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

by **Charles W. Jefford***, **Gérald Bernardinelli** and **Ernest C. McGoran**[1]

Department of Organic Chemistry and Laboratory of Crystallography, University of Geneva,
CH-1211 Geneva 4

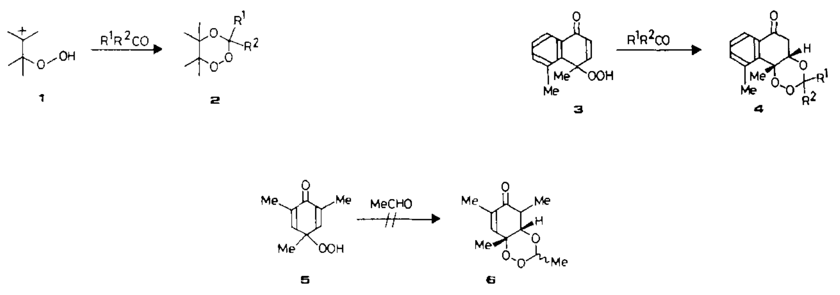
(8.VIII.84)

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.

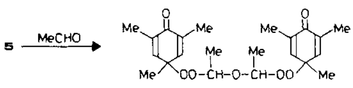
Scheme 1



---

[1] On leave from Eastern Washington University, Cheney, WA 99004.

Scheme 2



7

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 Mo$K\alpha$-radiation. The crystallographic data for $C_{22}H_{30}O_7$ 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 $|F_o| \leqslant 48$ 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} ($\times 10^3$ Å^2) *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)		

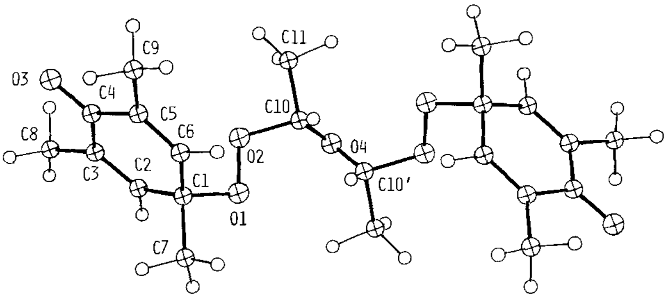


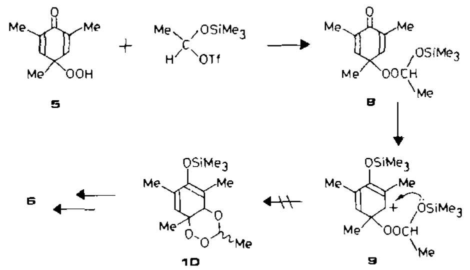
Figure. *Computer-generated perspective drawing of the structure of bis-peroxy acetal* **7**

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 ^{13}C-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 CH_3-substituents at C(2) and C(6). These substituents either pre-

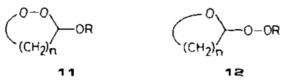
Scheme 3



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 acylic 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. ^{1}H- 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 Et_2O (100 ml) and then extracted with ice-cold H_2O (2 × 50 ml). The aq. layer was extracted with Et_2O (2 × 50 ml). The combined Et_2O-layers were washed with H_2O (3 × 25 ml), dried over anh. Na_2SO_4 and the solvent evaporated. Chromatography of the residue on *Kieselgel 60* (100 g, 70–230 mesh) with CH_2Cl_2 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, CH_2Cl_2 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 CH_2Cl_2 (15 ml) under an atmosphere of N_2 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 Et_3N (0.30 g, 3.0 mmol) dropwise. Et_2O (15 ml) and H_2O (25 ml) were added and the mixture allowed to warm to r.t. The aq. layer was extracted with Et_2O (2 × 25 ml). The combined org. layers were washed with 10% aq. $NaHSO_3$ (3 × 4 ml), brine (2 × 5 ml), dried over anh. Na_2SO_4 and the solvent evaporated. Prep. layer chromatography on two silica gel plates (*Merck* F_{254}, 60 mesh, thickness 2 mm) using two consecutive elutions with 3:1 light petroleum ether/Et_2O 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 (CCl_4): 2980*m*, 2922*m*, 1678*s*, 1648*s* br., 1443*s*, 1371*s*, 1335*m*, 1204*m*, 1056*s* br., 1014*m*, 955*s*, 898*s*, 862*s*. ^1H-NMR (360 MHz, $CDCl_3$): 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). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 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).

REFERENCES

[1] Qinghaosu Antimalarial Coordinating Research Group, Chinese Med. J. *92*, 811 (1979); *Liu Jing-ming, Ni Mu-yun, Fan Ju-fen, Tu You-you, Tu Zhao-hua, W Yu-lin & Zhou Wei-shan*, Acta Chim. Sinica *37*, 129 (1979); *L.J. Bruce-Chwatt*, Br. Med. J. *284*, 767 (1982); *Xu Xing-xiang, Zhu Jie, Huang Da-zhong & Zhou Wei-shan*, Acta Chim. Sinica *41*, 574 (1983); *Le Wen-ju, You Ji-qing, Yang Yuan-qing, Mei Jing-yan, Guo Hui-fang, Yang Hui-zhong & Zhang Chao-wei*, Acta Pharm. Sinica *17*, 187 (1982); *Wu Li-ju, Yang Hui-zhong & Yang Yan-qing*, Acta Pharm. Sinica *18*, 7 (1983).

[2] *G.B. Payne & C.W. Smith*, J. Org. Chem. *22*, 1682 (1957); *D. Creed, H. Werbin & E.T. Strom*, Chem. Commun. *1970*, 47; *W. Adam & A. Rios*, Chem. Commun. *1971*, 822; *H. Etoh, K. Ina & M. Iguchi*, Agric. Biol. Chem. *37*, 2241 (1973); *M. Schulz & K. Kirschke*, in 'Organic Peroxides', Vol. 3, ed. D. Swern, R.E. Krieger Publ. Co., Malabar, Florida, orig. 1972, reprint 1981, pp. 109–110; *V. Subramanyam, C.L. Brizuela & A.H. Soloway*, J. Chem. Soc., Chem. Commun. *1976*, 508; *H. Yamamoto, M. Akutagawa, H. Aoyama & Y. Omote*, J. Chem. Soc., Perkin Trans. 1 *1980*, 2300; *K. Maruyama, M. Muraoka & Y. Naruta*, J. Chem. Soc., Chem. Commun. *1980*, 1282, *M. Miura, M. Nojima & S. Kusabayashi*, J. Chem. Soc., Chem. Commun. *1981*, 581.

[3] *C.W. Jefford, J.C. Rossier & G.D. Richardson*, J. Chem. Soc., Chem. Commun. *1983*, 1064, *C.W. Jefford, D. Jaggi, J. Boukouvalas & S. Kohmoto*, J. Am. Chem. Soc. *105*, 6497 (1983); *C.W. Jefford, J. Boukouvalas & S. Kohmoto*, Helv. Chim. Acta *66*, 2615 (1983); *C.W. Jefford, D. Jaggi, J. Boukouvalas, S. Kohmoto & G. Bernardinelli*, Helv. Chim. Acta *67*, 1104 (1984); *C.W. Jefford, J. Boukouvalas & S. Kohmoto*, J. Chem. Soc., Chem. Commun. *1984*, 523.

[4] *C.W. Jefford, G. Bernardinelli, S. Kohmoto & J. Boukouvalas*, Helv. Chim. Acta, submitted for publication.

[5] Review: *R. Noyori, S. Murata & M. Suzuki*, Tetrahedron *37*, 3899 (1981).

[6] *P. Main, S.J. Fiske, S.E. Hull, L. Lessinger, G. Germain, J.P. Declercq & M.M. Woolfson*, 'MULTAN 80, A System for Computer Programs for the Automatic Solution of Crystal Structure from X-Ray Diffraction Data', University of York, 1980.

[7] *J.M. Stewart, P.A. Machin, C.W. Dickinson, H.L. Ammon, H. Heck & H.D. Flack*, 'The XRAY '76 System. Tech. Rep TR-446', Computer Science Center, University of Maryland, College Park, Maryland, 1976.

[8] *G. Simchen & W. Kober*, Synthesis *1976*, 259; *H. Emde & G. Simchen*, Synthesis *1977*, 867.

[9] Review: *M. Schulz & K. Kirschke*, in 'Organic Peroxides', Vol. 3, ed. D. Swern, J. Wiley & Sons, Inc., New York, 1972, Chap. 2; *Hong-Son Ryang & C.S. Foote*, Tetrahedron Lett. *1982*, 2551; *B. Maillard, C. Manigand, N. Pavlovna Tarassova, J.-J. Villenave & C. Filliatre*, Bull. Soc. Chim. Fr. II *1981*, 255.

[10] *H.H. Wasserman & J.E. Pickett*, J. Am. Chem. Soc. *104*, 4695 (1982).

[11] *D.H.R. Barton, P.D. Magnus & J.C. Quinney*, J. Chem. Soc., Perkin Trans. 1 1975, 1610.