Tetrahedron Letters, Vol. 22, No. 15, pp 1443 - 1446,1981
Printed in Great Britain

0040-4039/81/151443-04$02.00/0

A CROWN OZONIDE AND ITS REARRANGEMENT TO A MACROCYCLIC LACTONE

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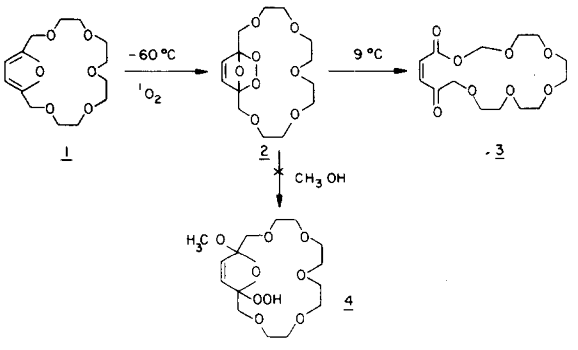
The addition of singlet oxygen to 2,5-furo-18-crown-6 yields a crown ozonide, which rearranges quantitatively to a macrocyclic lactone.

The [2+4]-cycloaddition of singlet oxygen to conjugated dienes is increasingly used as a facile way of introducing oxygen functionalities in a stereo-specific manner into unsaturated hydrocarbon compounds[1,2]. In our studies of sensitizer-substrate complexation and interaction effects in the photochemical dye-sensitized generation of $^1O_2$ we investigated the photo-oxidation of furo-crown ether 1. In this communication we report the preparation of a crown ozonide and the unusual rearrangement that followed the photo-oxidation of 1.

The sensitizer Rose Bengal is solubilized in apolar media via complexation to 1[3]. Photo-oxidation of 2,5-furo-18-crown-6 (1)[4] (1.0 mmol) in $CHCl_3$ or CH_2Cl_2 (2 ml) at 20 °C for 30 minutes with Rose Bengal (0.01 mmol) as the sensitizer afforded macrocylic lactone 3 (a colourless oil) in quantitative yield[5]. ^{1}H-NMR ($CDCl_3$): δ 6.57 (d, J = 12 Hz, 1 H), 6.19 (d, J = 12 Hz, 1 H), 5.41 (s, 2 H, OCH_2O), 4.43 (s, 2 H, OCH_2CO), 3.66 ppm (m, 16 H, CH_2); ^{13}C-NMR ($CDCl_3$): δ 70.9, 76.4 (t), 90.5 (t), 126.8 (d), 140.0 (d), 165.0 (s), 202.1 ppm (s). Lactone 3 is sensitive to hydrolysis and decomposed upon being chromatographed over alumina.

Photo-oxidations with methylene blue or tetraphenylporphyrin as sensitizer also yielded 3 as the sole product. The addition of radical scavengers had no effect on the oxidation; 1,4-diazabicyclo[2.2.2]octane, an efficient singlet-oxygen quencher, slowed down the photo-oxidation appreciably.

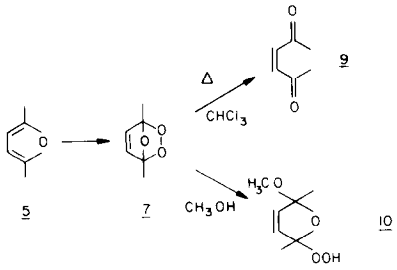


SCHEME 1

The formation of lactone 3 must be due to an anomalous ozonide rearrangement[6] of the singlet-oxygen adduct of 1. This hypothesis was tested by photo-oxygenation of 1 at -60 °C in $CDCl_3$. ^{1}H- and ^{13}C-NMR revealed that the singlet oxygen [4+2]-adduct 2 was the only product. The ozonide structure 2 was deduced from spectroscopic (Table) and chemical data. To support the ozonide structure of 2 we also photo-oxidized 2,5-dimethylfuran (5) and 2,5-di(methoxymethyl)furan (6) at -60 °C in $CHCl_3$. The corresponding ozonides 7 and 8 were formed quantitatively (for comparison of spectral data, see Table). Singlet-oxygen additions to furans have been extensively studied by Schenck and co-workers[7] and the products are generally explained in terms of initial formation of cyclobutadiene ozonides. Relatively stable ozonides have been isolated from the photo-oxidation of 2,5-diphenyl-substituted furans[8] and recently Adam and co-workers[9] have demonstrated the intermediacy of unstable alkyl-substituted ozonides by reduction to more stable cyclobutene ozonides. The macrocyclic cyclobutadiene ozonide 2 (a crown ozonide) is stable at temperatures below 0 °C.

On warming the solution of 2[10] a quantitative rearrangement to the macrocyclic lactone 3 was observed. This rearrangement was followed by NMR spectroscopy and showed first-order kinetics with $k = 2.5 \times 10^{-2}\ s^{-1}$ at 9 °C. Under the same conditions ozonide 7 remained unchanged. At 20 °C, 7 slowly decomposed into 1,2-di-acetylethylene (Scheme 2).

Photo-oxidation of 1 in methanol as the solvent at -60 °C with subsequent heating or at 20 °C also yielded lactone 3 as the only product. No trace of the hydroperoxide 4, due to methanol attack on ozonide 2, was detected. This is in strong contrast with the formation of 10 as the sole product of the photo-oxidation of dimethylfuran (5) in methanol (Scheme 2)[7,8,12].



5 7 9 10

SCHEME 2

The macrocyclic lactone 3 contains a γ-keto-α,β-unsaturated ester unit and this structural part is common to various natural antibiotic macrolides e.g. vermiculine[13] and pyrenophorin[14]. The mild and selective rearrangement described offers possibilities for an easy introduction of the γ-keto-α,β-unsaturated ester unit into macrocycles[15].

Notes and References

1. "Singlet Oxygen, Reactions with Organic Compounds and Polymers", (B. Rånby and J.F. Rabek eds.), John Wiley & Sons, New York, 1978; "Singlet Oxygen", (H.H. Wasserman and R.W. Murray, eds.), Academic Press, New York, 1979.
2. G. Ohloff, Pure Applied Chem., 481 (1975); G.W. Holbert and B. Ganem., J. Amer. Chem. Soc., 100, 352 (1978); D.J. Coughlin, R.S. Brown and R.G. Salomon, J. Amer. Chem. Soc., 101, 1533 (1979).
3. R.M. Boden, Synthesis, 783 (1975).
4. R.T. Gray, D.N. Reinhoudt, C.J. Smit and J. Veenstra, Rec. Trav. Chim. Pays Bas, 95, 258 (1976).
5. All photo-oxidation experiments were performed using a Philips high-pressure mercury-vapour (HPK 125 W) lamp in combination with a potassium chromate liquid filter.
6. W.G. Young, A.C.Mc. Kinnis, I.D. Webb and J.D. Roberts, J. Amer. Chem. Soc., 68, 293 (1946)
7. C.S. Foote, M.T. Wuesthoff, S. Wexler, I.G. Burstain, R. Denny, G.O. Schenck and K.H. Schulte-Elte, Tetrahedron, 23, 2583 (1967); K. Gollnick, G.O. Schenck in "1,4-Cycloaddition Reactions", (J. Hamer, ed.), Academic Press, New York, 1967, Chapter 10, p. 255.
8. See ref. 1, Chapter 9.
9. W. Adam and I. Erden, J. Org. Chem., 43, 2737 (1978); see also: W. Adam and A. Rodriquez, J. Amer. Chem. Soc., 102, 404 (1980).
10. The temperature-dependent ^{1}H NMR spectra as reported for the [2+4]-cycloadduct of 1 and dimethyl acetylenedicarboxylate[11], were not observed for ozonide 2 (temperatures -80 - 9 °C).
11. J.M. Timko, S.S. Moore, D.M. Walba, P.C. Hiberty and D.J. Cram, J. Amer. Chem. Soc., 99, 4207, (1977).
12. Addition of methanol to a chloroform solution of 7 also gives a clean conversion into 10 with second-order kinetics ($k = 1.81 \times 10^{-3}$ mol.l^{-1}.s^{-1} at 20 °C).

13. E.W. Colvin, T.A. Purcell and R.A. Raphael, J. Chem. Soc. Perkin Tr. I, 1718 (1976).

14. E.J. Corey, K.C. Nicolaou and T. Toru, J. Amer. Chem. Soc. 97, 2287 (1975).

15. We did not observe any significant effects on the photo-oxidation rates of 1 due to complexation of Rose Bengal.

Table: NMR data of ozonides 2, 7 and 8 ($CDCl_3$, ppm)

^{13}C-NMR

2	131.3 $(=\mathrm{C}{<}^{\mathrm{H}})$;	111.9 $({>}\mathrm{C}{<}^{\mathrm{O}}_{\mathrm{O}})$,	62.5 ($-CH_2O-$),	68.3, 69.0, 69.9 (OCH_2CH_2O)
8	131.5	, 112.5	, 65.3	, 59.0 (OCH_3)
7	133.2	, 111.7	,	12.6 (CH_3).

^{1}H-NMR

2	6.61 (s, $=\mathrm{C}{\diagup}^{\mathrm{H}}$),	4.18 (s, CH_2O), 4.24 (s, CH_2O),	3.68 (m, OCH_2CH_2O)
8	6.35 (s, $=\mathrm{C}{\diagup}^{\mathrm{H}}$),	4.13 (s, CH_2O),	3.54 (s, OCH_3)
7	6.38 (s, $=\mathrm{C}{\diagup}^{\mathrm{H}}$),		1.82 (s, CH_3)

(Received in UK 26 January 1981)