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OXYGENATION OF METHYL *p*-METHOXYPHENYLPYRUVATE. α-KETO-β-PEROXYLACTONE AND DIOXETANOL INTERMEDIATES.

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The way in which α-hydroperoxyketones decompose is a topic of current interest.[1] A relevant example is the oxygenation of the enol tautomer of *p*-hydroxyphenylpyruvic acid (1a).[2] The unstable α-hydroperoxyketo acid (2a) is formed, which promptly decomposes to *p*-hydroxybenzaldehyde (3a). Although the keto function in 2a is prone to attack by nucleophiles, the cyclization to the dioxetanol (4a) is not spontaneous and only occurs under basic, non-nucleophilic conditions. When hydroxylic solvents (R'OH) are present, they add preferentially to the keto function, giving the tetrahedral intermediate 5a, which subsequently cleaves to aldehyde 3a and oxalic acid or its ester 6. In non-nucleophilic media, fragmentation of 2a predominates, the oxides of carbon being formed together with 3a in an unspecified mechanism. We now report on the oxygenation of the enolic ester 1b.[3] The results amplify our previous observations and permit a clarification of the process of decarbonylation and decarboxylation.

Photo-oxygenation of 1b furnishes an aromatic fragment, *p*-methoxybenzaldehyde (3b) and the product of its further oxidation, the acid 7.[4] The rest of the molecule either simply breaks off as monomethyl oxalate (6) or fissures to the oxides of carbon (CO and CO_2) and presumable methanol (entry 1, Table). Dark oxygenation, under weakly basic, but essentially aqueous conditions, results in neat cleavage to aldehyde 3b and monomethyl oxalate 6 (entry 2). Dark oxygenation in methanol, under stronger basic conditions, also results in cleavage, accompanied by further oxidation of 3b to 7, giving exclusively dimethyl oxalate 8 (entry 3). Lastly, dark oxygenation in the presence of a strong bulky base, potassium *t*-butoxide, gives a spread of products, roughly the same as that seen on photo-oxygenation (entry 4).

Table. Products Arising from the Oxygenation of Methyl *p*-Methoxypyruvate (1b)

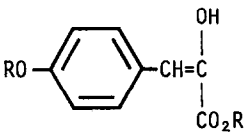
Entry	Conditions[a]	Aromatic Products[b]		Oxalate Esters[b]		Gaseous Products[c]	
		3b	7	6	8	CO	CO_2
1	MB/CH_3CN	80	20	50	-	32	52
2	Buffer, pH 7.5	100	-	85	-	-	-
3	MeONa/MeOH	68	32	-	100	-	*d*
4	*t*BuOK/DMSO	56	44	16	-	53	*d*

[a] Reactions were carried out by passing oxygen continuously through solutions containing 5.5 mmol of 1b. Irradiation with visible light of 10^{-3}M of methylene blue (MB) in 50 ml of CH_3CN at -20° for 6 hrs (entry 1). Dark reactions in 0.2 M sodium borate buffer at pH 7.5 at 0° for 48 hrs (entry 2); in 50 ml of methanol containing 55 mmol MeONa for 48 hrs (entry 3) and 50 ml DMSO containing 55 mmol *t*BuOK at 16° for 48 hrs (entry 4).

[b] Yields estimated by GLC[2] of reaction mixtures after acidification with dry HCl where necessary, followed by evaporation and treatment with *bis*-(trimethylsilyl)-acetamide. Structures isolated by HPLC and subsequently identified by comparison with authentic samples.

[c] Absolute yields.[2] Both gases were identified by IR analysis.

[d] Carbon dioxide could not be determined.



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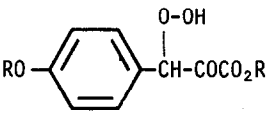

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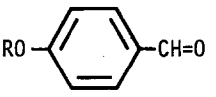

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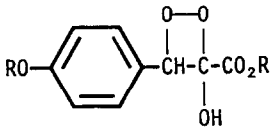

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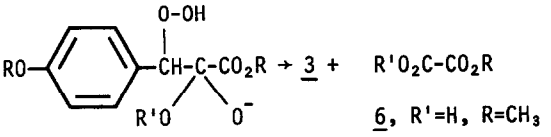
a, R=H



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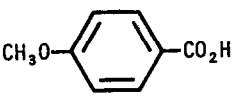
b, R=CH_3



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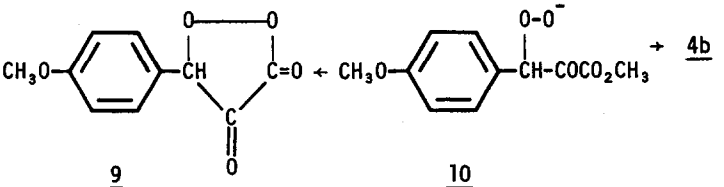

9 10

Although no intermediates could be isolated, the products of oxygenation are nicely rationalized in terms of the α-hydroperoxyketo ester 2b.[5] Dye-sensitized oxygenation of 1b produces 2b by either an ene-type or a free radical reaction.[6] At the same time, [2+2] addition of singlet oxygen gives the dioxetanol (4b) (entry 1).[7] Cleavage of the latter will account for monomethyl oxalate (6). The formation of the oxides of carbon means that 2b must initially lose a molecule of methanol under these conditions. In the absence of alternative explanations,[8] cyclization is most likely to give the peroxylactone (9). Fragmentation of 9 should be instantaneous, liberating aldehyde (3b) and the oxides of carbon.

Oxygenation in the dark (entries 2-4) gives only the α-hydroperoxyketo ester (2b), presumably by a free radical process.[2] In water (entry 2) and basic methanol (entry 3), 2b is attacked at the ketone function to give the hydroxy and methoxy tetrahedral intermediates 5b (R'=H and CH_3), which give respectively, on cleavage, monomethyl and dimethyl oxalates.[9] *p*-Methoxybenzaldehyde (3b), the other product, is oxidized under the alkaline conditions to the benzoic acid 7 (entry 3).

Finally, *t*-butoxide anion (entry 4), on account of its size, cannot attack the ketone function (no *t*-butyl oxalate was detected), but removes instead a proton from the α-hydroperoxy group. The resulting anion 10 now has the option of attacking either ester or ketone functions. Consequently, cyclization yields peroxylactone (9) and dioxetanol (4b). Fragmentation and simple scission of these generate carbon oxides and monomethyl oxalate (6), respectively.

The findings are significant in several respects. Firstly, they provide the second indirect instance of the intermediacy of α-keto-β-peroxylactones which are unknown as stable entities.[10] Such compounds are expected to be more unstable than β-peroxylactones which lose carbon dioxide on heating.[11] Secondly, the decomposition of 9 constitutes a mechanistic analogy for the reaction of ketonic five-membered cyclic peroxides, which undergo decarbonylation liberating two carbonyl units.[12,13] Lastly, the body of oxygenation experiments[14] carried out on 3-hydroxyflavones, such as quercetin, which resembles 1b, can be rationalized in terms of four and five-membered ring peroxides exemplified by 4b and 9. The apparent inconsistencies noted between different experiments can be reconciled by our finding that product composition depends on the conditions, *viz.* inert *vs.* hydroxylic solvents and the nature of the base.

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REFERENCES AND NOTES

(1) Y. Sawaki and Y. Ogata, J. Am. Chem. Soc. 99, 5412 (1977); 100, 856 (1978) and references cited therein.

(2) C.W. Jefford, W. Knöpfel and P.A. Cadby, J. Am. Chem. Soc., in press.

(3) The ester was prepared by addition of methanolic thionyl chloride (0.1 M) to methanolic *p*-methoxyphenylpyruvic acid at room temperature. Stirring for 3 hrs, followed by evaporation, washing with dilute aqueous $NaHCO_3$ and finally extraction with ether gave the product which was re-crystallized from ethyl acetate as colourless, unstable crystals, m.p. 90-93° (decomp.); ν_{max} $CHCl_3$; 3400, 1750, 1700 and 1600 cm^{-1}. NMR (d_6 acetone) δ: 3.8 (singlet, 3H), 3.9 (s, 3H), 6.55 (s, 1H), 6.90 (doublet, J = 9 Hz) and 7.75 ppm (d, 2H) Anal. C, 63.41; H, 5.90%, $C_{11}H_{12}O_4$ requires C, 63.46; H, 5.77%.

(4) Control experiments conducted under the same conditions confirmed this.

(5) This is well precedented, see ref. 2 and references cited therein.

(6) For reviews of the chemistry of singlet oxygen see: C.S. Foote, Acc. Chem. Res. 1, 104 (1968); Pure Appl. Chem. 27, 635 (1971); D.R. Kearns, Chem. Rev. 71, 395 (1971); R.W. Denny and A. Nickon, Org. React. 20, 133 (1973).

(7) Enamines, enols and their ethers give dioxetanes with singlet oxygen. See T. Matsuura and I. Saito in "Photochemistry of Hererocyclic Compounds", ed. O. Buchardt, John Wiley & Sons, Inc., New York, 1976, p. 480.

(8) It is unlikely that the hydroperoxide would undergo the Criegee rearrangement for electronic reasons (P.A.S. Smith in "Molecular Rearrangements", ed. P. de Mayo, Wiley-Interscience, New York, Vol. 2, p. 1 (1971)).

(9) α-Keto acids are notorious for their ease of hydration (A.J.L. Cooper and A.G. Redfield, J. Biol. Chem. 250, 527 (1975)). We also have discovered by NMR spectroscopy that formation of hemi-acetals is significant in deuteromethanol.

(10) D.A. Mayers and J. Kagan, J. Org. Chem. 39, 3147 (1974).

(11) W. Adam, O. Cueto, L.N. Guedes and L.O. Rodriguez, J. Org. Chem. 43, 1466 (1978) and references cited.

(12) W. Adam and I. Erden, Angew. Chem. Int. Ed. Engl. 17, 210 (1978).

(13) Such a bridged peroxyketone is the hypothetical intermediate which arises by addition of singlet oxygen to tetracyclone (N.M. Bikales and E.I. Becker, J. Org. Chem. 21, 1405 (1956); C.F. Wilcox, Jr., and M.P. Stevens, J. Am. Chem. Soc. 84, 1258 (1962)).

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