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Transformation of 1-Alkyl-Substituted Indene Ozonides and the Corresponding Solvent-Derived Ozonolysis Products to Tricyclic Peroxides: Isolation and Characterization of Novel Hexoxecane Derivatives

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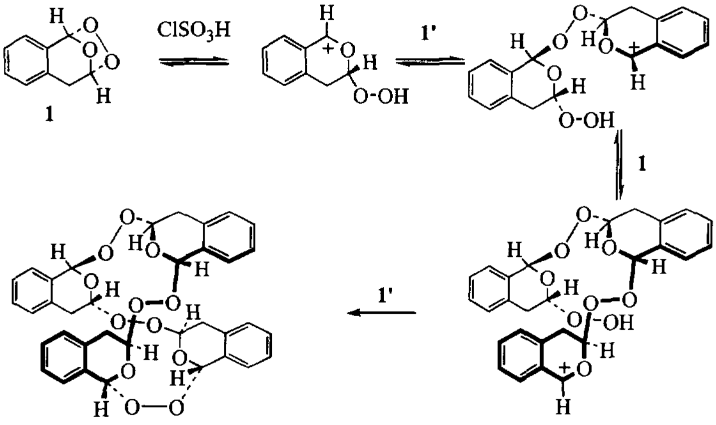
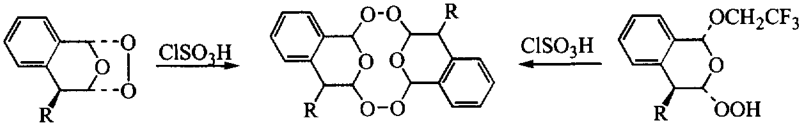
Abstract: Acidolysis of 1-alkyl-substituted indene ozonides **3a,c,d** or the corresponding solvent-derived ozonolysis products **5a-d** gave the hexoxecane derivatives **4a-d**. The structure of the compound **4a** was unambiguously established by the X-ray crystallographic analysis, which demonstrated that the hexoxecane **4a** is derived from dimerization of molecules of **3a** or **5a** of the same configuration.

The chemistry of mono- and polycyclic peroxides has attracted considerable recent attention since a significant number of peroxidic natural products with interesting pharmacological properties have been isolated.[1,2] In this respect, ozonides and the α-alkoxy-α'-hydroperoxy ethers derived from capture of the carbonyl oxides by protic solvents have recently been reported to be the useful precursors for the synthesis of medium-sized cyclic peroxides.[3] Thus, treatment of indene ozonide **1** with $ClSO_3H$ results in the stereoselective formation of the cyclic tetramer **2** having an unusual dodecaoxacycloicosane structure, derived from successive incorporation of, **1** and its enantiomer **1'** (Scheme 1).[3a]



Scheme 1

We now report the preliminary results of the acidolyses of a series of 1-alkyl-substituted indene ozonides **3a,c,d** or their corresponding α-alkoxy-α'-hydroperoxy ethers **5a-d**.[4] Treatment of a solution of 1-*tert*-butylindene ozonide **3a** with $ClSO_3H$ (0.1 equiv) in methylene chloride at 0 °C for 4 h., followed by column chromatography of the crude reaction mixture on silica gel gave a crystalline peroxidic product (57%); the unreacted ozonide **3a** was also recovered in 21% yield. Under similar conditions, the solvent-derived product **5a** afforded the same peroxidic product (60%) and the ozonide **3a** (7%). The NMR spectral data, elemental analysis, and molecular weight measurement suggested that the peroxidic product should be a symmetrical cyclic dimer **4a** of the indene ozonide **3a** rather than an analogue of the cyclic tetramer **2** obtained from ozonide **1** (Scheme 2).[5,6] Moreover, the hexoxecane derivatives **4b-d**, albeit in moderate to low yields, were also obtained. from the acidolyses of the corresponding indene ozonides **3b-c** and solvent-derived products **5b-d**.[7]

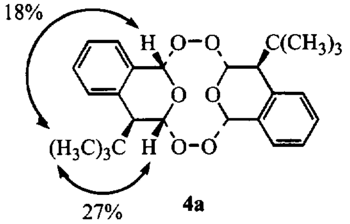


3 **4** **5**

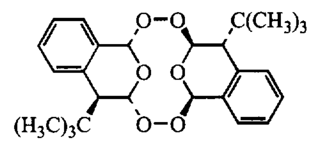
a; R = *t*-butyl b; R = 1,1-dimethylpropyl c; R = isopropyl d; R = 3-pentyl

Scheme 2

In the ^1H NMR spectrum of **4a**, the signals of the *tert*-butyl group and the remote methine hydrogen exhibited significant NOEs suggesting that these two substituents should be *syn* with respect to each other and consistent with either of the symmetrical structures **4a** and **4a'**. By analogy with the transformation of **1**→**2**, the cyclic dimer could be reasonably expected to be the centrosymmetrical isomer **4a'**. X-ray crystallographic analysis showed unambiguously that the cyclic dimer derived from **3a** or **5a** was in fact **4a** as depicted in Fig. 1.[8] The 10-membered 1,2,4,6,7,9- hexoxecane ring adopts a comformation which has a C_2-axis of symmetry perpendicular to the ring plane.



4a



4a'

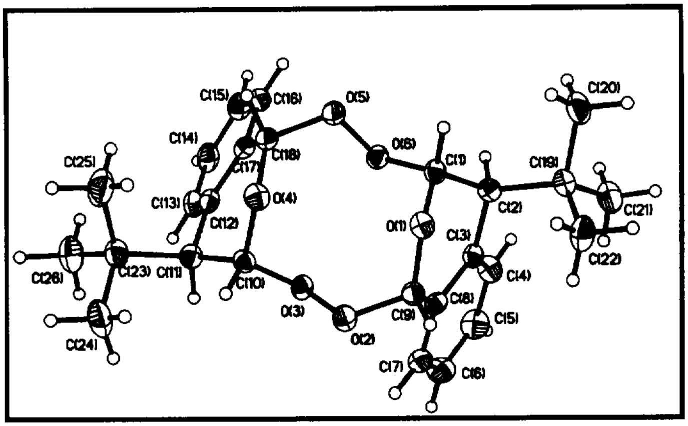
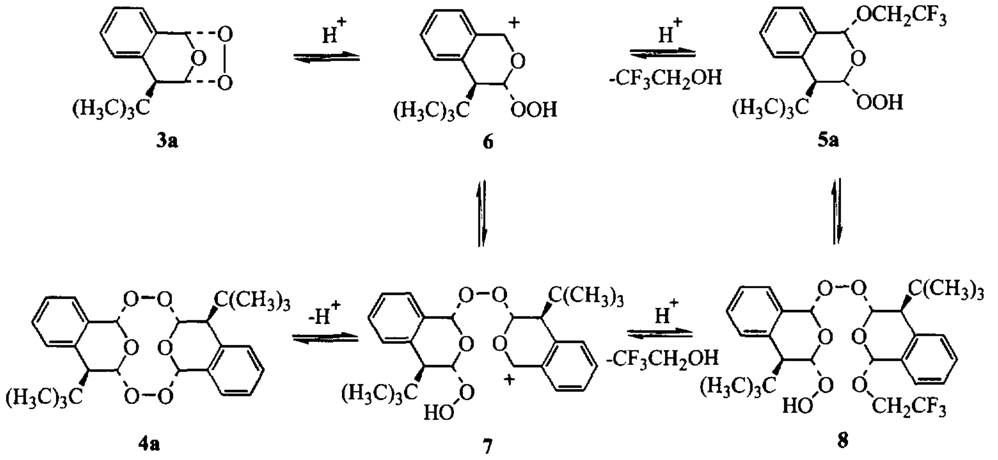


Figure 1. The crystal structure of cyclic dimer **4a**

By way of further support for the stereoselective formation of **4a**, the results of *ab initio* (PM3 package[9]) and molecular mechanics (MM2, MacroModel[10]) calculations suggest that isomer **4a'** is less stable than **4a** by *ca.* 9.5 and 6.0 kcal mol^{-1} respectively as a consequence of unfavourable repulsive interactions between the oxygen atom lone pairs.[5c]

From its relative stereochemistry, **4a** has been formed by the selective dimerization of molecules of 1-*tert*-butylindene ozonide **3a** or **5a** having the same configuration. Taking account of these stereochemical requirements, a plausible mechanism for the direct formation of **4a** from **3a** or **5a** is outlined in Scheme 3. An acid-catalyzed ring opening of ozonide **3a** or elimination of trifluoroethanol from **5a** would produce a common carbocationic intermediate **6**, which could in turn be captured by a second molecule of either **3a** or **5a**, having the same configuration, from the least sterically hindered face to give **7** or **8** (and then **7**) respectively. In each case, ring closure of **7** *via* intramolecular attack of the hydroperoxy group from the face *anti* to the bulky *tert*-butyl group establishes the *syn*-relationship between the peroxy moieties as observed in **4a**. The presence of the *tert*-butyl group is also likely to make the cyclization of **7** to **8** more favourable than the subsequent incorporation of further molecules of the substrates **3a** or **5a**.

In addition, given that the hexoxecane derivatives **4b-d** were isolated in only one stereoisomeric form., the bulky 1-alkyl substituents in precursors **3b,d** and **5b-d** must exert similar steric effects to the *tert*-butyl group described above.



Scheme 3

In conclusion, our investigations thus far suggest that the presence of a bulky substituent in either an indene ozonide or its related solvent-derived ozonolysis product plays an important role in determining the mechanism and extent of the cyclooligomerization process and also the stereochemistry of the resulting cyclisation products.

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REFERENCES AND NOTES

1. Casteel, D. A. *Natural Product Reports*, **1992**, *9*, 289.
2. (a) Patai, S. ed., '*The Chemistry of Peroxides*,' Wiley, New York, 1983. (b) Ando, W. ed., '*Organic Peroxides* ', Wiley, New York, 1992.
3. (a.) McCullough, K. J.;. Teshima, K; M. Nojima, *J. Chem. Soc., Chem. Commun.*, **1993**, 931. (b) Ushigoe, Y. ; Tanaka, S.;. Nojima, M; McCullough, K. J. *Tetrahedron Lett.*, **1994**, *52*, 9741 and references therein.
4. Teshima, K.; Kawamura, S.; Ushigoe, Y.; Nojima, M.; McCullough, K. J. *J. Org. Chem.*, **1995**, *60*, 4755.
5. For the synthesis of other hexoxecane derivatives, see (a) Rio, G.; Rio, M. J. *J. Chem. Soc., Chem. Commun.*, **1982**, 72. (b) Golnick, K.; Griesbeck, A. *Angew. Chem.*, **1983**, *95*, 751. (c) Griesbaum, K.; Kiesel, G.; Mertens, H.; Krieger-Beck, P.; Henke, H. *Can. J. Chem.*, **1994**, *72*, 2198.
6. All new compounds gave satisfactory elemental analyses.

   The hexoxecane **4a**: mp 141-142 °C (from diethyl ether-hexane); ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 18 H), 2.53 (s, 2 H), 5.98 (s, 2 H), 6.12 (s, 2 H), 7.0-7.7 (m, 8 H); ^{13}C NMR ($CDCl_3$) d 27.82, 34.93, 49.29, 97.58, 98.73, 125.96, 126.55, 127.18, 130.22, 131.25, 131.86; IR 1330, 1200, 1120, 1020, 960, 760 cm^{-1}; molecular weight (VPO, CH_2Cl_2) 486.
7. The yields of dimers **4b-d** from their respective precursors are shown in brackets:

   (i) **4b** (41%) from **5b**; (ii) **4c** (14%) from **3c** and (40%) from **5c**; (iii) 4d (14%) from **3d** and (31%) from **5d**. For **3c** and **3d**, the unreacted ozonide was recovered in *ca.* 40% in each case.
8. *Crystal data for 4a.*$C_{26}H_{32}O_6$, M = 440.52, colourless prisms, triclinic, space group $P\bar{1}$ (No. 2), ***a*** 7.0630 (14), ***b*** 13.125 (3), ***c*** 13.981 (3) Å, α = 112.58 (3), β = 101.75 (3) γ = 95.69 (3)°, U 1148.9 (4) $Å^3$, Z = 2, D_c 1.273 g cm^{-3}, F(000) 472, μ(Mo-K_α) 0.89 cm^{-1}.

   The intensity data were collected on an Enraf-Nonius CAD4 diffractometer equipped with a FAST detector (θ range: 1.81 – 25.02 °; ω -scanning; Mo-K_α X-radiation; 120 K). Refinement on F^2 (SHELXTL[11]); final discrepancy factors R and R_w were 0.048 and 0.120 respectively for 2771 intensities with $I > 2\sigma(I)$
9. Stewart, J. J. P. *J. Comput. Chem.*, **1989**, *10*, 209, 221.
10. Still, W. C., Columbia University, 1990.
11. Sheldrick, G. M., University of Göttingen, 1994.

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