109. A Vibrational Study of Some 1,2,4-Trioxanes

by **Martin Mohnhaupt, Hans Hagemann, Jean-Pascal Perler,** and **Hans Bill***
Department of Physical Chemistry

and **John Boukouvalas, Jean-Claude Rossier,** and **Charles W. Jefford***
Department of Organic Chemistry, University of Geneva, CH-1211 Geneva 4

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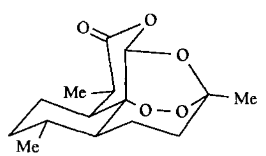
The vibrational spectra of some 1,2,4-trioxanes present two characteristic bands at 790 and 880 cm^{-1}. On the basis of ^{18}O-isotopic substitution and comparison with analogous compounds, these bands have been assigned to coupled C–O and O–O stretching modes of the C–O–O element.

Introduction. – Ever since the discovery that arteannuin (**1**) is a potent antimalarial agent [1–3], there has been a growing interest in the synthesis, chemistry, and physical properties of the intrinsic structural feature of this unique natural product, namely the 1,2,4-trioxane ring and its congeners [4–17]. From a study of the vibrational spectra of **1** and its lactol derivatives, it has been concluded [18] that the peroxide linkage contained therein is characterized by a frequency at 722 cm^{-1}. This is a plausible value since the O–O stretching mode is expected to lie between 600 and 900 cm^{-1} [19] [20]. Moreover, this mode is usually identified by two criteria; a *Raman*-active component which should show as a strong polarized band, and a corresponding IR band which should be either absent or weak. However, a *caveat* has been issued, namely that the O–O stretching mode cannot be regarded as a good group frequency because it is strongly coupled with other modes [21]. Consequently, we decided to investigate the vibrational spectra of appropriately labelled bicyclic 1,2,4-trioxanes in order to verify the above finding and to determine which bands comprise the 'fingerprint'.

The first set of trioxanes chosen are *cis*-fused derivatives consisting of two isotopically different pairs (**2**,**3** and **4**,**5**). Isotopic O-substitution is the best means of unambiguously identifying the vibrations of the peroxide linkage, since the aforementioned criteria are



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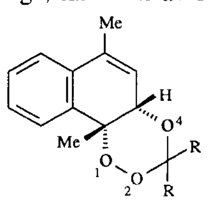


2 R = Me; O(1), O(2), O(4) = ^{16}O
3 R = Me; O(1), O(2) = ^{18}O; O(4) = ^{16}O
4 R = H; O(1), O(2), O(4) = ^{16}O
5 R = H; O(1), O(2) = ^{18}O; O(4) = ^{16}O

not infallible as they are qualitative. Secondly, the *cis*-fused trioxane **6** and its lower homologue, the acetal **7**, are identical except for the missing O-atom, thereby enabling the influence of the extra O-atom to be evaluated. Lastly, the *trans*-fused derivative **8** might reveal the effect of the ring fusion on the vibrational assignments. We now report the vibrational spectra of trioxanes **2**–**8**.

Results. – The *Raman* spectra of the methylated, isotopic pair **2** and **3** are virtually the same above 1000 cm^{-1}, but below 900 cm^{-1}, significant differences are observed *(Fig. 1)*. Bands ascribable to the non-trioxane part of the molecule are not expected to change on isotopic substitution. Consequently, the bands of greatest importance are precisely those

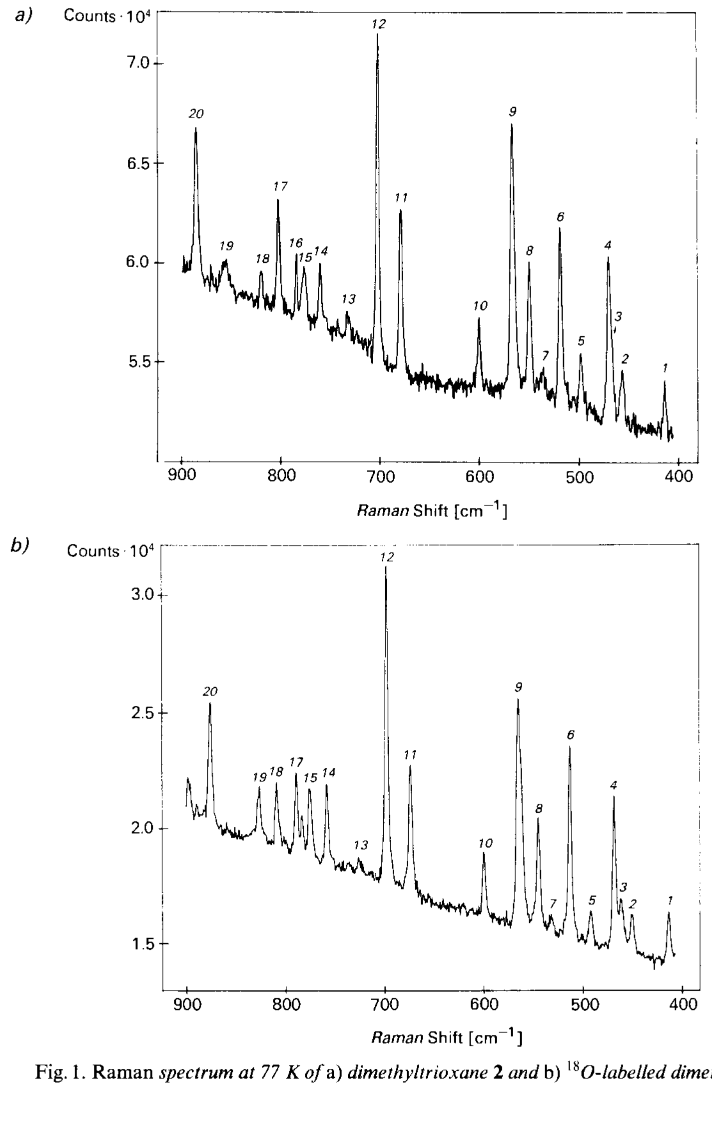


Fig. 1. Raman *spectrum at 77 K of* a) *dimethyltrioxane* **2** *and* b) ^{18}*O-labelled dimethyltrioxane* **3**

Table 1. *Observed* Raman *Shifts* (in cm^{-1}) *at 77 K for Trioxanes* **2** *and* **3** *in the Spectral Region 400–900* cm^{-1}

Band	**2**	**3**	$\tilde{\nu}(3)/\tilde{\nu}(2)$	*Band*	**2**	**3**	$\tilde{\nu}(3)/\tilde{\nu}(2)$
1	413.8	413.3	0.999	*11*	678.9	673.9	0.993
2	456.5	450.3	0.986	*12*	701.7	697.9	0.995
3	466.5	461.4	0.989	*13*	732.7	726.3	0.991
4	469.8	468.4	0.997	*14*	760.0	758.5	0.998
5	498.2	492.0	0.988	*15*	775.4	775.4	1.000
6	519.2	513.2	0.988	*16*	783.9	783.4	0.999
7	536.6	531.5	0.990	*17*	802.4	789.2	0.984
8	550.0	544.6	0.990	*18*	819.6	809.0	0.987
9	566.6	564.7	0.997	*19*	856.0	826.7	0.966
10	600.2	599.5	0.999	*20*	885.1	876.3	0.990

which display differences, namely bands *2, 3, 5–8, 11–13,* and *17–20 (Table 1)*. These isotopic differences also show to what extent the O–O vibration is coupled to other modes in the molecule. The four strongest bands lying between 600 and 900 cm^{-1} are all sensitive to isotopic substitution. The most intense band *(12)* which might have been expected to display strong O–O stretching character, is, in fact, the least sensitive to isotopic substitution *(Table 1)*. Conversely, the weak band *19* displays the greatest isotopic shift. Unfortunately, it cannot be used for comparison as it lacks good definition.

The previously mentioned four intense bands are also observed for the isotopic pair of parent trioxanes **4** and **5**. Isotopic substitution causes a shift in the same sense for all bands. The effect is most marked for bands *17* and *20*. The effect of Me substitution is also most marked for bands *17* and *20*. Consequently, it can be deduced that these two bands may constitute a possible fingerprint *(Table 2)*. Indeed, inspection of the *Raman* spectrum of the cyclopentene dimethyltrioxane **6** *(Fig. 2)* also shows two analogous

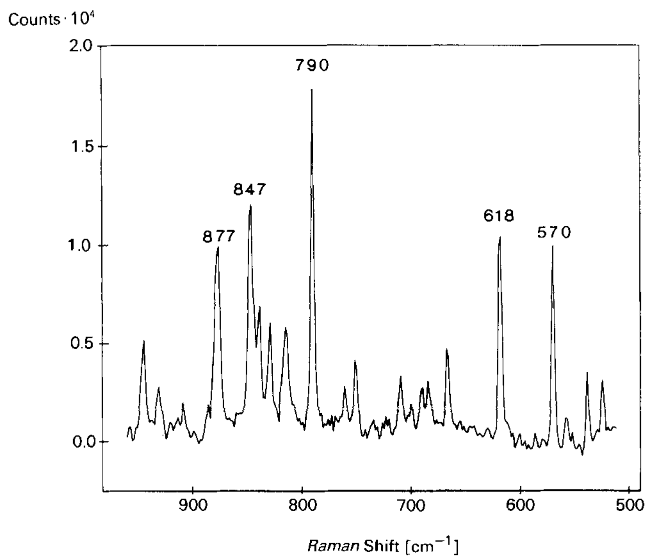


Fig. 2. Raman *spectrum at 77 K of* cis-*fused trioxane* **6**

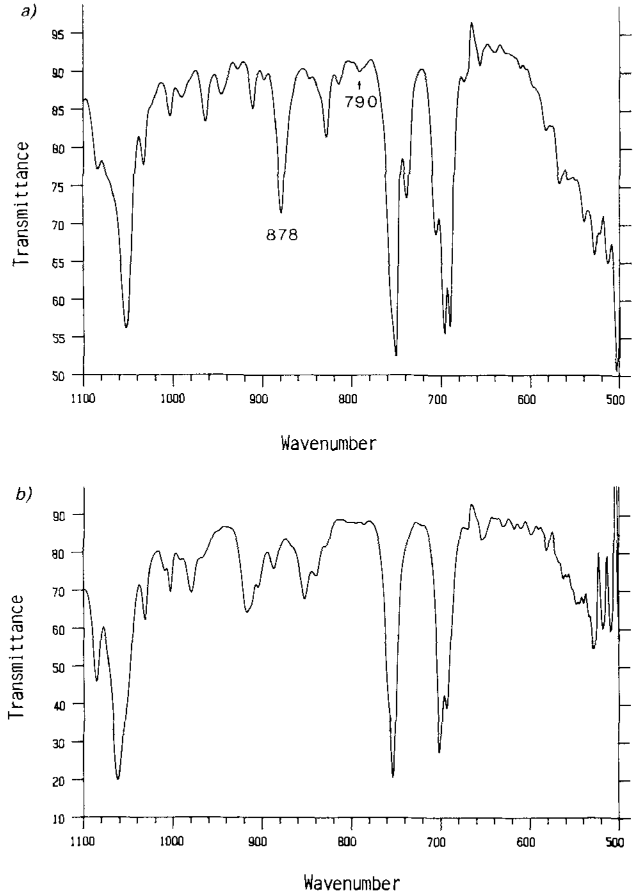


Fig. 3. *IR spectra (CS_2) of* a) *the* cis-*fused trioxane* **6** *and* b) *its acetal homologue* **7**

strong bands at 790 and 877 cm^{-1}. Interestingly, no strong band is seen around 700 cm^{-1}, which confirms that neither band *11* nor *12* is characteristic of the trioxane ring. Comparison of the IR spectrum of the trioxane **6** with its lower homologue, the acetal **7**, clearly reveals that the critical absorption at 878 cm^{-1} is present in the former and missing in the latter *(Fig. 3)*. Furthermore, the IR component of the band at 790 cm^{-1} is present in **6**, but very weak. In addition, the *Raman* spectrum of the acetal **7** does not show strong bands at 790 and 877 cm^{-1}.

Table 2. *Comparison of Selected Observed* Raman *Shifts* (in cm^{-1}) *at 77 K for Non-labelled and* ^{18}O*-Labelled Dimethyltrioxanes* **2** *and* **3** *and Parent Trioxanes* **4** *and* **5**

Band	**2**	**3**	$\Delta\tilde{\nu}$ (2–3)	**4**	**5**	$\Delta\tilde{\nu}$ (4–5)	$\Delta\nu$ (2–4)	$\Delta\nu$ (3–5)
11	679	674	5	672	665	7	7	9
12	702	698	4	706	701	5	–4	–3
17	802	789	13	816	783	33	–14	6
20	885	876	9	897	885	12	–12	–9

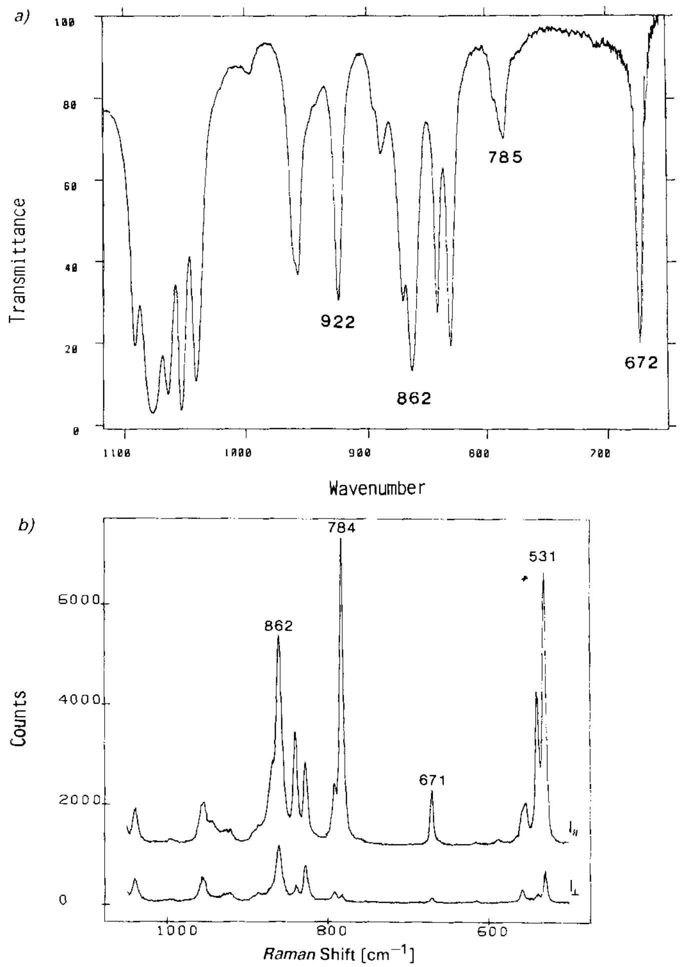
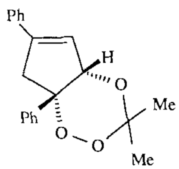


Fig. 4. a) *IR and* b) Raman *spectra of* trans-*fused trioxane* **8**



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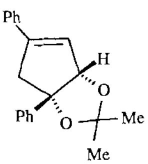

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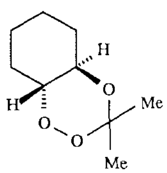

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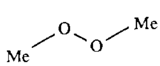

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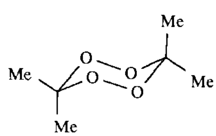

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Lastly, the vibrational spectrum of the *trans*-fused trioxane **8** shows a vibrational mode at 784 cm^{-1}, which has a weak IR, but a strongly polarized *Raman* component, and another at 862 cm^{-1} which is relatively strong in both *Raman* and IR spectra *(Fig. 4)*.

Discussion. – The results show that all 1,2,4-trioxanes examined display two bands at 780 ± 20 and 880 ± 10 cm^{-1} which are sensitive to isotopic and methyl substitution.

Table 3. *Frequencies of Characteristic Bands* (in cm^{-1}) *of 1,2,4-Trioxanes* **2**, **4**, **6**, *and* **8**, *Dimethyl Peroxide* (**9**) [6], *3,3,6,6-Tetramethyl-1,2,4,5-tetroxane* (**10**), *and Arteannuin* (**1**) [3]

Compound	**1**	**2**	**4**	**6**	**8**	**9**	**10**
Characteristic bands	789	802	816	790	784	779	759
	876	885	897	877	862	914	870

Therefore, each band contains both strong C—O and O—O stretching components which means that the bands actually characterize the O—O—C entity. Similar bands are also shown by dimethyl peroxide (**9**) [22] and 3,3,6,6-tetramethyl-1,2,4,5-tetroxane (**10**), which contain the same structural element *(Table 3)*. Normal-coordinate analysis for dimethyl peroxide [23] reveals that its own bands at 779 and 914 cm^{-1} are made up of the C—O stretching (48%), O—O stretching (40%), and C—O—O bending (11%) modes for the former and C—O stretching (58%) and O—O stretching (41%) modes for the latter band. This analysis is compatible with our findings for the trioxanes. Although the strong *Raman* polarization and weak IR intensity of the *ca.* 780 cm^{-1} band suggest that it displays stronger O—O character than the *ca.* 880 cm^{-1} band, nonetheless a pure single O—O stretching mode is simply not observed. ^{18}O-Substitution clearly reveals to what extent this mode is delocalized, but an important part of it is concentrated in the two aforementioned characteristic bands.

Our results invalidate the conclusion of a recent study on arteannuin (**1**) and its derivatives. On the basis of intensity and polarization arguments, the strong band at 722 cm^{-1} was ascribed to the O—O stretching mode. However, **1** is noteworthy in presenting relatively strong *Raman* bands at 789 and 876 cm^{-1} [18]. In keeping with the behavior of the trioxanes, the IR intensity of the 876-cm^{-1} component is strong.

The structures of arteannuin (**1**) and the *cis*-fused analogue **6** have been recently determined by X-ray and possess an additional point in common in that both contain twisted boat conformations for the trioxane ring. Consequently, we believe that the 722-cm^{-1} band reported for arteannuin must be of non-trioxane origin. On comparing the observed frequencies for the trioxanes and peroxides *(Table 3)*, variations are seen which arise partly from chemical differences. Although the frequencies are higher for the *cis*-fused trioxanes **2**–**5** adopting the chair conformation than those in which boats are preferred, **1** and **6** [24] [25], the generality of this finding needs yet to be proven.

Conclusion. – By means of isotopic and Me substitution, we have identified two bands at 780 ± 20 and 880 ± 10 cm^{-1} which arise from a combination of C—O, O—O stretching vibrations of the O—O—C entity. These can be regarded as the fingerprint of 1,2,4-trioxanes.

Experimental Part

1. *General.* All solvents were redistilled before use. $^{18}O_2$ (99%) was obtained from *ICN Stable Isotopes* (formerly *Stohler/KOR*). Column chromatography: *Merck* silica gel *60* (70–230 mesh) and *Fluka Florisil* (100–200 mesh). M.p.: *Reichert* hot-stage microscope; uncorrected. ^{1}H-NMR spectra: at 360-MHz, *Bruker-WM-360* or at 200 MHz, *Varian-XL-200* spectrometer; $CDCl_3$ solns. with TMS as internal standard (δ = 0 ppm); coupling constants *J* in Hz. MS (*m/z*): *Finnigan-GC/MS-4023* instrument using the *INCOS* data system. Elemental analyses were carried out by Dr. *H.J. Eder*, Service de Microchimie, Institut de Chimie Pharmaceutique, Université de Genève.

2. *Synthesis of Compounds* **2–8**. cis-*7,8-Dihydro-3,3-dimethyl-6,7a-diphenyl-4a*H-*cyclopenta[1,2-*e*]-[1,2,4]trioxine* (**6**) [24] and trans-*4a,5,6,7,8,8a-hexahydro-3,3-dimethylcyclohexa[1,2-*e*][1,2,4]trioxine* (**8**) [26] were prepared as previously described [24] [26].

*4a,10b-Dihydro-6,10b-dimethylnaphtho[2,1-*e*][1,2,4]trioxine* (**4**) was obtained in essentially quantitative yield from 1,4-epidioxy-1,4-dihydro-1,4-dimethylnaphthalene [27] and aq. formaldehyde according to our previous procedure [24], except that a short column (SiO_2, CH_2Cl_2) was used for purification.

*4a,10b-Dihydro-3,3,6,10b-tetramethylnaphtho[2,1-*e*][1,2,4]trioxine* (**2**) was prepared as previously described [6]: colorless crystals. M.p. 66–67°. R_f 0.47 (CH_2Cl_2). ^{1}H-NMR (360 MHz): 1.21 (*s*, 3 H); 1.30 (*s*, 3 H); 1.76 (*s*, 3 H); 2.16 (*d*, *J* = 1.6, 3 H); 4.33 (*d*, *J* = 6.4, 1 H); 5.88 (*dq*, *J* = 6.4, 1.6, 1 H); 7.25–7.43 (*m*, 3 H); 7.69 (*d*, *J* = 7, 1 H). MS: 246 (3, M^+), 159 (100), 156 (36), 146 (319), 115 (20). Anal. calc. for $C_{15}H_{18}O_3$ (246.33): C 73.15, H 7.37; found: C 73.29, H 7.13.

*4,6a-Dihydro-2,2-dimethyl-3a,5-diphenyl-3a*H-*cyclopenta[*d*][1,3]dioxolane* (**7**). To a soln. of 1,4-diphenylcyclopent-3-ene-*r*-1,*c*-2-diol [28] (157 mg, 0.6 mmol) in dry acetone (3.5 ml), powdered anh. $CuSO_4$ [29] (450 mg, 2.8 mmol) was added under Ar at 24°. Stirring at 24° for 63 h followed by filtration through *Celite* and evaporation gave a residue which, on chromatography (*Florisil*, CH_2Cl_2), gave **7** as colorless crystals. M.p. 65–66° (127 mg, 70%). R_f 0.87 (CH_2Cl_2). ^{1}H-NMR (200 MHz): 1.39 (*s*, 3 H); 1.50 (*s*, H); 3.06 (*ddd*, *J* = 17, 2, 0.5, 1 H); 3.38 (*dt*, *J* = 17, 2, 1 H); 5.34 (br. *t*, *J* = 2, 1 H); 6.28 (*q*, *J* = 2, 1 H); 7.20–7.50 (*m*, 10 H). Anal. calc. for $C_{20}H_{20}O_2$ (292.40): C 82.14, H 6,91; found: C 81.93, H 7.15.

*4a,10b-Dihydro-3,3,6,10b-tetramethylnaphtho[2,1-*e*](1,2-$^{18}O_2$)[1,2,4]trioxine* (**3**) *and 4a,10b-Dihydro-6,10b-dimethylnaphtho[2,1-*e*](1,2-$^{18}O_2$)[1,2,4]trioxine* (**5**). The procedures employed for the synthesis of **2** and **4** were followed, except that 1,4-($^{18}O_2$)epidioxy-1,4-dihydro-1,4-dimethylnaphthalene was used as a starting material [30] [31]. ^{18}O enrichment of ⩾ 95% was determined by MS and *Raman* measurements. ^{1}H-NMR of **3** and **5**: identical to those of **2** and **4**, resp. MS (**3**): 250 (4, M^+), 161 (100), 156 (44), 148 (28), 115 (23). MS (**5**): 223 (3, M^+), 174 (19), 161 (100), 141 (32), 115 (31).

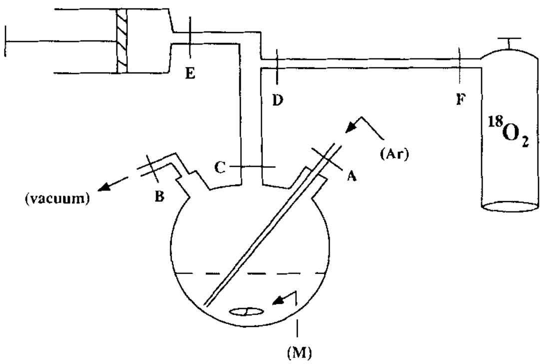

Fig. 5. *A simple apparatus for the preparation of 1,4-($^{18}O_2$)epidioxy-1,4-dihydro-1,4-dimethylnaphthalene*

1,4-($^{18}O_2$)Epidioxy-1,4-dihydro-1,4-dimethylnaphthalene. The apparatus used for its preparation is illustrated in *Fig. 5*. A 250-ml flask containing 1,4-dimethylnaphthalene (1.20 g, 7.7 mmol), dry CH_2Cl_2 (50 ml), methylene blue (10 mg), and a magnetic stirring bar (M), was cooled at −78° and the following operations were performed: *(i)* The soln. was purged for 30 min with Ar introduced through a capillary glass tube at port A with exit at port B (valves A, B, C open; D, E, F closed). *(ii)* A vacuum pump (1 Torr) was connected to port B (valves B, C, D open; A, E, F closed). *(iii)* 3 min later, Ar (*ca.* 200 ml) was introduced by syringe through port E (valves C, D, E open; A, B, F closed). *(iv)* Operations *(ii)*, *(iii)*, *(ii)*, *(iii)*, and finally *(ii)* were repeated in the sequence indicated. *(v)* $^{18}O_2$ (*ca.* 200 ml) was introduced *via* ports F, D, E to the syringe connected to the latter port (valves D, E, F open; A, B, C closed). *(vi)* Lastly, $^{18}O_2$ was introduced into the flask (valves E, C, D open; A, B, F closed). The flask was then allowed to warm to 0° and irradiated by a 500-W iodine lamp for 8 h. The contents of the flask were filtered through a short column (*Florisil*, CH_2Cl_2), and the solvent was evaporated at ≤ 0° to give 1,4-($^{18}O_2$)epidioxy-1,4-dihydro-1,4-dimethylnaphthalene as colorless crystals (m.p. 73°) with decomposition (1.44 g, 98%). According to MS and *Raman* spectroscopy, the desired trioxanes **3** ad **5** were enriched with ^{18}O to the extent of ⩾ 95%.

3. *Vibrational Spectra.* The *Raman* measurements were performed with a laboratory-assembled instrument consisting of a *Spectra Physics* Ar ion laser, a *Spex 1403* monochromator equipped with a photomultiplying detector and an *Ortec* photon counting system. The spectrometer is fully computer-controlled by a *DG30* computer in a multi-user environment. The experimental resolution was *ca.* 2 cm^{-1}, and the accuracy of the measured *Raman* shifts for sharp bands is estimated to be within 1 cm^{-1}. Samples were contained in conventional melting-point capillaries. Low temperature measurements were made using a home-built liquid-N_2 *Dewar* vessel. IR spectra were recorded on a *Mattson Cygnus 100 FTIR* instrument using a nominal resolution of 0.5 cm^{-1}.

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