Oxidation of the Dioximes of 1,3-Diketones with Lead Tetra-acetate

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The oxidation of dioximes of aliphatic and cyclic 1,3-diketones with lead tetra-acetate has been investigated. The formation of pyrazole and pyrazoline 1,2-dioxides in moderate yields has been established. A general reaction scheme is proposed.

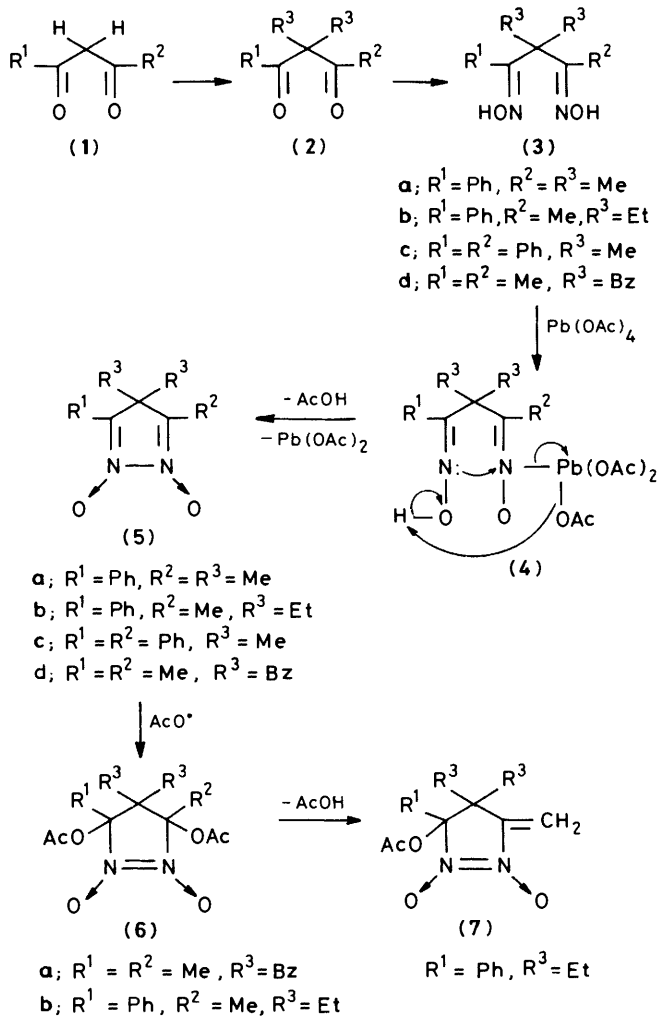
Nitrogen-containing derivatives of dicarbonyl compounds resulting from reactions of the carbonyl moiety are often used as intermediates for the preparation of biologically important heterocycles,[1] and several papers dealing with the oxidation of such compounds with lead tetra-acetate (LTA) have appeared.[2–10] The oxidation of α-dioximes with LTA gives a wide variety of important products depending on the nature of the adjacent groups.[11] The reaction of β-dioximes with LTA has attracted less attention and few papers discussing the subject have appeared[12–14] despite the fact that the products have been known to exhibit remarkable biological activity.[15] In an attempt to increase our understanding of the oxidation of β-dioximes we have studied the reaction of β-dioximes with LTA.

Results and Discussion

The 1,3-dioximes employed in this work are shown in Scheme 1. In their preparation we alkylated[16] the 2-position of the appropriate β-dioximes in order to avoid formation of tautomers. The alkylated compounds were subsequently treated with hydroxylamine. Oxidation with LTA resulted mainly in pyrazole 1,2-dioxides. In most cases other *N*-dioxides, mainly acetoxylated pyrazoline 1,2-dioxides, were also produced in substantial quantities (Table 1). Although the reasons for preferential formation of pyrazole *N*-dioxides rather than the acetoxylated compounds are uncertain, it appears that the substituents R^3 of the methylenic hydrogens in the β-diketone influence the progress of the reaction. Furthermore, influence is also exercised by alkyl or aryl groups adjacent to the =NOH moiety. Thus, the presence of two benzyl groups at the 2-position in 1,3-dioximes leads to oxidation products with two acetoxy groups at the 3- and 5-positions of the pyrazole (**6a**). Replacement of the benzyl groups with ethyl groups results in the formation of a similar product (**7**). However, in this case only one acetoxy group is present in the molecule. A plausible explanation for the formation of (**7**) is that it results from the abstraction of an $MeCO_2H$ molecule from (**6b**) (Scheme 1), the reaction not proceeding thus far when the *gem*-benzyl or *gem*-ethyl groups are replaced by other alkyls. For instance, the oxidation of (**3a**) (Scheme 1) with LTA resulted in (**5a**), a product with no acetoxy groups. The presence of phenyl groups (R^1=R^2=Ph) in the dioxime retards the progress of the reaction so that the 3,5-diphenyl derivative, the end product, has no acetoxy groups.

A plausible mechanism to explain the observed behaviour of the β-dicarbonyls towards LTA is given in Scheme 1. The action of LTA on compounds (**3**) is shown in step 3; formation of the *N*-dioxides (**4**) is thought to follow.

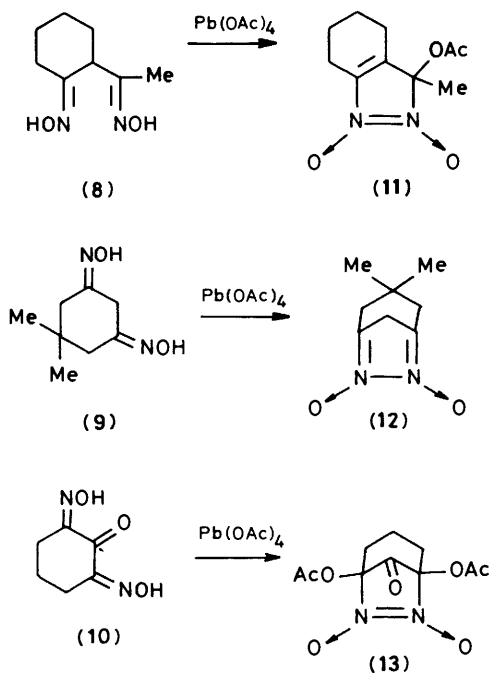
The formation of *N*-dioxides is thought of as an intermediate step in the acetoxylation which results from the presence of acetoxyl radicals produced from LTA in the course of the reaction.[11] Attempts to acetoxylate the *N*-dioxides with an excess of LTA proved successful after heating for *ca.* 2 h although the yield was low. We have found acetoxylation with $MeCO_2H$ much more efficient even at room temperature. The products isolated were either (**6**) or (**7**). It is envisaged that



Scheme 1.

product (**7**) results from the elimination of a $MeCO_2H$ molecule from (**6b**).

The investigation was extended to include β-dioximes in which one =NOH group was bonded to a carbocyclic ring; the oxidation of 2-acetylcyclohexanone dioxime (**8**) was examined. The only product obtained in reasonable yield (11%) was (**11**) (Scheme 2). There are certain similarities between compounds (**7**) and (**11**) in addition to the pyrazole ring which is a common feature in all products obtained. On this basis it is not unreasonable to assume that the oxidation mechanism suggested is also operative in cases where the =NOH is attached to a carbocyclic ring. Experiments were carried out to test the above assumption. Thus, the oxidation of cyclic dioximes such as the dimedone dioxime (**9**) and the cyclohexanetrione dioxime (**10**) by LTA was carried out. The only products of importance



Scheme 2.

Perkin-Elmer RMU-6L spectrometer and elemental analyses on a Perkin-Elmer **B** Analyser. 3,3-Disubstituted 2,4-diones were prepared according to a known procedure.[16] 2,2-Dimethyl-1-phenylbutane-1,3-dione had b.p. 135—138 °C/20 Torr.[17] 2,2-Diethyl-1-phenylbutane-1,3-dione had b.p. 128—130 °C/5 Torr. 2,2-Dimethyl-1,3-phenylpropane-1,3-dione was obtained in a mixture with 2-methyl-1,3-diphenylpropanedione. The mixture was subjected to column chromatography on silica gel (light petroleum–ethyl acetate 15:1), and the 2,2-disubstituted diketone was isolated, m.p. 94—95 °C (from EtOH).[17] Finally, 3,3-dibenzylpentane-2,4-dione had m.p. 104—105 °C (from EtOH).[16]

Preparation of the Dioximes (**3**).—To a solution of hydrochloric hydroxylamine (0.2 mol) in pyridine (200 ml), the appropriate diketone (0.05 mol) was added. The solution was heated, diluted with water, and the dioxime was filtered off. In this way we obtained the following compounds.

2,2-Dimethyl-1-phenylbutane-1,3-dione dioxime (**3a**), m.p. 189—191 °C (from EtOH).[17]

2,2-Diethyl-1-phenylbutane-1,3-dione dioxime (**3b**) (12 g, 98%), m.p. 129—131 °C (from EtOH) (Found: C, 67.85; H, 8.2; N, 11.5. $C_{14}H_{20}N_2O_2$ requires C, 67.7; H, 8.1; N, 11.3); $\nu_{max.}$(Nujol) 3 200 (OH) and 1 645 cm^{-1} (C=N); δ_H (60 MHz; $CDCl_3$) 0.70 (9 H, t, 2-Et, 3-Me), 2.00 (4 H, q, 2-Et), 7.32—7.75 (5 H, m, 1-Ph), and 10.50 (2 H, q, OH); *m/z* 248 (M^+, 1%), 231

Table 1. Analytical data of the pyrazole and pyrazoline 1,2 dioxides (**5**)—(**7**) and (**11**)—(**13**)

Compd. (Formula)	Yield (%)	Solvent*	M.p. °C	Found (%) (Required) C	H	N
(**5a**)	25	LP	158—160	66.25	6.6	12.85
($C_{12}H_{14}N_2O_2$)				(66.06)	(6.4)	(12.83)
(**5b**)	10	LP	169—170	68.1	7.1	11.3
($C_{14}H_{18}N_2O_2$)				(68.3)	(7.4)	(11.3)
(**5c**)	12	LP	56—57	72.5	5.6	10.1
($C_{17}H_{16}N_2O_2$)				(72.9)	(5.8)	(10.0)
(**5d**)	18	LP	202—203	74.2	6.3	9.1
($C_{19}H_{20}N_2O_2$)				(74.0)	(6.5)	(9.0)
(**6a**)	10	Oil–solid		64.7	6.1	6.6
($C_{23}H_{26}N_2O_6$)				(64.9)	(6.2)	(6.6)
(**7**)	12	EtOH	106—107	63.4	6.7	9.1
($C_{16}H_{20}N_2O_4$)				(63.2)	(6.6)	(9.0)
(**11**)	11	EtOH	169—170	53.5	6.0	12.4
($C_{10}H_{14}N_2O_4$)				(53.2)	(6.3)	(12.3)
(**12**)	10	Oil–solid		56.9	7.4	16.5
($C_8H_{12}N_2O_2$)				(57.1)	(7.2)	(16.6)
(**13**)	12	EtOH	348—350	43.9	4.2	10.4
($C_{10}H_{12}N_2O_7$)				(44.2)	(4.47)	(10.2)

* LP = light petroleum

obtained [(**12**) and (**13**)] both have the pyrazole ring. The choice of the cyclic β-dioximes might not seem judicious since the number of the acetoxy groups in the end products varies so that no information relating to the mode of action of LTA can be deduced.

Experimental

M.p.s were obtained on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^1H N.m.r. spectra were taken on a Varian Associates A-60A instrument with tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi-

(M^+ − OH, 7%), 217 (M^+ − NOH, 6%), 188 (217 − Et, 100%), 175 (188 − Me, 85%), and 145 (M^+ − PhCN, 27%).

2,2-Dimethyl-1,3-diphenylpropane-1,3-dione dioxime (**3c**), m.p. 100—101 °C.[17]

3,3-Dibenzylpentane-2,4-dione dioxime (**3d**) (10 g, 65%), m.p. 185—187 °C (from EtOH) (Found: C, 73.7; H, 7.3; N, 9.25. $C_{19}H_{22}N_2O_2$ requires C, 73.5; H, 7.14; N, 9.0); $\nu_{max.}$(Nujol) 3 210 (OH) and 1 655 cm^{-1} (C=N); δ_H (60 MHz; $CDCl_3$) 1.60 (6 H, s, 1-, 5-Me), 3.05 (4 H, s, 3-CH_2), 7.10 (10 H, s, Ph), and 10.50 (2 H, s, OH); *m/z* 310 (M^+ − OH, 5%), 279 (M^+ − NOH, 5%), 219 (M^+ − $PhCH_2$, 24%), 201 (293 − PhMe, 38%), and 187 (201 − CH_2, 100%). 2-Acetylcyclohexanone dioxime (**8**) prepared by a known procedure[18a] had m.p. 177—179 °C (from

Table 2. Spectral data of the pyrazole and pyrazoline 1,2-dioxides (**5**)—(**7**) and (**11**)—(**13**)

Compd.	i.r.	^{1}H N.m.r.	*m/z*	
	$\nu_{max.}$(Nujol) cm^{-1}	δ_H (60 MHz; $CDCl_3$ solvent; standard Me_4Si)		
(**5a**)	1 660	0.85 (6 H, s, 4-Me) 1.40 (3 H, s, 3-Me) 6.76—7.60 (5 H, m, 5 H)	218 (M^+, 9%) 188 (M^+ − NO, 6%) 153 (M^+ − 2NO, 13%)	143 (158 − Me, 66%) 103 (PhCN, 100%)
(**5b**)	1 650 (C=N)	0.60 (9 H, t, 4-Et, 1-Me) 2.00 (4 H, q, 4-Et) 7.35—8.00 (5 H, m, 5-Ph)	246 (M^+, 14%) 216 (M^+ − NO, 7%) 186 (M^+ − 2NO, 9%)	103 (PhCN, 100%) 77 (Ph, 65%)
(**5c**)	1 640 (C=N)	1.60 (6 H, s, 4-Me) 7.30—7.82 (10 H, m, 3-, 5-Ph)	280 (M^+, 2%) 250 (M^+ − NO, 90%) 220 (M^+ − 2NO, 4%)	103 (PhCN, 100%) 77 (Ph, 72%)
(**5d**)	1 640 (C=N)	2.24 (6 H, s, 3-, 5-Me) 3.24 (4 H, s, 4-CH_2) 7.11—7.68 (10 H, m, Ph)	308 (M^+, 1%) 278 (M^+ − NO, 0.5%) 217 (M^+ − CH_2Ph, 3%)	187 (217 − NO, 5%) 157 (187 − NO, 2%) 126 (217 − CH_2Ph, 4%) 91 (CH_2Ph, 100%)
(**6a**)	1 760 (CO)	1.99 (6 H, s, 3-, 5-Me) 2.16 (6 H, s, 3-, 5-OAc) 2.95 (4 H, s, 4-CH_2) 7.10 (10 H, s, Ph)	426 (M^+, 10%) 396 (M^+ − NO, 4%) 367 (M^+ − OAc, 7%) 366 (M^+ − 2NO, 10%)	335 (M^+ − NO − OAc, 27%) 305 (M^+ − 2NO − OAc, 10%) 276 (M^+ − NO − 20Ac, 100%)
(**7**)	1 745 (CO)	0.66 (6 H, t, 4-Et) 2.01 (7 H, s, 4-Et and 5-OAc) 5.01 (2 H, s, 3-CH_2) 7.61—8.11, m, 5-Ph)	304 (M^+, 10%) 274 (M^+ − NO, 2%) 244 (M^+ − 2NO, 3%) 215 (M^+ − NO − OAc, 27%)	103 (PhCN, 100%)
(**11**)	1 760 (CO)	2.05 (14 H, s)	226 (M^+, 2%) 196 (M^+ − NO, 20%) 167 (M^+ − OAc, 35%)	166 (M^+ − 2NO, 32%) 137 (M^+ − NO − OAc, 100%)
(**12**)	1 645 (C=N)	1.47 (6 H, s, 3-Me) 2.41 (6 H, s, 2-, 4-, 8-CH_2)	168 (M^+, 15%) 138 (M^+ − NO, 1%) 123 (M^+ − NO − Me, 48%)	108 (M^+ − 2NO, 3%) 67 (M^+ − 2NO − 2Me, 100%)
(**13**)	1 745 (CO)	2.08 (12 H, s)	272 (M^+, 1%) 242 (M^+ − NO, 2%) 212 (M^+ − 2NO, 2%) 183 (M^+ − NO − OAc, 100%)	124 (M^+ − NO − 20Ac, 33%)

EtOH). Dimedone dioxime[18b] (**9**) prepared in the same way, had m.p. 221—223 °C. Finally, cyclohexane-1,2,3-trione 1,3-dioxime[18c] (**10**) had m.p. 222—223 °C (from EtOH).

Oxidation of the Dioximes (**3**) *and* (**8**)—(**10**).—To a suspension of the corresponding dioxime (0.01 mol) in methylene chloride (30 ml), a solution of LTA (0.015 mol) in methylene chloride (30 ml) was added; the mixture was then stirred. The temperature and time of stirring was dependent on the nature of the dioxime. Thus, the dioximes (**3**) were heated at 40 °C; (**3a**) for 10 h, (**3b**) for 30 h, (**3c**) for 30 h, and (**3d**) for 2 h. The dioximes (**8**)—(**10**) were stirred at room temperature for 3 h. Subsequently the mixture was diluted with water and the precipitate, thus obtained, was filtered off. The organic layer was separated and washed with aqueous sodium carbonate and water and dried. Removal of the solvent left an oil, which was column chromatographed on silica gel [light petroleum–ethyl acetate; for (**3a**) 2:1, (**3b**) 4:1, (**3c**) 10:1, and for the dioximes (**4**) and (**8**)—(**10**) 5:1]. The analytical data of the products (**5**)—(**7**) and (**11**)—(**13**) are given in Tables 1 and 2. From Table 1 it is seen that the product yield ranges from 10—25%. The unchanged dioxime was recovered by column chromatography. The presence of resinous products was also observed.

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