Reactions of Relevance to the Chemistry of Aminoglycoside Antibiotics. Part 8.† Synthesis and Properties of *O*-Alkyl Selenoesters

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A wide range of aliphatic and aromatic *O*-alkyl selenoesters has been synthesised from the appropriate di-*N*-substituted imidoyl chloride with use of sodium hydrogen selenide to introduce selenium. The reduction of selenoesters to ethers has been demonstrated, as well as the ready reaction of these compounds with the methylene Wittig reagent.

UNTIL recently, few reports on the preparation of *O*-alkyl selenoesters had appeared. The aryl selenoesters (1) and (2) have been prepared [1] by the action of hydrogen selenide on the corresponding imidate esters, but the yields were prohibitively low. Attempts to adapt the method to the preparation of an aliphatic selenoester (*O*-methyl selenoacetate) failed. The yield of (1) has been improved by employing methyl benzimidate hydrochloride as starting material.[2] The aromatic selenoesters (1)—(4) have also been prepared [3] by the reaction of pentacarbonyl(methoxyarylcarbene)-chromium(0) complexes with selenium, but again yields were low (12—29%). *O*-Trimethylsilyl selenobenzoate (5) has been reported as the product from treatment of potassium selenobenzoate with chlorotrimethylsilane.[4]

A more general preparation of *O*-alkyl selenoesters has recently been reported from this laboratory.[5] Con-

† Part 7, D. H. R. Barton and R. Subramanian, preceding paper.

[1] C. Collard-Charon and M. Renson, *Bull. Soc. chim. belges*, 1962, **71**, 563.

[2] R. Mayer, S. Scheithauer, and D. Kunz, *Chem. Ber.*, 1966, **99**, 1393.

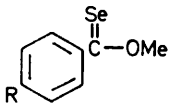
[3] E. O. Fischer and S. Riedmüller, *Chem. Ber.*, 1974, **107**, 915.

[4] H. Ishihara and S. Hato, *Tetrahedron Letters*, 1972, 3751.

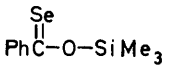
[5] D. H. R. Barton and S. W. McCombie, *J.C.S. Perkin I*, 1975, 1574.

densation of an alcohol with a di-*N*-substituted imidoyl chloride (prepared from phosgene and a tertiary amide) gives a salt which is converted into a selenoester on treatment with ethanolic sodium hydrogen selenide. The synthesis usually employs dimethylamides (Scheme 1), but piperidides are equally suitable.

By this method, *O*-cholesteryl and *O*-ethyl selenobenzoate were prepared in high yield. The first example of an aliphatic selenoester, *O*-cholesteryl selenoformate, was also obtained by this procedure. Another account



(1) R = H
(2) R = Me
(3) R = OMe
(4) R = Cl



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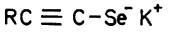


(6)

concerning the preparation of α-substituted selenoesters of the type $R^1CH_2{\cdot}C(:Se){\cdot}OR^2$ from the reaction of arylethynylselenolate salts (6) with alcohols at high dilution has also appeared.[6] However, the generality of this procedure as a preparative approach to selenoesters is limited by the fact that only α-monosubstituted selenoacetates are obtainable. The imidoyl chloride procedure, on the contrary, appeared particularly suitable for the synthesis of selenoesters with a variety of functionality.

TABLE 1

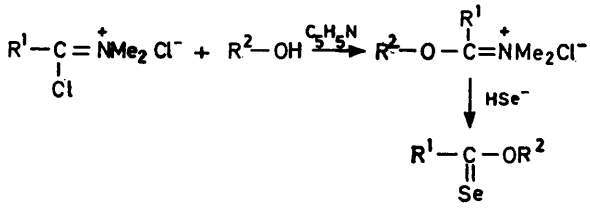
Yields (%) of selenobenzoates

O-Methyl (1) [1,3]	89
O-Isopropyl (7) *	92
O-Cholestanyl (8) †	89
O-Cholesteryl (9) [5]	87
O-Phenyl (10) ‡	87
Methyl 4,6-*O*-benzylidene-3-*O*-selenobenzoyl-α-D-glucopyranoside (11) §	49

* B.p. 76—78° at 0.1 mmHg, $\lambda_{max.}$ (EtOH) 254, 331, and 504 nm (ε 7 900, 8 800, and 130) (Found: C, 53.05; H, 5.5. $C_{10}H_{12}OSe$ requires C, 52.85; H, 5.3%). † D. H. R. Barton, R. V. Stick, and R. Subramanian, *J.C.S. Perkin I*, 1976, 2112. ‡ B.p. 164—166° at 0.4 mmHg, $\lambda_{max.}$ (EtOH) 261, 338, and 523 nm (ε 6 300, 9 000, and 160), *m/e* 262 (M^+) (owing to the instability of the compound, a satisfactory analysis was not obtained). § This compound, kindly supplied by Dr. R. Bielski, had m.p. 158—160° (from diethyl ether), $\lambda_{max.}$ (EtOH) 260, 332, and 489 nm (ε 9 000, 7 900, and 160) (Found: C, 56.40; H, 4.75. $C_{27}H_{22}O_6Se$ requires 5%). C, 56.15; H, 4.9

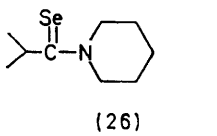
The selenobenzoates shown in Table 1 were prepared in high yield by the general sequence outlined in Scheme 1. The reaction did, however, fail for *O*-t-butyl selenobenzoate, almost certainly because of steric retardation of the initial condensation step between t-butyl alcohol and the imidoyl chloride.

A number of *O*-alkyl aliphatic selenoesters were also prepared, as shown in Table 2. Both *O*-cholestanyl and *O*-cholesteryl selenoformate decomposed rapidly under



SCHEME 1

the conditions used, and could be isolated in satisfactory yields only when work-up followed immediately after addition of the sodium hydrogen selenide solution. The selenoacetates (14)—(18) were obtained in high yield, but the attempted preparation of *O*-benzyl selenoacetate failed at the first stage when the intermediate salt (derived from the piperidide) was rapidly attacked by chloride ion to give benzyl chloride and *N*-acetylpiperidine. An attempted preparation of *O*-phenyl selenoisobutyrate was also unsuccessful. Although condensation with the imidoyl chloride from *N*-isobutyrylpiperidine proceeded normally, subsequent reaction with sodium hydrogen selenide resulted in expulsion of the phenoxy group to give *N*-selenoisobutyrylpiperidine (26). Reaction of 1,1′-adipoyldipiperidine with phosgene resulted in a red salt, which did not yield any of the desired di-*O*-methyl diselenoadipate on treatment with methanol and sodium hydrogen selenide. This failure was shown to be due to the formation of a cyclic condensation product, presumably (27), which was hydrolysed to (28) on treatment with water. With 1,1′-glutaryldipiperidine as starting material this complication was avoided, and the diselenoester (25) was isolated in 38% yield.



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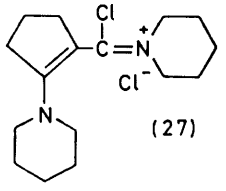

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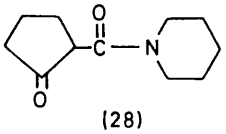

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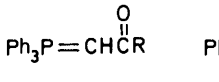

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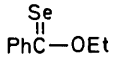
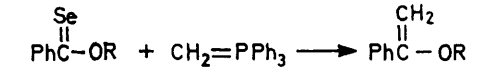


(30)

In view of the paucity of information on the chemical reactivity of aliphatic and aromatic selenoesters, the behaviour of these compounds towards a number of common reagents was investigated. It has been established that certain esters [7,8] and *S*-alkyl thioesters [9,10]

[6] F. Malek-Yazdi and M. Yalpani, *J. Org. Chem.*, 1976, **41**, 729.
[7] G. Wittig and U. Schöllkopf, *Chem. Ber.*, 1954, **87**, 1318.
[8] S. Trippett and D. M. Walker, *J. Chem. Soc.*, 1961, 1266.
[9] H. J. Bestmann and B. Arnason, *Tetrahedron Letters*, 1961, 455.
[10] H. J. Bestmann and B. Arnason, *Chem. Ber.*, 1962, **95**, 1513.

react with alkylidenephosphoranes to give β-oxoalkylphosphonium salts, which then yield stable β-oxoalkylidenephosphoranes (29) by elimination. In contrast, however, the selenobenzoates (1), (30),[5] and (7)—(10) reacted with methylenetriphenylphosphorane at room temperature to give α-alkoxystyrenes (Scheme 2). Because of their instability, the α-alkoxystyrenes could not be purified. They were identified by their characteristic n.m.r. spectra and their hydrolysis to acetophenone (Table 3). *O*-Cholesteryl selenoacetate was unreactive towards the reagent at room temperature, but was converted into the enol ether (37) at 50 °C.



(31) R = Me
(32) R = Et
(33) R = Pr^i
(34) R = cholestanyl
(35) R = cholesteryl
(36) R = Ph

SCHEME 2

The aliphatic selenoesters *O*-cholesteryl selenoformate and selenoacetate were rapidly reduced by ethanolic sodium borohydride to give the bis(alkoxyalkyl) diselenides (38) and (39), respectively, on oxidative (atmospheric oxygen) work-up. When the reaction mixture was quenched with methyl iodide the alkoxyalkyl alkyl selenides (41) and (42) were the products. *O*-Cholesteryl selenobenzoate reacted only slowly with the reducing agent, presumably because of the decreased electrophilicity of the selenocarbonyl carbon atom. With a large excess of sodium borohydride, similar reduction products, (40) and (43), were isolated.

In view of the high affinity phosphines possess for the formation of P–Se bonds, it appeared likely that the introduction of a phosphine might alter the course of the reduction. In the event, when *O*-cholesteryl selenoacetate (17) was subjected to reduction with sodium borohydride–triethylphosphine, cholesteryl ethyl ether was formed in high yield. Similarly, treatment of *O*-isopropyl selenoacetate (15) and *O*-cholesteryl selenopropionate (19) gave the corresponding ethers in 80% yield. If (17) was first reduced with sodium borohydride and then treated with triethylphosphine, the ether was again isolated in similar yield.

Attempts to prepare cholesteryl methyl ether and benzyl cholesteryl ether by treatment of (13) and (9) under the above conditions resulted in complex mixtures of products in which no trace of ethers was detected.

TABLE 2

Properties of aliphatic selenoesters

	$R^1C(:Se)\cdot OR^2$ R^1	R^2	M.p. (°C) *	B.p. (°C) [mmHg]	Yield (%)	$\lambda_{max.}$/nm (ε) †	C (%) ‡	H (%) ‡
(12)	H	cholestanyl	88—90		75	278 (7 700), 447 (43)	70.85 (70.1)	9.8 (10.1)
(13)	H	cholesteryl	125—127		69			
(14)	Me	Me		108—110 [763]	80 (total)	270 (7 300), 443 (50)	26.7 (26.3)	4.4 (4.4)
(15)	Me	Pr^i		139—141 [772]	76	277 (7 700), 443 (50)	35.95 (36.35)	6.1 (6.1)
(16)	Me	cholestanyl	104—105		74	282 (7 400), 435 (60)	70.4 (70.55)	10.35 (10.2)
(17)	Me	cholesteryl	144—145		83	283 (6 700), 438 (82)	70.65 (70.85)	9.95 (9.85)
(18)	Me	Ph		92 [0.7]	65	279 (6 300), 469 (50)	48.3 (48.25)	4.0 (4.05)
(19)	Et	cholesteryl	151—153		86	283 (8 000), 434 (60)	71.55 (71.25)	9.75 (9.95)
(20)	$CH_3[CH_2]_{16}$	Me	25—26 (solidified oil)		43	275 (8 200), 436 (60)	63.45 (63.5)	10.35 (10.1)
(21)	$PhCH_2$	Me		§	80	275 (7 800), 450 (45)	50.9 (50.7)	4.75 (4.75)
(22)	Pr^i	Et		72—74 [34]	69	274 (7 100), 443 (50)	40.5 (40.25)	6.8 (6.75)
(23)	Pr^i	Pr^i		82—84 [33]	61	278 (7 000), 444 (50)	43.75 (43.55)	7.3 (7.3)
(24)	Bu^t	Et		64 [14]	46	274 (7 950), 450 (50)	43.45 (43.55)	7.25 (7.3)
(25)	$EtO\cdot C(:Se)\cdot[CH_2]_3$	Et		§	38	274 (15 100), 446 (110)	34.85 (34.3)	5.55 (5.15)

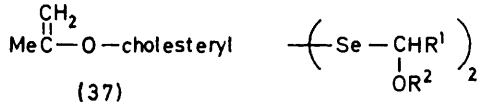
* From dry acetonitrile. † U.v. spectra of liquid selenoesters were determined for solutions in EtOH, and spectra of solid selenoesters in $CHCl_3$. ‡ Required values in parentheses. § Could not be distilled.

TABLE 3

Data for reactions of selenobenzoates with methylenetriphenylphosphorane

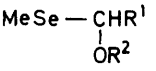
$PhC(:Se)\cdot OR$	δ_H for $PhC(:CH_2)\cdot OR$	Hydrolysis products of $PhC(:CH_2)\cdot OR$
R = Me (1)	7.76—7.11 (5 H, m), 4.39 (1 H, d, *J* 2.5 Hz), 3.94 (1 H, d, *J* 2.5 Hz), 3.54 (3 H, s)	Acetophenone (95 mg, 79%)
R = Et (30)	7.78—7.08 (5 H, m,), 4.67 (1 H, d, *J* 2.5 Hz), 4.16 (1 H, d, *J* 2.5 Hz), 3.89 (2 H, q, *J* 7 Hz), 1.34 (3 H, t, *J* 7 Hz)	Acetophenone (69 mg, 58%)
R = Pr^i (7)	7.69—7.21 (5 H, m), 4.64 (1 H, d, *J* 2.5 Hz), 4.32 (1 H, sept, *J* 6 Hz), 4.14 (1 H, d, *J* 2.5 Hz), 1.28 (6 H, d, *J* 6 Hz)	Acetophenone (91 mg, 76%)
R = cholestanyl (8)	7.60 (2 H, m), 7.29 (3 H, m), 4.65 (1 H, d, *J* 2.5 Hz), 4.20 (1 H, d, *J* 2.5 Hz), 4.05 (1 H, m)	Acetophenone (76 mg, 63%), Cholestanol (232 mg, 60%)
R = cholesteryl (9)	7.59 (2 H, m), 7.29 (3 H, m), 5.38 (1 H, m,) 4.68 (1 H, d, *J* 2.5 Hz), 4.01 (1 H, m)	Acetophenone (78 mg, 65%), cholesterol (230 mg, 60%)
R = Ph (10)	Not recorded	Acetophenone (87 mg, 73%)

This failure is ascribed to a rapid reaction between the selenoformate or selenobenzoate and triethylphosphine itself to give as yet uncharacterised products. When *O*-cholestanyl and *O*-cholesteryl selenobenzoate were treated with tri-n-butylphosphine in the presence of atmospheric oxygen, the corresponding esters were formed in high yields. *O*-Cholesteryl selenoacetate was inert to triethylphosphine at room temperature, but on heating a purple solution slowly developed. Saturation of the solution with oxygen resulted in rapid loss of the colour and formation of cholesteryl selenoacetate in high yield. It thus appears likely that the failure of



(37)

(38) R^1 = H, R^2 = cholesteryl
(39) R^1 = Me, R^2 = cholesteryl
(40) R^1 = Ph, R^2 = cholesteryl

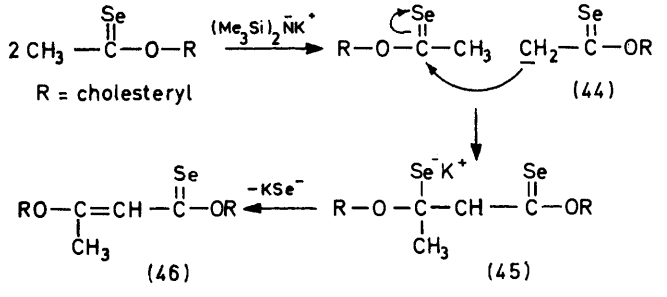


(41) R^1 = H, R^2 = cholesteryl
(42) R^1 = Me, R^2 = cholesteryl
(43) R^1 = Ph, R^2 = cholesteryl

(13) and (9) to give the desired products under the above conditions results from their enhanced reactivity towards triethylphosphine, which then alters the course of the reaction.

In an attempt to circumvent this difficulty, addition of triethylphosphine to the reduction mixture from (13) was delayed until reduction of the selenocarbonyl function was complete. Under these conditions, cholesteryl methyl ether was isolated in 64% yield. However, even under these modified conditions, only a low yield of benzyl cholesteryl ether was obtained.

Ellis and Schibeci [11] have reported the successful



SCHEME 3

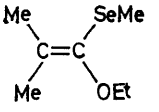
desulphurization of *O*-thioesters with Raney nickel to give ethers in fair yield. As selenoesters could be expected to be more easily reduced, it appears likely that the reagent would offer an alternative method of reduction. Treatment of *O*-cholestanyl selenobenzoate (8) with W-2 Raney nickel gave the desired ether in 64% yield. Deselenization of the selenobenzoates (30) and (11) afforded the corresponding benzyl ethers in similar yield.

Thus the reduction of selenoesters offers a new route to ethers. Alternative methods of ether formation often require strongly basic conditions which are incompatible with many functional groups. Selenoesters can now be synthesised in high yield and, although the method of reduction requires modification to suit the particular reactivity of certain members of this general class of compounds, the ease and mildness with which conversion into ethers can be accomplished offers some advantages.

The mechanism of the reduction of a selenoester with borohydride followed by treatment with triethylphosphine to yield an ether is of interest. It is, however, premature to speculate on this matter at present.

The reaction of selenoesters in strongly basic media was also of interest. Treatment of *O*-cholesteryl selenoacetate (17) with potassium bis(trimethylsilyl)amide yielded the selenocrotonate (46). The product presumably arises by attack of the anion (44) on a second molecule of selenoacetate to give an intermediate (45) which then expels KSe^- to give the product (Scheme 3).

In contrast *O*-alkyl thioesters are known to give normal Claisen products under similar conditions.[12]



(47)

When *O*-ethyl selenoisobutyrate (22) was treated under similar conditions, the product obtained on work-up with methyl iodide was the dimethylketen monoselenoacetal (47).

EXPERIMENTAL

M.p.s were determined with a Reichert hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 257 spectrometer and u.v. spectra with a Unicam SP 800 spectrometer. N.m.r. spectra were determined with a Varian T60 instrument for solutions in $CDCl_3$ with tetramethylsilane as internal standard. Mass spectra were recorded with an A.E.I. MS9 instrument and rotations were measured on a Perkin-Elmer 141 polarimeter for solutions in chloroform. 'Light petroleum' refers to the fraction b.p. 40—50 °C, and 'petroleum' to the fraction, b.p. 60—80 °C.

The 'usual work-up' refers to dilution with water, extraction with dichloromethane or ether, washing with dilute acid, sodium hydrogen carbonate solution, and water, and drying ($MgSO_4$).

Preparation of Selenobenzoates.—*NN*-Dimethylbenzamide (3.1 g, 20 mmol) was kept for 24 h at room temperature in dichloromethane (40 ml) containing phosgene (3.9 g, 40 mmol). The solution was then evaporated *in vacuo*, and the imidoyl chloride was redissolved in dichloromethane (75 ml) and treated with the alcohol (20 mmol) at room temperature. After stirring for the time shown, the

[11] J. Ellis and R. A. Schibeci, *Austral. J. Chem.*, 1974, **27**, 429.

[12] A. R. Hendrickson and R. L. Martin, *Austral. J. Chem.*, 1972, **25**, 257.

mixture was cooled to 0 °C and pyridine (4 ml) was added. The resulting mixture was added at −20 °C to a solution of sodium hydrogen selenide [from selenium (1.6 g, 20 mmol) and sodium borohydride (0.8 g, 20 mmol)] in ethanol (75 ml).[13] After stirring at room temperature for 10 min, the mixture was diluted with dichloromethane (100 ml) and worked up in the usual way. The pure selenobenzoates were obtained by chromatography on alumina (grade III) with petroleum–diethyl ether (20 : 1) as eluant.

The selenobenzoates obtained by the above method are shown in Table 1. N.m.r. and mass spectra of new compounds were consistent with the structures indicated. The times allowed for reaction of the imidoyl chloride with the alcohol in each preparation were as follows: (1) 0.25 h, (7) 0.25 h, (8) 0.5 h, (9) 0.5 h, (10) 2 h, and (11) 0.5 h.

Attempted preparation of O-t-butyl selenobenzoate. Attempts to prepare *O*-t-butyl selenobenzoate by the standard method, with introduction of a t-butoxy-group under the following conditions, were unsuccessful: (*a*) t-butyl alcohol, 24 h reflux; (*b*) t-butyl alcohol and imidazole, 12 h reflux; (*c*) potassium t-butoxide, 12 h reflux.

Preparation of Aliphatic Selenoesters.—The general procedure utilised is described below for the preparation of *O*-cholesteryl selenopropionate.

O-*Cholesteryl selenopropionate* (19). *NN*-Dimethylpropionamide (3.0 g, 30 mmol) in benzene (50 ml) was treated with a solution of phosgene (5.9 g, 60 mmol) in benzene (50 ml) at room temperature and the mixture was set aside for 4 h. Evaporation *in vacuo* gave the imidoyl chloride (4.34 g, 28 mmol) as a white solid, which was then treated with cholesterol (5.8 g, 15 mmol) in dichloromethane (150 ml) at 0 °C. After stirring for 30 min at room temperature, the mixture was again cooled to 0 °C and pyridine (6 ml) was added. The resulting mixture was added at −20 °C to a solution of sodium hydrogen selenide [from selenium (2.2 g) and sodium borohydride (1.1 g)] in ethanol (100 ml). The yellow mixture was stirred without cooling for 30 min and, after the usual work-up and evaporation, the product was chromatographed on silica gel. Elution with petroleum–diethyl ether (20 : 1) gave the *selenopropionate* (19), which crystallised from dry acetonitrile as yellow needles (6.5 g, 86%), m.p. 151—153 °C.

Data for the aliphatic selenoesters prepared by this method are given in Table 1. N.m.r. and mass spectra were consistent with the structures shown. Modifications to the above general procedure are shown below.

O-*Cholestanyl selenoformate* (12) *and* O-*cholesteryl selenoformate* (13). The imidoyl chloride was prepared by treatment of dimethylformamide with phosgene in dichloromethane (20% w/v) for 30 min. The alcohol in dichloromethane–tetrahydrofuran (1 : 1), precooled to −20 °C, was then added to the solid chloride. After the addition of pyridine, the solution was maintained at 0 °C for 10 min and then treated as above. Immediately upon addition to the sodium hydrogen selenide solution, the mixture was worked up and rapidly chromatographed to give the crude products.

O-*Methyl selenoacetate* (14) *and* O-*isopropyl selenoacetate* (15). The imidoyl chloride was prepared from *N*-acetyl piperidine in dry diethyl ether by treatment with ethereal phosgene. After 45 min the precipitated salt was filtered off under dry conditions, dried *in vacuo*, and converted into the selenoesters by the standard procedure. Sodium hydrogen selenide was generated in dry methanol for the preparation of the *O*-methyl ester. Because of the volatility of the products, solutions were carefully concentrated (60 cm Vigreux column). Light petroleum–ether (20 : 1) was used as chromatography solvent.

O-*Cholestanyl selenoacetate* (16) *and* O-*cholesteryl selenoacetate* (17). The imidoyl chloride was prepared from *NN*-dimethylacetamide under standard conditions. Stirring was continued for 10 min after addition of the alcohol and addition to the sodium hydrogen selenide solution.

O-*Phenyl selenoacetate* (18). The imidoyl chloride was prepared as above. After addition of phenol, the mixture was stirred for 3 h at room temperature and then treated as in the general procedure. *NN*-Dimethylselenoacetamide (27) was also isolated on elution with petroleum–diethyl ether (2 : 1) as a yellow oil, b.p. 81—83° at 768 mmHg (lit.,[14] 82—84° at 770 mmHg).

The selenoacetate was also prepared in 41% yield from *N*-acetylpiperidine. *N*-Selenoacetylpiperidine (53%) was isolated as a yellow oil, b.p. 62—64° (lit.,[15] 64.5—65°).

O-*Methyl seleno-octadecanoate* (20). *NN*-Dimethyloctadecanamide in benzene cooled in ice was converted into the imidoyl chloride by treatment with a stream of phosgene for 15 min. The salt was filtered off, dried, and treated under standard conditions. The sodium hydrogen selenide was generated in dry methanol.

O-*Methyl phenylselenoacetate* (21). The imidoyl chloride was prepared by stirring a solution of *NN*-dimethylphenylacetamide in benzene overnight with phosgene. Conversion into the selenoester was performed as above.

O-*Ethyl selenoisobutyrate* (22) *and* O-*isopropyl selenoisobutyrate* (23). The imidoyl chloride prepared from *N*-isobutyrylpiperidine and phosgene (48 h) was treated with the alcohol in dichloromethane at −20 °C. The homogeneous solution was then treated with pyridine, and the resulting mixture was immediately added to a solution of sodium hydrogen selenide as described in the general procedure. During work-up, solutions were concentrated with use of a Vigreux column (60 cm).

O-*Ethyl selenopivalate* (24). Treatment of *N*-pivaloylpiperidine in benzene with phosgene for 120 h gave the imidoyl chloride which, after filtration and drying, was treated with ethanol in dichloromethane at −40 °C. After 10 min the homogeneous mixture was treated with pyridine and the resulting suspension was then added to a solution of sodium hydrogen selenide as previously described.

Di-O-*ethyl diselenoglutarate* (25). The imidoyl chloride was prepared from 1,1′-glutaryldipiperidine with phosgene in benzene for 1 h. The salt was filtered off and converted into the diselenoester by addition of ethanol (1 mol. equiv.) and sodium hydrogen selenide (1 mol. equiv.) as in the general preparation.

Attempted preparation of O-*benzyl selenoacetate.* The imidoyl chloride was treated with benzyl alcohol as described in the preparation of *O*-methyl selenoacetate. After the usual work-up, evaporation left a residue which was chromatographed on silica gel. Elution with petroleum–diethyl ether (20 : 1) gave benzyl chloride (89%); elution with diethyl ether yielded *N*-acetylpiperidine (72%), both identical with authentic samples.

Attempted preparation of O-*phenyl selenoisobutyrate.* The

[13] D. L. Klayman and T. S. Griffin, *J. Amer. Chem. Soc.*, 1973, **95**, 197.

[14] C. Collard-Charon and M. Renson, *Bull. Soc. chim. belges*, 1963, **72**, 304.

[15] K. A. Jensen, H. Mygind, and P. H. Mielsen, unpublished results (personal communication to Dr. Hansen).

imidoyl chloride was treated with phenol as described under *O*-ethyl selenoisobutyrate, but in this experiment the addition was carried out at 0 °C. After 2 h, the solution became homogeneous and was then treated with pyridine and sodium hydrogen selenide at −20 °C as previously described. After the usual work-up and evaporation, the product was chromatographed on silica gel [elution with petroleum–diethyl ether (4 : 1)] to give N-*selenoisobutyryl-piperidine* (26) as a yellow oil (77%), b.p. 140—142° at 2 mmHg, $\nu_{max.}$ (film) 1 490s, 1 440s, 1 380w, 1 360w, 1 280m, 1 240s, 1 180m, 1 145w, 1 130w, 1 085w, 1 065w, 1 020m, 1 010w, 975m, 950w, 870m, and 865w cm^{-1}, $\lambda_{max.}$ (EtOH) 310 and 396 nm (ε 12 000 and 150), δ 4.46 (2 H, m), 3.77 (2 H, m), 3.12 (1 H, sept, *J* 6.5 Hz), 1.75 (6 H, m), and 1.25 (6 H, d, *J* 6.5 Hz), *m/e* 219 (M^+), 138, and 124 (Found: C, 49.85; H, 7.9; N, 6.15. $C_9H_{17}NSe$ requires C, 49.55; H, 7.85; N, 6.4%).

Preparation of 1-(2-*Oxocyclopentylcarbonyl*)*piperidine* (28). —1,1′-Adipoyldipiperidine (1.3 g, 5 mmol) in benzene (75 ml) was treated with a solution of phosgene (3.0 g, 30 mmol) in benzene (50 ml) at room temperature. After stirring for 1 h at room temperature, crushed ice was added and the mixture was then vigorously stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried and evaporated. Distillation gave the amide (28) as an oil (0.44 g, 45%), b.p. 156—159° at 0.45 mmHg (lit.,[16] 128—130° at 0.05 mmHg), which slowly crystallised; m.p. 25° (lit.,[17] 24.5—26°).

Reactions of Selenobenzoates with Methylenetriphenylphosphorane.—Methyl-lithium (1.0 ml; 2M in diethyl ether) was added dropwise to a stirred suspension of triphenylmethylphosphonium bromide (0.52 g, 1.5 mmol) in toluene (30 ml). After stirring at room temperature for 4 h, a solution of the selenobenzoate (1.0 mmol) in toluene (10 ml) was added. After 30 min stirring, the mixture was washed with water, dried, and evaporated, and the residue was chromatographed on dehydrated florisil [elution with petroleum–diethyl ether (20 : 1)] to give the α-alkoxystyrene, identified by its ^1H n.m.r. spectrum and its hydrolysis products.

Hydrolysis of α-Alkoxystyrenes.—The α-alkoxystyrene (1 mmol) was dissolved in ethanol–water (5 : 1) and 4 drops of concentrated sulphuric acid were added. After 3 h, the mixture was neutralised with sodium hydrogen carbonate and extracted with dichloromethane. The extracts were dried and chromatographed on alumina (grade III) to give acetophenone and the alcohol products on elution with petroleum–diethyl ether (4 : 1). The results are shown in Table 3.

Reaction of O-Cholesteryl Selenoacetate with Methylenetriphenylphosphorane.—*O*-Cholesteryl selenoacetate (0.246 g, 0.5 mmol) was treated with methylenetriphenylphosphorane as described for the selenobenzoates, but with benzene instead of toluene as solvent. After 1 h at 50 °C, the mixture was diluted with diethyl ether, washed with water, dried, and evaporated; the residue was chromatographed on dehydrated florisil. Elution with petroleum–diethyl ether (19 : 1) gave crude 2-cholesteryloxypropene (37) (0.162 g), δ 5.42 (1 H, m), 3.87 (3 H, m), and 1.79 (3 H, s), and cholestanol (0.065 g, 34%).

2-Cholesteryloxypropene was then dissolved in ethanol–ether (1 : 1) (10 ml) and treated with 2,4-dinitrophenylhydrazine (0.15 g) and concentrated sulphuric acid (8 drops) in ethanol–water (5 : 1). After 3 h at room temperature the mixture was diluted with dilute aqueous ammonia and extracted with ether. After drying and concentration, 2,4-dinitrophenylhydrazine was filtered off and the residue was chromatographed on silica gel. Elution with petroleum–diethyl ether (19 : 1) gave acetone 2,4-dinitrophenylhydrazone (0.051 g, 43%), m.p. 122—124° (lit.,[18] 128°), identical with an authentic sample; elution with petroleum–diethyl ether (9 : 1) yielded cholesterol (0.108 g, 56%).

Reaction of O-Cholesteryl Selenoformate with Sodium Borohydride.—(*a*) *O*-Cholesteryl selenoformate (0.12 g, 0.25 mmol) dissolved in benzene (5 ml) was treated with sodium borohydride (0.010 g) in ethanol (2 ml) under argon. After stirring for 1 h at room temperature, the mixture was diluted with water and extracted with dichloromethane; the extract was dried and evaporated. Chromatography on grade III alumina [elution with petroleum–diethyl ether (99 : 1)] gave *bis*(*cholesteryloxymethyl*) *diselenide* (38) (0.10 g, 83%), which crystallised from ether–methanol as cream, microcrystalline plates, m.p. 135—136°, $[\alpha]_D$ −44.2° (*c* 0.6), $\nu_{max.}$ ($CHCl_3$) 1 605w, 1 465m, 1 370m, 1 050s, and 945w cm^{-1}, $\lambda_{max.}$ (cyclohexane) 311 nm (ε 550), δ 5.42 (6 H, m) and 3.50 (2 H, m), *m/e* 451, 449, 386, 368, and 353 (Found: C, 69.95; H, 9.7. $C_{56}H_{94}O_2Se_2$ requires C, 70.25; H, 9.9%).

(*b*) The above reaction was repeated with the addition of methyl iodide (2 ml) before work-up. The product was purified by preparative t.l.c. on silica gel [development in light petroleum–diethyl ether (19 : 1)] to give *cholesteryloxymethyl methyl selenide* (41) (0.108 g, 87%), which crystallised from ether–acetone at −78 °C as prisms, m.p. 105—107°, $[\alpha]_D$ −34.6° (*c* 0.5), $\nu_{max.}$ ($CHCl_3$) 1 605w, 1 460m, 1 370m, and 1 060s cm^{-1}, $\lambda_{max.}$ (cyclohexane) 247sh (ε 110), δ 5.37 (1 H, m), 4.97 (2 H, s), 3.47 (1 H, m), and 2.07 (3 H, s), *m/e* 386, 369, and 353 (Found: C, 70.5; H, 10.4. $C_{29}H_{50}OSe$ requires C, 70.55; H, 10.2%).

Reaction of O-Cholesteryl Selenoacetate with Sodium Borohydride.—(*a*) Sodium borohydride (0.020 g) in ethanol (2.5 ml) was added, under argon, to a solution of *O*-cholesteryl selenoacetate (0.246 g, 0.5 mmol), in benzene (10 ml). After stirring for 2 h at room temperature, the mixture was worked up by dilution with water, extraction with dichloromethane, drying, and evaporation. Chromatography on grade III alumina gave *bis*-(1-*cholesteryloxyethyl*) *diselenide* (39) (0.175 g, 71%) [eluted with petroleum–diethyl ether (99 : 1)] and cholesterol (0.043 g) [eluted with petroleum–diethyl ether (1 : 1)]. The former was recrystallised from ether–acetone at −78 °C to give cream prisms, m.p. 79—81°, $[\alpha]_D$ −45.3° (*c* 0.6), $\nu_{max.}$ ($CHCl_3$) 1 605w, 1 460m, 1 370m, 1 100s, 995w, and 900m cm^{-1}, $\lambda_{max.}$ (cyclohexane) 308 nm (ε 570), δ 5.38 (2 H, m), 5.22 (2 H, q, *J* 6 Hz), 3.56 (2 H, m), and 1.75 (6 H, d, *J* 6 Hz), *m/e* 412, 409, 385, 368, and 353 (Found: C, 70.5; H, 9.9. $C_{58}H_{98}O_2Se_2$ requires C, 70.7; H, 10.05%). Only 0.070 g of crystalline material was obtained from the recrystallisation.

(*b*) The above reaction was repeated with the addition of methyl iodide (2 ml) after 1 h. After work-up, the product was subjected to preparative t.l.c. [silica gel; petroleum–diethyl ether (19 : 1)] to give cholesterol (0.031 g) and

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[17] H. Möhrle and H. Baumann, *Arch. Pharm.*, 1966, **299**, 355.

[18] J. Heilbron, ' Dictionary of Organic Compounds,' 4th edn., Eyre and Spottiswoode, London, 1965.

1-*cholesteryloxyethyl methyl selenide* (42) (0.188 g, 74%), which crystallised from ether at −78 °C as prisms, m.p. 131—133°, $[\alpha]_D$ +0.8° (*c* 0.6), $\nu_{max.}$ ($CHCl_3$) 1 605w, 1 460m, 1 375m, 1 100s, 960w, and 900m cm^{-1}, $\lambda_{max.}$ (cyclohexane) 250sh nm (ε 95), δ 5.36 (1 H, m), 5.00 (1 H, q, *J* 6 Hz), 3.50 (1 H, m), 1.96 (3 H, s), and 1.68 (3 H, d, *J* 6 Hz), *m/e* 414, 411, 369, and 353 (Found: C, 70.65; H, 10.05. $C_{30}H_{52}OSe$ requires C, 70.95; H, 10.35%).

Reaction of O-Cholesteryl Selenobenzoate with Sodium Borohydride.—(*a*) *O*-Cholesteryl selenobenzoate (0.554 g, 1 mmol) in benzene (20 ml) was treated under argon with ethanol (10 ml) and sodium borohydride (0.3 g). After stirring for 3 h at room temperature, the mixture, which had become colourless, was evaporated to dryness *in vacuo* at room temperature. The residue was then shaken with water and dichloromethane and, following saturation with oxygen, the organic phase was separated, dried, and evaporated at room temperature. Chromatography on alumina (grade III) gave *bis(cholesteryloxyphenylmethyl) diselenide* (40) (0.104 g, 19%), on elution with light petroleum–diethyl ether (99 : 1). The diselenide, which rapidly deposited red selenium from solution at room temperature, crystallised from ether–methanol at −50 °C as a yellow microcrystalline solid, m.p. 79—81°, $[\alpha]_D$ −46.5° (*c* 0.6), $\nu_{max.}$ ($CHCl_3$) 1 600w, 1 455s, 1 375m, 1 340m, 1 300w, 1 055s, and 950m cm^{-1}, $\lambda_{max.}$ (cyclohexane) 320sh and 245sh (ε 1 280 and 12 300), δ 7.27 (10 H, m), 5.88br (2 H, s), 5.32 (2 H, m), and 3.54 (2 H, m), *m/e* 476, 461, 459, 443, 419, 385, 370, 368, 355, and 353 (Found: C, 73.7; H, 9.25. $C_{68}H_{102}O_2Se_2$ requires C, 73.6; H, 9.25%).

(*b*) The reaction was repeated as above with addition of methyl iodide (5 ml) after 2.5 h. After work-up and chromatography on alumina (grade III), *cholesteryloxyphenylmethyl methyl selenide* (43) (0.374 g, 66%) was recrystallised from light petroleum at −45 °C to give prisms, m.p. 125—130° (decomp.), $[\alpha]_D$ +12.0° (*c* 0.6), $\nu_{max.}$ ($CHCl_3$) 1 605w, 1 455s, 1 375m, 1 335m, 1 305w, 1 065s, 950w, and 905w cm^{-1}, $\lambda_{max.}$ (cyclohexane) 265sh nm (ε 760), δ 7.28 (5 H, m), 6.00 (1 H, s), 5.32 (1 H, m), 3.50 (1 H, m), and 1.82 (3 H, s), *m/e* 465, 386, 369, and 353 (Found: C, 73.8; H, 9.5. $C_{35}H_{54}OSe$ requires C, 73.8; H, 9.55%).

Reaction of O-Cholesteryl Selenoacetate with Sodium Borohydride–Triethylphosphine.—*O*-Cholesteryl selenoacetate (0.246 g, 0.5 mmol) in benzene (10 ml) was treated with sodium borohydride (0.020 g) and triethylphosphine (0.3 ml) in ethanol (2.5 ml). After stirring at room temperature for 2 h, the mixture was evaporated to dryness. Aqueous acetic acid (20% v/v) was then added and the mixture was extracted with dichloromethane, washed (dilute $NaHCO_3$), dried, and evaporated. Chromatography on alumina (grade III) gave, on elution with petroleum, cholesteryl ethyl ether, which crystallised from ethanol as needles (0.154 g, 75%), m.p. 88—89°, $[\alpha]_D$ −38.4° (*c* 0.5) (lit.,[19] m.p. 88.5°, $[\alpha]_D$ −39.4°).

Reaction of O-Isopropyl Selenoacetate with Sodium Borohydride–Triethylphosphine.—*O*-Isopropyl selenoacetate (2 mmol) in ethanol (25 ml) was treated with sodium borohydride (0.076 g, 2 mmol) and triethylphosphine (0.944 g, 8 mmol) in ethanol. The mixture was stirred at room temperature until the yellow colour had disappeared (10 min) and then worked up by adding methyl iodide (2.0 g), diluting with water, and extracting into dichloromethane. Column chromatography of the residue from the dried and evaporated extract on alumina (grade III) [elution with petroleum–diethyl ether (20 : 1)] gave ethyl isopropyl ether (80%), identical with an authentic sample, and triethylphosphine selenide.

Reaction of O-Cholesteryl Selenopropionate with Sodium Borohydride–Triethylphosphine.—*O*-Cholesteryl selenopropionate (2 mmol) was treated with sodium borohydride–triethylphosphine as above. After stirring for 2 h at room temperature and work-up, cholesteryl propyl ether was isolated in 80% yield, and identified by comparison with an authentic specimen.[19]

Reaction of O-Cholesteryl Selenoacetate with Sodium Borohydride and Subsequent Addition of Triethylphosphine.—*O*-Cholesteryl selenoacetate (0.246 g, 0.5 mmol) in benzene (10 ml) was treated with sodium borohydride (0.020 g) in ethanol (3 ml) under argon. After stirring for 30 min, triethylphosphine (0.3 ml) was added and the mixture was stirred for 1 h. Work-up as previously described yielded cholesteryl ethyl ether (0.148 g, 71%).

Reaction of O-Cholesteryl Selenoformate with Sodium Borohydride–Triethylphosphine.—*O*-Cholesteryl selenoformate was treated with sodium borohydride–triethylphosphine as described for *O*-cholesteryl selenoacetate. No methyl ether was isolated.

Reaction of O-Cholesteryl Selenobenzoate with Sodium Borohydride–Triethylphosphine.—*O*-Cholesteryl selenobenzoate was treated as above. Only traces of benzyl cholesteryl ether were detected (n.m.r. and t.l.c.).

Reaction of the Selenobenzoates (8) *and* (9) *with Tri-n-butylphosphine in the Presence of Atmospheric Oxygen.*—The selenobenzoate (1 mmol) in benzene (15 ml) was treated with tri-n-butylphosphine (2.0 g, 10 mmol) over 3 h. Methyl iodide (3 ml) was then added, the mixture was evaporated, and the residue was extracted with petroleum. Evaporation of the extracts and chromatography of the residue on silica gel [elution with petroleum–diethyl ether (4 : 1)] gave the benzoates and tri-n-butylphosphine selenide, identical with authentic samples. *O*-Cholestanyl selenobenzoate (8) gave cholestanyl benzoate (0.477 g, 97%) and *O*-cholesteryl selenobenzoate (9) yielded cholesteryl benzoate (0.461 g, 94%).

Reaction of O-Cholesteryl Selenoacetate (17) *with Triethylphosphine.*—*O*-Cholesteryl selenoacetate (17) (1 mmol) in benzene (10 ml) was heated at 70 °C for 4 h with triethylphosphine (0.472 g, 4 mmol) under argon. The purple mixture was then exposed to the atmosphere until the colour had disappeared. Work-up by addition of methyl iodide, filtration, evaporation, and chromatography on alumina (grade III) [elution with petroleum–ethyl acetate (4 : 1)] gave cholesteryl acetate (0.382 g, 87%) and triethylphosphine selenide (0.179 g, 95%), both identical with authentic samples.

Reaction of O-Cholesteryl Selenoformate with Sodium Borohydride and Subsequent Addition of Triethylphosphine.—*O*-Cholesteryl selenoformate (0.48 g, 1 mmol) in benzene (20 ml) was treated with sodium borohydride (40 mg) in ethanol (5 ml) under argon at 0 °C. After 2 min, the colourless solution was treated with triethylphosphine (0.6 ml) and was then stirred at room temperature for 6 h. The mixture was worked up as described for *O*-cholesteryl selenoacetate and the product chromatographed on alumina (grade III). Elution with petroleum gave cholesteryl methyl ether, leaflets (0.256 g, 64%) from methanol, m.p. 84—85°, $[\alpha]_D$ −43.4° (*c* 0.6) (lit.,[19] m.p. 84.5—85°, $[\alpha]_D$ −45.8°).

Reaction of O-Cholesteryl Selenobenzoate with Sodium Boro-

[19] E. Müller and J. H. Page, *J. Biol. Chem.*, 1933, **101**, 127

hydride and Subsequent Addition of Triethylphosphine.—*O*-Cholesteryl selenobenzoate (0.277 g, 0.5 mmol) in benzene (10 ml) was treated with sodium borohydride (0.150 g) suspended in ethanol (7.5 ml) under argon. After the mixture had become colourless (4 h), triethylphosphine (0.6 ml) was added and the mixture was then stirred at room temperature for 15 h and at 70 °C for 5 h. Work-up as described for the reaction of *O*-cholesteryl selenoacetate and chromatography on alumina (grade III) (elution with petroleum) gave benzyl cholesteryl ether (0.024 g, 10%), m.p. 118—119° (lit.,[18] 118.5°), identical with an authentic sample, and a mixture of cholesterol and triethylphosphine selenide (0.238 g), eluted with diethyl ether.

Reduction of the Selenobenzoates (8), (30), *and* (11) *with Raney Nickel.*—Raney nickel (W2; 1 g per 0.5 mmol of selenoester) was added to a solution of the selenobenzoate in dry tetrahydrofuran (10 ml). After stirring at 0 °C until the mixture was colourless, the nickel was filtered off and the solution was evaporated. The benzyl ethers were purified as described below.

(*a*) *O*-Cholestanyl selenobenzoate (8) (0.277 g, 0.5 mmol) afforded, after chromatography on alumina (elution with petroleum), *benzyl cholestanyl ether*, which crystallised from ethanol as prisms (0.154 g, 64%), m.p. 106—107°, $[\alpha]_D$ +15.1° (*c* 0.7), $\nu_{max.}$ ($CHCl_3$) 1 605w, 1 455s, 1 365s, 1 305w, 1145w, 1 135w, 1 070s, and 950w cm^{-1}, $\lambda_{max.}$ (cyclohexane) 257 nm (ε 170), δ 7.23 (5 H, m), 4.51 (2 H, s), and 3.32 (1 H, m), *m/e* 478 (M^+), 469, 463, 421, 387, 370, and 355 (Found: C, 85.0; H, 11.35. $C_{34}H_{54}O$ requires C, 85.3; H, 11.35%), identical with a sample prepared by treatment of cholestanol with potassium hydride and benzyl chloride.

(*b*) *O*-Ethyl selenobenzoate (30) (0.852 g, 4 mmol) yielded, after chromatography on alumina (elution with petroleum), benzyl ethyl ether, b.p. 185—187° (lit.,[18] 189°).

(*c*) (With Dr. R. Bielski.) Methyl 4,6-*O*-benzylidene-3-*O*-selenobenzoyl-α-D-glucopyranoside (11) (0.090 g, 0.2 mmol) gave methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (0.048 g, 65%), m.p. 186—188° (from diethyl ether), $[\alpha]_D$ +75.1° (*c* 0.9) (lit.,[20] m.p. 185°, $[\alpha]_D$ +84°).

O-*Cholesteryl* 3-*Cholesteryloxyselenocrotonate* (46).—Potassium hydride (*ca.* 0.15 g) suspended in tetrahydrofuran (10 ml) was treated with hexamethyldisilazane (1.0 g). After hydrogen evolution had ceased, 0.5 ml of the solution was added dropwise to a solution of *O*-cholesteryl selenoacetate (0.246 g, 0.5 mmol) in tetrahydrofuran (10 ml) under nitrogen. Further portions (3 × 10 ml) of the basic solution were added at 1 h intervals, and the mixture was stirred at room temperature overnight. The resulting red-brown suspension was diluted with water and extracted with ether; the extracts were dried and evaporated and the residue was chromatographed on alumina (grade III). Elution with light petroleum gave the crude *selenocrotonate* (46) (0.133 g, 59%), which crystallised from light petroleum as yellow needles, m.p. 189—191°, $[\alpha]_D$ −116° (*c* 0.25), $\nu_{max.}$ ($CHCl_3$) 1 560s, 1 370m, 1 105m, and 1 000m cm^{-1}, $\lambda_{max.}$ (cyclohexane) 344 and 267 (ε 14 900 and 10 800), δ 6.20 (1 H, s), 5.36 (3 H, m), 4.00 (1 H, m), and 2.07 (3 H, s), *m/e* 532, 530, 528, 386, 369, and 353 (Found: C, 77.05; H, 10.35. $C_{58}H_{94}O_2Se$ requires C, 77.2; H, 10.5%).

Dimethylketen O-*Ethyl* Se-*Methyl Monoselenoacetal* (47).—*O*-Ethyl selenoisobutyrate (0.72 g, 4 mmol) in tetrahydrofuran (10 ml) under nitrogen was treated with a solution of potassium bis(trimethylsilyl)amide (2 ml) [from potassium hydride (*ca.* 0.4 g) and hexamethyldisilazane (2.4 g) in tetrahydrofuran (10 ml)]. Further portions (3 and 5 ml) of the basic solution were added to the mixture at 0.5 h intervals. After 1 h at room temperature, methyl iodide (5 ml) was added and the mixture was then diluted with water and extracted with dichloromethane; the extracts were dried and evaporated. The residue was chromatographed on alumina (grade III) and the fraction eluted with petroleum was concentrated and distilled to give the dimethylketen monoselenoacetal (47) (0.42 g, 54%) as a pale yellow oil, b.p. 40—42° at 5 mmHg, $\nu_{max.}$ ($CHCl_3$) 1 645m, 1 440m, 1 385m, 1 130s, 1 020m, 960w, 910m, 880m, and 855m cm^{-1}, $\lambda_{max.}$ (EtOH) 264 nm (ε 1 270), δ 3.82 (2 H, q, *J* 7 Hz), 2.03 (3 H, s), 1.81 (3 H, s), 1.77 (3 H, s), and 1.24 (3 H, q, *J* 7 Hz).

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