Oxidation with lead tetraacetate. IV. Cyclization of phenylhydrazones of levulinic acid, levulinanilide, 5-ketohexanoic acid, 4-keto-1-pentanol, and of levulinic acid oxime

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The phenylhydrazones of levulinic acid (**3***a*) and 5-ketohexanoic acid (**4**) are cyclized by lead tetraacetate (LTA) to γ-phenylazo-γ-valerolactone (**9***a*) and δ-phenylazo-δ-caprolactone (**11**), respectively. Oxidation of levulinanilide phenylhydrazone (**3***b*) leads, by analogous oxygen-to-carbon ring closure, to γ-phenylazo-α-phenylimino-γ-valerolactone (**15**) which is hydrolyzed to **9***a*. Similarly, the phenylhydrazone of 4-keto-1-pentanol (**5**) is cyclized to 2-phenylazo-2-methyl tetrahydrofuran (**12**) and the oxime of levulinic acid (**7**) is converted to γ-nitroso-γ-valerolactone which is isolated as the dimer, *trans*-bis[γ-nitroso-γ-valerolactone] (**14**).

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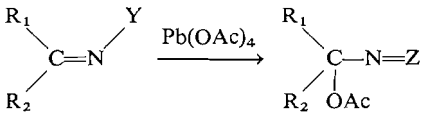
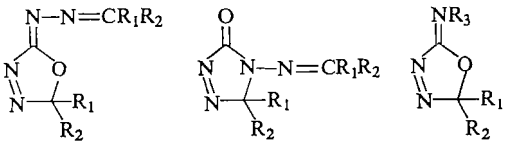
Introduction

Among the many organic compounds that have been oxidized with lead tetraacetate (LTA) are carbonyl derivatives such as oximes (1), hydrazones (2), carbohydrazones (3), and semicarbazones (4). Hydrazones and oximes react according to the generalized equation [1], forming azoacetates and nitrosoacetates, respectively (1,2).

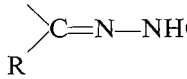
[1] 

Y = NHR, OH Z = NR, O

Carbohydrazones, on the other hand, are cyclized by LTA and it is now established that the products are oxadiazolines (**1***a*) (3) rather than triazolinones (**1***b*) (5). Semicarbazones are cyclized to analogous oxadiazolines (**2**) (4).



1*a* **1***b* **2**

These cyclizations probably involve organolead intermediates which undergo ring closure to carbonyl oxygen through cationic transition states (6). Such a mechanistic picture led us to look for other heterocyclic systems, arising from attack of a nucleophilic center in R of 

on the erstwhile carbonyl carbon. The present work adds to the variety of heterocyclic compounds now available by oxidative cyclization with LTA.

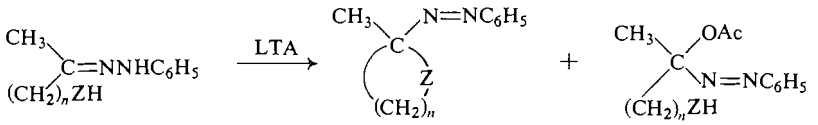
Results and Discussion

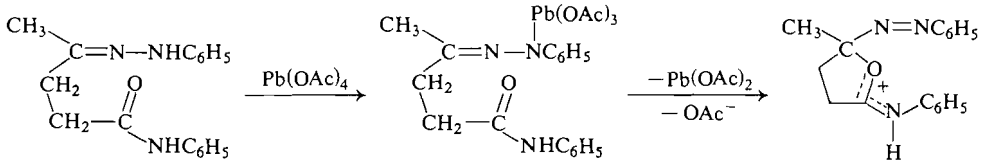
The systems studied include aryl hydrazones of substituted ketones with the substituent so situated that cyclization would produce either a 5-membered or a 6-membered ring, eq.[2]. Cyclization was pitted against azoacetate formation (eqs. [1] and [2]) which is the major reaction in systems lacking the potential for cyclization.

Aryl hydrazones of levulinic acid (**3***a*, **3***d*) gave mainly the corresponding γ-arylazo-γ-valerolactones, **9***a* and **9***b*, with small amounts of the azoacetates, **10***a* and **10***b*.[1] Similarly, **4** and **5** gave mainly **11** and **12**, respectively. The oxime **7** was also smoothly oxidized to form, presumably, γ-nitroso-γ-valerolactone which dimerized to **14**.[2] The dimer is stable for several days at room temperature, in contrast to the ready decomposition of bis-nitrosoacetates and nitrosoacetates (1). At its melting point, **14** decomposes to levulinic acid and other, unidentified products.

[1]The presence of azoacetate in the crude product, after acetic acid had been removed with bicarbonate, (see Experimental) was inferred from the proton magnetic resonance spectrum and from the infrared spectrum. Since our interest was primarily in the cyclic compounds no effort was made, in general, to isolate the azoacetates.

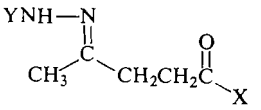
[2]The product does not show typical N=O absorption near 1555 cm^{-1} but absorbs instead at 1200 cm^{-1}. Nitroso dimers (1) are said to absorb in the region 1185–1195 cm^{-1}. The low value (Table II) obtained for the molecular weight (Rast) suggests that the dimer is partly dissociated at higher temperatures. The *trans* configuration is assigned by analogy (1).

[2] 

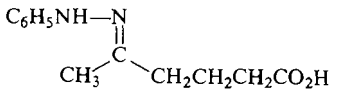
[3] 

The phenylhydrazone of levulinanilide (**3***b*) was oxidized by LTA to a crude product which absorbed at 1691 cm^{-1} and less strongly at 1750 and 1787 cm^{-1}. The 1787 cm^{-1} band was assigned to **9***a* which, together with aniline, was the product of hydrolysis during workup. An *N*-aryl-5-membered lactam is expected to resist hydrolysis and to show carbonyl absorption near 1715 cm^{-1}, well above the 1691 cm^{-1} band observed. On the basis of the infrared (i.r.), the ease of hydrolysis, and the hydrolysis products, it is likely that a major component of the crude product was the iminolactone **15**.

This preference for closure to oxygen rather than nitrogen in the case of **3***b* is readily rationalized in terms of a likely mechanism (eq. [3]) for the cyclization.[3] The organolead intermediate is formulated as having a nitrogen-to-lead bond (6)



3*a* X = OH; Y = C_6H_5
3*b* X = NHC_6H_5; Y = C_6H_5
3*c* X = OC_2H_5; Y = C_6H_5
3*d* X = OH; Y = $C_6H_3(NO_2)_2$-2,4



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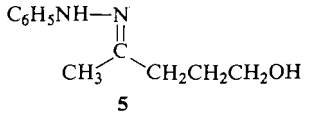

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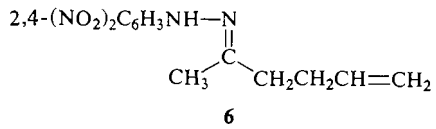

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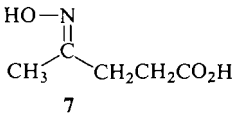

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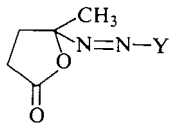
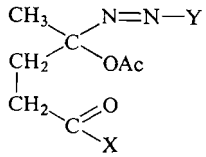
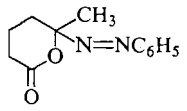


9*a* Y = C_6H_5
9*b* Y = $C_6H_3(NO_2)_2$-2,4



10*a* Y = C_6H_5; X = OH
10*b* Y = $C_6H_3(NO_2)_2$-2,4; X = OH
10*c* Y = C_6H_5; X = OC_2H_5



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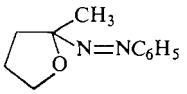

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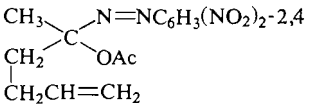

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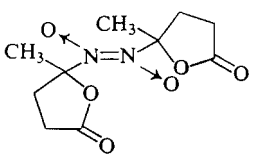

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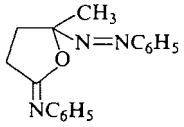

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[3]The same rationale applies to oxadiazoline formation (3,4). Cyclization to sulfur rather than nitrogen is probably also preferred. The yield of a Δ^3-1,3,4-thiadiazoline prepared from acetone thiocarbohydrazone (3) was not high enough, however, to prove such a preference.

TABLE I

Spectra of the oxidation products

Compound	i.r. (vC=O, cm^{-1})	Solvent	(p.m.r.) ($CDCl_3$), δ, type (relative area)
9*a*	1797* 1787* 1780*	CCl_4 neat $CHCl_3$	1.73, s (3); 2.44, m (4); 7.55, m (5)
9*b*	1800	KBr	1.86, s (3); 2.60, m (4); 7.50, d (1); 8.62, m (1); 8.93, d (1)
10*c*	1750	neat	1.10, t (3); 1.73, s (3); 2.05, s (3); 2.35, m (4); 4.02, q (2); 7.22–7.85, m (5)
11	1756* 1750* 1737*	CCl_4 neat $CHCl_3$	1.18–2.66, m (6); 1.73, s (3); 7.24–7.91, m (5)
12	1135†	neat	1.17–2.50, m (4); 1.55, s (3); 4.03, m (2); 7.00–8.00, m (5)
14	1800	KBr	1.82, s (3); 1.99, s (3); 2.62, m (8)‡

*Perkin-Elmer 521 instrument.
†Ether chromophore.
‡The nitrosodimer must be a mixture of diastereoisomers and therefore has more than one methyl signal.

although the allylic alternative has been suggested (7) and a π-bonded species is also conceivable. Whatever its structure, ready heterolysis is to be expected and the cationic precursor (eq. [3]) of **15** should be considerably more stable than that resulting from use of the amide nitrogen in cyclization.

Neither **3***c* nor **6** were cyclized by LTA; azoacetates **10***c* and **13** being formed instead.[1] The double bond is probably not sufficiently nucleophilic to allow cyclization to compete with azoacetate formation. Whether the ester (**3***c*) cyclizes in the sense of eq. [3], with subsequent ring opening faster than displacement on the ethyl group, is not known.

The carbonyl stretching frequencies (Table I) of the azo-substituted lactones are increased slightly by the arylazo substituents.[4] Carbonyl stretching frequencies of δ-valerolactone and of γ-lactones in $CHCl_3$ are 1732 and 1775–1777 cm^{-1}, respectively (8).

Experimental

Infrared spectra and proton magnetic resonance (p.m.r.) spectra were obtained with Perkin-Elmer, Model 337 and Varian Associates, A-60 instruments, respectively, unless otherwise indicated. Melting points were determined with a Thomas "Unimelt" capillary-melting-point apparatus. Analyses were by Alfred Bernhardt, Elbach, Germany and by A. B. Gygli, Toronto, Canada.

Chemicals

Methylene chloride was used as supplied by Matheson, Coleman and Bell (MCB). Lead tetraacetate (MCB), wet with acetic acid, was washed with petroleum ether (30–60°) before use. Levulinic acid, 4-keto-1-pentanol, 5-ketobutyric acid, 5-hexene-2-one, phenylhydrazine,2,4-dinitrophenylhydrazine, and aniline were obtained from the Aldrich Chemical Co., Milwaukee. Florisil (60–100 mesh), for column chromatography, was obtained from the Fisher Scientific Co., Toronto.

Levulinic Acid Phenylhydrazone (3a)

Levulinic acid (20 g, 0.17 mole) and phenylhydrazine (18.6 g, 0.19 mole) in 20 ml of ether gave 32 g (91%) of **3***a*, m.p. 108–109° (lit. (9) m.p. 109–110°).

Levulinic Acid-2,4-dinitrophenylhydrazone (3d)

Levulinic acid (11.6 g, 0.1 mole) was refluxed for 6 h in benzene with 2,4-dinitrophenylhydrazine (19.8 g, 0.1 mole). After cooling, the precipitate was filtered off and recrystallized from ethanol to give 21 g (71%) of yellow **3***d*, m.p. 204° (lit. (10) m.p. 206°).

5-Ketohexanoic Acid Phenylhydrazone(4)

5-Ketohexanoic acid (5 g, 0.038 mole) was mixed with phenylhydrazine (4.15 g, 0.038 mole) in 10 ml of ether. A yellow oil was obtained which crystallized after several days to yield 7.2 g (86%) of **4**, m.p. 48–51°; p.m.r. ($CDCl_3$) δ 1.71 (s, 3, CH_3), 1.72–2.55 (m, 6, CH_2),

[4]The direction of the effect is that expected from inductive electron withdrawal by the arylazo function. Its magnitude (ca. 5 cm^{-1}) is appreciable when compared with the effect of equatorial bromine and chlorine *alpha* to carbonyl of cyclohexanones (Δ vCO = 15 and 20 cm^{-1}, respectively).

TABLE II

Analyses and physical properties

Compound	Yield (%)	Properties (mm Hg), °C	Analysis* C	H	N	Mol.wt.
9*a* from **3***a*	67	b.p. (0.25), 106–108; n_D^{22}, 1.5510	64.69 64.61	5.92 5.39	13.72 13.91	— —
9*b*	40	m.p. 115–117	44.91 44.62	3.43 3.61	19.04 18.84	294.2 295
9*a* from **3***b*	41	b.p. (0.01), 92–93	64.69 64.87	5.92 5.49	13.72 13.92	— —
11	55	b.p. (0.6), 128	66.03 66.07	6.47 6.47	12.84 12.80	218.3 228
12	79	b.p. (0.1), 44	69.44 69.35	7.42 7.42	14.73 14.96	190.2 189
14	56	m.p. 118–119	46.51 46.31	5.47 5.48	10.85 10.69	258.3 236

*Calculated values in the upper rows. Analytical results in the lower rows.

6.59–7.41 (m, 5, C_6H_5), 8.32 (s, 2, *NH* and *OH*); i.r. (neat) 1780 cm^{-1} (C=O).

4-Keto-1-pentanol Phenylhydrazone (5)

Heating phenylhydrazine (10.8 g, 0.1 mole) with 4-keto-1-pentanol (10.2 g, 0.1 mole) for 0.5 h in 6 ml of acetic acid at 100° gave, after addition of NH_4OH and extraction with ether, 15 g (78%) of **5**, m.p. 64–65° (lit. (11) m.p. 60–66°).

Ethyllevulinate Phenylhydrazone (3c)

To a saturated solution of phenylhydrazine hydrochloride (43.2 g, 0.3 mole) in water was added ethyllevulinate (43.2 g, 0.3 mole). The mixture was shaken and after a few h the crystals which had separated were recovered and recrystallized from benzene. The yield of **3***c*, m.p. 108–109° (lit. (12) m.p. 103–104°), was 54 g (77%).

Levulinanilide Phenylhydrazone (3b)

Levulinic anilide (19.1 g, 0.1 mole) and phenylhydrazine (10.8 g, 0.1 mole) gave 22 g (78%) of **3***b*, m.p. 110–111°; p.m.r. ($CDCl_3$) δ 1.71 (s, 3, CH_3), 2.65 (s, 4, CH_2), 6.70–7.60 (m, 10, C_6H_5), 8.42 (s, 2, *NH*); i.r. (KBr) 1670 cm^{-1} (C=O).

5-Hexen-2-one-2,4-dinitrophenylhydrazone (6)

2,4-Dinitrophenylhydrazine (18.2 g, 0.1 mole) was refluxed briefly with 5-hexen-2-one (9.8 g, 0.1 mole) in 100 ml of ethanol. The mixture was cooled, 5 ml of conc. HCl was added, and the resulting mixture was heated again for 2 min. After cooling there was obtained 10.5 g (38%) of **6**, m.p. 104° (lit. (13) m.p. 104°).

Levulinic Acid Oxime (7)

Hydroxylamine hydrochloride (50 g, 0.72 mole) and levulinic acid (8.3 g, 0.07 mole) were dissolved in a little water and a hot, saturated solution of Na_2CO_3 (38 g) in H_2O was added. On cooling 6.7 g (76%) of **7** precipitated, m.p. 95–96° (lit. (14) m.p. 95–96°).

Oxidation of Phenylhydrazones

The general procedure involved gradual addition of 0.03 mole of the hydrazone in methylene chloride solution to a stirring solution of 20 g (0.045 mole) LTA in methylene chloride at 0–5°. The mixture was allowed to warm to room temperature and stirred another h after which time cold water was added. Filtration through a bed of Celite, separation of the organic layer, washing with cold water and with cold bicarbonate solution, drying with Na_2SO_4, and evaporation of the solvent gave the reaction product. Preliminary purification was done by chromatography on Florisil with methylene chloride as eluent. The first small fraction contained mainly azobenzene, the second fraction contained the desired reaction product while the azoacetates remained on the column.[5] Further purification was achieved by recrystallization or distillation. Analyses and physical constants of the oxidation products are in Table II.

Oxidation of Levulinic Acid Oxime

To 33.3 g (0.075 mole) of LTA in 150 ml of methylene chloride was added, gradually and with stirring, 9.82 g (0.075 mole) of the oxime at 0–5 °C. The reaction mixture was kept 2 h at room temperature, water was added, the organic layer was separated, washed with cold water and bicarbonate solution, dried, and the solvent evaporated. After recrystallization from methylene chloride–petroleum ether, 5.4 g (56%) of *trans*-bis[γ-nitroso-γ-valerolactone] (**14**) was obtained, m.p. 118–119 °C.

Acknowledgments

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We are grateful also to the National Research Council of Canada for financial assistance.

[5]Azoacetates **10***c* and **13**, which lack the polar functional groups of the other azoacetates, were eluted.

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