Dispiro-1,2,4,5-tetraoxanes via Ozonolysis of Cycloalkanone *O*-Methyl Oximes: A Comparison with the Peroxidation of Cycloalkanones in Acetonitrile−Sulfuric Acid Media

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Introduction

Dispiro-1,2,4,5-tetraoxanes, also known as ketone diperoxides, dimeric peroxides, or carbonyl oxide dimers, are probably best known as precusors to macrocyclic hydrocarbons and lactones via thermal decomposition.[1] We recently found[2] that certain dispiro-1,2,4,5-tetraoxanes possess potent antimalarial activity comparable to artemisinin (qinghaosu), a clinically useful endoperoxide sesquiterpene lactone. To optimize activity and elucidate the mechanism of action for this novel class of antimalarial peroxides, the synthesis of structurally diverse dispiro-1,2,4,5-tetraoxanes was required.

The most direct method for dispiro-1,2,4,5-tetraoxane synthesis[3] is by acid-catalyzed peroxidation of cycloalkanones using aqueous hydrogen peroxide, a reaction optimized by Sanderson et al.[4] and by McCullough et al.,[5] or by the use of bis(trimethylsilyl)peroxide in the presence of trimethylsilyl trifluoromethanesulfonate in an anhydrous variant on this reaction.[6] Unfortunately, in some cases, a complex mixture of peroxidic products is formed including trispiro-1,2,4,5,7,8-hexaoxonanes and various hydroperoxide intermediates along with the desired dispiro-1,2,4,5-tetraoxanes.[4a,7]

Alternatively, dispiro-1,2,4,5-tetraoxanes can be obtained by ozonolysis of cycloalkylidenecycloalkanes[8] or cycloalkanone enol ethers[9] and conceivably by ozonolysis of cycloalkanone *O*-methyl oximes. Indeed, ozonolysis of the *O*-methyl oximes of acetophenone and several of its analogues by Ito et al.[10] afforded the corresponding 1,2,4,5-tetraoxane products, which were not readily available via the acid-catalyzed peroxidation route due to a preference for the Baeyer−Villiger reaction. More recently, Griesbaum[11] has developed the coozonolysis of *O*-methyl oximes and ketones as a convienent route to prepare a variety of ozonides (1,2,4-trioxolanes), suggesting carbonyl oxides are formed upon ozonolysis of *O*-methyl oximes. In this work, we show that ozonolysis of cycloalkanone *O*-methyl oximes is a useful alternative synthetic route to dispiro-1,2,4,5-tetraoxanes, some of which could not be obtained via acid-catalyzed peroxidation of the corresponding cycloalkanones.

Results and Discussion

O-Methyl oximes **1** (Table 1) were readily prepared by oximation of commercially available cyclic ketones with *O*-methylhydroxylamine hydrochloride and pyridine in methanol.[12] With the exception of **1e**, ozonolysis of the *O*-methyl oximes proceeded smoothly in methylene chloride at −75 °C and dispiro-1,2,4,5-tetraoxanes **2a**−**f** were obtained in yields of 2−49%. We suggest that the low to modest yields obtained in this reaction derive from formation of *N*-methoxy lactam and cycloalkanone byproducts, which compete with dimerization of the very reactive and short-lived carbonyl oxide intermediates to form the desired dispiro-1,2,4,5-tetraoxanes. In no case was the corresponding trispiro-1,2,4,5,7,8-hexaoxonane formed based on ^{1}H NMR spectra of crude products. For **1a**, **1c**, and **1d**, a 1−1.5 mol equiv of ozone was required; for **1b** and **1f**, a 2−3 mol equiv of ozone was necessary for a complete reaction. As the reaction of *O*-methyl oxime **1e** with ozone was extremely sluggish at −75 °C, the temperature was increased to −40 °C, and a 12 mol equiv of ozone was used in order to achieve a complete reaction. The lower reactivities of **1b** and **1e** toward ozone are probably due to steric effects associated with a bridged methylene group and a bulky *tert*-butyl group, respectively; the lower reactivity of **1f** toward ozone derives from the inductive effect of the tetrahydropyran oxygen atom. We also note that although *O*-methyl 2-*tert*-butylcyclohexanone oxime (**1e**) afforded a very low yield (2%) of dispiro-1,2,4,5-tetraoxane **2e**, *O*-methyl *tert*-butyl phenyl ketone oxime formed no tetraoxane product.[10,13]

Dispiro-1,2,4,5-tetraoxanes **2a**,[14] **2c**,[4a] **2d**,[4a] and **2f**[6] are known compounds, of which **2d** was isolated as a 9:1

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(13) In the paper,[11a] a tetraoxane obtained in 20% yield was incorrectly cited and should refer to *n*-butyl phenyl ketone diperoxide not *tert*-butyl phenyl ketone diperoxide (yield:[10] 0%).

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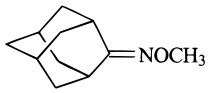
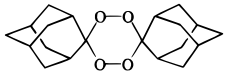
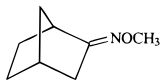
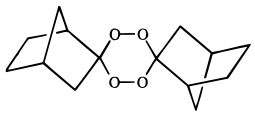
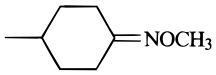
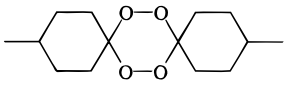
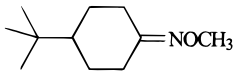
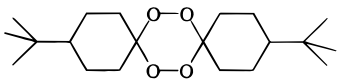
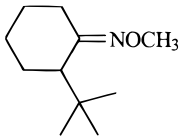
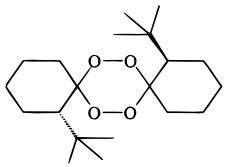
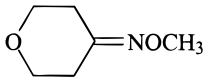
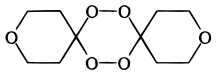
Table 1. Ozonolyses of *O*-Methyl Oximes

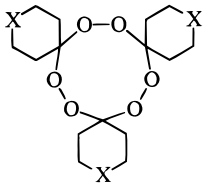
O-Methyl oximes **1**		Tetraoxanes **2**		Yield
	**1a**		**2a**	49%
	**1b**		**2b**	20%
	**1c**		**2c**	19%
	**1d**		**2d**	17%
	**1e**		**2e**	2%
	**1f**		**2f**	6%

mixture of tetraoxane and hexaoxonane by the acid-catalyzed ketone peroxidation method.[4a] In contrast, **2d** obtained via ozonolysis was readily isolated in pure form, and its structure was confirmed along with those of the new **2b** and **2e** by elemental analyses and ^{1}H and ^{13}C NMR spectra. The assigned structure of **2d** was additionally supported by the vapor pressure osmometry (VPO) molecular weight analysis.

Dispiro-1,2,4,5-tetraoxanes **2a** and **2f** were isolated as single isomers as they were formed from achiral *O*-methyl oximes. As the acid-catalyzed peroxidation of 2-methylcyclohexanone affords a single meso dispiro-1,2,4,5-tetraoxane isomer,[2,5] so also did we isolate **2b** and **2e** as single isomers, both of which were derived from ozonolysis of 2-substituted *O*-methyl oximes. This result suggests that for both synthetic methods the adjacent substituent may control the last cyclization step. Dispiro-1,2,4,5-tetraoxanes **2c** and **2d** were isolated as diastereomeric mixtures, as they were formed from *O*-methyl oximes with remote substituents that had little impact on tetraoxane ring formation.

We had initially attempted to synthesize dispiro-1,2,4,5-tetraoxanes **2a**−**f** via peroxidation of appropriate cycloalkanones using 50% aqueous H_2O_2 in acetonitrile−sulfuric acid media following a modified method of McCullough et al.[5] In the peroxidation of 2-norbornanone, 2-*tert*-butylcyclohexanone, and tetrahydro-4*H*-pyran-4-one, the usual precipitation of crude product did not occur, and ^{1}H NMR spectra of extracted crude products showed none of the signals expected for tetraoxane products **2b**, **2e**, and **2f**. For 2-norbornanone and 2-*tert*-butylcyclohexanone, no peroxidic products could be characterized, while for tetrahydro-4*H*-pyran-4-one, the novel hexaoxonane **3** was isolated in 12% yield (Chart 1). The structural assignment of **3** was based on ^{1}H and ^{13}C NMR spectra and elemental and VPO MW analysis. The reaction of 2-adamantanone gave a precipitate from which tetraoxane **2a** was isolated via chromatography in 4% yield. 4-Methylcyclohexanone afforded principally hexaoxonane **4** with only a trace of tetraoxane **2c**[15] in the crude product, whereas 4-*tert*-butylcyclohexanone afforded a 4:1 mixture of hexaoxonane **5** and tetraoxane **2d** in the crude product. Hexaoxonanes **4** and **5** were purified by recrystallization and were obtained in yields of 21% and 37%, respectively.

Chart 1



3 X = O
4 X = $CHCH_3$
5 X = $CHC(CH_3)_3$

The reason for preferential formation of hexaoxonanes rather than tetraoxanes from 4-methylcyclohexanone, 4-*tert*-butylcyclohexanone, and tetrahydro-4*H*-pyran-4-one is unclear. However, this outcome has also been observed in the peroxidation of 2-indanone,[5] 5,7-dihydro-

(15) It should be noted that the NMR data for tetraoxane **2c** reported previously[2] was that of hexaoxonane **4** not tetraoxane **2c**.

6*H*-dibenzo[a,c]cyclohepten-6-one[5] and diethyl ketone.[7] Story et al.[1] argue that the hexaoxonane is the kinetically controlled product that is subsequently converted to the thermodynamically favored tetraoxane. This interpretation is disputed by McCullough et al.[5] who note that while tetraoxanes are more thermodynamically stable than hexaoxonanes, which of these is kinetically preferred depends on the relative rates of the multiple equilibria between starting material ketone and products. More specifically, Hardy and Whalen[16] suggest that intramolecular ring closure of the penultimate precursors for the hexaoxonane and tetraoxane is considerably less hindered for the hexaoxonane than for the tetraoxane. At this point, a preference for tetraoxane versus hexaoxonane formation cannot easily be predicted and is a subject of our ongoing investigations.

In summary, this work reveals that ozonolysis of *O*-methyl oximes can be extended to the preparation of dispiro-1,2,4,5-tetraoxanes, some of which are inaccessible by acid-catalyzed peroxidation methods. In comparison with ozonolysis of enol ethers to form tetraoxanes[9] (yields of 11−37%) this method has the advantage of using the more easily accessible *O*-methyl oximes despite their lower reactivities toward ozone. As the current most reliable method used to differentiate tetraoxanes from hexaoxonanes is VPO MW analysis,[17] we also note that ozonolysis of *O*-methyl oximes can be used as an independent means of tetraoxane structural verification, since only tetraoxanes, not hexaoxonanes, are formed. Finally, this ozonolysis procedure is an attractive alternative method for tetraoxane synthesis, as many acid-catalyzed peroxidation methods[4b,5] apparently require commercially unavailable highly concentrated H_2O_2 to proceed efficiently.

Experimental Section

The melting points are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 spectrometer using $CDCl_3$ as a solvent. All chemical shifts are reported in parts per million (ppm) and are relative to internal $(CH_3)_4Si$ for ^{1}H and $CDCl_3$ (77.0 ppm) for ^{13}C NMR. Microanalyses were performed by M-H-W-laboratories, Phoenix, AZ. Molecular weights were determined via the vapor pressure osmometry (VPO) method by Galbraith Laboratories, Inc., Knoxville, TN.

All ketones were purchased from Aldrich Chemical Co. *O*-Methyl oximes were prepared according to a slightly modified published method.[12] Ozone was generated using an OREC model 03V5-0 ozonator (percent volt amperes 60; oxygen flow rate 0.6 L/min).

General Procedure for Synthesis of Dispiro Tetraoxanes. A solution of an *O*-methyl oxime (20 mmol) in 100 mL of dichloromethane was treated with ozone at −75 or −40 °C (**1f**) until the *O*-methyl oxime was consumed. The solution was flushed with oxygen and then concentrated in vacuo at room temperature. From the residue, tetraoxanes **2a**−**d** were isolated by flash chromatography using silica gel and petroleum ether/ether in a ratio of 97:3, and tetraoxanes **2e** and **2f** were purified by crystallization from ethanol.

Adamantane-2-spiro-3′-1′,2′,4′,5′-tetraoxane-6′-spiro-2″-adamantane (2a). Yield, 49%; colorless solid, mp 167 °C dec (CH_3CN) (lit.[14] mp 172 °C); ^{1}H NMR 1.50−2.10 (m, 26H), 3.20 (br s, 2H); ^{13}C NMR 27.10, 30.23 (br s), 33.20, 34.25 (br s), 37.00, 110.10.

Norbornane-2-spiro-3′-1′,2′,4′,5′-tetraoxane-6′-spiro-2″-norbornane (2b). Yield, 20%; colorless solid, mp 149−151 °C dec (pentane); ^{1}H NMR 1.05−1.90 (m, 16H), 2.28 (s, 2H), 3.30 (s, 2H); ^{13}C NMR 22.08, 28.09, 35.01, 37.41, 41.89, 42.22, 117.51. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.79; H, 7.79.

3,12-Dimethyl-7,8,15,16-tetraoxadispiro[5.2.5.2]-hexadecane (2c). Yield, 19%; colorless solid, mp 71−72 °C (CH_3CN) (lit.[4a] mp 71−72 °C); ^{1}H NMR 0.94 (d, J = 6.5 Hz, 6H), 1.09−1.38 (m, 4H), 1.39−1.99 (m, 12H), 3.05 (br s, 2H); ^{13}C NMR 21.47, 28.99 (br), 29.93 (br), 30.45 (br), 31.35 (br), 31.64, 31.74, 108.15, 108.19. VPO MW ($CHCl_3$) 257; calcd MW 256.

3,12-Di-*tert*-butyl-7,8,15,16-tetraoxadispiro[5.2.5.2]-hexadecane (2d). Yield, 17%; colorless solid, mp 196−198 °C dec (CH_3CN) (lit.[4a] mp 90−95 °C, mixture of tetraoxane and hexaoxonane); ^{1}H NMR 0.88 (s, 18H), 0.99−1.58 (m, 10H), 1.59−2.00 (m, 6H), 3.19 (br s, 2H); ^{13}C NMR 22.74 (br), 23.13 (br), 27.57, 27.61, 29.70 (br), 31.98 (br), 32.32, 47.37, 47.52, 108.14. Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.70; H, 10.56. VPO MW ($CHCl_3$) 323; calcd MW 341.

1,10-Di-*tert*-butyl-7,8,15,16-tetraoxadispiro[5.2.5.2]-hexadecane (2e). Yield, 2%; colorless solid, mp 128 °C dec (ethanol); ^{1}H NMR 1.05 (s, 18H), 0.80−1.95 (m, 16H), 3.38 (br s, 2H); ^{13}C NMR 22.34, 24.87, 26.45, 30.28, 33.82, 34.08, 55.78, 113.80. Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.80; H, 10.51.

3,7,8,12,15,16-Hexaoxadispiro[5.2.5.2]hexadecane (2f). Yield, 6%; colorless solid, mp 158−159 °C (CH_3OH) (lit.[6] mp 157−158 °C); ^{1}H NMR 1.74 (br s, 4H), 2.48 (br s, 4H), 3.75 (br s, 4H), 3.78 (br s, 4H); ^{13}C NMR 30.83 (br), 32.29 (br), 63.28 (br), 64.62 (br), 106.12.

General Procedure for the Peroxidation of Ketones.[5] A solution of a cycloalkanone (10 mmol) in acetonitrile (2 mL) [or in 1:1 acetonitrile/CH_2Cl_2 (4 mL) for 2-adamantanone] was added dropwise to a stirred, cold (−30 °C) solution of 50% hydrogen peroxide (0.60 mL, 11 mmol) and concentrated sulfuric acid (1.0 mL) in acetonitrile (4.0 mL). After being stirred for another 1 h at −30 to −20 °C, the solution was kept at −20 °C overnight.

Adamantane-2-spiro-3′-1′,2′,4′,5′-tetraoxane-6′-spiro-2″-adamantane (2a). From the precipitated crude product, tetraoxane **2a** was isolated by flash chromatography using silica gel and petroleum ether/ether in a ratio of 97:3. Yield, 4%; data are identical to that reported above.

3,7,8,12,15,16,20,23,24-Nonaoxatrispiro[5.2.5.2.5.2]-tetracosane (3). Hexaoxonane **3** was obtained by addition of water to the reaction mixture to induce precipitation, followed by filtration and successive recrystallizations from methanol and pentane. Yield, 12%; colorless solid, mp 137−139 °C; ^{1}H NMR 1.75−2.25 (m, 12H), 3.50−4.10 (m, 12H); ^{13}C NMR 31.28, 64.58, 105.53. Anal. Calcd for $C_{15}H_{24}O_9$: C, 51.72; H, 6.94. Found: C, 51.68; H, 6.85. VPO MW ($CHCl_3$) 342; calcd MW 348.

3,12,20-Trimethyl-7,8,15,16,23,24-hexaoxatrispiro-[5.2.5.2.5.2]tetracosane (4). Hexaoxonane **4** was isolated by filtration and was purified by recrystallization from acetonitrile. Yield, 21%; colorless solid, mp 106−107 °C (CH_3CN) (lit.[18] mp 107−109 °C); ^{1}H NMR 0.80−1.03 (m, 9H), 1.04−1.80 (m, 21H), 2.05−2.37 (m, 6H); ^{13}C NMR 21.54, 21.62, 21.66, 28.51, 28.57, 30.78, 30.94, 30.97, 31.06, 31.11, 31.16, 31.67, 31.74, 31.77, 31.83, 107.54, 107.60, 107.74. VPO ($CHCl_3$) MW 374; calcd MW 385.

3,12,20-Tri-*tert*-butyl-7,8,15,16,23,24-hexaoxatrispiro-[5.2.5.2.5.2]tetracosane (5). Hexaoxonane **5** was isolated by filtration and was purified by recrystallization from acetonitrile. Yield, 37%; colorless solid, mp 195−196 °C ($CHCl_3$) (lit.[18] mp 216−218 °C); ^{1}H NMR 0.87 (s, 27H), 0.95−1.85 (m, 21H), 2.15−2.45 (m, 6H); ^{13}C NMR 23.31, 23.50, 23.63, 23.66,

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(17) Bertrand, M.; Fliszár, S.; Rousseau, Y. J. *J. Org. Chem.* **1968**, *33*, 1931−1934. Although these investigators were able to get a small molecular ion for the dispiro-1,2,4,5-tetraoxane of cyclohexanone using EI-MS, the intensity was very low (0.2% of the total ionic current). We have also found MS (even FAB-MS) to be an inconsistent method for MW assignment as the molecular ions are not always present. When the M^+ peak was observed, it was uniformly of very low intensity.

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23.69, 27.51, 27.56, 27.64, 29.06, 32.30, 32.50, 32.54, 47.21, 47.28, 47.50, 107.45, 107.53, 107.81. VPO (THF) MW 497; calcd MW 511.

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Supporting Information Available: The synthetic procedure and ^{1}H NMR data for *O*-methyl oximes (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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