Methods in Selenium Chemistry. II. Bis(methoxymagnesium) Diselenide, a Novel Reagent for the Introduction of Selenium into Organic Molecules[1,2]

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The reaction of magnesium and selenium in methanol yields a reagent, tentatively described as bis(methoxymagnesium) diselenide, suitable for the direct introduction of the diselenide moiety into organic molecules by nucleophilic displacement reactions on halides and γ-lactones. In combination with morpholine the reagent converts benzaldehyde into dibenzyl diselenide.

Many laboratory methods for the introduction of selenium into organic molecules are based upon conversion of the element into a nucleophilic species which is then capable of displacing a suitable active leaving group. This can be accomplished through the intermediate formation of a variety of inorganic selenium compounds such as hydrogen selenide, potassium selenocynate,[4-6] potassium selenosulfate,[7,8] or of compounds carrying a protective organic group such as benzyl selenol[9] or selenourea.[10] In all these cases a separate preparative step is frequently required to remove the protecting group. To eliminate this extra effort, a number of procedures have been devised which lead directly from elemental selenium to alkylselenols or to the closely related diselenides. Instances are the reaction of selenium with Grignard reagents[11] or the use of selenium dissolved in strong alkali[5] or of selenium solutions in aqueous Rongalite.[12] A very elegant method[13] consists in reacting elemental selenium and metallic sodium in liquid ammonia giving a reagent which, on alkylation, affords the corresponding diselenides in a single step. The possible disadvantages of work in liquid ammonia are the high reactivity of the solvent and the comparatively low temperatures at which the reactions have to be carried out. It has now been found that powdered selenium and magnesium shavings, "activated" by iodine and suspended in absolute methanol, react vigorously to give a dark brown clear solution which can similarly be employed to produce diselenides directly from the corresponding halides. Reaction with α-chlorotoluene, for instance, gives dibenzyl diselenide (I) in good yield and from 2-bromoethylamine the corresponding bis(2-aminoethyl) diselenide ("selenocystamine," III)[4,8,14] is obtained without the necessity of protecting the amino group. The new reagent is also capable of nucleophilic attack on the γ-carbon of lactones such as γ-butyrolactone or phthalide, giving 4,4′-diselenodibutyric acid (IV) and α,α′-diselenodi-*o*-toluic acid (V), respectively. The latter compound was difficult to purify, giving consistently low selenium values in the elemental analysis. It was, therefore, converted into 2-selenophthalide[15] by heating with hypophosphorous acid in a reaction similar to the procedure used to prepare selenobutyrolactone[2] from 4,4′-diselenodibutyric acid. Reaction of the selenophthalide with *n*-butylamine in the presence of oxygen gave the corresponding N,N′-*n*-butyl-α,α′-diselenodi-*o*-toluamide (VII) as a further derivative.

Reactions in which a selenium nucleophile displaces the ester oxygen of lactones have been reported before; thus, sodium methylselenolate reacted with α-amino-γ-butyrolactone to yield the selenium analog of methionine,[16] 4,4′-diselenodibutyric acid was obtained from γ-butyrolactone and potassium selenosulfate in aqueous medium,[2] and sodium benzylselenolate has been shown to give the corresponding benzylselenoalkylcarboxylic acids from a number of β-, γ-, and δ-lactones.[17,18] Except for β-lactones, which react very readily, fairly high reaction temperatures had to be employed to get reasonable yields of products, while the present reaction proceeds readily in refluxing methanol.

In addition to these nucleophilic displacement reactions, which could be expected from any reagent containing diselenide anions, the direct conversion of an aldehyde into a dialkyldiselenide has also been observed. When an equimolar mixture of benzaldehyde and morpholine was treated with a reagent prepared from 2 equiv of magnesium and 1 equiv of selenium, an excellent yield of dibenzyl diselenide was obtained. A similar reaction in the absence of the amine failed to produce the diselenide; a number of evil-smelling products have not yet been identified.

Reactions of aldehydes with polysulfides or sulfur in the presence of morpholine are well known[19] to yield thiocarboxylic acid morpholides and a similar formation of selenobenzomorpholide (II) was originally expected here. This compound has recently been obtained[20] from O-methyl selenobenzoate[21,22] and morpholine but it could not be detected in the present reaction.

Little is known, at this point, about the nature of the new diselenide reagent. When the amount of hy-

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(2) Paper I in this series: W. H. H. Günther, *J. Org. Chem.*, **31**, 1202 (1966).

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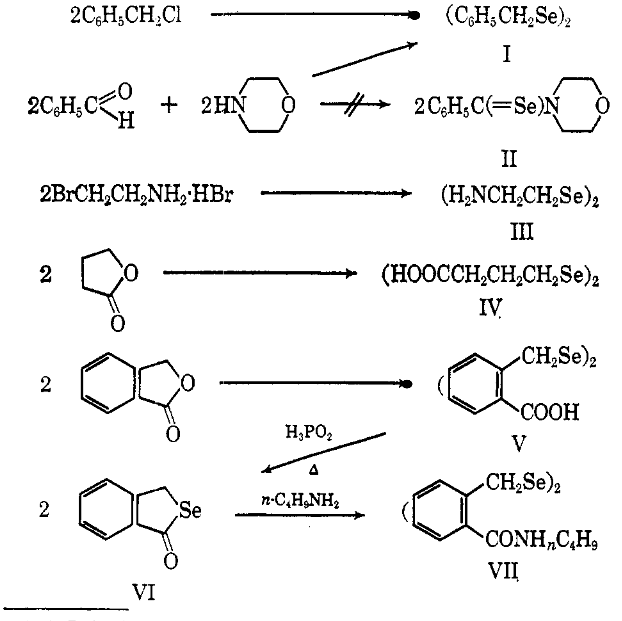
drogen evolved from a mixture of equal gram-atoms of magnesium and selenium in methanol was compared to the hydrogen produced in the absence of selenium, a ratio of 0.735:1.0 was found, indicating that three molecules of methanol had reacted with two atoms each of magnesium and selenium. This stoichiometry does not appear to satisfy any of the simple valence rules which could be applied to the elements involved here. On slow cooling the reagent solution deposited large, sepia crystals which were insoluble in ethanol, ether, or acetone but which formed brown solutions in methanol, ethylene glycol, methylene chloride, or chloroform. Decomposition of the dissolved material with formation of elemental selenium occurred very readily, however, in the presence of oxygen and moisture. The elemental composition of the crystalline product gave an empirical formula of $C_3H_{11}O_3Se_{1.1}Mg$ which indicated that at least a portion of the reagent has the structure of a bis(methoxymagnesium) diselenide which contains four molecules of methanol of crystallization. The high selenium value may be due to the presence of triselenide chains which are known to be formed readily as contaminants of most diselenides. Attempts to remove the solvent of crystallization by heating in a stream of nitrogen lead to decomposition of the product and formation of a volatile material with an extremely disagreeable odor. When the escaping gases were passed through a solution of mercuric chloride, a solid adduct precipitated. Only a portion of this was crystallizable from ethanol, giving a final melting point of 151–152° dec. Dransfield and Challenger[23] quote 152–153° as the melting point for the mercuric chloride adduct of dimethyl selenide. A considerable portion of the initial precipitate could not be dissolved in ethanol and this portion of the product was not identified further.

It is interesting to note that, similar to the reduction of only diselenides with hypophosphorous acid,[2] the reaction of selenium with magnesium and methanol to give diselenide ions appears to be specific to this member of the chalcogen family (Scheme I). Tellurium powder did not react under the same conditions and sulfur was completely reduced to hydrogen sulfide. Selenium also appeared to be inert to combinations of magnesium with higher alcohols or to aluminum granules, activated with mercuric chloride, in methanol or ethanol.

SCHEME I
REACTIONS WITH BIS(METHOXYMAGNESIUM)
DISELENIDE IN METHANOL



Experimental Section

Preparation of Bis(methoxymagnesium) Diselenide Reagent.—Magnesium turnings (3.0 g, 0.125 g-atom) contained in a 1-l. round-bottom flask were "activated" by heating them over a gas flame with a small crystal of iodine. Dry methanol (150–250 ml) was then added and the flask fitted with a reflux condenser and a magnetic stirrer. When the reaction between magnesium and methanol had started and after the yellow iodine color had been discharged, dry selenium powder (7.9 g, 0.1 g-atom) was added and the mixture stirred until the initial vigorous reaction had ceased and all solids had gone into solution. This takes from 15 to 30 min.

Solutions prepared by this method were routinely used for the synthetic experiments outlined below. When the dark brown solution (about 150 ml) was kept at room temperature for 2 days, large chunky crystals (10.5 g) had deposited. These were collected, rinsed with absolute methanol and ether, and analyzed without recrystallization.

Anal.[24] Calcd for $C_6H_{22}O_6Se_2Mg_2$: C, 18.16; H, 5.59; Se, 39.80; Mg, 12.25. Found: C, 17.51; 17.91; H, 5.60; 5.80; Se, 42.62; Mg, 11.92.

The evolution of hydrogen in the reaction of equiatomic proportions of magnesium and selenium with excess methanol was monitored and compared with the amount of gas given off by the reaction in the absence of selenium. The ratio of Mg–Se–MeOH/Mg–MeOH = 0.735 ± 0.03 (average of six determinations).

Dimethyl Selenide.—Crystalline bis(methoxymagnesium) diselenide (2.0 g, 0.01 equiv of Se) was calcined by heating over an open flame in a stream of nitrogen. The escaping gases were passed through an aqueous solution of mercuric chloride (200 ml of 5% $HgCl_2$) and the cream precipitate (3.05 g, 80%, of $(CH_3)_2Se\cdot HgCl_2$; mp 120–124°) recrystallized from absolute ethanol to raise the melting point to 151–152° (lit.[23] mp 152–153° for the mercuric chloride adduct of dimethyl selenide). A large portion (*ca.* 90%) of the initial precipitate did not readily dissolve in ethanol and was not further identified.

Dibenzyl Diselenide (I). 1.—Benzyl chloride (12.6 g, 0.1 mole) was dropped slowly (15 min) into a stirred solution of the magnesium diselenide reagent (from 0.1 g-atom of Se). When the reddish brown color of the solution appeared discharged (5–10 min), water (200 ml) and concentrated hydrochloric acid (10 ml) were added, the solution was cooled, and the dark product was collected by filtration. The solid was recrystallized from ethanol to give yellow crystals (14.0 g, 82%); mp[25] 94°) with an infrared spectrum identical with that of an authentic sample of dibenzyl diselenide.

2.—To a magnesium diselenide reagent prepared from 0.1 g-atom of Se and 0.2 g-atom of Mg was added a mixture of benzaldehyde (10.6 g, 0.1 mole) and morpholine (8.3 g, 0.1 mole). The mixture was heated under reflux, with stirring, for about 18 hr, then water (200 ml) and hydrochloric acid (20 ml of 12 *N*) were added and the product was extracted with ether. The yellow ethereal solution was washed with dilute hydrochloric acid, aqueous sodium bicarbonate, and water, dried over anhydrous sodium sulfate, and evaporated to dryness. The yellow residue was recrystallized from ethanol or petroleum ether (bp 30–60°) to give dibenzyl diselenide (13.5 g, 79%), identical in all respects with an authentic sample.

Bis(2-aminoethyl) Diselenide (III).—To the magnesium diselenide reagent (0.1 equiv) was added, with stirring, a solution of 2-bromoethylamine hydrobromide (20.4 g, 0.1 mole) in methanol (50 ml). In the resulting exothermic reaction the color of the solution became much lighter and some solid precipitated. The solution was heated under reflux for 30 min, the methanol evaporated under reduced pressure, water and sodium hydroxide were added, and the yellow product was extracted continuously with ether. The ether solution was reextracted with 2 *N* hydrochloric acid and the aqueous layer evaporated under reduced

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[23] P. B. Dransfield and F. Challenger, *J. Chem. Soc.*, 1153 (1955).

[24] Microanalyses were carried out at the Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

[25] All melting points are uncorrected.

pressure to yield bis(2-aminoethyl) diselenide dihydrochloride (8.8 g, 55%; mp 179° dec). The compound had an infrared spectrum identical with that of an authentic sample.[14]

4,4'-Diselenodibutyric Acid (IV).—The selenium–magnesium reagent (0.1 equiv) was heated for 20 hr under reflux with butyrolactone (10.1 g, 0.12 mole). The solvent was then evaporated, water added, and the acidified solution extracted with ether. The yellow ether solution was reextracted with sodium hydroxide and the 4,4'-diselenodibutyric acid (11.0 g, 66%; mp 84–86°) precipitated by addition of hydrochloric acid. The dried product was recrystallized from carbon tetrachloride to give platelets, mp 88°, which had an infrared spectrum identical with that of an authentic sample.

α,α'-Diselenodi-*o*-toluic Acid (V).—Phthalide (13.4 g, 0.1 mole) was heated for 20 hr under reflux and stirring with the selenium–magnesium reagent (from 0.1 g-atom of Se). The clear supernatant liquid was then decanted and discarded and the dark solid was shaken with water (300 ml) and hydrochloric acid (30 ml of 12 *N*) until it was thoroughly dispersed. The crude product was collected by filtration, dissolved in 2 *N* aqueous sodium hydroxide, and aerated until precipitation of selenium appeared complete. Elemental selenium was removed by filtration with Celite and the clear, orange filtrate acidified with hydrochloric acid. The yellow precipitate of α-α'-diselenodi-*o*-toluic acid (18 g, 82%; mp 215–218°) was collected and dried over phosphorous pentoxide. For analysis a sample was recrystallized from ethanol. The compound dissolves very slowly in boiling ethanol and crystallizes over a period of days; the melting point was not changed by this treatment.

Anal. Calcd for $C_{16}H_{14}O_4Se_2$: C, 44.88; H, 3.30; Se, 36.88. Found: C, 44.77; H, 3.47; Se, 35.14.

Discrepancy in the selenium values necessitated the preparation of the two derived compounds given below.

2-Selenophthalide (VI).—α,α-Diselenodi-*o*-toluic acid (10.7 g, 0.05 mole) and 50% aqueous hypophosphorous acid (8 ml) were heated together in a 250-ml erlenmeyer flask on an electric hot plate until the water had evaporated and a sudden vigorous reaction set in. The yellow product was dissolved in ether and passed through a column of activated alumina (Woelm, neutral, activity grade I). The colorless effluent was evaporated to dryness and the residue crystallized from petroleum ether (bp 36–55°) to give colorless scales of 2-selenophthalide (6.7 g, 62%), mp 56.5–58° (lit.[15] mp 58°).

Anal. Calcd for C_8H_6OSe: C, 48.75; H, 3.07; Se, 40.06. Found: C, 48.99; H, 3.10; Se, 40.09.

N,N'-*n*-Butyl-α,α-diselenodi-*o*-toluamide (VII).—2-Selenophthalide (2.0 g, 0.01 mole) was dissolved in ethanol (25 ml) and *n*-butylamine (2 ml) added. The reaction was allowed to proceed in an open flask overnight; water was then added until crystallization set in to give yellow needles of VII (2.7 g, quantitative yield), mp 144–146°.

Anal. Calcd for $C_{24}H_{32}N_2O_2Se_2$: C, 53.53; H, 5.99; N, 6.20. Found: C, 53.45; H, 5.90; N, 6.16.

Registry No.—I, 1482-82-2; III, 3542-13-0; IV, 14362-48-2; V, 10352-20-2; VII, 14310-08-8; bis(methoxymagnesium) diselenide, 14310-09-9.

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Methods in Selenium Chemistry. III.[1,2]
The Reduction of Diselenides with Dithiothreitol

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The interaction of aliphatic diselenides and dithiothreitol in aqueous solution leads to the quantitative formation of selenols. A new ultraviolet absorption peak in the 243–253-mμ range is attributed to the aliphatic selenol anion.

Selenols are readily oxidized to the corresponding diselenides upon exposure to atmospheric oxygen. In addition they are extremely powerful hydrogen donors capable of reducing disulfides, sulfoxides, and aromatic azo compounds[1] as well as other mild oxidizing agents such as 2,4-dichlorophenolindophenol.[4] Chemical or biological work with dilute solutions of organic selenols must, therefore, be carried out with the strict exclusion of air and this limitation has frequently prevented the accumulation of accurate data. Diselenides, on the other hand, are relatively stable compounds that can be prepared conveniently by the oxidation of selenols[5] or from other suitable intermediates, such as selenocyanates,[5] or selenosulfate Bunte salts.[6] In aqueous solution diselenides are conveniently converted to selenols by reaction with sodium borohydride[6] under alkaline conditions, or with hypophosphorous acid[1] if an acidic medium is preferred. In both cases the progress of the reaction can be followed by measuring the disappearance of the low intensity ultraviolet absorption peak near 300 mμ which is characteristic of aliphatic diselenides[7] or, in preparative work, by observing the disappearance of the yellow color in the solution. Quantitative determinations of diselenides based on ultraviolet absorption are, however, quite unsatisfactory if the molar concentration is lower than 10^{-3}. A more sensitive assay for diselenides is based on the observation[8] that iodine in the presence of bicarbonate buffer converts diselenides into the corresponding seleninic acids and that this reaction is reversed upon acidification of the solution, allowing the liberated iodine to be determined by standard procedures. A variation of this latter method has been used to detect small amounts of selenols, diselenides, and monoselenides on paper and thin layer chromatograms.[9] The recent observation[10] that dithio-

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[1] Papers I and II in this series: W. H. H. Günther, *J. Org. Chem.*, **31**, 1202 (1966); **32**, 3929 (1967).

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[10] W. H. H. Günther and H. G. Mautner, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, C-78.