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Bis(methylsulfonoxymethyl) Ether

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Reaction of acetyl mesylate (3) with trioxane and certain other polyoxymethylene derivatives gives the previously unknown title compound in yields as high as 70%. This extremely active compound undergoes the expected dialkylation reactions with mercaptides and with pyridine, but in a few other reactions cleavage occurs leading to derivatives of formaldehyde. Reaction of 3 with paraformaldehyde gives good yields of methylene dimesylate which is the main product from trioxane when a substantial amount of free methanesulfonic acid is present.

Restrictions on the use of bis(chloromethyl) ether (BCME) because of its high level of carcinogenicity to man[1] have produced a need for a suitable substitute for this useful intermediate. Obviously, the bromo- or iodomethyl ethers would serve this purpose, but because of their close relationship to BCME they also are suspect. Utilization of a sulfonate ester, such as bis(methylsulfonoxymethyl) ether (1), appeared

$$RSO_3CH_2OCH_2OSO_2R$$

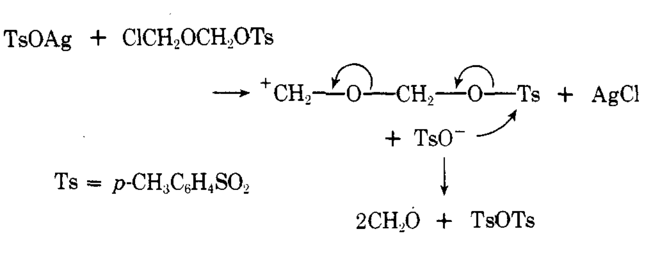
$$1, R = CH_3$$

$$2, R = p\text{-}CH_3C_6H_4$$

to offer the advantages of easier containment, due to a very low vapor pressure, and quite different physiological activity because of its high chemical reactivity as exemplified by a monofunctional analogue, methoxymethyl methanesulfonate.[2] [This compound was found to be 10^4 times more reactive with pure benzene (no catalyst) than is the corresponding chloromethyl ether (in acetic acid).] In fact, recent tests of 1 for mutagenic activity by microbial assay, with and without mammalian metabolic activation (Ames test[3]), gave negative results,[4] in contrast to BCME. (A positive test is suggestive that a chemical may be carcinogenic; on the other hand, a negative result cannot be taken as conclusive evidence to the contrary.[5])

A search of the literature produced no reference to a sulfonate analogue of BCME.[6] An early attempt to prepare for study bis(tosyloxymethyl) ether (2) by the direct reaction of silver tosylate with BCME led only to the isolation of *p*-toluenesulfonic anhydride in fair yield. A possible reaction path is shown in Chart I. This result might explain the absence in the literature of any reference to either 1 or 2. Other examples of failures of double displacements on BCME have been noted elsewhere.[7]

Chart I



Synthesis of Bis(methylsulfonoxymethyl) Ether (1). In 1968 Karger and Mazur[8a] first reported a new, facile synthesis of mixed carboxylic–sulfonic anhydrides which are powerful electrophilic reagents capable of selective ether cleavage without added Lewis acid catalysts.[8b] The cleavage of several cyclic ethers to give good yields of mixed acetate–sulfonate diesters was described. The only formal investigated was dimethoxymethane, which underwent reaction with acetyl methanesulfonate to form methoxymethyl methanesulfonate.[2] It has now been found that this reaction, when applied to certain polyoxymethylene compounds, gives bis(alkylsulfonoxymethyl) ethers such as the dimesylate 1.

The most convenient source of 1, in 60–70% yield, has proved to be from the neat reaction[9] of acetyl methanesulfonate (3) with trioxane at 90 °C (Chart II). Addition of ca. 3.5% methanesulfonic acid reduced the reaction time from 20–24 h to 4 h. With a larger amount of acid (ca. 7.5%), although 1 was formed initially (ca. 30% detected by NMR after 3 h), it gradually declined, paraformaldehyde was evolved, and the major reaction product was methylene dimesylate.[10] Reaction times are also reduced by elevated temperatures; for example, at 110 °C, without added acid, reaction was complete in 5 h but the yield suffered (52%) due to thermal instability of the product. Isolation of 1 by distillation (at 10–20 μ) is possible, but crystallization from tetrahydrofuran is more convenient and equally productive of pure product. Tetroxane was reacted with 3 under similar conditions to give 1 in 70% yield. In this case, the volatile by-product contained a high percentage of bis(acetoxymethyl) ether (8), as indicated by the reaction path in Chart III.

Chart II

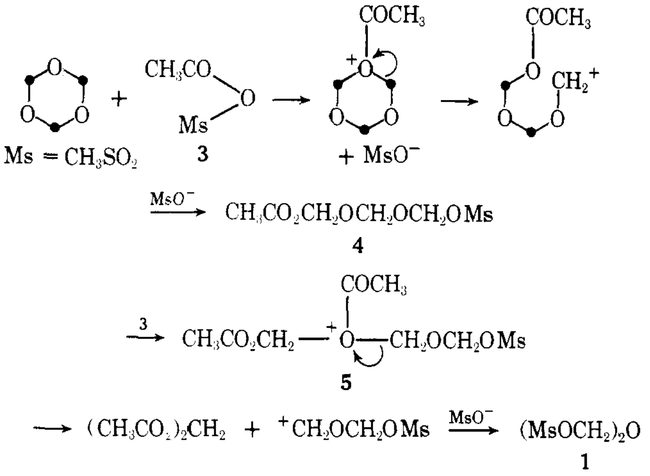
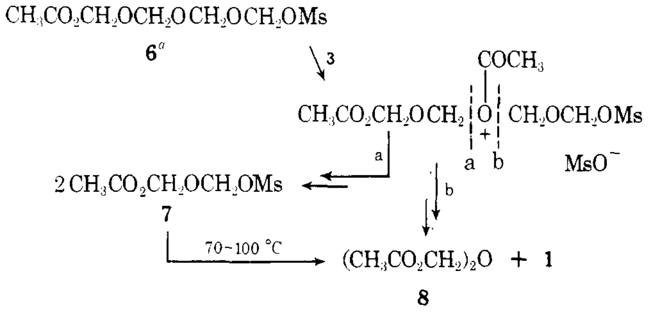


Chart III



[a] From tetroxane, analogous to 4 in Chart II.

The reaction of trioxymethylene diacetate with an equimolar amount of acetyl mesylate was explored with the primary aim of preparing the mixed ester 7, one of the suggested by-products in the preparation of 1 from tetroxane. Based on NMR analysis of the crude product mixture, at 25 °C about 60% of the trioxymethylene diacetate reacted to form 7. Distillation at 65–115 °C, however, caused an unexpected disproportionation resulting in the total disappearance of 7 in favor of the dimesylate 1, which was isolated in 29% yield, and diacetate 8.

Equimolar amounts of 3 and bis(acetoxymethyl) ether (8) heated at 70–80 °C for 3.5 h under vacuum (0.5 mm) produced an approximately 2:1:1 (molar basis by NMR analysis) mixture of ester 7, dimesylate 1, and unreacted 8 with acetic anhydride as the volatile by-product. Distillation of a portion of the reaction mixture gave a 57% yield of 1 and only traces of 7 in the forerun. In a similar reaction, a 2:1 molar ratio of 3 and 8, heated at 65 °C for 32 h under vacuum, afforded a 2:1 molar ratio of 1 and 7 with only a trace of 8 remaining. Crystallization of the reaction mixture from dry tetrahydrofuran gave a 33% yield of pure dimesylate 1.

Reaction of 3 with paraformaldehyde, rather unexpectedly, produced 75% of methylene dimesylate and only about 7% 1. This dimesylate, which has been of considerable pharmacological interest,[11] had been prepared previously from methylene iodide and silver mesylate.[10] No other synthesis appears to have been reported.

Possible Reaction Pathways for the Acetyl Mesylate Reactions. Charts II and III show possible reaction pathways for the reaction of acetyl mesylate (3) with trioxane and tetroxane, respectively. Both proceed via attack of acetylium ion on a ring oxygen atom. The mixed esters 4 and 6 are again attacked by acetylium ion, preferentially on the *least* electron-deficient oxygen atom, with subsequent cleavage to form the more stable carbonium ion. In the trioxane case (Chart II) the dimesylate 1 and methylene diacetate are the expected and observed products. Catalysis of the reaction by a small amount of methanesulfonic acid could be due to protonation of the carbonyl group as was observed in the Karger and Mazur studies.[8b] The higher concentrations of acid undoubtedly protonate the trioxane, resulting in ring cleavage and formation of formaldehyde and the symmetrical final products methylene dimesylate and methylene diacetate, also observed in the reaction of 3 with paraformaldehyde.

As shown in Chart III the oxonium ion resulting from acetylium ion attack on 6 can cleave with nearly equal apparent ease at bond a or b. Cleavage at b leads directly to 1 and 8, while cleavage of bond a produces the mixed ester 7, which, being thermally unstable, disproportionates to give the same product mixture. The reaction of 3 and trioxymethylene diacetate also leads to the intermediate formation of 7 by an analogous pathway. The disproportionation is likely promoted by methanesulfonic acid, known to be ever present in unpurified 3. This is reminiscent of acid-catalyzed mixed-anhydride disproportionations observed by Karger and Mazur.[12] In reactions of 3 and bis(acetoxymethyl) ether (8) the unexpected formation of 7 and 1 (presumably from initially formed 7), with acetic anhydride as the only volatile product, must be due to a preferential attack of acetylium ion on the carbonyl oxygen of 8 rather than the ether oxygen, owing to inhibition by the inductive influence of the two acetoxy groups.

The fact that different products are obtained with paraformaldehyde than are usual with trioxane and tetroxane may not be surprising in view of the poor solubility of the polymer in 3 and the probable formation of a significant amount of methanesulfonic acid from the acetylation, by 3, of the hydroxyl end groups of paraformaldehyde. As has already been mentioned, increasing amounts of methanesulfonic acid in the reaction of 3 with trioxane favor the formation of methylene dimesylate at the expense of 1.

These reactions provide further examples of the unusually high order of selectivity of ether cleavage by the mixed anhydrides observed by Karger and Mazur.[8b]

Physical Properties, Stability, and Reactions.

Bis(methylsulfonoxymethyl) ether is a low-melting solid (mp 57–59 °C) which can be distilled at low pressures (5–15 μ). Like methoxymethyl mesylate it is so reactive that even aromatic hydrocarbons undergo reaction and cannot be used as solvents. However, it reacts only slowly with THF at 25 °C from which solvent it is readily recrystallized. It can also be purified by precipitation with ethyl ether in which it is insoluble. Reaction mixtures and *distilled* dimesylate are stable for weeks at room temperature if kept in tightly capped containers. However, 1 which has been crystallized from THF degrades with a half-life of a few days at room temperature (presumably owing to reaction with traces of THF) but it can be stored for months at −35 °C.

The reactions of 1 with mercaptans are somewhat complicated owing to the severe limitation on the choice of solvent imposed by the ease of solvolysis of 1 in some hydroxylic solvents, the usual choice for such reactions. The solvents which *were* found suitable required either sodium or sodium hydride as base in order to form the mercaptide without introducing or forming water or methanol in the reaction mixture. Dioxane or THF can be used to dissolve 1, and EtOH (at −20 °C) or 2-PrOH (at 0–30 °C) serves as an appropriate reaction medium with mercaptides. In MeOH, even at −20 °C, considerable solvolysis occurs. There is no apparent problem, even with 2-mercaptoethanol, at 25–30 °C in 2-PrOH, and yields are 80–90%.

Pyridine reacts readily with 1 to give the expected 2-oxapropane-1,3-bis(pyridinium mesylate). Secondary amines, such as pyrrolidine, on the other hand, cause ether cleavage of 1 leading to aminals of formaldehyde, a reaction typical of methoxymethyl mesylate.[2] Similar reactions occur with primary alcohols and aromatic hydrocarbons under ambient conditions; for example, 1 in butanol produced the formal derivative, and in toluene a mixture of isomeric ditolylmethanes was formed. However, reaction of 1 with sodium *n*-butoxide afforded the bis(butoxymethyl) ether as the major product.

Analogues of 1. Bis(ethylsulfonoxymethyl) ether, a liquid, was prepared from acetyl ethanesulfonate and trioxane in 36% yield. As expected, it is essentially as reactive as 1, giving the same reaction with toluene, for example. Since it was isolated by distillation, it was quite stable to ambient conditions in tightly capped bottles.

Efforts to obtain bis(tosyloxymethyl) ether (2) by reaction of acetyl tosylate with trioxane under a variety of conditions failed, although the NMR spectra of reaction mixtures held at 25 °C showed strong evidence of its formation. Instability of the compound very likely prevented its isolation. Attempts to prepare a methyl homologue of 1 by reaction of 3 with paraldehyde led only to exothermic polymerizations, initiating at temperatures as low as 10 °C.

Experimental Section

^{1}H NMR spectra were determined on a Varian T-60 spectrometer in $CDCl_3$. Small variations in δ values were observed for a given group depending on other components where mixtures were involved, slight temperature changes, etc.

IR spectra were obtained on a Perkin-Elmer 137 spectrophotometer.

Bis(methylsulfonoxymethyl) Ether (1). A. From *s*-Trioxane. Acetyl methanesulfonate[12] (285.2 g, 2.06 mol, undistilled) was transferred by syringe to a dry-N_2-filled flask fitted with thermometer, stirrer, N_2 inlet, and vacuum take-off. The anhydride was cooled to −5 °C, and 92.9 g (1.03 mol) of trioxane was added over a 10-min period with good stirring at <0 °C. When solution was complete (ca. 20 min) it was heated slowly to 90 °C, with a 0.5-mm vacuum applied when the temperature reached 35 °C. Heating, with stirring under vacuum, was continued for 24 h,[13] during which time 118.5 g (90%) of methylene diacetate, containing a small amount of bis(acetoxymethyl) ether, was collected in a cold trap. The brown reaction mixture was brought to ambient conditions under dry N_2, dissolved in 120 mL of dry THF, treated with carbon, and filtered. The filtrate was seeded and cooled to −35 °C. The crystalline product was collected under N_2 in a glove box, washed with cold THF, then ether, and dried, yield 168.4 g (70%), mp 52–58 °C. It was stored in a well-sealed container at −35 °C. Alternatively, isolation by distillation using a short-path pot still [pot temperature 105–122 °C (7–10 μ)] gave a 60% yield of pure compound, mp 57–59 °C.

Anal. Calcd for $C_4H_{10}O_7S_2$: C, 20.5; H, 4.3; S, 27.4. Found: C, 20.3; H, 4.9; S, 27.6. NMR δ 3.13 (s, 6 H), 5.52 (s, 4 H).

B. With Methanesulfonic Acid Catalysis. In a reaction using the procedure of A above 5 mol % (3.5% by weight based on the mixed anhydride) of methanesulfonic acid was added to the freshly prepared acetyl methanesulfonate just before the trioxane. After 3.5 h of heating the reaction at 90 °C at 0.5 mm pressure, an NMR of the reaction mixture was essentially identical with the NMR of the reaction without methanesulfonic acid (A) after 24 h.

C. From *s*-Tetroxane. Substitution of an equivalent amount of tetroxane[14] for the trioxane in A gave a similar yield of 1. The byproduct in this case consisted of nearly equal amounts of bis(acetoxymethyl) ether (8) and methylene diacetate.

D. From Trioxymethylene Diacetate. To 9.15 g (0.066 mol) of acetyl mesylate at 0 °C was added 12.7 g (0.066 mol) of trioxymethylene diacetate.[15] After stirring for 18 h at 25 °C NMR indicated the presence of approximately 4 mol % 1 (16% by weight of theory), and 31 mol % (62% by weight of theory) of the expected mixed ester 7 (methylene peaks at δ 5.40 and 5.47). Distillation, using a short-path pot still, produced 4.5 g (29% yield) of 1, mp 57–59 °C, and lower boiling fractions consisting almost entirely of methylene diacetate and 8 (methylene peak δ 5.33).

E. From Bis(acetoxymethyl) Ether (8). 1. 1:1 Reaction. Acetyl methanesulfonate (27.03 g, 0.196 mol) was placed in the apparatus described above (A) and cooled to 0 °C. Neat 8 (31.73 g, 0.196 mol) was added dropwise, and the solution was allowed to warm to 25 °C and stirred for 30 min. The reaction was slowly heated to 75 °C under reduced pressure, held there for 3.5 h, and cooled to 25 °C, and the vacuum was broken under dry N_2. The NMR spectrum of the *crude* product (34.9 g) contained eight singlets assigned to 1 (3.13, 5.51), 7 (2.13, 3.10, 5.40, 5.47), and 8 (2.09, 5.35). The trap contents gave a singlet at 2.23 ppm in the NMR spectrum and the IR spectrum contained anhydride bands at 1750 and 1825 cm^{-1}. Based on the integral of the four singlets in the δ 5 region of the NMR the approximate composition of the crude product mixture was 33% (by weight) 1, 51% 7, and 16% 8.

A 25-g portion of the crude product was distilled in an oil-jacketed pot still to give 8.7 g (53% of theoretical yield) (105–121 °C, 8–3 μ) of the dimesylate 1. Only traces of the mixed ester 7 were seen in the NMR spectrum of the forerun.

2. 2:1 Reaction. Using the procedure described above, 53.54 g (0.388 mol) of acetyl methanesulfonate was reacted with 31.42 g (0.194 mol) of 8. To ensure a nearly complete reaction the heating period of 65 °C under vacuum was extended to 32 h. Based on the NMR, the crude product mixture contained 70% (by weight) 1, 27% 7, and 3% 8. The reaction mixture was worked up as in A to give 14.8 g (33%) of 1 (mp 56–59 °C).

F. Attempt with Paraformaldehyde. To 69 g (0.50 mol) of acetyl mesylate, in the system already described, was added 22.5 g (0.75 mol of CH_2O) of paraformaldehyde. The mixture was slowly warmed to 40 °C and after 16 h evacuated to 0.5 mmHg (vigorous bubbling). The temperature was raised to 75 °C during 4 h and finally heated at 80 °C for 4 h. Distillation of the reaction mixture in a short-path pot still produced a 25.0-g main fraction [pot temperature 76–82 °C (11–18 μ)] consisting almost entirely of methylene dimesylate. Analysis by NMR of the total distillate showed that it consisted of ca. 75% of the latter, 7% of 1, and some methanesulfonic acid and anhydride. Recrystallization from THF–ether produced 17.6 g of methylene dimesylate: mp 74–74.5 °C (lit.[10] 75–76 °C); NMR δ 3.20 (s, 6 H), 5.78 (s, 2 H).

Bis(ethylsulfonoxymethyl) Ether. Acetyl ethanesulfonate[16] (76.1 g, 0.50 mol) was placed in the apparatus described for the preparation of 1 above (A) and cooled to −5 °C, and 22.5 g (0.25 mol) of trioxane was added over a 20-min period. After the solution was heated at 60 °C with stirring under dry N_2 for 1 h, a 0.5-mm vacuum was applied and the reaction continued at 80 °C for 18 h. The dark brown reaction mixture was brought to ambient conditions under dry N_2. Distillation in a short-path pot still [pot temperature 110–113 °C (3–8 μ)] afforded 23.8 g (36%) of colorless liquid product: NMR δ 1.43 (t, 6 H), 3.22 (q, 4 H), 5.50 (s, 4 H).

Anal. Calcd for $C_6H_{14}O_7S_2$: C, 27.5; H, 5.4; S, 24.4. Found: C, 27.5; H, 5.7; S, 24.0.

Attempted Preparation of Bis(*p*-tolylsulfonoxymethyl) Ether

(2). A. From Bis(chloromethyl) Ether.[17] A 2:1 mixture of silver tosylate and BCME dissolved in dry acetonitrile was held at 25 °C for 18 h, protected from light, and filtered. Evaporation of the solvent at 30 °C and recrystallization of the crystalline residue from dry acetone gave a 36% yield of *p*-toluenesulfonic anhydride: mp 124–129 °C (lit.[18] 125 °C); NMR δ 2.51 (s, 6 H), 7.86 (m, 8 H).

B. From Acetyl Tosylate. Several attempts to isolate the ditosylate from the reaction of acetyl tosylate and trioxane were unsuccessful, apparently owing to instability of the product. A strong singlet at δ 5.33 in the NMR spectra of reaction mixtures held at 25 °C, and before attempted isolation, was indicative of product formation.[19] The only solid isolated from such mixtures was some unreacted acetyl tosylate.

Reaction of 1 with Mercaptans. A. 7-Oxa-5,9-dithiatridecane. To a suspension of sodium butylmercaptide, prepared from 1.53 g of butanethiol and 0.6 g of NaH (1.2 g of 50% oil suspension) in 40 mL of dry THF, was added under a nitrogen atmosphere at 0 °C a solution of 2.0 g of 1 in 10 mL of THF. After 2.5 h at 25 °C 2 mL of MeOH was added, and after filtration and evaporation the residue was extracted with ethyl acetate. Evaporation produced 1.9 g (85%) of product, the NMR of which matched that of an authentic sample: δ 0.88 (t, 6 H), 1.5 (m, 8 H), 2.53 (t, 4 H), 4.7 (s, 4 H).

B. 5-Oxa-3,7-dithia-1,9-nonanediol. To a suspension of sodium isopropoxide, under nitrogen, prepared from 9.2 g (0.40 mol) of sodium and 500 mL of dry 2-PrOH,[20] was added 31 g (0.40 mol) of 2-mercaptoethanol, followed by the dropwise addition of a solution of 46.5 g of 1 in 200 mL of dry THF at 25–30 °C. After 1 h the mixture was neutralized with concentrated HCl in 2-PrOH, charcoal added, and the sodium mesylate removed by filtration. Evaporation yielded 32.2 g (81%) of pale yellow oil, the NMR of which matched that of an authentic sample prepared from BCME: δ 2.77 (t, 4 H), 3.72 (t, 4 H), 4.75 (s, 4 H).

Reaction of 1 with Toluene. Addition of 11.7 g of 1 to 100 mL of dry toluene at 25 °C produced a dark brown mixture which after 18 h was poured into water. The organic layer upon evaporation yielded 14.7 g (76%) of a light oil identified by NMR and mass spectroscopy as a mixture of ditolylmethanes: NMR δ 2.24 (3 s, 6 H), 3.89 (2 s, 2 H), 7.12 (m, 8 H). The mass spectrum was run on a Perkin-Elmer RMS-4 instrument at 70 eV with all-glass reservoir inlet at 175 °C, ion source 200 °C, acceleration voltage 1500: *m/e* (rel intensity) 197 (14), 196 (82), 182 (15), 181 (100), 180 (8). 179 (10), 178 (11), 166 (20), 165 (24), 105 (15), 104 (40), 77 (10).

Reaction of 1 with Amines. A. Pyridine. A solution of 8.8 g (0.038 mol) of 1 in 20 mL of dry MeCN was added dropwise to a solution of 6 g (0.075 mol) of pyridine in 40 mL of MeCN at 25 °C. After 1 h the mixture was cooled to −40 °C and filtered. Recrystallization from MeOH produced 11.1 g (79%) of 2-oxapropane-1,3-bis(pyridinium mesylate), mp 187–189 °C.

Anal. Calcd for $C_{14}H_{20}N_2O_7S_2$: C, 42.8; H, 5.1; N, 7.1. Found: C, 42.5; H, 5.0; N, 7.1.

B. Pyrrolidine. To a solution of 8.09 g (0.114 mol) of pyrrolidine in 75 mL of dry ether was added 6.66 g (0.028 mol) of 1. The suspension gradually became pasty. After 2 h the ether solution was decanted and evaporated to a pale oil (2.9 g, 66%) which proved to be the aminal, dipyrrolidinomethane: NMR δ 1.78 (t, 8 H), 2.63 (t, 8 H), 3.28 (s, 2 H).

Reaction of 1 with 1-Butanol. A 5.7-g (0.024 mol) sample of 1 was dissolved in 10 mL of dry MeCN and added dropwise to 50 mL of dry 1-butanol at 25 °C. The reaction mixture was stirred for 1 h, 5 g of anhydrous sodium bicarbonate added, and the mixture filtered. The crude product solution, analyzed by gas chromatography–mass spectroscopy, contained the formal, dibutoxymethane. The instrument used was an AEI MS-30 equipped with a 0.125 in. × 7 ft glass column with a 10% Carbowax 20M packing. A membrane separator at 150 °C was used, ion source temperature 200 °C, spectrum run at 70 eV. The gas chromatography column was held at 50 °C. For the major peak of the chromatogram: *m/e* (rel intensity) 159 (2), 117 (2), 103 (3), 101 (2), 87 (52), 57 (100).

Reaction of 1 with Sodium *n*-Butoxide. Sodium (1.12 g, 0.049 mol) was reacted with 50 mL of dry 1-butanol and a solution of 5.7 g (0.0244 mol) of 1 in 10 mL of dry MeCN added dropwise, with stirring at 25 °C. After 0.5 h the precipitated sodium mesylate was removed by filtration and the crude product solution analyzed by gas chromatography–mass spectroscopy. The two major peaks, area ratio ~2:1, were examined by mass spectroscopy. The larger peak was identified as bis(butoxymethyl) ether and the smaller peak was tentatively identified as bis(butoxymethoxy)methane because of the *m/e* 147 peak ($BuOCH_2OCH_2OCH_2$–) in the mass spectrum. The AEI MS-30 was used as above with the Carbowax 20M column held at 50 °C for 2 min, then heated at 10 °C/min to 150 °C. Bis(butoxymethyl) ether: *m/e* (rel intensity) 189 (1), 159 (8), 117 (49), 116 (22), 103 (16), 101 (6), 87 (47), 86 (39), 57 (100), 56 (78). Bis(butoxymethoxy)methane: *m/e* (rel intensity) 189 (1), 159 (4), 147 (1), 117 (8), 116 (3), 103 (6), 101 (3), 87 (98), 57 (100), 56 (25).

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Registry No.—1, 62609-70-5; **3**, 5539-53-7; **7**, 62609-71-6; **8**, 4082-91-1; trioxane, 110-88-3; tetroxane, 291-15-6; trioxymethylene diacetate, 62609-72-7; paraformaldehyde, 30525-89-4; methylene dimesylate, 156-72-9; bis(ethylsulfonoxymethyl) ether, 62609-73-8; acetyl ethanesulfonate, 6744-63-4; 7-oxa-5,9-dithiatridecane, 62609-74-9; sodium butylmercaptide, 4779-86-6; 5-oxa-3,7-dithia-1,9-nonanediol, 36727-72-7; 2-mercaptoethanol, 60-24-2; toluene, 108-88-3; ditolylmethane, 1335-47-3; pyridine, 110-86-1; 2-oxapropane-1,3-bis(pyridinium mesylate), 62609-75-0; pyrrolidine, 123-75-1; dipyrrolidinomethane, 7309-47-9; 1-butanol, 71-36-3; dibutoxymethane, 2568-90-3; bis(butoxymethyl) ether, 5614-25-5; bis(butoxymethoxy)methane, 62609-76-1.

References and Notes

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(13) When 2.5% by weight of methanesulfonic acid was present the reaction time was reduced to 4 h. Heating for 5 h at 110 °C gave a 52% yield of slightly less pure product.

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(16) Prepared from ethanesulfonic acid and acetyl chloride according to ref 12 and used without purification.

(17) Use now restricted.[1]

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(19) The δ 5.33 value for the methylene protons vs. δ 5.52 for those in **1** is consistent with the relative values for the methyl protons in methyl tosylate (3.70 ppm) and methyl mesylate (3.88 ppm).

(20) EtOH has also been used successfully but a reaction temperature of −20 °C must be used to avoid solvolysis.