Synthesis and Stereochemistry of 2,5-Dimethoxy 3,6-Disubstituted 1,4-Dioxanes Obtained from α-Hydroxy Dimethyl Acetals

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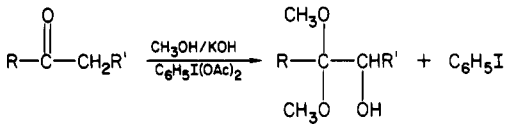
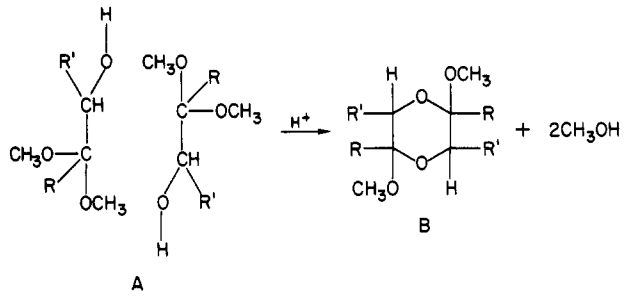
Several α-hydroxy dimethyl acetals were shown to undergo bimolecular loss of CH_3OH under acid catalysis to yield the corresponding 1,4-dioxane. In the case of the 3,3-dimethoxy-2-pentanol (**5**) rearrangement accounts for the formation of 3,6-diethyl-2,5-dimethoxy-2,5-dimethyl-1,4-dioxane (**6**). ^1H NMR and ^{13}C NMR methods were used to establish the stereochemistry of the products as *trans*-2,5-dimethoxy-1,4-dioxanes.

Recently we described a useful reaction for the conversion of ketones containing an active methylene group into α-hydroxy dimethyl acetals.[1-4]



In the course of defining conditions under which the acetal could be hydrolyzed to the corresponding α-hydroxy ketone we adventitiously found conditions under which the α-hydroxy dimethylacetals could be converted to the 1,4-dioxane in very high yield (Table I) (A → B). The



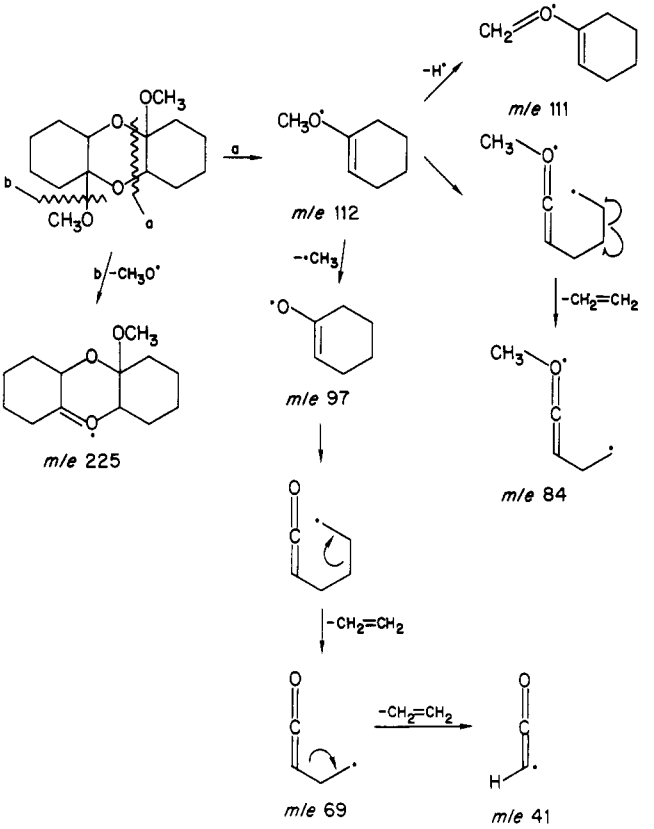
1,4-dioxanes presented in Table I are obtained by treating a methanolic solution of the α-hydroxy dimethyl acetal with a trace of *p*-toluenesulfonic acid. Under these conditions the product crystallizes out of the solution. The yields referred to in Table I are for the product obtained by such direct crystallization.

The gross structure of the 1,4-dioxanes was revealed by their composition and infrared spectra. The dimeric nature of the products was obvious from examination of the mass spectrum particularly by the presence of the parent molecular ion. The fragmentation pattern for 8 is given in Scheme I.

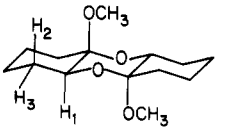
Route a yields two characteristic fragments at *m/e* 112 and *m/e* 111. These are related as ring cleavage and hydrogen loss. Loss of methyl yields *m/e* 97 and a retro-Diels-Alder process yields *m/e* 69 followed by loss of another $CH_2{=}CH_2$ unit. A second retro-Diels–Alder proceeds from *m/e* 112 to yield *m/e* 84. Loss of $M^+ - OCH_3$ in all cases is observed. The base peak in all cases was $(M^+/2) - 16$.

The next point regards the stereochemistry of the various compounds. The fact that the compounds are crystalline is indicative of stereochemical homogeneity al-

Scheme I. Mass Spectrum Fragmentation Pattern of Compound 8



though, a priori, this homogeneity may not persist in solution. The ^1H NMR spectra, however, indicated that in all cases we had stereochemically pure substances. The central stereochemical issue is the configuration of the methoxyl groups in this series of compounds. The ^1H NMR spectrum of 8 (200 MHz) revealed this information. The C*H*–O absorption was clearly identifiable at 3.72–3.83 ppm, doublet of doublet, with $J_{12} = J_{aa} = 11.5$ Hz and $J_{13} = J_{ea} = 4.9$ Hz.



This is close to values quoted in the literature, $J_{aa} = 11.4$ Hz, and $J_{ae} = 4.2$ Hz for an equatorial acetoxycyclohexane derivative.[5] The coupling pattern, together with the

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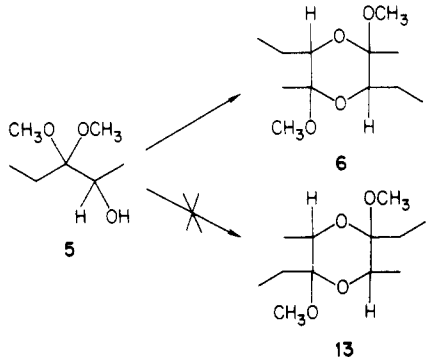
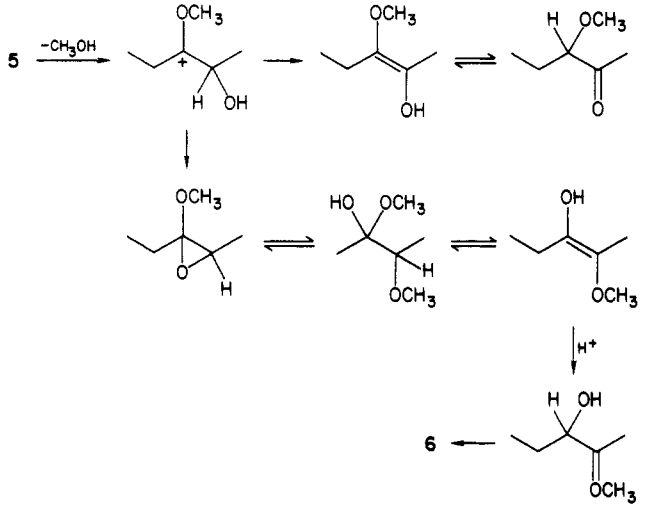
presence of a single OCH_3 group in the ^1H NMR and ^{13}C NMR (Table I) established the trans diaxial stereochemistry of the two methoxyl groups for **8**. The axial methoxyl group is also favored by a stereo electronic effect involving the lone pair electrons on the $O-CH_3$ group and the adjacent $-O-$ group.[6]

Compound **6** does not conform to a simple incorporation of two molecules of **5** upon loss of two molecules of CH_3OH. ^1H NMR showed that 3,3-dimethoxy-2-pentanol (**5**)



yielded 3,6-diethyl-2,5-dimethoxy-2,5-dimethyl-1,4-dioxane (**6**) and not 2,5-diethyl-2,5-dimethoxy-3,6-dimethyl-1,4-dioxane (**13**) by the fact that the ring proton at δ 3.48 was a triplet as demanded by **6**. Furthermore, the methyl resonance at δ 1.27 was a singlet peak.

The rearrangement of **5** to a mechanistically reasonable precursor of **6** is well-known from the work of Creary and Rollins.[7]



Transformations **1** → **2** and **3** → **4** proceed without rearrangement probably because of the stability of the benzylic carbenium ion. Transformations **7** → **8** and **9** → **10** may proceed with rearrangement analogous to **5** → **6** but this cannot be detected because of symmetry. No allylic rearrangement occurs in the case of **11** → **12**.

Finally the five-, eight-, and twelve-membered ring α-hydroxy dimethyl acetals did not undergo 1,4-dioxane formation under the standard conditions employed in our study. Reactions closely related to those disclosed in this paper are the conversion of dimethylethynylcarbinol into 3,3-dimethoxy-2-methyl-2-butanol and its 1,4-dioxane dimer upon treatment with a catalytic amount of HgO and BF_3/Et_2O,[8] the conversion of arylmethoxyoxiranes or arylchlorooxiranes into 1,4-dioxanes,[9-11] the conversion of glyco aldehyde acetals into 1,4-dioxanes under acidic condition in alcohol,[12,13] and the conversion of 1,2-bis(trimethylsiloxy)cyclohexane to the 1,4-dioxane via the α-hydroxy ketone.[14]

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 727B spectrometer. ^1H NMR spectra were recorded on a Varian A-60 or Varian EM-360 spectrometer and a Bruker WP 200 (200 MHz) was used to analyze the stereochemistry of 1,4-dioxane ring. ^{13}C NMR spectra were recorded on a Bruker WP 80 spectrometer. Mass spectra were determined on a Perkin-Elmer GC–MS 5985 spectrometer. Microanalyses were performed by Microtech Labs, Skokie, IL.

General Procedure. Preparation of 1,4-Dioxane Derivatives 2, 4, 6, 8, 10, and 12. α-Hydroxy dimethyl acetal (0.01 mol) was added to 0.10 mol of methanol and placed in a 25-mL round-bottom flask equipped with a stirrer bar. After a small crystal of *p*-toluenesulfonic acid was added, the reaction mixture was heated to boiling, and within 30 min, the white solid 1,4-dioxane derivative precipitated. The reaction was chilled in ice bath for another 30 min. Filtration and recrystallization from $CHCl_3$/hexane yielded the product.

2,5-Dimethoxy-2,5-diphenyl-1,4-dioxane (2). 2,2-Dimethoxy-2-phenylethanol (**1**) (1.82 g, 0.01 mol) was treated according to the general procedure. **2** (1.17 g, 78%) was obtained: mp 190–191 °C (lit.[11] mp 198 °C); IR (KBr) 3050, 2945, 1445, 1240, 1200, 1165, 1038, 900, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25–7.78 (m, 10 H), 3.78 (s, 4 H), 3.08 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.3, 128.6, 126.7, 96.7 67.0, 49.7; mass spectrum (70 eV), *m/e* 300 (M^+, 4.16), 269 ($M^+ - OCH_3$, 3.13), 134 ($M^+/2 - 16$, 100), 133 (134 - 1, 78.77), 119 (134 - CH_3, 18.39), 105 (18.85), 91 (12.89). Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.80; H, 6.96.

2,5-Dimethoxy-3,6-dimethyl-2,5-diphenyl-1,4-dioxane (4). The general procedure was used by proceeding from 1.0 g (0.0051 mol) of 1,1-dimethoxy-1-phenyl-2-propanol (**3**); 0.60 g (72%) of **4** was obtained: mp 238–240 °C (lit.[9b] mp 244–245 °C); IR (KBr) 3060, 2990, 2950, 2920, 2840, 1490, 1450, 1240, 1180, 1083, 1030, 940, 760, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23–7.77 (m, 10 H), 3.92 (q, 2 H, J = 7 Hz), 3.15 (s, 6 H), 1.20 ppm (d, 6 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$ and Me_2SO-d_6) δ 138.4, 128.0, 127.7, 99.5, 70.7, 49.4, 14.3; mass spectrum (20 eV), *m/e* 297 ($M^+ - OCH_3$, 1.1), 148 ($M^+/2 - 16$, 100), 147 (148 - 1, 88.8), 133 (148 - 15, 9.6), 105 (70.7), 77 (64.1). Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.17; H, 7.31. Found: C, 72.91; H, 7.25.

3,6-Diethyl-2,5-dimethoxy-2,5-dimethyl-1,4-dioxane (6). About 2.0 g (0.0135 mol) of 3,3-dimethoxy-2-pentanol was allowed to stand at room temperature for two weeks and a white crystalline

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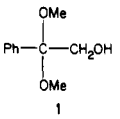
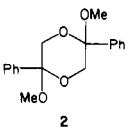
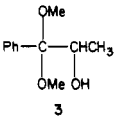
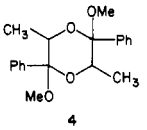
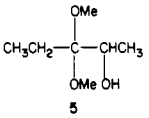
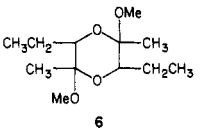
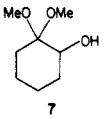
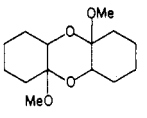
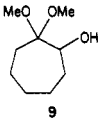
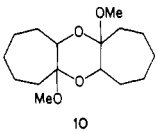
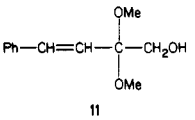
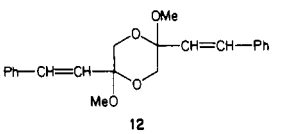
Table I. 1,4-Dioxane Derivatives Obtained from α-Hydroxy Dimethyl Acetals

α-hydroxy dimethyl acetal	1,4-dioxane derivatives	mp, °C	^{1}H NMR,[a] δ		^{13}C NMR,[a] ppm			yield
			CH_3O	CHO (ring)	CH_3O	CHO (ring)	$OCOCH_3$	
 1	 2	190–191	3.08	3.78	49.7	67.0	96.7	78
 3	 4	238–240	3.15	3.92	49.4	70.7	99.5	72
 5	 6	73–75	3.23	3.48	47.8	75.4	97.2	53
 7	 8	156–158	3.20	3.77	46.9	73.1	97.7	69
 9	 10	183–186	3.23	3.97	48.0	74.2	98.6	62
 11	 12	168–170	3.36	3.72				41

[a] $CDCl_3$ as solvent, tetramethylsilane as internal standard.

solid appeared. After filtration and recrystallization, pure **6** was obtained: 0.83 g (53% yield); mp 73–75 °C; IR (KBr) 2960, 2900, 2860, 2820, 1458, 1436, 1380, 1195, 1128, 1085, 1055, 1030, 990, 895, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.48 (t, 2 H, J = 7 Hz), 3.23 (s, 6 H), 1.43 (quin, 4 H, J = 7 Hz), 1.27 (s, 6 H), 1.00 ppm (t, 6 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) 97.2, 75.4, 47.8, 22.3, 19.9, 10.4 ppm; mass spectrum (20 eV), m/e 232 (M^+, 0.8), 201 ($M^+ - OCH_3$, 7.7), 100 ($M^+/2 - 16$, 100), 99 (100 − 1, 29.7), 85 (100 − CH_3, 95.8).

2,5-Dimethoxy-2,3:5,6-bis(tetramethylene)-1,4-dioxane (8). The general procedure was used with 1.60 g (0.01 mol) of 2,2-dimethoxycyclohexanol (**7**); 0.88 g (69% yield) of **8** was obtained: mp 156–158 °C (lit.[15] mp 155–156 °C); IR (KBr) 2950, 2850, 2825, 1450, 1325, 1270, 1200, 1135, 1100, 1080, 1040, 960, 910, 850 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.77 (m, 2 H), 3.20 (s, 6 H), 1.13–2.27 (m, 16 H); ^{1}H NMR (200 MHz) (3–4 ppm range) δ 3.78 (d, d, 2 H, J = 11.5 Hz, J = 4.9 Hz), 3.22 (s, 6 H); ^{13}C NMR ($CDCl_3$) 97.7 (s), 73.1 (d), 46.9 (q), 29.9 (t), 27.6 (t), 24.6 (t), 22.0 (t); mass spectrum (20 eV), m/e 256 (M^+, 4.3), 225 ($M^+ - OCH_3$, 4.1), 112 ($M^+/2 - 16$, 100), 111 (112 − 1, 47.3), 97 (112 − CH_3, 44.8). Anal. Calcd for $C_{14}H_{24}O_4$: C, 62.65; H, 9.37. Found: C, 62.37; H, 9.34.

2,5-Dimethoxy-2,3:5,6-bis(pentamethylene)-1,4-dioxane (10). 2,2-Dimethoxycycloheptanol (**9**) (1.74 g, 0.01 mol) was treated according to the general procedure; 0.88 g (62% yield) of **10** was obtained: mp 183–186 °C; IR (KBr) 2925, 2850, 2830, 1440, 1290, 1220, 1180, 1160, 1080, 1020, 920, 880 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.57 (m, 2 H), 3.23 (s, 6 H), 1.40–1.81 (m, 20 H); ^{13}C NMR δ 98.6, 74.2, 48.0, 31.9, 29.3, 25.9, 23.0, 20.9; mass spectrum (15 eV), m/e 284 (M^+, 1.3), 253 ($M^+ - OCH_3$, 3.47), 126 ($M^+/2 - 16$, 100), 125 (126 − 1, 17.48), 111 (126 − CH_3, 18.65), 98 (37.72). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.60; H, 9.86. Found: C, 67.35; H, 9.97.

2,5-Dimethoxy-2,5-distyryl-1,4-dioxane (12). 2,2-Dimethoxy-4-phenyl-3-buten-1-ol (**11**) (0.40 g, 1.9 mmol) in 2 mL of $CDCl_3$ was stored at room temperature for about 2 months. A solid formed which, after recrystallization, yielded 0.12 g of pure **12**: mp 168–170 °C; IR (KBr) 3025, 3000, 2950, 2925, 2830, 1480, 1440, 1315, 1300, 1200, 1185, 1150, 1040, 980, 920, 745, 730, 675 cm^{-1}; ^{1}H NMR δ 7.38 (m, 10 H), 6.86 (d, 2 H, J = 16 Hz), 6.08 (d, 2 H, J = 16 Hz), 3.72 (d, 4 H, J = 4 Hz), 3.36 (s, 6 H); mass spectrum (14 eV), m/e 352 (M^+, 1.1), 321 ($M^+ - OCH_3$, 3.2), 160 ($M^+/2 - 16$, 100), 159 (160 − 1, 28.8), 145 (160 − CH_3, 8.1), 129 (160 − OCH_3, 28.8). Anal. Calcd for $C_{22}H_{24}O_4$: C, 75.00; H, 6.82. Found: C, 73.98; H, 7.08.

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Registry No. **1**, 28203-05-6; **2**, 1231-51-2; **3**, 73611-99-1; **4**, 21069-18-1; **5**, 90054-91-4; **6**, 92720-83-7; **7**, 63703-34-4; **8**, 33372-00-8; **9**, 90054-92-5; **10**, 92720-84-8; **11**, 90054-96-9; **12**, 92720-85-9.