The Oxidation of Azines with Lead Tetraacetate[1]

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The oxidation of aldazines (RCH=NN=CHR) with lead tetraacetate has been found to yield 1,3,4-oxadiazolines (**2**) when R = alkyl or aryl. Compound **2a** could be converted to the 1,3,4-oxadiazole (**3**) upon further oxidation with lead tetraacetate. The oxidation of aliphatic ketazines ($RCH_2C(R')$=NN=$C(R,)CH_2R$) with lead tetraacetate has been found to give α,β-unsaturated azo acetates **4**, **5**, and **6**. Aromatic ketazines failed to react with lead tetraacetate. The spectra of the α,β-unsaturated azo acetates **5** and **6** are very similar to those of known α,β-unsaturated azo compounds. The compounds **4**, **5**, and **6** are stable when stored at low temperatures but rearrange to α-acetoxy ketazines upon heating.

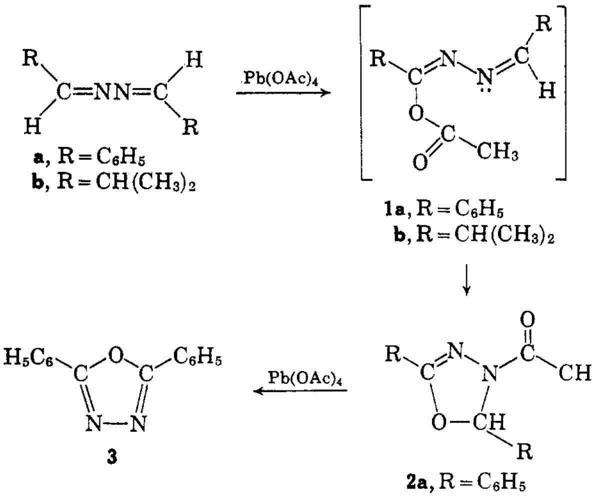
In our further investigation of the oxidation of nitrogen derivatives of carbonyl compounds,[2] we were led to the oxidation of azines with lead tetraccetate—a reaction which has not been previously reported in in the literature. The oxidation of N-alkylhydrazones with lead tetraacetate has been investigated by many workers[3] and was found to give azo acetates.

It was anticipated that lead tetraacetate might react with azines to give α,α'-diacetoxy azo compounds either by a free-radical or an ion mechanism. Such a reaction would find a parallel in the addition of chlorine to azines to give the α,α'-dichloroazo compounds.[4] In our reactions, however, we observed a different type of reaction, one involving an abstraction of hydrogen and addition of an acetate moiety. In the case of the aldazines, the abstraction and addition of the acetate are viewed to occur at the aldehyde carbon similar to the results observed in the lead tetraacetate oxidation of aromatic aldehyde alkylhydrazones[5] and the peracetic acid oxidation of aliphatic aldehyde alkylhydrazones.[3d] In the case of the ketazines, the abstraction of hydrogen and addition of an acetate group do not occur at the same atom site and probably go through radical intermediates.

Thus, when isobutyraldehyde azine was treated with 1 equiv of lead tetraacetate in benzene, the iminoanhydride (**1**) was probably formed as a nonisolable intermediate which rapidly underwent acyl migration and cyclized to form 3-acetyl-2,3-dihydro-2,5-diisopropyl-1,3,4-oxadiazole (**2b**), whose structure was shown clearly by pmr and infrared spectroscopy and microanalysis. The rapid cyclization also accounts for the nonformation of a bisiminoanhydride. Similar cyclization occurs when alkylidene hydrazides are heated with acetic anhydride.[6,7]

When benzal azine was treated with 1 equiv of lead tetraacetate in benzene, again the first isolable product formed was 3-acetyl-2,3-dihydro-2,5-diphenyl-1,3,4-oxadiazole (**2a**) which could only be isolated in about 35% yield. This low yield was due to the further oxidation of **2a** by lead tetraacetate to give 2,5-diphenyl-1,3,4-oxadiazole (**3**) (Scheme I). The latter compound could be isolated in 90% yield by the reaction of benzal azine with 2 equiv of lead tetraacetate. In the case of the benzal azine oxidation, it is believed that the iminoanhydride is a nonisolable intermediate as it is in the case of the oxidation of isobutyraldehyde azine. Further oxidation of **2a** then gives rise to the oxadiazole (**3**). Identification of compounds **2a** and **3** was made on the basis of melting points, mixture melting point determinations, and comparison of their infrared spectra with those of authentic samples.

SCHEME I



When 1-phenyl-2-propanone azine was oxidized with 1 equiv of lead tetraacetate, the previously unknown aromatic α,β-unsaturated azo system (**4**) was formed in 42% yield. Assignment of this structure was possible on the basis of ultraviolet, infrared, and pmr evidence and microanalysis. Compound **4** was subsequently found to rearrange to the α-acetoxy azine (**7**) upon heating. Compound **7** was not isolated pure, but a mixture of **4** and **7** was obtained (Scheme II). The pmr spectra showed both products to be present and the ultraviolet spectra showed it to be about a 2:1 mixture of **4** and **6** by using the ultraviolet chromaphore and ϵ of **4**, since aliphatic azines have only terminal absorption. The pmr spectrum of the mixture contained not only peaks of the α,β-unsaturated azo acetate (**4**) but also peaks for **7** at 1.83, 1.94, and 3.75 ppm (similar to starting azine). The acetyl and phenyl protons showed the same chemical

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(2) B. T. Gillis and K. F. Schimmel, *J. Org. Chem.*, **27**, 413 (1962).

(3) (a) D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Am. Chem. Soc.*, **83**, 747 (1961); (b) W. A. F. Gladstone and R. C. Norman, *J. Chem. Soc.*, 3048, 5177 (1965); (c) F. L. Scott and R. N. Butler, *ibid.*, 1202 (1966); (d) B. T. Gillis and K. F. Schimmel, *J. Org. Chem.*, **32**, 2865 (1967); (e) J. P. Freeman, *ibid.*, **28**, 885, 2508 (1963).

(4) S. Goldschmidt and B. Acksteiner, *Ann.*, **618**, 173 (1958).

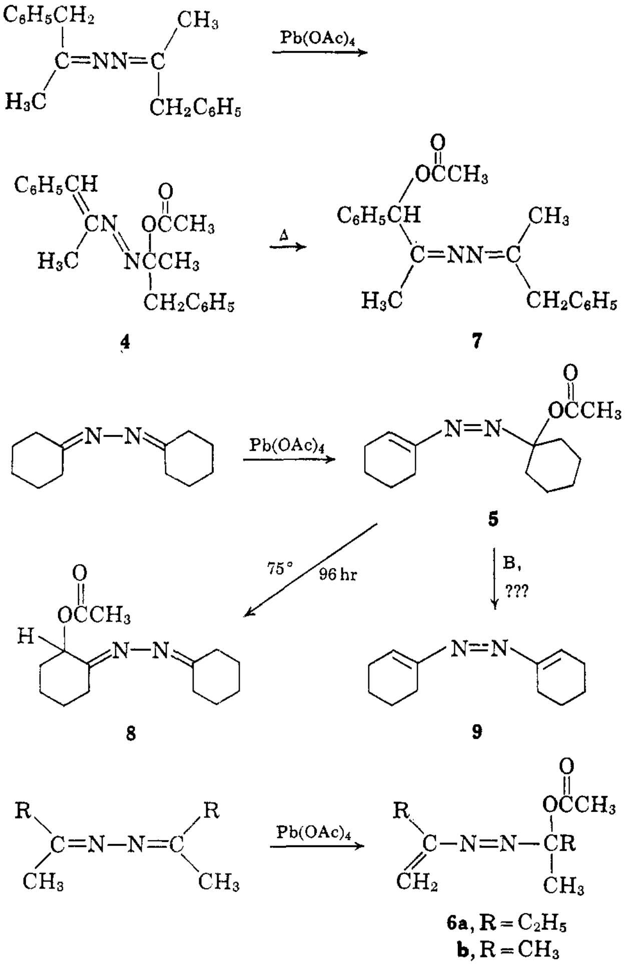
(5) F. L. Scott and R. N. Butler, *J. Chem. Soc.*, 1202 (1966), wherein they also review the evidence for the intermediacy of iminoanhydride prior to rearrangement.

(6) R. Stolle and E. Münch, *J. Prakt. Chem.*, [2] **70**, 410 (1904).

(7) H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry, and J. Bernstein, *J. Am. Chem. Soc.*, **75**, 1937 (1953).

shift in both **4** and **7** and the tertiary proton in **7** was also buried under the phenyl peaks. This rearrangement of **4** was considerably more sluggish than that of **5** under similar conditions.

Scheme II



Treatment of cyclohexanone azine with 1 equiv of lead tetraacetate resulted in the formation of the α,β-unsaturated azo acetate (**5**) in 60% yield. Here again structural assignment is corroborated by ultraviolet, infrared, and pmr spectral data along with microanalysis. The ultraviolet and infrared spectral properties of this compound are very similar to that of 1-(methylazo)cyclohexene[8] which showed an absorption maximum at 249 mμ (ϵ 9570). Compound **5** was found to rearrange to the α-acetoxy azine (**8**) upon heating to about 75° for a prolonged period of time.

When methyl ethyl ketazine was treated with 1 equiv of lead tetraacetate, the α,β-unsaturated azo acetate (**6a**) was isolated in 70% yield. In this case the terminal methylene product was the only one formed. The methyl hydrogens are more acidic and less sterically hindered than the methylene hydrogens, possibly pointing to a radical abstraction mechanism. Once again structural assignment has been made on the basis of spectral data and microanalysis. The ultraviolet and infrared spectral properties of this compound are very similar to those of 2-(methylazo)propene[8] which showed an absorption maximum at 232 mμ (ϵ 6060).

When dimethyl ketazine was treated with lead tetraacetate, the α,β-unsaturated azo acetate (**6b**) was isolated in about 40% yield. This product is less stable than any of the other α,β-unsaturated azo acetates that we prepared. Once again the structural assignment of **6b** is made on the basis of spectral evidence and microanalysis.

These α,β-unsaturated azo acetates are rather stable when stored in the refrigerator but decompose at the rate of approximately 5% per day at room temperature, as measured by the decrease in ϵ in the ultraviolet spectra of a dilute solution.

The products **4**, **5**, and **6** are particularly interesting in that they may be a potential source of the unknown chromophore shown in **9**.

Experimental Section[9]

Preparation of Azines.—Benzal azine was prepared in 80% yield according to the procedure of Zimmerman and Somasekhara.[10a] Isobutyraldehyde azine was prepared in 70% yield according to the method of Kost and Grandberg.[10b] Cyclohexanone azine was prepared in 70% yield according to the method of Perkin and Plant.[10c] Methyl ethyl ketazine and acetone azine were prepared according to the method of Kost and Grandberg[10d] in 73 and 60% yield, respectively. Phenyl-2-propanone azine was prepared by the slow addition of 40.2 g of phenyl-2-propanone to 9.0 g of hydrazine hydrate (85% solution). The reaction mixture was cooled in an ice-water bath during the addition of the ketone and was allowed to warm to room temperature subsequent to the addition. The mixture was then allowed to stir at room temperature for 3 hr. Diethyl ether was then added and the layers were separated. The ether layer was then washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the oily residue was distilled to give a pale yellow liquid: bp 148° (0.43 mm); $n^{29}\text{D}$ 1.5685. The infrared spectrum showed a strong C=N absorption at 1630 cm^{-1} but no N-H or C=O bands.

Oxidation of Isobutyraldehyde Azine with Lead Tetraacetate.—To a stirred solution of 10.5 g (0.075 mole) of isobutyraldehyde azine dissolved in 200 ml of reagent grade benzene was added slowly with cooling in an ice-water bath 39.0 g (0.075 mole) of lead tetraacetate (85% active). The reaction mixture was allowed to stir for 2 hr at room temperature. The lead diacetate was removed by filtration and the filtrate was washed several times with water and saturated sodium bicarbonate solution. The washed benzene was then dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. This liquid was then distilled to give 7.5 g (52%) of a colorless liquid bp 53.5-54° (0.23 mm), $n^{25}\text{D}$ 1.4552. The pmr spectrum of this material (**2b**) showed a doublet at 5.85 ppm, a septet between 3.0 and 2.0 ppm, a sharp singlet at 2.1 ppm, and a multiplet of methyl peaks between 1.3 and 0.8 ppm. The relative intensities were 1:2:3:12, respectively. The infrared spectrum of **2b** showed neither acetate carbonyl absorption nor N-H stretch, but it did have a strong amide carbonyl peak at 1675 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.63; H, 9.09; N, 14.13. Found: C, 60.48; H, 9.06; N, 13.96.

Oxidation of Benzal Azine with 1 Equiv of Lead Tetraacetate.—To a stirred solution of 10.4 g (0.05 mole) of benzal azine in 150 ml of reagent grade benzene was added slowly 26.1 g (0.05 mole) of lead tetraacetate (85% active). The solution was allowed to stir overnight at room temperature. The lead diacetate was then filtered and the benzene was washed several times with water and sodium bicarbonate solution. The benzene was then

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[8] B. T. Gillis and J. D. Hagarty, *J. Am. Chem. Soc.*, **87**, 4576 (1965).

[9] Boiling points and melting points are uncorrected. Microanalyses were performed by A. Bernhardt, Mülheim, (Ruhr), Germany. The spectra were measured with a Cary Model 14 ultraviolet-visible spectrophotometer and a Perkin-Elmer Model 137 double-beam infrared spectrophotometer. The nmr spectra were measured on a Varian Model A-60 spectrophotometer at 60 Mc/sec with tetramethylsilane as an internal standard.

[10] (a) H. Zimmerman and S. Somasekhara, *J. Am. Chem. Soc.*, **82**, 5865 (1960); (b) A. N. Kost and I. I. Grandberg, *Zh. Obshch. Khim.*, **26**, 2319 (1956); (c) W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **125**, 1508 (1924); (d) A. N. Kost and I. I. Grandberg, *Zh. Obshch. Khim.*, **26**, 1717 (1956).

dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The oily residue was slurried in petroleum ether (bp 30–60°) and the insoluble white solid obtained was recrystallized from hot 95% ethanol to give 4.1 g (35%) of 2-acetyl-2,3-dihydro-2,5-diphenyl-1,3,4-oxadiazole (**2a**), mp 98–99°. An infrared spectrum of this product was identical with that of an authentic sample of **2a** prepared by the reaction of benzylidinebenzoylhydrazine with acetic anhydride according to the procedure of Stolle and Münch.[6]

Oxidation of Benzal Azine with 2 Equiv of Lead Tetraacetate.—To a solution of 10.4 g of benzal azine (0.05 mole) in 150 ml of reagent grade benzene was added 52.0 g (0.10 mole) of lead tetraacetate (85% active). The mixture was allowed to stir overnight at room temperature. The lead diacetate was then filtered and the benzene solution was washed several times with water and a saturated sodium bicarbonate solution. The washed benzene was then dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give 9.9 g (90%) of a white solid which was recrystallized from hot 95% ethanol to give 7.6 g of pure 2,5-diphenyl-1,3,4-oxadiazole (**3**), mp 138–139°. The infrared spectrum of compound **3** was identical with that of 2,5-diphenyl-1,3,4-oxadiazole.[11]

Oxidation of Phenyl-2-propanone Azine with Lead Tetraacetate.—To 10.0 g (0.038 mole) of phenyl-2-propanone azine in 150 ml of reagent grade benzene was added with stirring and cooling in an ice–water bath 19.5 g (0.38 mole) of lead tetraacetate (85% active). After stirring for 5 hr at ice-bath temperature the lead diacetate was filtered and the benzene filtrate was washed several times with water and a saturated sodium bicarbonate solution. The benzene was then dried over anhydrous sodium sulfate and the solvent was then removed under reduced pressure. The orange, oily residue weighed 12.2 g. This oil was then chromatographed on an acid-washed alumina column and eluted with petroleum ether to give 5.0 g (42%) of 2-(1-phenyl-1-propen-2-ylazo)-1-phenylpropan-2-ol acetate (**4**), a yellow-orange oil: $\lambda_{\max}^{\text{EtOH, 95\%}}$ 297 mμ (ϵ 4200) and 400 (100). The infrared spectrum of the oil showed strong acetate peaks at 1760 and 1230 and sharp peaks at 1645 and 1500 cm^{-1}. The pmr showed a phenyl peak centered at 7.4, a singlet at 3.6, a sharp singlet at 2.0, a methyl singlet at 1.79, and a methyl singlet at 1.75 ppm. The relative intensities were 11:2:3:3:3. The olefinic proton was buried under the phenyl absorption at 7.5–7.2 ppm.

Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69 Found: C, 74.75; H, 7.04; N, 8.87.

Oxidation of Cyclohexanone Azine with Lead Tetraacetate.—To 9.6 g (0.05 mole) of cyclohexanone azine dissolved in 200 ml of reagent grade benzene was added slowly with stirring and cooling in an ice–water bath 26.1 g (0.05 mole) of lead tetraacetate (85% active). The reaction mixture was allowed to stir at ice-bath temperature for 8 hr after which time the lead diacetate was filtered. The benzene was then washed several times with water and a saturated sodium bicarbonate solution. The benzene was then dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The yellow oil (12.4 g) was then chromatographed on an acid-washed alumina column and eluted with petroleum ether to give 6.9 g of 1-[1-(cyclohexenyl azo)]-cyclohexanol acetate (**5**) a yellow oil which was shown by ultraviolet absorption intensity to be about 90% pure. An analytical sample was prepared by careful distillation of this purified liquid. A yellow oil (bp 70° (0.10 mm), n^{25}D 1.5120) was collected as pure **5**. The ultraviolet spectrum of **5** had $\lambda_{\max}^{\text{EtOH, 95\%}}$ 254 mμ (ϵ 14,700) and 390 (97). The infrared spectrum of **5** showed strong acetate absorptions at 1760 and 1230, a sharp C=C stretch at 1670, and a strong, sharp N=N stretch at 1500 cm^{-1}. The pmr spectrum of **5** showed a broad triplet at 6.7, a broad cyclohexyl multiplet between 2.4 and 1.4, and a sharp singlet at 2.1 ppm, with relative intensities of 1:18:3.

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.85; N, 11.19. Found: C, 67.05; H, 9.00; N, 11.20.

Thermal Rearrangement of 5.—Cyclohexanone azine (9.6 g) was oxidized with 1 equiv of lead tetraacetate as described above. The crude reaction product obtained by work-up similar to that described above was then heated to 70° for 4 days. The oil was then distilled and a yellow-orange liquid, α-acetoxycyclohexanone azine (**8**), was collected, bp 70° (0.15 mm). The infrared spectrum of this oil showed no N=N stretch at 1500 cm^{-1} and the pmr showed only a cyclohexyl multiplet between 2.4 and 1.6 ppm and a sharp acetate singlet at 2.1 ppm with relative intensities of 6.5:1. There was no olefinic proton.

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.85; N, 11.19. Found: C, 67.06; H, 8.69; N, 11.44.

Oxidation of Methylethyl Ketazine with Lead Tetraacetate.—To 10.0 g (0.071 mole) of methylethyl ketazine in 200 ml of reagent grade benzene was added slowly with stirring and cooling in an ice–water bath 37.0 g (0.71 mole) of lead tetraacetate (85% active). The mixture was allowed to stir at ice-bath temperature for 9 hr after which time the lead diacetate was filtered. The benzene filtrate was washed several times with water and a saturated sodium bicarbonate solution. The washed benzene was then dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The yellow liquid residue (14 g) was then chromatographed on an acid-washed alumina column and eluted with petroleum ether. The yellow band moving down the column was collected and the solvent was removed to give 9.5 g (70%) of a yellow liquid, 2-(1-buten-2-ylazo)-butan-2-ol acetate (**6a**) which was shown by ultraviolet absorption intensity to be about 95% pure. An analytical sample was prepared by careful distillation of this purified liquid, and pure **6a**, a yellow oil (bp 80–81° (7.5 mm), n^{25}D 1.4531) was collected. The ultraviolet spectrum of **6a** had $\lambda_{\max}^{\text{EtOH, 95\%}}$ 240 mμ (ϵ 7700) and 397 (60). The infrared spectrum of **6a** showed strong acetate peaks at 1755 and 1240, a sharp C=C stretch at 1640, and a sharp N=N stretch at 1500 cm^{-1}. The pmr spectrum of **6a** showed a terminal methylene doublet at 5.85 and 5.65, a singlet at 2.05, a singlet at 1.55, a methylene multiplet between 2.3 and 1.9, and two methyl triplets between 1.2 and 0.7 ppm with relative intensities of 2:3:3:4:6, respectively.

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.59; H, 9.14; N, 14.13. Found: C, 60.68; H, 9.19; N, 14.03.

Oxidation of Dimethyl Ketazine with Lead Tetraacetate.—To 11.2 g (0.10 mole) of dimethyl ketazine in 200 ml of pure benzene was added slowly with stirring and cooling in an ice–water bath 52.5 g (0.10 mole) of lead tetraacetate (85% active). The mixture was allowed to stir at ice-bath temperature for 4 hr after which time the lead diacetate was removed by filtration. The benzene filtrate was then washed several times with water and a saturated sodium bicarbonate solution. The washed benzene was then dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The red-orange liquid residue wash then placed on an acid-washed alumina column and eluted with petroleum ether. The yellow band was collected and the solvent removed to give 6.3 g (40%) of a yellow liquid, 2-(1-propen-2-ylazo)-propan-2-ol acetate (**6b**): n^{20}D 1.4480; bp 51° (5.5 mm). The ultraviolet spectrum of **6b** had $\lambda_{\max}^{\text{EtOH, 95\%}}$ 240 mμ (ϵ 9500) and 397 (66). The infrared spectrum of **6b** showed strong acetate peaks at 1760 and 1250, a sharp C=C stretch at 1650, and a sharp N=N stretch at 1500 cm^{-1}. The pmr of spectrum of **6b** showed a terminal methylene doublet centered at 5.85, an acetate singlet at 2.05, a methyl singlet at 1.83, and a methyl singlet at 1.5 ppm with relative intensities of 2:3:3:6, respectively.

Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.29; H, 8.45; N, 16.32.

Registry No.—**2a**, 13864-76-1; **2b**, 13864-77-2; **3**, 725-12-2; **4**, 13864-79-4; **5**, 13970-27-9; **6a**, 13864-80-7; **6b**, 13864-74-9; **8**, 13864-75-0; lead tetraacetate, 546-67-8.

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[11] E. Muller and D. Ludsteck, *Ber.*, **88**, 923 (1955).