefly discussed.

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VITA

The author was born June 21, 1945, in Chicago, Illinois. He attended Austin High School in that city and was graduated in June 1963. In June, 1967 he received the Bachelor of Science degree from Purdue University and entered the Graduate School of Western Michigan University in August of that year.