

# Organic Synthesis by the Pummerer Reaction. I.

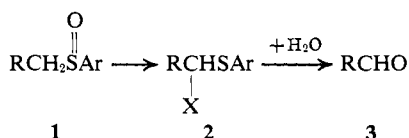
## Synthesis of $\alpha$ -Hydroxyaldehydes from $\beta$ -Hydroxy Sulfoxides

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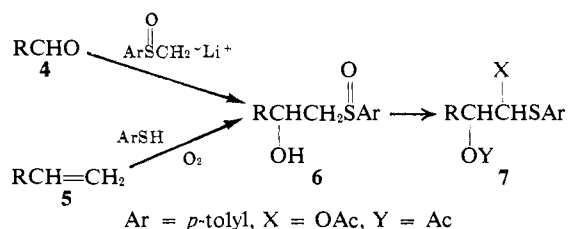
Contribution from the Sagami Chemical Research Center,  
Nishi-Ohnuma, Sagami-hara, Kanagawa 229, Japan. Received October 25, 1973

**Abstract:** The Pummerer reaction of  $\beta$ -hydroxy sulfoxides with acetic anhydride in the presence of sodium acetate afforded in excellent yields the corresponding  $\alpha,\beta$ -diacetoxy sulfides which can be regarded as a protected form of  $\alpha$ -hydroxyaldehydes. For example, the reaction of 3-acetoxy-2-hydroxypropyl *p*-tolyl sulfoxide derived from allyl acetate by a cooxidation with *p*-toluenethiol and oxygen gave 1,2,3-triacetoxypropyl *p*-tolyl sulfide, a derivative of glyceraldehyde, in 87% yield. The reaction of 2-methoxy-2-phenylethyl *p*-tolyl sulfoxide furnished 1-acetoxy-2-methoxy-2-phenylethyl *p*-tolyl sulfide quantitatively. The latter produced 2-methoxy-2-phenylacetaldehyde by alkaline hydrolysis, 2-hydroxy-3-methoxy-3-phenylpropionitrile by the reaction with NaCN, and 2-amino-3-methoxy-3-phenylpropionitrile by the reaction with NaCN followed by  $\text{NH}_4\text{Cl}$  and concentrated aqueous ammonia. The aminonitrile was hydrolyzed to give DL-*threo*-O-methylphenylserine. The present work, in conjunction with the synthesis of  $\beta$ -hydroxy sulfoxides either by the cooxidation of olefins and thiols with oxygen or by the condensation of  $\alpha$ -sulfinylcarbanions with aldehydes, constitutes a simple synthesis of  $\alpha$ -hydroxyaldehyde derivatives from olefins or aldehydes.

The Pummerer reaction of sulfoxides is a well-known rearrangement which gives sulfides with concomitant oxidation of the  $\alpha$  carbon.<sup>1</sup> It may also be regarded as a transfer of the oxidative state of sulfur to the  $\alpha$  carbon. For example, the reaction of sulfoxides (1) produces  $\alpha$ -oxidized sulfides (2) (e.g., X = OAc) which may give aldehydes (3) on hydrolysis. This ex-



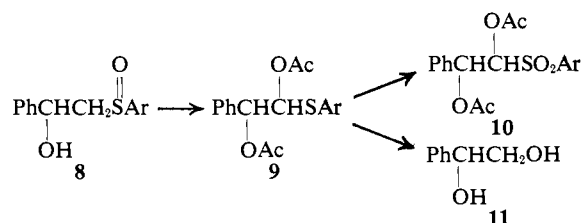
ample shows that the  $\alpha$ -sulfinylmethylene carbon can be "aldehyde equivalent" by the Pummerer reaction. Accordingly, the application of this reaction to  $\beta$ -hydroxy sulfoxides (6), which are easily obtained by the



condensation of  $\alpha$ -sulfinylcarbanions with aldehydes (4)<sup>2</sup> or the cooxidation of olefins (5) and thiols by oxygen,<sup>3</sup> will produce  $\alpha$ -hydroxyaldehyde derivatives (7). However, no substantial work on synthesizing  $\alpha$ -

hydroxyaldehydes from 6 by the Pummerer reaction has been reported. After some experimentation to effect conversion of 6 to 7, we have found that the reaction with acetic anhydride in the presence of sodium acetate is particularly suitable for this transformation. The addition of sodium acetate is required for (1) acetylating the hydroxy group prior to the Pummerer reaction and (2) keeping the medium in the buffered condition so that the Pummerer products exist in a stable state.<sup>4</sup>

The Pummerer reaction of 2-hydroxy-2-phenylethyl *p*-tolyl sulfoxide (8)<sup>2,6</sup> with acetic anhydride in the presence of sodium acetate afforded 1,2-diacetoxy-2-phenylethyl *p*-tolyl sulfide (9) in 95% yield as an oil of a ca. 1:1 diastereomeric mixture. The oxidation of 9 with hydrogen peroxide gave the corresponding crystalline sulfone (10) while the reduction with sodium borohydride furnished styrene glycol (11).



The Pummerer reaction of 3-acetoxy-2-hydroxypropyl *p*-tolyl sulfoxide (13), which is obtained in 82% yield by the cooxidation of allyl acetate (12) and *p*-toluenethiol (ArSH) with oxygen under the irradiation of a black-light fluorescent lamp,<sup>3b</sup> produced in 90% yield 1,2,3-triacetoxypropyl *p*-tolyl sulfide (14) which is considered a protected form of glyceraldehyde. This is a two-step synthesis of the glyceraldehyde from 12. In

(1) (a) R. Pummerer, *Chem. Ber.*, **42**, 2282 (1909); **43**, 1401 (1910); (b) J. A. Smythe, *J. Chem. Soc.*, **95**, 349 (1909); (c) L. Horner and P. Kaiser, *Justus Liebigs Ann. Chem.*, **626**, 19 (1959); (d) W. E. Parham and L. D. Edwards, *J. Org. Chem.*, **33**, 4150 (1968); (e) C. R. Johnson and W. G. Phillips, *J. Amer. Chem. Soc.*, **91**, 682 (1969); (f) see also T. Durst in "Advances in Organic Chemistry," Vol. 6, E. C. Taylor and H. Wymberg, Ed., Interscience, New York, N. Y., 1966, pp 356-365.

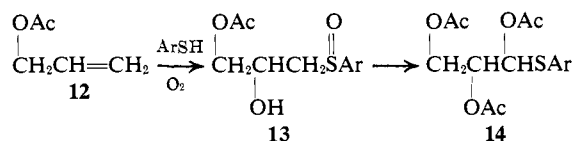
(2) G. Tsuchihashi, S. Iriuchijima, and M. Ishibashi, *Tetrahedron Lett.*, 4605 (1972).

(3) (a) For a review, see A. A. Oswald and T. J. Wallace in "The Chemistry of Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, Oxford, 1966, pp 217-232. (b) We have found that irradiation of a black-light fluorescent lamp is effective for the cooxidation of  $\alpha$ -olefins which are not conjugated with the electron-attracting groups such as aromatic rings, esters, and nitriles: S. Iriuchijima, K. Maniwa, T. Sakakibara, and G. Tsuchihashi, *J. Org. Chem.*, **39**, 1170 (1974).

(4) This is particularly true in the Pummerer reaction of 2-methoxy-2-phenylethyl *p*-tolyl sulfoxide (15) (see the next paragraph), pentyl *p*-tolyl sulfoxide, and isobutyl phenyl sulfoxide. The reaction of the latter two sulfoxides with acetic anhydride in the presence of sodium acetate gave  $\alpha$ -acetoxy sulfides in good yields whereas the reaction in the absence of sodium acetate resulted in the formation of  $\alpha,\beta$ -unsaturated sulfides.<sup>5</sup> Similar results affording  $\alpha,\beta$ -unsaturated sulfides were also reported; see ref 1c and d.

(5) Our unpublished results.

(6) H. Brederecker, A. Wagner, and A. Kottenhahn, *Chem. Ber.*, **93**, 2415 (1960).



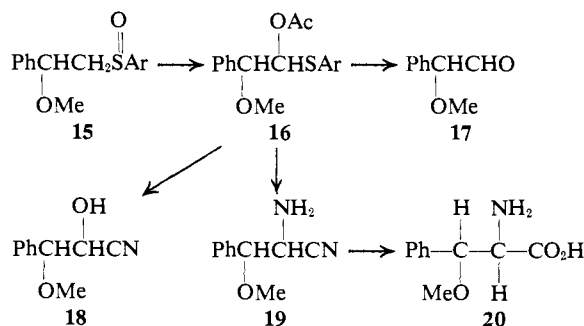
a similar way, the various types of **7** were obtained in high yields (see Table I).

**Table I.** Synthesis of  $\alpha$ -Hydroxyaldehydes (**7**) from  $\beta$ -Hydroxy Sulfoxides (**6**)

R	Reflux time, hr	Yield, %
CH <sub>3</sub> <sup>a</sup>	3	90
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> <sup>b</sup>	2	71
AcOCH <sub>2</sub> <sup>b</sup>	3	90
PhCH <sub>2</sub> OCH <sub>2</sub> <sup>b</sup>	3	97
CH <sub>3</sub> CH(OAc) <sup>b</sup>	3	87
3-Cyclohexenyl <sup>b</sup>	4	92
PhCH <sub>2</sub> <sup>b</sup>	3	74
4-Acetoxy-3-methoxybenzyl <sup>b</sup>	5	84
Ph <sup>a, b</sup>	3	95
<i>p</i> -Chlorophenyl <sup>a</sup>	2	76
3,4-Methylenedioxyphenyl <sup>a</sup>	6	99

<sup>a</sup> The materials (**6**) were prepared from aldehydes (**4**).<sup>b</sup> The materials (**6**) were prepared from olefins (**5**).<sup>3</sup>

The Pummerer reaction of 2-methoxy-2-phenylethyl *p*-tolyl sulfoxide (**15**), obtained quantitatively by the treatment of **8** with methyl iodide and silver oxide, produced 1-acetoxy-2-methoxy-2-phenylethyl *p*-tolyl sulfide (**16**) in quantitative yield.<sup>7</sup> The alkaline hydrolysis of **16** gave 2-methoxy-2-phenylacetaldehyde (**17**) which was identified as its semicarbazone, isolated in 65% yield. The treatment of **16** with sodium cyanide in aqueous methanol followed by stirring the solution at pH *ca.* 8 (with dilute sulfuric acid) gave 2-hydroxy-3-methoxy-3-phenylpropionitrile (**18**) as a 6:4 diastereomeric mixture in 88% yield. The major isomer was characterized as the corresponding benzoate. Similar treatment of **16** with sodium cyanide followed by reaction with ammonium chloride and concentrated aqueous ammonia afforded 2-amino-3-methoxy-3-phenylpropionitrile (**19**) as a 9:1 diastereomeric mixture in 79% yield. The major isomer, which was isolated as the crystalline hydrochloride, gave on acid hydrolysis DL-*threo*-O-methylphenylserine (**20**)<sup>8</sup> in 57% yield.



The present work together with the cooxidation reaction<sup>3</sup> constitutes a new and simple synthesis of  $\alpha$ -hydroxyaldehyde derivatives from olefins while in conjunction with the asymmetric synthesis using chiral  $\alpha$ -

(7) The addition of sodium acetate is necessary for this quantitative reaction.

(8) T. Suami and S. Umezawa, *Bull. Chem. Soc. Jap.*, **30**, 537 (1957).

sulfinylcarbanions<sup>2</sup> it gives a method for the synthesis of optically active  $\alpha$ -hydroxyaldehydes from aldehydes.

Moreover,  $\alpha$ -hydroxyaldehyde derivatives obtained by this method can be easily converted to the corresponding "sulfur-free" products such as cyanohydrins and aminonitriles. The cyanohydrins are useful for the sugar synthesis<sup>9</sup> while the aminonitriles can be converted to  $\beta$ -hydroxy- $\alpha$ -amino acids or  $\beta$ -hydroxy- $\alpha$ -aminoaldehydes.<sup>10</sup>

## Experimental Section

**General.** Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. Unless otherwise stated, infrared spectra were determined in Nujol mull on a Hitachi EPI-G3 spectrometer, mass spectra were recorded on a Hitachi RMU-6E spectrometer, and nmr spectra were measured in CDCl<sub>3</sub> solution on Varian HA-100, T-60, and Hitachi R-20B spectrometers; chemical shifts are given in  $\delta$  with TMS as internal standard. The Pummerer products were always produced as an oil in a *ca.* 1:1 diastereomeric mixture and their nmr spectra are expressed as a 1:1 mixture. Chromatography was done with silica gel (Wakogel C-200). Thin-layer plates were made of Wakogel B-5FM. It was suspended in dichloromethane, and the plates were dipped and dried in an atmosphere. They were detected with iodine and uv light.

**Preparation of 1,2-Diacetoxy-2-phenylethyl *p*-Tolyl Sulfide (**9**) as a General Procedure for the Pummerer Reaction.** A stirred mixture of 2-hydroxy-2-phenylethyl *p*-tolyl sulfoxide (**8**) (1.79 g, 6.86 mmol) and sodium acetate (1.79 g, an equal weight) in acetic anhydride (20 ml) was heated from room temperature to reflux during 0.5 hr and then refluxed for 3 hr. After excess acetic anhydride and acetic acid were removed under reduced pressure, the residue was suspended in benzene and passed through silica gel. The evaporation of the solvent followed by drying under vacuum gave an oil (2.25 g, 95%) of **9**: ir (film) 700, 1021, 1210, 1235, 1370, 1493, 1750 cm<sup>-1</sup>; nmr (100 MHz) 1.97 (s, 3, CH<sub>3</sub>CO<sub>2</sub>), 2.05 (s, 3, CH<sub>3</sub>CO<sub>2</sub>), 2.08 (s, 3, CH<sub>3</sub>CO<sub>2</sub>), 2.14 (s, 3, CH<sub>3</sub>CO<sub>2</sub>), 2.35 (s, 6, 2  $\times$  aryl CH<sub>3</sub>), 5.97, 6.05, 6.30, 6.37 (AB q, 2, *J* = 7 Hz, C<sub>1</sub>H and C<sub>2</sub>H of one isomer), 5.99, 6.05, 6.29, 6.34 (AB q, 2, *J* = 5.5 Hz, C<sub>1</sub>H and C<sub>2</sub>H of another isomer), 7.0–7.5 (18, aryl H); mass spectrum (70 eV) *m/e* (rel intensity) 344 (M<sup>+</sup>, 8), 221 (34), 124 (80), 119 (39), 91 (40), 43 (100). The product thus obtained was almost homogeneous in tlc with benzene and can be used immediately for the further reaction. It was chromatographed with hexane-benzene (8:2) and eluted with hexane-benzene (6:4), but its recovery is low and the sample, though homogeneous in tlc, did not give a satisfactory elemental analysis. Therefore, **9** was characterized as crystalline sulfone (**10**) as follows.

A solution of the crude product (**9**) (1.055 g, 2.93 mmol) and 30% hydrogen peroxide (1 ml, 10 mmol) in acetic acid (6 ml) was warmed at 45° overnight. After the evaporation of the solvent, the residue was dissolved in dichloromethane, washed with dilute sodium bicarbonate, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated giving 1.10 g (96%) of white crystals (**10**) as a diastereomeric mixture: mp 134–150° (chloroform-hexane); ir 1040, 1197, 1324, 1594, 1744, 1752, 1770 cm<sup>-1</sup>; nmr 1.72 (s, 3 H), 1.99 (s, 3 H), 2.02 (s, 3 H), 2.04 (s, 3 H), 2.45 (s, 6 H), 6.06 (d, *J* = 4 Hz, 1 H), 6.20 (s, 2 H), 6.54 (d, *J* = 4 Hz, 1 H), 7.2–7.5 (14 H), 7.63–7.93 (4 H) (as a 1:1 mixture). *Anal.* Calcd for C<sub>16</sub>H<sub>20</sub>O<sub>6</sub>S: C, 60.62; H, 5.36. Found: C, 60.62; H, 5.45.

**1,2,3-Triacetoxypropyl *p*-Tolyl Sulfide (**14**).** The residue obtained by concentration of the reaction mixture was chromatographed with benzene and fractionated. After a few fractions were discarded, **14** was obtained as a clear oil (90%): ir (film) 1015, 1045, 1212, 1369, 1746 cm<sup>-1</sup>; nmr 2.00–2.15 (9, 3  $\times$  CH<sub>3</sub>CO<sub>2</sub>), 2.35 (s, 3 H), 4.27–4.45 (2 H), 5.15–5.45 (1, C<sub>2</sub>H), 6.15–6.3 (1, C<sub>1</sub>H), 7.0–7.55 (4 H) (two diastereomers were superimposed); mass spectrum (70 eV) *m/e* 340 (M<sup>+</sup>, 5), 217 (33), 124 (92), 115 (42), 91 (42), 43 (100). *Anal.* Calcd for C<sub>18</sub>H<sub>20</sub>O<sub>6</sub>S: C, 56.46; H, 5.92; S, 9.42. Found: C, 56.47; H, 5.66; S, 9.37.

**1,2-Diacetoxypentyl *p*-Tolyl Sulfide (**7**; R = CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>).** The product obtained by passage through silica gel gave two spots in tlc with benzene. Therefore it was chromatographed. The elution

(9) R. Kuhn and H. Grassner, *Justus Liebig's Ann. Chem.*, **612**, 55 (1958); R. Kuhn and P. Klesse, *Chem. Ber.*, **91**, 1989 (1958).

(10) R. Kuhn and H. Fischer, *Justus Liebig's Ann. Chem.*, **641**, 152 (1961), and references therein.

with hexane gave acetoxymethyl *p*-tolyl sulfide (ca. 20%) as an oil: ir (film) 808, 978, 1017, 1212, 1748  $\text{cm}^{-1}$ ; nmr 2.08 (s, 3 H), 2.34 (s, 3 H), 5.36 (s, 2 H), 7.25 (m, 4 H). The further elution with hexane-benzene (1:1) afforded 7 ( $\text{R} = \text{CH}_2\text{CH}_2\text{CH}_2$ ) (71%) as an oil: ir (film) 1020, 1215, 1240, 1370, 1750  $\text{cm}^{-1}$ ; nmr 0.7–2.0 (14 H), 2.05 (s, 12 H), 2.34 (s, 6 H), 5.0–5.4 (2,  $\text{C}_2\text{H}$ ), 6.10 (d, 1,  $J = 6$  Hz,  $\text{C}_1\text{H}$ ), 6.18 (d, 1,  $J = 3.5$  Hz,  $\text{C}_1\text{H}$ ), 7.0–7.55 (8 H). *Anal.* Calcd for  $\text{C}_{16}\text{H}_{22}\text{O}_4\text{S}$ : C, 61.91; H, 7.14; S, 10.33. Found: C, 61.58; H, 7.02; S, 10.78.

**1,2-Diacetoxypropyl *p*-Tolyl Sulfide (7;  $\text{R} = \text{CH}_3$ ).** The product obtained by passage through silica gel gave almost homogeneous tlc and reasonable ir and nmr spectra: ir (film) 813, 1016, 1215, 1240, 1371, 1745  $\text{cm}^{-1}$ ; nmr 1.34 (d,  $J = 6.7$  Hz, 3 H), 1.35 (d,  $J = 6.7$  Hz, 3 H), 2.02 (s, 6 H), 2.06 (s, 6 H), 2.32 (s, 6 H), 4.9–5.42 (2,  $\text{C}_2\text{H}$ ), 6.06 (d, 1,  $J = 7$  Hz,  $\text{C}_1\text{H}$ ), 6.15 (d, 1,  $J = 4.5$  Hz,  $\text{C}_1\text{H}$ ), 7.0–7.55 (8 H). The product was chromatographed with hexane-benzene (4:1) and eluted with hexane-benzene (1:1) giving an analytically pure sample. *Anal.* Calcd for  $\text{C}_{14}\text{H}_{18}\text{O}_4\text{S}$ : C, 59.55; H, 6.43; S, 11.35. Found: C, 59.87; H, 6.25; S, 11.73.

**1,2-Diacetoxy-2-(3,4-methylenedioxyphenyl)ethyl *p*-Tolyl Sulfide (7;  $\text{R} = 3,4\text{-Methylenedioxyphenyl}$ ).** The product obtained by passage through silica gel was almost homogeneous in tlc with benzene and gave reasonable ir and nmr spectra: ir (film) 810, 1035, 1230, 1750  $\text{cm}^{-1}$ ; nmr 1.95 (s, 3 H), 2.00 (s, 6 H), 2.06 (s, 3 H), 2.28 (s, 6 H), 5.88 (s, 4 H), 5.86–6.45 (4,  $\text{C}_1\text{H}$  and  $\text{C}_2\text{H}$ ), 6.6–7.45 (14 H). The product was chromatographed with hexane-benzene (4:1) and eluted with hexane-benzene (6:4) to afford an analytically pure sample. *Anal.* Calcd for  $\text{C}_{20}\text{H}_{20}\text{O}_6\text{S}$ : C, 61.84; H, 5.19; S, 8.26. Found: C, 61.85; H, 5.15; S, 8.27.

**Spectral Properties of Other Pummerer Products (7).** The products obtained by passage through silica gel were almost homogeneous in tlc with benzene and gave reasonable ir and nmr spectra which are analogous to those of the compounds characterized above: all of the nmr signals were assigned to the proposed structures.

**1,2-Diacetoxy-3-phenylpropyl *p*-Tolyl Sulfide (7;  $\text{R} = \text{PhCH}_2$ ).** ir (film) 700, 750, 815, 1020, 1225, 1370, 1748  $\text{cm}^{-1}$ ; nmr 1.91 (s, 3,  $\text{CH}_3\text{CO}_2$ ), 1.95 (s, 3,  $\text{CH}_3\text{CO}_2$ ), 2.02 (s, 3,  $\text{CH}_3\text{CO}_2$ ), 2.05 (s, 3,  $\text{CH}_3\text{CO}_2$ ), 2.33 (s, 6, 2  $\times$  aryl  $\text{CH}_3$ ), 2.8–3.35 (4, 2  $\times$   $\text{CH}_2$ ), 5.2–5.6 (2,  $\text{C}_2\text{H}$ ), 6.10 (d, 1,  $J = 7.5$  Hz,  $\text{C}_1\text{H}$ ), 6.18 (d, 1,  $J = 5$  Hz,  $\text{C}_1\text{H}$ ), 7.0–7.6 (18, aryl H).

**1,2-Diacetoxy-3-(4-acetoxy-3-methoxyphenyl)propyl *p*-Tolyl Sulfide (7;  $\text{R} = 4\text{-Acetoxy-3-methoxyphenyl}$ ).** ir (film) 1035, 1200–1220, 1370, 1605, 1745–1770  $\text{cm}^{-1}$ ; nmr 1.95 (s, 3,  $\text{CH}_3\text{CO}_2$ ), 1.98 (s, 3,  $\text{CH}_3\text{CO}_2$ ), 2.03 (s, 3,  $\text{CH}_3\text{CO}_2$ ), 2.07 (s, 3,  $\text{CH}_3\text{CO}_2$ ), 2.29 (s, 6, 2  $\times$  aryl  $\text{CH}_3\text{CO}_2$ ), 2.33 (s, 6, 2  $\times$  aryl  $\text{CH}_3$ ), 2.85–3.2 (4, 2  $\times$   $\text{CH}_2$ ), 3.79 (s, 3,  $\text{CH}_3\text{O}$ ), 3.80 (s, 3,  $\text{CH}_3\text{O}$ ), 5.2–5.6 (2,  $\text{C}_2\text{H}$ ), 6.05–6.25 (2,  $\text{C}_1\text{H}$ ), 6.6–7.55 (14, aryl H).

**1,2-Diacetoxy-2-(*p*-chlorophenyl)ethyl *p*-Tolyl Sulfide (7;  $\text{R} = p\text{-chlorophenyl}$ ).** ir (film) 1015, 1210, 1230, 1370, 1750  $\text{cm}^{-1}$ ; nmr 1.96 (s, 3,  $\text{CH}_3\text{CO}_2$ ), 2.04 (s, 6, 2  $\times$   $\text{CH}_3\text{CO}_2$ ), 2.10 (s, 3,  $\text{CH}_3\text{CO}_2$ ), 2.31 (s, 6, 2  $\times$  aryl  $\text{CH}_3$ ), 5.9–6.4 (4,  $\text{C}_1\text{H}$  and  $\text{C}_2\text{H}$ ), 7.0–7.4 (16, aryl H).

**1,2-Diacetoxy-3-benzyloxypropyl *p*-Tolyl Sulfide (7;  $\text{R} = \text{PhCH}_2\text{-OCH}_2$ ).** ir (film) 1020, 1108, 1210, 1235, 1370, 1750  $\text{cm}^{-1}$ ; nmr 2.00–2.10 (6, 2  $\times$   $\text{CH}_3\text{CO}_2$ ), 2.34 (s, 3, aryl  $\text{CH}_3$ ), 3.65–3.8 (2,  $\text{CH}_2$ ), 4.50–4.57 (2, aryl  $\text{CH}_2$ ), 5.15–5.5 (1,  $\text{C}_2\text{H}$ ), 6.24–6.36 (1,  $\text{C}_1\text{H}$ ), 7.0–7.5 (9, aryl H) (two diastereomers were superimposed).

**1,2,3-Triacetoxypentyl *p*-Tolyl Sulfide (7;  $\text{R} = \text{CH}_2\text{CHOAc}$ ).** ir (film) 1220, 1375, 1750  $\text{cm}^{-1}$ ; nmr 1.10–1.35 (3,  $\text{CH}_3$ ), 1.95–2.2 (9, 3  $\times$   $\text{CH}_3\text{CO}_2$ ), 2.34 (s, 3, aryl  $\text{CH}_3$ ), 5.05–5.5 (2,  $\text{C}_2\text{H}$  and  $\text{C}_3\text{H}$ ), 6.0–6.26 (1,  $\text{C}_1\text{H}$ ), 7.0–7.55 (4, aryl H) (four isomers superimposed).

**2-(3-Cyclohexenyl)-1,2-diacetoxyethyl *p*-Tolyl Sulfide (7;  $\text{R} = 3\text{-Cyclohexenyl}$ ).** ir (film) 812, 1016, 1215, 1233, 1369, 1747  $\text{cm}^{-1}$ ; nmr 1.2–2.45 (16 H), 5.0–5.3 (1,  $\text{C}_2\text{H}$ ), 5.6–5.75 (2, olefinic H), 6.15–6.30 (1,  $\text{C}_1\text{H}$ ), 7.0–7.55 (4, aryl H) (four isomers were superimposed).

**Isolation of Styrene Glycol (11) from 9.** To a solution of 9 (172 mg, 0.50 mmol) in ethanol (5 ml) was added a solution of sodium borohydride (47 mg, 1.24 mmol) in 1 *N* sodium hydroxide (1.5 ml), and the mixture was stirred at room temperature overnight. The addition of water followed by extraction with dichloromethane, drying ( $\text{Na}_2\text{SO}_4$ ), and evaporation of the solvent afforded 43 mg of white crystals. Recrystallization from benzene-hexane gave 25 mg of 11, identified by infrared and nmr spectra with the authentic sample.

**Preparation of 2-Methoxy-2-phenylethyl *p*-Tolyl Sulfoxide (15).** To a solution of 8 (1.72 g, 6.6 mmol) and methyl iodide (2.81 g, 19.8 mmol) in dimethylformamide (20 ml) was added silver oxide (1.53 g, 6.6 mmol) at room temperature, and the mixture was stirred for 6 hr. After evaporation of the solvent, the residue was suspended in

benzene and chromatographed with silica gel. The elution with benzene-ethyl acetate (95:5) gave 15 (1.79 g, 99%) which crystallized on standing. The crystals were recrystallized from benzene-hexane affording a ca. 6:4 diastereomeric mixture: mp 78–87°; ir 706, 800, 1036, 1045, 1112  $\text{cm}^{-1}$ ; nmr of the major isomer 2.43 (s, 3 H), 3.13 (s, 3 H), 4.35 (q,  $J = 5.7$  and 7.8 Hz, 1 H), 7.2–7.7 (9 H). *Anal.* Calcd for  $\text{C}_{16}\text{H}_{18}\text{O}_2\text{S}$ : C, 70.04; H, 6.61. Found: C, 69.70; H, 6.60.

**Preparation of 1-Acetoxy-2-methoxy-2-phenylethyl *p*-Tolyl Sulfide (16).** A mixture of 15 (685 mg, 2.5 mmol) and sodium acetate (700 mg) in acetic anhydride (10 ml) was refluxed for 3 hr. The work-up gave 16 (785 mg, 99%) as an oil of a 6:4 diastereomeric mixture: ir (film) 700, 1219, 1750  $\text{cm}^{-1}$ ; nmr of the major isomer 1.95 (s, 3 H), 2.30 (s, 3 H), 3.31 (s, 3 H), 4.49 (d,  $J = 5.5$  Hz, 1 H), 6.30 (d,  $J = 5.5$  Hz, 1 H), 6.95–7.5 (9 H).

**Isolation of 2-Methoxy-2-phenylacetaldehyde (17) Semicarbazone.** To a stirred solution of 16 (300 mg, 0.95 mmol) in ethanol (3 ml) was added 1 *N* sodium hydroxide (1.5 ml), and the mixture was stirred at room temperature for 1 hr. After the addition of acetic acid (0.1 ml), semicarbazide hydrochloride (150 mg, 1.34 mmol) and sodium acetate (200 mg) were added portionwise, and the mixture was stirred overnight. Water was added, and the mixture was extracted with ethyl acetate. The extract was dried ( $\text{Na}_2\text{SO}_4$ ), concentrated, and chromatographed using silica gel with dichloromethane. The elution with dichloromethane-ethyl acetate (1:1) gave a semicarbazone<sup>11</sup> of 17 (127 mg, 64.5%): mp 138–140° (ethyl acetate-hexane); ir 703, 1095, 1597, 1661, 1718, 3270, 3465  $\text{cm}^{-1}$ . *Anal.* Calcd for  $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_2$ : C, 57.96; H, 6.32. Found: C, 57.77; H, 6.25.

**Preparation of 2-Hydroxy-3-methoxy-3-phenylpropionitrile (18).** A solution of 16 (158 mg, 0.5 mmol) and sodium cyanide (49 mg, 1 mmol) in methanol (8 ml)-water (2 ml) was stirred at 50° for 6 hr. The solution was neutralized to pH 8 with dilute sulfuric acid and stirred at room temperature overnight. Water was added, and the mixture was extracted with dichloromethane. The extract was dried ( $\text{Na}_2\text{SO}_4$ ), concentrated, and chromatographed with benzene. The elution with benzene-ethyl acetate (98:2) gave 18 (78 mg, 88%) as an oil of a 6:4 diastereomeric mixture: ir (film) 700, 714, 762, 1075, 1112, 2250, 3400  $\text{cm}^{-1}$ ; nmr of the major isomer 3.28 (m, 1 H), 3.38 (s, 3 H), 4.47 (m, 2 H), 7.41 (s, 5 H).

**Characterization of 18 as Benzoate.** A solution of 18 (298 mg, 1.68 mmol) and benzoyl chloride (355 mg, 2.52 mmol) in pyridine (4 ml) was stirred at 50° for 4 hr. After water was added, the mixture was stirred at room temperature for 8 hr and extracted with dichloromethane. The extract was washed with 1 *M* sodium carbonate, dried ( $\text{Na}_2\text{SO}_4$ ), concentrated, and chromatographed with benzene-hexane (1:1). The elution with benzene furnished a benzoate of 18 (410 mg, 86.8%) as a diastereomeric mixture which crystallized on standing. The major isomer was isolated by fractional crystallizations from benzene-hexane: mp 102–105°; ir 709, 1096, 1264, 1722  $\text{cm}^{-1}$ ; nmr 3.45 (s, 3 H), 4.67 (d,  $J = 5.2$  Hz, 1 H), 5.70 (d,  $J = 5.2$  Hz, 1 H), 7.45 (m, 8 H), 8.0 (m, 2 H). *Anal.* Calcd for  $\text{C}_{17}\text{H}_{15}\text{NO}_8$ : C, 72.59; H, 5.37. Found: C, 72.59; H, 5.35.

In a similar way, 3,5-dinitrobenzoate of the major isomer of 18 was obtained: mp 170–172° (benzene-hexane); ir (KBr) 1100, 1270, 1345, 1540, 1740  $\text{cm}^{-1}$ ; nmr 3.41 (s, 3 H), 4.70 (d,  $J = 5.6$  Hz, 1 H), 5.70 (d,  $J = 5.6$  Hz, 1 H), 7.50 (s, 5 H), 8.95–9.3 (3 H). *Anal.* Calcd for  $\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_7$ : C, 54.99; H, 3.53. Found: C, 55.06; H, 3.54.

**Synthesis of DL-threo-O-Methylphenylserine (20).** A mixture of 16 (604 mg, 1.90 mmol) and sodium cyanide (186 mg, 3.8 mmol) in ethanol (10 ml) and water (3 ml) was stirred at room temperature overnight. Then to this were added ammonium chloride (203 mg, 3.80 mmol) and concentrated aqueous ammonia (2 ml), and the mixture was stirred at 60° for 4.5 hr. After the mixture was cooled, water was added and the mixture was extracted with dichloromethane. The organic layer was extracted with dilute sulfuric acid which was basified with 1 *N* sodium hydroxide and reextracted with dichloromethane. The organic extract was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated giving 2-amino-3-methoxy-3-phenylpropionitrile (19) (265 mg, 79.2%) as an oil of a 9:1 diastereomeric mixture: ir (film) 710, 758, 1111, 2225, 2925, 3300, 3365  $\text{cm}^{-1}$ ; nmr of the major isomer 1.67 (s, 2 H), 3.25 (s, 3 H), 3.86 (d,  $J = 5.6$  Hz, 1 H), 4.24 (d,  $J = 5.6$  Hz, 1 H), 7.32 (s, 5 H). The corresponding hydrochloride was crystalline, and the major isomer was obtained in a

(11) This compound was first synthesized by K. Ogura and G. Tsuchihashi. For the synthesis of 2-methoxy-2-phenylacetaldehyde, see *Tetrahedron Lett.*, 2681 (1972).

pure state by recrystallization from ethanol-ethyl acetate: mp 184–185° dec; ir 700, 765, 1096, 1503, 1587, 2020, 2470–2800  $\text{cm}^{-1}$ . *Anal.* Calcd for  $\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}$ : C, 56.48; H, 6.16; N, 13.17. Found: C, 56.39; H, 5.86; N, 12.89.

A solution of 19 (316 mg, 1.795 mmol) in 6 *N* hydrochloric acid (4 ml) was stirred at 130° for 6.5 hr. The solution was concentrated, dried *in vacuo*, dissolved in concentrated aqueous ammonia (1 ml), and concentrated again giving the crystals which were recrystallized from ethanol-water-ether to afford 200 mg (57.1%) of 20. The pure sample which showed mp 220–222° after a few recrystalliza-

tions from the same solvents was identified as *DL-threo-O*-methylphenylserine (mp 218–220°)<sup>8</sup> by the infrared spectrum (KBr) of the authentic specimen.

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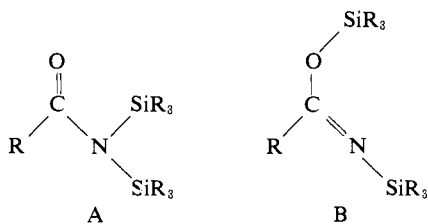
## The Structure of Trimethylsilyl Amides

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**Abstract:** The structures of a series of bis(trimethylsilyl) amides have been investigated by nmr and ir spectroscopy. A study of the  $^{15}\text{N}$  derivative of bis(trimethylsilyl)formamide provides definitive evidence for the amide structure and the free energy of activation for the rotational process is found to be 11.6 kcal/mol. The structures of the other amides were determined from their nmr characteristics, and all were found to have the imidate structure. The free energies of activation for the intramolecular exchange of trimethylsilyl groups range from 15.0 to 22.1 kcal/mol and are related to the electronic and steric properties of the substituent at the carbonyl carbon. The structures of mono- and bis(trimethylsilyl) amides, hindered rotation in the amide tautomers, and exchange of the trimethylsilyl group are discussed.

One of the interesting peculiarities of the trimethylsilyl group is its lability in many compounds in which alkyl groups are nonmobile. This is particularly well illustrated by the stereochemical nonrigidity of the popular silylating agent bis(trimethylsilyl)acetamide (BSA). Although this compound has been reported to have the amide structure (A)<sup>1</sup> and the imidate structure



(B),<sup>2</sup> the imidate assignment has been confirmed by a spectroscopic study of the  $^{15}\text{N}$  derivative.<sup>3</sup> The nmr spectrum of BSA at room temperature contains a singlet in the trimethylsilyl region which collapses to a doublet as the temperature decreases. This behavior is attributable to a temperature-dependent intramolecular exchange of trimethylsilyl groups. Recently, bis(trimethylsilyl)formamide has also been prepared, and its spectral behavior has been interpreted as evidence for the amide<sup>4</sup> and imidate forms.<sup>5</sup>

We report here: (a) the results of our investigation of the  $^{15}\text{N}$  derivative of bis(trimethylsilyl)formamide,

(1) L. Birkhofer and A. Ritter, *Angew. Chem., Int. Ed. Engl.*, **4**, 417 (1965).

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(3) C. H. Yoder and D. Bonelli, *Inorg. Nucl. Chem. Lett.*, **8**, 1027 (1972).

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(5) W. Kantlehner, W. Kugel, and H. Bredereck, *Chem. Ber.*, **105**, 2264 (1972).

and a series of bis(trimethylsilyl) compounds of the type  $\text{RCON}[\text{Si}(\text{CH}_3)_3]_2$ , where  $\text{R} = \text{C}_2\text{H}_5$ ,  $\text{CH}(\text{CH}_3)_2$ ,  $\text{C}(\text{CH}_3)_3$ , and  $\text{CF}_3$ , and (b) our conclusions regarding the determinants of the structure and exchange rate in both mono- and bis(trimethylsilyl) amides.

### Experimental Section

**Compounds.** All reactions and operations were carried out under nitrogen in oven-dried glassware with dry solvents and compounds.

**Bis(trimethylsilyl)formamide.** The  $^{14}\text{N}$  and  $^{15}\text{N}$  isotopomers (96 atom %  $^{15}\text{N}$  formamide was obtained from Merck, Sharpe and Dohme of Canada) were prepared by the reaction of 0.01 mol of formamide with 0.02 mol of trimethylchlorosilane and 0.022 mol of triethylamine in 5 ml of benzene at room temperature. After 1 hr of reflux the mixture was filtered and the filtrate distilled at reduced pressure through a 13-cm column packed with glass helices. Product was obtained at 68° (25 mm); a second fraction (which contained some trimethylsilylformamide) was obtained at 78° (25 mm) (lit.<sup>4</sup> bis(trimethylsilyl)formamide, 57° (13 mm)).

**Bis(trimethylsilyl)propionamide** was prepared by the treatment of propionamide with trimethylchlorosilane in triethylamine, bp 55° (10 mm). (*Anal.* Calcd for  $\text{C}_8\text{H}_{23}\text{NOSi}_2$ : C, 49.77; H, 10.59; N, 6.45. Found: C, 49.17; H, 10.67; N, 6.19.)

**Bis(trimethylsilyl)dimethylacetamide** was obtained from the reaction of isobutyramide with trimethylchlorosilane in the presence of triethylamine, bp 52° (9 mm). (*Anal.* Calcd for  $\text{C}_{10}\text{H}_{25}\text{NOSi}_2$ : C, 51.88; H, 10.89; N, 6.05. Found: C, 52.07; H, 10.78; N, 6.92.)

**Bis(trimethylsilyl)trimethylacetamide** was obtained from the reaction of the lithium salt of hexamethyldisilazane with trimethylacetyl chloride in hexane, bp 72–74° (15 mm) (lit.<sup>2b</sup> 79–80° (16 mm)).

**Bis(trimethylsilyl)trifluoroacetamide** was a commercial sample.

**Nmr and Ir Measurements.** Nmr spectra were obtained on a Varian A-60D spectrometer equipped with variable-temperature accessory V-4341/V-6057. Temperatures were measured with methanol and ethylene glycol samples and the equations of Van Geet.<sup>6</sup> Variables used in the determination of free energies of

(6) A. L. Van Geet, *Anal. Chem.*, **42**, 679 (1970).