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THE OXIDATION OF SOME ENAMINES WITH METAL OXIDANTS

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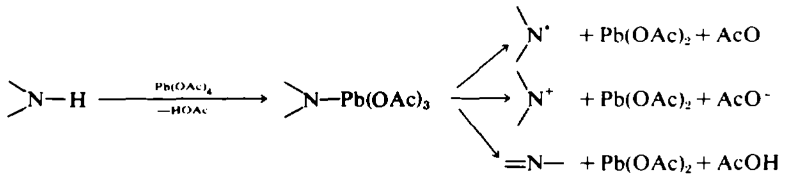
Abstract—4-(1-cyclohexen-1-yl)-morpholine, 1-morpholino-styrene and 1-morpholino-2-methylstyrene were treated with lead tetraacetate. The products obtained were N-acetyl-morpholine, the 2-acetoxy-ketone and in the case of the first substrate its enamine. The 2-morpholino-ketone was also formed in the reactions with 4-(1-cyclohexen-1-yl)-morpholine and 1-morpholino-2-methylstyrene. 4-(1-cyclohexen-1-yl)-morpholine reacted with thallium triacetate and mercuric diacetate, giving very similar results. A mechanistic scheme is discussed, where an intermediate product derived from the addition of two acetoxy groups to the enamine double bond is cleaved via an α-elimination path.

The oxidation of nitrogen compounds with lead tetraacetate has received much attention in the past few years, and a review[1] reports the results obtained in the treatment of various substrates with this reagent.

A particular field of investigation is constituted by the study of the reactivity of unsaturated nitrogen compounds with metal oxidants. Here, the three possibilities indicated by Aylward[1] for the oxidation of a nitrogen compound (Scheme 1), have to be considered with other reaction pathways involving nitrogen cation radicals, formed from tertiary N atoms,[2] nitrene intermediates,[3] and the reactivity of the metal oxidant towards double bonds.[4-6]



SCHEME 1

Our approach to this complex problem was directed to the study of the oxidation of imines, enamines and compounds capable of imine–enamine tautomerism.[7] Preliminary results[3] have shown that aromatic imines are oxidised by lead tetraacetate through the intermediate formation of an aryl nitrene, and this subject is at present being further investigated. The oxidation of enamines, derived by the reaction of a ketone and morpholine, are the subject of the investigation reported.

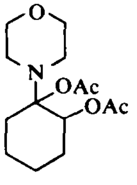
The reaction of 4-(1-cyclohexen-1-yl)-morpholine (**1**) with 1 mol. eq. of acetic acid–free lead tetraacetate was described in a preliminary communication.[8] The reaction was complete within 20′ and the reaction products were N-acetyl-morpholine (**2**), 22%, 2-acetoxy-cyclohexanone (**3**), 10%, the 2-morpholino-ketone (**4**), 49% and the two acetates (**5**), 7% and (**6**), 10%. In some runs, a small amount of the unsaturated morpholino–ketone (**7**), (< 5%) was also noted. Distillation of the crude reaction mixture followed by preparative GLC and silica-gel chromatography allowed the separation of **2**, **3**, **4** and the acetate **5**. The acetate **6** was obtained as a mixture with **5** and its structure was deduced from the NMR, the IR spectra and the analytical data of this mixture, and from the MS spectrum obtained from GLC-MS.

In attempting to confirm the structures of compounds **5** and **6**, 2-acetoxy-cyclohexanone (**3**) was treated with an equimolecular amount of morpholine in diethyl ether in the presence of Linde 4 Å molecular sieves. This gave **2**, 12%; **3**, 29%; **4**, 24%; **5**, 30% and **6**, 4%.

When the oxidation of **1** with lead tetraacetate was repeated under controlled conditions (temp below 15°) in addition to compounds **2**–**6** the precursor **8** was also present, as evidenced by the MS spectrum obtained by GLC–MS. The alternative structure **8a** could be excluded as gem-diacetates, once formed, rapidly regenerate the starting ketone with Lewis acids, and do not give enolacetates such as **5**.[9]

Compound **8** could be converted into **2**–**6** by heating or by silica-gel chromatography.

The oxidation of compound **1** with thallium triacetate in dry benzene gave **3** together with a small amount (< 10%) of the mixture of the morpholino-ketone **4** and the acetate **5**. This reac-



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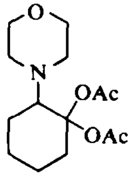
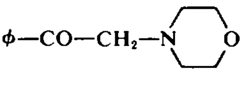


8a

tion has also been carried out by Kühne and Giacobbe[10] who, using an acetic acid or chloroform solution of the substrate, obtained **3** only. With mercuric acetate as oxidant **2** and **3** could be detected among the products together with much resinous material.

Lead tetraacetate oxidations were carried out on two other enamines: 1-morpholino-styrene (**9**) and 1-morpholino-2-methyl-styrene (**14**). The products from compound **9** were **2**, 46%, phenacyl acetate (**10**), 54% and, in some instances, phenylglyoxal diacetate (**13**), (< 5%). Similarly compound **14** gave **2**, 14%, 2-acetoxy-propiophenone (**15**), 48% and 1-morpholino-1-phenyl-acetone (**17**), 38%, identical with material prepared by the reaction of 1-bromo-1-phenyl-acetone (**18**) and morpholine in benzene solution.[11] In this case, the treatment of phenacyl acetate **10** with morpholine in diethyl ether in the presence of Linde 4 Å molecular sieves gave only traces of **19** by nucleophilic displacement of an acetate ion by the basic nitrogen compound. A prolonged boiling of this reaction mixture yielded **19** in 39% yield.



ϕ—CO—CH$_2$—N

19

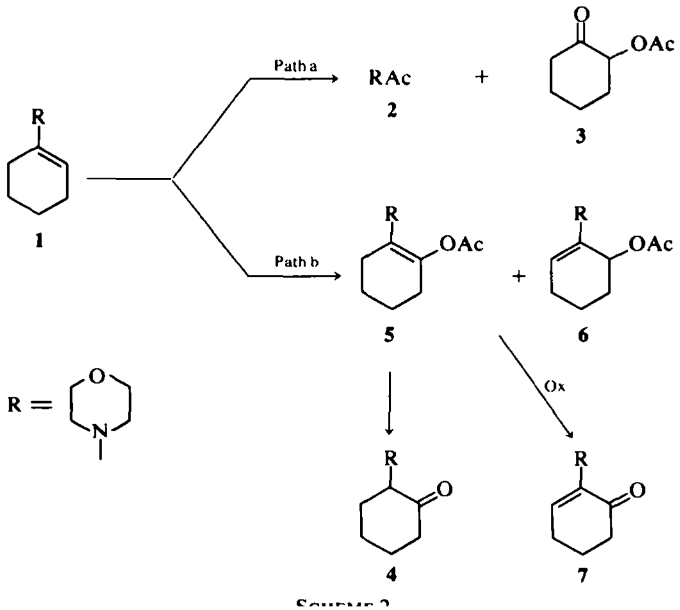
Cyclohexanone, 2-acetoxy-cyclohexanone, acetophenone, phenacyl acetate, propiophenone, 2-acetoxy-propiophenone were recovered unchanged when submitted to the action of lead tetraacetate in benzene solution for several days.

These observations tend to suggest that the first step of the transformation of the enamines is the addition of two acetate groups to the double bond to yield an intermediate such as **8**. A compound of this type could undergo two different transformations: an α-elimination path to give N-acetylmorpholine (**2**) and a 2-acetoxy-ketone such as **3**, **10** or **15**, or alternatively a β-elimination path to give compounds with an enamine-enol acetate structure as **5** or **6**. Compounds of the type **5** could then undergo an acid-catalysed transformation to give the 2-morpholino-ketones **4** or **17**. This is supported by the formation of **4** together with **5** and **6** on treating 2-acetoxy-cyclohexanone with morpholine in the presence of molecular sieves. It also seems reasonable to assume that this transformation can occur both in acidic and in basic conditions.

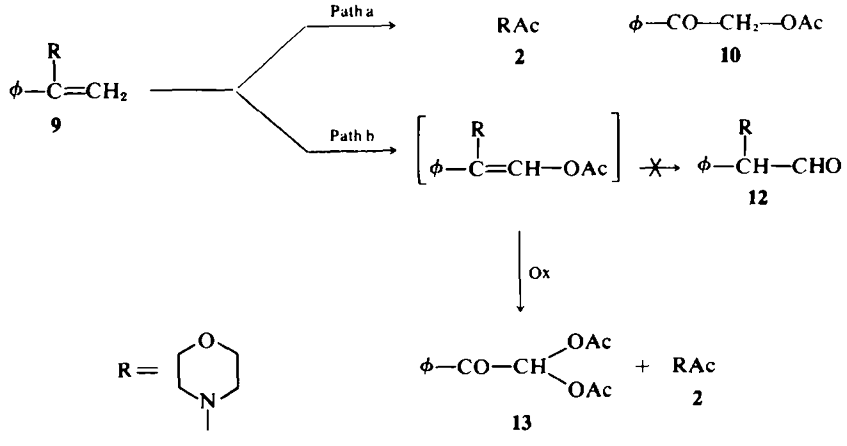
Schemes 2, 3 and 4 illustrate the experimental observations from the oxidation of the three enamines.

These observations require an appraisal of the factors which govern the choice between paths *a* and *b* and in the case of the latter path the fate of the acetates formed.

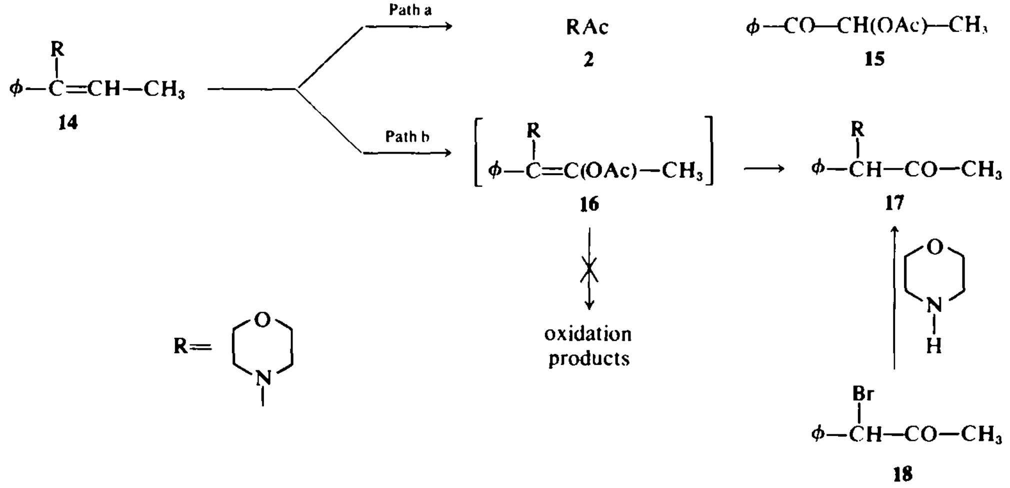
Four factors could come into play in the first problem: (1) the relief of steric crowding associated with the α-elimination path; (2) the availability of β-hydrogens in *anti-trans* position relative to the acetate group which is eliminated in path *b*; (3) the possibility of an equilibrium between **3** and **5**; **10**



SCHEME 2



Scheme 3

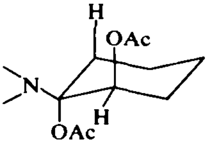


Scheme 4

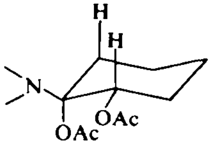
and **11**; **15** and **16**; (4) the properties as Lewis acids of the reagents used and their solubility in benzene (although never isolated, compounds **11** and **16** appear to be key intermediates in the formation of oxidised products such as **7** or **13**).

In our opinion, the most important factor is the possibility of 2-acetoxy-ketones existing in equilibrium with the corresponding enamines thus interrelating the two reaction paths. In fact, the similarity of the results of the oxidation of **1** with lead tetraacetate and the results of the reaction between 2-acetoxy-cyclohexanone and morpholine indicate the possibility of an equilibrium, in the oxidation reaction conditions, between the 2-acetoxy-ketone and its enamine. In the latter reaction direct nucleophilic substitution of the acetate group of **2** with morpholine to yield **5** could constitute a side reaction. The fact that the reaction of phenacyl acetate with morpholine led to the formation of **19** instead of **11** or the aldehyde **12** indicates that the equilibria **11**$\rightleftharpoons$**10** and **16**$\rightleftharpoons$**15** could be completely shifted to the right hand side under the oxidation reaction conditions. A minor contribution to the evaluation of the difference between the two reaction paths may also be ascribed to the properties of the metal oxidants, and to the relief of steric crowding in path *a*.

A further indication could be obtained by considering the availability of β-hydrogens for the elimination of acetic acid in intermediate **8**. Conformations **20** or **21** may be assigned to this compound, deriving respectively from a *trans*- or a *cis*-addition in the oxidation reaction. Although a decision between **20** and **21** could not be made (conformations



20



21

having the morpholino group in axial position can be excluded by thermodynamic considerations), the distribution of hydrogens *anti-trans* to the acetate group being eliminated showed that **20** could give rise, in the β-elimination reaction, to **6** and **21** to **5** and **6**. The observed ratio of 5 : 1 for **4** + **5** to **6** in the reaction of **1** with lead tetraacetate and the isolation of **4** and **5** with thallium triacetate suggested that the oxidative attack to the enamine in this case occurred predominantly with a *cis* stereochemistry, although the formation of the *trans* derivative (**20**) could not be entirely excluded.

The fate of the acetates, which would be formed in path *b*, can be explained as follows. Compounds **5**, **11** and **16** are reactive both as enamines and as enol acetates. The former reactivity accounts for their transformation into the 2-acetoxy-ketones and the resulting competition with the starting material in the oxidation reaction. Their "enol acetate reactivity" is responsible for the formation of the 2-morpholino-ketones via acid catalysis effected by the metal oxidant. This reaction also occurs under the conditions used in the treatment of 2-acetoxy-cyclohexanone with morpholine. Compound **5**, once formed, undergoes all these transformations. The experimental difference in the behaviour of **11** and **16** can be attributed to the major "enamine reactivity" of **11** as opposed to **16**, leading to a further oxidation to phenylglyoxal diacetate (**13**). Compound **16**, reacting primarily via its "enol acetate reactivity", accordingly gave the 2-morpholino-ketone in good yield.

In conclusion it can be noted that the formation of carbonyl compounds through the intermediacy of enol acetates could be a general pattern in the oxidation of unsaturated compounds with metal oxidants. The ease of oxidation of enamines could be due to the extra nucleophilicity of the β-carbon thus activating electrophilic attack by the metal reagent.

Furthermore, this reaction seems to be complementary to the hydroboration of enamines[12] which has been used for the transformation of a ketonic group in complex molecules.

EXPERIMENTAL

NMR spectra were recorded for solutions in $CDCl_3$ with a Perkin-Elmer R10 instrument (TMS as internal reference). IR spectra were measured for $CHCl_3$ soln with a Perkin-Elmer 257 spectrophotometer. Analytical GLC was performed with a Varian 1740 gas chromatograph equipped with a glass column (6 ft × 0·3 in) packed with 1% NPGS on Chromosorb W (oven temp 160°, injection temp 200°, flame ionisation detector temp 200°, carrier gas N_2 at 28 ml/min); product yields were determined by tracing the curves on paper and cutting out and weighing the paper. Preparative GLC was performed on an Aerograph-Autoprep A-700 instrument. MS spectra were obtained with a LKB 9000 (70 eV) GLC-linked instrument. Microanalyses were obtained with a Perkin-Elmer Elemental Analyser 240.

Oxidation of the enamines. 1 mol. eq. of acetic acid-free metal oxidant was added to a 0·16 M soln of enamine in anhyd benzene, and the resulting suspension was left at room temp with stirring until the oxidant had disappeared. Reaction time: 10–20′ for the oxidations with lead tetraacetate, 1 day for thallium triacetate or mercuric diacetate. The reaction mixture was then filtered, the ppt washed with benzene and the organic solns evaporated to dryness under vacuum and analysed by GLC and GLC-MS. Reaction yields 90–98%. The new compounds, resulting from the reaction of **1** with lead tetraacetate, were isolated by distillation of the crude mixture at 5 mm/Hg. The fraction boiling at 140–180° (0·67 g) was chromatographed over silica-gel Merck 0·05–0·2 mesh (45 g) (15 ml each fraction). 12 fractions were eluted with chloroform, the solvent was changed to $CHCl_3$/EtOAc 4 : 1, and gave in the fractions 19–20 35 mg of **5**, b.p. 140° at 4 mm/Hg; ν_{max} 1745 cm^{-1}; $m/e = 225, 183, 166, 165, 125, 110$; NMR signals at 1·80–2·20 δ (4H, m, $-C\underline{H}_2-C\underline{H}_2-$); 2·06 δ (3H, s, $-O-CO-C\underline{H}_3$); 2·45 δ (4H, m, $-C\underline{H}_2-\overset{|}{C}=\overset{|}{C}-C\underline{H}_2-$); 2·83 δ (4H, m, $-C\underline{H}_2-N-C\underline{H}_2-$); 3·73 δ (4H, m, $-C\underline{H}_2-O-C\underline{H}_2-$). (Found C: 63·62; H: 8·81; N: 6·32. $C_{12}H_{19}NO_3$ requires: C: 63·98; H: 8·50; N: 6·22%). Fractions 25–27 contained 67 mg of a mixture of **5** and **6**. Compound **6** could not be further purified. It had ν_{max} 1735 cm^{-1} and the NMR spectrum showed a singlet at 1·97 δ, assigned to the Me protons of the acetate group, and a multiplet at 5·19 δ assigned to an olefinic proton. Its mass spectrum had the same peaks as **5** with different relative intensities. (Found C: 64·23; H: 8·34; N: 6·01%). Fractions 30–33 contained 87 mg of **4**. When the reaction between **1** and lead tetraacetate was performed by carefully avoiding any heating during the reaction or in the work-up procedure, GLC-MS showed the presence of ≈ 70% of **8**, $m/e = 285, 243, 225, 201, 183, 127$ together with ≈ 30% of the mixture **2**–**6**. Attempts to purify compound **8** by silica-gel chromatography or by distillation transformed it quantitatively into **2**–**6**.

Treatment of 2-acetoxy-cyclohexanone **3** *with morpholine.* 1·8 ml of morpholine and 8 g of Linde 4 Å molecular sieves were added to a soln of **3** (2·7 g) in 8 ml anhyd diethyl ether. After 1 day with stirring at room temp, the resulting suspension was filtered, the solvent removed under vacuum and the residue was analysed by GLC-MS.

Treatment of phenacyl acetate (**10**) *with morpholine.* 0·6 g of morpholine and 3·5 g of Linde 4 Å molecular sieves were added to a soln of **10** (1 g) in 7 ml anhyd diethyl ether. After 1 day with stirring at room temp the resulting suspension was filtered and the solvent evaporated. The residue was shown to consist of unreacted **10** and traces of **19**. Compound **19** was obtained in 39% yield by prolonged heating of this mixture.

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