Organic Disulfides and Related Substances. 36. Some Oxodisulfide Cleavage Reactions to Form Disulfides and Trisulfides[1]

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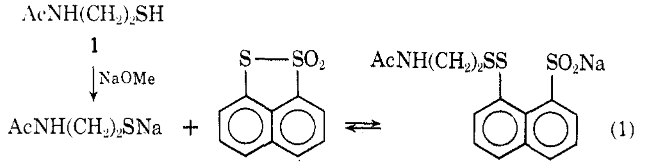
Several applications of 1,2-dithiane 1,1-dioxide and 1,1,2,2-tetroxide to synthesis of otherwise difficultly obtainable classes of disulfides were described earlier.[2] Preparation of similar products containing a varied number of substituted or unsubstituted methylene groups separating an –SS– moiety from a functional group based on a sulfinate moiety should be possible, since cyclic disulfides containing from 3 to 13 methylene groups are known.[3]

This paper reports further tests of the generality and nature of reactions of disulfide dioxides, which for convenience are called "oxodisulfide cleavages." 2-Acetamidoethanethiol (**1**) and sodium sulfide were used to afford disulfides and trisulfides, respectively. The thiol **1** was used as a model in the hope that the products also might be of interest as antiradiation drugs.[4] Disulfide 1,1-dioxides were used that would begin to afford insight into the effect on the cleavage of fused-on aromatic systems and of chain substitution.

The most striking neighboring-group effect of $-SO_2Na$ on –SS– yet encountered was seen at the outset. Thioalkylation of **1** with the known disulfide dioxide **2**[5] evidently led by oxodisulfide cleavage to a hydrate of the sulfinate salt **3** (eq 1). This presumed hydrate could not be obtained analytically pure. The cyclization shown in eq 2 occurs in *ca.* 1 hr in a water–benzene mixture at 60° and, when the salt of the thiol **1** was trapped with *N*-ethylmaleimide, 1,2-dithiane 1,1-dioxide was isolated in 39% yield.[1a] The sulfinate salt **3** shows a similar neighboring-group attack of SO_2Na on –SS– even more dramatically; for example, warming for 5 min led to 33% of **2** (MeOH, 50°). In another experiment, an aqueous solution of **3** was extracted from time to time with chloroform. Isolation and characterization by ir and mixture melting point confirmed the rapid cyclization of **3** to give **2**, the cumulative per cent yield of **2** being as follows (hours in parentheses, ~25°): 43 (0.17), 59 (4), 69 (8), 77 (16). The rapid cyclization of **3** to **2**, complicated by disproportionation of the unsymmetrical disulfide **3** to the two possible symmetrical ones, presumably is a cause of the inability to obtain analytically pure **3**. Indeed, a major problem with **3** lies in preventing the ring closure of the salt **3** to the starting material **2**. Efforts to trap **3** were unpromising. These included attempts to make the ferric sulfinate (hopefully, too sparingly soluble to revert to **1**), the sulfinic acid (**2** separated in 49% yield) or its formaldehyde adduct, or sulfones. Presumably, the coplanarity of **3** greatly enhances the neighboring-group attack of $-SO_2Na$ on the –SS– bond, thus causing the extremely facile reversion of **3** to **2** observed in all these efforts.

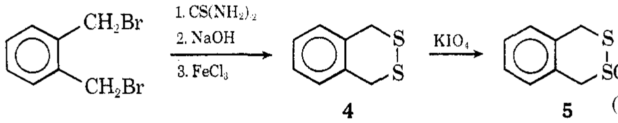


2 **3** (1)

$$AcNH(CH_2)_2SS(CH_2)_4SO_2Na \rightleftharpoons AcNH(CH_2)_2SNa + \overline{S(CH_2)_4SO_2} \quad (2)$$

Confirmation that the reaction of eq 1 occurs as formulated is afforded by several kinds of evidence. (1) Thiolate disappears, since the solution of the thiolate salt of **1** is very basic but after reaction with **2** is neutral; furthermore, a strong nitroprusside test at the beginning becomes negative after *ca.* 2 min. The strong absorption by $-SO_2-$ of **2** at 1110 and 1290 cm^{-1} is not seen in the product; hence **2** is consumed as well. (2) The product shows one major tlc spot, although one to two minor ones also always were seen (presumably caused by equilibrium *via* eq 1 and/or disproportionation of **3** to two symmetrical disulfides). The product shows very strong *new* ir bands at *ca.* 1000 cm^{-1}, as expected for the $-SO_2Na$ moiety of **3**, as well as the ir absorption expected for the amide linkage of **3**. (3) Ferric chloride at pH *ca.* 6 gave an abundant precipitate with the product, consistent with expectation for an arenesulfinic acid from **3**;[6] that the yield was 99% of expectation for the usual 1:3 stoichiometry is strong confirmation for the sulfinate moiety. (4) The product was initially insoluble in acetone but dissolved (and could not be reprecipitated) after *ca.* 0.3 hr, consistent with cyclization of **3**. (5) As mentioned, the product **3** reverted readily to **2** under a variety of conditions (neutral, acidic, and weakly basic), as formulated for **3** in eq 1.

The dioxide **5** should lead to a product with a thiol quite different from **3** in ease of reconversion to the dioxide, since this product would not be constrained into the coplanar arrangement that seems to be the root of trouble with **3**. First, we attempted to prepare dioxide **5** according to a sequence developed by Lüttringhaus and Hägele (eq 3).[7] We were able to prepare **4** in 83% yield (lit.[7] 84%), but oxidation with *m*-chloroperbenzoic acid under a variety of conditions gave very low yields (*ca.* 4%) of **5**. Fortunately, in light of a report that a sulfide can be oxidized to a sulfone by so-



4 **5** (3)

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[1] (a) Paper 35: Y. H. Khim and L. Field, *J. Org. Chem.*, **37**, 2714 (1972). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DADA 17-69-C-9128.

[2] L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 1792 (1969).

[3] *Cf.*, for example, A. Schöberl and H. Gräfje, *Justus Liebigs Ann. Chem.*, **614**, 66 (1958).

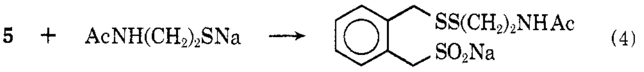
[4] *Cf.* earlier papers in this series for other such uses of this compound as a model.

[5] A. Zweig and A. K. Hoffmann, *J. Org. Chem.*, **30**, 3997 (1965).

[6] (a) L. Ackerman, *Ind. Eng. Chem., Anal. Ed.*, **18**, 243 (1946); (b) J. Thomas, *J. Chem. Soc.*, **95**, 342 (1909).

[7] A. Lüttringhaus and K. Hägele, *Angew. Chem.*, **67**, 304 (1955).

dium metaperiodate in refluxing methanol,[8] we have been able recently to oxidize *trans*-1,2-dithiane-4,5-diol diacetate to the corresponding dioxide by use of potassium metaperiodate in aqueous isopropyl alcohol with iodine as a catalyst.[9] Dioxide **5** could be obtained in 60% yield by oxidizing a solution of **4** by essentially the latter procedure. This dioxide (**5**) then was cleaved with the sodium salt of the thiol **1** to give disulfide sulfinate **6** in 73% yield (eq 4). The ir spectrum was consistent with structure **6**.

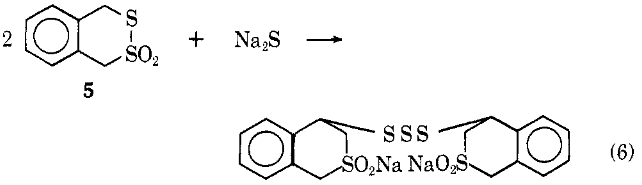


6

Recently the trisulfide **7** was prepared as a highly hygroscopic salt that forms a dihydrate (eq 5).[10] Promising activity of **7** as an antiradiation drug is noteworthy, since **7** does not contain a nitrogen function.[10] Hence we were tempted to prepare the corresponding trisulfides **8** and **10** from dioxides **5** and **9** using Na_2S as a nucleophile. For synthesis of **8** (eq 6), a solution of

$$2\,\overline{O_2S(CH_2)_4S} + Na_2S \longrightarrow [NaO_2S(CH_2)_4S]_2S \qquad (5)$$

7



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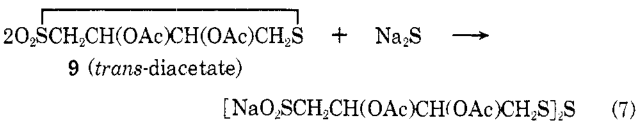

$$2\,\overline{O_2SCH_2CH(OAc)CH(OAc)CH_2S} + Na_2S \longrightarrow [NaO_2SCH_2CH(OAc)CH(OAc)CH_2S]_2S \qquad (7)$$

9 (*trans*-diacetate)

10

Na_2S was added slowly to one of the dioxide **5**; the pH of the mixture went below 7 at first but finally became *ca.* 7. Addition of a large amount of ether then precipitated **8** (84%), which was purified by reprecipitation. A similar procedure gave **10** in 90% yield (eq 7), possibly as a mixture of two diastereoisomers.

It is worth adding that most of the sulfinate salts discussed (**3**, **8**, and **10**) are quite hygroscopic and acquire enough moisture during ordinary handling to give hydrates (without contact with water *per se*, except possibly from $Na_2S \cdot 9H_2O$). Only **6** gave no such problem. Hydration, combined with the difficulty of purifying sensitive salts that presumably both cyclize and disproportionate readily, precluded fully satisfactory elemental analyses in several instances. Unfortunate also was the fact that nmr was of little help in confirming structures of disulfides because changes of the spectrum occurred during observation. Infrared spectra, however, as well as the very fact of conversion of starting materials to highly water-soluble salts in each instance, reassured us as to the identity of **3**, **6**, **8**, and **10**.

Experimental Section[11]

Sodium 8-(2-Acetamidoethyldithio)naphthalene-1-sulfinate (3).—Naphtho[1,8-*cd*]-1,2-dithiole 1,1-dioxide (**2**) was prepared essentially by the procedure of Zweig and Hoffmann.[5] 1-Aminonaphthalene-8-sulfonic acid (60 g) was diazotized using 30 g of $NaNO_2$. The solid diazonium sulfonate obtained, treated with aqueous Na_2S_2, gave 47 g (67%) of crude disodium 8,8′-dithiodi-(1-naphthalenesulfonate). This material was dried and powdered, and, in our modification, was treated with 30 g (0.14 mol) of PCl_5, added slowly so that the reaction mixture did not rise above −5°; any higher temperature led to much lower yields. This mixture was allowed to warm to *ca.* 25° and then to stand for 5 hr. It was then extracted with benzene, as usual.[5] The extracts were concentrated, and the residue was taken up in hot MeOH and treated with charcoal. Cooling gave 7 g (17%) of **2** as pale yellow needles, mp 148–149° (lit.[5] mp 148–149°); **2** had ir maxima at 1110 and 1290 cm^{-1} ($-SO_2-$).

For its conversion to **3**, the dioxide **2** (1.11 g, 5.0 mmol) was dissolved in MeOH (100 ml). A solution prepared by dissolving sodium (0.115 g, 5.0 mg-atoms) in MeOH (10 ml) and mixing in 2-acetamidoethanethiol (**1**, 0.59 g, 4.95 mmol)[12] then was added dropwise with stirring during 0.5 hr. Dry acetone then was added until no more precipitate appeared. This solid was separated, and purification was attempted by adding dry ether to a solution in MeOH at 0–5° until no more precipitate formed: yield of **3**, 1.20 g (67%); mp 200–202° dec; ir 3400 (CONH), 3020, 1690, 1630 (CONH), 1580 (CONH), 1540, 1470, 1400, 1000 (SO_2Na), 960, 940, 800, 740, 690 cm^{-1}. *Anal.* Calcd for $C_{14}H_{14}NNaO_3S_3 \cdot H_2O$: C, 44.09; H, 4.19; S, 25.2. Found: C, 44.14; H, 4.13; S, 21.58. The following experiments illustrate the ease with which **3** cyclizes to **2**. (a) When **3** (1.0 g, 2.7 mmol) was dissolved in MeOH (5 ml) and was warmed for *ca.* 5 min at 50°, on cooling and dilution 0.2 g (33%) of **2** was isolated, mp and mmp 147–148°. (b) The salt **3** (1 g, 2.7 mmol) was dissolved in H_2O (100 ml) and HCl was added (pH *ca.* 3). Within *ca.* 3 min, **2** separated. Filtration gave 0.3 g (49%) of **2**, mp and mmp 147–148°.

2,3-Benzodithian (4).[7]—Thiourea (250 mmol), α,α′-dibromo-*o*-xylene (100 mmol), and EtOH (250 ml) were refluxed (6 hr). The EtOH was removed, the residue was dissolved in H_2O (500 ml), and NaOH (16 g) in H_2O (150 ml) was added. After 6 hr of reflux, cooling, acidification, and extraction gave α,α′-dimercapto-*o*-xylene (82%). To this thiol (82.3 mmol) in 200 ml each of MeOH and AcOH, $FeCl_3 \cdot 6H_2O$ (119 mmol) in AcOH (50 ml) was added at 60–70° (1 hr, to a faint color of $FeCl_3$). Removal of MeOH and addition of H_2O gave **4** (83%), mp 78–79° (lit.[7] mp 80°).

2,3-Benzodithian 2,2-Dioxide (5). A. *Via* ***m*-Chloroperbenzoic Acid (*cf.* Ref 7).**—The peracid (29.5 mmol) in $CHCl_3$ was added slowly to **4** (10 mmol) in $CHCl_3$ at 0°. After 4 hr, solvent was removed and excess oxidant was destroyed (aqueous Na_2SO_3). Extraction ($CHCl_3$) left polymer. Concentration, then washing with aqueous $NaHCO_3$, left **5** (4%): mp (from MeOH) 108–109° (lit.[7] mp 108°); ir bands at 1090 and 1280 cm^{-} ($-SSO_2-$).

B. *Via* **Potassium Metaperiodate (KIO_4).**—A solution of **4** (0.84 g, 5.0 mmol) in *i*-PrOH (200 ml) was added to KIO_4 (3.4 g, 14.8 mmol) in H_2O (100 ml) containing a crystal of iodine. The reaction mixture was stirred continuously at *ca.* 80° for 4 hr. The *i*-PrOH then was removed, and the residue was extracted with $CHCl_3$. Removal of $CHCl_3$ gave 0.6 g (60%) of dioxide **5**, which was recrystallized from MeOH, mp 108–109°. This **5** showed ir bands at 1090 and 1280 cm^{-1} ($-SSO_2-$) and was identical with **5** obtained by the oxidation of **4** in A.

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[8] L. L. Replogle and J. R. Maynard, *J. Org. Chem.*, **32**, 1909 (1967).

[9] L. Field and Y. H. Khim, *J. Org. Chem.*, **37**, 2710 (1972).

[10] L. Field and Y. H. Khim, *J. Med. Chem.*, **15**, 312 (1972).

[11] Melting points are corrected. Ir spectra were obtained using KBr pellets and a Beckman Model IR-10 spectrophotometer; bands reported were at least of medium intensity. Tlc spots were obtained using Brinkmann F-254 sheets of silica gel (0.25 mm) on aluminum and were developed by exposure to I_2 vapor in a sealed container. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Moist extracts ordinarily were dried over anhydrous $MgSO_4$, and solvent then was removed using a rotating-flask evaporator. Yields of materials which became hydrated were calculated on an anhydrous basis, since the point at which water was acquired was uncertain.

[12] R. Kuhn and G. Quadbeck, *Chem. Ber.*, **84**, 844 (1951).

Sodium [2-(2-Acetamidoethyldithiomethyl)phenyl]methanesulfinate (6).—Sodium (460 mg, 20 mg-atoms) dissolved in MeOH (20 ml) was added dropwise to a mixture of 5 (4.00 g, 20.0 mmol) and 1 (2.38 g, 20.0 mmol) in MeOH (50 ml) with stirring at *ca.* 25°. After addition was complete (*ca.* 10 min), dry Et_2O (*ca.* 500 ml) was added to the reaction mixture until no more precipitate appeared. Solvent was decanted, and the white precipitate was redissolved in MeOH (10 ml) and reprecipitated with dry Et_2O. Decantation and drying at 0.1 mm for 24 hr at 25° gave 5.00 g (73%) of white 6, mp 110–112° dec. Tlc showed one spot (1:1 MeOH:Me_2CO); ir 3400, 1650, 1530, 1010, 960, and 750 cm^{-1}. Additional tlc spots appeared a few minutes after dissolution of 6 in H_2O or (more slowly) MeOH.

Anal. Calcd for $C_{12}H_{16}NNaO_3S_3$: C, 42.22; H, 4.69; N, 4.10; S, 28.15. Found: C, 42.33; H, 4.65; N, 3.74; S, 27.95.

Disodium 2,2′-(Trithiodimethyl)bis(phenylmethanesulfinate) (8).—A solution of commercial $Na_2S \cdot 9H_2O$ (1.5 mmol) in MeOH (5 ml) was added slowly to the dioxide 5 (0.60 g, 3.00 mmol) in MeOH (25 ml) at 0–5° with good stirring during 30 min. After the addition was complete (the pH then was 7), the reaction mixture showed only one spot for 8 by tlc (1:1 MeOH:Me_2CO) and none for 5. Addition of Et_2O (600 ml) at 0° gave a white precipitate. Most of the solvent was decanted, after which drying at 0.1 mm gave 0.60 g (84%) of white 8, mp 192–194° dec. This 8 was dissolved in a little MeOH, and a small amount of dry Et_2O was added until a cloudy precipitate began to appear. A colorless, clear solution then resulted upon removal of the small amount of precipitate by centrifugation as quickly as possible. Dry Et_2O again was added to this solution until appearance of a white precipitate was complete. Decantation and drying at 0.1 mm for 24 hr at *ca.* 25° gave 0.50 g (70%) of 8, mp 192–194 dec. Tlc showed one spot (1:1 MeOH:Me_2CO); ir 3400 (H_2O), 1640 (H_2O), 1010 and 970 (very strong, SO_2^-), and 760 cm^{-1}. Additional tlc spots appeared a few minutes after dissolution of 8 in H_2O or (more slowly) MeOH.

Anal. Calcd for $C_{16}H_{16}Na_2O_4S_5 \cdot 3H_2O$ (dried at 25°): C, 36.09; H, 4.13; S, 30.07. Found: C, 36.28, 36.36; H, 4.24, 4.40; S, 29.60, 29.45.

Drying to constant weight (100° overnight) gave hygroscopic, anhydrous 8.

Anal. Calcd for $C_{16}H_{16}O_4S_5Na_2$: C, 40.17; H, 3.34; S, 33.47. Found: C, 39.42; H, 3.81; S, 31.66.

When the analyst kindly exposed anhydrous 8 for *ca.* 2 days to ambient air and then redried, the weight loss was 10.64% (calcd for $8 \cdot 3H_2O$, 10.13%).

Disodium 4,4′-Trithiobis(*threo*-2,3-diacetoxybutanesulfinate) (10).—A solution of $Na_2S \cdot 9H_2O$ (3.6 mmol) in MeOH (20 ml) was added dropwise to the *trans*-diacetate dioxide 9 (2.00 g, 7.46 mmol)[13] in MeOH (50 ml) at 0–5° with good stirring. After addition was complete (the pH then was *ca.* 7), the reaction mixture showed one spot for 10 by tlc (1:1 MeOH:Me_2CO). Addition of Et_2O (500 ml) at 0° gave a white precipitate. As with 8, the 10 was redissolved in a little MeOH and a little dry Et_2O was added until a precipitate began to appear. Centrifugation as quickly as possible again removed a little solid and left a clear solution. Dry Et_2O was added to this solution until appearance of a white precipitate was complete. Decantation and drying at 0.1 mm for 24 hr at 25° gave 2.0 g (90%) of 10, mp 178–180° dec. Tlc showed one spot (1:1 MeOH:Me_2CO); ir 3440 (H_2O), 1730, 1620 (H_2O), 1380, 1220, 1030 (broad), 950 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}Na_2O_{12}S_5 \cdot H_2O$: C, 30.37; H, 4.11; S, 25.31; H_2O, 2.84. Found: C, 29.80; H, 4.19; S, 26.19; H_2O, 3.15.

Drying to constant weight (100° overnight, then 120°) of a sample moderately dried for the foregoing analysis removed only 1.02% H_2O.

Anal. Calcd for $C_{16}H_{24}O_{12}S_5Na_2$: C, 31.27; H, 3.90; S, 26.05. Found: C, 29.85, 29.75; H, 4.04, 4.24; S, 26.40, 26.36.

Registry No.—3, 36540-20-2; 6, 36540-21-3; 8, 36540-22-4; 10, 36540-23-5.

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(13) We are indebted to Dr. Y. H. Khim for the preparation of 9, as reported by L. Field and Y. H. Khim in ref 9.

Preparation of Orthocarbonates from Thallous Alkoxides and Carbon Disulfide

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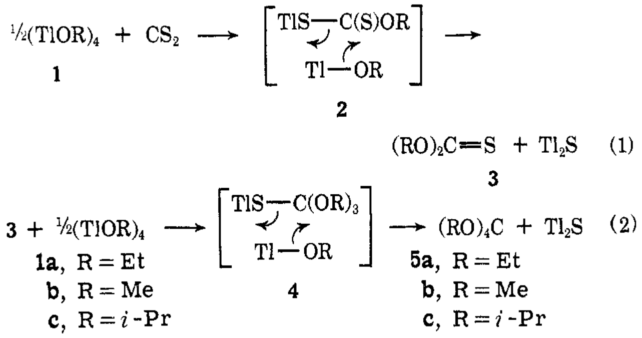
During our studies on new types of orthocarbonate syntheses from organometallic alkoxides and carbon disulfide,[2,3] Lee reported that dimethylthallium alkoxide reacted with carbon dioxide, carbon disulfide, and sulfur dioxide to form insertion products across the thallium(III)–oxygen bond.[4] Although insertion reactions of heterocumulenes are well known for R_3SnOR[5] and other organometallic alkoxides, the syntheses of orthocarbonates could be realized only in the case of the reactions of bis(trialkyltin) glycolates[2] and dialkyltin dialkoxides[3] with carbon disulfide.

In this note, we report the reaction of thallium(I)–oxygen compounds with carbon disulfide and dioxide, and show a new type of utilization of thallous alkoxides for orthocarbonate syntheses.

Thallous ethoxide reacted with an equimolar amount of carbon disulfide in dry methylene dichloride to afford tetraethyl orthocarbonate in 97% yield. The orthocarbonate formed was identified by comparison with the melting point and ir and nmr spectra of an authentic sample.[3] Tetramethyl orthocarbonate was also obtained in good yield by the reaction of thallous methoxide with carbon disulfide.

Furthermore, when thallous ethoxide was treated with an excess of carbon disulfide, the ir spectrum of the reaction mixture indicated the presence of a small amount of diethyl thioncarbonate. Consequently, the reaction scheme may be formulated by eq 1 and 2, as in the reactions of dialkyltin dialkoxides with carbon disulfide.[2]



The adducts of carbon disulfide with trialkyltin alkoxides[5] [$R_3SnSC(S)OR'$], dimethylthallic alkoxide, and thallous phenoxide[4,6] were found to be stable at room temperature, while the adducts of thallous alkoxides are unstable and decomposed to give thioncarbonates, 3, or orthocarbonates, 5. These results are in-

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(1) Department of Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu, 430 Japan.

(2) S. Sakai, Y. Kiyohara, K. Itoh, and Y. Ishii, *J. Org. Chem.*, **35**, 2347 (1970).

(3) S. Sakai, Y. Kobayashi, and Y. Ishii, *ibid.*, **36**, 1176 (1971).

(4) A. G. Lee, *J. Chem. Soc. A*, 467 (1970).

(5) A. G. Davies, *Synthesis*, 56 (1969); *J. Chem. Soc. C*, 1309, 1313 (1967).

(6) A. G. Lee, *Organometal. Chem. Rev., Sect. B*, 310 (1970).