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Polycyclic Ozonides and Peroxides Derived from Hexamethyl(Dewar Benzene)

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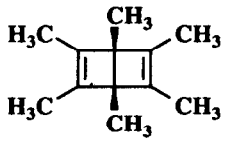
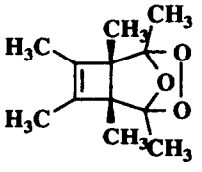
Abstract: A stable, crystalline diozonide, derived from Hexamethyl(Dewar Benzene) **1**, has been shown by X-ray crystallographic analysis to be the *endo,endo*-isomer **3c** which had been predicted to be less stable than the *endo,exo*-isomer **3b**. Acidolysis of the *trans*-ozonide **5** in CF_3CO_2H/CH_2Cl_2 gave a stable crystalline tricyclic peroxide **6** whereas the isomeric *cis*-ozonide **7** decomposed under similar conditions.

Introduction

Hexamethyl(Dewar benzene) [HMDB, 1,2,3,4,5,6-hexamethylbicyclo[2.2.0]hexa-2,5-diene] **1** had been reported previously to produce a mono- **2** and a di-ozonide **3** on treatment with one or two equivalents of ozone respectively.[1] Although ozonides would normally be expected by reputation to undergo decomposition readily, diozonide **3** was described as being highly thermally stable and indeed melts without decomposition.



1



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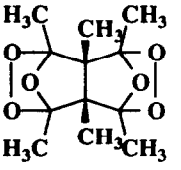
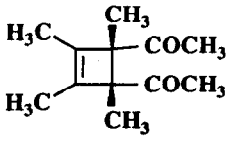


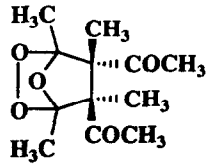
3

Ozonization of a related *cis*-diacetylcyclobutane derivative **4**, obtained by oxidative cleavage of **1** using potassium permanganate,[1] at low temperature in aprotic solvents such as carbon tetrachloride or trichlorofluoromethane afforded predominantly the ozonide **5** whereas, in methanol, the isomeric tricyclic peroxide **6** was the major product isolated.[2] The structure of **6** has been established by X-ray crystallographic analysis.[3]

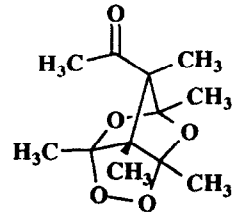
We report herein the results of a recent investigation of the structures of the intriguing ozonides **2** and **3**, the ozonolysis of cyclobutene **4** to give either ozonide **5** or polycyclic peroxide **6**, and the acidolysis of ozonide **5**.



4



5



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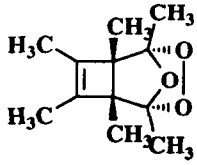
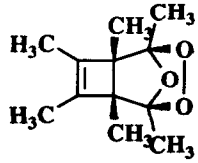
Results and Discussion

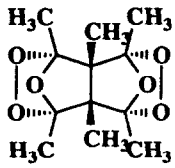
Although the general structural features of the ozonides **2** and **3** were generally consistent with the conventional analytical data available, their precise structures had not been definitively determined.[1] From their respective structures and assuming that no skeletal rearrangements had occurred during the ozonolysis reaction, ozonide **2** could potentially exist as two isomers, the *exo*-**2a** and the *endo*-**2b**, and diozonide **3** as three isomers, the *exo,exo*-**3a**, the *endo,exo*-**3b** and the *endo,endo*-**3c**.[4] An initial investigation of the structures of **2** and **3** was carried out using molecular mechanics calculations [5] which has been shown to be useful for modelling the structures of a variety of acyclic and cyclic peroxide systems.[6]



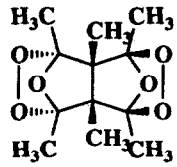
2a



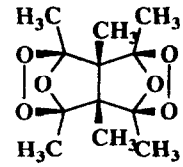
2b



3a



3b



3c

Structural minimisation of mono-ozonides **2a** and **2b** using both MacroModel[7] and Chem3DPlus[8] indicated that the latter *endo*-isomer should be more stable by around 1.6 kcal mol^{-1}. The calculated structures for compounds **2a** and **2b** were found to be symmetrical and corresponding bond lengths and angles were comparable. Apart from the central carbon-carbon bond which was slightly shorter than that reported for Dewar benzene or cyclobutene (1.55 Å cf. 1.567 Å),[5] the calculated geometrical parameters were found to be generally within expected ranges.[9]

The results of similar molecular mechanics calculations on the isomeric diozonides **3a-c** predicted a relative order of structural stability of **3b** > **3c** > **3a** with energy differences between **3b** and **3c**, and **3c** and **3a** of around 5.5 and 1.2 kcal mol^{-1} repectively. As observed for the mono-ozonides, corresponding calculated structural parameters were in reasonable agreement between the structures obtained for **3a-3c**, and their magnitudes did not vary significantly from the expected ranges.

Cursory inspection of the calculated structure for the *exo,exo*-isomer **3a** suggested that intramolecular steric interactions between the eclipsed peroxide bridges would destabilise this structure (Figure 1). Similarly, the *endo,endo*-isomer **3c** would be destabilised by steric interactions between the peroxide linkages and the adjacent *syn*-methyl groups though the ozonide rings are slightly distorted in order to minimise these interactions (Figure 2). Nonetheless, it would be surprising if the diozonide **3** were to be formed as the *endo,exo*-isomer **3b** since that mono-ozonide **2b** appears to be structurally favoured over **2a**.

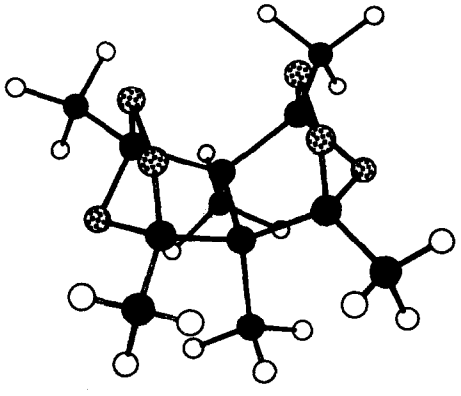


Figure 1. Minimised structure of *exo, exo*-isomer **3a**

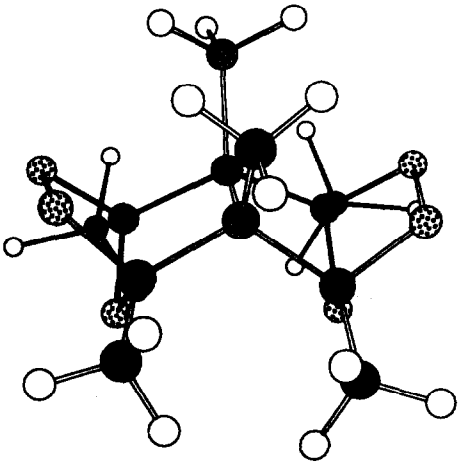


Figure 2. Minimised structure of *endo,endo*-isomer **3c.**

Since diozonide **3**, which was considered to be a single stereoisomer on the basis of its available spectroscopic data, afforded suitable single crystals, its structure was, therefore, investigated by X-ray crystallographic analysis to resolve this apparent structural ambiguity. The results of the X-ray crystallographic analysis show clearly that the the diozonide **3** is a single isomer corresponding to the *endo,endo*-isomer as depicted in structural formula **3c** and Figure 3 together with the numbering scheme adopted in the X-ray structural study.

The crystal structure consists of discrete, well-separated molecules of **3c** (no significant intermolecular contacts less than 3.2 Å were observed). As a result of small torsional distortions (*ca.* 0.7-2.3 °), most notably around the 1,2,4-trioxolane rings and in the region of the eclipsed methyl groups C(11) and C(12), the molecule does not have ideal C_{2v} point group symmetry. The 1,2,4-trioxolane rings are forced to adopt slightly distorted envelop conformations by the rigid polycyclic molecular framework. Corresponding bond lengths and angles around the ozonide rings are, however, in good agreement and are comparable with those reported for analogous polycylic mono-ozonides.[10,11] Although the observed O–O

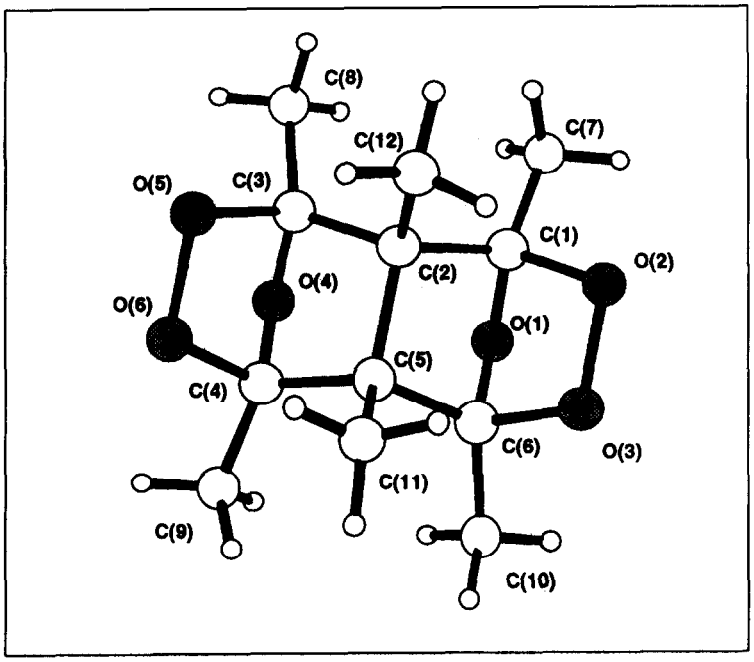
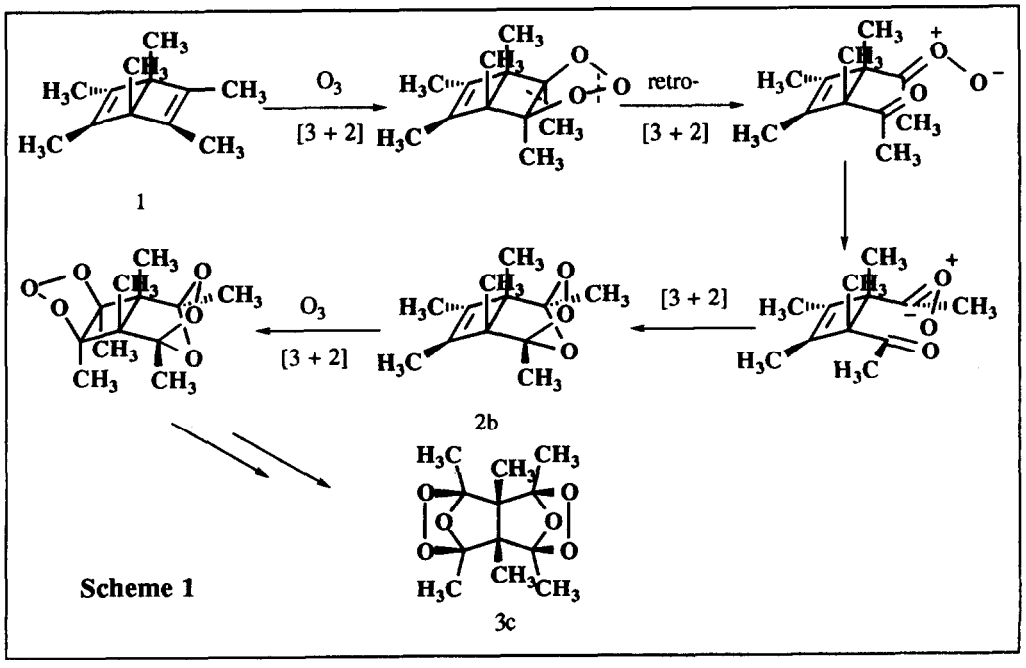


Figure 3. The crystal structure of diozonide **3** with the crystallographic numbering system. Hydrogen atom labels have been omitted for clarity.



bond lengths [1.4867 (20) and 1.4833 (21) Å] are at the upper end of the expected range, they are not significantly longer than that reported for compound **6** and probably indicate that structurally rigid diozonide **3c** is not highly strained (cf. O–O bond length 1.501 (2) Å in 1,4-diphenyl-2,3-dioxabicyclo[2.2.1]heptane [12]).[13] The ring junction bond C(2)–C(5) [1.586 (3) Å] is, however, significantly longer than expected for a typical C–C single bond, a feature which was not adequately reproduced in the molecular mechanics calculations.

A tentative reaction mechanism for the formation of diozonide **3c** from HMDB **1** is outlined in Scheme 1. Consistent with the structure of diozonide **3c** , it is likely that the initial attack of ozone took place on the convex face of HMDB **1**, *syn* to the ring junction methyl groups, to give the corresponding primary ozonide which subsequently decomposed according to the conventional Criegee mechanism[14] to a carbonyl oxide/carbonyl pair. Reorientation of the sterically less hindered acetyl group followed by recombination would give *endo*-**2b**. The addition of a second molecule of ozone to *endo*-**2b** on the same face as described above followed by a similar cycloreversion-recombination sequence would give rise to the *endo,endo*-diozonide **3c** as obtained. Thus, the formation of the less thermodynamically stable diozonide **3c** arises from the apparent ease of approach of ozone to the substrates **1** and **2b**. Like its precursor HMDB **1**, the diozonide **3c** is inherently stable because the activation barriers to other rearrangement processes are relatively high. The molecule is, therefore, considered to be located in a local energy minimum.

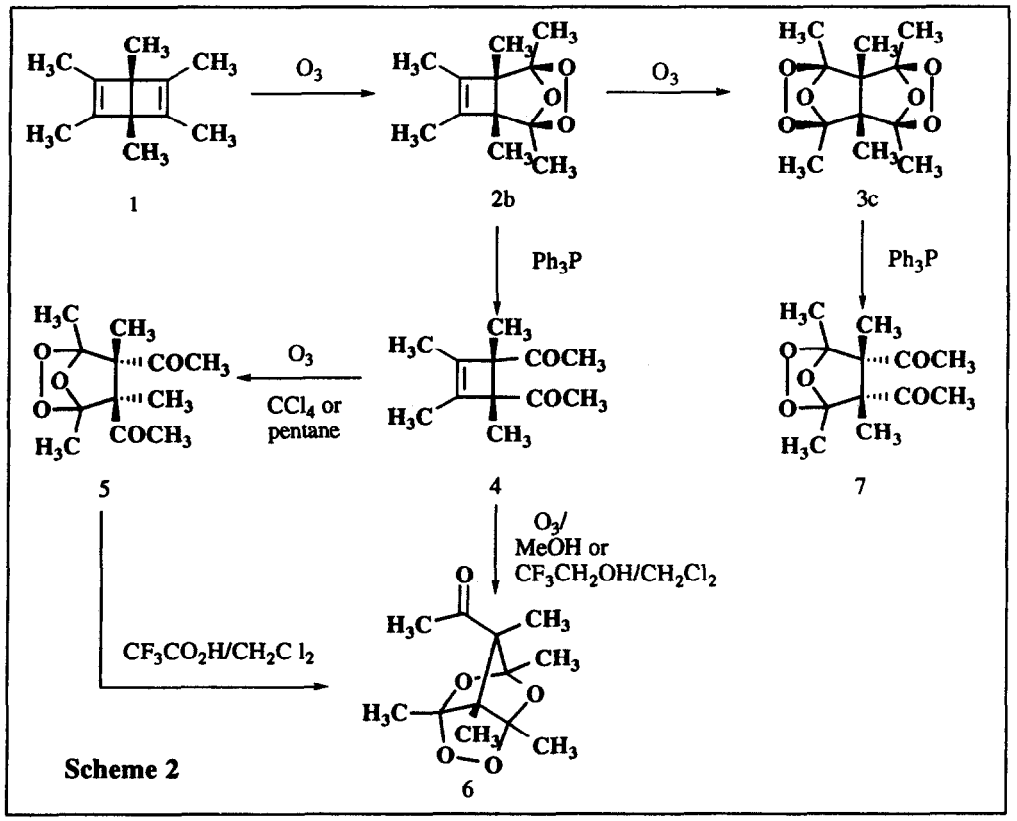
Having unambiguously assigned the structure of the ozonide **3c**, and by inference that of **2b** also , the ozonolysis reactions of the cyclobutene derivative **4**, obtained by reduction of ozonide **2b** with triphenylphosphine, were investigated [Scheme 2].

Ozonolysis of **4** in the non-polar solvents, pentane and carbon tetrachloride, afforded the *trans*-ozonide **5** as the major product in agreement with previous findings.[2] In polar, protic solvent systems such as methanol or trifluoroethanol/ dichloromethane, the predominant product from the ozonization of **4** was the rearranged peroxide **6**. An extended [3 + 2 + 2] cycloaddition process had been proposed previously to account for the formation of **6**.[2]

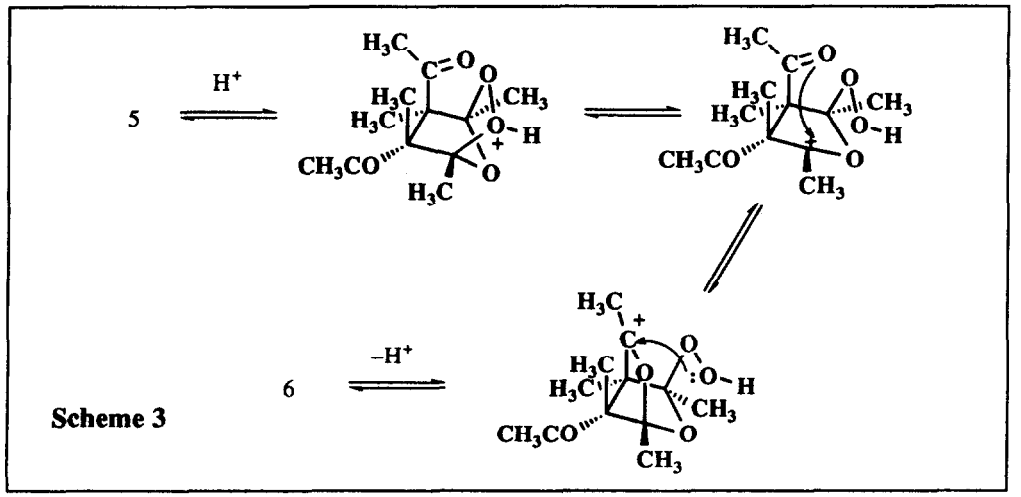
Partial reduction of diozonide **3c** with 1 equivalent of triphenylphosphine in benzene allowed the independent synthesis of the *cis*-ozonide **7**, the geometrical isomer of **5**.

Treatment of ozonide **5** with trifluoroacetic acid in dichloromethane gave the tricyclic peroxide **6** in 48% yield. Under similar conditions, acidolysis of the *cis*-compound **7** resulted in the formation of a complex mixture of unidentifiable products. The acidolysis of ozonide **5** appears to be a highly stereoselective process involving exclusively the adjacent acetyl group which is *syn* to the peroxide moiety. Thus, the formation of **6** from **5** can be rationalised by the stepwise sequence outlined in Scheme 3 which requires selective protonation of the distal peroxy oxygen atom, heterolytic C–O bond cleavage, participation of the neighbouring *syn*-acetyl group and finally ring closure by terminal oxygen atom of the peroxyl group. The polycyclic nature of **6**, being composed exclusively of 5- and 6-membered rings, render it immune to further rearrangement uner the mild reaction conditions employed.

Conversely, both acetyl groups in ozonide **7** are too remote from the peroxide moiety to participate in an analogous rearrangement sequence, thus extensive decomposition of **7** resulted instead. In addition, the acidolysis reaction conditions do not appear to favour the interconversion of the isomeric ozonides **5** and **7** which is, in principle, possible via their common acyclic carbonyl oxide intermediate.



Scheme 2



Scheme 3

Experimental Section

General

^{1}H- and ^{13}C-NMR spectra were measured on JEOL JNM-PS-100 and JNM-GSX-400 spectrometers respectively with $CDCl_3$ as solvent (unless otherwise stated). Mass spectral data were obtained with a Hitachi RMU-6H spectrometer and infrared spectra recorded with a Hitachi 215 spectrometer.

Hexamethyl(Dewar benzene) was purchased from the Aldrich Chemical Company and used without further purification.

Column chromatography was performed on silica gel YMC-Gel (70-230 mesh). Solvents were dried and purified by standard methods.

Ozone was generated using a Nippin Ozone ON-I-2 Ozonator (O_2 flow rate 50 l h^{-1}).

CAUTION: Since organic ozonides and peroxides are potentially hazardous compounds, they must be handled with due care; avoid exposure to strong heat or light, or mechanical shock, or oxidisable organic materials or transition metal ions.

In the course of this work, no particular difficulties were encountered in handling any of the organic ozonides or peroxides synthesised using the reaction scales and procedures described below together with the general safeguards mentioned above.

***Synthesis of Mono-ozonide* 2b *from HMDB* 1**

To a solution of HMDB **1** (500 mg, 3.09 mmol) in dichloromethane (15 ml), was passed a slow stream of ozone (1 equiv.) at -70 °C. After evaporation of the solvent, the crude product mixture was subjected to column chromatography on silica gel. Elution with diethyl ether-hexane (1:20) gave *endo*-ozonide **2b** (362 mg, 56% yield).

1,2,3,4,5,6-Hexamethyl-7,8,9-trioxatricyclo[4.2.1.$0^{2,5}$]non-3-ene **2b**: mp 53-54 °C (Lit.[1] 53-54 °C) (from methanol); ^{1}H NMR (CCl_4) δ 1.00 (s, 6 H), 1.37 (s, 6 H), 1.57 (s, 6 H). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63 %. Found: C, 68.50; H, 8.65 %.

***Synthesis of Diozonide* 3c *from HMDB* 1**

To a solution of HMDB **1** (1.25 g, 7.72 mmol) in carbon tetrachloride (30 ml) was passed a slow stream of ozone (3 equiv.) at 0 °C. After evaporation of the solvent, the precipitated diozonide **3c** was collected (1.58 g, 79% yield).

Tetrahydro-1,4,4a,5,8,8a-hexamethyl-1:4,5,8-diepoxy-1*H*,4*H*-*o*-dioxino[4,5-d]-*o*-dioxin **3c**: mp 190 °C (Lit.[1] 184-186 °C) (from methanol); ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 6 H), 1.61 (s, 12 H); ^{13}C NMR ($CDCl_3$) δ 10.25, 13.09, 58.26, 114.49; IR 1460, 1380, 1230, 1195, 1145, 1075, 920, 855, 800, 630 cm^{-1}.

***Transformation of Ozonide* 2b *to Cyclobutene* 4**

A solution of *endo*-ozonide **2b** (362 mg, 1.72 mmol) and triphenylphosphine (451 mg, 1.72 mmol) in benzene (15 ml) was stirred at room temperature for 1 day. After evaporation of the solvent, cyclobutene **4**

(228 mg, 68%) was isolated from the crude product mixture by column chromatography on silica gel, eluting with diethyl ether-hexane (3:17).

3,4-Diacetyl-1,2,3,4-tetramethylcyclobutene **4**: mp 58-59 °C (Lit.[2] 58 °C) (from aqueous MeOH); ^{1}H NMR (CCl_4) δ 1.20 (s, 6 H), 1.62 (s, 6 H), 1.88 (s, 6 H).

Transformation of Cyclobutene 4 to trans-Ozonide 5

A solution of cyclobutene **4** (228 mg, 1.18 mmol) in carbon tetrachloride (15 ml) was treated with 3 equiv. of ozone at 0 °C. After evaporation of the solvent, the crude residue was subjected to column chromatography on silica gel. Elution with diethyl ether-hexane (3:17) gave *trans*-ozonide **5** (165 mg, 58%).

1,1'-(1,4,5,6-Tetramethyl-2,3,7-trioxabicyclo[2.2.1]heptane-5,6-diyl)bis-(1α,4α,5α,6β)ethanone **5**: mp 62-64 °C (Lit.[2] 63-64 °C) (from MeOH-H_2O); ^{1}H NMR (CCl_4) δ 0.97 (s, 3 H), 1.32 (s, 3 H), 1.51 (s, 3 H), 1.67 (s, 3 H), 2.20 (s, 3 H), 2.30 (s, 3 H). Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H,7.43 %. Found: C, 59.40; H, 7.44 %.

Transformation of Cyclobutene 4 to a Tricyclic Peroxide 6

A solution of cyclobutene **4** (254 mg, 1.31 mmol) in trifluoroethanol-methylene chloride (15 ml; 1:2, v/v) was treated with 1.5 equiv. of ozone at 0 °C. After evaporation of the solvent, the major components of the crude product mixture were separated by column chromatography on silica gel. Elution (a) with diethyl ether-hexane (1:4) gave ozonide **5** (12 mg, 4%) and (b) with diethyl ether-hexane (1:3) gave the tricyclic peroxide **6** (79 mg, 29% yield).

1-(Tetrahydro-3,3a,4,5,6a-pentamethyl-3,5-epoxy-3*H*-furo[2,3-c]-1,2-dioxol-4-yl)ethanone **6**: mp 144-148 °C (Lit.[2] 156-157 °C) (from methanol); ^{1}H NMR (CCl_4) δ 1.20 (s, 3 H), 1.34 (s, 6 H), 1.50 (s, 3 H), 1.70 (s, 3 H), 2.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 7.97, 12.86, 15.42, 16.16, 16.73, 28.56, 66.15, 66.52, 105.21, 110.39, 111.48, 206.04.

Transformation of Diozonide 3c to cis-Ozonide 7

A solution of diozonide **3c** (1.55 g, 6.0 mmol) and triphenylphosphine (1.58 g, 6.0 mmol) in benzene (15 ml) was stirred at room temperature for 1 day. After evaporation of the solvent, crude products were separated by column chromatography on silica gel. Elution with diethyl ether-benzene (1:19) gave *cis*-ozonide **7** (626 mg, 43%).

1,1'-(1,4,5,6-tetramethyl-2,3,7-trioxabicyclo[2.2.1]heptane-5,6-diyl)bis-(1α,4α,5α,6α)ethanone **7**: mp 104-110 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 6 H), 1.65 (s, 6 H), 2.05 (s, 6 H). Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.43 %. Found: C, 59.78; H, 7.22 %.

Rearrangement of trans-Ozonide 5 to Tricyclic Peroxide 6

A solution of ozonide **5** (170 mg, 0.70 mmol) and trifluoroacetic acid (80 mg, 0.70 mmol) in methylene chloride (8 ml) was stirred at room temperature for 2 h. Diethyl ether (50 ml) was added and the mixture was poured into aqueous $NaHCO_3$. The organic layer was washed with saturated brine, dried over anhydrous MgSO4, and concentrated. The resulting residue was subjected to column chromatography on silica gel (elution with ether-hexane (1:3)) to give tricyclic peroxide **6** (81 mg, 48%).

Attempted Rearrangement of cis-Ozonide 7

A mixture of ozonide **7** (97 mg, 0.40 mmol) and trifluoroacetic acid (46 mg, 0.40 mmol) in methylene chloride (5 ml) was stirred at room temperature for 1 day. After work-up as described above, isolation of the reaction products was attempted by column chromatography on silica gel. Elution with ether-hexane (1:70 gave the unchanged ozonide **7** (33 mg, 33%). Subsequent elution with ether-hexane (1:1) gave a complex mixture of unidentified products (30 mg).

X-ray Crystal Structure Determination of the diozonide 3c

A single crystal of **3c** (from dichloromethane/hexane, approximate size 0.5 x 0.3 x 0.25 mm), mounted in a Lindemann tube, was used for X-ray data collection.

Crystal data. $C_{12}H_{18}O_6$, M = 258.2, colourless prisms, orthorhombic, space group Pbca (No. 61), *a* 8.7915 (13), *b* 12.4048 (4), *c* 22.584 (4) Å, U 2462.9 (8) $Å^3$, Z = 8, D_C 1.393 g cm^{-3}, F(000) 1104, μ(Mo-K_α) 1.05 cm^{-1}.

Data Collection, Structure Solution and Refinement. The intensity data were collected on an Enraf-Nonius CAD4 diffractometer fitted with a FAST detector over the hemisphere (2θ range: 1.0 – 60.0 °; ***h***: -12 - +12, ***k***: -17 - +17, ***l***: 0 - +31) using Mo-K_α X-radiation (λ 0.710693 Å). Further details of the diffractometer settings have been published elsewhere.[15] Of the 3260 unique data measured, 1753 had $I > 2\sigma(I)$ and were used in subsequent structural solution and refinement. The data were corrected for Lorentz and polarisation effects, but not for absorption. The structure was solved by direct methods (SHELXS86 [16]) and refined by full-matrix least squares methods (SHELX76 [17]) using anisotropic temperature factors for all the non-hydrogen atoms. All the hydrogen atoms of the methyl groups were located on difference Fourier maps and included in the refinement process as idealised rigid tetrahedra (d_{C-H} 0.95 Å) with group isotropic temperature factors. At convergence, the discrepancy factors R and R_w were 0.036 and 0.047 respectively. The weighting scheme, $w^{-1} = [\sigma^2(F) + 0.00206\ (F)^2]$ was found to give satisfactory analyses of variance. Apart from one peak ca. 0.32 e $Å^{-3}$ of no chemical significance, the final difference Fourier map was essentially featureless (general noise level less that $\pm$0.17 e $Å^{-3}$). Incidental crystallographic calculations and compilation of tables were carried using the computer program CALC.[18] Figure 1 was prepared using the plotting program Ball & Stick (Version 3.0).[19]

Acknowledgements

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