**Table I. Product Yields and Direct vs. Intrachain Cyclization Ratios**

| Leaving group X | Yield % product[a] 1 | 2 | 3 | 4 | Ratio (1 + 3/2 + 4) |
|---|---|---|---|---|---|
| Br | 14.83 | 0 | 3.09 | 2.42 | 7.46 |
| Cl | 7.92 | Trace | 0.88 | 4.31 | 2.05 |

[a] Based on direct addition of 0.5 M ethylene halide–ethanol solution to 0.5 M 3-thiapentane-1,5-dimercaptide–ethanol solution under nitrogen. Reactants maintained below 5 °C for reaction duration; column chromatographic isolation.[1]

conveniently improved by use of high dilution conditions, which were investigated over a 50-fold dilution range.

The change in reaction course from a slight modification of reactants and conditions is consistent with our earlier observations[1] that leaving group, solvent polarity, and temperature could have a critical effect on intrachain cyclization, by which **1** and **3** arise, in competition with direct cyclization leading to the intended products **2** and **4**. The results in Table I illustrate the effect of leaving group on cyclization. The intrachain cyclization process is enhanced by better leaving group, by virtue of lower nucleophilicity of the chain-interior thia function relative to the ω-mercaptide function which affords direct cyclization. Thus the lesser polarizability of chloro relative to bromo leaving group could represent the boundary at which the enthalpy of nucleophilic displacement by mercaptide and thia functions, respectively, is sufficiently differentiated as to significantly diminish the difference in total enthalpy for formation of the six- and nine-membered ring systems.

However, two additional observations suggest that formation of **2** might in fact be due to a fortuitous solvation effect of ethanol media at a particular stage in the two-step cyclization process. The reaction of 1,5-dichloro-3-thiapentane with the dimercaptide of ethanedithiol should give rise to the same intermediate, and therefore **2**, as could be postulated in the present experimental design. As previously noted, **2** was not observed from these reactants in butanol media,[1] nor when subsequently investigated in ethanol media. Secondly, the use of less polar butanol media was found in all previous cases to inhibit intrachain cyclization and enhance direct cyclization relative to linear polymerization with better leaving groups than chloride. This observation also held true when chloride was displaced from 1,11-dichloro-3,6,9-trithiaundecane by 3-thiapentane-1,5-dimercaptide to yield macrocycle **4**.[1] Thus the results in Table I are anomalous with respect to the usual solvent effect.

## Experimental Section

**General.** Nuclear magnetic resonance spectra were obtained on a Varian Associates T-60 NMR, $Me_4Si$ as internal reference. Infrared spectra were recorded on a Perkin-Elmer 283 infrared spectrometer. Molecular weights were determined with a Hitachi Perkin-Elmer 115 vapor pressure osmometer. Column chromatography was performed on Baker's Analyzed silica gel (60–200 mesh) and HPL chromatography was carried out with a Waters Associates 660 solvent programmable chromatograph. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. All other general experimental details were as reported earlier.[1]

**1,4,7-Trithiacyclononane (2).** To a sodium ethoxide solution generated and maintained under a nitrogen atmosphere by dissolving sodium (8.0 mol) in 4 L of ethanol was added all at once 605.2 g (3.93 mol) of 3-thiapentane-1,5-dithiol.[1] The solution was allowed to equilibrate for 1 h, then cooled and maintained below 5 °C for the duration of the reaction. To the mercaptide solution was added 385.1 g (3.93 mol) of ethylene chloride in dropwise fashion. After 3 days of efficient stirring, the reaction mixture was filtered cold and filtrate concentrated. The filter cake was air dried, powdered, loosely packed in a 8 × 30 cm column, and leached by elution of 5 L of hexane–ethyl acetate, 80:20 volume ratio solvent. The leaching concentrates and original reaction filtrate concentrates were combined as a 1-L solution of methylene chloride, washed with two 500-mL portions of 5% sodium hydroxide, dried with sodium sulfate, and reconcentrated to yield 87.5 g of white solid residue. TLC analysis by comparison to authentic samples on silica gel H with 4% ethyl acetate–hexane revealed in descending order *p*-dithiane **1**, traces of unreacted dithiol, substantial quantities of 1,4,7,10,13,16-hexathiacyclooctadecane (**4**), and finally higher polymers. The 1,4,7,10-tetrathiacyclododecane (**3**) is highly insoluble and may be leached directly from the filter cake as previously described.[1] Only at very high plate loading could an additional component be detected immediately following unreacted dithiol. The 87.5 g of residue was dispersed on 400 g of sand and loaded onto a 6 × 70 cm silica gel column. Elution with hexane yielded all of **1** and a portion of the unreacted dithiol in the first 2.6 L of eluent. The first traces of **4** did not appear until an additional 2.8 L of hexane was eluted. This void fraction was concentrated and yielded 0.630 g of oil. TLC analysis established the oil to be only unreacted dithiol and the presumed trithia macrocycle **2**. No additional **2** in the presence of **4** could be detected in further column aliquots. The 0.630 g oil residue was taken up in 150 mL of hexane and filtered hot with three consecutive 0.3-g portions of charcoal. Cooling overnight at −20 °C deposited 283 mg (0.04%) of fine white crystals, mp 81–82 °C.[6] Further recrystallizations from hexane had no effect on the melting point. The data obtained are consistent with the structure assigned **2**: NMR ($CDCl_3$) s, δ 3.08 (500-Hz sweep width) and in expansion mode m, $J \sim 0.2$ Hz (25-Hz sweep width); mol wt (in benzene), calcd 180.35, found 178 ± 1; IR (KBr) (s) 2922, (s) 2896, (w) 2805, (s) 1455, (m) 1408, (s) 1414, (s) 1420, (m) 1295, (s) 1283, (w) 1183, (s) 1135, (w) 1125, (m) 920, (s) 875, (m) 837, (s) 822, (w) 669, (w) 617, (w) 410.

Anal. Calcd for $C_6H_{12}S_3$: C, 39.95; H, 6.71; S, 53.33. Found: C, 39.60; H, 6.75; S, 53.55.

**Acknowledgment.** This research was supported by the National Institute of General Medical Sciences under Grant GM-20424.

**Registry No.**—**1**, 505-29-3; **2**, 6573-11-1; **3**, 25423-56-7; **4**, 296-41-3; 3-thiapentane-1,5-dithiol, 3570-55-6; ethylene chloride, 107-06-2; ethylene bromide, 106-93-4.

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(6) The previously reported melting point of 113 °C from ethanol, ref 4, is only 1 °C from the long-established value for compound **1**. Compound **2** failed to crystallize from ethanol.

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# Convenient and General Method for Aliphatic and Aromatic Selenonester and N-Mono- and N,N-Disubstituted Selenoamide Synthesis

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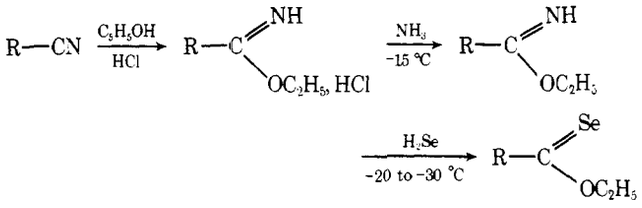
Selenonesters have been prepared by the treatment of arylethynylselenoate salts with alcohols,[1] or by addition of hydrogen selenide to imidoester or its hydrochloride,[2,3] or a less direct method.[4] These preparations are either not general, or require restrictive conditions or, in some cases, reagents that

**Table I. Aliphatic and Aromatic Selenonesters R-CSeOC$_2$H$_5$**

| Registry no. | | R | Bp, °C | Yield, % |
|---|---|---|---|---|
| 62448-73-1 | 1 | $CH_3$[a] | 129 | 26 |
| 62448-74-2 | 2 | $C_2H_5$[a] | 147 | 34 |
| 62448-75-3 | 3 | $CH_3CH_2CH_2$[a] | 46[10] | 46 |
| 62448-76-4 | 4 | $(CH_3)_2CH$[a] | 41[8] | 48 |
| 62448-77-5 | 5 | $CH_3(CH_2)_3$[a] | 60[9] | 57 |
| 62448-78-6 | 6 | $CH_3(CH_2)_4$[a] | 66[10] | 60 |
| 57444-31-2 | 7 | $C_6H_5CH_2$ | 105[2] | 80 |
| 57701-22-1 | 8 | $C_6H_5$ | 106[9] | 86 |
| 62448-79-7 | 9 | $p$-$CH_3C_6H_4$[a] | 105[8] | 90 |

[a] New compounds.

are not readily available. We wish to describe a method for the preparation of aliphatic and aromatic selenonesters via the imidoesters, which, in turn, are conveniently prepared from addition of ethanol to different nitriles.[5]



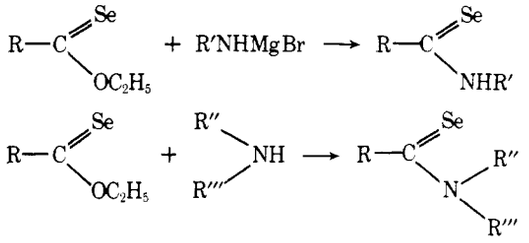
Initially, aliphatic and aromatic nitriles were converted to their imidoester salts by treatment with 2 equiv of ethanol and anhydrous hydrochloric acid in diethyl ether at 0 °C. After 5 days in refrigeration, simple treatment of these imidoester salts with anhydrous ammonia gave the desired imidoester bases. The addition of hydrogen selenide to these later compounds at −20 to −30 °C in the presence of pyridine–triethylamine affords respective selenonesters.

The IR spectra of the selenonesters (Table I) showed a selenocarbonyl absorption band at 1250–1220 cm$^{-1}$. The NMR spectra of all aliphatic and aromatic selenonesters prepared (Table I) showed a shift of the $-CH_2-$ of the ethoxy group at 4.5–4.7 ppm.

The overall advantage of the synthesis of the selenonesters described is that the procedure is straightforward and employs readily available starting materials.

The aliphatic selenonesters are yellow liquids; the aromatic esters are deep-red oils. The aromatic selenonesters are more stable than aliphatic ones; however, after 2 or 3 days, they begin to deposit elemental selenium, but in refrigeration there is no change after a few months.

The availability of the selenonesters has permitted the preparation of a series of selenoamides, which are little-studied compounds. A few examples have been prepared by the reaction of phosphorus pentaselenide with tertiary amines such as *N*,*N*-dimethylbenzylamine.[6] Yalpani and Malek-Yazdi have been able to obtain mono- and disubstituted selenoamides by reacting 5-unsubstituted 1,2,3-selenadiazoles with various amines.[7] We now wish to describe the synthesis of selenoamides from the corresponding selenonesters. Aliphatic selenonesters with various primary alkylamide magnesium bromides in diethyl ether give N-monosubstituted selenoamides, whereas direct addition of secondary amines to selenonesters after 15 days afford N,N-disubstituted selenoamides. With primary amines, formation of the imido ester and $H_2Se$ was a significant side reaction.

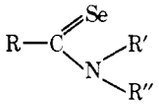


R = alkyl; R′ = alkyl, aryl; R″, R‴ = alkyl

The structures were determined by elemental analyses and spectroscopic data. The NMR spectra of all substituted selenoamides prepared (Table II) showed $-CH_2N$ proton signal at 3.60–4.70, $-CH_2C{=}Se$ proton signal at 2.28–3.72, and $-CHC{=}Se$ proton signal at 3.04–3.30.

The N-mono- and N,N-disubstituted alkyl aliphatic selenoamides are liquids and the N-monosubstituted aromatic ones are solids. Substituted selenoamides are more stable than

**Table II. Substituted Selenoamides**



| Registry no. | | R | R′ | R″ | Bp, °C (mm) (mp, °C) | Yield, % |
|---|---|---|---|---|---|---|
| 62448-80-0 | 10 | $CH_3$ | $p$-$BrC_6H_4$ | H[a] | (156) | 82 |
| 62448-81-1 | 11 | $CH_3$ | $p$-$CH_3C_6H_4$ | H[a] | (132) | 85 |
| 62448-82-2 | 12 | $CH_3CH_2$ | $p$-$C_2H_5OC_6H_4$ | H[a] | (93) | 74 |
| 62448-83-3 | 13 | $CH_3CH_2$ | $CH_3CH_2$ | $CH_3CH_2$ | 122 (7) | 70 |
| 62448-84-4 | 14 | $(CH_3)_2CH$ | $p$-$CH_3C_6H_4$ | H[a] | (99) | 83 |
| 62448-85-5 | 15 | $(CH_3)_2CH$ | $p$-$CH_3OC_6H_4$ | H[a] | (82) | 75 |
| 62448-86-6 | 16 | $(CH_3)_2CH$ | $CH_3CH_2$ | $CH_3CH_2$[a] | 110–112 (8) | 30 |
| 62448-87-7 | 17 | $CH_3CH_2CH_2$ | $p$-$CH_3OC_6H_4$ | H[a] | (113) | 80 |
| 62448-88-8 | 18 | $CH_3CH_2CH_2$ | $p$-$C_2H_5OC_6H_4$ | H[a] | (84) | 87 |
| 62460-39-8 | 19 | $CH_3CH_2CH_2$ | $p$-$BrC_6H_4$ | H[a] | (109) | 78 |
| 62448-89-9 | 20 | $CH_3(CH_2)_3$ | $p$-$BrC_6H_4$ | H[a] | (104) | 92 |
| 62448-90-2 | 21 | $CH_3(CH_2)_3$ | $p$-$C_2H_5OC_6H_4$ | H[a] | (87) | 78 |
| 62448-91-3 | 22 | $CH_3(CH_2)_3$ | $(CH_3)_2CH(CH_2)_2$ | H[a] | 150 (8) | 65 |
| 62448-92-4 | 23 | $CH_2(CH_2)_3$ | $CH_3CH_2$ | $CH_3CH_2$[a] | 132 (8) | 60 |
| 62448-93-5 | 24 | $(CH_3)_2CH(CH_2)_2$ | $p$-$BrC_6H_4$ | H[a] | (112) | 70 |
| 62448-94-6 | 25 | $(CH_3)_2CH(CH_2)_2$ | $p$-$CH_3OC_6H_4$ | H[a] | (86) | 86 |

[a] New compounds.

corresponding selenonesters and in refrigeration there is no change after 6 months.

## Experimental Section

**General.** Proton magnetic resonance spectra were determined with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. A Beckman IR-20A spectrophotometer was used for IR spectra. Microanalyses were performed by CNRS (Service Central de Microanalyse, 94 Thiais, France) and Dornis U. Kolbe, Hohenweg 17, West Germany.

**Aliphatic and Aromatic Imido Esters.** The above-mentioned compounds were obtained by the method of Reynaud and Moreau.[5]

**General Procedure for Synthesis of Aliphatic and Aromatic Selenonesters.** The following description for the conversion of imido esters to selenonesters (Table I, 1) may be considered general. A solution of 8.7 g (0.1 mol) of ethyl acetimidate, 30 mL of dry pyridine, and 10 mL of triethylamine in a 100-mL round bottom flask is cooled to −30 °C. About 25 g (0.3 mol) of anhydrous hydrogen selenide (hydrogen selenide is generated from aluminum selenide by addition of water and passed through the calcium chloride tube) is passed through the solution in 30 min at −30 to −20 °C. The flask temperature is allowed to come to 0 °C and immediately poured into 200 mL of ice water. The mixture is extracted with three 50-mL portions of ether. The extracts are combined and treated with diluted hydrochloric acid and washed with water. The ether solution is dried over anhydrous sodium sulfate, concentrated, and distilled to afford 4 g of *O*-ethyl selenoacetate (26%), bp 129 °C.

**General Method for Synthesis of N-Monoalkyl or Aryl Aliphatic Selenoamides.** The following preparation of *N*-*p*-bromophenylselenoacetamide (Table II, **10**) will serve as general procedure for the preparation of the above-mentioned selenoamides. To 0.96 g (0.04 mol) of magnesium turnings covered with 20 mL of anhydrous diethyl ether in the usual Grignard apparatus, a solution of 4.36 g (0.04 mol) of ethyl bromide in diethyl ether was added dropwise. A solution of 6.88 g (0.04 mol) of *p*-bromoaniline in anhydrous diethyl ether was added dropwise during 30 min, at such a rate that the mixture refluxed. To the resulting suspension, a solution of 3.02 g (0.02 mol) of *O*-ethyl selenoacetate in diethyl ether was added at once. After the addition was completed, the mixture was refluxed 1 h, cooled, and poured into 400 mL of ice water. The reaction mixture was treated with dilute hydrochloric acid. The mixture was extracted with three 50-mL portions of ether. The combined ether phases were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent leaves a solid which after recrystallization from benzene–petroleum ether gave 4.54 g (82%) of **10**, mp 156 °C. The solid-substituted selenoamides listed in Table II were recrystallized from benzene–petroleum ether to afford analytically pure products.

The N-monoalkyl-substituted aliphatic selenoamides were prepared in dipropyl ether.

**General Procedure for Synthesis of *N,N*-Dialkyl Aliphatic Selenoamides.** The following description for the preparation of *N,N*-diethylselenopropionamide (Table II, **13**) may be considered general. To 3.30 g (0.02 mol) of *O*-ethyl selenopropionate, a solution of 2.19 g (0.03 mol) of diethylamine in 5 mL of anhydrous ethanol was added. After 15 days, the alcohol solution was fractionated to give 2.69 g (70%) of **13**, bp 122 °C (7 mmHg).

**Registry No.**—Ethanimidic acid ethyl ester, 1000-84-6; propanimidic acid ethyl ester, 1070-17-3; butanimidic acid ethyl ester, 998-97-0; isopropylimidic acid ethyl ester, 1069-52-9; pentanimidic acid ethyl ester, 999-09-7; hexanimidic acid ethyl ester, 1001-25-8; benzenethanimidic acid ethyl ester, 4971-77-1; benzenecarboximidic acid ethyl ester, 825-60-5; benzenecarboximidic acid 4-methyl ethyl ester, 827-71-4; $H_2Se$, 7783-07-5; *O*-ethyl selenoisohexanoic ester, 62448-97-9; magnesium, bromo(4-bromobenzenaminato), 58655-99-5; magnesium, bromo(4-methylbenzenaminato), 58655-94-0; magnesium, bromo(4-ethoxybenzenaminato), 62448-95-7; diethylamine, 109-89-7; magnesium, bromo(4-methoxybenzenaminato), 58655-97-3; magnesium, bromo(isopentanaminato), 62448-96-8.

## References and Notes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# Reaction of Methylmagnesium Iodide with Methyl Propiolate. A Correction


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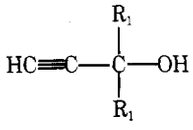
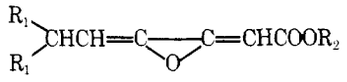
Rhinesmith[1] has recently reported the reaction of methylmagnesium iodide or ethylmagnesium bromide with methyl or ethyl propiolate. Beside the expected acetylenic carbinol **1** ($R_1$ = $CH_3$ or $C_2H_5$) resulting from the addition of 2 mol of Grignard reagent to the ester function, a higher boiling, labile compound was found to which the structure of a doubly unsaturated epoxy ester **2** ($R_1$ = $CH_3$ or $C_2H_5$; $R_2$ = $CH_3$ or $C_2H_5$)

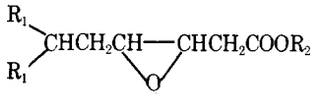


**1**

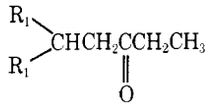


**2**

was assigned based on a combustion analysis, the uptake of 2 mol of hydrogen on catalytic hydrogenation, the IR spectrum, and negative tests for the functional groups –HC=O, >C=O, and –C≡CH. In each case these compounds presumed to have structure **2** were reduced to the alleged saturated β,γ-epoxy esters **3**, which on treatment with methanolic

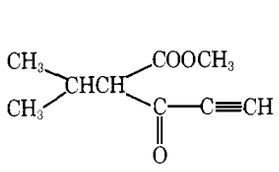


**3**

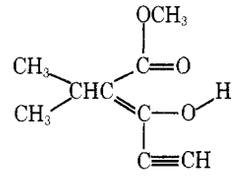


**4**

potassium hydroxide gave the corresponding ethyl ketones **4** ($R_1$ = $CH_3$ or $C_2H_5$) identified with authentic material. The isolation of a monoepoxide of a 1,2,3-triene such as **2** from a Grignard reaction is unexpected in view of the known instability of epoxides of simple allenes.[2] We therefore repeated the reaction of excess methylmagnesium iodide with methyl propiolate under the conditions described by Rhinesmith[1] while slightly modifying the workup to minimize secondary reactions. VPC analysis of the crude product showed the presence of 3-methyl-1-butyn-3-ol (**1**, $R_1$ = $CH_3$, 20–50% of the volatile material), two further major components (20–30% each), and several minor components (less than 5% each) which were not investigated. Distillation, column chromatography, and preparative VPC led to the isolation of methyl 2-isopropyl-3-oxo-4-pentynoate (**5**) and methyl (*Z*)-2-ethyl-



**5**



**6**

idene-3-hydroxy-3-methyl-4-pentynoate (**7**) besides the known[3] alcohol **1**.

The structure of **5** follows from spectroscopic evidence. The IR spectrum shows the presence of an acetylenic proton at 3305 $cm^{-1}$, a peak of medium intensity for a conjugated triple bond at 2095 $cm^{-1}$, and two carbonyl absorptions at 1745 and 1685 $cm^{-1}$. The $^1H$ NMR spectrum confirms the presence of an ester methyl group, of an acetylenic proton, and of an iso-