SYNTHESIS AND REACTIONS OF THIO- AND SELENOESTERS

by

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DEDICATION

To

My Wife

for her understanding

and support at all times

CONTENTS

PART III

ABSTRACT

A brief review of the preparation and properties of seleno-carbonyl compounds is presented.

The preparation of the thioesters was accomplished via the corresponding amidochloride/imidate ester with subsequent reaction with hydrogen sulphide. O-Cholestanyl o-nitrothiobenzoate was prepared from the corresponding imidoyl chloride.

The dithiocarbonates were prepared by the reaction between the O-cholestanyl anion and the respective halogenated hydrocarbon.

Treatment of the imidate ester derived from N,N-dimethyl-o-benzoylbenzamide and cholestanol with hydrogen sulphide resulted in the formation of O-cholestanyl o-benzoylthiobenzoate and O-cholestanyl o-thiobenzoylbenzoate.

The irradiation of the O-cholesteryl thioesters gave cholesta-3,5-diene.

The irradiation of O-cholestanyl thioacetate and O-cholestanyl thioformate resulted in the formation of the corresponding S-cholestanyl thioesters, both epimers.

The irradiation of O-cholestanyl S-phenacyl dithiocarbonate gave acetophenone and di-O-cholestanyl dithiobis thioformate.

The irradiation of O-cholestanyl o-benzoylthiobenzoate and O-cholestanyl S-(2,4-dinitrophenyl) dithiocarbonate resulted in the rupture of the thiocarbonyl carbon atom oxygen atom bond.

Explanations for the photochemical reactions are suggested.

A general synthesis of selenoesters has been developed. The different complications that can arise in this preparation is discussed.

The selenobenzoates reacted with methylenetriphenylphosphorane

and gave the corresponding α-alkoxystyrenes.

The reaction between triethylphosphine and the selenobenzoates gave the corresponding benzyl ethers and the disubstituted dialkoxystilbenes.

The reaction between the aliphatic selenoesters and triethylphosphine gave a purple intermediate which gave the corresponding α-alkoxytriethylphosphonium iodide and dimethyl selenide when reacted with methyl iodide.

The reaction between the selenoesters and triethylphosphine in the presence of atmospheric oxygen gave the corresponding esters.

Based on its reactivity and its physical data a structure of the purple intermediate is presented.

The reaction between the selenobenzoates and triethylphosphine gave the carbene trapped product when performed in cyclohexane. This same reaction gave the Wittig product when performed in the presence of benzaldehyde.

Based on these reactions and the recorded physical data a mechanism for these reactions is presented.

The aliphatic selenoesters gave when treated with sodium borohydride the corresponding dialkyl diselenides and the corresponding alcohols.

When the aliphatic selenoesters were treated with sodium borohydride in the presence of triethylphosphine the corresponding ethers were produced.

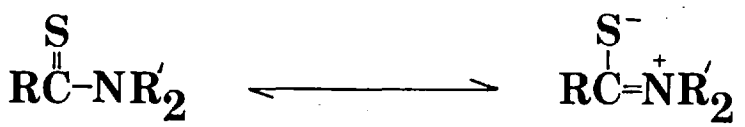
PART I.

CHAPTER 1.

SYNTHESIS AND PROPERTIES OF SELENOCARBONYL COMPOUNDS.

A. INTRODUCTION.

Selenium is the third member of group VIb in the periodic table, and is therefore expected to have properties similar to sulphur. A number of different thiocarbonyl compounds are well documented in the literature. Most of these compounds have, however, one thing in common, a heteroatom with a free lone pair next to the thiocarbonyl carbon atom (e.g. thioamides). This stabilizes the thiocarbonyl function through resonance.



This principle also applies to thiocarbonyl compounds with a heteroatom situated in the molecule in such a way that it can stabilize the thiocarbonyl function through resonance (e.g. pyran-4-thiones).

Nevertheless, thiocarbonyl compounds without this kind of stabilization are also known, though these compounds are rather unstable. Aliphatic thioaldehydes are still unknown, whereas aliphatic thioketones have been known since 1964 [1,2]. Aromatic thioketones and thioaldehydes are also well known because of their ability to be stabilized by the aromatic system. The aliphatic thiocarbonyl compounds are unstable in the monomeric form because sulphur does not easliy form a P_π-P_π double bond with the carbon atom. These two elements belong to different groups. Overlap of the $2P_\pi$ orbital of the carbon atom with the $3P_\pi$ orbital of the sulphur atom is therefore rendered more difficult. Thus the thiocarbonyl group tends to turn into a carbon-sulphur single bond, by enethiolization, dimerisation,

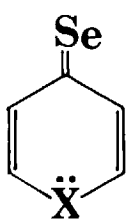
trimerisation or polymerisation.

Taking these observations into account it is therefore not surprising to find that the bulk of information about selenocarbonyl compounds in the literature deals with compounds that have two heteroatoms with a free lone pair next to the selenocarbonyl carbon atom.

In this review the selenocarbonyl compounds are accordingly divided into three groups.

1. Those with two stabilizing heteroatoms next to the selenocarbonyl carbon atom.

2. Those with only one stabilizing heteroatom next to the selenocarbonyl carbon atom or situated in such a way that it can stabilize the selenocarbonyl function through resonance.



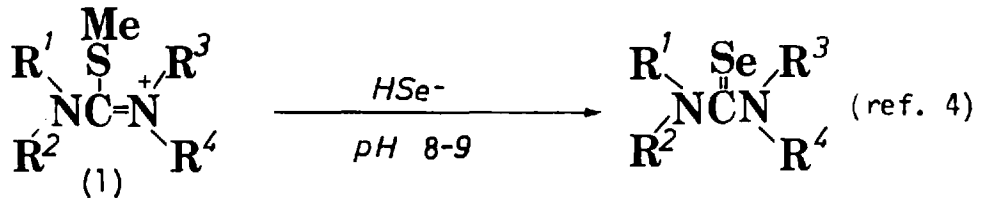
3. Aliphatic and aromatic selenoketones and selenoaldehydes.

B. SYNTHESIS AND PROPERTIES OF SELENOCARBONYL COMPOUNDS.

1. TWO STABILIZING HETEROATOMS.

The preparation of selenoureas are usually accomplished in one of the three following ways:

1. $RN{=}C{=}Se + R'NH_2 \longrightarrow RNH\overset{\overset{Se}{\|}}{C}NHR'$ (ref. 3)

2. 

3. $CSe_2 + 2RNH_2 \longrightarrow RNH\overset{\overset{Se}{\|}}{C}NHR + H_2Se$ (ref. 5)

The most general of these methods is probably the displacement of the methylthio group from the thiopseudourea(1) by the hydroselenide ion, especially for tetrasubstituted selenoureas which are difficult to prepare by other methods. Method 1 has been used to make mono, di and trisubstituted selenoureas, whereas method 3 usually is used to make symmetrically disubstituted selenoureas.

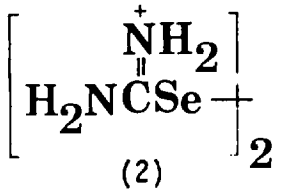
The selenoureas are crystalline stable solids, and normally stable to air and light.

The selenoureas behaves analogously to the thioureas with regards to alkylation and oxidation. They are readily alkylated on selenium by alkyl sulphates, alkyl halides [6] or conjugated carbon-carbon multible bonds [7].

$$2\,H_2N\overset{\overset{Se}{\|}}{C}NH_2 + Me_2SO_4 \longrightarrow \left[H_2NC(\overset{SeMe}{|})=NH\right]_2\cdot H_2SO_4$$

$$CH_2{=}CHCO_2H + H_2N\overset{\overset{Se}{\|}}{C}NH_2 \xrightarrow{HCl} H_2NC(\overset{SeCH_2CH_2CO_2H}{|})=\overset{+}{N}H_2\,Cl^-$$

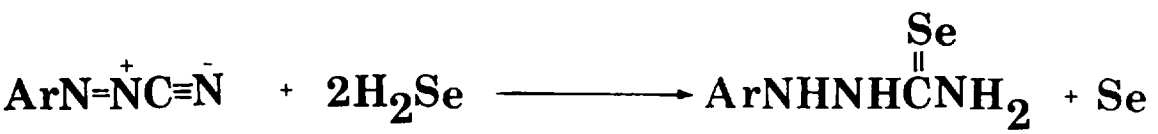
When subjected to oxidation by hydrogen peroxide [8], selenoureas form the α,α'-diselenobisformamidinium cation (2).



(2)

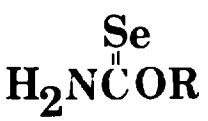
The preparation of selenosemicarbazides is usually accomplished by the reaction between an isoselenocyanate and a hydrazine [9], or the

reaction between an aromatic diazonium cyanide and hydrogen selenide [10]



The selenosemicarbazides are generally stable crystalline solids. In analogy with the semicarbazides, the selenosemicarbazides react with aldehydes and ketones to give selenosemicarbazone derivatives [11], and when subjected to alkyl halides or alkyl sulphates, alkylation on selenium occurs [9].

Other selenocarbonyl compounds with two stabilizing heteroatoms are the selenocarbamates(3), the selenothiocarbamates(4), the diselenocarbamates(5) and the Se-carboxymethyl-O-alkyl diseleno-carbonates(6).



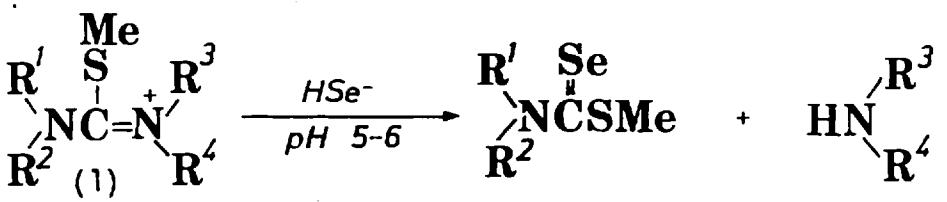
(3)

(4)

(5)

(6)

The selenothiocarbamates(4) have been prepared by displacement of the amino group from the thiopseudourea(1) by the hydroselenide ion at pH 5-6 [4].



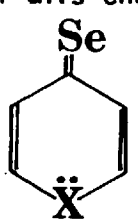
The selenocarbamates(3) can be prepared by the addition of hydrogen selenide to alkyl cyanates [12], and the esters of diselenocarbamates(5) have been prepared by alkylation of sodium dialkyl diselenocarbamate [13].

Derivatives of Se-carboxymethyl-O-alkyl diselenocarbonates(6) have been prepared by the reaction between potassium O-ethyl diselenocarbonate and chloroacetic acid [30]. It was observed that these compounds decomposed slowly at room temperature.

The properties and chemistry of these last four mentioned compounds have yet to be thoroughly investigated.

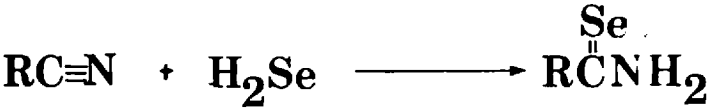
2. ONE STABILIZING HETEROATOM.

Of the compounds with only one stabilizing heteroatom, the selenoamides are best known. Other types of compounds with this feature are, O-alkyl and O-aryl monoselenoates, S-alkyl and S-aryl selenothioates, diselenoates and selenohydrazides. The selenocarbonyl compounds of the type 8 are also included in this chapter.



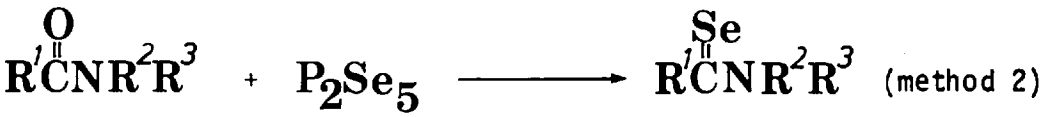
(7)

The selenoamides can be prepared by adding hydrogen selenide to a nitrile [14].



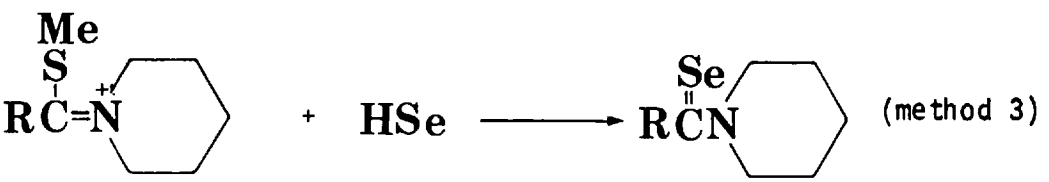
(method 1)

Phosphorus pentaselenide has also been used to prepare selenoamides. However, this method gives poor yields [15].



(method 2)

The best method for preparing tertiary selenoamides is the displacement of the methylthio group from the S-methylated thioamide(8) [16].

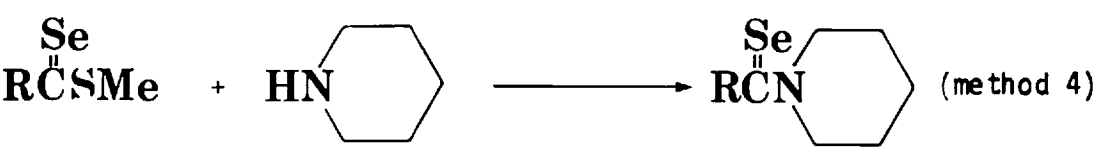


(method 3)

(8)

This is in principle the same method used for the preparation of tetrasubstituted selenoureas.

The reaction between S-alkyl thioselenocarboxylates and piperidine have also been employed in the synthesis of selenoamides [17].

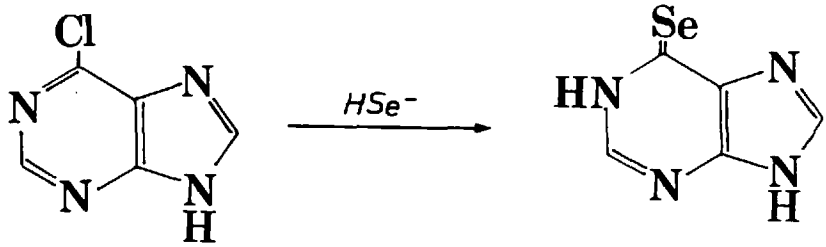


(method 4)

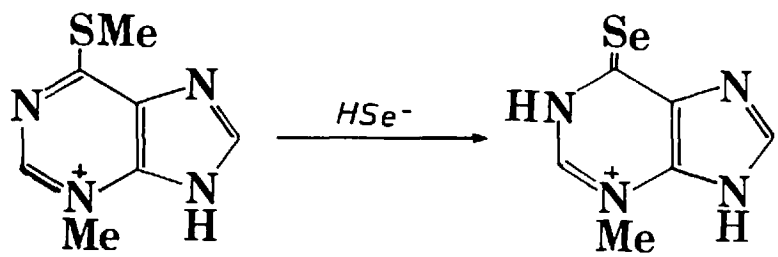
By this method the following series has been made in good yield: R=Ph, p-MeOPh, benzyl and Me [17].

Interest in the synthesis of the selenium analogues of biologically important sulphur compounds, has received much attention, and some heterocyclic compounds containing the selenocarbonyl function have been made. These derivatives have either been prepared by the reaction

between the corresponding chlorocompound and sodium hydrogen selenide [45,46].



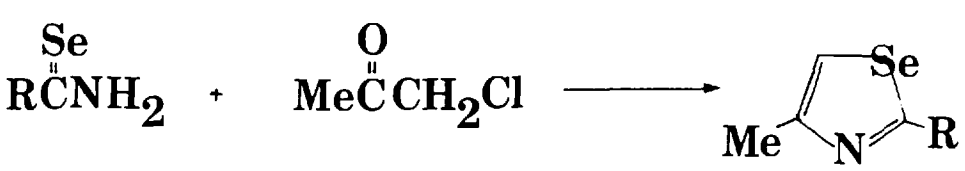
or analogously to the preparation of selenoureas via displacement of the methylthio group from a thiopseudourea with sodium hydrogen selenide [4,47].



As for the generality of the above mentioned methods, method 1 is only applicable to promary selenoamides, method 2 only to secondary and tertiary selenoamides and method 3 only to tertiary selenoamides. Method 4 should, however, be applicable to primary, secondary and tertiary selenoamides. This method has yet to be explored.

The primary selenoamides are reported [14] to be unstable solids that discolour rapidly in light. The stability of the selenoamides increases from primary to tertiary.

The primary selenoamides when reacted with α-chloroacetone condenses to give selenazoles(9) [18,19].



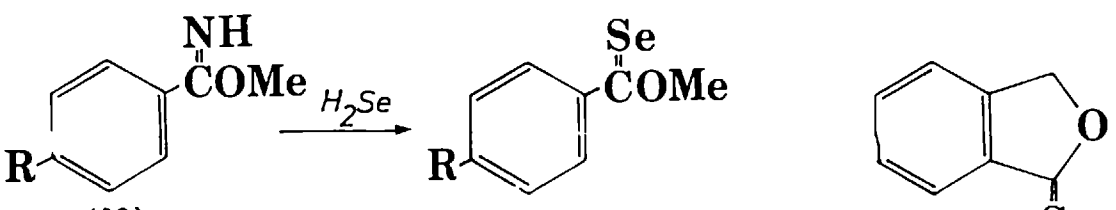
(9)

Cyclic products also arise when selenoamides are oxidated with iodine [20], and alkylation has been shown to take place on selenium giving selenoamidium salts [15]. In recent years the selenoamide group has been studied in order to determine the importance of the resonance form(II).

I II

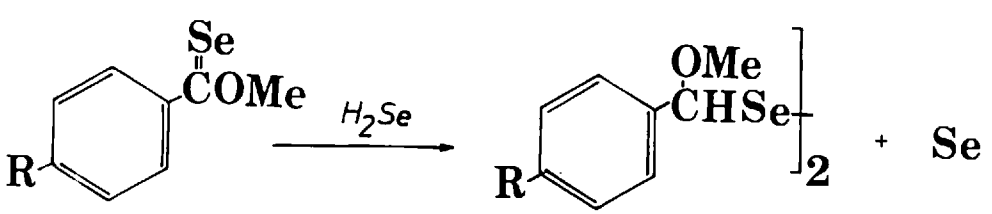
From ^{1}H n.m.r. studies it has been concluded that the form(II) is the more important [21,22].

Of the esters that can be derived from monoselenocarboxylic acid, Se-alkyl (or -aryl) momoselenoates or O-alkyl (or -aryl) monoselenoates, the Se-alkyl and -aryl monoselenoates are best known [48,49]. The first ester of the other type to appear were O-methyl selenobenzoate and O-methyl seleno-p-toluate [23]. These were prepared by the reaction between the imidoester(10) and hydrogen selenide in 5,6% and 3,0% yield, respectively



(10) R=H, Me. (11) (12)

These selenoesters are red stable oils. Further reaction of the selenoester(11) with hydrogen selenide explaines the low yield in this preparation.



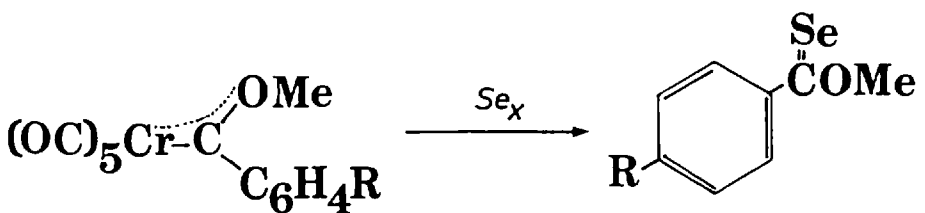
(11) R=H, Me.

This preparation have been improved [24], by reacting the imidoester(10) hydrochloride in pyridine with hydrogen selenide. The yield in this modification was 36%.

An internal selenoester(12) has also been prepared using this same method [25].

When this method was used in an attempt to prepare an aliphatic selenoester (O-methyl selenoacetate), a product was isolated whose elemental analysis and i.r. spectrum showed that it was not the desired compound [23].

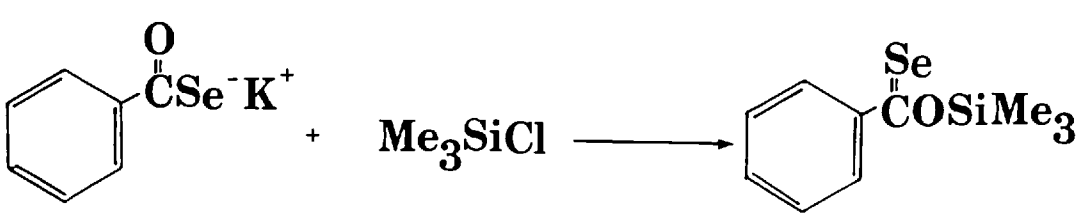
The aromatic selenoester(11) was also prepared by the reaction between pentacarbonyl(methoxyarylcarbene)chromium(0) complexes and selenium [26], with yields ranging from 12% to 29%.



(11)

R=H, Me, OMe, Cl.

A preparation of a compound which also must be classified as a selenoester, namely (selenobenzoyloxy) trimethylsilane(13), has also appeared [27]. This molecule is prepared by the reaction between chlorotrimethylsilane and potassium selenobenzoate.

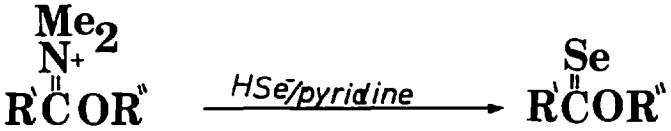


(13)

This compound is also a red oil.

Recently the best method for making selenoesters appeared [28].

This method employs the reaction between an imidoester hydrochloride, pyridine and sodium hydrogen selenide. In this way O-ethyl selenobenzoate(14) and O-cholesteryl selenobenzoate(15) have been made in high yields (97% and 78%).



R' =H, R'' =Cholesteryl(16).

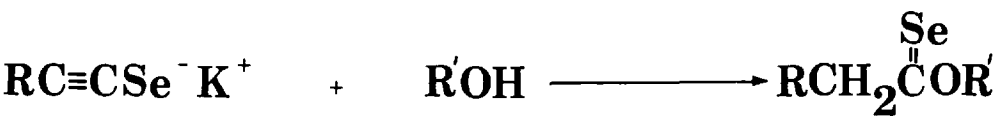
R' =Ph, R'' =Et (14).

R' =Ph, R'' =Cholesteryl (15).

R' =H, R'' =Cholesteryl (17).

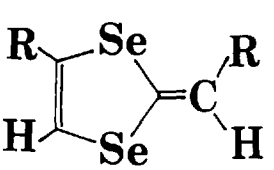
This method afforded also the first known aliphatic selenoester, by reacting cholesteryl N,N-dimethylformimidate hydrochloride(16) with pyridine and sodium hydrogen selenide. O-Cholesteryl selenoformate(17) is a rather unstable yellow solid [28].

Another account concerning the preparation of selenoesters has recently appeared [29]. This preparation deals with the reaction between arylethynylselenolate salts(18) and alcohols.



(18)

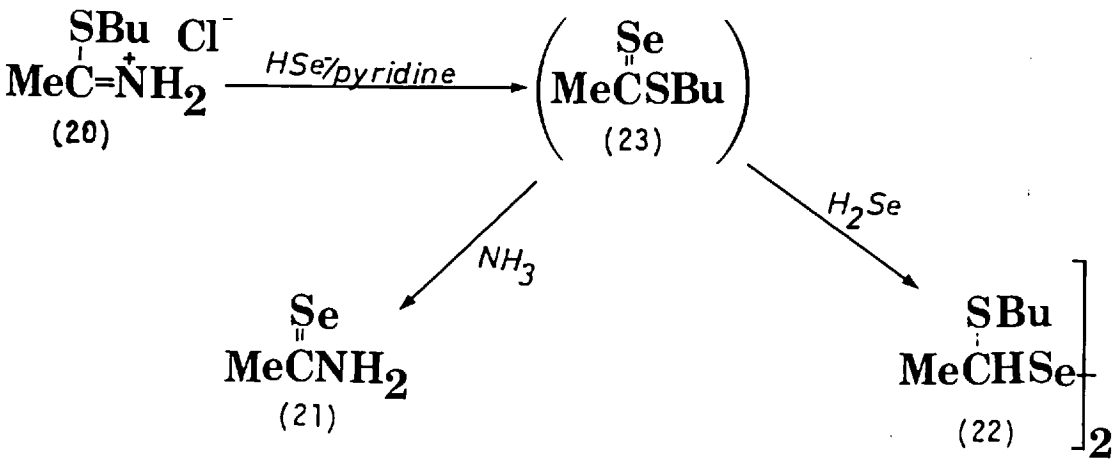
A series of α-aryl substituted selenoesters were prepared in this way. By using a technique of slow addition to a slightly acidified solution, such that the concentration of (18) never exceeded 10^{-5} M, the formation of a side product could be kept low. The side product in question is the fulvene(19).



(19)

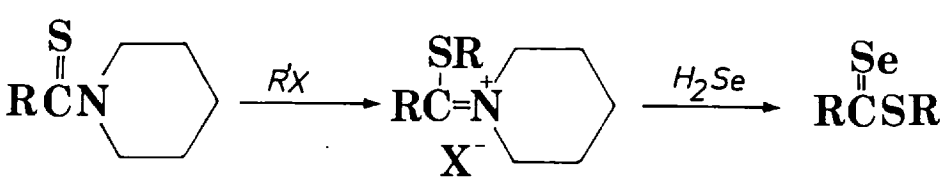
The properties and chemistry of these selenoesters have not yet been investigated.

S-Alkyl and -aryl selenothioates are also known from the literature. The first attempt to make this class of compound employed the reaction between S-butyl thioimidoacetate hydrochloride(20) and hydrogen selenide in pyridine [23]. The isolated products from this reaction were, however, the selenoamide(21) and the dialkyl selenide(22). The formation of these products has been explained via the S-butyl selenothioacetate(23), and its reaction with ammonia and hydrogen selenide.



The preparation of S-ethyl selenothiobutyrate has been reported [31]. It is, however, doubtful whether this was the isolated product, as neither analytical nor spectral data were given.

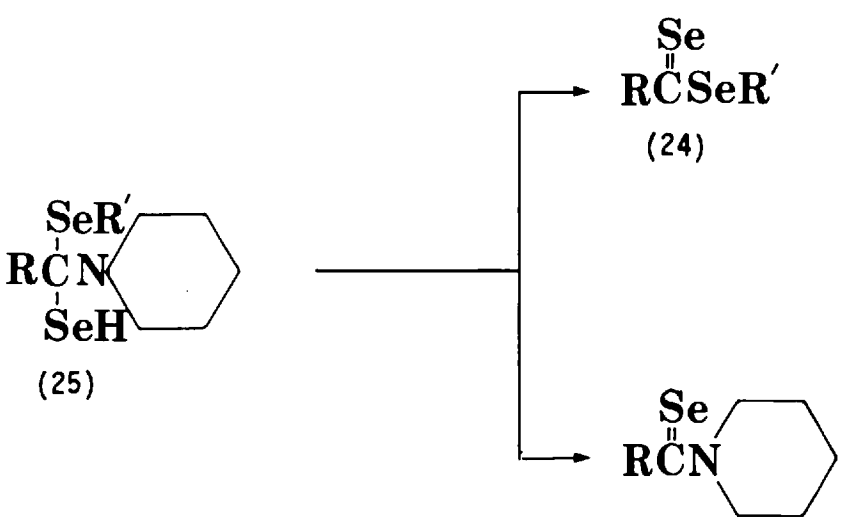
Extension of the method used for the preparation of esters of dithiocarboxylic acid [32] proved successful when applied to the preparation of S-alkyl selenothioates [17].



R'X= MeI, $BrCH_2COOH$.

This preparation was performed under oxygen free conditions, and with low concentration of hydrogen selenide. The principle of low concentration of hydrogen selenide was necessary in order to avoid the previously observed redoction [23] of the formed S-alkyl selenothioates. This low concentration of hydrogen selenide was achieved by leading the hydrogen selenide gas into the reaction mixture without letting it bubble thruogh the solution. In this way several selenothioates were made. The aliphatic esters were redviolet to violet compounds and the aromatic esters were green. The stability of these compounds appeared to be greatest when R' was carboxymethyl, whereas when R' was methyl a somewhat lower stability was observed. These compounds could be stored for several months at -30°C under oxygen free conditions without any destruction.

Esters of diselenocarboxylic acid(24) have been prepared analogously to the selenothioates[17]. A competing reaction was, however, observed in this preparation. The intermediate(25) eliminated with cleavage of both the C-N bond and the C-Se bond, giving diselenoates(24) and selenoamides.

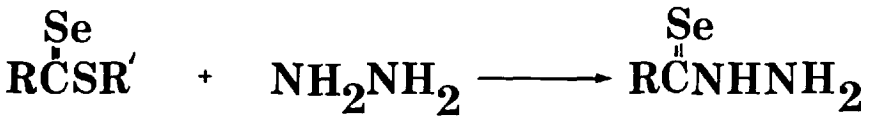


The only diselenoate prepared in high yield with correct analytical data was Se-methyl diselenobenzoate. Se-carboxymethyl diselenobenzoate

was isolated as a dark green impure oil. Several other Se-methyl and Se-carboxymethyl selenoacyl piperidinium salts gave purple to green solutions on treatment with hydrogen selenide, but the pure diselenoates could not be obtained.

Very little is known about the properties and reactivities of these compounds.

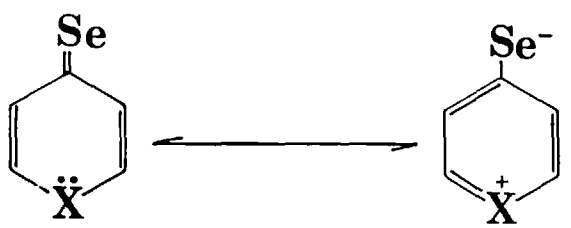
As the last selenocarbonyl compound with a stabilizing heteroatom next to the carbonyl carbon atom, the selenohydrazides should be mentioned. These compounds were prepared analogously to the method used for the preparation of thiohydrazides [33,17].



R= t-Bu, p-MeOPh, Ph.

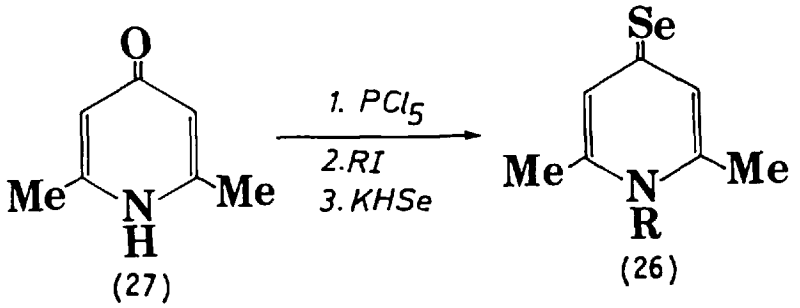
This method gave the hydrazides in yields ranging from 9% to 31%.

Selenocarbonyl compounds of the type 7, can also be regarded as compounds which are stabilized by the lone pair of the heteroatom.



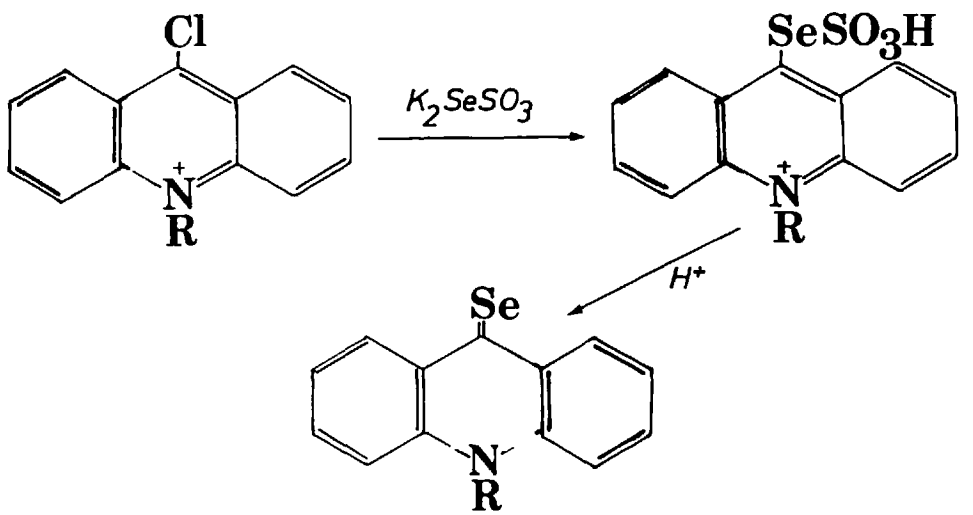
(7) X= O, S, NR.

The first member in this class of compounds to appear was the γ-selenolutidone(26). This compound was prepared from the lutidone(27), by chlorination, alkylation and treatment with potassium hydrogen selenide [34].



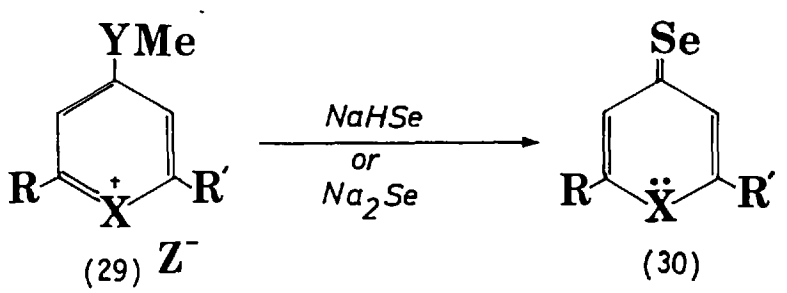
(27) (26)

A similar route was employed to prepare the N-methyl, N-ethyl and N-phenyl selenoacridones(28) [35]. Instead of using sodium hydrogen selenide, the selenium was introduced using potassium selenosulphate.



(28)

4-Seleno-γ-pyrones and thiopyrones(30) have been prepared in 50% yield, by displacing the methylthio or methyloxy group from the pyrylium salt(29), using sodium hydrogen selenide or sodium selenide [36,37].



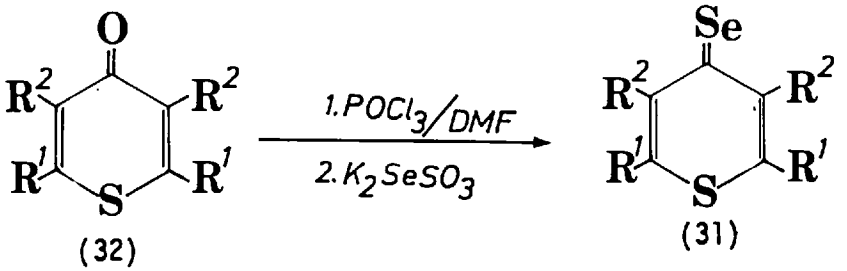
(29) (30)

X= O, S.

Y= O, S.

Z= ClO_4^- , I^- , $MeSO_4^-$.

4-Seleno-4H-thiopyran-4-ones(31) have also recently been prepared by reacting the corresponding 4H-thiopyran-4-ones(32) with phosphoryl chloride in dimethylformamide, and subsequently with potassium selenosulphate[38].



(32) (31)

$R^1=R^2=H$ (31a)

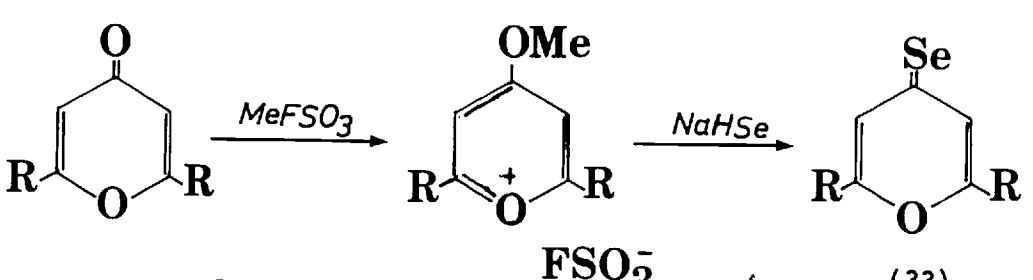
$R^1=H$. $R^2=Me$ (31b)

$R^1=Ph$. $R^2=H$ (31c)

The advantages in using selenosulphate in place of selenide or hydroselenide ion for the introduction of selenium come from the fact that it is a non-reducing, non-toxic, easily handled solid.

The selenoketone(30. X=S, R=R'=Me) is reported to be thermally unstable [36], and the selenoketone (30. X=O, R=R'=Ph) could not be isolated due to its instability [36]. Isolation of the selenoketones (31a and 31c) resulted in extensive deposition of selenium, and this decomposition was especially rapid in the case of compound 31c [38]. The selenoketone(31b) however was isolated and characterized [38].

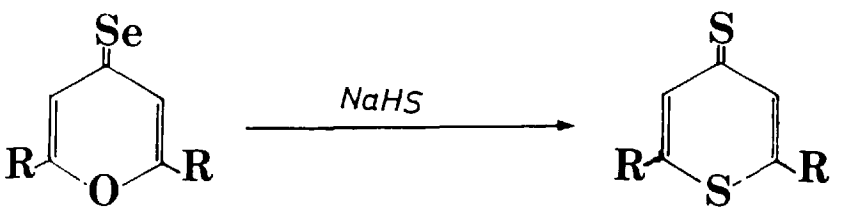
A modification of the synthesis of the pyran-4-selones(33) has also appeared [39]. In this modification the 4-pyrones were methylated on oxygen using methyl fluorosulphate, and the salt was then treated with sodium hydrogen selenide.



R=H, Me. (34) (33)

Only the previously known dimethyl selenoketone(33. R=Me)[37] was isolated and characterized. It was found that these compounds were moderately stable and extruded selenium with ease to form 4,4'-bipyranylidene derivatives.

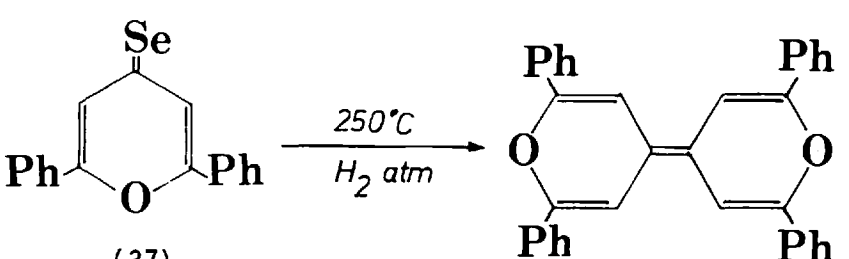
The selenoketones described in this section are all highly coloured compounds (from blue to red). The chemistry of these compounds have been investigated to some extent. Alkylation occured on selenium [36,37,40]. The selenoketone(35) was transformed into the dithiopyrone(36) when it was treated with two equivalents of sodium hydrogen sulphide.



(35) (36)

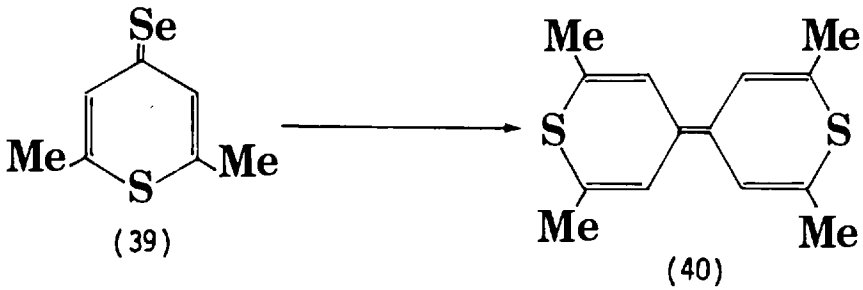
This dithiopyrone(36) could be further transformed into the selenoketone(30, X=S) by treatment with methyl iodide and sodium hydrogen selenide [36,37].

When the selenoketone(37) was heated in a hydrogen atmosphere, a dimer(38) was formed [36].



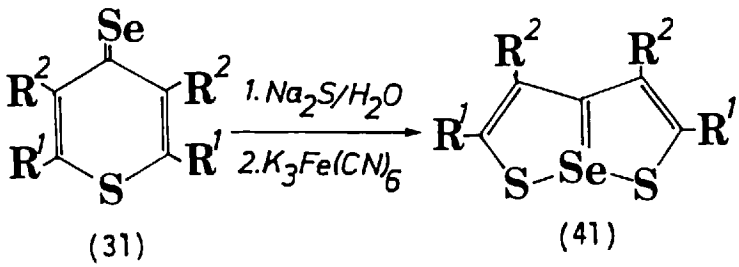
(37) (38)

Likewise was the selenoketone(39) transformed into a dimer(40) when boiled in ligroin (70-90°C) [36].

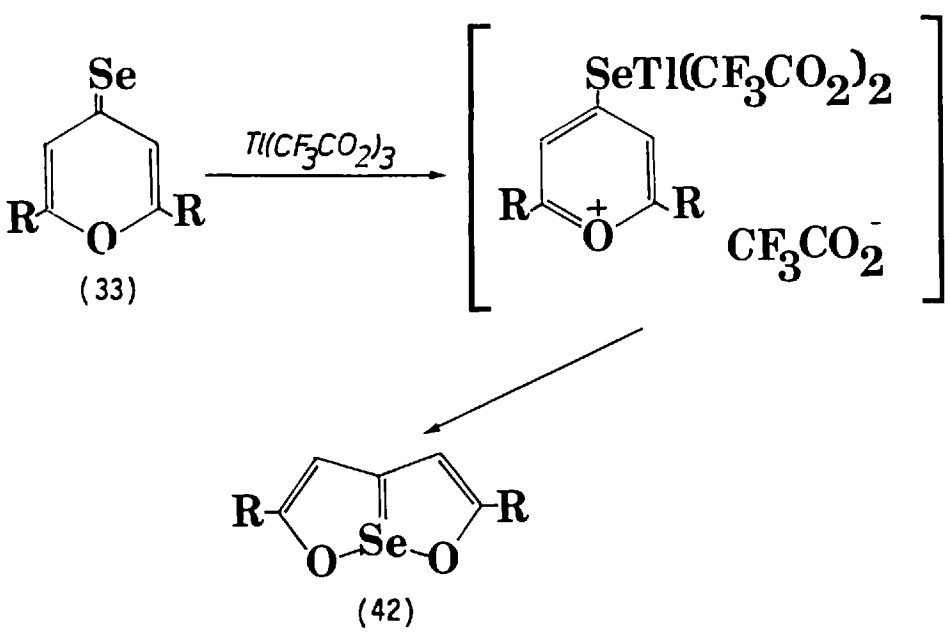


(39) (40)

The selenoketones(31 and 33) have been used in the synthesis of the heterocyclic compounds(41) and (42) [38,39].



(31) (41)

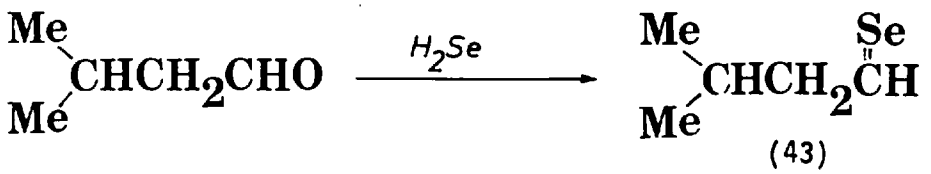


(33) (42)

3. ALIPHATIC AND AROMATIC SELENOKETONES AND SELENOALDEHYDES:

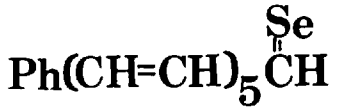
The preparation of aliphatic or aromatic selenoketones and selenoaldehydes with no heteroatom stabilization has received some

attention over the years. However, in most cases the isolated products had structures of dimeric or trimeric nature. In one account the seleno-aldehyde(43) has been isolated, but since the method used ih this preparation has failed with other aliphatic aldehydes, its authenticity is questionable [41,42].



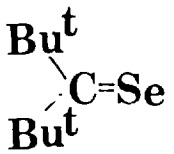
(43)

One other selenoaldehyde(44) has been claimed to have been made by a similar method [43].

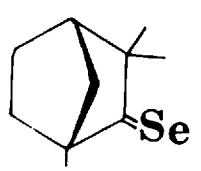


(44)

To the best of my knowledge only one well documented account dealing with monomeric selenoketones has appeared in the literature. This deals with the preparation of the selenoketones(45) and (46) [44].



(45)



(46)

These compounds have been prepared by heating the corresponding triphenylphosphoranylidene hydrazones with selenium powder. The ketone (45) was isolated as a blue oil and the ketone(46) as blue crystals. Both selenoketones are stable under nitrogen on prolonged heating at 150 C.

The chemistry of these compounds is at present under investigation in this laboratory.

REFERENCES

1. M. Demuynck and J. Vialle, Bull. Soc. Chim. France, 1967, 2748.
2. R. Mayer, J. Morgenstern and J. Fabian, Angew. Chem. Intern. Ed. Engl, 1964, 3, 277.
3. H. Stolte, Ber., 1886, 19, 2350.
4. D. L. Klayman and R. J. Shine, J. Org. Chem., 1969, 34, 3549.
5. J. S. Warner, J. Org. Chem., 1963, 28, 1642.
6. A. Senning and O. N. Sørensen, Acta. Chem. Scand., 1966, 20, 1445.
7. E. G. Kataev, L. K. Konovalova and E. G. Yarkova, Zh. Org. Khim., 1969, 5, 621.
8. A. Chiesi, G. Grossoni, M. Nardelli and M. E. Vidoni, J. C. S. Chem. Comm., 1969, 404.
9. C. Collard-Charon, R. Huls and M. Renson, Bull. Soc. Chim. Belges, 1962, 71, 541.
10. C. Collard-Charon, R. Huls and M. Renson, Bull. Soc. Chim. Belges, 1962, 71, 554.
11. E. Bulka, W. Dietz, H. G. Patzwaldt and H. Beyer, Chem. Ber., 1963, 96, 1996.
12. K. A. Jensen, M. Due, A. Holm and C. Wentrup, Acta. Chem. Scand., 1966, 20, 2091.
13. M. L. Shankaranarayana, Acta. Chem. Scand., 1970, 24, 351.
14. C. Collard-Charon and M. Renson, Bull. Soc. Chim. Belges., 1963, 72, 304.
15. K. A. Jensen and P. H. Nielsen, Acta, Chem. Scand., 1966, 20, 597.
16. H. Hartman, Z. Chim., 1971, 11, 60.
17. K. A. Jensen, H. Mygind and P. H. Nielsen, Unpublished results.
18. G. Hofmann, Ann. Chem., 1889, 250, 294.

19. L. G. S. Brooker, G. H. Keyes and F. L. White, J. Am. Chem. Soc., 1935, 57, 2492.

20. W. Becker and J. Meyer, Ber., 1904, 37, 2550.

21. P. Hampson and A. Mathias, J. Mol. Phys., 1967, 13, 361.

22. G. Schwenker and H. Rosswag, Tetrahedron Lett., 1967, 4237.

23. C. Collard-Charon and M. Renson, Bull. Soc. Chim. Belges, 1962, 71, 563.

24. R. Mayer, S. Scheithauer and D. Kunz, Chem. Ber., 1966, 99, 1393.

25. M. Renson and R. Collienne, Bull. Soc. Chim. Belges., 1964, 73, 491.

26. E. O. Fischer and S. Riedmüller, Chem. Ber., 1974, 107, 915.

27. H. Ishihara and S. Kato, Tetrahedron Lett., 1972, 3751.

28. D. H. R. Barton and S. W. McCombie, J. C. S. Perkin I, 1975, 1574.

29. F. Malek-Yazdi and M. Yalpani, J. Org. Chem., 1976, 41, 729.

30. K. A. Jensen, P. A. A. Frederiksen and L. Henriksen, Acta. Chem. Scand., 1970, 24, 2061.

31. P. J. W. Schuijl, L. Brandsma and J. F. Arens, Rec. Trav. Chim. Pays-Bas, 1966, 85, 889.

32. K. A. Jensen and C. Pedersen, Acta. Chem. Scand., 1961, 15, 1087.

33. K. A. Jensen and C. Pedersen, Acta. Chem. Scand., 1961, 15, 1097.

34. A. Michaelis and A. Hölken, Ann. Chem., 1904, 331, 245.

35. K. Gleu and R. Schaarschmidt, Ber., 1939, 72, 1246.

36. G. Traverso, Ann. Chim. (Rome)., 1957, 47, 1244.

37. G. Traverso, Ann. Chim. (Rome)., 1957, 47, 3.

38. D. H. Reid, J. Chem. Soc.(C)., 1971, 3187.

39. D. H. Reid and R. G. Webster., J. C. S. Perkin I, 1975, 775.

40. A. Edinger and J. C. Ritsema, J. Prakt. Chem., 1903, 68, 72.

41. W. E. Bradt and M. Van Valkenburgh, Proc. Indiana Acad. Sci., 1929, 39, 165.

42. W. E. Bradt, J. Chem. Educ., 1935, 12, 363.

43. R. Kuhn, Angew. Chem., 1937, 50, 703.

44. T. G. Back, D. R. R. Barton, M. R. Britten-Kelly and F. S. Guziec Jr, J. C. S. Chem. Comm., 1975, 539.

45. H. G. Mautner, J. Am. Chem. Soc., 1956, 78, 5292.

46. H. G. Mautner, S. H. Chu, J. J. Jaffe and A. C. Sartorelle, J. Med. Chem., 1963, 6, 36.

47. F. Bergmann and M. Rashi, Israel J. Chem., 1969, 7, 63.

48. M. Renson and C. Draquet, Bull. Soc. Chim. Belges, 1962, 71, 260.

49. M. Renson and J. L. Prette, Bull. Soc. Chim. Belges, 1964, 73, 507.

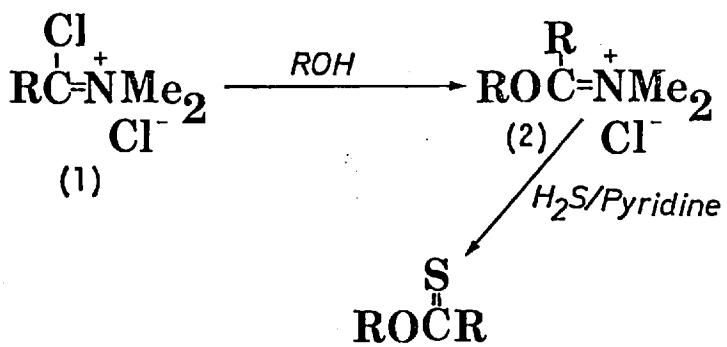
PART II

CHAPTER 1.

PREPARATION OF THIOCARBONYL ESTERS.

A. BY THE AMIDOCHLORIDE METHOD.

The preparation of this class of compounds has been accomplished by a variety of methods [1-7]. Of these methods there is one which is clearly outstanding in giving high yields, in simplicity and in easy accessibility of starting materials. This method stems from initial observations by Eilingfeld [6] which have been developed into a general synthesis in this laboratory [7]. Condensation of an alcohol with an amidochloride(1) (prepared from phosgene and a tertiary amide) gives an intermediate(2) which is converted into a thioester by reaction with hydrogen sulphide and pyridine (scheme 1).



Scheme 1.

Since this preparation is performed under essentially neutral conditions, it is possible to make aliphatic thioesters. Table 1 summarizes the steroidal thioesters prepared by this method.

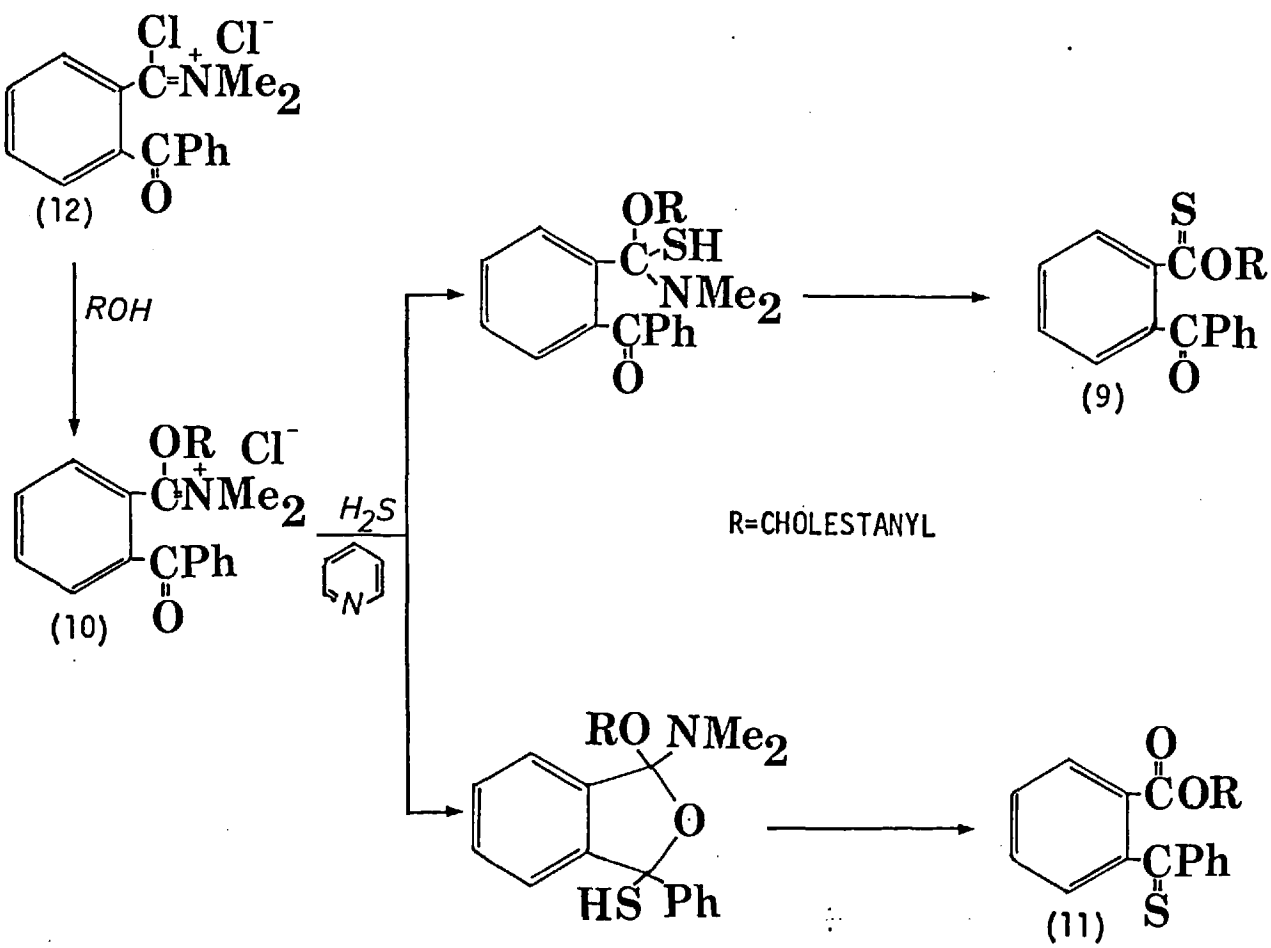
Table 1.

COMPOUND	YIELD (in %)
O-Cholestanyl thioformate [7] (3)	81
O-Cholesteryl thioformate [7] (4)	82
O-Cholestanyl thioacetate (5)	80

Table 1 contd.

O-Cholesteryl thioacetate [7] (6)	79
O-Cholestanyl thiocinnamate (7)	90
O-Cholesteryl thiocinnamate (8)	90
O-Cholestanyl o-benzoylthiobenzoate (9)	6,5

The only case in which this preparation failed to give a resonable yield was in the preparation of the o-benzoylthiobenzoate(9). The reason for this compound being an exception is that the intermediate(10) contains two possible positions which a nucleophile can attack. Attack of the hydrosulphide ion at the imidate carbon atom will give the desired product, whereas attack at the carbonyl carbon atom will give the thioketone(11) (scheme 2).



Scheme 2.

The reaction between N,N-dimethyl-o-benzoylbenzamide and phosgene was very slow, probably due to steric hindrance, but after 120 hours the reaction had gone to completion. This reaction was monitored by ^{1}H n.m.r. The two N-methyl groups of the amide gives rise to a singlet at τ=7,13, whereas these two N-methyl groups resonate as two singlets in the amidochloride(12) at τ=6,18 and τ=5,81. The reaction could therefore conveniently be followed by monitoring the disappearance of the singlet at τ=7,13 and the appearance of the two singlets at τ=6,18 and τ=5,81. By using the disappearance of the singlet at τ=7,13 as a criterion for complete transformation, it was found that this reaction took 120 hours.

The reaction between the amidochloride(12) and 3β-cholestanol was complete in 24 hours (disappearance of 3β-cholestanol on t.l.c.). When the intermediate(10) was treated with hydrogen sulphide/pyridine, the reaction mixture did not turn yellow as expected, but instead deep green, and t.l.c. of the reaction mixture, after washing with dilute hydrochloric acid and sodium hydrogen carbonate, showed two non-polar products. These were separated on a silica gel column, and were identified as the desired thiobenzoate(9) and the thioketone(11).

It was noticed that the column chromatography of the reaction-mixture gave extensive destruction of both compounds(9 and 11). This conclusion was drawn on the basis of the following observations:

A. The amount of crude material put on the column did not correspond to the amount of isolated products(9 and 11).
B. A large amount of 3β-cholestanol was also isolated from the column.
C. ^{1}H n.m.r. of the material put on the column did not indicate the presence of 3β-cholestanol (absence of the broad singlett at τ=6,45).

Integration of the two 3α-protons due to the thiobenzoate(9) (τ=4,73) and the thioketone(11) (τ=5,40) in the crude reaction-mixture,

indicated the composition to be 4:1 thioketone(11)/thiobenzoate(9).

It appeared therefore that the intermediate imidate ester(10) had been attacked by the hydrosulphide anion at both the imidate carbon atom and at the carbonyl carbon atom, with the last mentioned attack as the preferred process.

The question as to why attack at the carbonyl position should be preferred to attavk at the imidate ester position can be explained by steric and electronic considerations. The carbonyl position is the less hindered and hence more susceptible to attack. Also, the oxygen atom of the carbonyl group is polarized by the neighbouring carbon-nitrogen double bond and its electrophilicity is therefore enhanced.

B. BY OTHER METHODS.

It was also of interest to investigate the photolysis of compounds that contained a second photolabile group in addition to the thiocarbonyl group. These compounds are summarized in table 2.

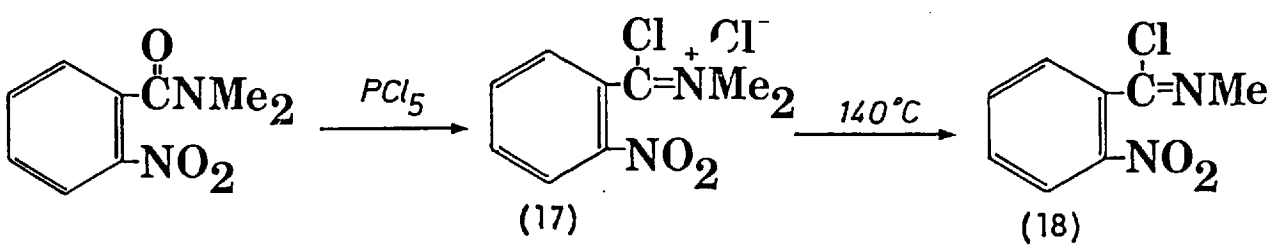
Table 2.

COMPOUND	YIELD (in %)
O-Cholestanyl o-nitrothiobenzoate (13)	65
O-Cholestanyl S-(2,4-dinitrophenyl) dithiocarbonate (14)	72
O-Cholestanyl S-phenacyl dithiocarbonate (15)	82
O-Cholestanyl S-nitromethyl dithiocarbonate (16)	0

Preparation of the o-nitrothiobenzoate(13) could not be accomplished along the pathway outlined in scheme 1. It turned out that N,N-dimethyl-

o-nitrobenzamide did not, even after 7 days, react with phosgene. Since O-cholestanyl p-nitrothiobenzeate could be prepared by this route [7], and a nitro group ortho or para to an amide function has approximately the same electron withdrawing effect on the amide function, it would appear that the reason why N,N-dimethyl-o-nitrobenzamide fails to react is due to steric hindrance of the o-nitro group.

By using a more powerful chlorinating agent it was considered that it should be possible to convert N,N-dimethyl-o-nitrobenzamide into the corresponding amidochloride. Thionyl chloride in refluxing benzene did not react with N,N-dimethyl-o-nitrobenzamide. Some experiments using phosphorus pentachloride were then initiated, and after several variations in the temperature (50-130°C) and the amount of phosphorous pentachloride (1-4 equivalents), it seemed that at the best only 40% of the amide had been transformed into product(s). Based upon analysis of the ^1H n.m.r. spectrum of the reaction mixture there was, however, some uncertainty regarding the structure of the product. N,N-Dimethyl-o-nitrobenzamide itself gives rise to two singlets at τ=6,81 and 7,13 due to the two N-methyl groups, and if the product was the corresponding amidochloride (17) it was also expected to give two N-methyl singlets. This was, however, not the case as only one new singlet was observed in the spectrum. A demethylated product was thus indicated, i.e. a von Braun degradation [22] has taken place. It is well established that this reaction takes place when amidochlorides are heated to 130-150°C [8]. It seems therefore likely that the reactions outlined in scheme 3 have taken place.



(17) (18)

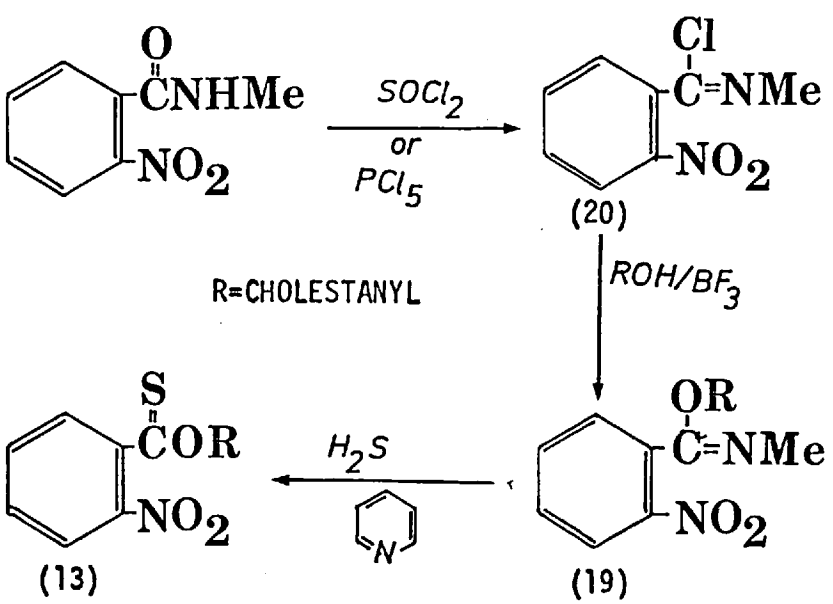
Scheme 3.

Preparation of the o-nitrothiobenzoate(13) via the amidochloride(18) was therefore abandoned.

It is known that it is possible to make imidates of the type 19 by reacting an imidoyl chloride with an alcohol [19]. This reaction is probably involved in the Pinner synthesis [20] of imidates. Subsequent reaction of the imidate(19) with hydrogen sulphide-pyridine should then give the desired o-nitrothiobenzoate(13).

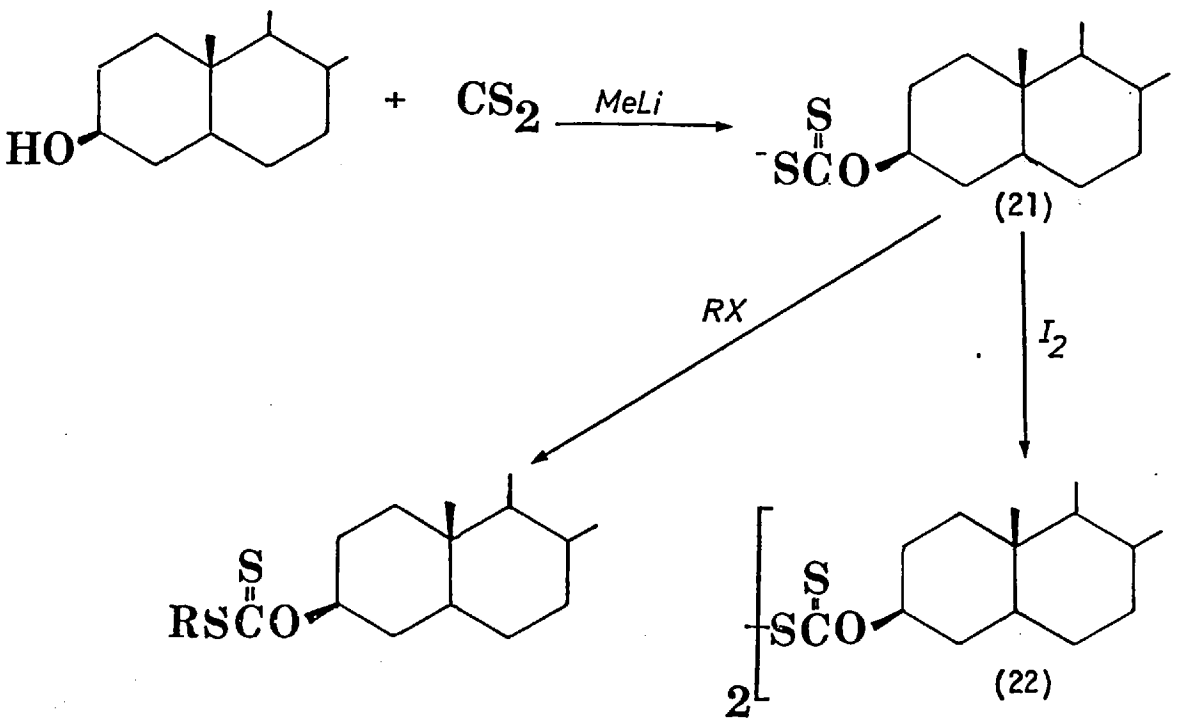
Preparation of the imidoyl chloride(20) was accomplished equally well by treating N-methyl-o-nitrobenzamide with thionyl chloride at 50°C or phosphorus pentachloride at room temperature [21]. In both cases the imidoyl chloride(20) was isolated as a crystalline hygroscopic solid in high yield. This reaction was again monitored by ^1H n.m.r. N-Methyl-o-nitrobenzamide showed two N-methyl singlets at τ=7,15 and 7,23, indicating the presence of both syn and anti isomers, whereas the product showed only one N-methyl singlett at τ=6,46.

Treatment of the imidoyl chloride(20) with 3β-cholestanol and boron trifluoride etherate for 24 hours and subsequent treatment with hydrogen sulphide-pyridine gave the desired o-nitrothiobenzoate(13). This reaction sequence is outlined in scheme 4.



Scheme 4.

The preparations of the dithiocarbonates(14,15,16) were based on the well established [9] formation of dithiocarbonate salts by treating an alcohol with carbon disulphide in the presence of a base. Using the dithiocarbonate anion as a nucleophile it should then be possible to make the desired dithiocarbonates from the corresponding halides by a nucleophilic displacement (scheme 5).



R=2,4-Dinitrophenyl (14)

R=Phenacyl (15)

R=Nitromethyl (16)

Scheme 5.

Both the aromatic nucleophilic substitution of 1-chloro-2,4-dinitrobenzene and the aliphatic nucleophilic substitution of phenacyl bromide with the dithiocarbonate anion(21) gave the desired products. On attempting the same procedure using bromonitromethane a crystalline product that did not contain the nitromethyl group was isolated.

The physical properties of this compound indicated its structure to be a dimeric dithiocarbonate (22). This was shown to be the case by preparing the dimer (22) by an unambiguous route. This was accomplished by oxidative coupling of the dithiocarbonate anion (21) with iodine. A resonable explanation for the failure of bromonitromethane to give the desired product is offered by the postulate that bromonitromethane fragments into a bromo and a nitromethyl radical, either of which can then remove an electron from the dithiocarbonate anion (21). The dithiocarbonate radical so formed can then react with another radical to give the product.

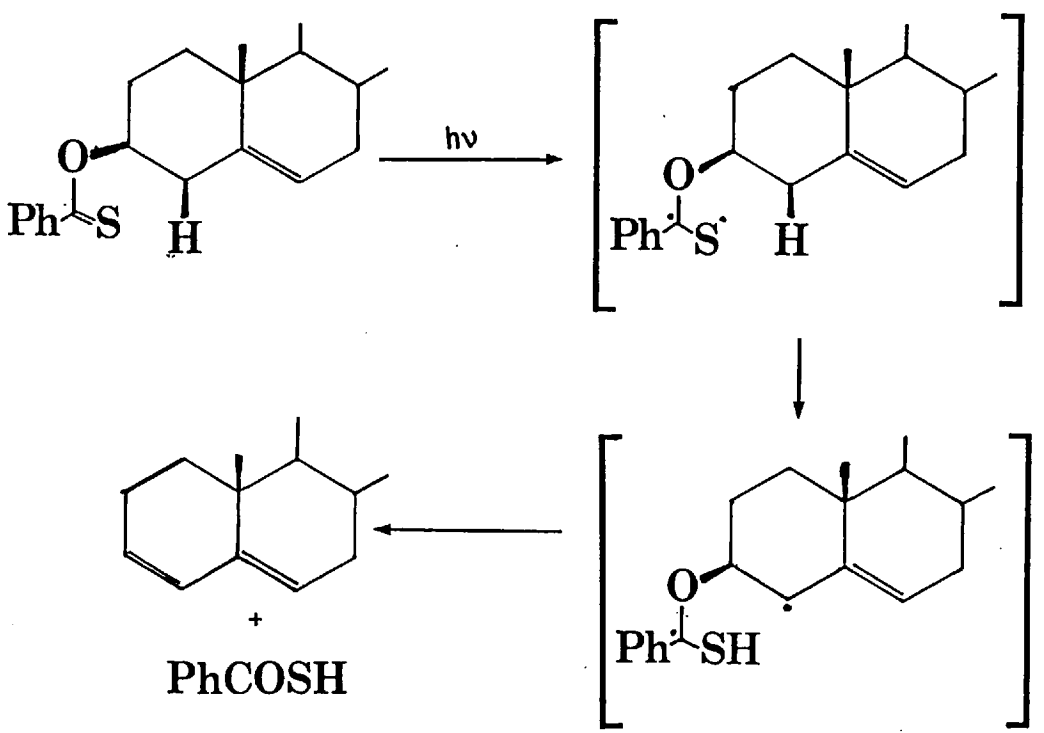
Finally the exchange of oxygen with sulphur in ester-carbonyls using phosphorus pentasulphide was explored. This reaction has recently been published [10], and has been employed on ketones, esters, amides and S-alkyl thioesters. The reaction worked best for ketones and not very good for esters. In spite of this the reaction was investigated using cholesteryl benzoate. The results gave, however no indications of any exchange. Neither variations in the solvent (acetonitrile, tetrahydrofuran, diglyme) nor prolonged heating at reflux caused consumption of the starting material.

CHAPTER 2.

PHOTOLYSIS OF THIOCARBONYL ESTERS.

A. PHOTOLYSIS OF THE O-CHOLESTERYL THIOESTERS.

It has previously been shown [1] that O-cholesteryl thiobenzoate rapidly photoeliminates thiobenzoic acid, and gives cholesta-3,5-diene in high yield, whereas O-cholestanyl thiobenzoate does not give any photoelimination product, but a complex mixture from which the two epimeric 3S-thioesters can be isolated [1.4]. The photoelimination has been shown to proceed via a triplet state radical [4,23.], as shown in scheme 6.



Scheme 6

The difference in the photoreactivity between O-cholestanyl and

O-cholesteryl thiobenzoate has been attributed to the double bond, i.e. the double bond provides, in the transition state, some conjugative stabilisation of the newly forming double bond [1]. If this stabilisation is not present other photoreactions will take place. It was therefore of interest to have a closer look at the photochemistry of the "non" activated O-alkyl thioesters, and determine how a second photolabile function would affect these reactions.

Irradiation of the O-cholesteryl thioesters (table 3) gave, as expected, cholesta-3,5-diene in high yield.

Table 3.

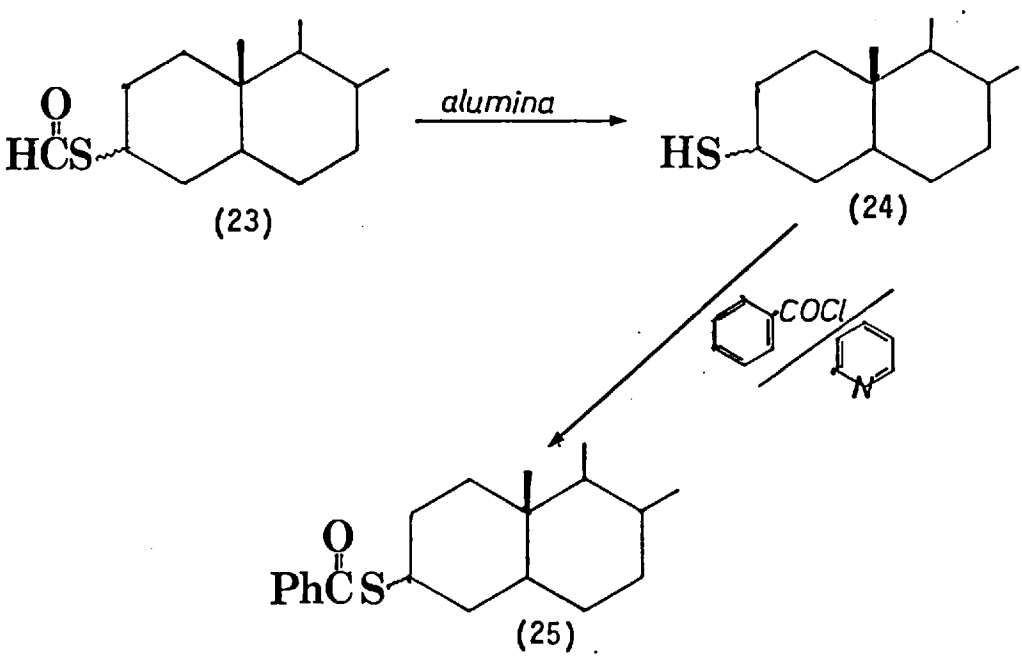
COMPOUND	CHOLESTA-3,5-DIENE (%).
O-cholesteryl thioformate (4)	79
O-cholesteryl thioacetate (6)	90
O-cholesteryl thiocinnamate (8)	77

It has previously [1] been observed that the eliminated thioacid readily readded to the newly generated diene system, thus forming the two epimeric 3S-cholesteryl thiobenzoates. This readdition has been prevented by performing the photoelimination in the presence of triethylamine or bis-p-nitrobenzoyl peroxide. In the photoelimination of the three thioesters (4), (6) and (8), however, it was not necessary to use a trapping agent in order to prevent readdition of the thioacid. The readdition occured only if the irradiation was prolonged after the elimination reaction had gone to completion.

B. PHOTOLYSIS OF THE O-CHOLESTANYL THIOESTERS.

Irradiation of the saturated thioesters (3), (5) and (7) gave,

as expected, results which were analogous to the irradiation of O-cholestanyl thiobenzoate [1]. It was found that the thioformate (4) was consumed in 105 minutes. The reaction was monitored on t.l.c., aliquots were taken out every 5 minutes. Isolation of the primary photoproducts from the reaction mixture could not be accomplished because of their facile hydrolysis. However, on the basis of the ^1H n.m.r. and the i.r. spectra of these primary photoproducts (ν=1720 cm^{-1} and τ=0,6 ppm) it was resonable to assume that these products were the rearranged thioformates (23). By stirring the crude reaction mixture with neutral alumina under an atmosphere of argon, both the formate proton and the carbonyl band disappeared. These observations were in accord with a hydrolysis of the thioformate (23). The thiols (24) were identified as their S-cholestanyl thiobenzaotes (25) [24] by reacting the thiols with benzoyl chloride in pyridine (scheme 7).



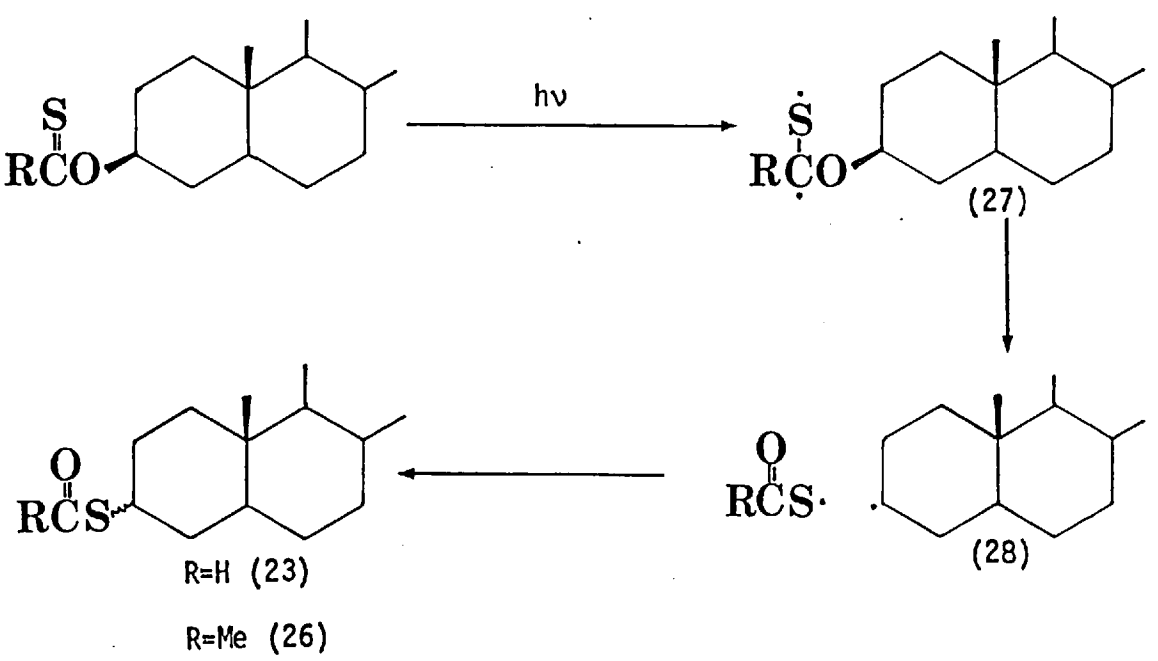
Scheme 7

The thioacetate(5) was found to be less reactive than the

thioformate (3), when irradiated under the same conditions. Complete consumption of the thioacetate was found to take 6 hours. The reaction mixture was chromatographed on an alumina column, and a fraction containing two products was isolated. Analysis of the ^1H n.m.r. and the i.r. spectra of this fraction showed a strong carbonyl stretch 1715 cm^{-1} and two signals at τ=6,36 and 5,63. Based on the results from the irradiation of 3-cholestanyl thiobenzoate [1] and 3-cholestanyl thioformate (3), and the width at half-height [25] of the two above-mentioned ^1H n.m.r. signals (18 and 6 cps.), it was assumed that the products were the two epimeric 3S-cholestanyl thioacetates (26). These products were, however, not separated and isolated.

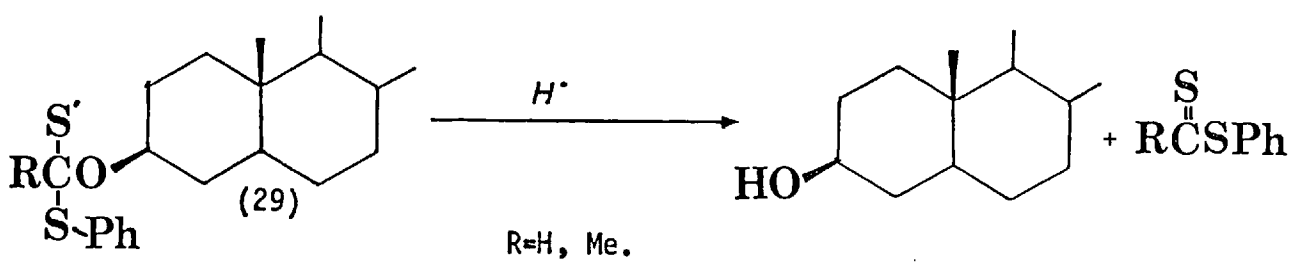
The thiocinnamate (7) was found to be photostable under the conditions used in the irradiation. After 6 hours the thiocinnamate (7) could be recovered unchanged.

The photorearrangement explained as shown in scheme 8. The initially formed diradical (27) causes a homolytic rupture of the oxygen-C_3 carbon bond, creating the two radicals (28), which terminate the reaction by making a carbon-sulphur bond. This mechanism also explaines the loss of stereochemistry at C_3.



Scheme 8

Assuming this mechanism to be correct, it should in principle be possible to trap the cholestanyl radical. Attempted trapping, using thiophenol, thioglycollic acid or benzyldimethylsilane as a hydrogen radical source, did not result in the isolation of 5α-cholestane. With thiophenol and thioglycollic acid, the steroidal part of the thioesters was isolated as 3β-cholestanol, and with benzyldimethylsilane only the rearranged 3S-esters (23,26) could be isolated. A blank experiment showed that the thioesters(3,5) did not react with thiophenol or thioglycollic acid, it would therefore appear that the initially formed diradical(27) was trapped and gave an intermediate that was responsible for the formation of 3β-cholestanol. An intermediate of the type 29 could be responsible for this process (scheme 9). This could fragment into phenyl dithioacetate (formate) and the cholestanyloxy radical, which could pick up a hydrogen radical, and thus give 3β-cholestanol. No attempts was, however, made to isolate phenyl dithioacetate (formate) from the reaction mixture.



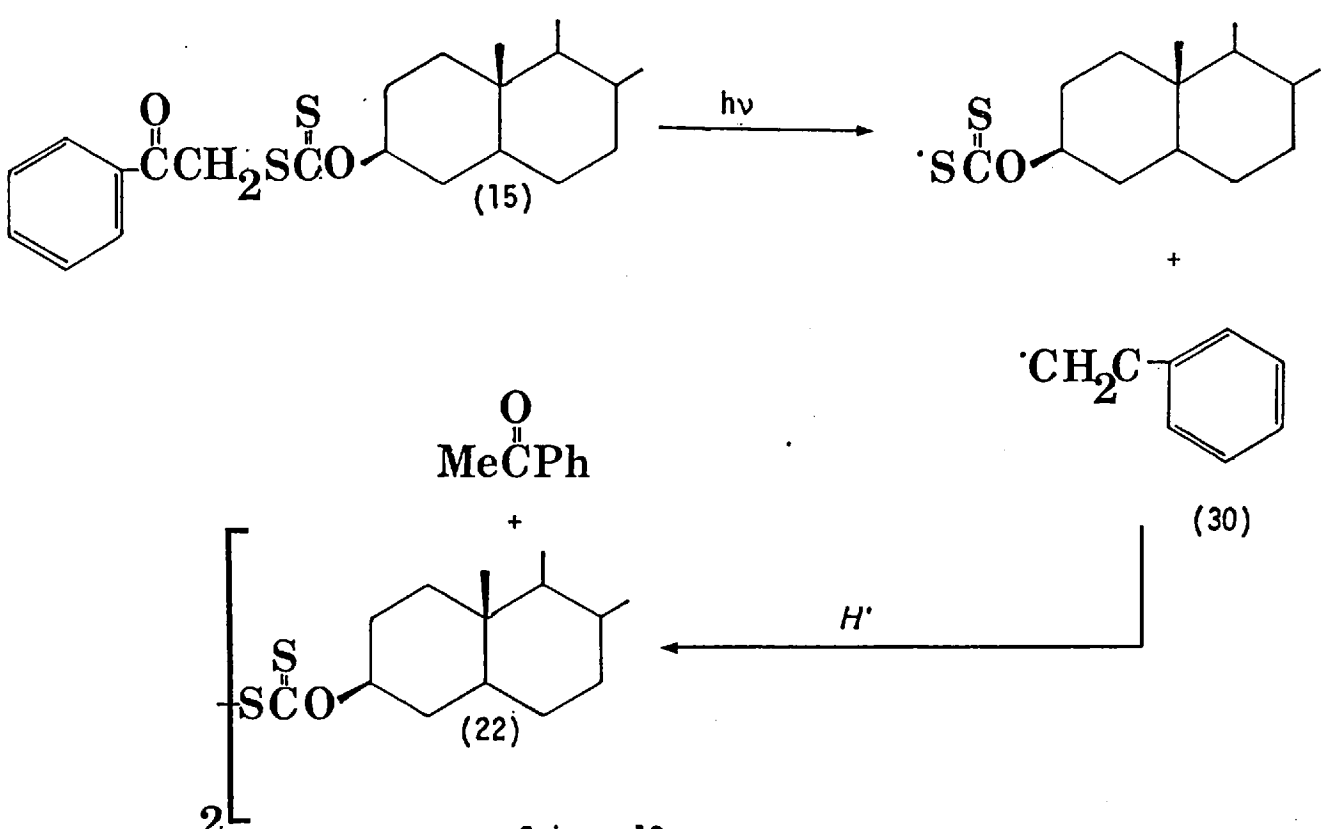
Scheme 9.

C. PHOTOLYSIS OF THE THIOESTERS CONTAINING AN ADDITIONAL PHOTOLABILE GROUP.

Irradiation of the nitrocompounds (13,14) produced in both cases

complex mixtures, in which the products had polarities greater than cholestanol. Treatment of the crude reaction mixtures with sodium hydroxide produced in both cases cholestanol. Attempted isolation of other products from these reactions produced intractable mixtures.

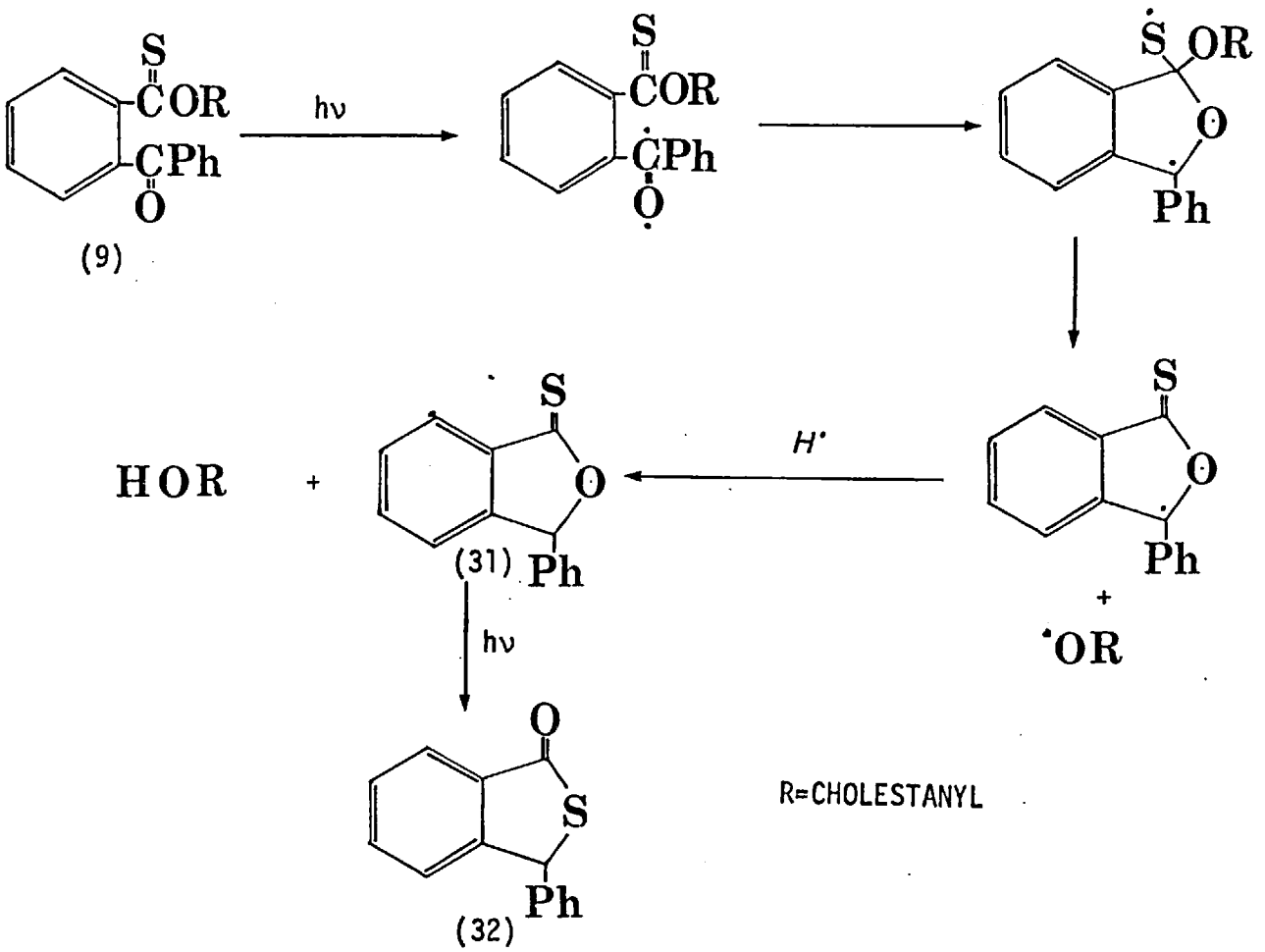
The phenacyl dithiocarbonate (15) gave upon irradiation identifiable products. After 100 minutes the reaction had gone to completion (absence of starting material on t.l.c.), and upon work-up acetophenone (identified as its 2,4-dinitrophenylhydrazone derivative) and di-O-cholestanyl dithio-bis-thioformate (22) were isolated. Since it is known that O-alkyl S-alkyl dithiocarbonate is photostable [26], it would appear that it is the phenacyl moiety that is responsible for the carbon-sulphur bond rupture. This will create the two radicals (30) (scheme 10) which terminate the reaction by a dimerisation and a hydrogen radical abstraction.



Scheme 10

The benzoylthiobenzoate (9) was consumed in 35 minutes when

it was subjected to irradiation. Separation of the reaction products gave 3β-cholestanol as the only identifiable product. Formation of 3β-cholestanol could be explained by the process outlined in scheme 11, but since neither the thiolactone (31), nor the phthalthiolide (32) (this could be formed by a photorearrangement of the thiolactone (31)) could be found among the reaction products, this seems unlikely.



Scheme 11.

CHAPTER 3.

EXPERIMENTAL.

GENERAL.

Unless otherwise stated, the following data applies to the experiments described in this section.

Melting points were taken on a Kofler block and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer as Nujol mulls.

Ultraviolet spectra were measured on a Unicam SP 800 instrument in ethanol solution.

N.m.r. spectra were determined for solutions in (^{2}H)chloroform with tetramethylsilane as internal standard. The following abbreviations refer to the n.m.r. data: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

Rotations were measured on a Perkin-Elmer 141 polarimeter and are for chloroform solutions.

The progress of the reactions and the course of column chromatograms were monitored by thin layer chromatography on silica gel GF_{254} (Merck) with ethyl acetate/petroleum ether (b.p. 60-80°C) 1:4 as eluent. Development was effected by spraying with 2N sulphuric acid and heating at 120°C. Column chromatography was on grade III alumina or silica gel MFC grade (Hopkins and Williams).

Mass spectra were recorded with an A. E. I. MS 9 high resolution spectrometer.

Ether refers to diethyl ether.

Toluene, benzene and ether were dried over sodium wire. Petroleum ether was destilled to remove high boiling impurities. Pyridine was destilled from calcium hydride and stored over molecular sieves (4A). Tetrahydrofuran was destilled from sodium hydride.

The lamp used for photolysis was: Philips HPK 125W BA15D TYP 57203B/00 high pressure mercury lamp.

The "usual work-up" refers to dilution with water, extraction with dichloromethane, washing with dilute hydrochloric acid (2N), sodium hydrogen carbonate solution, and water, and drying ($MgSO_4$).

The ester, in degassed solvent, was irradiated in a container which had a sintered disc at its base through which argon could be passed. The container was fitted with 2 necks. One for a condenser and a drying tube and the other for removing aliquots. The lamp was fixed to the end of a probe in a pyrex water cooled thimble which dipped into the solution. The whole system was wrapped in aluminium foil to act as a reflector.

Nitrogen or argon used as an inert atmosphere in reactions was freed of oxygen by passing through a bottle containing Fieser's solution, and then dried by passing through concentrated sulphuric acid.

Preparation of O-cholestanyl Thioformate (3).[7]

N,N-Dimethylformamide (2,2g. 10mmol) was added to a solution of phosgene in dichloromethane (10% w/v, 40ml) with stirring. After 30 minutes at room temperature, the solvent was evaporated in vacuo and the residue was stirred with dichloromethane (40ml) and cooled to -20°C. A solution of cholestanol (7,75g, 20mmol) in dichloromethane (30ml) and tetrahydrofuran (30ml) was added during 15 minutes, and stirring was continued while the temperature was raised to 0°C during 15 minutes. Dry pyridine (3ml) was added, and a stream of dry hydrogen sulphide was passed through the solution for 5 minutes. After the usual work-up, evaporation gave the crude thioester, which was dried at 0,1 mmHg, dissolved in 2:1 petroleum ether (b.p. 60-80°C)/dichloromethane, and filtered down a short column of silica gel (elution with the same solvent mixture). Evaporation and recrystallisation gave the thioformate (3) (7,13g, 81%), m.p. 104-105°C (from ether/methanol).

Preparation of O-cholesteryl Thioformate (4) [7].

The method described in the foregoing preparation was followed, the cholestanol being replaced by cholesterol (7,72g, 20mmol). Recrystallisation from ethanol gave the thioformate (4) (7.2g, 82%) as long, pale yellow needles, m.p. 124-126°C.

Preparation of O-cholestanyl Thioacetate (5).

N,N-Dimethylacetamide (4,2g, 48mmol) was stirred in dichloromethane

(25ml) and a solution of phosgene in toluene (12,5% w/v, 40ml) was added during 5 minutes. The semisolid mixture was diluted with 1:1 dichloromethane/toluene (25ml), stirred at room temperature for 30 minutes, after which a solution of cholestanol (4,85g, 12,5mmol) in dichloromethane (50ml) was added. After stirring for 10 minutes, the mixture was cooled to 0°C and treated with a stream of dry hydrogen sulphide during dropwise addition (5 minutes) of pyridine (15ml). After 10 minutes, the mixture was worked up in the usual way, and chromatographed on silica gel (eluting with 2:1 petroleum ether (b.p. 60-80°C)/dichloromethane) to give the crude thioacetate (5), obtained as plates (4,4g, 80%), m.p. 93-94°C (from ethanol).

ν_{max} 1340(m), 1280(s), 1270(s), 1250(s), 1230(s), 1150(w), 1135(w), 1080(w), 1030(s), 930(m), cm^{-1}.

λ_{max} 245 and 366 nm (ε 6700 and 12). Ethanol

τ 4,67 (1H, broad s). 7,46 (3H, s). 7,75-9,50 (46H, m).

$\{\alpha\}_D^{22}$ -4,82° (c 2). Ethanol.

Found: C 77,69. H. 11,04. S 6,84. $C_{29}H_{50}OS$ requires

C 77,96. H 11,28. S 7,18.

Preparation of O-cholesteryl Thioacetate (6).[7]

The method described in the foregoing preparation was followed, the cholestanol being replaced by cholesterol (4,82g, 12,5mmol). Recrystallisation from ethanol gave the thioacetate (6) (4,38g, 79%) as yellow plates, m.p. 141-142°C.

Preparation of O-cholestanyl Thiocinnamate (7).

N-cinnamoylpiperidine (trans) (2,15g, 10mmol) was dissolved in dichloromethane (25ml) containing phosgene (10% w/v). After stirring for 30 minutes, dichloromethane and excess phosgene were removed in vacuo, and the residue was suspended in dichloromethane (20ml). To this mixture cholestanol (3,8g, 10mmol) dissolved in tetrahydrofuran (10ml) was added. After 30 minutes pyridine (3ml) was added to the homogeneous solution, and the solution saturated with hydrogen sulphide. After 20 minutes the mixture was worked up in the usual way and after evaporation the residue was chromatographed on alumina (grade III) (eluting with benzene/petroleum ether (b.p. 60-80°C) 1:1) to give the crude thiocinnamate (7), obtained as yellow prisms (3,8g, 90%), m.p. 165-167°C (from ethanol).

ν_{max} 1615(w), 1330(m), 1315(m), 1290(s), 1260(s), 1205(m), 1190(m), 1160(m), 1020(m), 970(m), 755(s), 690(m), cm^{-1}.

λ_{max} 240 and 325 nm (ε 6000 and 15700). Ethanol.

τ 9,73-7,67 (45H, m). 4,53 (1H, broad s). 3,02 (1H, d. J=16Hz). 2,77-2,30 (5H, m). 2,25 (1H, d. J=16Hz).

$[\alpha]_D^{22}$ +8,25° (c 2). Ethanol.

MS 534 (M^+). 473 (M-CHSO). 370 (M-C_9H_8SO).

Found: C 80,58. H 10,04. S 6,09. $C_{36}H_{54}OS$ requires C 80,84. H 10,18. S 5,99.

Preparation of O-cholesteryl Thiocinnamate (8).

The method described in the foregoing preparation was followed, the cholestanol being replaced by cholesterol (3,8g, 10mmol). Recrystallisation from ethanol gave the thiocinnamate (8) (3,8g, 90%) as yellow plates, m.p. 146-148°C.

ν_{max} 1630(w), 1305(m), 1290(m), 1250(m), 1175(s), 975(m), 750(w), 690(w), cm^{-1}.

λ_{max} 236 and 326 nm (ε 7500 and 16800). Ethanol.

τ 9,50-7,30 (43H, m). 4,63 (2H, broad s). 3,11 (1H, d. J=16Hz). 2,30-2,44 (5H, m). 2,22 (1H, d. J=16Hz).

$\{\alpha\}_D^{22}$ -24,33° (c 2). Ethanol.

MS 532 (M^+). 368 ($M-C_9H_8OS$).

Found: C 80,98. H 9,87. S 5,79. $C_{36}H_{52}OS$ requires

C 81,14. H 9,84. S 6,02.

Preparation of O-cholestanyl o-Benzoylthiobenzoate (9) and O-cholestanyl o-Thiobenzoylbenzoate (11).

N,N-Dimethyl-o-benzoylbenzamide (8,85g, 35mmol) was dissolved in a solution of phosgene in dichloromethane (20% w/v, 50ml). The phosgene solution was changed every 24 hours. After 120 hours the reaction was completed as seen on ^1H n.m.r. (disappearance of the methyl singlet). To the evaporated and redissolved amidochloride (dichloromethane, 40ml), cholestanol (7,75g, 20mmol), dissolved in tetrahydrofuran (25ml), was added. After 24 hours pyridine (9ml) was added and the mixture was treated with a stream of dry hydrogen sulphide for 15 minutes. The reaction mixture turned blue-green upon this treatment. After the usual work-up, the mixture was chromatographed on silica gel, (elution with benzene/petroleum ether (b.p. 60-80°C) 2:1) to give the crude thiobenzoyl-benzoate (11) as an oil, which crystallized as blue plates (3,2g, 26%), m.p. 44-45°C upon standing at 0°C.

ν_{max} 1725(s), 1320(m), 1295(s), 1270(m), 1220(w), 1180(w), 1130(m), 775(w), 765(m), 705(w), 690(w), cm^{-1}.

λ_{max} 250, 325 and 576 nm (ε 9900, 12000 and 120). Chloroform.

τ 1,87-2,87 (9H, m). 5,40 (1H, broad s). 7,60-9,77 (45H, m).

$\{\alpha\}_D^{22}$ not recorded (UV absorbance).

MS 612 (M^+). 371 ($M-C_{14}H_9SO_2$).

Found: C 80,20. H 9,07. S 5,14. $C_{41}H_{56}SO_2$ requires
C 80,34. H 9,21. S 5,23.

Continued elution with benzene gave a yellow fraction. The yellow fraction was evaporated and the residue was crystallized from ethanol/dichloromethane. The last traces of the thiobenzoylbenzoate (11) was removed by chromatography of the crystallized benzoylthiobenzoate (9) on a preparative plate (silica gel GF_{254}), eluting with petroleum ether (b.p. 60-80°C)/ethyl acetate 4:1 Crystallisation from ethanol/dichloromethane gave the pure benzoylthiobenzoate (9) (800mg, 6,5%), m.p. 128-129°C.

ν_{max} 1675(s), 1300(w), 1290(m), 1265(s), 1245(m), 1030(m), 940(w), 770(w), 715(m), cm^{-1}.

λ_{max} 249, 283 and 410 nm (ε 16000, 8700 and 340). Chloroform.

τ 1,54, 2,84 (9H, m). 4,73 (1H, broad s). 7,84-9,73 (45H, m).

$[\alpha]_D^{22}$ not recorded (UV absorbance).

MS 612 (M^+). 371 ($M-C_{14}H_9SO_2$).

Found: C 80,39. H 9,32. S 5,17. $C_{41}H_{56}SO_2$ requires
C 80,34. H 9,21. S 5,23.

Preparation of N-methyl-o-Nitrobenzimidoyl Chloride (18).

A. Thionyl Chloride.

N-Methyl-o-nitrobenzamide (3,6g, 20mmol) and thionyl chloride (6,0g, 50mmol) were mixed together and heated at 50°C for 3 hours. Upon cooling the crystalline solid was collected and dried in vacuo, (3,9g, 81%).

τ 6,43 (3H, s). 2,59-1,90 (5H, m).

B. Phosphorus Pentachloride.

To a solution of N-methyl-o-nitrobenzamide (3,6g, 20mmol) in dichloromethane (30ml), phosphorus pentachloride (2,2g, 10,5mmol) was added in portions (0,5g). The addition was accompanied with evolution of hydrogen chloride gas. The reaction mixture was stirred for 2 hours at room temperature after the addition of phosphorus pentachloride. was complete. The imidoyl chloride (18) (4,0g. 85%), which crystallized as white plates, was filtered off and dried in vacuo.

τ 6,43 (3H, s). 2,59-1,90 (5H, m).

The imidoyl chloride was very sensitive to moisture.

Preparation of O-cholestanyl o-Nitrothiobenzoate (13).

N-Methyl-o-nitrobenzimidoyl chloride (18) (2,0g, 8,5mmol) was suspended with stirring in dichloromethane (30ml), and cholestanol (3,3g, 8,5mmol) dissolved in tetrahydrofuran (10ml) was added. To this mixture boron trifluoride etherate (2,5ml, 2 equivalents) was added, and the mixture was stirred for 48 hours at room temperature after which time t.l.c. indicated the absence of cholestanol. The mixture was then treated with pyridine (3ml) and saturated with dry hydrogen sulphide gas. The saturation was repeated at 2 hourly intervals over a period of 8 hours, and then worked up in the usual way. The residue was chromatographed on alumina (grade III) (eluting with benzene/petroleum ether (b.p. 60-80°C) 1:1) to give the crude o-nitrothiobenzoate (13), (5,0g, 65%), as a yellow solid, m.p. 150-152°C. Repeated attempts to crystallize the crude o-nitrothiobenzoate from a variety of solvents gave gels. A sample for analysis was rechromatographed on alumina and dried at 80°C in vacuo.

ν_{max} 1530(s), 1355(m), 1270(m), 1240(m), 1030(w), 735(w), cm^{-1}.

λ_{max} 260 and 398 nm (ε 8100 and 290). Ethanol

τ 9,67-7,70 (45H, m). 4,50 (1H, broad s). 2,55-2,00 (3H, m).

$\{\alpha\}_D^{22}$ +3,67°(c 3). Ethanol.

MS 553 (M^+). 537 (M-O). 523 (M-NO). 507 ($M-NO_2$).

Found: C 73,83. H 9,55. N 2,78. S 6,03. $C_{34}H_{51}NO_3S$ requires

C 73,73. H 9,28. N 2,53. S 5,79.

Preparation of O-cholestanyl S-(2,4-dinitrophenyl) Dithiocarbonate (14).

A solution of cholestanol (1,54g, 4mmol) in tetrahydrofuran (25ml), under an atmosphere of argon, was titrated with methyllithium (2ml, 2M in diethyl ether), using triphenylmethane as an indicator. To this mixture carbon disulphide (5ml) was added, and stirring was continued for 30 minutes . After the reaction mixture had been heated to 70°C, 1-chloro-2,4-dinitrobenzene (1,01g, 5mmol) was added. The reaction mixture turned deep red upon this treatment. After washing once with water and drying ($MgSO_4$), the solvent was evaporated. The dithiocarbonate (14) (1,72g, 72%) was obtained as pale yellow plates, m.p. 163-164°C (from ethanol).

ν_{max} 1600(w), 1545(m), 1525(m), 1340(s), 1260(m), 1230(m), 1020(w), 730(w), cm^{-1}.

λ_{max} 243, 272 and 337 nm (ε 9600, 10400 and 4900). Ethanol.

τ 9,52-7,83 (45H, m). 4,70 (1H, broad s). 2,04 (1H, d. J=8Hz). 1,50 (1H, d of d. J=9Hz). 1,11 (d. J=3,5Hz).

$\{\alpha\}_D^{22}$ not recorded (UV absorbance).

MS 370 ($M-C_7H_4N_2O_5S_2$).

Found: C 64,47. H 7,78. N 4,33. S 9,85. $C_{34}H_{50}O_5N_2S_2$ requires

C 64,72. H 8,00. N 4,44. S 10,16.

Preparation of O-cholestanyl S-phenacyl Dithiocarbonate (15).

A solution of the lithium salt of O-cholestanyl dithiocarbonate, prepared as in the previous preparation, was cooled to 10°C and phenacyl bromide (990mg, 5mmol), dissolved in tetrahydrofuran (10ml), was added dropwise. After 1 hour's stirring at room temperature, the reaction mixture was washed once with water and dried ($MgSO_4$). The dithiocarbonate (15) (1,91g, 82%) was obtained as light yellow needles, m.p. 135-137°C, (from ethanol).

ν_{max} 1690(m), 1680(m), 1230(s), 1220(s), 1190(m), 1060(m), 750(m), 690(w), cm^{-1}.

λ_{max} 245, 278 and 349 nm (ε 9700, 8600 and 3800). Ethanol.

τ 9,50-7,83 (45H, m). 5,40 (2H, s). 4,63 (1H, broad s). 2,70-1,84 (5H, m).

$\{\alpha\}_D^{22}$ +7,16° (c 3). Ethanol.

MS 582 (M^+). 370 ($M-C_9H_8S_2O_2$).

Found: C 73,89. H 9,05. S 10,62. $C_{36}H_{54}O_2S_2$ requires

C 74,17. H 9,34. S 11,00.

Preparation of Cinnamoyl Chloride (trans).

Cinnamoyl chloride was prepared by treating cinnamic acid with thionyl chloride at 50°C in benzene. M.p 34-36°C., b.p. 138-141°C/33mmHg., (lit., [11] m.p. 36°C., b.p. 251-253°C).

Preparation of N-cinnamoylpiperidine (trans).

N-Cinnamoylpiperidine was prepared by treating cinnamoyl chloride with piperidine in dry benzene. M.p. 121-123°C., (lit., [12] m.p. 122°C).

Preparation of o-Benzoylbenzoic Acid.

o-Benzoylbenzoic acid was prepared by treating phthalic anhydride with benzene and aluminium chloride. M.p. 126-128°C., (lit., [13] m.p. 127°C).

Preparation of o-Benzoylbenzoyl Chloride.

o-Benzoylbenzoyl chloride was prepared by treating o-benzoylbenzoic acid with thionyl chloride at 60°C in benzene. M.p. 56-58°C., (lit., [14] m.p. 59-60°C).

Preparation of N,N-dimethyl-o-Benzoylbenzamide.

N,N-Dimethyl-o-benzoylbenzamide was prepared by treating o-benzoylbenzoyl chloride with aqueous dimethylamine in benzene. M.p. 80°C., (lit., [15] m.p. 81-83°C).

Preparation of o-Nitrobenzoyl Chloride.

o-Nitrobenzoyl chloride was prepared by treating o-nitrobenzoic acid with thionyl chloride in benzene at reflux. B.p. 84-86°C/0,5mmHg., (lit., [11] b.p. 148°C/9mmHg).

Preparation of N-methyl-o-Nitrobenzamide.

N-Methyl-o-nitrobenzamide was prepared by treating o-nitrobenzoyl

chloride with aqueous methylamine in benzene. M.p. 107-109°C., (lit., [16] m.p. 109-111°C).

Preparation of N,N-dimethyl-o-Nitrobenzamide.

N,N-Dimethyl-o-nitrobenzamide was prepared by treating o-nitrobenzoyl chloride with aqueous dimethylamine in benzene. M.p. 78-79°C., (lit., [17] m.p. 78°C).

Attempted preparation of N,N-dimethyl-o-Nitrobenzamidochloride (17).

A. Phosgene.

N,N-Dimethyl-o-nitrobenzamide (2,0g, 10mmol) was treated with phosgene in dichloromethane (10% w/v, 30ml) at room temperature for 7 days. ^{1}H n.m.r. after this period indicated no reaction, and work-up gave only starting material (1,9g, 95%).

B. Thionyl Chloride.

N,N-Dimethyl-o-nitrobenzamide (2,0g, 10mmol) was treated with thionyl chloride (2,4g, 20mmol) in refluxing dry benzene (30ml) for 24 hours. Evaporation in vacuo gave only starting material (1,94g, 97%).

C. Phosphorus Pentachloride.

A mixture of N,N-dimethyl-o-nitrobenzamide (2,0g, 10mmol) and phosphorus pentachloride (2,7g, 13mmol) was refluxed in toluene (10ml) for 20 hours. Evaporation of the homogeneous solution in vacuo left a syrupy oil which was analysed on ^{1}H n.m.r. By comparison with ^{1}H n.m.r.

of authentic samples, the three singlets in the spectrum were assigned to the two N-methyl groups of the starting material (τ=6,86 and 7,20), and the N-methyl group of N-methyl-o-nitrobenzimidoyl chloride, (18) (τ=6,56).

Preparation of Bromonitromethane.

Bromonitromethane was prepared by reacting the sodium salt of nitromethane (prepared by reacting nitromethane with sodium in ethanol) with bromine in carbon disulphide. B.p. 61°C/15-20mmHg., (lit., [18] b.p. 70-72°C/40-50MmHg).

Attempted preparation of O-cholestanyl S-nitromethyl Dithiocarbonate (16).

To a solution of the lithium salt of O-cholestanyl dithiocarbonate, (prepared as described in the preparation of O-cholestanyl S-(2,4-dinitrophenyl) dithiocarbonate (14)), bromonitromethane (700mg, 5mmol) dissolved in tetrahydrofuran (10ml), was added. After 1 hour's stirring at room temperature the solution was washed once with water and dried ($MgSO_4$). Crystallization (ethanol) gave a light yellow crystalline compound (1,64g.), m.p. 169-171°C. By comparison with an authentic sample this was shown to be di-O-cholestanyl dithiobis-thioformate (22), m.p. and mixed m.p.

Preparation of Di-O-cholestanyl Dithiobis-thioformate (22).

A solution of cholestanol (1,54g, 4mmol) in tetrahydrofuran (25ml),

under an atmosphere of argon, was titrated with methyllithium (2ml, 2M in diethyl ether) using triphenylmethane as an indicator. To this carbon disulphide (5ml) was added, and after stirring for 30 minutes at room temperature, iodine (1,02g, 4mmol) was added. After washing with sodium thiosulphate, water and drying ($MgSO_4$), the crude product was crystallized from ethanol (1,62g, 88%), m.p. 169-171°C.

ν_{max} 1330(m), 1270(s), 1245(m), 1150(w), 1130(w), 1020(s), 985(w), 960(w), 900(w), 855(w), cm^{-1}.

λ_{max} 243 and 280 nm (ε 12300 and 8500). Ethanol.

τ 9,47-7,78 (92H, m). 4,59 (2H, broad s).

$\{\alpha\}_D^{22}$ +9,63° (c 3). Ethanol.

MS 370 ($M-C_{29}H_{47}S_4O_2$).

Found: C 70,69. H 9,83. S 14,89. $C_{56}H_{94}S_4O_2$ requires

C 72,51. H 10,21. S 13,83.

It was not possible to prepare an analytical sample, even after several recrystallizations from ethanol.

Treatment of Cholesteryl Benzoate with Phosphorus Pentachloride .

A mixture of cholesteryl benzoate (1,0g, 2mmol), phosphorus pentachloride (0,91g, 2mmol) and sodium hydrogen carbonate (0,25g) in tetrahydrofuran (30ml) was heated at reflux for 14 hours. After this period of time no change was discernible on t.l.c., and work up gave only starting material.

Photolysis of O-cholesteryl Thioesters.

O-cholesteryl thioester (1mmol) in degassed dry diethyl ether (400ml) was irradiated with a high pressure mercury lamp for X minutes. The reaction was monitored on t.l.c., by taking aliquots every 5 minutes. After evaporation, the residue was chromatographed on alumina (grade III). Elution with petroleum ether (b.p. 60-80°C) gave cholesta-3,5-diene as needles, m.p. 77-79°C (methanol/acetone), identified by comparison with an authentic sample, m.p. and mixed m.p.

THIOESTER	TIME (X)	DIENE
O-cholesteryl thioformate (4)	7 min.	281mg. 79%.
O-cholesteryl thioacetate (6)	9 min.	346mg. 90%.
O-cholesteryl thiocinnamate (8)	4 hours	287mg. 77%.

Photolysis of O-cholestanyl Thioformate (3).

O-cholestanyl thioformate (432mg, 1mmol) in degassed dry diethyl ether (400ml) was irradiated for 105 minutes. T.l.c. then indicated the absence of the starting material. After evaporation and redissolving in chloroform (50ml), alumina (neutral) (5g) was added and the mixture was stirred in an atmosphere of argon over night. When the alumina had been removed, pyridine (2ml) and benzoyl chloride (1,5g) was added, and the solution was refluxed for 1 hour. Upon cooling, water (20ml) was added dropwise, and the mixture was washed first with dilute hydrochloric acid and then with sodium hydrogen carbonate. After drying ($MgSO_4$) and evaporation, the residue was chromatographed on silica gel. Elution with petroleum ether (b.p. 60-80°C)/dichloromethane (3:1) gave

the two 3S-cholestanyl thiobenzoates, identified by comparison with authentic samples [24].

3α isomer 95mg., 18%.

3β isomer 124mg., 24%.

Photolysis of O-cholestanyl Thioacetate (5).

O-cholestanyl thioacetate (446mg, 1mmol) in degassed dry diethyl ether (400ml) was irradiated for 6 hours. After evaporation, the residue was chromatographed on alumina (grade III). Elution with benzene/petroleum ether (b.p. 60-80°C) (3:1) gave a fraction containing two compounds.

ν 1715 cm^{-1}.

τ 5,63 (W/2=6 cps). 6,36 (W/2=18 cps).

Photolysis of O-cholestanyl Thiocinnamate (7).

O-cholestanyl thiocinnamate (530mg, 1mmol) in degassed dry diethyl ether (400ml) was irradiated for 6 hours. Evaporation and crystallization (ethanol) gave the starting material (498mg, 94%).

Photolysis of O-cholestanyl Thioacetate with added Thiophenol.

O-cholestanyl thioacetate (445mg, 1mmol) in degassed dry diethyl ether (400ml), containing thiophenol (165mg, 1,5mmol), was irradiated for 6 hours. T.l.c. then indicated absence of the thioacetate. After evaporation, the residue was chromatographed on alumina (grade III).

Elution with dichloromethane/petroleum ether (b.p. 60-80°C) (1:2) gave 3β-cholestanol as plates (322mg, 83%) (ethanol), identified by comparison with an authentic sample, m.p. and mixed m.p.

A similar experiment was performed by substituting thiophenol with thioglycollic acid. This resulted, however, also in the isolation of 3β-cholestanol (317mg, 81%).

Photolysis of O-cholestanyl Thioacetate (5) with added Benzyldimethylsilane.

O-cholestanyl thioacetate (445mg, 1mmol) in degassed dry diethyl ether (400ml), containing benzyldimethylsilane (5ml), was irradiated for 2 hours. After evaporation, the residue was chromatographed on alumina (grade III). Elution with benzene/petroleum ether (b.p. 60-80 C) (3:1) gave a fraction containing two compounds, which on comparison with the data recorded in the photolysis of the thioacetate (5) without any added trapping agent, proved to be identical.

These experiments (thiophenol, thioglycollic acid and benzyldimethylsilane) were also performed with the thioformate (3). Similar results were obtained as shown below.

thiophenol	3β-cholestanol (306mg, 79%).
thioglycollic acid	3β-cholestanol (294mg, 76%).
benzyl dimethyl silane	3α- and 3β-S-cholestanyl thioformates

Photolysis of O-cholestanyl o-Nitrothiobenzoate (13).

O-cholestanyl o-nitrothiobenzoate (570mg, 1mmol) in degassed dry diethyl ether (400ml) was irradiated for 9 hours. T.l.c. then indicated the absence of the starting material and the presence of some product(s) more polar than cholestanol. The reaction mixture was evaporated and the residue was refluxed (1 hour) in 5% potassium hydroxide in ethanol (50ml). The basic solution was diluted with water and acidified with dilute hydrochloric acid. After extraction with dichloromethane and drying ($MgSO_4$), the residue was chromatographed on alumina (grade III). Elution with benzene/petroleum ether (b.p. 60-80°C) (1:1) gave 3β-cholestanol as white plates (364mg, 92%) (ethanol), m.p. 140-141°C, identified by comparison with an authentic sample, m.p. and mixed m.p.

Photolysis of O-cholestanyl S-(2,4-dinitrophenyl) Dithiocarbonate.(14).

O-cholestanyl S-(2,4-dinitrophenyl) dithiocarbonate (647mg, 1mmol) in degassed dry diethyl ether was irradiated for 7 hours. T.l.c. then indicated the absence of the starting material and the presence of some product(s) more polar than cholestanol. After treatment with potassium hydroxide and work-up (see the previous experiment), 3β-cholestanol (359mg, 90%) was isolated.

Photolysis of O-cholestanyl S-phenacyl dithiocarbonate (15).

O-cholestanyl S-phenacyl dithiocarbonate (530mg, 1mmol) in degassed dry diethyl ether (400ml) was irradiated for 100 minutes. T.l.c. then indicated the absence of the starting material. Evaporation and chromatography of the residue on a silica gel column (eluting with petroleum ether (b.p. 60-80°C)/benzene (10:1)) gave two products.

The first was identified to by acetophenone (as its 2,4-dinitrophenylhydrazone derivative). The second product crystallized from dichloromethane/petroleum ether (b.p. 60-80°C) as pale yellow needles, m.p. 169-171°C, identified to be di-O-cholestanyl dithiobis-thioformate (22) (450mg, 93%) by comparison with an authentic sample, m.p. and mixed m.p.

Photolysis of O-cholestanyl o-benzoylthiobenzoate (9).

O-cholestanyl o-benzoylthiobenzoate (306mg, 0,5mmol) in degassed dry diethyl ether (300ml) was irradiated for 35 minutes. After evaporation, the residue was chromatographed on a preparative plate (silica gel GF_{254}). This gave 3β-cholestanol (174mg, 90%) (ethanol), and an inseparable mixture of compounds.

Preparation of Benzyldimethylsilane.

Benzyldimethylsilane was prepared by treating benzyldimethylchlorosilane with lithium aluminium hydride in dry diethyl ether at reflux. B.p 92-94°C/35mmHg., (lit. [27] b.p. 114-115°C/145mmHg).

REFERENCES

1. S. Achmantowicz, D. H. R. Barton, P. D. Magnus, G. A. Poulton and P. J. West, J. C. S. Perkin I., 1973, 1567.
2. G. J. Janz, I. Ahmad and H. V. Venkatasetty, J. Phys. Chem., 1964, 68, 889,
3. R. Roger and D. G. Neilson, Chem. Rev., 1961, 61, 179, and references cited therein.
4. D. H. R. Barton, M, Bolton, P. D. Magnus, G. A. Poulton and P. J. West., J. C. S. Perkin I., 1973, 1580.
5. D. H. R. Barton, C. Chavis, M. K. Kaloustian, P. D. Magnus, G. A. Poulton and P. J. West, J. C. S.Perkin I., 1973, 1571.
6. H. Eilingdfeld, M. Seefelder and H. Weidinger, Chem. Ber., 1963, 96, 2899.
7. D. H. R. Barton and S. W. McCombie, J. C. S. Perkin I., 1975, 1574.
8. J. von Braun and J. Weismantel, Ber., 1922, 55, 3165.
9. A. Zeise, Ann., 1835, 16, 178.
10. J. W. Scheeren, P. H. J. Ooms and R. J. F. Nivard, Synthesis, 1973, 3, 149.
11. H. Meyer, Monats., 1901, 22, 428.
12. B. Herstein, Chem. Ber., 1889, 22, 2265.
13. T. C. McMullen, J. Am. Chem. Soc., 1922, 44, 2055.
14. H. C. Martin, J. Am. Chem. Soc., 1916, 38, 1142.
15. H. W. Bersch, K. H. Fischer and V. Banniza, Arch. Pharm., 1961, 294, 601.
16. R. M. Herbst, C. W. Roberts, H. T. F. Givens and E. K. Harvill, J. Org. Chem., 1952, 17, 262.
17. A. Reissert, Chem. Ber., 1908, 41, 3815.
18. R. Scholl, Chem. Ber., 1896, 29, 1824.
19. R. C. Cookson,.J. Chem. Soc., 1953, 643.
20. A. Pinner and F. Klein, Chem. Ber., 1877, 10, 1889.

21. O. Wallach, Ann. Chem., 1877, 184, 79.

22. W. R. Vaughan and R. D. Carlson, J. Am. Chem. Soc., 1962, 84, 779.

23. J. Wirz, J. C. S. Perkin II., 1973, 1307.

24. J. H. Turnbull, Chem. and Ind., 1959, 515.

R. Bourdon, Bull. Soc. Chim, France, 1962, 844.

25. P. West, Ph. D. Thesis. Imperial College.

26. G. L. O'Connor and H. R. Nace, J. Am. Chem. Soc., 1953, 75, 2118.

27. F. K. Cartledge and K. H. Riedel, J. Organom. Chem., 1972, 34, 11.

J. W. Jenkins and H. W. Post, J. Org. Chem., 1950, 15, 552.

PART III.

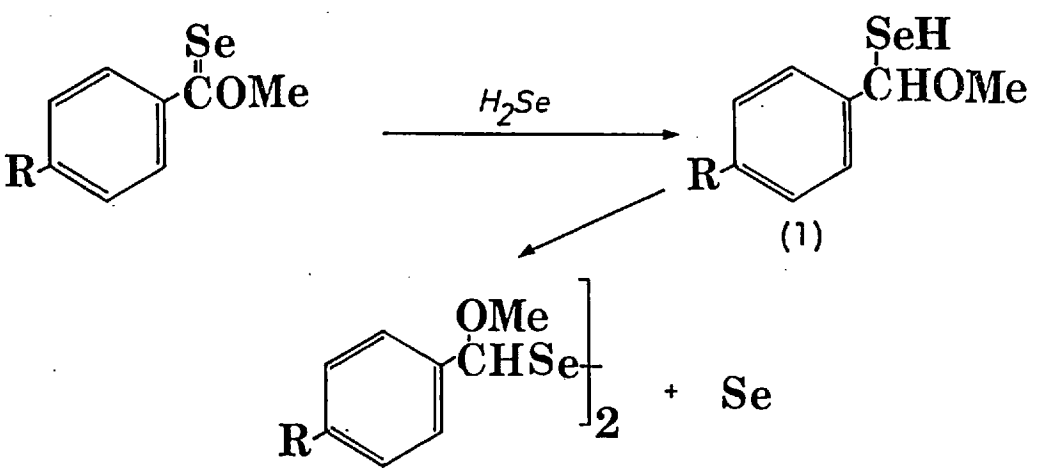
CHAPTER 1.

PREPARATION OF O-ALKYL AND O-ARYL SELENOESTERS.

A. AROMATIC O-ALKYL AND O-ARYL SELENOESTERS.

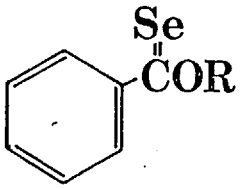
Preparation of aromatic selenoesters has previously been accomplished using two different reagents to introduce the selenium. Gray or black selenium (Se_x) has been found to react with pentacarbonyl-(methoxyarylcarbene)chromium(0)complexes to give aromatic O-alkyl selenoesters [1]. A series of O-methyl p-substituted selenobenzoates was made in this way. This method suffers, however, two disadvantages, firstly the chromium(0)complexes must be made from hexacarbonylchromium and phenyllithium, followed by acidification with boron trifluoride etherate [2,3]. Incidentally this also places the limitation on the preparation that only O-methyl esters can be made. Secondly, this method gives poor yield of the selenoesters. The yields are ranging from 10 to 29% based upon the amount of chromium(0)complex used. This method has also been used to make aromatic O-methyl thioesters and esters [1]. This method could possibly be extended to make O-methyl tellurobenzoates as well?.

The second reagent used to introduce selenium into this class of compounds was sodium hydrogen selenide or hydrogen selenide/pyridine [4,5]. The modification using hydrogen selenide/pyridine [4,5] suffers, however, a serious drawback. Once the selenoester has been formed hydrogen selenide reduces the selenocarbonyl function and gives an α-alkoxyselenol (1), which dimerizes under the reaction conditions (scheme 1).



Scheme 1.

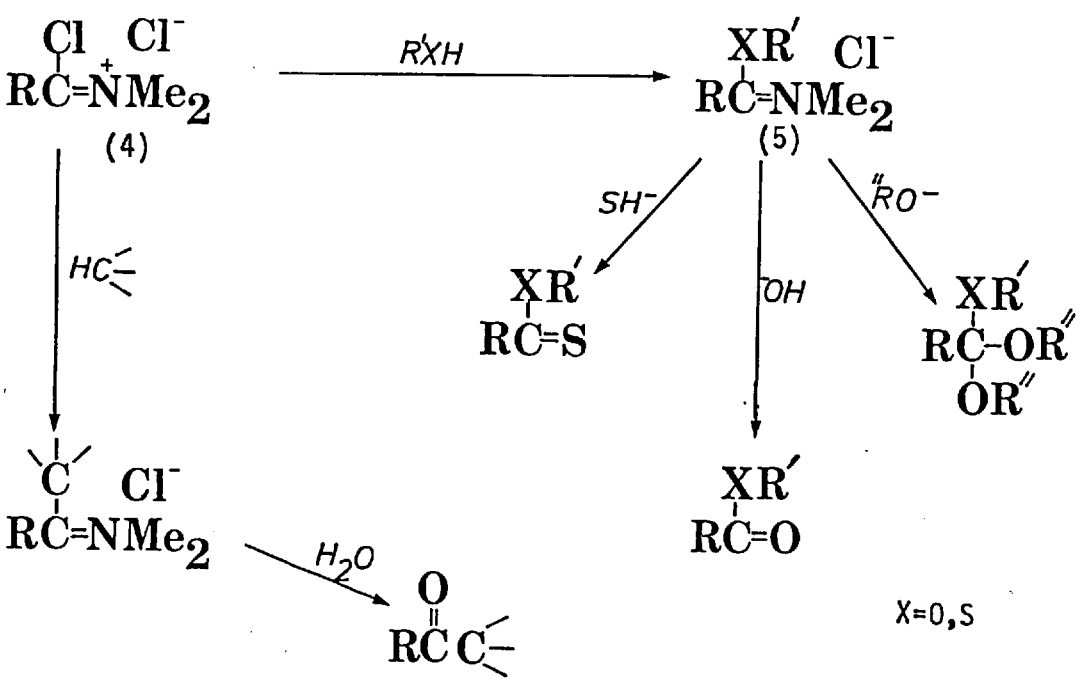
This reduction was, however, not observed when the modification using sodium hydrogen selenide/pyridine was used [6]. In this way excellent yields of the selenobenzoates (2) and (3) could be obtained.



R=Et (2)

R=CHOLESTERYL (3)

The idea to use an amidochloride of the type (4) as an intermediate in this preparation was based upon its reactivity towards nucleophiles. It has previously been established [8,9] that esters, thiolesters, thioesters, dithioesters, amidoacetals, orthoesters, heterocyclic compounds and ketones are formed by the reaction of an amidochloride of the type (4) with the respective nucleophile In many cases an intermediate imidate ester (5) could be isolated. Subsequent reaction with the respective nucleophile gave the products shown in scheme 2.



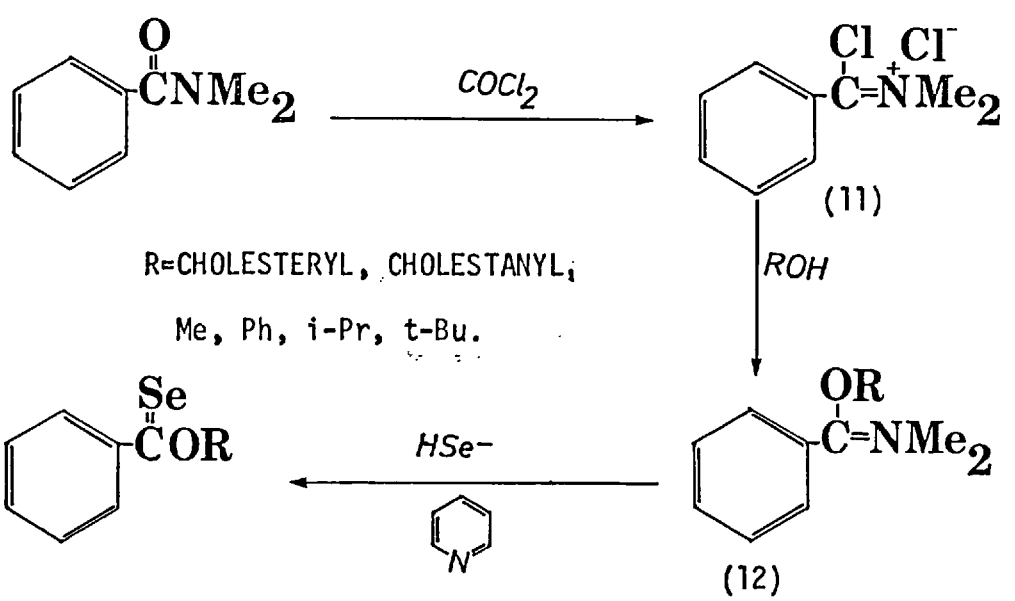
Scheme 2.

The method used for the preparation of the sodium hydrogen selenide solution makes this reagent easily accessible. This is done by reducing elemental selenium with sodium borohydride in ethanol an inert atmosphere [7].

Applying this method (scheme 3) the preparation of the selenobenzoates summarized in table 1 was attempted.

Table 1.

COMPOUND	YIELD (in %)
O-cholesteryl selenobenzoate [6] (3)	82
O-cholestanyl selenobenzoate [10] (6)	89
O-methyl selenobenzoate (7)	89
O-phenyl selenobenzoate (8)	87
O-isopropyl selenobenzoate (9)	92
O-t-butyl selenobenzoate (10)	0



Scheme 3.

Formation of N,N-dimethylbenzamidochloride (11) [8] from N,N-dimethylbenzamide and phosgene was complete in 24 hours (85-90%).

N,N-Dimethylbenzamidochloride (11) reacted smoothly with the alcohols, and subsequent treatment of the imidate esters (12) with sodium hydrogen selenide/pyridine gave the red coloured selenobenzoates.

Incorporation of the t-butoxy moiety into the imidate ester (12) was, however, not successful. Neither t-butanol, potassium t-butoxide nor t-butanol/imidazole reacted with the amidochloride (11) in the desired way. The failure to incorporate this moiety is probably due to steric hindrance.

The selenobenzoates, except O-phenyl selenobenzoate (8), were all stable in air. O-Phenyl selenobenzoate (8) extruded selenium with ease when exposed to air. The selenobenzoates, except O-phenyl selenobenzoate (8), could all be destilled (vacuum). O-Phenyl selenobenzoate (8) was destroyed when destilled, this compound was therefore purified by column chromatography, and it could be stored under argon for several weeks. Satisfactory elemental analysis could, however, not be obtained.

B. ALIPHATIC O-ALKYL AND O-ARYL SELENOESTERS.

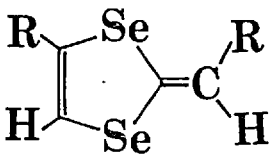
Preparation of aliphatic selenoesters has previously been accomplished along the pathway shown in scheme 3, using the N,N-dimethylformamide [6].

During these studies a report on a new method for preparing α-substituted selenoesters has appeared [11]. In this method the selenoesters were made from arylethynylselenolate salts (13), by treatment with an alcohol. This method suffered, however, two draw-

$$\underset{(13)}{RC{\equiv}CSe^{-}K^{+}} + R'OH \longrightarrow RCH_2\overset{\overset{Se}{\|}}{C}OR'$$

backs. Firstly the preparation must be performed in high dilution in

order to minimize the competing reaction which gives the fulvene (14).

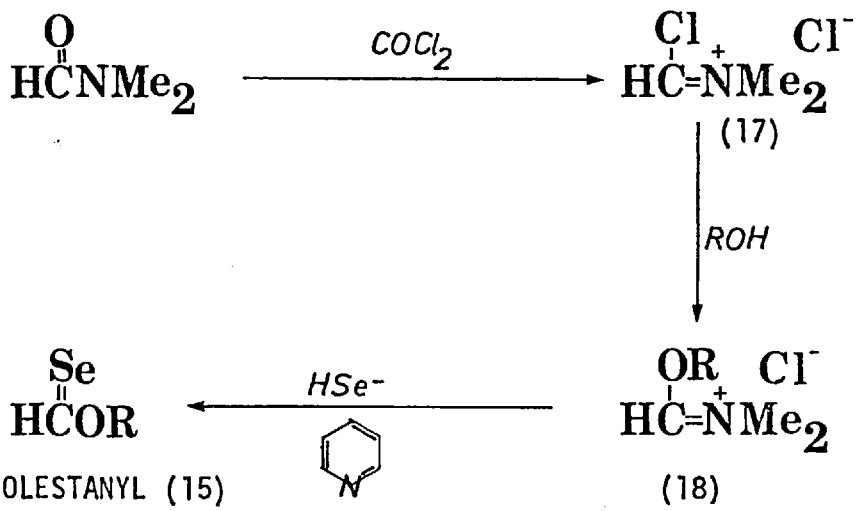


(14)

Secondly it was not possible to isolate the volatile low molecular weight selenoesters in this method. The yield in this method was approximately 50%.

1. SELENOESTERS WITHOUT α-HYDROGENS. (selenoformates).

Preparation of O-cholestanyl and O-cholesteryl selenoformate (15 and 16) was accomplished along the pathway outlined in scheme 4.



Scheme 4.

Phosgene reacted fast with N,N-dimethylformamide and gave the amidochloride (17). The structure of the amidochloride (17) has been established by ^{1}H n.m.r. [12]. Reaction of the amidochloride (17) with cholestanol or cholesterol took place within 5 minutes, and gave the imidate ester (18). Treatment of this imidate ester (18) with sodium hydrogen selenide/pyridine at -20°C, caused, however some difficulties. It appeared that the formation of the selenoformates (15 and 16) took

place (yellow solution), but a rapid precipitation of black selenium took also place, and work-up did not afford any selenoformate. The obvious reason for this process was that the selenoformates were not stable in the reaction medium. The stability of the selenoformates (15 and 16) towards pyridine and hydrogen chloride, which were both present in the reaction mixture, was therefore investigated. Upon dissolving the selenoformate (15) in an ethanolic solution containing pyridine or hydrogen chloride, it became apparent that the selenoformate (15) was destroyed by pyridine (instantaneous precipitation of black selenium). Hydrogen chloride, however, seemed not to affect the selenoformate (15). The preparation was therefore repeated without using pyridine. This resulted in no reaction. Instead a large amount of hydrogen selenide was produced. Since hydrogen chloride (pK=-7) is a stronger acid than hydrogen selenide (pK=3,88), the following acid-base reaction has taken place.

$$HCl + HSe^- \longrightarrow H_2Se + Cl^-$$

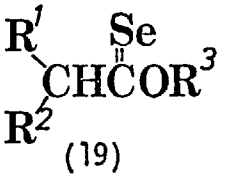
Hydrogen chloride is present in the reaction mixture from the reaction between the amidochloride (17) and cholestanol. This experiment also indicates that it is the hydroselenide anion that is the attacking nucleophile.

In an another attempt to change the method of isolation, the wet work-up procedure was omitted. After reaction with sodium hydrogen selenide/pyridine, the reaction mixture was evaporated in vacuo and quickly filtered through a silica gel column. This resulted in a vigorous reaction on the column, with complete destruction of the selenoformate.

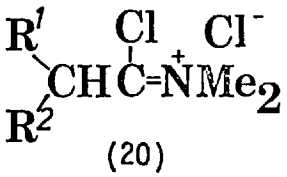
Successful isolation of the selenoformates (15 and 16) was accomplished when pyridine was washed out of the reaction mixture with hydrogen chloride immediately after the mixing of the imidate ester (18) solution and the sodium hydrogen selenide solution. With this modification, the selenoformates (15 and 16) could be isolated in 75% yield.

2. ALIPHATIC SELENOESTERS WITH α-HYDROGENS.

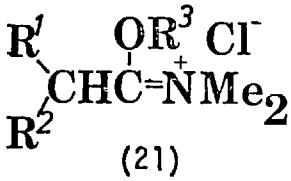
In the preparation of aliphatic selenoesters containing α-hydrogens (19), it was found that the intermediate amidochloride (20) and imidate ester (21) could participate in competing reactions.



(19)

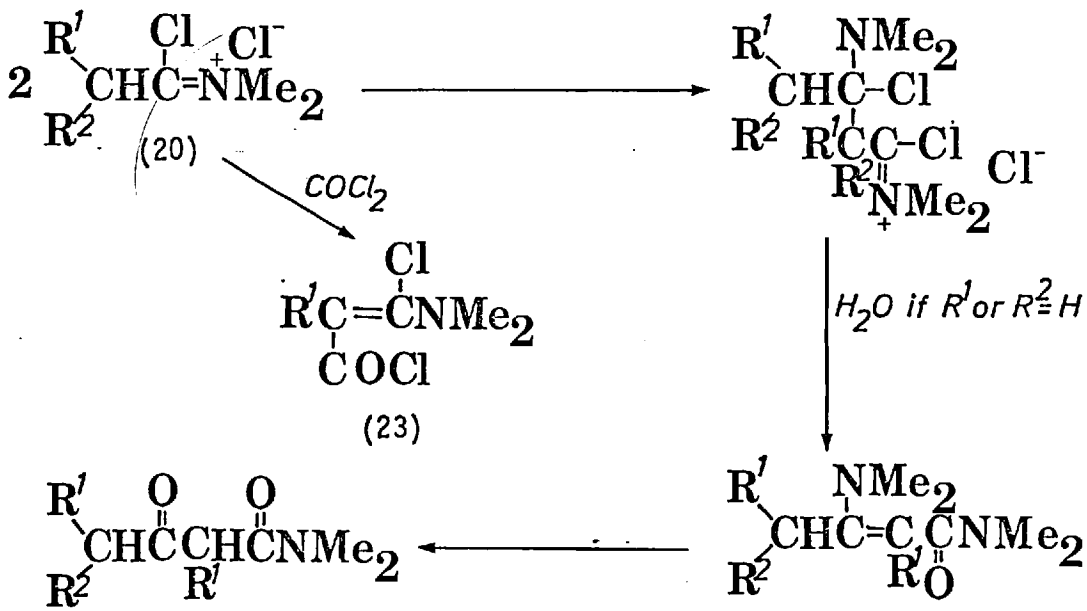


(20)



(21)

It has been established that amidochlorides of the type 20 can react with another molecule of amidochloride in a Claisen type condensation [9].(scheme 5).



Scheme 5.

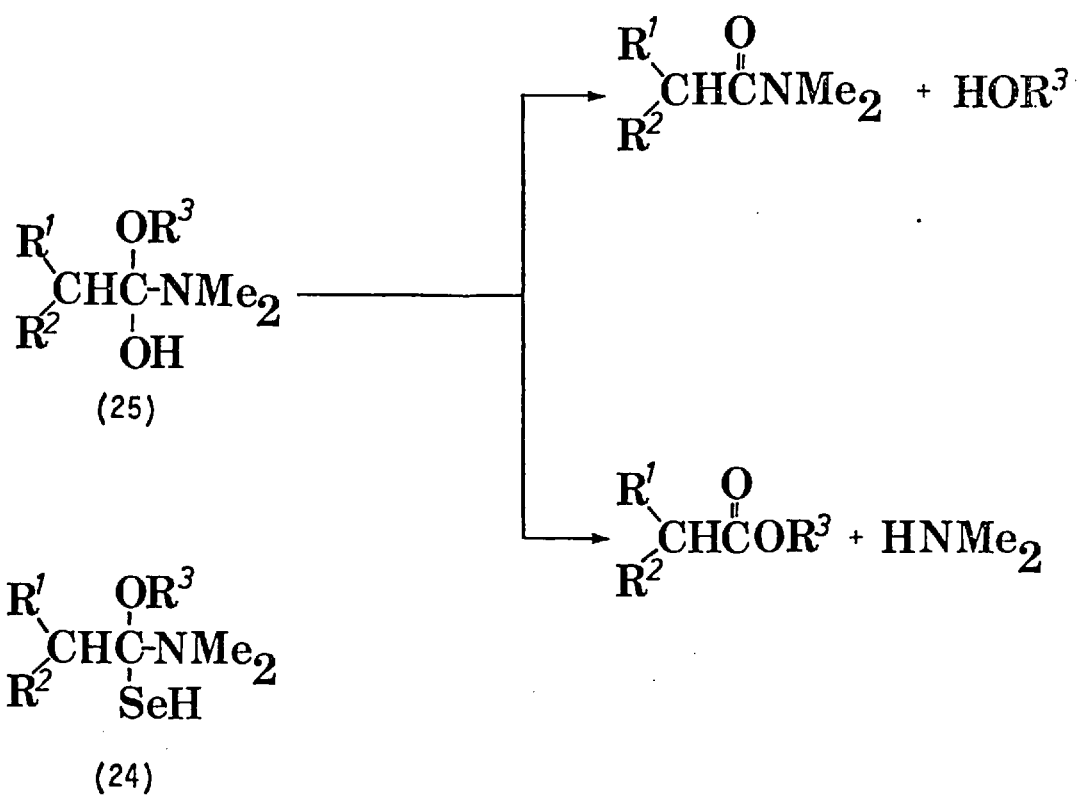
This will lead to β-keto amides after hydrolysis.

A second competing process has also been found to occur when tertiary aliphatic amides are treated with phosgene, i.e. the initially formed amidochloride (20) reacts further with phosgene giving an

enamine derivative (23) [13]. Formation of the β-keto amides and the enamine derivatives (23) requires that R^2 is hydrogen.

The imidate esters of the type 21 are known to fragment into alkyl halides and amides [8,14]. This process requires normally moderate heating over a period of some hours, nevertheless this is a complication when dealing with this type of intermediates.

In the last step in the preparation of the selenoesters a tetrahedral intermediate of the type 24 is probably involved. Recently a theory dealing with the cleavage of tetrahedral intermediates of the type 25 has been put forward [15]. The problem is whether the intermediate will cleave to give ester/amine or amide/alcohol.



According to this theory it is the orientation of the lone pairs on the two oxygen atoms relative to the carbon-nitrogen bond that determines which set of products that are formed. If the two lone pairs on the oxygen atoms are orientated antiperiplanar to the carbon-nitrogen

bond, only ester/amine will be formed, if this is not the case the intermediate will rotate its bonds to give conformers in which this orbital assisted elimination can take place. This implied that if the rotation of the bonds takes place before the orbital assisted elimination a mixture of both ester/amine and amide/alcohol will result. If these principles determine the product-composition resulting from the elimination of the tetraherdral intermediate (24) it can be expected that two sets of products will be formed, either selenoester/amine or selenoamide/alcohol or both.

Taking these considerations into account the preparation of the following selenoesters was attempted (table 2).

Table 2.

O-cholestanyl selenoacetate (26)

O-cholesteryl selenoacetate (27)

O-methyl selenoacetate (28)

O-methyl selenooctadecanoate (29)

O-methyl phenylselenoacetate (30)

O-cholesteryl selenopropionate (31)

O-phenyl selenoacetate (32)

O-ethyl selenoisobutyrate (33)

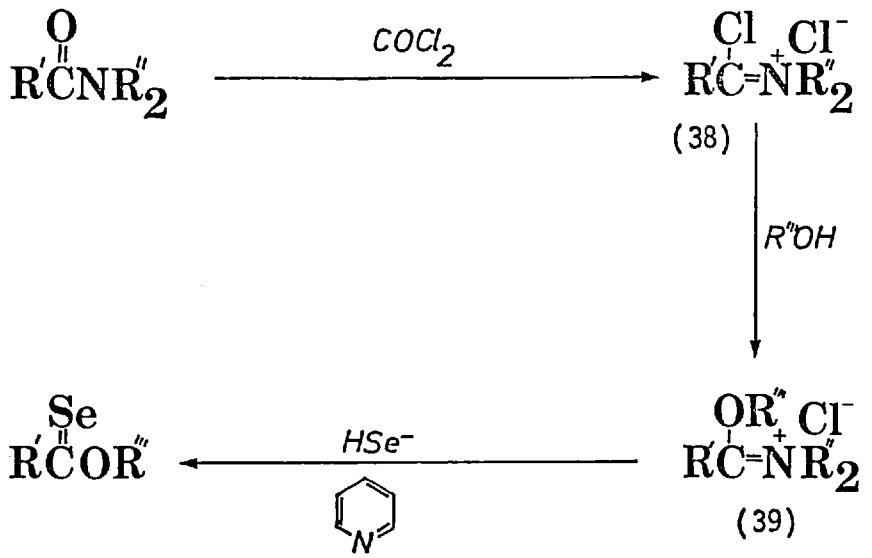
O-benzyl selenoacetate (34)

O-phenyl selenoisobutyrate (35)

O-isopropyl selenoacetate (36)

O-isopropyl selenoisobutyrate (37)

In order to avoid the Claisen type condensation, the preparation of the amidochlorides (38) (scheme 6) was conducted in a solvent in which they precipitated once they were formed. Benzene and diethyl ether

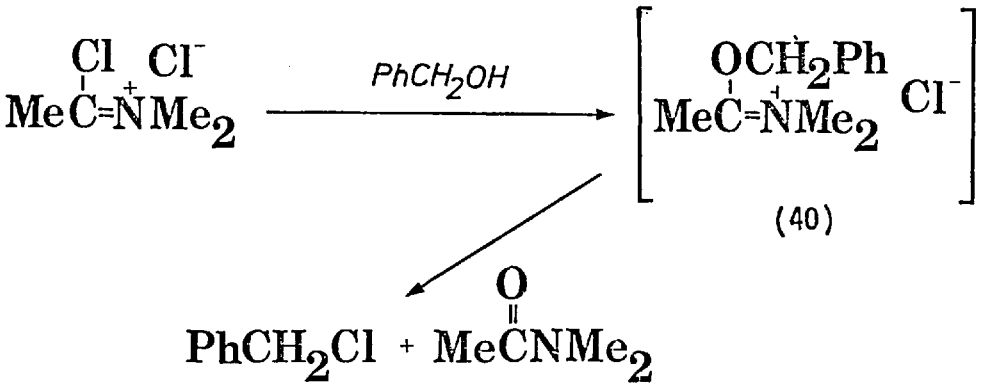


Scheme 6.

were found to be excellent solvents in this respect. This modification also completely blocked the further reaction of the amidochlorides with phosgene to give enamine derivatives. In this way the amidochlorides could be isolated as white crystalline materials. The preparation of the amidochlorides was in the majority of the cases based on the corresponding N,N-dimethylamides. N,N-Dimethylisobutyramide reacted, however, too slowly with phosgene, and the amidochloride formed did not readily precipitate out of the reaction mixture, thus enhancing the Claisen type condensation. Upon changing to the piperidine type amide these difficulties were overcome. The amidochloride derived from N-isobutyrylpiperidine was isolated as a nice crystalline material. The amidochlorides were all very hygroscopic, but could be kept for several days under dry conditions without any loss in reactivity.

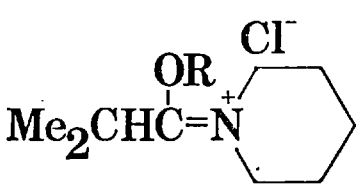
Subsequent reaction of the amidochlorides with the various alcohols gave the corresponding imidate esters. This reaction was performed in such a way that the Claisen type condensation was suppressed, i.e. the amidochloride was added to a solution of the alcohol in dichloromethane/diethyl ether. Some of the imidate esters (39) fragmented into the corresponding chlorohydrocarbon and amide. The

imidate ester derived from from N,N-dimethylacetamide and benzyl alcohol(40) fragmented into benzyl chloride and N,N-dimethylacetamide before it could be treated with sodium hydrogen selenide/pyridine. Performing the reaction at -20°C did not change the course of this reaction.



The driving force for this reaction is probably the formation of the benzyl cation. The selenoester (34) could therefore not be made by this method.

The imidate esters derived from N-isobutyrylpiperidine and ethanol or isopropanol fragmented also into the corresponding chlorohydrocarbons and N-isobutyrylpiperidine. These fragmentations were not as fast as the fragmentation of the imidate ester (40), thus it was possible to convert them into the corresponding selenoesters. The formation and the fragmentation of the two imidate esters (41 and 42) were followed by ^1H n.m.r. This showed that the reaction between the amidochloride and ethanol or isopropanol was fast. After 5 minutes the signals corresponding to the alcohols could not be detected, whereas the signals corresponding to the chlorohydrocarbons could be detected after 15 minutes. The ^1H n.m.r. observations are summarized in table 3.



R=ETHYL (41)

R=ISOPROPYL (42)

R=PHENYL (43)

Table 3.

Reaction time				
	Ethanol			
8 min.	5,27 (q)	6,38 (septet)		
6 h.	5,27 (q)	6,38 (septet)	6,46 (q)	6,59 (septet)
24 h.			6,46 (q)	6,59 (septet)
	Isopropanol			
8 min.	4,64 (septet)	6,38 (septet)		
2 h.			5,76 (septet)	6,59 (septet)

The signals in the first column correspond to the imidate esters and the signals in the second column correspond to the chlorohydrocarbons.

These reactions were also performed on a preparative scale, and after 24 hours at room temperature the corresponding chlorohydrocarbons could be isolated in excellent yields.

Reaction of the imidate esters (39) with sodium hydrogen selenide/pyridine resulted in the formation of the selenoesters mentioned in table 2, i.e. except O-benzyl selenoacetate and O-phenyl selenoisobutyrate.

The selenoacetate (34) could not be made because of the previously mentioned fragmentation of the imidate ester (40). Treatment of the imidate ester (43) with sodium hydrogen selenide/pyridine resulted in exclusive formation of N-selenoisobutyrylpiperidine. The tetrahedral intermediate (44) has apparently undergone elimination with cleavage of the carbon-oxygen bond.

(44) (51)

The preparation of O-phenyl selenobenzoate (8) and O-phenyl selenoacetate (32) was therefore reinvestigated. Preparation of O-phenyl selenobenzoate (8) starting either from N,N-dimethylamide or N-benzoylpiperidine did not alter the outcome. The selenobenzoate (8) was isolated in high yield in both cases. The corresponding selenoamide could not be detected in either of the cases. In the case of O-phenyl selenoacetate (32), starting either from N,N-dimethylamide or N-acetylpiperidine, both the selenoester (32) and the selenoamide could be isolated. When N,N-dimethylamide was the starting material the selenoester (32) was the major product, but when N-acetylpiperidine was the starting material both the selenoamide and the selenoester (32) were isolated.

If the previously mentioned orbital assisted mechanism [15] should be used to explain these results this must indicate that only in the cases of O-phenyl selenoacetate and O-phenyl selenoisobutyrate, the lone pairs on oxygen and selenium are not properly orientated to assist in the cleavage of the carbon-nitrogen bond. The tetrahedral intermediate must reorientate its orbitals on oxygen and selenium through bond rotation, thus giving conformers that will give both amide/alcohol and ester/amine.

These results can, however, equally well be explained by considering which one of the groups on the central carbon atom is the best leaving group. It was therefore to be expected that the formation of the selenoamides should be enhanced in these cases. The difference in the product composition seemed to be influenced by the aryl or alkyl residue on the central carbon atom, i.e. the competetion between the two leaving groups.

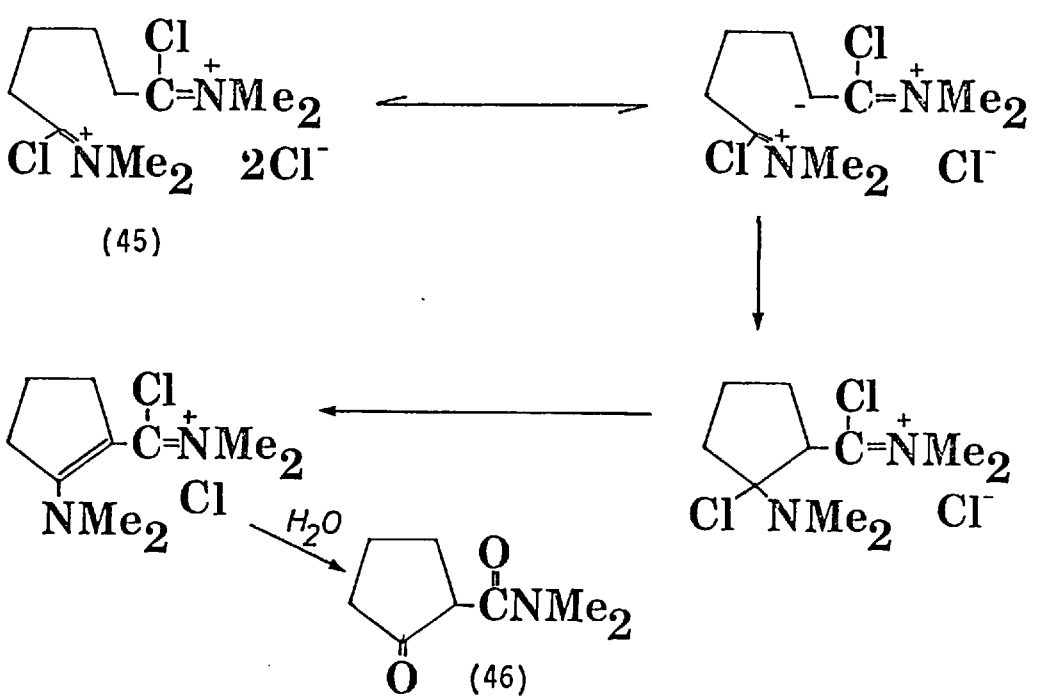
Isolation of the low molecular weigth selenoacetates (28 and 36) was not possible when benzene or petroleum ether (b.p. 60-80°C)

was used in the preparation. Upon changing to diethyl ether and petroleum ether (b.p. 40-50°C) and by careful removal of these solvents using a 60 cm. Vigreux column, these selenoesters could be isolated.

3. SELENOESTERS CONTAINING TWO SELENOCARBONYL FUNCTIONS.

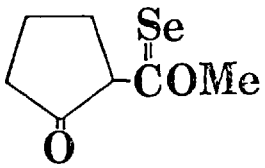
The preparation of this class of compounds was attempted along the pathway used in the preparation of the aliphatic selenoesters.

Treatment of di-N-pentamethyleneadipdiamide with phosgene gave a red coloured intermediate, which on treatment with methanol and sodium hydrogen selenide/pyridine gave an unstable selenium containing molecule. The structure of this compound was not established. A reaction similar to the above mentioned has previously been investigated [9]. It was established that the initially formed diamidochloride (45) condensed intramolecularly and gave a five-membered ring, which upon hydrolysis gave a cyclopentanone derivative (46) (scheme 7).



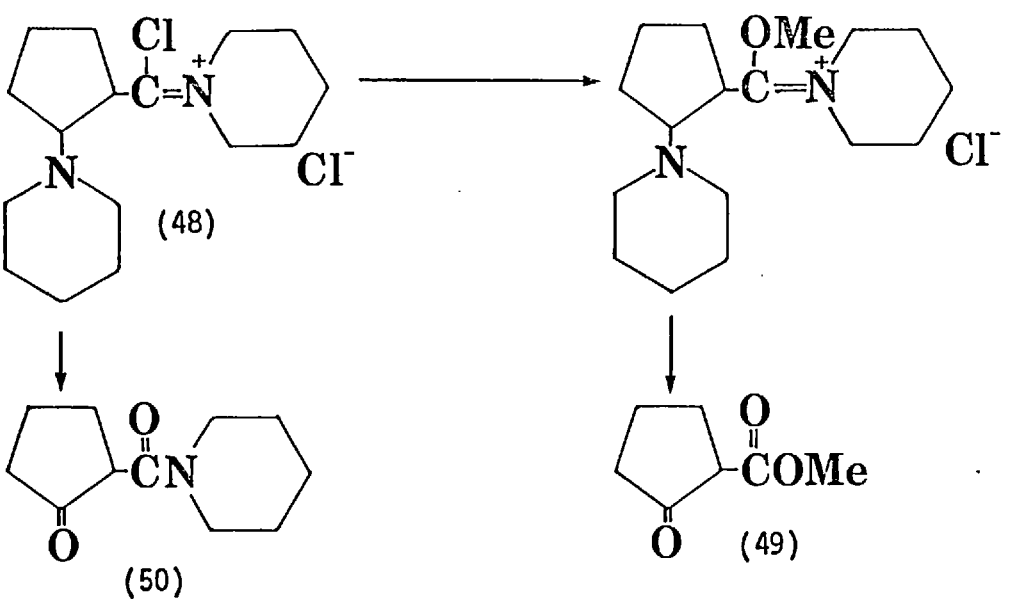
Scheme 7.

It was therefore reasonable to assume that the structure of the isolated product was (47).



(47)

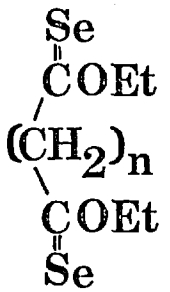
The intermediacy of the five-membered ring (48) was established by conducting the following experiments: Treatment of the red intermediate with methanol and subsequent hydrolysis gave methyl 2-oxocyclopenta-1-carboxylate (49) [17], and hydrolysis of the red intermediate gave the amide (50) [18] (scheme 8).



Scheme 8.

In order to avoid the intramolecular selfcondensation, a diselenoester based on glutaric acid was investigated. Treatment of di-N-pentamethyleneglutardiamide with phosgene produced the desired diamidochloride, and subsequent reaction with ethanol and sodium hydrogen selenide/pyridine resulted in the isolation of the diselenoester (52) in 40% yield. The low yield in this preparation was due to some intermolecular

condensation of the diamidochloride.



n=3 (52)

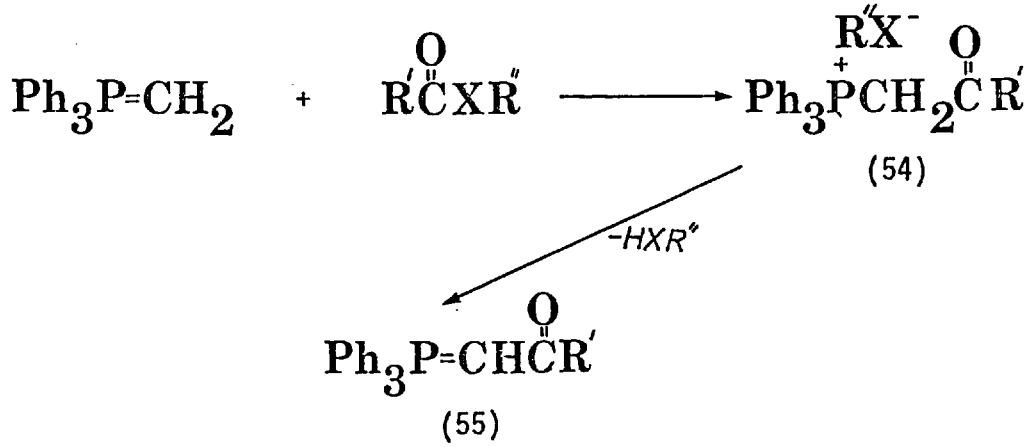
n=4 (53)

CHAPTER 2.

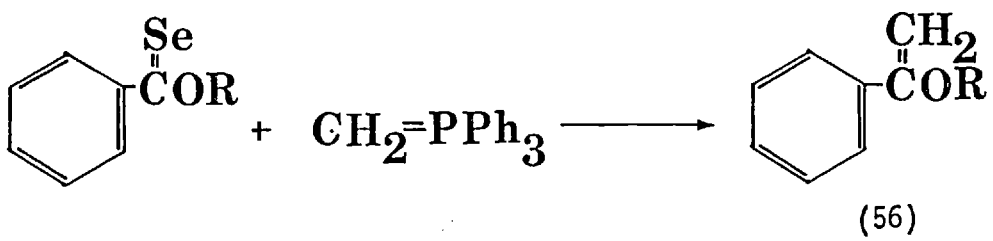
REACTIONS OF O-ARYL AND O-ALKYL SELENOESTERS.

A. REACTION WITH METHYLENETRIPHENYLPHOSPHORANE.

It has previously been established that esters [35,36] and thioesters [37] reacted with alkylidenephosphoranes, not as in the normal Wittig reaction, but instead to give β-ketoalkylphosphonium salts (54). This salt then eliminated HOR or HSR to give the stable β-ketoalkylidenephosphorane (55).



On performing this reaction with the selenobenzoates and methylenetriphenylphosphorane, only the normal Wittig product was formed (scheme 9), i.e. α-alkoxystyrenes (56). The product, acetophenone, that should be formed according to the above mentioned reaction could not be detected.



Scheme 9.

The α-alkoxystyrenes were identified on the basis of their ^1H n.m.r. spectra, and the products that arose from their hydrolysis. In fact ,

the α-alkoxystyrenes hydrolysed with ease. This was, however, to be expected since protonation of α-alkoxyalkenes (vinyl ethers) does not take place on oxygen, but on the β-carbon atom [38]. Acetophenone will therefore be the leaving group.

The aliphatic selenoesters did not react with methylenetriphenylphosphorane under the same conditions as the selenobenzoates did. They could be recovered unchanged from the reaction mixtures.

B. REACTIONS WITH TRIALKYLPHOSPHINES.

1. INTRODUCTION.

Irradiation of the selenoesters (3,6,26,27,) in degassed dry diethyl ether with a high pressure mercury lamp, resulted in extrusion of a small amount of selenium. The selenium was finely divided throughout the solution, and after a few minutes it settled on the glass walls of the reaction wessel, thus preventing the light from reaching the reaction mixture and no further reaction took place. From these experiments the selenoesters could be recovered in 90% yield. In an attempt to overcome this difficulty, tri-n-butylphosphine was added to the reaction mixture before the irradiation was started. Selenium should thus be prevented from blocking the light, i.e. selenium would react with tri-n-butylphosphine and give tri-n-butyl phosphine selenide which would stay in solution. It is well known that selenium reacts readily with trialkylphosphines [42].

Irradiation of the selenoesters (3,6,26,27) under these conditions gave the corresponding esters and tri-n-butylphosphine selenide. When these results are compared with the results obtained

from the irradiation of the corresponding thioesters, it appeared unlikely that these reactions could have been caused by a photoreaction. A reaction between the selenoesters and tri-n-butylphosphine, giving an intermediate that reacted either with oxygen or water appeared to be more likely.

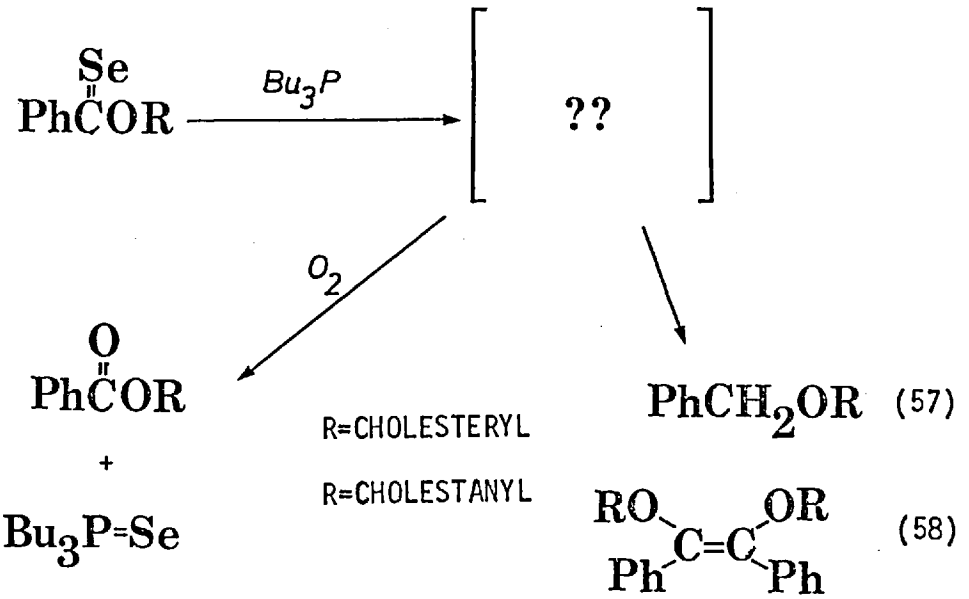
2. THE AROMATIC SELENOESTERS.

The selenobenzoates (3) and (6) were treated with tri-n-butylphosphine in dry benzene. After 1 hour the red colour had disappeared and the corresponding esters and tri-n-butylphosphine selenide could be isolated in high yield.

Upon repeating this experiment under completely oxygen free conditions (see experimental part for details), the ester could not be found among the reaction products. T.l.c. indicated two non-polar products. Attempted separation of these on a silica gel column resulted in the isolation of the benzyl ether (57). The second non-polar product had been hydrolysed in this attempt. Attempted separation on an alumina column (grade III) gave the same result. From the polar material left on the column after isolation of the benzyl ether (57), cholestanol, benzoin and tri-n-butylphosphine selenide could be isolated. This suggested that benzoin and cholestanol had been formed by a hydrolysis of the second non-polar material. The second non-polar compound was eventually isolated by crystallisation from the reaction mixture, and was identified as the disubstituted alkoxy-stilbene (58).

It was established that these compounds readily hydrolysed to give benzoin and cholesterol (cholestanol).

These results can be interpreted in the following way: Tri-n-butylphosphine reacted with the selenoester and gave an intermediate (?) which reacted with oxygen and gave the ester. This intermediate (?) must also be responsible for the formation of the benzyl ether (57) and the disubstituted alkoxystilbene (58) (scheme 10).



Scheme 10.

Because of its low volatility tri-n-butylphosphine was exchanged with triethylphosphine. The reaction between the selenobenzoates (3) and (6) and triethylphosphine was also conducted in toluene, tetrahydrofuran and triethylphosphine. These experiments gave all the same result,i.e. formation of the benzyl ether (57), the dimer (58) and triethylphosphine selenide. However, when triethyl orthoformate was used as a solvent, the formation of the benzyl ether (57) was enhanced at the expense of the dimer. The ratio between the benzyl ether and the dimer was 1:1 in the previously mentioned experiments, whereas in the case of triethyl orthoformate the ratio was 7:3.

Since the formation of the benzyl ether (57) was enhanced when the reaction was performed in a hydrogen source (triethyl orthoformate) it was also explored if thiophenol would have the same effect. The

products isolated from this experiment were cholestanol and triethylphosphine selenide. It appeared that thiophenol reacted with the intermediate (?) and caused the rupture of the carbon-oxygen bond.

The ratio between the benzyl ether (57) and the dimer (58) was also dependent of the O-alkyl residue. The formation of the benzyl ether was enhanced at the expense of the dimer when the O-alkyl residue grew in size from methyl to isopropyl. These results are summarized in table 4.

Table 4.

O-R	benzyl ether/dimer
methyl	only dimer
ethyl	only dimer
isopropyl	1:1
cholestanyl	5:4
cholesteryl	5:4
phenyl	only dimer

It was also investigated if triphenylphosphine would react with the selenobenzoates in a similar way. 24 hours reaction at room temperature resulted only in recovery of the starting material. Reaction in a sealed tube at 150°C with or without added benzyldimethylsilane resulted also in recovery of the starting material. The failure of triphenylphosphine to react compared to the trialkylphosphines can be ascribed to the lower nucleophilicity of triphenylphosphine.

If the benzyl ethers were formed when the reaction was performed in a non hydrogen containing solvent, the only source of hydrogen would be triethylphosphine, thus proving triethylphosphine to be the hydrogen source. A number of halogen containing solvents were investigated in this

respect. The solvents in question were: Carbon tetrachloride, tetrachloroethylene, carbon disulphide, 1,2,2-trifluoro-1,1,2-trichloroethane and 1,1,1-trifluoro-2,2,2-trichloroethane. Triethylphosphine reacted , however, with these solvents. With carbon disulphide a red 1:1 adduct was formed [43]. With the halogenated solvents black tars were formed. Triethylphosphine reacted probably with the aliphatic halogenated hydrocarbons in a similar way as triphenylphosphine reacted with carbon tetrachloride [44]. The intended experiment could therefore not be performed.

A phosphorus containing molecule was, however, isolated from the reaction between the selenobenzoate (9) and triethylphosphine. On the basis of ^{31}P n.m.r. and ^{1}H n.m.r. data its structure was assumed to be (59).

$$\begin{array}{l} MeCHPEt_2 \\ MeCHPEt_2 \end{array}$$

(59)

The ^{1}H n.m.r. assignements were as follows: The signal at τ=5,93ppm. (m) is due to the two methine protons (coupling to methyl and phosphorus), τ=7,93ppm. (m) is due to the two methylene groups of the ethyl group and τ=8,83ppm. (m) is due to the methyl groups. These signals integrated as 1:2:6. The chemical shift for the phosphorus in ^{31}P n.m.r. (16,40ppm.) is reasonable for a trivalent phosphorus atom. This chemical shift is relative to triethylphosphine.

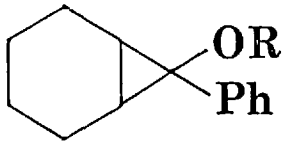
This compound was not, however, further characterized.

The above mentioned experiments were all performed with four equivalents of triethylphosphine. If less triethylphosphine was used the reactions were not completed within 24 hours.

In order to gain information concerning the mechanism in the above mentioned reactions the experiments described on the following pages were conducted.

The reaction with triethylphosphine was carried out in cyclohexene.

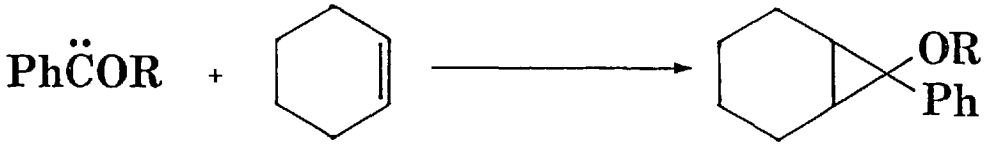
This resulted in the isolation of the benzyl ether (57), phenyl cyclohexyl ketone and triethylphosphine selenide. The two isomeric 7,7-disubstituted norcarane derivatives (60) were also detected (^{1}H n.m.r.). These compounds (60) were not characterized as such, but hydrolyzed to phenyl cyclohexyl ketone.



(60)

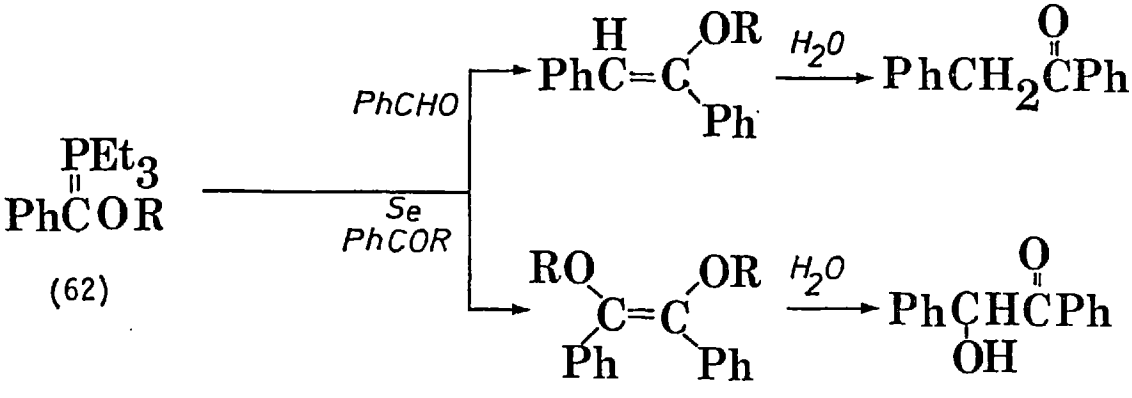
When the reaction with triethylphosphine was carried out with benzaldehyde present, deoxybenzoin was obtained as one the products. Using 0,5 equivalents of benzaldehyde, deoxybenzoin, benzoin, benzyl ether (57) and triethylphosphine selenide were isolated. When 1,0 qquivalent of benzaldehyde was present benzoin was not formed.

These results suggested that both a carbene and a Wittig type ylid were involved in the reaction. Formation of the norcarane derivatives (60) gave strong indication of a carbene intermediate.



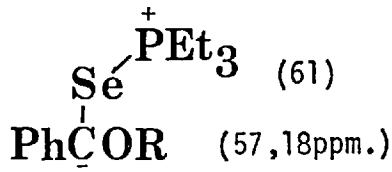
(60)

At the same time the formation of deoxybenzoin and benzoin pointed to a Wittig reaction.

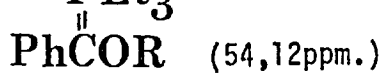


Benzoin and deoxybenzoin have both been formed during the work-up.

The reaction between triethylphosphine and the selenobenzoate (9) in benzene was also monitored on ^{31}P n.m.r., and this revealed two different intermediate phosphorus atoms. These were observed when the spectrum was recorded immediately after the mixing of the two reagents. When the spectrum was rerecorded after 30 minutes these two phosphorus atoms had disappeared. The chemical shifts of these two phosphorus atoms were 54,12ppm. and 57,18ppm. relative to triethylphosphine. A reasonable interpretation of these two signals would be to assign them to the phosphorus atoms in the intermediates (61) and (62).



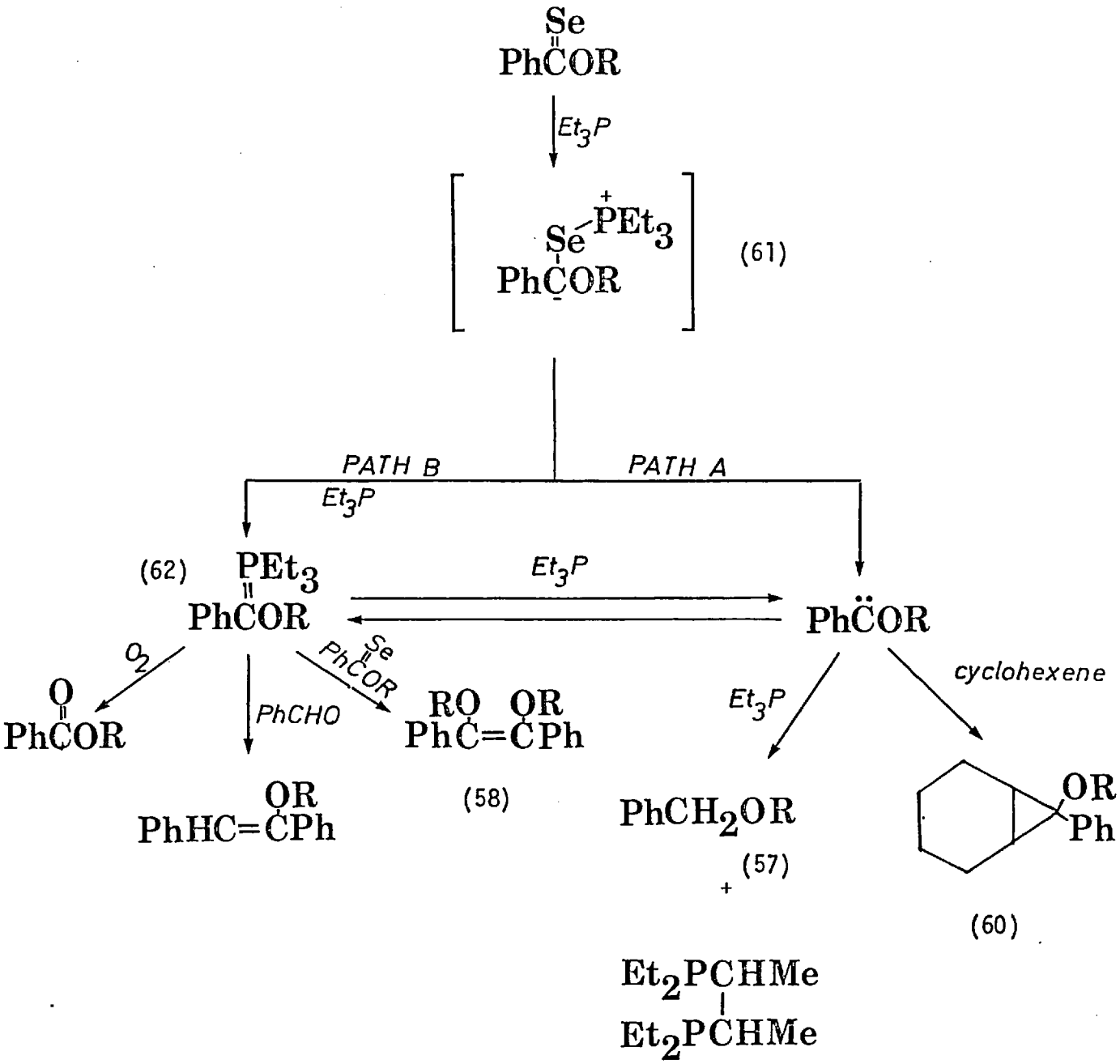
(61) (57,18ppm.)



(62) (54,12ppm.)

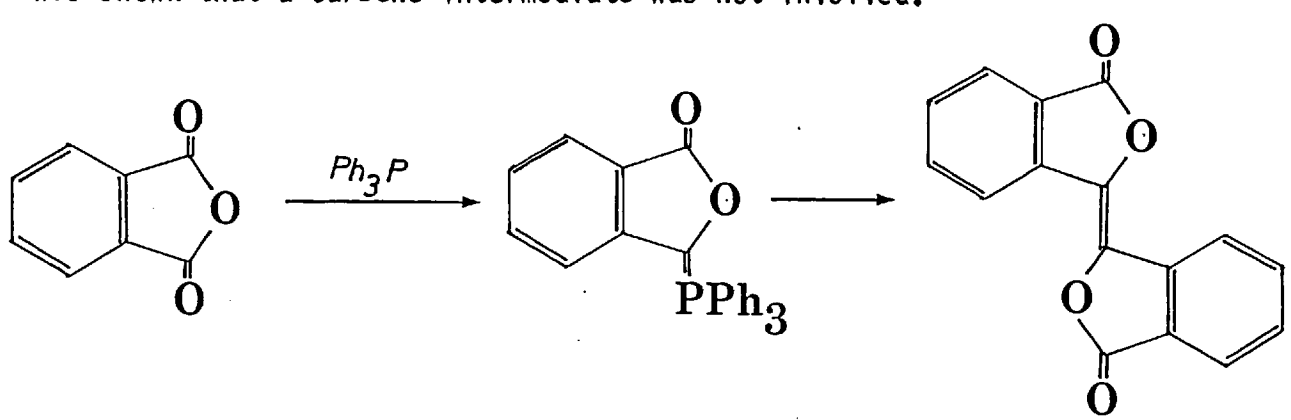
The assignements were based upon the ^{31}P n.m.r. spectra of the aliphatic selenoesters/triethylphosphine (see section 3), and the fact that $Et_3P{=}CH_2$ resonates at higher field than $Et_3\overset{+}{P}MeI^-$ [45]. Spectra of a number of alkyl substituted methylenetriethylphosphoranes have been recorded, with chemical shifts ranging from 44,0ppm. to 35,0ppm relative to triethylphosphine [45]. Thus it would be expected to find the chemical shift at lower field when the alkyl substituents are replaced by two electronegative substituents. Because of the unstability of α-alkoxyphosphoranes not much is known about their ^{31}P n.m.r. [46].

Based on these results a reasonable mechanism regarding the reaction between the selenobenzoates and triethylphosphine is outlined in scheme 11. Triethylphosphine reacts with the selenobenzoate and gives the 1,3 dipolar intermediate (61), which in turn reacts with a second molecule of triethylphosphine and gives the Wittig type ylid (62). Analogy for this reaction stems from the reaction between phthalic anhydride and triphenylphosphine [47,48]. In this case it

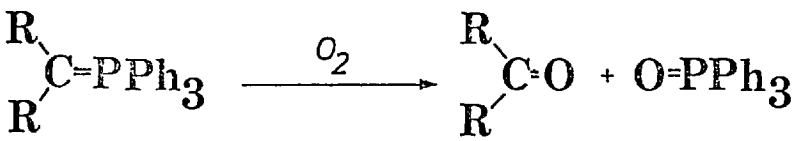


Scheme 11.

was shown that a carbene intermediate was not involved.



The Wittig type ylid (62) is a very reactive ylid, and can hence react with oxygen. It has been shown that reactive Wittig ylids (no stabilizing groups on the carbon atom) reacts readily with oxygen and gives ketones and phosphine oxides [49,50].



Reaction of the ylid (62) with benzaldehyde or a second molecule of selenobenzoate accounts for the formation of the Wittig products (benzoin and deoxybenzoin).

(62)

It has been suggested that ylids of the type 62 can collapse to give a carbene and triethylphosphine [51,52]. If this was the case this would account for the formation of the carbene trapped product (phenyl cyclohexyl ketone).

Formation of the benzyl ether would then require that the α-alkoxycarbene abstracts hydrogen from triethylphosphine. Very little is known about the reactivity of α-alkoxycarbenes. They are, however, considered to be highly reactive species. Since the benzyl ether could not be found among the reaction products from the trapping experiment with benzaldehyde (only a small trace was found), it appeared that the formation of the benzyl ether was connected with the carbene.

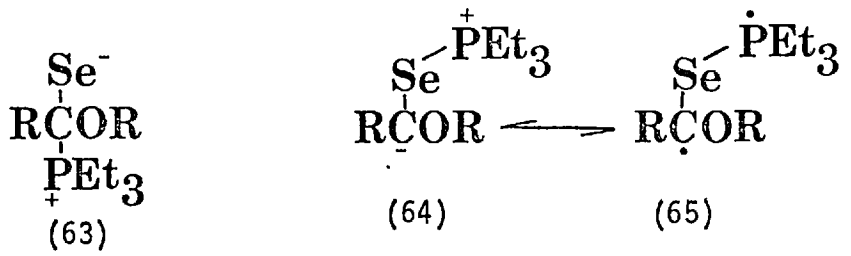
Formation of the carbene can also be postulated from the collapse of the 1,3 dipolar (61) (path A). The carbene formed can then react with a second molecule of triethylphosphine and give the Wittig ylid (62). This would be in analogy with the established reaction between dihalo-carbenes and triphenylphosphine [53,54,55,56].

3. THE ALIPHATIC SELENOESTERS.

The selenoacetates (26,27) behaved analogously to the selenobenzoates (3,6) when they were treated with triethylphosphine in the presence of oxygen,i.e. a deep colour developed rapidly which faded after 4 hours. Work-up gave the corresponding esters and triethylphosphine selenide. When the selenoacetates (26,27) were treated with triethylphosphine under completely oxygen free conditions the purple colour developed rapidly and increased in intensity during 4 hours. This colour did not change as long as oxygen was kept away from the reaction mixture. The reaction mixture could be kept in this state for several days without any visible change. Treatment of the purple reaction mixture with water free oxygen resulted in a rapid discoloration and the isolation of the corresponding esters and triethylphosphine selenide. In an another experiment the purple reaction mixture was treated with oxygen free water, and this resulted in no visible change. It was therefore assumed that oxygen was responsible for the formation of the esters.

The thermal stability of the purple intermediate was also investigated. Heating at 110°C in a sealed tube resulted in no visible change. Heating at 150°C for 6 hours caused the colour to fade away. From the intermediate derived from the selenoacetate (26) it was possible to isolate cholestanol and triethylphosphine selenide, and from the intermediate derived from the selenoacetate (27) cholesterol, cholesta-3,5-diene and triethylphosphine selenide could be isolated.

The nature of this purple intermediate could be radical or dipolar. Triethylphosphine can attack the selenocarbonyl function either at the carbon atom or the selenium atom, giving the corresponding intermediate,(63) or (64).



(63) (64) (65)

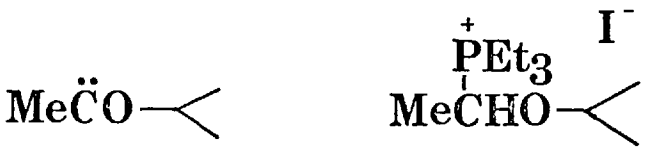
Applying the principle of hard/soft acids and bases (HSAB) it is not very likely that triethylphosphine will attack the carbon atom. Triethylphosphine is considered to be a very soft base and similarly is selenium considered to be a soft acid, hence a bonding between the two will be stabilized, and a bonding between triethylphosphine and carbon will be destabilized [57,58]. It would therefore seem that the structure (64) is most reasonable.

A resonance form of this intermediate is the diradical (65). It was, however, shown that the radical form could not be important. The ESR spectrum of the purple intermediate showed that no radicals were present. It is, however, possible that a 1,3 diradical of the type 65 could interact through space with itself and thereby give a triplet state. Scanning under conditions (-180°C) where triplets would be detected gave negative result .

In order to gain information regarding the purple intermediate a number of experiments were performed. Adding benzaldehyde, acetone or benzyldimethylsilane to the purple intermediate resulted in no reaction. Methyl iodide, however, reacted rapidly with the purple intermediate and gave a very volatile product. In order to bypass this problem the purple intermediate was reacted with octadecyl iodide. This resulted in the isolation of dioctadecyl selenide (in collaboration with Dr. Hulshof). This was based upon ^{1}H n.m.r., i.r., mass spectrometry and analysis (Dr. Hulshof). ^{1}H n.m.r. showed only one large peak at τ=8,73 ppm., and mass spectrometry gave the molecular ion at m/e=586. The fragmentation pattern showed rupture of the carbon-selenium bond as

the major process. A metastable peak was found in the spectrum for this process. A peak at m/e=666 could also be found in the spectrum. This is probably due to dioctadecyl diselenide.

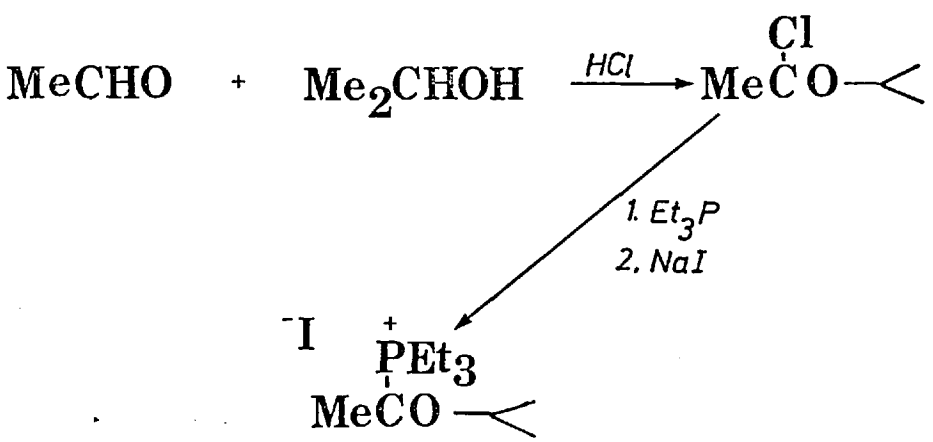
Repeating this reaction with methyl iodide on the intermediate derived from O-isopropyl selenoacetate (36) and triethylphosphine, resulted in the isolation of dimethyl selenide as the previously mentioned volatile product. From the residue it was possible to isolate triethylphosphine selenide and the phosphonium salt (66).



(68)

(66)

The identity of this compound was established on the basis of ^1H n.m.r. and comparison with an authentic sample. The preparation of the phosphonium iodide (66) is outlined in scheme 12.



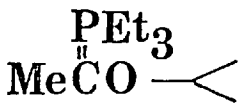
(66)

Scheme 12.

The α-chloroether was prepared by reacting paraldehyde with isopropanol in the presence of dry hydrogen chloride [59]. Reaction with triethylphosphine at room temperature in dry benzene gave the phosphonium chloride. Subsequent treatment of the chloride with sodium iodide in acetone gave the iodide (66). The phosphonium iodide (66) crystallized

from acetone with acetone in its crystal lattice. By dissolving the phosphonium iodide (66) in benzene and evaporation in vacuo, the phosphonium iodide (66) crystallized without any solvent. The phosphonium iodide (66) was an unstable hygroscopic compound. In solution it decomposed to give isopropanol. Similar observations have been made with other α-alkoxyphosphonium salts [60,61].

Formation of the phosphonium iodide (66) can be explained if the reaction between O-isopropyl selenoacetate (36) and triethylphosphine gave the Wittig type ylid (67). There are, however, a number of things wrong with this assumption. The stability of the purple intermediate is much too great for it to be a Wittig type ylid (67). Ylids of this type are known to be extremely unstable at room temperature [46,62,63,64].



(67)

Treatment of an ylid of the type (67) with methyl iodide should give a C-alkylated phosphonium salt, and lastly, the ylid should give an α,β-unsaturated ether when treated with benzaldehyde. None of these products arose when the purple intermediate was treated with methyl iodide or benzaldehyde.

In order to get information regarding the Wittig ylid (67), it was investigated if it could be possible to generate it from the phosphonium iodide (66). Treatment of the phosphonium iodide (66) with methyllithium at -40°C gave, however, no strongly coloured compound. Subsequent reaction with benzaldehyde and work-up gave a mixture of compounds, none of which were the desired Wittig product.

The ylid could also have been formed by the collapse of the 1,3 dipolar intermediate (64) to give the carbene (68). The carbene

could then react with triethylphosphine and give the ylid (67). On performing the reaction between O-isopropyl selenoacetate (36) and triethylphosphine in cyclohexene no carbene trapped product could be found. This reaction gave the same result as if it had been performed in benzene.

The formation of the phosphonium iodide (66) must therefore arise from the reaction between the purple intermediate and methyl iodide.

This leaves the 1,3 dipolar structure as the most reasonable structure for the purple intermediate.

The purple intermediate has also been investigated on ^{31}P n.m.r. These results are given in table 5.

Table 5.*

SAMPLE	^{31}P ***	^{13}C ****
$Et_3P{=}Se$ **	63,93	104,03. 120,68. 105,81. 120,85.
$PhC(O)(Se)<$ + Et_3P	16,40. 54,12. 57,18. 63,28.	
Et_3P	0,00.	108,66. 117,91, 109,20. 118,45.
$CH_3C(O)(Se)<$		-101,65. 86,52. 47,97. 107,12.
$CH_3C(O)(Se)<$ + Et_3P	59,37. 63,14.	COMPLEX PATTERN:
$CH_3CHO(P^+Et_3)<$ I^-	59,36.	42,80. 43,39. 47,67. 51,96. 85,10. 92,90. 94,00. 99,91. 103,81. 106,86. 109,40. 109,73.

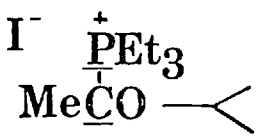
*The spectra were recorded in C_6D_6.

**^{31}P-^{77}Se coupling 683Hz.

***The chemical shifts are relative to triethylphosphine.

****The chemical shifts are relative to the middle peak of C_6D_6.

The ^{31}P n.m.r. spectrum of the purple intermediate shows two different phosphorus atoms. On comparison with the ^{31}P n.m.r. of triethylphosphine selenide (63,93ppm.), one of these (63,15ppm.) is assigned to triethylphosphine selenide. This compound is considered to be an impurity in the reaction mixture. The other phosphorus atom has a chemical shift (59,37ppm.) very close to the phosphorus atom in the phosphonium iodide (66) (59,36ppm.). Comparison of the ^{13}C spectra of these compounds shows, however, that the phosphonium iodide (66) can not be involved in the purple reaction mixture. In the spectrum of (66) the coupling between the phosphorus atom and the carbon atom (underlined in the figure) can be found (62Hz). This



(66)

value is in accord with other phosphonium salts [66,67]. This coupling can not be found in the spectrum of the purple intermediate.

The spectrum of the purple intermediate was also monitored on ^{31}P n.m.r. as a function of time. The first recording took place immediately after the mixture of triethylphosphine and O-isopropyl selenoacetate. After 20 minutes the signal at 59,37ppm. could be detected. The intensity of this signal increased as a function of time. After 4 hours it had reached maximum intensity. The spectrum did not change after this period of time. This indicates that only

one phosphorus atom is involved in the formation of the purple intermediate.

In the ^{31}P n.m.r. spectrum of triethylphosphine selenide the coupling between ^{77}Se and ^{31}P can be found (683Hz). J_{P-Se} has previously been determined to be in the range 850-1100Hz [65].

It was also established that the selenoesters mentioned in table 2 reacted with triethylphosphine and gave a purple intermediate.

4. THE SELENOFORMATES.

The selenoformates (15,16) reacted rapidly with triethylphosphine (15 minutes). No coloured intermediate was formed. There are, however, some doubt about the products from this reaction (the author has not been able to reproduce the results), and this reaction will therefore not be further commented.

This reaction is under investigation in this laboratory.

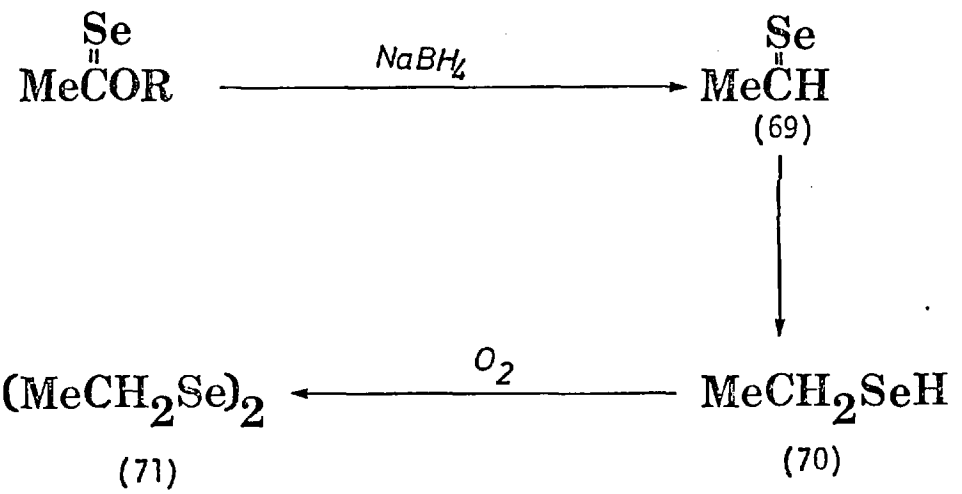
C. REACTION WITH SODIUM BOROHYDRIDE.

If the assumption that triethylphosphine reacts with O-isopropyl selenoacetate (36) and gives the 1,3 dipolar intermediate (64) is correct it should be possible to transform this into the corresponding ether. Upon performing the reaction in triethyl orthoformate and quenching the purple reaction mixture with acetic acid it was possible to isolate ethyl isopropyl ether in moderate yield (50%).

It was also of interest to investigate how the aliphatic seleno-esters behaved towards moderately reducing agents, such as sodium boro-

hydride. O-Isopropyl selenoacetate (36) reacted readily with sodium borohydride in ethanol. The selenium containing product from this reaction was identified to be the corresponding dialkyl diselenide (diethyl diselenide).

It appeared that the selenoesters behaved towards sodium borohydride in the same way as esters behaved towards lithium aluminum hydride. The initial product in this reaction was the selenoaldehyde (69), which was further reduced to the selenol (70). The selenol was then converted into the diselenide (71) by atmospheric oxygen.



The selenosters (26), (27), (31) and (33) gave also the corresponding diselenides upon treatment with sodium borohydride.

If, however, this reaction was carried out in the presence of triethylphosphine a different reaction took place. In this modification the corresponding ethers were formed. It appears that the presence of triethylphosphine prevents the rupture of the carbon-oxygen bond, and a straightforward reduction of the selenocarbonyl function takes place.

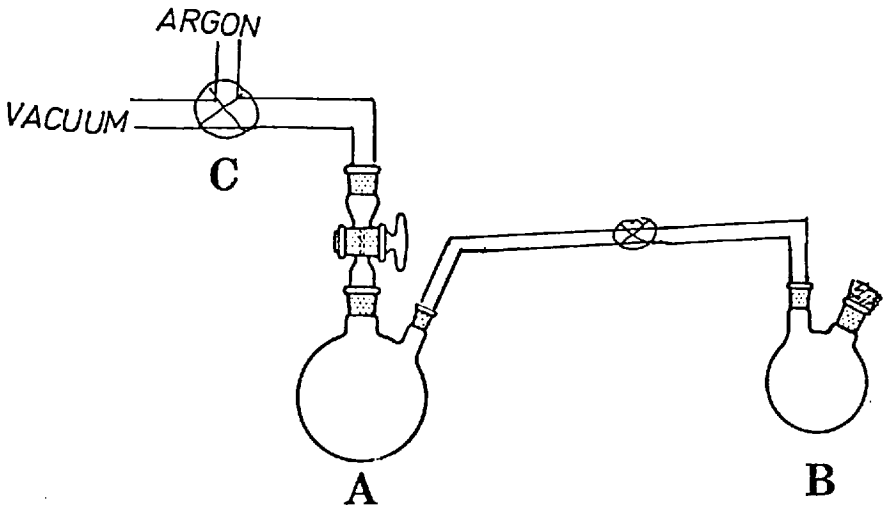
CHAPTER 3.

EXPERIMENTAL.

GENERAL.

See page 41.

The experiments involving trialkylphosphines were performed under oxygen free conditions, unless otherwise stated.



The apparatus shown in the figure was used in the reactions involving trialkylphosphines. The atmosphere in the apparatus was exchanged with argon by alternate application of vacuum and inlet of argon through the three way valve C.The volatile selenoesters were introduced into the reaction vessel B by vacuum destillation from the vessel A. The non volatile selenoesters were dissolved in benzene and introduced into the reaction vessel B and freeze-dried. The solvent used in these reactions and the trialkylphosphines were introduced into the reaction vessel by vacuum destillation from the vessel A. The reaction vessel was kept at -70°C when the reagents were introduced by vacuum destillation.

Preparation of the Selenobenzoates.

N,N-Dimethylbenzamide (3,1g, 20mmol) was kept for 24 hours at room temperature in dichloromethane (40ml) containing phosgene (3,9g, 40mmol). Evaporation in vacuo gave the amidochloride (11) (4,1g, 20mmol).

The amidochloride was redissolved in dichloromethane (75ml) and the alcohol (20mmol) was added at room temperature. After stirring for X minutes, the reaction mixture was cooled in ice/water and pyridine (4ml) was added.

The resulting mixture was added at -20°C to a solution of sodium hydrogen selenide, prepared from selenium (1,6g, 20mmol) and sodium borohydride (800mg, 20mmol) in ethanol (75ml) [7].

After stirring at room temperature for 30 minutes, the reaction mixture was diluted with dichloromethane (100ml) and worked up in the usual way.

The pure selenobenzoates were obtained by chromatography on alumina (grade III) with petroleum ether (b.p. 60-80°C)/diethyl ether 20:1 as eluent.

O-cholestanyl Selenobenzoate (6).

Reaction time with cholestanol, 30 minutes. Red plates (9,88g. 89%), m.p. 136-137°C (dichloromethane/ethanol) [10].

O-cholesteryl Selenobenzoate (3).

Reaction time with cholesterol, 30 minutes. Red needles (9,62g. 87%), m.p. 159-161°C., (lit., [6] m.p. 160-162°C), (dichloromethane/ethanol).

O-methyl Selenobenzoate (7).

Reaction time with methanol, 15 minutes. Red oil (3,54g. 89%), b.p. 86-88°C/0,5mmHg., (lit., [4] 90-91°C/1,8mmHg).

ν_{max} 3060(w), 3020(w), 2985(w), 2940(m), 2840(w), 1600(w), 1455(s), 1440(m), 1320(m), 1260(s), 1230(s), 1180(m), 1150(m), 1100(w), 1080(w), 1020(s), 925(w), 770(s), 690(s), 670(m), cm^{-1}.

λ_{max} 254, 325 and 502 nm (ε 6200, 8700 and 140).

τ 1,80 (2H, m). 2,63 (3H, m). 5,60 (3H, s).

MS 200 (M^+). 169 ($M-OCH_3$). 105 ($M-(Se+CH_3)$).

Found: C 48,60. H 4,24. C_8H_8OSe requires C 48,26. H 4,05.

O-phenyl Selenobenzoate (8).

Reaction time with phenol, 2 hours. Deep purple oil (4,54g. 87%), b.p. 164-166°C/0,4mmHg.

ν_{max} 3060(w), 1595(m), 1495(m), 1455(m), 1320(w), 1270(s), 1195(s), 1175(s), 1160(m), 1100(w), 1075(m), 1030(w), 1010(w), 970(m), 770(m), 690(s), cm^{-1}.

λ_{max} 261, 338 and 523 nm (ε 6300, 9000 and 160).

τ 1,62 (2H, m). 2,55 (8H, m).

MS 262 (M^+). 169 ($M-C_6H_5O$). 105 ($M-(Se+Ph)$).

Owing to its unstable nature a satisfactory analysis could not be obtained.

This compound was also prepared from N-benzoylpiperidine in good yield (83%).

O-isopropyl Selenobenzoate (9).

Reaction time with isopropanol, 15 minutes. Red oil (4,17g. 92%),

b.p. 76-78°C/0,1mmHg.

ν_{max} 3060(w), 2980(w), 2930(w), 1595(w), 1455(m), 1385(w), 1375(w), 1315(m), 1260(s), 1230(s), 1175(w), 1095(m), 985(m), 905(w), 770(m), 690(m), cm^{-1}.

λ_{max} 254, 331 and 504 nm (ε 7900, 8800 and 130).

τ 1,88 (2H, m). 2,63 (3H, m). 3,97 (1H, septet. J=6Hz). 8,47 (6H, d. J=6Hz).

MS 228 (M^+). 186 ($M-C_3H_6$). 105 ($M-(Se+C_3H_7)$).

Found: C 53,03. H 5,48. $C_{10}H_{12}OSe$ requires

C 52,87. H 5,32.

Attempted preparation of O-(t-butyl) Selenobenzoate (10).

N,N-Dimethylbenzamidochloride (11), prepared as previously described, was treated with the following reagents:

1. t-Butanol, 24 hours reflux.
2. t-Butanol and imidazole, 12 hours reflux.
3. Potassium t-butoxide, 12 hours reflux.

These reactions were performed in dichloromethane. Subsequent treatment of the reaction mixtures with sodium hydrogen selenide/pyridine and the usual work-up did not give the desired selenobenzoate.

Preparation of N,N-dimethylbenzamide.

N,N-Dimethylbenzamide was prepared by treating benzoyl chloride with aqueous dimethylamine in benzene. M.p. 38-40°C., (lit., [16] m.p. 41-42°C).

Preparation of N-benzoylpiperidine.

N-Benzoylpiperidine was prepared by treating benzoyl chloride with piperidine in dry benzene. B.p. 123-125°C/0,5mmHg., m.p. 46°C., (lit., [22] b.p. 180°C/15mmHg., m.p. 48°C).

Preparation of O-cholestanyl Selenoformate (15).

N,N-Dimethylformamide (1,1g. 15mmol) was added to phosgene in dichloromethane (20% w/v. 20ml) with stirring. After 30 minutes, the solvent was evaporated off with exclusion of moisture and a solution of cholestanol (3,8g. 10mmol) in dichloromethane (15ml) and tetrahydrofuran (15ml), precooled to -20°C, was added to the solid amidochloride. The mixture was stirred with ice cooling, pyridine (3ml) was added, and stirring was continued for 10 minutes at 0°C. The resulting mixture was added at -20°C to a solution of sodium hydrogen selenide, prepared from selenium (900mg) and sodium borohydride (600mg) in ethanol (50ml).

The yellow reaction mixture was rapidly washed twice with dilute hydrochloric acid. After drying ($MgSO_4$) and evaporation the residue was rapidly chromatographed on degassed silica gel (elution with petroleum ether (b.p. 60-80°C)/ethyl acetate 4:1) to give the crude selenoformate (15), obtained as yellow needles (3,6g. 75%), m.p. 88-90°C (dry acetonitrile).

ν_{max} 1365(m), 1250(s), 1240(s), 1130(w), 920(w), 805(w), 785(w), cm^{-1}.

λ_{max} 278 and 447 nm (ε 7700 and 43). Chloroform.

τ -2,10 (1H, s). 4,37 (1H, broad s). 7,80-9,50 (45H, m).

$\{\alpha\}_D^{22}$ not recorded (UV absorbance),

MS 480 (M^+). 387 (M-HCSe). 371 (M-HCOSe).

Found: C 70,87. H 9,81. $C_{28}H_{48}OSe$ requires
C 70,11. H 10,08.

Preparation of O-cholesteryl Selenoformate (16).

The method described in the foregoing preparation was followed, the cholestanol being replaced by cholesterol (3,8g. 10mmol). Recrystallisation from dry acetonitrile gave the selenoformate (16) (3,3g. 69%) as yellow needles, m.p. 125-127°C., (lit., [6] m.p. 126-128°C).

Preparation of O-cholestanyl Selenoacetate (26).

N,N-Dimethylacetamide (2,2g. 25mmol) was stirred in dry benzene (25ml) and a solution of phosgene (5,0g. 50mmol) in dry benzene (40ml) was dropwise added during 5 minutes. After 30 minutes, the reaction mixture was evaporated in vacuo with exclusion of moisture. The amido-chloride was suspended in benzene (50ml), and a solution of cholestanol (4,85g. 12,5mmol) in dichloromethane (50ml) was rapidly added. After stirring for 10 minutes, the mixture was cooled to 0°C and pyridine (3ml) was added.

The resulting mixture was added at -20°C to a solution of sodium hydrogen selenide, prepared from selenium (1,2g.) and sodium borohydride (1,0g.) in ethanol (75ml) [7].

The yellow mixture was stirred without cooling for 10 minutes. After the usual work-up and evaporation, the residue was chromatographed on silica gel, (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 20:1) to give the crude selenoacetate (26), obtained as yellow plates

(4,56g. 74%), m.p. 104-105°C.(dry acetonitrile).

ν_{max} 1270(s), 1245(m), 1170(w), 1150(w), 1130(w), 1070(w), 1025(m), 1005(w), 920(w), cm^{-1}.

λ_{max} 282 and 435 nm (ε 7400 and 60). Chloroform.

τ 4,51 (1H, broad m). 7,62 (3H, s). 7,75-9,92 (45H, m).

$\{\alpha\}_D^{22}$not recorded (UV absorbance).

MS 494 (M^+). 371 ($M-C_2H_3OSe$).

Found: C 70,41. H 10,33. $C_{29}H_{50}OSe$ requires

C 70,55. H 10,21.

Preparation of O-cholesteryl Selenoacetate (27).

The method described in the foregoing preparation was followed, the cholestanol being replaced by cholesterol (4,85g. 12,5mmol). Recrystallisation from dry acetonitrile gave the selenoacetate (27) (5,11g. 83%) as yellow plates, m.p. 144-145°C.

ν_{max} 1270(s), 1260(m), 1240(w), 1185(w), 1030(w), 1005(w), 920(w), cm^{-1}.

λ_{max} 283 and 438 nm (ε 6700 and 82). Chloroform.

τ 4,54 (2H, broad m). 7,56 (3H, s). 7,23-9,57 (43H, m).

$\{\alpha\}_D^{22}$not recorded (UV absorbance).

MS 492 (M^+). 385 ($M-C_2H_3Se$). 369 ($M-C_2H_3OSe$).

Found: C 70,63. H 9,95. $C_{29}H_{48}OSe$ requires

C 70,84. H 9,83.

Preparation of O-methyl Selenoacetate (28).

N-Acetylpiperidine (12,7g. 100mmol) in dry diethyl ether (100ml)

was treated with a solution of phosgene (14,7g. 150mmol) in dry diethyl ether (100ml), whilst the reaction mixture was stirred vigorously for 45 minutes, after which the precipitated amidochloride was filtered off under dry conditions and dried in vacuo. This gave the amidochloride as a light yellow solid.

The amidochloride was suspended in diethyl ether (100ml) and methanol (1,6g 50mmol), dissolved in dichloromethane (150ml), was added. This gave after 30 minutes a homogeneous solution, which was cooled to -20°C and treated with pyridine (8ml).

The resulting yellow mixture was added at -20°C to a solution of sodium hydrogen selenide, prepared from selenium (4,0g) and sodium borohydride (2,0g) in dry methanol (75ml) [7].

The yellow mixture was stirred without cooling for 30 minutes. After the usual work-up, the dried reaction mixture was carefully concentrated to 20 ml. using a Vigreux column (60 cm). The concentrated solution was chromatographed on a silica gel column. Elution with petroleum ether (b.p. 40-50°C)/diethyl ether (20:1) gave a yellow fraction, which subsequently was concentrated using a Vigreux column (60 cm). This gave a solution which on destillation gave a fraction boiling at 60-65°C, and the pure selenoester (28) as an evil smelling volatile oil, (2,2g. 32%), b.p. 108-110°C/763mmHg.

The amount of O-methyl selenoacetate in the fraction boiling at 60-65°C, determined by UV, was 3,3g. By adding this to the isolated selenoacetate, the total yield comes out at 80% (5,5g).

ν_{max} 3010(w), 2980(w), 2935(w), 1440(m), 1360(w), 1255(s), 1210(s), 1150(w), 1040(m), 910(m), cm^{-1}.

λ_{max} 270 and 443 nm (ϵ 7300 and 50).

τ 5,86 (3H, s), 7,61 (3H, s).

MS 138 (M^+).

Found: C 26,68. H 4,38. C_3H_6OSe requires

C 26,29. H 4,41.

Preparation of O-methyl Selenooctadecanoate (29).

N,N-Dimethyloctadecanamide (5,0g. 16mmol) in benzene (50ml) was cooled in ice/water and a stream of phosgene was bubbled through the solution for 15 minutes. Filtration with exclusion of moisture and drying in vacuo gave the amidochloride (5,0g. 14mmol) as a white solid.

The amidochloride was suspended in benzene (75ml) and dry methanol (450mg. 14mmol) dissolved in dichloromethane (25ml) was dropwise added, whilst the reaction mixture was cooled in ice/water. After stirring for 30 minutes at room temperature, the reaction mixture was cooled to 0°C, and pyridine (3ml) was added.

The resulting yellow mixture was added at -20°C to a solution of sodium hydrogen selenide, prepared from selenium (1,1g) and sodium borohydride (600mg) in dry methanol (75ml) [7].

The reaction mixture was stirred without cooling for 30 minutes. After the usual work-up and evaporation, the residue was chromatographed on silica gel, (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 20:1) to give the selenooctadecanoate (29) (2,2g. 43%) as an oil, which crystallized upon standing, m.p. 25-26°C.

ν_{max} 1445(s), 1250(s), 1190(s), 1135(w), 1075(m), 725(w), all broad bands, cm^{-1}.

λ_{max} 275 and 436 nm (ε 8200 and 60). Chloroform.

τ 5,83 (3H, s). 7,37 (2H, m). 8,73 (33H, m).

MS 362 (M^+). 281 (M-SeH).

Found: C 63,46. H 10,36. $C_{19}H_{38}OSe$ requires

C 63,48. H 10,10.

Preparation of O-methyl Phenylselenoacetate (30).

N,N-Dimethylphenylacetamide (3,0g. 18mmol) dissolved in benzene (25ml) was stirred overnight with a solution of phosgene (3,5g. 36mmol) in benzene (25ml). Filtration with exclusion of moisture and drying in vacuo gave the white amidochloride (3,3g. 15mmol).

The amidochloride was added to a solution of dry methanol (512mg. 16mmol) in dichloromethane (50ml), whilst the temperature was kept at 0°C, and stirring was continued for 30 minutes at room temperature.

The resulting mixture was added at -20°C to a solution of sodium hydrogen selenide, prepared from selenium (1,2g) and sodium borohydride (600mg) in dry methanol (75ml) [7]. Pyridine (3ml) was added simultaneously.

The reaction mixture was stirred without cooling for 30 minutes. After the usual work-up and evaporation, the residue was chromatographed on silica gel, (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 20:1) to give the phenylselenoacetate (30) (2,6g. 80%) as an yellow oil. Vacuum destillation of the phenylselenoacetate resulted in destruction of the compound.

ν_{max} 3060(w), 3030(w), 2940(w), 1605(w), 1495(m), 1455(s), 1445(s), 1325(m), 1295(m), 1260(s), 1200(m), 1190(m), 1175(m), 1095(s), 1005(m), 885(w), 765(m), 705(s), cm^{-1}.

λ_{max} 275 and 450 nm (ε 7800 and 45).

τ 2,77 (5H, s). 5,87 (2H, s). 6,00 (3H, s).

MS 214 (M^+). 183 ($M-OCH_3$). 134 (M-Se). 118 ($M-(Se+CH_4)$). 91 ($M-(Se+C_2H_3O)$).

Found: C 50,88. H 4,77. $C_9H_{10}OSe$ requires
C 50,71. H 4,73.

Preparation of O-cholesteryl Selenopropionate (31).

N,N-Dimethylpropionamide (3,0g. 30mmol) dissolved in benzene (50ml) was treated with a solution of phosgene (5,9g. 60mmol) in benzene (50ml) at room temperature for 4 hours. Evaporation and drying in vacuo gave the amidochloride (4,34g. 28mmol) as a white solid.

The amidochloride was added to a solution of cholesterol (5,8g. 15mmol) dissolved in dichloromethane (150ml), whilst the reaction mixture was cooled in ice/water. After 30 minutes stirring at room temperature. the reaction mixture was cooled to 0°C and pyridine (6ml) was added.

The resulting mixture was added at -20°C to a solution of sodium hydrogen selenide, prepared from selenium (2,2g) and sodium borohydride (1,1g) in ethanol (100ml) [7].

The yellow reaction mixture was stirred without cooling for 30 minutes. After the usual work-up and evaporation, the residue was chromatographed on silica gel, (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 20:1) to give the crude selenopropionate (31), obtained as yellow needles (6,5g. 86%), m.p. 151-153°C (dry acetonitrile).

ν_{max} 1335(w), 1320(w), 1285(m), 1225(s), 1170(m), 1070(m), 995(w), 970(w), 965(w), 955(w), 940(w), 925(w), 845(w), 805(w), 740(w), cm^{-1}.

λ_{max} 283 and 434 nm (ε 8000 and 60).

τ 4,62 (1H, m). 4,66 (1H, m). 7,18-9,48 (48H, m). The signals from the ethyl group are hidden in the methylene envelope from the steroid.

$\{\alpha\}_D^{22}$ not recorded (UV absorbance).

MS 506 (M^+). 369 ($M-C_3H_5OSe$).

Found: C 71,55. H 9,77. $C_{30}H_{50}OSe$ requires

C 71,25. H 9,97.

Preparation of O-isopropyl Selenoisobutyrate (37).

N-(1-chloro-2-methylpropylidene)piperidinium chloride (6,3g. 30mmol) was suspended in diethyl ether (50ml) and isopropanol (900mg. 15mmol) dissolved in dichloromethane (150ml) was added at -20°C. This gave rapidly a homogeneous solution which was kept at -20°C and treated with pyridine (5ml).

The resulting mixture was immediately added at -20°C to a solution of sodium hydrogen selenide, prepared from selenium (1,2g) and sodium borohydride (600mg) in ethanol (75ml) [7].

The yellow reaction mixture was stirred without cooling for 30 minutes. After the usual work-up and evaporation, the residue was chromatographed on silica gel, (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 20: 1) to give the crude selenoisobutyrate (37) as an evil smelling oil (1,8g. 61%), b.p. 82-84°C/33mmHg.

ν_{max} 2985(s), 2925(m), 2870(m), 1465(m), 1380(m), 1360(s), 1245(s), 1195(m), 1150(m), 1090(s), 1050(m), 1005(m), 950(m), 915(w), 880(w), 845(w), 805(w), cm^{-1}.

λ_{max} 278 and 444 nm (ε 7000 and 50).

τ 4,14 (1H, septet. J=6Hz). 7,01 (1H, septet. J=6,5Hz). 8,61 (6H, d. J=6,5Hz). 8,80 (6H, d. J=6Hz).

MS 194 (M^+). 151 (M-C_3H_7). 114 (M-Se).

Found: C 43,76. H 7,31. $C_7H_{14}OSe$ requires
C 43,53. H 7,31.

Preparation of N-(1-chloro-2-methylpropylidene)piperidinium Chloride.

N-Isobutyrylpiperidine (37,5g. 240mmol) dissolved in benzene (75ml) was treated with phosgene (47,0g. 480mmol) in benzene (75ml) for 48 hours. Filtration with exclusion of moisture and drying in vacuo gave the

piperidinium chloride as a crystalline salt (43,0g. 85%). The amidochloride prepared in this way could be stored for several weeks in a desiccator without any loss in activity.

τ 5,46 (4H, m). 6,01 (1H, septet) J=6,5Hz). 8,03 (6H, m). 8,55 (6H, septet. J=6,5Hz).

Preparation of O-ethyl Selenoisobutyrate (33).

This compound was prepared exactly as O-isopropyl selenoisobutyrate (37), substituting isopropanol with ethanol (700mg).

After the usual work-up, the dried reaction mixture was carefully concentrated to 20 ml. using a Vigreux column (60 cm). The concentrated solution was chromatographed on a silica gel column. Elution with petroleum ether (b.p. 40-50°C)/diethyl ether (20:1) gave a yellow fraction, which subsequently was concentrated using a Vigreux column (60 cm). This gave a solution which on destillation gave the selenoisobutyrate (33) as an evil smelling oil (1,85g. 69%), b.p. 72-74°C/34mmHg.

ν_{max} 2965(m), 2930(w), 2865(w), 1465(m), 1370(m), 1330(m), 1290(w), 1235(s), 1195(s), 1155(m), 1090(m), 1055(w), 1005(w), 905(w), 854(w), 810(w), cm^{-1}.

λ_{max} 274 and 443 nm (ε 7100 and 50).

τ 5,38 (2H, q. J=7Hz). 7,01 (1H, septet. J=6,5Hz). 8,53 (3H, t. J=7Hz). 8,77 (6H, d. J=6,5Hz).

MS 180 (M^+). 137 ($M-C_3H_7$). 100 (M-Se).

Found: C 40,52. H 6,80. $C_6H_{12}OSe$ requires C 40,23. H 6,75.

Attempted preparation of O-phenyl Selenoisobutyrate (35).

N-(1-chloro-2-methylpropylidene)piperidinium chloride (6,2g. 30mmol) was suspended in diethyl ether (50ml) and phenol (1,4g. 15mmol) dissolved in dichloromethane (150ml) was added at 0°C. This gave after 2 hour's a homogeneous solution which was cooled to -20°C and treated with pyridine (5ml).

The resulting mixture was added at -20°C to a solution of sodium hydrogen selenide, prepared from selenium (1,2g) and sodium borohydride (600mg) in ethanol (75ml) [7].

The yellow reaction mixture was stirred without cooling for 30 minutes. After the usual work-up and evaporation, the residue was chromatographed on silica gel, (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 4:1) to give the crude N-selenoisobutyrylpiperidine (51) as an yellow oil (2,5g. 77%), b.p. 140-142°C/2mmHg.

ν_{max} 2925(s), 2860(m), 1490(s), 1440(s), 1380(w), 1360(w), 1280(m), 1240(s), 1180(m), 1145(w), 1130(w), 1085(w), 1065(w), 1020(m), 1010(w), 975(m), 950(w), 870(m), 865(w), cm^{-1}.

λ_{max} 310 and 396 nm (ε 12000 and 150).

τ 5,54 (2H, m). 6,23 (2H, m). 6,88 (1H, septet. J=6,5Hz). 8,25 (6H, m). 8,75 (6H, d. J=6,5Hz).

MS 219 (M^+). 138 (M-SeH). 124 (M-CH_3Se).

Found: C 49,86. H 7,92. N 6,17. $C_9H_{17}NSe$ requires C 49,54. H 7,85. N 6,42.

Preparation of O-isopropyl Selenoacetate (36).

This compound was prepared and worked up exactly as O-methyl

selenoacetate (28). Destillation gave the selenoacetate (36) as an evil smelling oil (6,3g. 76%), b.p. 139-141°C/772mmHg, 58-59°C/23mmHg.

ν_{max} 2975(m), 2930(w), 1385(w), 1375(m), 1365(w), 1265(s), 1200(m), 1170(m), 1140(w), 1090(m), 1015(m), 900(w), 825(w), cm^{-1}.

λ_{max} 277 and 443 nm (ε 7700 and 50).

τ 4,27 (1H, septet. J=6,5Hz). 7,61 (3H, s). 8,58 (6H, d. J=6,5Hz).

MS 166 (M^+). 123 ($M-C_3H_7$).

Found: C 35,93. H 6,08. $C_5H_{10}OSe$ requires

C 36,37. H 6,10.

Attempted preparation of O-benzyl Selenoacetate.(34).

This experiment was performed in exactly the same way as O-methyl selenoacetate (28), by substituting isopropanol with benzyl alcohol (5,4g. 50mmol).

After the usual work-up and evaporation the residue was chromatographed on silica gel, (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 20:1) to give benzyl chloride (5,6g. 89%) and N-acetylpiperidine (9,14g. 72%) (elution with diethyl ether). Both compounds were identified by comparison with authentic samples.

Preparation of O-phenyl Selenoacetate (32) from N,N-dimethyl-acetamide.

N,N-Dimethylacetamide (8,7g. 100mmol) dissolved in benzene (100ml) was treated with a solution of phosgene (14,7g. 150mmol) in benzene (100ml), whilst the reaction mixture was vigorously stirred for 45 minutes, after which the reaction mixture was filtered with exclusion of moisture and

dried in vacuo.

The amidochloride was added to a solution of phenol (4,7g. 50mmol) in dichloromethane (75ml). After 3 hours stirring at room temperature the homogeneous solution was cooled to -20°C and pyridine (8ml) was added.

The resulting mixture was added at -20°C to a solution of sodium hydrogen selenide, prepared from selenium (4,0g) and sodium borohydride (2,0g) in ethanol (100ml) [7].

The yellow reaction mixture was stirred without cooling for 30 minutes. After the usual work-up and evaporation, the residue was chromatographed on silica gel, (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 20:1) to give the selenoacetate (32) as a brown-yellow oil (6,4g. 65%), b.p. 92°C/0,7mmHg.

ν_{max} 3060(w), 2920(w), 1595(m), 1490(m), 1460(m), 1430(w), 1365(m), 1225(s), 1210(s), 1075(m), 1025(m), 995(m), 905(w), 830(m), 820(m), 765(m), 695(m), cm^{-1}.

λ_{max} 279 and 469 nm (ε 6300 and 50).

τ 2,44-3,07 (5H, m). 7,43 (3H, s).

MS 200 (M^+). 105 ($M-CH_3Se$). 93 (M-OPh).

Found: C 48,30. H 3,99. C_8H_8OSe requires
C 48,26. H 4,05.

Continued elution with petroleum ether (b.p. 60-80°C)/diethyl ether (2:1) gave N,N-dimethylselenoacetamide (2,0g. 27%) as a yellow oil (b.p. 81-83°C/768mmHg., (lit., [19] b.p. 82-84°C/770mmHg)).

Preparation of O-phenyl selenoacetate (32) from N-acetylpiperidine.

The method described in the foregoing preparation was followed,

N,N-dimethylacetamide being replaced by N-acetylpiperidine (12,7g. 100mmol).

After the usual work-up and evaporation, the residue was chromatographed on silica gel, (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 20:1) to give the selenoacetate (32) (4,0g. 41%).

Continued elution with diethyl ether gave N-selenoacetylpiperidine (5,0g. 53%) as an yellow oil (b.p. 62-64°C., (lit., [20] b.p. 64,5-65°C)).

Attempted preparation of di-O-methyl Diselenoadipate (53).

Di-N-pentamethyleneadipdiamide (1,8g. 6,5mmol) dissolved in benzene (75ml) was treated with a solution of phosgene (3,0g. 30mmol) in benzene (50ml) at 0°C. The reaction mixture became red by this treatment. After stirring for 30 minutes at room temperature, the reaction mixture was filtered with exclusion of moisture and dried in vacuo.

The red solid was suspended in benzene (50ml), and methanol (500mg. 13mmol) dissolved in dichloromethane (25ml) was added. After stirring for 30 minutes the reaction mixture was cooled to -20°C and pyridine was added (2ml).

The resulting mixture was added at -20°C to a solution of sodium hydrogen selenide, prepared from sodium borohydride (500mg) and selenium (1,0g) in methanol (75ml) [7].

The yellow reaction mixture was stirred without cooling for 30 minutes. After the usual work-up and evaporation, the residue was chromatographed on silica gel, (elution with diethyl ether) to give an unseparable mixture of compounds.

Preparation of 2-(N-piperidylcarbonyl)-Cyclopentanone (50).

Di-N-pentamethyleneadipdiamide (1,3g. 5mmol) dissolved in benzene (75ml) was treated with a solution of phosgene (3,0g. 30mmol) in benzene (50ml) at room temperature. After stirring for 1 hour at room temperature, crushed ice was added, and the mixture was vigorously stirred for 1 hour. The organic layer was separated. The aqueous layer was extracted with dichloromethane and the combined organic extracts were dried ($MgSO_4$). Destillation of the evaporated extract gave the amide (50) as an oil (440mg. 45%), b.p. 156-159°C/0,45mmHg., (lit.,[18] b.p. 124-126°C/0,05mmHg), which crystallized upon standing, m.p. 25°C., (lit.,[21] m.p. 24-26°C).

Preparation of Methyl 2-Oxocyclopentan-1-Carboxylate (49).

Di-N-pentamethyleneadipdiamide (1,3g. 5mmol) dissolved in benzene (75ml) was treated with a solution of phosgene (3,0g. 30mmol) in benzene at room temperature. After 1 hour the reaction mixture was evaporated in vacuo , and the residue was suspended in benzene (50ml). Methanol (320mg. 10mmol), dissolved in dichloromethane (50ml), was added and the reaction mixture was stirred for 1 hour. Water (50ml) was then added and the reaction mixture was stirred vigorously for 4 hours. After separation of the organic layer, the aqueous layer was extracted with dichloromethane, and the combined organic extracts were dried ($MgSO_4$). Destillation of the evaporated extract gave the ester (49) as an oil (360mg. 51%), b.p. 108-110°C/33mmHg., (lit.,[17] b.p. 93-95°C/11mmHg).

Preparation of Di-O-ethyl Diselenoglutarate (52).

Di-N-pentamethyleneglutardiamide (3,6g. 13,5mmol) dissolved in benzene (50ml) was treated with a solution of phosgene (4,4g. 44mmol) in benzene (50ml) at 0°C. After stirring for 1 hour at room temperature, the reaction mixture was filtered with exclusion of moisture and dried in vacuo.

The amidochloride was suspended in benzene (50ml), and ethanol (700mg. 13mmol) dissolved in dichloromethane (75ml) was added at 0°C. After 1 hour the reaction mixture was cooled to -20°C and pyridine (8ml) was added.

The resulting mixture was added at -20°C to a solution of sodium hydrogen selenide, prepared from selenium (1,1g) and sodium borohydride (700mg) in dry ethanol (50ml) [7].

The yellow reaction mixture was stirred without cooling for 1 hour. After the usual work-up and evaporation, the residue was chromatographed on silica gel, (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 20:1) to give the diselenoester (52) as a foul smelling oil (1,55g. 38%), b.p. not recorded.

ν_{max} 2980(m), 2930(w), 1445(m), 1370(s), 1305(s), 1240(s), 1185(s), 1090(m), 1050(m), 1015(m), 960(w), 875(w), 810(w), cm^{-1}.

λ_{max} 274 and 446 nm (ε 15100 and 110).

τ 5,38 (4H, q. J=7Hz). 7,31 (4H, m). 7,75 (2H, m). 8,53 (6H, t. J=7Hz).

MS 315 (M^+).

Found: C 34,83. H 5,57. $C_9H_{16}O_2Se_2$ requires

C 34,41. H 5,13.

Preparation of N-acetylpiperidine.

N-Acetylpiperidine was prepared by treating acetyl chloride with piperidine in dry benzene. B.p. 40-42°C/0,5mmHg., (lit., [22] b.p. 125°C/30mmHg).

Preparation of Octadecanoyl Chloride.

Octadecanoyl chloride was prepared by treating octadecanoic acid with thionyl chloride in benzene at reflux. B.p. 168-171°C/0,3mmHg., (lit., [23] b.p. 200-215°C/13-15mmHg).

Preparation of N,N-dimethyloctadecanamide.

N,N-Dimethyloctadecanamide was prepared by treating octadecanoyl chloride with aqueous dimethylamine in benzene. M.p. 45-47°C., (lit., [24] m.p. 48,5°C).

Preparation of N,N-dimethylphenylacetamide.

N,N-Dimethylphenylacetamide was prepared by treating phenylacetyl chloride with aqueous dimethylamine in benzene. M.p. 42-44°C., (lit., [25] m.p. 43-44°C).

Preparation of Propionyl Chloride.

Propionyl chloride was prepared by heating phosphorus trichloride with propionic acid for 1 hour. B.p. 79-81°C., (lit., [26] b.p. 75-82°C).

Preparation of N,N-dimethylpropionamide.

N,N-Dimethylpropionamide was prepared by treating propionyl chloride with aqueous dimethylamine in benzene. B.p. 94-96°C., (lit., [27] b.p. 175,5°C/765mmHg).

Preparation of Phthaloyl Chloride.

Phthaloyl chloride was prepared by heating phthalic anhydride with phosphorus pentachloride at 150°C. B.p 89-91°C/0,5mmHg., (lit., [28] b.p. 131-133°C/9-10mmHg).

Preparation of Isobutyryl Chloride.

Isobutyryl chloride was prepared by dropwise addition of isobutyric acid to phthaloyl chloride at 135°C. The chloride was collected as the destillate from the reaction. Redestillation gave the pure chloride. B.p 89-91°C., (lit., [29] b.p. 92°C).

Preparation of N,N-dimethylisobutyramide.

N,N-Dimethylisobutyramide was prepared by treating isobutyryl chloride with aqueous dimethylamine in benzene. B.p. 90-92°C., (lit., [25] b.p. 178-179°C).

Preparation of N-isobutyrylpiperidine.

N-Isobutyrylpiperidine was prepared by treating isobutyryl chloride with piperidine in dry benzene. B.p. 66-68°C/0,4mmHg., (lit., [30] b.p. 114°C/15mmHg).

Preparation of Adipoyl Dichloride.

Adipoyl dichloride was prepared by treating adipic acid with thionyl chloride in benzene at reflux. B.p. 70°C/0,3mmHg., (lit., [31] b.p. 130-132°C/18mmHg).

Preparation of Di-N-pentamethyleneadipdiamide.

Di-N-pentamethyleneadipdiamide was prepared by treating adipoyl dichloride with piperidine in dry benzene at 0°C. M.p 62-64°C., (lit., [32] m.p. 61-62°C).

Preparation of Glutaryl Dichloride.

Glutaryl dichloride was prepared by treating glutaric acid with thionyl chloride in benzene at reflux. B.p. 66-68°C/0,7mmHg., (lit., [33] b.p. 107-108°C/16mmHg).

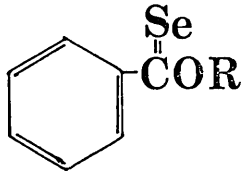
Preparation of Di-N-pentamethyleneglutardiamide.

Di-N-pentamethyleneglutardiamide was prepared by treating glutaryl dichloride with piperidine in dry benzene at 0°C. M.p. 52-54°C., (lit., [34] m.p. 53-54°C).

Reaction between the Selenobenzoates and Methylenetriphenylphosphorane.

To a stirred suspension of triphenylmethylphosphonium bromide (520mg. 1,5mmol) in toluene (30ml), methyllithium (1,0ml. 2M in diethyl ether) was dropwise added. After stirring at room temperature for 4 hours, a solution of the selenobenzoate (1,0mmol) in toluene (10ml) was added. After 30 minutes stirring at room temperature, the reaction mixture was washed with water, dried ($MgSO_4$), evaporated and chromatographed on dehydrated florisil, (elution with petroleum ether (b.p. 60-80°C/diethyl ether 20:1) to give the α-alkoxysubstituted styrene.

The α-alkoxystyrenes were identified on the basis of their ^1H n.m.r. spectra and the products that arose from their hydrolysis.

	^1H n.m.r. (in τ)	Products after hydrolysis
R= CHOLESTERYL	2,41 (2H, m). 2,71 (3H, m). 4,62 (1H, broad s). 5,32 (1H, d. J=2,5Hz). 5,80 (1H, d. J=2,5Hz). 5,99 (1H, broad s). 7,49-9,60 (43H, m).	ACETOPHENONE (78mg). CHOLESTEROL (230mg).
CHOLESTANYL R=	2,40 (2H, m). 2,71 (3H, m). 5,35 (1H, d. J=2,5Hz). 5,80 (1H, d. J=2,5Hz). 5,95 (1H, broad s). 7,61-9,50 (45H, m).	ACETOPHENONE (76mg). CHOLESTANOL (232mg).

CONTD.

R= ETHYL	2,22-2,92 (5H, m). 5,33 (1H, d. J=2,5 Hz). 5,84 (1H, d. J=2,5Hz). 6,11 (2H, q. J=7Hz). 8,66 (3H, t. J=7Hz).	ACETOPHENONE (69mg).
R= ISOPROPYL	2,31-2,79 (5H, m). 5,36 (1H, d. J=2,5 Hz). 5,68 (1H, septet. J=6Hz). 5,86 (1H, d. J=2,5Hz). 8,72 (6H, d. J=6Hz).	ACETOPHENONE (91mg).
R= METHYL	2,24-2,89 (5H, m). 5,61 (1H, d. J=2,5 Hz). 6,06 (1H, d. J=2,5Hz). 6,46 (3H, s).	ACETOPHENONE (95mg).
R= PHENYL	NOT RECORDED	ACETOPHENONE (87mg).

References: ETHYL 39, Methyl 40, PHENYL 41.

General procedure for the hydrolysis of the vinyl ethers.

The vinyl ether (1mmol) was dissolved in aqueous ethanol (ethanol/water 5:1) and 4 drops of concentrated sulphuric acid was added. After 3 hours the reaction mixture was neutralised with sodium hydrogen carbonate, extracted with dichloromethane and dried ($MgSO_4$). Chromatography on alumina (grade III) (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 4:1) gave the ketone and the alcohol. The ketone was identified as the 2,4-dinitrophenylhydrazone derivative.

Photolysis of the Selenoactates (26) and (27) and the Selenobenzoates (3) and (6).

The selenoester (1mmol) in degassed dry diethyl ether (400ml) was irradiated with a high pressure mercury lamp for 4 hours. After filtration and evaporation the selenoesters could be recovered in 90% yield.

Photolysis of the Selenoacetates (26) and (27) and the Selenobenzoates (3) and (6) with added Tri-n-butylphosphine.

The selenoester (1mmol) in degassed dry diethyl ether containing tri-n-butylphosphine (2,0g. 25mmol) was irradiated for 4 hours. After evaporation, the residue was dissolved in petroleum ether and cooled in ice. To this solution methyl iodide (3ml) was added, and after 30 minutes the reaction mixture was filtrated and evaporated. The residue was chromatographed on silica gel (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 4:1) to give the following results:

O-cholestanyl selenoacetate (26) ⟶ cholestanyl acetate (391mg).

O-cholesteryl selenoacetate (27) ⟶ cholesteryl acetate (384mg).

O-cholestanyl selenobenzoate (6) ⟶ cholestanyl benzoate (483mg).

O-cholesteryl selenobenzoate (3) ⟶ cholesteryl benzoate (494mg).

and

tri-n-butylphosphine selenide (243mg).

These products were identified by comparison with authentic samples.

Reaction between the Selenobenzoates (6) and (3) and Tri-n-butylphosphine in the presence of atmospheric oxygen.

The selenobenzoate (1mmol) dissolved in benzene (15ml) was treated with tri-n-butylphosphine (2,0g. 25mmol) over a period of 3 hours. After this time methyl iodide (3ml) was added to the reaction mixture. Evaporation and washing the residue with petroleum ether gave a solution which was evaporated and chromatographed on silica gel (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 4:1) to give the benzoates and tri-n-butylphosphine selenide, identified by comparison with authentic samples.

O-cholestanyl selenobenzoate (6) ⟶ cholestanyl benzoate (477mg).

O-cholesteryl selenobenzoate (3) ⟶ cholesteryl benzoate (461mg).

tri-n-butylphosphine selenide (232mg).

Reaction between the Selenobenzoates (6) and (3) and Tri-n-butylphosphine under oxygen free conditions.

The selenobenzoate (1mmol) dissolved in benzene (3ml) and tri-n-butylphosphine (804mg. 4mmol) was kept at room temperature for 4 hours. After evaporation in vacuo, dry ethanol was added to the residue and the precipitated solid was collected. Crystallisation of this solid gave dicholesteryloxy stilbene (dicholestanyloxy stilbene) as white plates.

Dicholesteryloxy Stilbene.

204mg. 43%. M.p. 289-291°C, (ethanol).

ν_{max} 1604(w), 1255(w), 1245(w), 1145(s), 1075(w), 1030(w), 1015(w), 995(w), 950(w), 840(w), 805(w), 775(m), 705(m), cm^{-1}.

λ_{max} 224 and 284 nm (ε 25000 and 12000). Carbon disulphide.

τ 2,30 (4H, m). 2,70 (6H, m). 4,92 (2H, broad s). 6,88 (2H, broad s). 7,75-9,65 (86H, m). Carbon disulphide.

$\{\alpha\}_D^{22}$ not recorded.

MS 948 (M^+). 475 ($M-C_{34}H_{49}O$). 369 ($M-C_{41}H_{55}O_2$).

Found: C 85,90. H 10,57. $C_{68}H_{100}O_2$ requires C 86,01. H 10,62.

Dicholestanyloxy Stilbene.

195mg. 41%. M.p. 281-283°C, (ethanol).

ν_{max} 1604(w), 1250(w), 1145(s), 1130(m), 1075(m), 1010(m), 970(w), 935(w), 770(s), 705(s), cm^{-1}.

λ_{max} 222 and 280 nm (ε 25000 and 12000). Carbon disulphide.

τ 2,00-2,43 (4H, m). 2,60-2,94 (6H, m). 6,72 (2H, broad s). 7,94-9,72 (92H, m). Carbon disulphide.

$\{\alpha\}_D^{22}$ not recorded.

MS 952 (M^+). 477 ($M-C_{34}H_{51}O$). 371 ($M-C_{41}H_{57}O_2$).

Found: C 85,51. H 10,87. $C_{68}H_{104}O_2$ requires C 85,65. H 10,99.

The ethanolic solution was cooled in ice and methyl iodide (3ml) was added. After 30 minutes the mixture was filtrated and evaporated, and the residue was chromatographed on alumina (grade III) (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 4:1) to give the benzyl ether and tri-n-butylphosphine selenide (243mg).

Benzyl Cholesteryl Ether (248mg. 52%) m.p. 118-119°C., (lit.,[68] m.p. 118-119° C).

Benzyl Cholestanyl Ether.

253mg. 53%. M.p. 112-113°C, (ethanol).

ν_{max} not recorded.

λ_{max} not recorded.

τ 2,37-2,94 (5H, m). 5,43 (2H, s). 6,14 (1H, broad s). 7,87-9,61 (45H, m).

$\{\alpha\}_D^{22}$ not recorded.

MS 478 (M^+). 91 ($M-C_{27}H_{47}O$).

Found: C 84,95. H 11,15. $C_{34}H_{54}O$ requires C 85,29. H 11,37.

This experiment was also carried out in the following solvents:

O-cholesteryl Selenobenzoate.

Solvent	Benzyl Ether	Stilbene
Toluene	44%	49%
Tetrahydrofuran	30%	41%
Tri-n-butylphosphine	56%	--
Triethyl orthoformate	72%	33%

O-cholestanyl Selenobenzoate.

Solvent	Benzyl Ether	Stilbene
Toluene	40%	51%
Tetrahydofuran	32%	42%
Tri-n-butylphosphine	51%	--
Triethyl orthoformate	74%	21%

Hydrolysis of the stilbene derivatives.

To a solution of the stilbene (0,2mmol) in tetrahydrofuran (5ml) 2M aqueous sulphuric acid was added (5ml), and the reaction mixture was stirred at room temperature for 16 hours. Extraction with dichloromethane

washing with sodium hydrogen carbonate, drying ($MgSO_4$) and evaporation gave a residue which on chromatography on alumina (grade III) (elution with petroleum ether (b.p. 60-80°C)/ethyl acetate 2:1) gave benzoin (35mg) and cholestanol (113mg) (cholesterol (110mg)).

Reaction between O-cholesteryl Selenobenzoate (3) and Triethylphoshine with added Thiophenol.

O-cholesteryl selenobenzoate (567mg. 1mmol) and triethylphosphine (472mg. 4mmol) dissolved in toluene (15ml) was stirred with thiophenol (2ml) for 3 hours at room temperature. After evaporation, the residue was chromatographed on alumina (grade III) (elution with petroleum ether (b.p. 60-80°C)/dichloromethane 8:1) to give cholestanol (260mg. 65%) and triethylphosphine (174mg. 88%). Both compounds were identified by comparison with authentic samples.

Reaction between the selenobenzoates (7), (8), (9), O-ethyl and Triethylphosphine.

O-ethyl selenobenzoate was kindly supplied by Dr. McCombie.

The selenobenzoate (1mmol) dissolved in benzene (15ml) was treated with triethylphosphine (472mg. 4mmol) for the required time at room temperature. Benzene and excess triethylphosphine were evaporated off *in vacuo*. The residue was chromatographed on silica gel (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 10:1) to give the products. These are summarized below.

O-ethyl selenobenzoate	Triethylphosphine selenide (101mg). Benzoin (95mg).	30 min.
O-methyl selenobenzoate	Triethylphosphine selenide (110mg). Benzoin (81mg).	30 min.
O-isopropyl selenobenzoate	Triethylphosphine selenide (96mg). Isopropyl benzyl ether (45mg). Benzoin (63mg).	6 Hours
O-phenyl selenobenzoate	Triethylphosphine selenide (103mg). Benzoin (97mg).	5 min.

Attempted reaction between O-cholesteryl Selenobenzoate and Triphenylphosphine.

The following three experiments were conducted:

1. O-cholesteryl selenobenzoate (567mg. 1mmol) dissolved in toluene (15ml) was treated with triphenylphosphine (1,06g. 4mmol) at room temperature for 48 hours.

2. O-cholesteryl selenobenzoate (567mg. 1mmol) and triphenylphosphine (1,06g. 4mmol) dissolved in toluene (15ml) was heated in a sealed tube for 6 hours,(150°C).

3. The experiment 2 was also conducted with benzyldimethylsilane (2ml) present.

From these three experiments O-cholesteryl selenobenzoate could be recovered unchanged.

Reaction between O-isopropyl Selenobenzoate and Triethylphosphine in Cyclohexene.

O-Isopropyl selenobenzoate (454mg. 2mmol) dissolved in cyclohexene (10ml) was treated with triethylphosphine (944mg. 8mmol). After 30 minutes the precipitated triethylphosphine selenide (373mg. 95%) was filtered off. The resulting filtrate was worked up by adding methyl iodide (3ml), filtration of the precipitated iodide and evaporation. The residue was chromatographed on alumina (grade III) (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 20:1) to give two fractions. The least polar fraction was evaporated and redissolved in ethanol (10ml) containing sulphuric acid (1ml 2M aqueous sulphuric acid). After 30 minutes at room temperature water was added and the reaction mixture was extracted with dichloromethane, washed with sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated. The residue was chromatographed on alumina (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 10:1) to give benzyl isopropyl ether(120mg. 40%) and cyclohexyl phenyl ketone (155mg. 30%). Benzyl isopropyl ether was identified by comparison with an authentic sample. Cyclohexyl phenyl ketone was identified on the basis of its spectral data, i.r. 1695 cm^{-1},, ^1H n.m.r. τ=1.83-2,74 (5H, m), 7,01 (1H, q. J=7Hz), 7,95-9,18 (10H, m)., and its 2,4-dinitrophenylhydrazone derivative m.p. 190-192°C., (lit., [69] m.p. 191-193°C).

The second fraction contained cyclohexyl phenyl ketone (133mg. 35%).

Reaction between O-isopropyl Selenobenzoate and Triethylphosphine in the presence of Benzaldehyde.

O-isopropyl selenobenzoate (454mg. 2mmol) dissolved in benzene

was treated with triethylphosphine (944mg. 8mmol) in the presence of benzaldehyde (106mg. 1mmol). After 1 hour the reaction mixture was worked up by adding methyl iodide (3ml), filtration of the precipitated iodide and evaporation. Hydrolysis of the residue in ethanolic sulphuric acid (2M, 10ml) gave after dilution with water, washing with sodium hydrogen carbonate and extraction with dichloromethane, a residue which was chromatographed on alumina (grade III) (elution with ethyl acetate/petroleum ether (b.p. 60-80°C) 3:1) to give benzyl isopropyl ether (trace), triethylphosphine selenide (359mg. 91%), deoxybenzoin (206mg. 52%) and benzoin (151mg. 44%). These compounds were identified by comparison with authentic samples.

This experiment was repeated using 1 equivalent benzaldehyde. In this experiment the following compounds were identified: Triethylphosphine selenide (341mg. 86%) and deoxybenzoin (304mg. 78%).

Generation of the purple intermediate derived from the Seleno-acetates (26), (27) and (36).

The selenoacetate (1mmol) dissolved in benzene (10ml) was heated to 70°C for 4 hours in the presence of trietylphosphine (472mg. 4mmol). This gave the purple intermediate.

The work-up in the reactions involving this purple intermediate consists of adding methyl iodide, filtration, evaporation and chromatography on alumina (grade III) (elution with petroleum ether (b.p. 60-80°C)/ethyl acetate 4:1).

Reaction of the purple intermediate derived from O-cholesteryl Selenoacetate (27) with atmospheric oxygen.

The purple intermediate was work-up by exposing it to atmospheric oxygen. This gave cholesteryl acetate (382mg. 87%) and triethylphosphine selenide (179mg. 95%). Both compounds were identified by comparison with authentic samples.

Addition of oxygen free water (1ml) did not affect the purple colour.

The purple intermediate derived from O-cholestanyl selenoacetate (26) gave upon work-up in atmospheric oxygen cholestanyl acetate (360mg. 82%) and triethylphosphine selenide (181mg. 96%).

Reaction between the Selenoacetates (26) and (27) and Triethylphosphine at 150°C.

The selenoacetate (1mmol) dissolved in toluene (15ml) was heated to 150°C in a sealed tube in the presence of triethylphosphine (472mg. 4mmol). After 6 hours the reaction mixture was colourless and was worked up in the usual way.

O-cholesteryl selenoacetate	cholesta-3,5-diene (220mg) cholesterol (115mg) triethylphosphine selenide (173mg).
O-cholestanyl selenoacetate	cholestanol (211mg) triethylphosphine selenide (163mg).

Attempted reaction between the purple intermediate derived from O-cholesteryl Selenoacetate (27) and Benzaldehyde, Acetone or Benzyldimethylsilane.

Benzaldehyde, acetone and benzyldimethylsilane were added separately to three different samples of the purple intermediate. The purple colour was not affected by these additions. After exposure to air the reaction mixtures were worked up in the usual way to give in all three cases cholesteryl acetate and triethylphosphine selenide.

Reaction between the purple intermediate derived from O-cholesteryl Selenoacetate (27) and Octadecyl Iodide.

Octadecyl iodide (380mg. 1mmol) dissolved in oxygen free benzene (5ml) was added to the purple reaction mixture. After 1 hour the colourless reaction mixture was worked up in the usual way. The material collected from the column was dissolved in benzene (15ml) and treated with triethylamine at reflux for 15 minutes. The evaporated reaction mixture was then chromatographed on a silica gel plate to give dioctadecyl selenide (70mg) m.p. 60°C (ethanol).

ν_{max} 2910(s), 2840(s), 1460(m), 1375(w), 730(w), 720(w), cm^{-1}.

τ 8,73 (68H, m). 9,12 (6H, m).

MS 586 (M^+). 558 ($M-C_2H_2$). 333 ($M-C_{18}H_{37}$). 253 ($M-C_{18}H_{37}Se$).

This compound has been completely characterized by Dr. Hulshof.

Reaction between the purple intermediate derived from the Selenoacetate (36) and methyl Iodide.

O-Isopropyl selenoacetate (330mg. 2mmol) dissolved in benzene (3ml) was heated at 70°C for 4 hours in the presence of triethylphosphine (944mg. 8mmol). Benzene and excess triethylphosphine was then destilled off under reduced pressure, and a solution of methyl iodide (1,1g) in benzene was destilled in. After 5 minutes at room temperature the reaction mixture was evaporated under reduced pressure and the destillate was trapped in liquid nitrogen. This gave a benzene solution containing dimethyl selenide (isolated as trimethylselenonium iodide (100mg. 20%) m.p. 143-144°C., (lit., [70] m.p. 150-151°C).

The residue was chromatographed on alumina (grade III) (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 10:1) to give triethylphosphine selenide (216mg. 75%). Continued elution with methanol gave α-isopropoxyethyl triethylphosphonium iodide (604mg.91%).

α-Isopropoxyethyl triethylphosphonium iodide was identified by comparison with an authentic sample.

Preparation of α-Chloroethyl Isopropyl Ether. [71]

α-Chloroethyl isopropyl ether was prepared by treating a mixture of acetaldehyde (trimer) and isopropanol with dry hydrogen chloride gas at -5°C, b.p. 32-34°C/35mmHg., (lit., [72] b.p. 40°C/60mmHg).

Preparation of α-Isopropoxyethyl Triethylphosphonium iodide.

To a stirred solution of α-chloroethyl isopropyl ether (6,1g. 55mmol) in benzene (30ml) a solution of triethylphosphine (5,9g. 50mmol) in benzene (10ml) was added at 0°C.

After 4 hours the precipitated salt was filtered off and dried.

This gave the phosphonium salt as the chloride. The chloride was exchanged with iodide by mixing one equivalent of the phosphonium chloride with one equivalent of sodium iodide in acetone. After filtration, evaporation and washing with benzene the residue was dried in vacuo at 70°C for 12 hours. The iodide crystallized when it was cooled to room temperature (14,3g. 86%) m.p. 70°C (decomp.)

ν_{max} 2980(s), 2890(s), 1460(s), 1360(m), 1330(m), 1315(w), 1275(w), 1180(w), 1100(s), 1050(m), 1020(w), 960(m), 920(s), 810(w), 780(s), 730(s), 645(w), cm^{-1}.

τ 4,72 (1H, pentet. J=7Hz). 6,03 (1H, septet. J=6,5Hz). 7,13-7,85 (6H, m). 8,13-8,97 (18H, m).

MS 332 (M^+).

Due to the compounds rapid decomposition in solution an analytical sample cuold not be made.

Reaction between the purple intermediate derived from O-isopropyl Selenoacetate and Acetic Acid in Triethyl Orthoformate.

O-Isopropyl selenoacetate (330mg. 2mmol) dissolved in triethyl orthoformate (5ml) was heated at 70°C for 4 hours in the presence of triethylphosphine (944mg. 8mmol). After cooling to room temperature a solution of acetic acid in triethyl orthoformate (240mg. in 3ml) was transfered into the reaction mixture. The resulting colourless reaction mixture was destilled under reduced pressure and the destillate was trapped in liquid nitrogen. Redestillation of the destillate at atmospheric pressure gave ethyl isopropyl ether (79mg. 47%) b.p. 55°C (lit., [73] b.p. 53°C).

The ether was identified by comparison with an authentic sample.

Reaction between the Selenoesters (36), (27), (26), and Sodium Borohydride.

The selenoester (2mmol) suspended in dry ethanol (50ml) and sodium borohydride (76mg. 2mmol) was stirred at room temperature until the yellow colour had disappeared. The reaction mixture was diluted with water, extracted with dichloromethane and dried ($MgSO_4$). The residue after evaporation was chromatographed on alumina (elution with petroleum ether (b.p. 60-80°C)/diethyl ether 20:1) to give the alcohols and the diselenides.

	Reaction time	Products.
O-isopropyl selenoacetate	15 min.	Isopropanol Diethyl diselenide
O-cholesteryl selenoacetate	15 min.	Cholesterol Diethyl diselenide
O-cholesteryl selenopropionate	2 h.	Cholesterol Dipropyl diselenide.

This reaction gave the diselenide in 90% yield. The products were identified by comparison with authentic samples.

Reaction between the Selenoesters (36), (31) and Sodium Borohydride/Triethylphosphine.

To a suspension of the selenoester (2mmol) in ethanol, sodium borohydride (76mg. 2mmol)/triethylphosphine (944mg. 8mmol) was added. The reaction mixture was stirred at room temperature until the yellow colour had disappeared. After the usual work-up, the residue

was chromatographed on alumina (elution with petroleum ether (b.p.60-80°C)/diethyl ether 20:1) to give the ether and triethylphosphine selenide.

	Reaction time	Products
O-isopropyl selenoacetate	10 min.	Ethyl isopropyl ether Triethylphosphine selenide
O-cholesteryl selenopropionate	2 h.	Propyl cholesteryl ether Triethylphosphine selenide

The ethers were isolated in 80% yield, and were identified by comparison with authentic samples.

Preparation of Benzyl Isopropyl Ether.

Benzyl isopropyl ether was prepared by treating sodium isopropoxide with benzyl chloride. B.p. 83°C/16mmHg., (lit., [74] b.p. 178°C).

Preparation of Ethyl Isopropyl Ether.

Ethyl isopropyl ether was prepared by treating ethyl iodide with isopropanol in the presence of potassium hydroxide. B.p. 54-55°C., (lit., [73] b.p. 53°C).

Preparation Cholesteryl Propyl Ether.

Cholesteryl propyl ether was prepared by treating cholesteryl p-toluenesulphonate with propyl alcohol. M.p. 99-101°C., (lit., [75] m.p. 99°C).

Preparation of Diethyl Diselenide.

Diethyl diselenide was prepared by treating ethyl bromide with sodium hydrogen selenide and hydrogen peroxide. B.p. 126°C/10mmHg., (lit., [76] b.p. 186°C).

Preparation of Dipropyl Diselenide.

Dipropyl diselenide was prepared by treating propyl bromide with sodium hydrogen selenide and hydrogen peroxide. B.p. 96-98°C/10mmHg., (lit., [77] b.p. 103-104°C/15mmHg).

Preparation of Triethylphosphine Selenide.

Triethylphosphine selenide was prepared by treating triethylphosphine with selenium. M.p. 111-113°C., (lit.,[78] m.p. 112°C).

Preparation of Tri-n-butylphosphine Selenide.

Tri-n-butylphosphine selenide was prepared by treating tri-n-butylphosphine with selenium. B.p 134°C/0,1mmHg., (lit., [42] b.p. 167°C/10mmHg).

REFERENCES.

1. E. O. Fischer and S. Riedmüller, Chem. Ber., 1974, 107, 915.
2. E. O. Fischer, C. G. Kreiter, H. J. Kollmeier, J. Müller and R. D. Fischer, J. Organomet. Chem., 1971, 28, 237.
3. E. O. Fischer, B. Heckl, K. H. Dötz, J. Müller and H. Werner, J. Organomet. Chem., 1969, 16, P29.
4. C. Collard-Charon and M. Renson, Bull, Soc. Chim. Belges, 1962, 71, 563.
5. R. Mayer, S. Scheithauer and D. Kunz, Chem. Ber., 1966, 99, 1393.
6. D. H. R. Barton and S. W. McCombie, J. C. S. Perkin I, 1975, 1574.
7. D. L. Klayman and T. S. Griffin, J. Am. Chem. Soc., 1973, 95, 197.
8. H. Eilingsfeld, M. Seefelder and H. Weidinger, Chem. Ber., 1963, 96, 2671.
9. H. Eilingsfeld, M. Seefelder and H. Weidinger, Chem. Ber., 1963, 96, 2899.
10. B. Stick, Unpublished results.
11. F. Malek-Yazdi and A. Yalpani, J. Org. Chem., 1976, 41, 729.
12. M. L. Filleux-Blanchard, M. T. Querneneur and G. J. Martin, J. C. S. Chem. Comm., 1968, 836.
13. R. Buyle and H. G. Viehe, Tetrahedron., 1968, 24, 4217.
14. D. R. Hepburn and H. R. Hudson, J. C. S. Perkin I., 1976, 754.
15. P. Deslongchamps, C. Lebreux and R. T. Taillefer, Can. J. Chem., 1973, 51, 1665.

    P. Deslongchamps, Tetrahedron report, Tetrahedron, 1975, 31, 2463.
16. F. Hallmann, Chem. Ber., 1876, 9, 846.
17. R. F. C. Briwn and M. Butcher, Aust. J. Chem., 1971, 24, 2421.
18. R. H. Rynbrandt and F. L. Schmidt, J. Med. Chem., 1971, 14, 54.
19. C. Collard-Charon and M. Renson, Bull. Soc. Chim. Belges, 1963, 72, 304.
20. K. A. Jensen, H. Mygind and P. H. Nielsen, Unpublished results.
21. H. Mörhle and H. Bauman, Arch. Pharm., 1966, 299, 355.
22. H. Staudinger and H. Schneider, Chem. Ber., 1923, 56, 699.

23. A. W. Ralston and W. M. Selby, J. Am. Chem. Soc., 1939, 61, 1019.

24. E. F. Jordan Jr. and W. S. Pont, J. Am. Oil. Chem. Soc., 1961, 38, 600.

25. H. Rapoport and R. M. Bonner, J. Am. Chem. Soc., 1950, 72, 2783.

26. A. Dodrowsky, Monatsh., 1951, 82, 140.

27. J. R. Ruhoff and E. Reid, J. Am. Chem. Soc., 1937, 59, 401.

28. H. Ott, Org. Synth. Coll. Vol 2., 1943, 528.

29. S. Kasman and A. Tauris, Can. J. Chem., 1956, 34, 1261.

30. H. Bestian and D. Guentker, Angew, Chem., 1963, 75, 841.

31. W. Triebs and G. Leichssering, Chem. Ber., 1951, 84, 52.

32. J. H. Paden and H. Adkins, J. Am. Chem. Soc., 1936, 58, 2487.

33. K. von Awers and M. Schmidt, Chem, Ber., 1913, 46, 457.

34. J. D. D'Ianni and H. Adkins, J. Am. Chem. Soc., 1939, 61, 1675.

35. G. Wittig and U. Schöllkopf, Chem. Ber., 1954, 87, 1318.

36. S. Trippet and D. M. Walker, J. Chem. Soc., 1961, 1266.

37. H. J. Bestmann and H. Schulz, Angew. Chem., 1961. 73, 620.

38. D. M. Jones and N. F. Wood, J. Chem. Soc., 1964, 5400.

39. Y. Ogata, A. Kawasaki and K. Tsulimura, Tetrahedron., 1971, 27, 2765.

40. R. Tanaka, M. Rodgers, R. Simonanitis and S. I. Miller, Tetrahedron., 1971, 27, 2651.

41. P. A. El'tsova, M. M. Koton, O. K. Mineva and O. K. Surning, J. Gen. Chem. USSR., 1960, 30, 947.

42. A. Schmidpeter and H. Brecht, Z. Naturforsch., 1969, 24b, 179.

43. C. Screttas and A. F. Isbell, J. Org. Chem., 1962, 27, 2573.

44. I. M. Downie, J. B. Holmes and J. B. Lee, Chem. Ind., 1966, 900.

45. R. Köster, D. Simic and M. A. Grussberger, Ann., 1970, 739, 211.

46. G. Wittig and W. Böll, Chem. Ber., 1962, 95, 2526.

47. F. Ramirez, H. Yamanaka and D. H. Baselow, J. Am. Chem. Soc., 1961, 83, 173.

48. C. W. Bird and D. Y, Wong, J. C. S. Chem. Comm., 1969, 932.

49. H. J. Bestmann and O. Kratzer, Angew. Chem. Intern. Ed. Engl., 1962, 1, 512.

50. H. J. bestmann and O. Kratzer, Chem. Ber., 1963, 96, 1899.

51. V. Franzen and G. Wittig, Angew. Chem., 1960, 72, 417.

52. V. Franzen, Chem. Ber., 1960, 93, 557.

53. A. J. Speziale and K. W. Ratts, J. Am. Chem. Soc., 1962, 84, 854.

54. D. Seyfarth, S. Grim and T. O. Read, J. Am. Chem. Soc., 1960, 83, 1510.

55. G. Wittig and M. Schlosser, Angew. Chem., 1960, 72, 324.

56. V. Franzen, Angew. Chem., 1960, 72, 566.

57. Tse-Lok Ho, Chem. Rev., 1975, 75, 1.

58. Hard and soft acids and bases. Ed. R. G. Pearson. Dowden, Hutchinsons and Stroudsburg 1973.

59. O. Grummit, E. P. Budewitz and C. C. Chudd, Org. Synth., 1963, Coll. Vol. 4, 748.

60. R. J. Anderson, C. A. Henrick, J. B. Siddall and R. Zurfluh, J. Am. Chem. Soc., 1972, 94, 5379.

61. D. R. Coulson, Tetrahedron Lett., 1964, 3323.

62. G. Wittig and M. Schlosser, Chem. Ber., 1961, 94, 1373.

63. G. Wittig and W. Böll, Chem. Ber., 1962, 95, 2514.

64. S. Trippet, Proc. Chem. Soc., 1963,19.

65. I. A. Nuretdinov and E. I. Loginova, Bull. Acad. Sci. USSR., 1971, 2252.

66. W. McFarlane, Proc. Roy. Soc. Ser., 1968, A306, 185.

67. P. R. Wells. NMR Spectra of Heavier Elements in: F. C. Nachod and J. J. Zuckerman Ed., Determination of Organic Structures by Physical Methods. Vol 4. Academic Press, New York, London 1971.

68. J. H. Beynon, I. M. Heilbron and F. S. Spring, J. Chem. Soc., 1936, 907.

69. Dictionary of Organic Compounds. Fourth Ed. Eye and Spottiswode, London.

70. W. van Döring and A. K. Hoffmann, J. Am. Chem. Soc., 1955, 77, 521.

71. See reference 59.

72. M. F. Shostakovskii and F. P. Sidelkovskaya, Bull, Acad, Sci. USSR., 1959, 859.

73. G. M. Bennet and W. G. Philip, J. Chem. Soc., 1928, 1930.

74. J. B. Niederl and S. Natelson, J. Am. Chem. Soc., 1931, 53, 1928.

75. C. E. Bills and F. G. McDonald, J. Biol. Chem., 1927, 72, 1.

76. B. Rathke, Ann., 1869, 152, 212.

77. H. J. Backer and W. van Dam, Rec. Trav. Chim., 1935, 54, 531.

78. A. Cahours and A. W. Hofman, Ann., 1857, 104, 1.