

226. The Reaction of 4-Hydroperoxy-2,4,6-trimethylcyclohexa-2,5-dienone with Acetaldehyde. Formation of the Bis(peroxyacetal)

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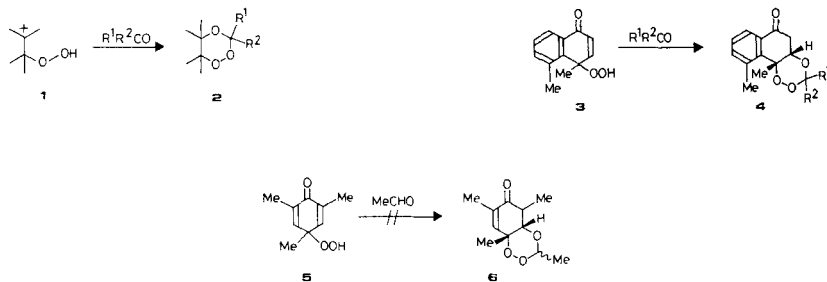
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Summary

The reaction of 4-hydroperoxy-2,4,6-trimethylcyclohexa-2,5-dienone with acetaldehyde using trimethylsilyl trifluoromethanesulfonate as catalyst gives 1,1'-bis[(1,3,5-trimethyl-4-oxo-2,5-cyclohexadienyl)peroxy]diethyl ether (**7**) in 70% yield. The structure of this unusual acetal was determined by X-ray analysis.

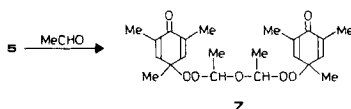
Introduction. – Interest attaches to the 1,2,4-trioxane ring since it is the crucial part of *Qinghaosu* and some of its derivatives which are active against malaria and *Schistosoma japonicum* [1]. In the past, few syntheses of 1,2,4-trioxanes were available [2]. Recently, however, we have shown that β -hydroperoxy cations **1** and their equivalents are engendered from 1,4-endoperoxides, 1,2-dioxetanes, and allylic hydroperoxides by catalysis with *Amberlyst-15* or trimethylsilyl trifluoromethanesulfonate (TMSOTf) and that they react with ketones and aldehydes to give 1,2,4-trioxanes **2** in high yield [3] (*Scheme 1*). 4-Hydroperoxy-4,5-dimethyl-1,4-dihydronaphthalen-1-one (**3**) is typical. Aldehydes and ketones condense with **3** on catalysis with *Amberlyst-15* to give the *cis*-fused trioxanes **4** [4]. We wished to exploit this reaction by using structurally simpler molecules such as 4-hydroperoxy-2,4,6-trimethylcyclohexa-2,5-dienone (**5**). Acetaldehyde on catalysis with TMSOTf should add to **5** to give the trioxanes **6**. However, the reaction took an unprecedented course, details of which are reported here.

Scheme 1



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Scheme 2



Results and Discussion. – The treatment of **5** with an excess of acetaldehyde and more than 1 equiv. of TMSOTf [5] gave the bis-peroxy acetal **7** in 70% yield (Scheme 2). Its structure was elucidated by X-ray analysis. The lattice parameters and diffracted intensities were measured at room temperature using an automatic four-circle diffractometer (Philips, model PW1100) with graphite-monochromated MoK α -radiation. The crystallographic data for C₂₂H₃₀O₇ are: orthorhombic, space group *Pccn*; $a = 8.237(1)$, $b = 27.567(4)$, $c = 10.375(2)$ Å; $Z = 4$, $F_{000} = 872$; $D_c = 1.146$ g·cm⁻³.

The structure was solved by direct methods [6] and refined by full-matrix least-squares analysis [7] with anisotropic temperature factors for non-H-atoms and isotropic terms for hydrogen and the O(4) oxygen. All H-atoms were calculated. The final *R*-value, based on 726 reflections ($|F_o| > 3\sigma(F_o)$ and $|F_o| > 8$), was 0.100 ($R = 0.058$ with $\omega = (|F_o|/48)^2$ for $|F_o| \leq 48$ and $\omega = (48/|F_o|)^2$ for $|F_o| > 48$).

The positional and vibrational parameters (Table 1) together with the bond lengths and principal torsional angles were determined (Table 2)².

The molecule adopts a linear zig-zag conformation which is symmetrical with respect to the mean position of the central ether O-atom (Fig.). The O(4)-atom is situated on a two-fold crystallographic axis parallel to *c*. Its co-ordinates correspond to an average position on the symmetry element, but O(4) is actually slightly displaced

Table 1. Fractional Co-ordinates, Equivalent Isotropic Temperature Factors, U_{eq} ($\times 10^3$ Å²) with e.s.d.'s in Parentheses, and Population Parameters for **7**^{a)}

Atom	X	Y	Z	U_{eq}	PP
O(1)	0.2836(7)	0.16027(20)	0.8494(6)	60(3)	1.0
O(2)	0.1400(7)	0.17575(22)	0.7748(6)	65(3)	1.0
O(3)	-0.2013(9)	0.0450(3)	0.9560(8)	104(4)	1.0
C(1)	0.2340(13)	0.1164(3)	0.9200(10)	53(4)	1.0
C(2)	0.1802(12)	0.0785(3)	0.8258(9)	51(4)	1.0
C(3)	0.0406(14)	0.0547(3)	0.8392(10)	52(4)	1.0
C(4)	-0.0718(14)	0.0673(4)	0.9433(12)	71(6)	1.0
C(5)	-0.0309(13)	0.1082(4)	1.0313(11)	61(5)	1.0
C(6)	0.1094(14)	0.1306(3)	1.0206(9)	57(4)	1.0
C(7)	0.3947(12)	0.1033(4)	0.9847(9)	69(5)	1.0
C(8)	-0.0066(12)	0.0141(3)	0.7509(12)	74(5)	1.0
C(9)	-0.1527(12)	0.1205(4)	1.1350(9)	82(5)	1.0
C(10)	0.1490(13)	0.2305(4)	0.7837(10)	106(6)	1.0
C(11)	-0.0240(17)	0.2379(4)	0.7368(14)	148(7)	1.0
O(4)	0.25	0.25	0.7084(13)	11(4)	0.5

^{a)} The numbering of atoms is that shown in the Figure.

²⁾ Observed and calculated structure factors may be obtained on request from G. B. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

Table 2. Bond Lengths (Å) and Torsion Angles (°) with *e.s.d.*'s in Parentheses for 7^a)

O(1)–O(2)	1.476(8)	C(2)–C(1)–O(1)–O(2)	58.9(9)
O(1)–C(1)	1.471(11)	C(6)–C(1)–O(1)–O(1)	– 67.8(9)
O(2)–C(10)	1.515(11)	C(1)–O(1)–O(2)–C(10)	– 142.3(7)
O(3)–C(4)	1.239(14)	O(1)–O(2)–C(10)–C(11)	– 154.5(8)
O(4)–C(10)	1.261(13)	O(1)–O(2)–C(10)–O(4)	78.9(10)
O(4)–C(10')	1.261(8)	O(2)–C(10)–O(4)–C(10')	– 116.7(7)
C(1)–C(2)	1.499(13)		
C(1)–C(6)	1.515(14)		
C(1)–C(7)	1.528(14)		
C(2)–C(3)	1.331(14)		
C(3)–C(4)	1.464(16)		
C(3)–C(8)	1.498(14)		
C(4)–C(5)	1.489(16)		
C(5)–C(6)	1.315(15)		
C(5)–C(9)	1.509(14)		
C(10)–C(11)	1.520(17)		

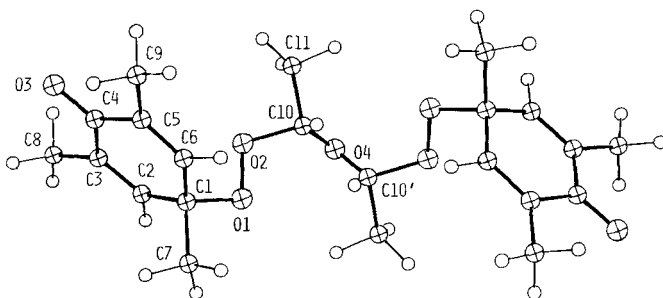


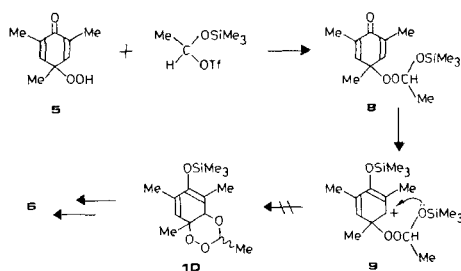
Figure. Computer-generated perspective drawing of the structure of bis-peroxy acetal 7

from the two-fold axis. The short bond length between O(4) and C(10) (1.261 (14) Å) confirms that O(4) is disordered. The six-membered ring, comprising atoms C(1) to C(6), is quasi-planar with a maximum deviation of 0.045 Å and is almost perpendicular (87.9°) to the plane defined by atoms C(1), O(1), O(2). The dihedral angle between the mean planes of the two six-membered rings is 75.2°.

The most significant structural feature is the fact that the *threo*-diastereoisomer is formed. The two asymmetric C-atoms (C(10) and C(10')) have the same configuration (*RR* in the configuration shown). The anisotropic effect springing from the C(10)- and C(10')-atoms is not far reaching as it is only revealed by the non-equivalent ¹³C-NMR signals displayed by the C(3)- and C(5)-atoms (135.6 and 135.8 ppm) and the C(2)- and C(6)-atoms (144.3 and 144.4 ppm).

The stereoselectivity of this unusual condensation is conferred in the ether-forming step. Initially the hydroperoxide **5** may add to acetaldehyde under catalysis by TMSOTf to furnish the silylated acetal **8** [8] (*Scheme 3*). Closure to the 1,2,4-trioxane would be aided by silylation of the ketone function in **8**. Intramolecular nucleophilic attack by the acetal on the resultant allylic cation **9** would produce the siloxy trioxane **10** and eventually **6**. Cyclization without catalysis to **6** is also possible. In any event, neither trioxane **6** or **10** was formed. The reason may be the potential steric impediment offered by the CH₃-substituents at C(2) and C(6). These substituents either pre-

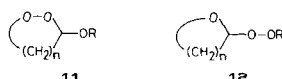
Scheme 3



vent the silylation of the intervening carbonyl function, or hinder the creation of the *cis*-fused trioxane ring. Consequently, the monoperoxy acetal **8** reacts with itself to lose a molecule of hexamethyldisiloxane, thereby giving the bis-peroxy acetal **7**. How this happens is open to conjecture. Whatever the mechanism, self-condensation is strongly favored between a pair of acetals **8** having *opposite* configurations, either *R* with *S* or *vice versa*, but not *R* with *R* or *S* with *S*. As a result, the bulk, perhaps all, of the bis-peroxy acetal formed, at least that furnishing crystalline material, is a racemic mixture of (R,R) -**7** and (S,S) -**7**.

Conclusion. – The structure of **7** is unusual. We are unaware of any other reports of acyclic peroxy or bis-peroxy acetals. The closest examples are cyclic peroxy acetals having the alkoxy group exocyclic, e.g. **11**, and cyclic acetals with the peroxy grouping exocyclic, e.g. **12** [9].

Scheme 4



We thank Messrs. *J.-P. Saulnier* and *A. Pinto* for performing the NMR spectral measurements and Mrs. *A. D'Ascoli* for the MS measurements. We are indebted to the *Swiss National Science Foundation* (grant No. 2.036-0.83) and *UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases* for support of this work.

Experimental Part

General. Physical constants and spectra were determined as follows. Melting points (m.p., uncorrected): *Büchi* m. p. apparatus. IR: *Perkin-Elmer 681* spectrometer. ^1H - and ^{13}C -NMR spectra (chemical shifts in ppm relative to internal TMS ($= 0$ ppm) coupling constants *J* in Hz): *Bruker WH 360* and *Varian XL-100* spectrometers. MS: *CH-4 MAT*.

4-Hydroperoxy-2,4,6-trimethylcyclohexa-2,5-dienone (5). The photo-oxygenation method for preparing 4-hydroperoxy-4-methylcyclohexa-2,5-dienone [10] was adapted as follows. A solution of 2,4,6-trimethylphenol (4 g, 29.4 mmol) in CHCl_3 (30 ml) was added to a sat. solution of Bu_4NF (10.2 g, 32.3 mmol) in 95% EtOH. The solvent was evaporated initially at 12 Torr and finally at 0.3 Torr for 30 min. The residue was dissolved in dry CHCl_3 (80 ml) and *Rose Bengal B* (40 mg, 0.039 mmol) was added. The solution was placed in a jacketed irradiation vessel and its temp. maintained at 25° by circulation of H_2O . The solution was irradiated with two 500-W *Sylvania FFX* bulbs screened with a UV cut-off filter (418 nm) while dry oxygen was passed. The course of the reaction was monitored by TLC on silica gel *G* using Et_2O as solvent. R_f values = 0.57, 0.50, and 0.38 were noted for 2,3,4-trimethylphenol, **5**, and an unknown side product, respectively. After 16 h of photolysis,

the solvent was evaporated at 20°, the residue was dissolved in Et₂O (100 ml) and then extracted with ice-cold H₂O (2 × 50 ml). The aq. layer was extracted with Et₂O (2 × 50 ml). The combined Et₂O-layers were washed with H₂O (3 × 25 ml), dried over anh. Na₂SO₄ and the solvent evaporated. Chromatography of the residue on *Kieselgel* 60 (100 g, 70–230 mesh) with CH₂Cl₂ gave **5** (1.22 g) as white needles after recrystallization from hot hexane. An additional 0.42 g of product was obtained by further chromatography over *Florisil* (20 g, 70–230 mesh, CH₂Cl₂ as eluant). Total yield of **5** was 1.64 g (33%), m.p. 99.5–100.0° ([11]: 98–99.5°). ¹H-NMR (100 MHz): 1.38 (s, 3H); 1.92 (s, 6H); 6.66 (s, 2H); 8.20 (s, 1H).

1,1'-Bis[(1,3,5-trimethyl-4-oxo-2,5-cyclohexadienyl)peroxy]diethyl Ether (7). To a magnetically stirred solution of **5** (0.20 g, 1.2 mmol) in CH₂Cl₂ (15 ml) under an atmosphere of N₂ at –78° was added dropwise by syringe, first acetaldehyde (0.88 g, 20 mmol) and then TMSOTf (0.29 g, 1.3 mmol). After stirring for 1 h at –78°, the reaction was quenched by adding Et₃N (0.30 g, 3.0 mmol) dropwise. Et₂O (15 ml) and H₂O (25 ml) were added and the mixture allowed to warm to r.t. The aq. layer was extracted with Et₂O (2 × 25 ml). The combined org. layers were washed with 10% aq. NaHSO₃ (3 × 4 ml), brine (2 × 5 ml), dried over anh. Na₂SO₄ and the solvent evaporated. Prep. layer chromatography on two silica gel plates (*Merck F₂₅₄*, 60 mesh, thickness 2 mm) using two consecutive elutions with 3:1 light petroleum ether/Et₂O yielded a colorless oil 0.17 g (70% of theory) which crystallized on standing. Orthorhombic crystals, m.p. 95/96°, were obtained on recrystallization from pentane. IR (CCl₄): 2980m, 2922m, 1678s, 1648s br., 1443s, 1371s, 1335m, 1204m, 1056s br., 1014m, 955s, 898s, 862s. ¹H-NMR (360 MHz, CDCl₃): 1.33 (d, *J* = 5.7, 6H); 1.36 (s, 6H); 1.92 (d, *J* = 1.8, 12H); 5.38 (q, *J* = 5.7, 2H); 6.61 (br. s, 4H). ¹³C-NMR (90.6 MHz, CDCl₃): 15.8 (q); 18.2 (q); 23.4 (q); 77.6 (s); 103.0 (d); 135.6 (s); 135.8 (s); 144.3 (d); 144.4 (d); 186.5 (s). MS: 162 (53), 147 (81), 146 (98), 145 (100), 131 (82), 119 (62), 91 (59).

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