STUDIES RELATED TO THE SYNTHESIS OF TETRACYCLINE

a thesis presented by

NIGEL JOHN CUSSANS

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WHIFFEN LABORATORY,
CHEMISTRY DEPARTMENT,
IMPERIAL COLLEGE,
LONDON, SW7 2AY.

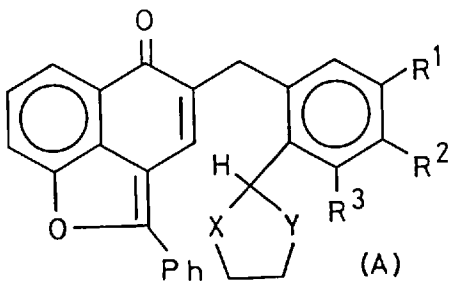
Nigel John Cussans,

Studies Related to the Synthesis of Tetracycline.

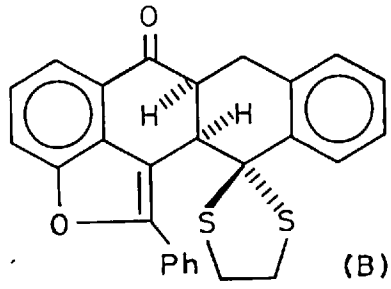
ABSTRACT

Previous and contemporary achievements are reviewed related to the structure, biosynthesis, chemistry, and total synthesis of the tetracycline antibiotics. Aspects of recent organoselenium and sulphur chemistry relevant to this work are also reviewed.

An established approach to the formation of ACD-tricyclic intermediates (A, $R^1=R^2=R^3=H$ and $R^1=R^3=OH$, $R^2=CONH_2$) was extended and improvements effected in the overall yield of starting materials. The utility of oxazoline (A, X=O, Y=NH), thiazolidine (A, X=S, Y=NH/Me), and 1,3-dithiolane (A, X=Y=S) derivatives (A, $R^1=R^2=R^3=H$) was investigated during a subsequent base-catalysed photocyclisation step, and optimisation of the conditions gave increased yields of the masked model tetracyclic compound (B).

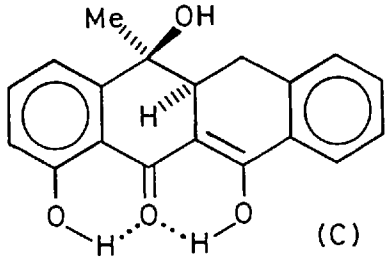


(A)



(B)

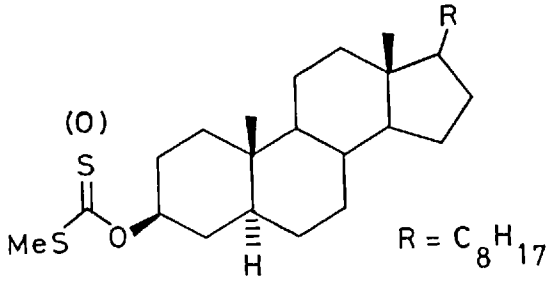
The preparation of 6-methyl-6-hydroxy derivatives is discussed together with the attempted regeneration of the 12-keto functionality from its 1,3-dithiolane by literature procedures and with benzenesulphenyl and benzeneselenenyl chloride. Successful deprotection with benzeneseleninic anhydride ($Ph_2Se_2O_3$) and subsequent transformations afforded the ring-A unsubstituted Tetracycline (C).



(C)

The capacity of $Ph_2Se_2O_3$ to regenerate ketones and aldehydes from acyclic and cyclic dithioacetals and from cyclic hemithioacetals was demonstrated and the scope of the reaction exemplified. A proposed mechanism is presented.

$Ph_2Se_2O_3$ was also found to convert thio- and selenocarbonyl compounds to their corresponding *oxo*- derivatives, even in the presence of other sulphur moieties, e.g. (D) and (E). The generality of this reaction is compared with existing literature procedures and its utility demonstrated with suitable simple substates and more complex natural products. A mechanistic interpretation is tentatively proposed.



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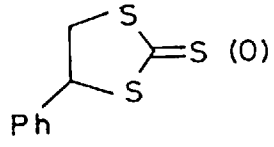
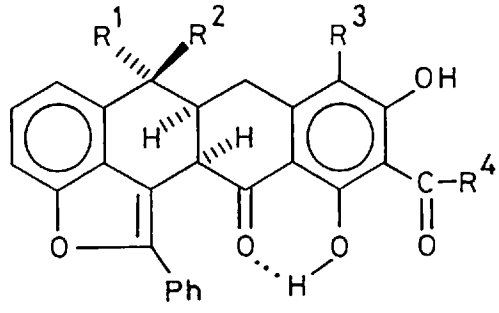


(E)

Application of the above methodology to Tetracycline synthesis afforded limited success in the preparation of C-10,11-masked ring-A substituted tetracyclic intermediates (F, R^1R^2=O, R^3=H, R^4=OMe;- R^1R^2=O, R^3=H, R^4=NH_2 ; and R^1=Me, R^2=OH, R^3=$PhSe(O)_2$, R^4=NH_2).

(F)



TO MY PARENTS and BEVERLEY.

The three Princes of Serendip, Balakrama, Vijayo, and Rajahsigha, as they travelled ...

".... were always making discoveries, by accident and sagacity, of things they were not in quest of ...." *

* Horace Walpole, in a letter of January 28th., 1754, as quoted in " The Three Princes of Serendip ", by E.J. Hodges, Atheneum Press, New York, 1964.

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I wish to thank Professor Sir Derek Barton, F.R.S. *for granting me the opportunity to work with him and for his stimulating supervision and patient guidance at all times. I also thank* Dr. Steven V. Ley *for his friendship and invaluable help throughout this work.*

I wish to record my sincere thanks to all my colleagues and friends in the Whiffen *and* Hofmann *laboratories, both past and present, and in particular to* José Cardoso, Andrew Brewster, Alex Markham, Peter Setiloane, David Lester, *and special thanks to* Roman *and* Maria Bielski.

My thanks are also due to Mr. K.I. Jones *and his staff for their microanalytical service,* Mrs. J. Lee *and* Mr. J. Bilton *for mass-spectra,* Mr. J. Burgess *for provision of XL-100 n.m.r. spectra,* Dr. J.F. Gibson *for his assistance with e.s.r. spectroscopy,* Mrs. B.Day *and* Mrs. I. Hamblin *for their friendship and help in the organic stores, and* Mr. T. Adey, Mr. A. Ellis, *and* Mr. R. Carter *for their technical assistance.*

I offer my gratitude to Mr. P.J. Scott, Dr. J.G. Broadhurst, Dr. T.N. Huckerby, and Dr. S. Breuer *for inspiring me throughout my education in chemistry, and my thanks to my wife* Beverley, *for all her help and understanding, and to my parents* Charles and Margaret Cussans, *for their continual guidance and encouragement.*

Finally, I wish to thank the Science Research Council *for a studentship.*

Nigel J. Cussans,
Whiffen Laboratory,
September, 1978.

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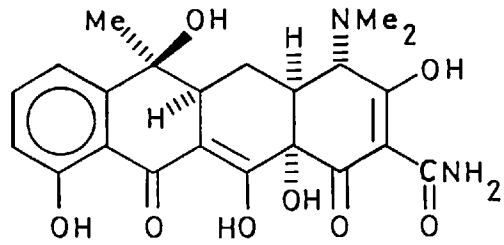
INTRODUCTION

The object of the work presented in this thesis has been to extend an established approach to the total synthesis of Tetracycline, and to evaluate new chemical transformations for this purpose. By utilising the valuable properties of sulphur and the versatility of a new organoselenium reagent, some of these objectives were achieved. Therefore, it is fitting to review the relevant areas of tetracycline, recent organoselenium and sulphur chemistry, as presented below.

REVIEWS

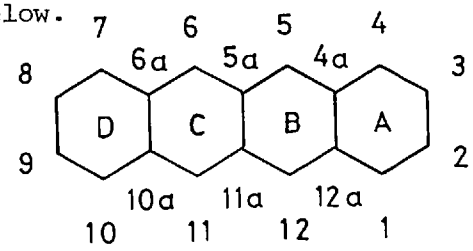
A. TETRACYCLINE.

Tetracycline (1) is the parent compound of a family of broad spectrum antimicrobial agents, active orally and parenterally against both Gram-positive and negative bacteria and large viruses, and is exceeded only by the spectrum of chloramphenicol [1]. Thus, the tetracycline antibiotics continue to play an important role in human and veterinary medicine.



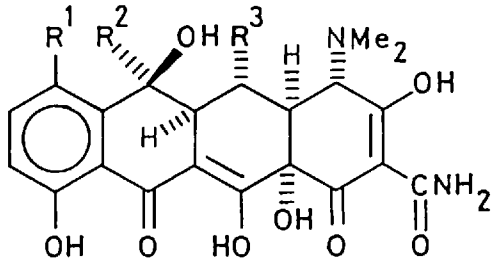
(1)

The linearly fused four ring system (A-D) is numbered according to the scheme for the 1,4,4a,5,5a,6,11,12a-octahydronaphthacene shown below.



A.1. The Tetracycline Antibiotics.

Aureomycin (2) was the first tetracycline isolated by Duggar [2] in 1948 from a culture of *Streptomyces aureofaciens*, followed by Terramycin (3) from *S. rimosus* by Finlay *et al.*[3] in 1950. These two antibiotics represent the standard metabolites of the two species, although the careful selection of mutant strains has furnished over 20 new tetracyclines, the first being 6-demethylchlortetracycline (4) discovered by McCormick *et al.*[4] in 1957.



	R^1	R^2	R^3
(2)	Cl	Me	H
(3)	H	Me	OH
(4)	Cl	H	H

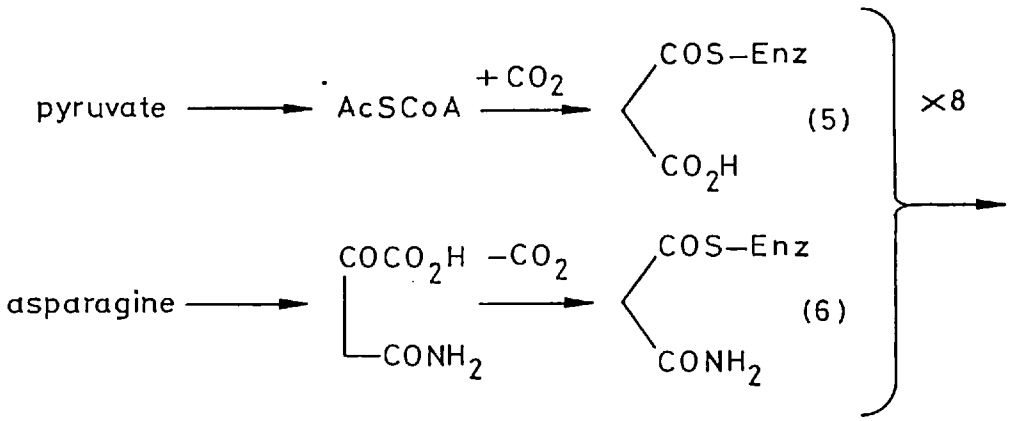
The parent Tetracycline (1) was originally prepared by catalytic hydrogenation of (2) [5], but was later available as a fermentation product from mutants of *S. aureofaciens*, blocked in the chlorination step [6]. Its isolation accompanied the structure elucidation of Terramycin (3) by Woodward *et al.* at Chas. Pfizer and Co.[7], which was later confirmed by X-ray studies [8], which also established the relative stereochemistry of the five common centres of asymmetry: C-4,4a,5a,6, and 12a [9,10]. The relative chirality of the 5-OH group in (3) was deduced from nuclear magnetic resonance (N.M.R.) studies [11].

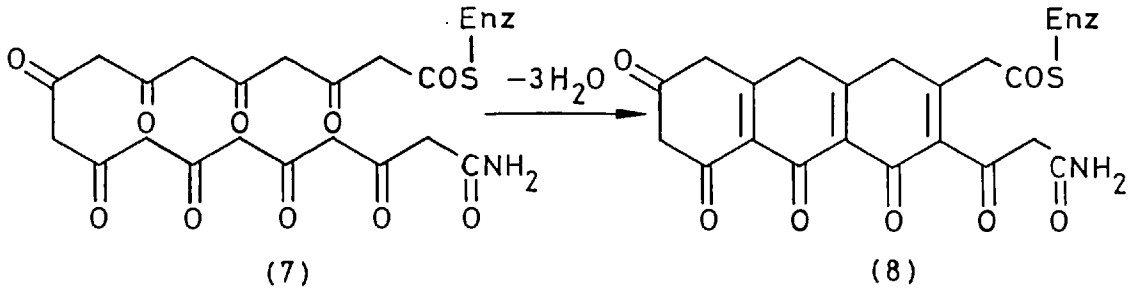
Mutant strains of *S. aureofaciens* and *S. rimosus* are commonly prepared by subjecting cultures to U.V., X-ray, or gamma radiation, or by the application of chemical mutagens such as *N*-methyl-*N'*-nitro- *N*-nitrosoguanidine [12]. The selection of suitable mutants has produced enhanced yields or modified tetracyclines of medicinal interest. Hybridisation by genetic recombination can also incorporate desirable properties, such as high yield and resistance to the production

metabolite. Although a genetic map of *S. rimosus* has been constructed by analysis of the loci controlling the biosynthesis of essential metabolites [13], the information is still fragmentary. Consequently, the selection of strains improved by mutagenesis or hybridisation is practically at random. To improve this rather empirical approach, it is necessary to understand the biosynthetic steps and the genetic control of the formation of tetracyclic metabolites.[14]

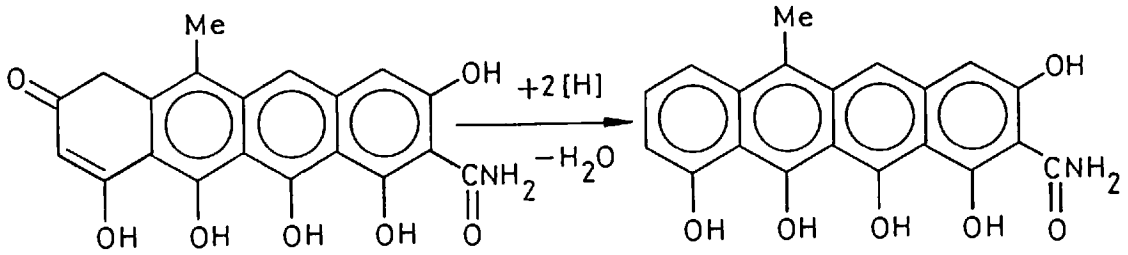
A.2. Biosynthesis of Tetracyclines.

After McCormick had confirmed the polyketide origin of the tetracyclines [15], Vanêk *et al.*[16] in 1971 formulated a theoretical concept of the genetic regulation of chlortetracycline biosynthesis, divided into three sections based on the established intermediates. Firstly, the conversion of glucose to acetylCoA and secondly, the carboxylation of acetylCoA to malonylCoA (5). Condensation of the malonylamide (6), derived from asparagine, with eight units of (5) leads, *via* the hypothetical nonaketide (7) to the tricyclic skeleton (8).



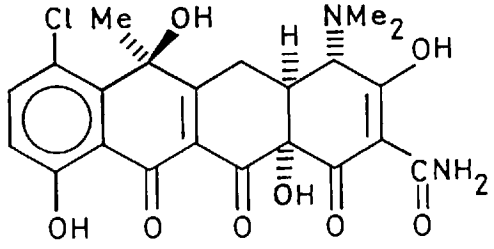


Thirdly, methylation at C-6 precedes the ring-A cyclisation and aromatization to the anthracene (9). Subsequent reduction and dehydration affords 6-methylpretetramid (10) [17], which is the first isolable precursor [18].



(9) (10)

A further seven enzyme catalysed reactions, namely: hydroxylation at C-4, oxidation of ring-A, hydration at C-4a/12a, chlorination at C-7, transamination to C-4, double *N*-methylation, and hydroxylation at C-6 leads to the dehydrochlortetracycline (11), and finally by reduction to the chlortetracycline (2).



(11)

A total of 72 metabolites derived from (8) are implicated in the biosynthetic scheme, of which 27 are already known and 45 remain hypothetical.

A.3. Genetic Control of Biosynthesis.

If the correspondence of one gene: one enzyme exists, then at least 11 structural genes are involved in the latter stages of biosynthesis (from 8) and about 300 genes overall. The assumption [16] that the loci of the latter genes are grouped together into a chlortetracycline *operon* (expected for biosynthesis in a defined sequence)

has been supported by a recent genetic analysis on *S.rimosus* [19] and *S. aureofaciens* [20]. Thus, mutations causing blocks or retardations cannot predictably result in the increased production of a standard metabolite, e.g. (2) from *S. aureofaciens*.

Blocks which cause lack of end-product control, or the uncoupling of a rate limiting reaction, can result in the formation of high molar concentrations of an intermediate metabolite. For example, interference with the final 2{H} reduction step can produce an excessive amount of dehydrochlortetracycline(11) [21]. Due to the high structural and/or conformational specificity of the feed-back mechanism, this leads to a loss of end-product control in the biosynthetic process, which incidentally is connected with the low antimicrobial activity of dehydrotetracyclines. Mutations which enhance the synthesis of an involved enzyme can accelerate a rate-limiting step and similarly increase the production yield.

Genetic changes alone however, cannot account for the broad variability of *Streptomyces* in their production of tetracyclines. The expression of genes which are transcribed to produce the necessary enzymes for metabolite synthesis is probably governed by a group of regulatory genes, whose switching action is influenced by metabolic and environmental factors, as in the classic example of the *lac-operon* of *E. coli* [22]. For example, acetylCoA, used in the tricarboxylic acid cycle, could be diverted towards the energetically less demanding production of tetracyclines by suitable adjustment of the cultivation conditions to reduce the rate of respiration.

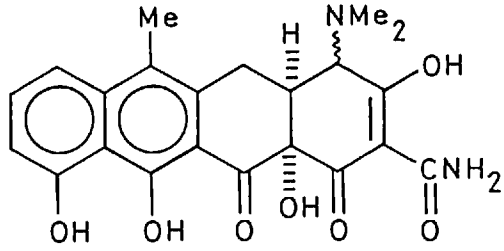
From an evolutionary aspect, the production of such non-essential metabolites probably represents a detoxicating shunt of organic polymers with low energy requirements, which operates in response to environmental factors. Thus, choosing strains of micro-organisms with wider tolerance to cultivation conditions and whose

genotype suppresses metabolic pathways which compete for common precursors, will lead to the optimisation of the production of tetracyclines by fermentation processes.

A.4. Chemistry and Structure-Activity of the Tetracyclines.

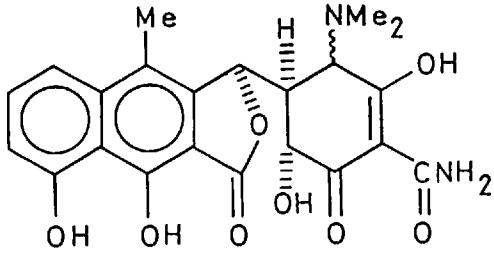
The chemistry of the tetracyclines has been extensively reviewed in the literature [23,24,25] and in earlier theses from these laboratories [26]. Tetracyclines are slightly soluble in water at physiological pH levels and show amphoteric behaviour [27]. They exhibit characteristic U.V. absorption spectra; ring-A chromophore 262 nm, rings-BCD chromophores: 225, 285, 320, and 360 nm with a composite absorption at 275 nm [28].

The alternating oxygenation pattern renders the tetracyclines sensitive to both acids and bases. The tertiary C-6 hydroxyl group lies *trans* to the 5a-proton in natural epimers, allowing facile acid-catalysed elimination of water to form 5a,6-anhydrotetracyclines (12) [5,29].



(12)

Acids also cause epimerisation at C-4 in the pH range 2-6 [30]. Oxytetracycline (3) undergoes a series of rapid degradations in acid to form C-4-epimeric α- and β-apooxytetracyclines (13) [25].

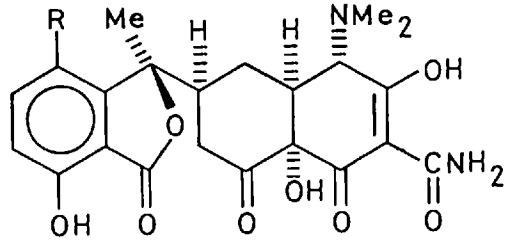


(13)

The presence of a chloro- group at C-7 or the lack of a methyl- group at C-6 can improve the tolerance to acidic media [23].

Weak bases readily isomerise tetracyclines to the γ-lactonic isotetracyclines (14) [7,31] and whilst the 6-demethyl series also shows enhanced stability towards base, the 7-chloro compounds are particularly labile; chlortetracycline (2) forms isochlortetracycline (15) at pH 7.5 [25].

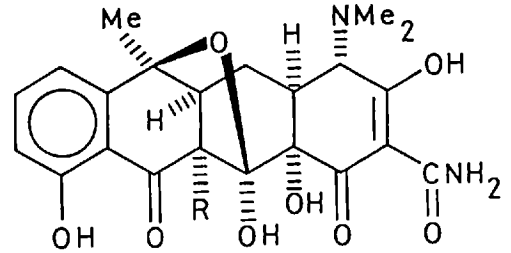
	R
(14)	H
(15)	Cl



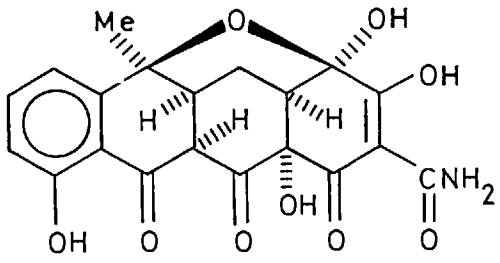
Between pH 3-7.5 the tetracyclic phenol-keto-enol system can form chelates with many metal cations, noteably Mg^{2+} and Ca^{2+} [32]. These complexes show enhanced base stability and their strong fluorescence is utilised in assays for the drug in biological material[33]. Predictably, the simultaneous administration of tetracyclines and foodstuffs rich in such ions (e.g. milk) can lead to disturbances [34] and reduction in serum levels of the drug [35].

The treatment of Tetracycline (1) with perchloryl fluoride ($FClO_3$) and base (1 equiv.) gives the crystalline 11a-fluoro-6,12-hemiketal (16) [36]. Also, (1) and *N*-chlorosuccinimide (NCS) under anhydrous conditions is reported to yield the analogous 11a-chloro - compound (17) [36]. The fluoro derivative (16) shows remarkable resistance to acid (boiling MeOH/HCl [37]).

	R
(16)	F
(17)	Cl
(18)	H

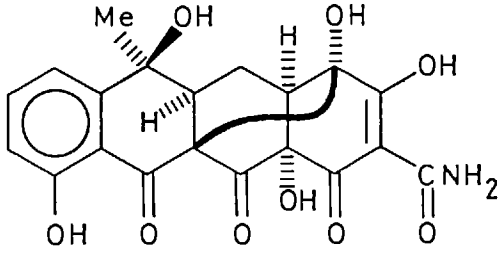


In contrast, (1) and aqueous NCS is reported to afford the 4,6-tetracycloxide (19) [38], which is interconvertible with Tetracycline (1) [30] and thus stands as an important synthetic target [26]. However, Gurevich *et al.* [39] have obtained both products (18) and (19) from this reaction, to which they assign the major product structure (18).



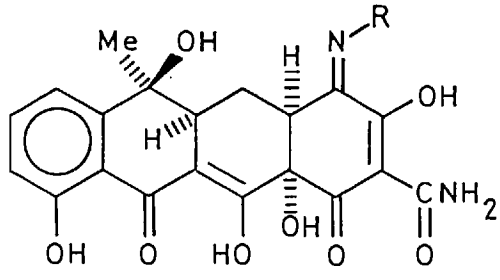
(19)

Recently, Meguro has repeated this reaction in these laboratories and by careful comparison of U.V., I.R., and N.M.R. spectroscopic data, has assigned the *minor* product structure (19) and the *major* product, crystallised from methanol, the novel 4,11a-bridged compound (20). This structure was confirmed by X-ray crystallographic analysis of the dimethanolate [40].



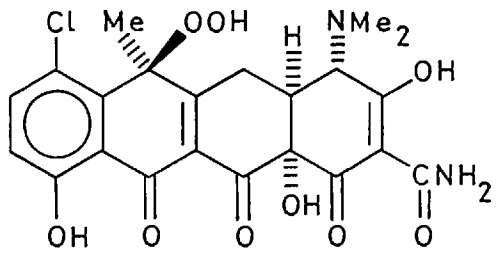
(20)

Compound (20) undergoes typical reactions of the 4-keto-isomer, to which it is related *via* a retro-aldol reaction, to form the 4-oxime (21) and the 4-hydrazone (22).



	R
(21)	OH
(22)	NH_2

Hydroxylation at C-6, which occurs relatively late during biosynthesis [41], has been simulated chemically by the oxygenation of 5a,6-anhydro-7-chlorotetracycline with U.V. light and a photosensitizer [42,43]. The resultant hydroperoxide (23) was hydrogenated to a mixture of chlortetracycline (2) and 5a-epichlortetracycline [44].

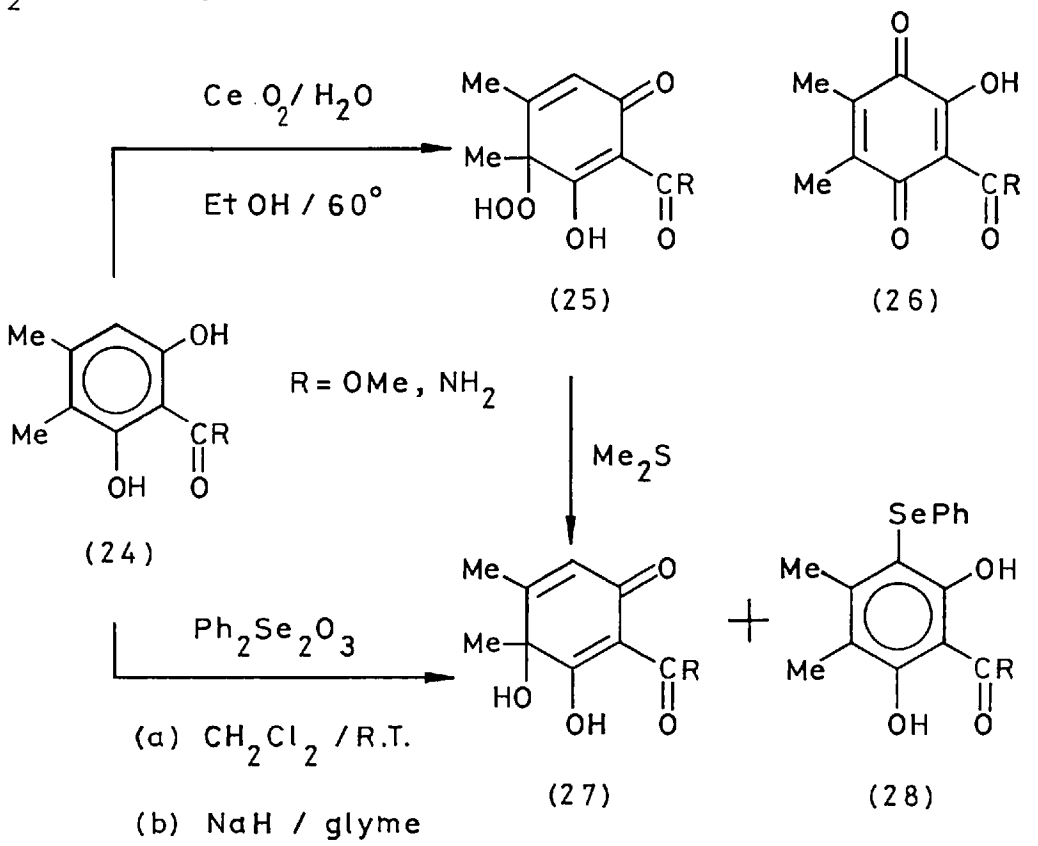


(23)

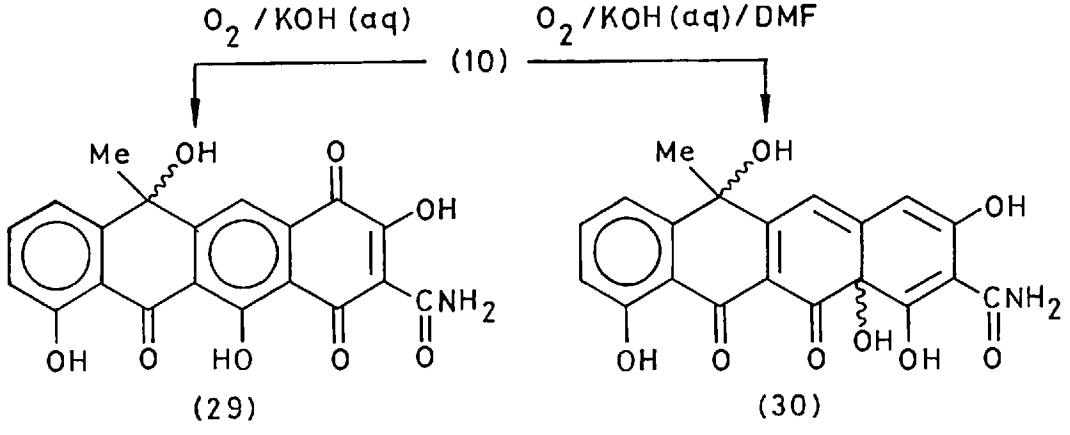
The hydroxyl group at C-12a is less easily removed than that at C-6, to form 4a,12a-anhydrotetracyclines. When required, 12a-deoxytetracyclines can be prepared by the action of zinc dust in aqueous ammonia [17,45], or by hydrogenolysis of the 12a-*O*-formate [46]. The reintroduction of the 12a-OH is of major importance in any synthetic scheme and has been achieved in a number of ways; e.g. the use of peroxyacids [47], oxygen in the presence of noble metals [48]or transition metal ions [49], and such *ortho*-hydroxylation of the phenol generates α-hydroxycyclohexadienones [50]. Barton's group have provided further examples in this field. Quinney [51] demonstrated that oxidation of the Tetracycline ring-A model compound (24) with activated ceric oxide gave an 80% yield of the hydroperoxycyclohexadienone (25, R=NH_2) free from the alternative quinone product (26) found to be the sole product from ammonium molybdate/hydrogen peroxide systems. Quantitative conversion to the desired hydroxydienone (27) was achieved with dimethylsulphide.

Additionally, Rosenfeld [52] found that treatment of (24) with benzeneseleninic anhydride afforded a mixture of products; R=OMe: (27) 35%, (28) 55%, and R=NH_2: (26) 20%, (27) 25%, and (28) 45%.

However, greater *ortho*-selectivity was achieved by prior generation of the phenolate with sodium hydride, which suppressed the formation of quinone (26), to yield R=OMe : (27) 75%, (28) 17% and $R=NH_2$: (27) 68%, alone.

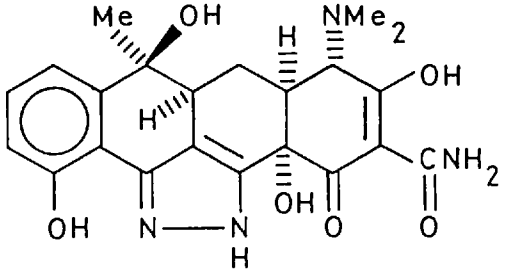


The oxidative hydroxylation of 6-methylpretetramid (10) has been studied by Hassall [53]. Oxygen in alkali performed simultaneous oxygenation at C-4 and hydroxylation at C-6 to yield the quinone (29). However, Hassall has recently claimed [54] that this same reaction performed in 0.1M potassium hydroxide/dimethylformamide (DMF) 1:1 does not give (29), but proceeds to afford the C-6 *and* C-12a hydroxylated product (30).



The evidence for C-12a hydroxylation is indirect and that against C-4 oxygenation in (30), for which five tautomers exist, is presented through the interpretation of an extensive ^{1}H N.M.R. study and the analysis of dubious chemical degradations; the significant role of DMF is not discussed. However, confirmation of this result would prove it to be a useful contribution towards a biogenetic approach to tetracycline synthesis.

The basic structural requirements for full biological activity of the tetracyclines comprise an intact, linear, 4-ring keto-enol chromophoric system; extension or shortening of the chromophore, or modification as in pyrazolotetracycline (31), leads to inactivity. Furthermore, an aromatic ring-D and retention of the natural configuration at C-4,4a, and 12a appears to be essential. Beyond this, many modifications of the basic structure are possible, and some of these are mentioned briefly below.



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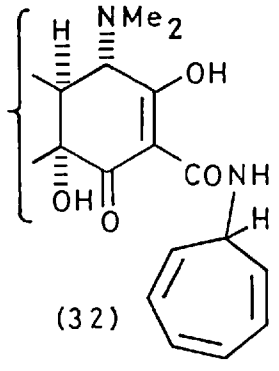

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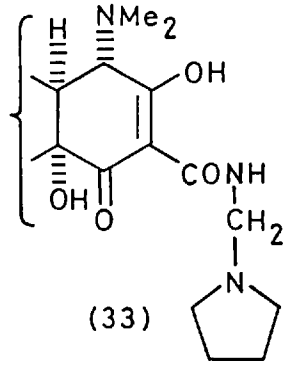
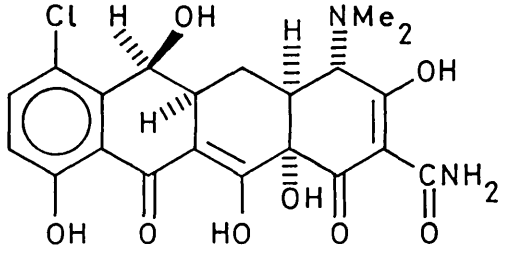


(33)

Although monoalkylation of the C-2 carboxamide group generally leads to the loss of *in-vitro* activity, notably useful modifications include the preparation of the *N*-cycloheptatrienyl derivative (32) [55] or the Mannich reaction of (1) to give pyrrolidinotetracycline (33) [56], which are soluble in water at physiological pH and readily hydrolysed after primary absorption *in-vivo*.

The C-4 dimethylamino group may be replaced by an amino group although any other changes, including epimerisation to the β-configuration [57], decreases the bacteriostatic activty. Modifications of the hydrophilicity at centres C-5 to C-7 are more flexible and *in-vivo* activity is maintained or enhanced in each of the examples (34) to (37) shown below. Changes in the -OH funtionality at C-5 are less critical than at C-6, although neither the C-6 methyl or hydroxyl groups are necessary for antibacterial activity, as illustrated by 6-demethyl-chlortetracycline (34) and Doxycycline (35). Whilst the combined 6-demethyl-6-deoxy compounds generally show decreased activity, this is offset in Minocycline (37) by the incorporation of a C-7 dimethyl-amino group, thus making it one of the most potent tetracyclines [57].



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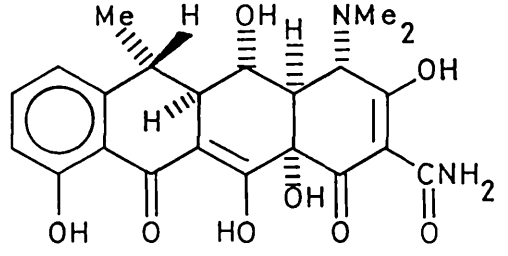

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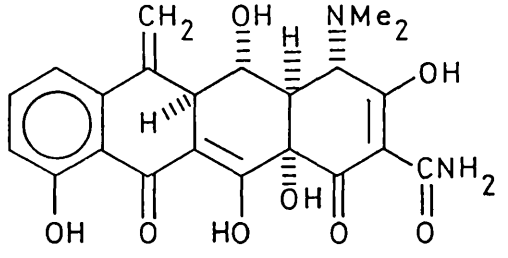

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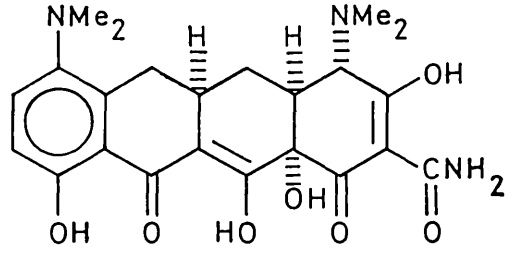


(37)

Increased efficacy due to the above modifications results less from an enhanced inherent structural activity, than from an increase in favourable pharmacokinetics. It is clear that any drug,or pro-drug, has to be first absorbed then traverse a number of both passive and active-transport membranes [58] and other biological interfaces, before reaching its site of action. The process is complex

and involves inactivation, excretion and resorption in the living tissue, but of major importance is the initial uptake upon administration which has been shown by Hansch [59] to be largely dependent upon the relative lipophilicity of the drug and the semi-permeable membrane through which it must first pass.

Microorganisms which are resistant to tetracyclines are believed to contain an R-factor [60] which limits uptake of the drug. Since cell-free extracts of both R-factor resistant and sensitive strains of *E. coli* are equally inhibited by tetracyclines, the R-factor must be associated with an active mechanism of drug concentration across the cell membrane. Therefore, altering the relative lipid/water solubility of tetracycline analogues could lead to an increase in passive diffusion into the bacterial cells, and thus offset the R-factor resistance to active transport. A rough measure of relative lipophilicity is the partition coefficient of a drug between octanol and an aqueous buffer solution. Recently Miller *et al.* [61] studied a number of tetracyclines (T.C.) in this way and related the partition coefficients (P.C.) to the structure-activity of the compounds. Several selected examples are reproduced in the table below.

T.C.	P.C. ($C_8H_{17}OH/H_2O$)
(a) 5a,6-anhydro-	6.00
(b) 4-dedimethylamino-	4.95
(c) 6-demethyl-6-deoxy-	0.99
(d) 7-chloro-	0.37
(e) 5-hydroxy-	0.12 (0.087) [62]
(f) unsubstituted (1)	0.09
(g) 5a,11-dehydro-7-chloro-	0.057

The loss of an hydroxyl- e.g. (a), (c), loss of an amino - e.g. (b), or the presence of a chloro- group e.g. (d) increases lipid solubility relative to Tetracycline (f). The result for (e) suggests that a 5-OH group makes little difference, although an earlier study [62] did place the P.C.'s of (e) and (f) in the expected order, rather than the reverse order presented by Miller.

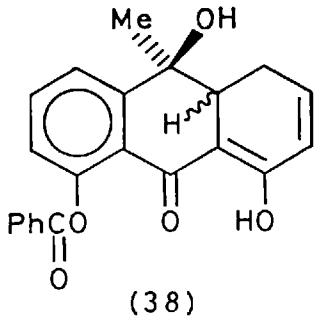
The exact mode of action of the tetracyclines still remains unclear, but principally they interfere with protein biosynthesis [63]. Translation of the base sequence of *m*-RNA occurs at the cell ribosomes, whereupon *t*-RNA's are directed to deliver the specific amino acids which they carry for incorporation into the growing polypeptide chain. Tetracyclines apparently interfere with recognition of the ribosomal codon by the aminoacyl *t*-RNA anticodon, which leads to lack of specific binding, and translocation and termination steps [64] are also affected.

In addition to chemotherapy, some tetracyclines, noteably (2) and (3), have been fed in nutritive doses to healthy animals in order to increase growth. This has led to an increase in the number of resistant strains of bacteria, due to aquired chromosomal resistance caused by needless overexposure of intestinal bacteria to the drug. Unfortunately, such R-factor resistance can be transmitted to other microorganisms *via* DNA plasmids, thus leading to new tetracycline-resistant strains, which is potentially very harmful to man. Government restrictions have recently limited such misuse of these and related drugs. However, much has yet to be achieved in the synthesis of tetracycline analogues, to defeat the ever widening pool of bacterial strains already resistant to the existing antibiotics.

A.5. Achievements in the Synthesis of Tetracyclines.

During the past 25 years since the structure elucidation of Tetracycline was achieved [7-11] the literature has become replete with examples of attempted and some successful syntheses of tetracyclines. Some of the more noteable examples will be discussed briefly below.

By sequential elaboration of the BCD-dienediolone (38) through the nitro-derivative (39), Shemyakin *et al.* [65,66] produced, among others, compounds (40) and (41). Although the C-6 hydroxyl group was inefficiently lost during subsequent transformations of (39), Shemyakin believed that the photooxidation of (41) followed by reduction of the hydroperoxide would reintroduce the C-6-OH along with the C-12a-OH, thus providing a formal total synthesis of (±)-Tetracycline. However, Muxfeldt [25] has claimed that such a photooxidation only succeeds in the case of 7-chlortetracyclines.



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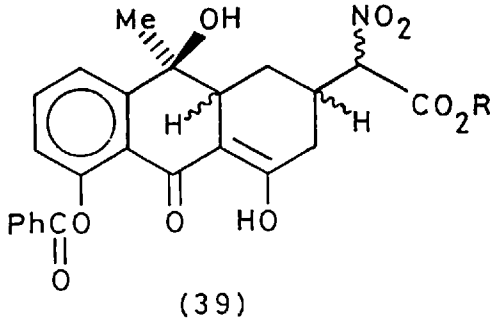

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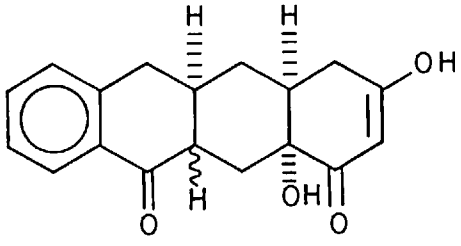

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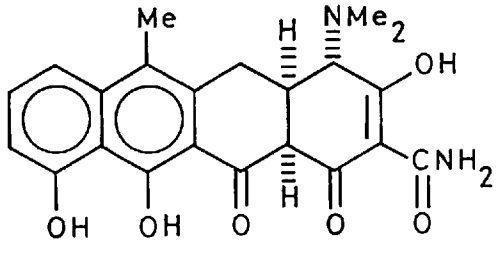
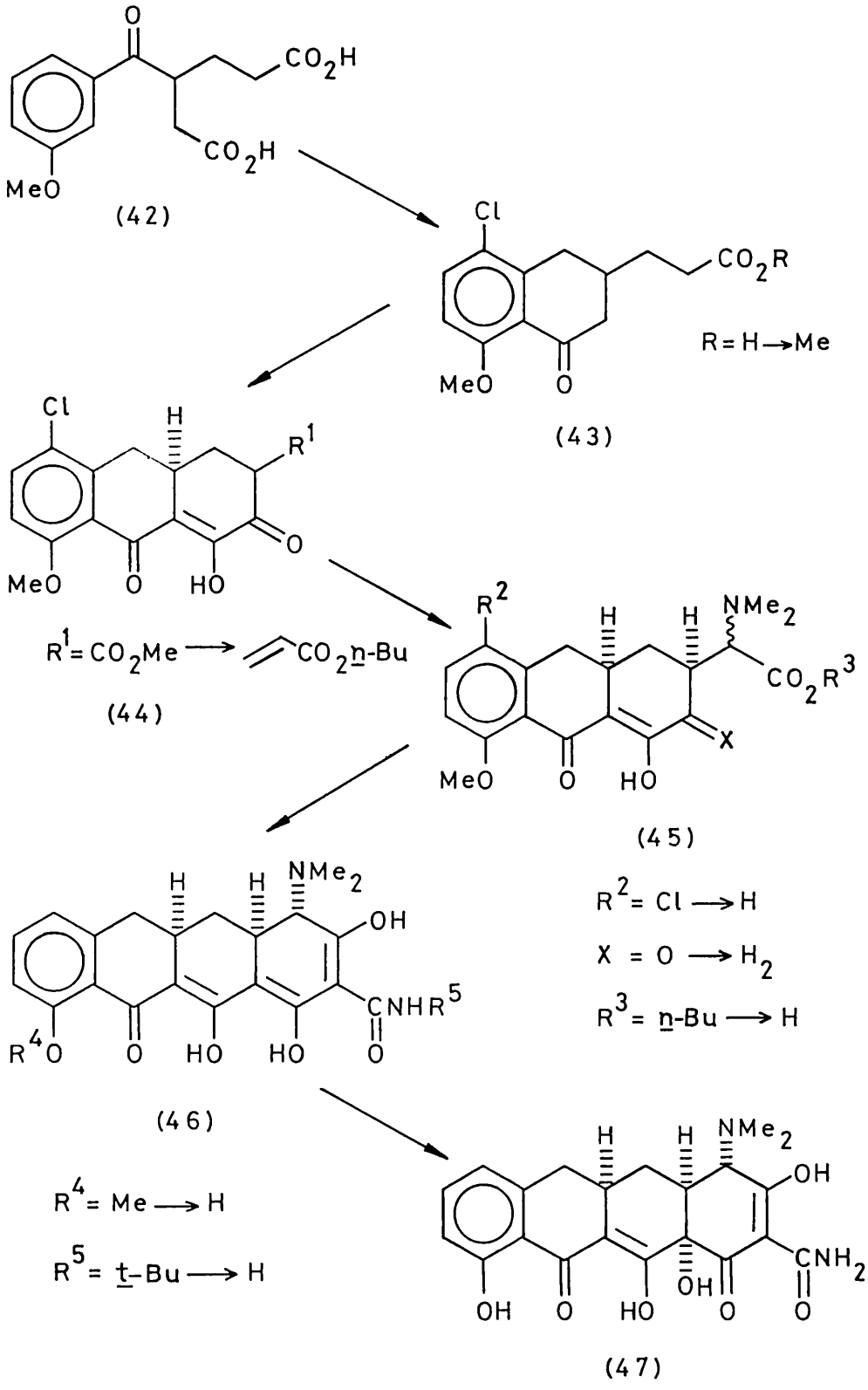


(41)

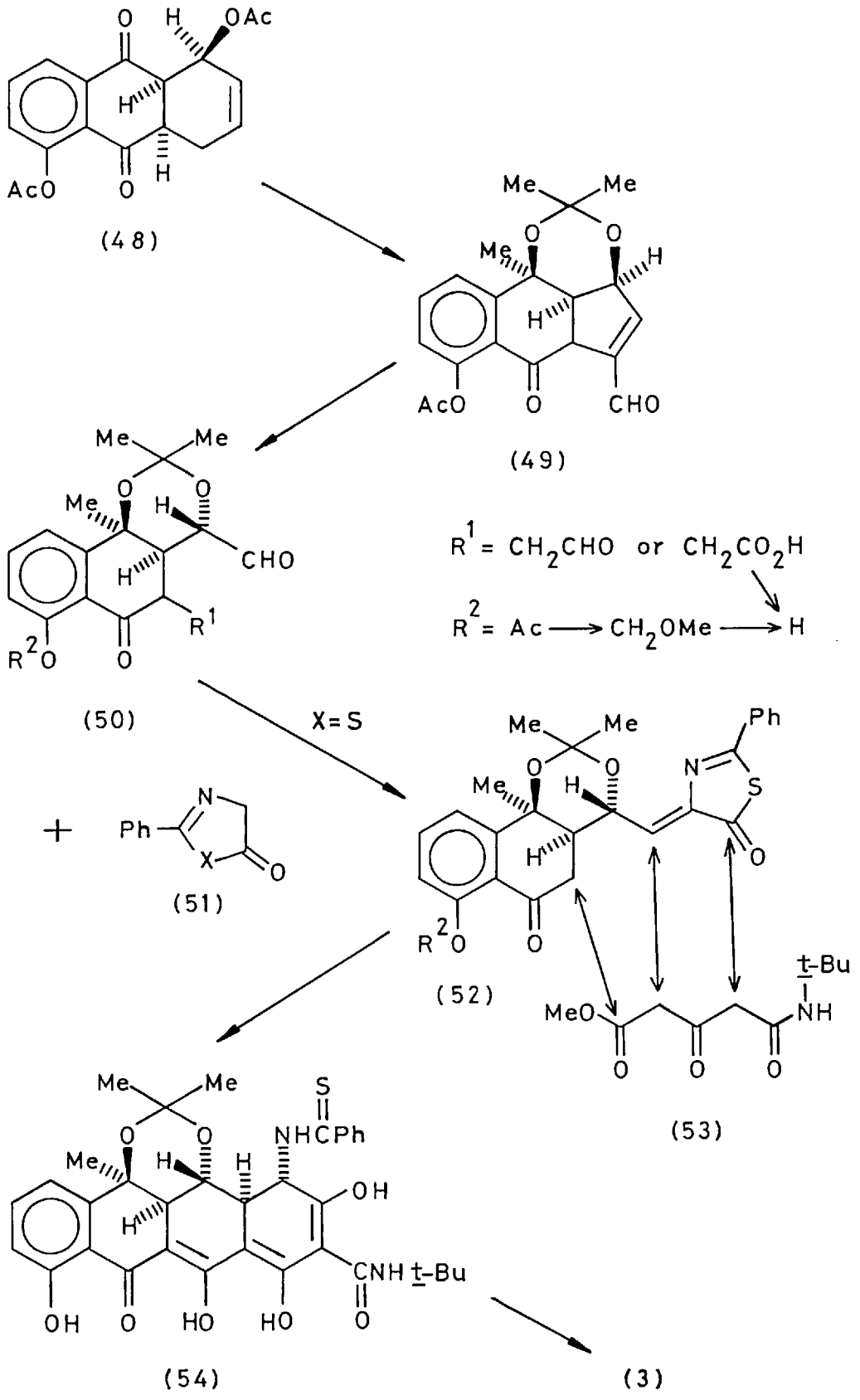
In 1962 Woodward *et al.* [67] communicated the results of the first total synthesis of the simplest biologically active tetracycline, namely (±)-6-demethyl-6-deoxytetracycline (47). A full account of the synthesis

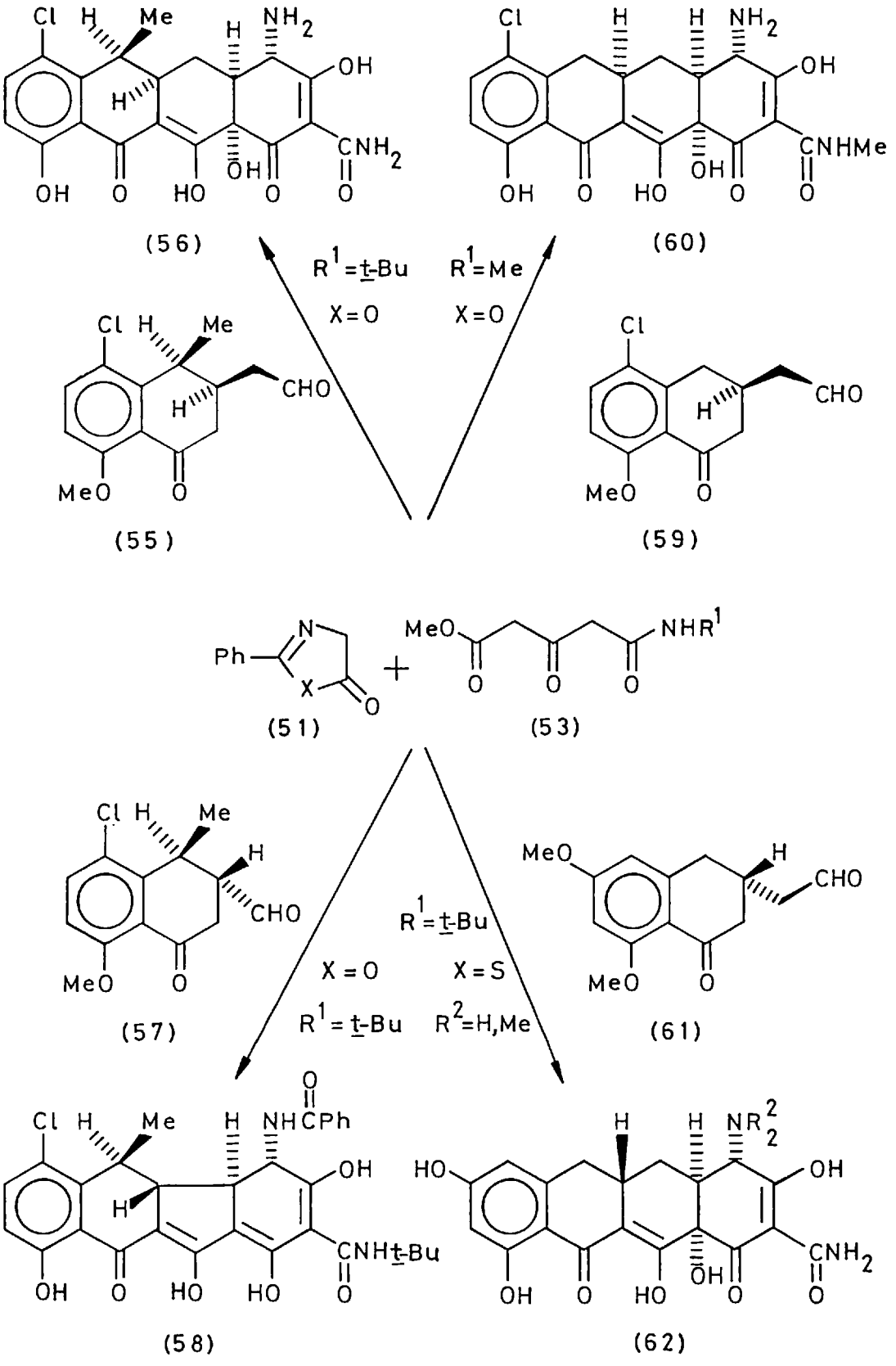

O
CO2H
CO2H
MeO
(42)
Cl
CO2R
R=H→Me
MeO
O
(43)
Cl
H
R1
O
MeO
O
HO
R1= CO2Me → CO2n-Bu
(44)
R2
H
H
NMe2
CO2R3
X
MeO
O
HO
(45)
R2= Cl → H
X = O → H2
R3= n-Bu → H
H
H
NMe2
OH
CNHR5
R4O
O
HO
HO
O
(46)
R4= Me → H
R5= t-Bu → H
H
H
NMe2
OH
CNH2
OH
OH
O
HO
O
O
(47)

appeared in 1968 [68], from which the following description is abstracted.

The Claisen condensation product from methyl-*meta*-methoxybenzoate and dimethylsuccinate was reacted with methyl acrylate, then hydrolysis to form the keto-diacid (42). After hydrogenation of the ketone and C-7 chlorination, cyclodehydration in liquid HF gave the tetralone (43, R=H). Double condensation of (43, R=Me) with dimethyl oxalate gave the triketo-ester (44, $R^1=CO_2Me$), which upon hydrolysis and decarboxylation gave (44, R^1=H). Further condensation with *n*-butyl glyoxylate gave (44, $R^1=$  CO_2-*n*-Bu), which with dimethylamine gave the C-4 epimers (45, R^2=Cl, R^3=*n*-Bu, X=O) which equilibrated to the thermodynamically most stable, natural, α-configuration. Reduction of the ketone and removal of the 7-chloro group by hydrogenolysis gave, after hydrolysis, the acid (45, $R^2=R^3$=H, $X=H_2$). Stepwise conversion to the mixed isopropyl anhydride, acylation with *N*-*t*-butyl malonamate and cyclisation with NaH/DMF afforded the C-12a-deoxy compound (46, R^4=Me, R^5= *t*-Bu). Removal of the blocking groups and treatment of the derived hydrochloride with O_2/Ce^{2+} converted (46, $R^4=R^5$=H) in 6.5% yield to the desired product (47). The overall yield from this 22 step synthesis was *ca.* 10^{-3}% of the racemic product.

A more flexible synthetic strategy was adopted by Muxfeldt and his group, who prepared (47) in a simpler and more elegant manner in 1965 [69]. The principal route employed is exemplified by its application to the synthesis of oxytetracycline (3) [70]. The Diels-Alder adduct from juglone acetate and 1-acetoxybutadiene (48) was converted in 7 steps to the aldehyde (49). Ozonolysis, then hydrolysis gave a mixture of epimeric aldehydes, which could be equilibrated to the desired single epimer *via* the piperidine enamine, and subsequent reaction with chloromethyl methyl ether then afforded the specific aldehyde (50, R^1=H, $R^2=CH_2OMe$). Condensation of this key aldehyde with 2-phenyl-4-thiazolone (51, X=S) gave (52), whereupon a strategic triple condensation with methyl-*N*-*t*-butyl


(48)
(49)
(50)
(51)
(52)
(53)
(54)
(3)
X=S
R^1 = CH_2CHO or CH_2CO_2H
R^2 = Ac → CH_2OMe → H

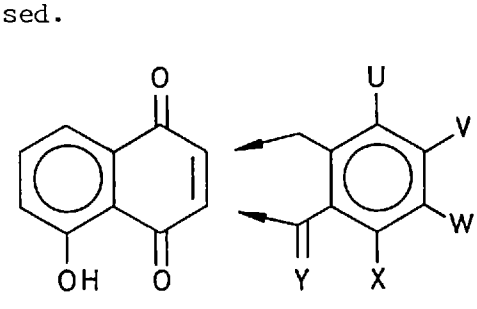

(56)
(60)
R1=t-Bu
X=O
R1=Me
X=O
(55)
(59)
(51)
(53)
(57)
(61)
R1=t-Bu
X=O
X=S
R1=t-Bu
R2=H,Me
(58)
(62)

-3-oxoglutaramate (53) yielded the thioamide derivative (54). Subsequent removal of the protecting groups and introduction of the C-12a hydroxyl group by aerial oxidation in NaH/DMF led to oxytetracycline (3).

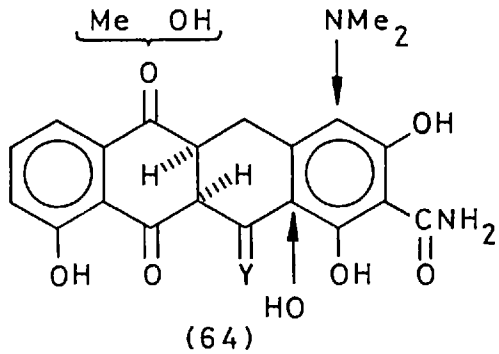
The flexibility of the approach is due largely to the number of variations possible in the constitution of the basic aldehyde moiety. For example, a group at Hoechst [71] condensed the oxazolone (51, X=O) and (53) with the aldehyde (55) to afford the 6-*epi*-chlortetracycline (56). A similar reaction with the truncated aldehyde (57) [25] led to the novel 5a,6-*epi*-chlortetracycline analogue (58) which contains a five-membered ring-B. Analogously, aldehyde (59) and the *N*-methylglutaramate (53, R^1=Me) gave the tetracycline (60), cleanly monomethylated at the 2-carboxamide group [72]. Finally, condensation of the thiazolone (51, X=S) and a suitable aldehyde (61) has furnished a group of 8,10-dihydroxy-4,5a-*epi*-tetracyclines (62, R^2=H, Me).[73] The overall yields of the tetracyclines by the Muxfeldt approach is *ca.* 0.05-0.1%, with the additional advantage that intermediate isomers are readily separated and purified by fractional crystallisation.

A.6. Synopsis of the Imperial College approach to Tetracycline Synthesis.

This well established approach by Barton's group has been extensively reviewed in the past [26], and most recently by Cardoso [74]. Here the more pertinent aspects of the projected synthesis will be discussed.



(63)

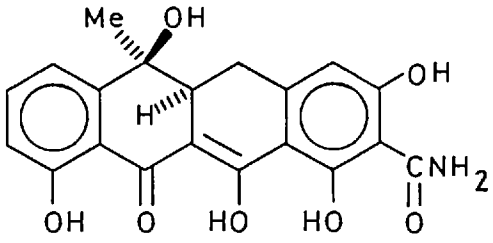


(64)

The basic concept involves the conversion of the suitably protected and masked form of the ring-A and ring-CD components (63) into

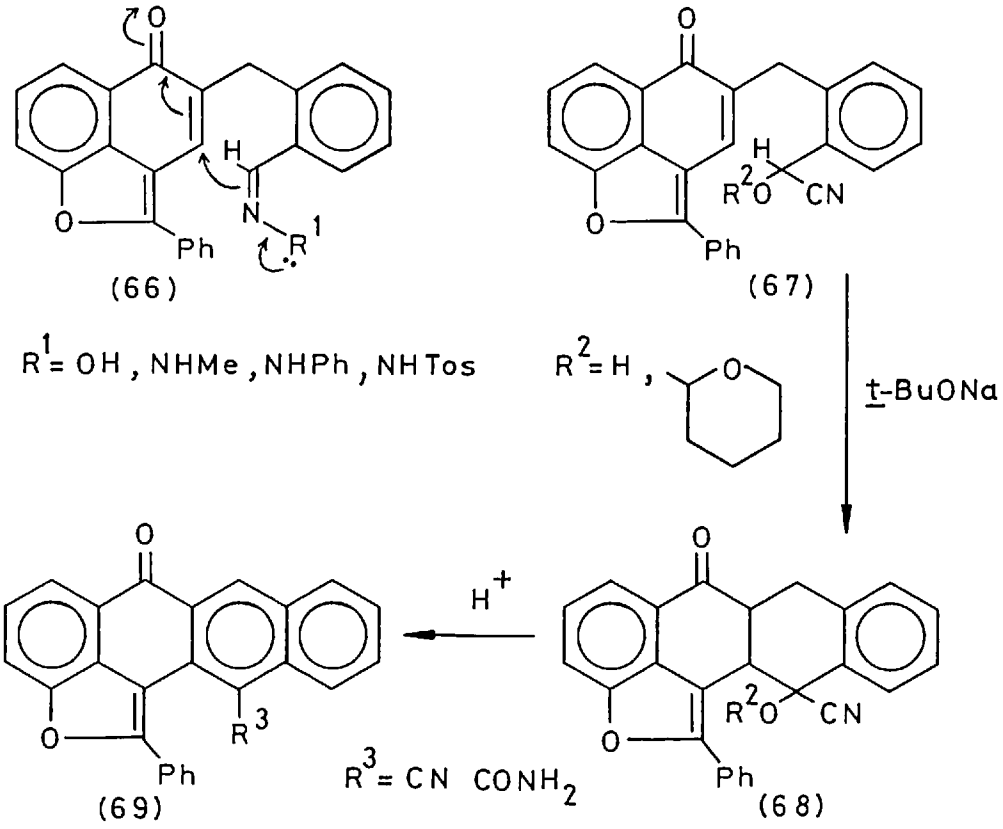
the linear tetracyclic species (64) which, after introduction of the additional functionalities at C-4,6, and 12a, and suitable adjustment of the ring-A oxidation level, should yield (1).

Whilst the earlier synthetic objective of this scheme was the preparation of the 4,6-tetracycloxide (19), based upon the reported, reversible, degradations of (1) to (19), the recent efforts of Mills, Meguro and Monteil in this laboratory [75], have now established the tetracyclic "diphenol" (65) as the desired "relay" intermediate.



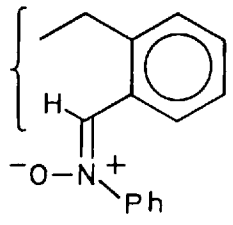
(65)

The closure of ring-B by a Michael-type addition of a suitably masked C -12 functionality to a CD-enone, was attempted for a number of derivatives, namely the oxime, methyl-, phenyl- , and tosyl-hydrazones, in the ring-A unsubstituted model series (66) [76].



Whilst this 6-*endo-trig* reaction is favoured [77] it is unfortunately also reversible, and all attempts failed to produce tetracyclic compounds. Turning to the "tetrahedral" cyanohydrin derivatives (67), cyclisation with base gave (68). However, although chromatography of (68) on alumina did yield the desired model 6,12-diketone, generally acidic work-up afforded only ABD-aromatic products (69). Furthermore, this cyclisation method was later shown to be incompatible with ring-A substituted derivatives, so this route was abandoned.

The use of 1,3-dipolar intermediates [78] was similarly without success. Thus, whilst cyclisation of the nitrone (70) occurred spontaneously to give a mixture of isomeric isoxazolidines (71) and (72) in 80% and 11% yield respectively, (71) resisted conversion to a 12-keto derivative. Although hydrogenolysis of (71) over palladium, or treatment with chromous chloride, did cleave the isoxazolidine (N-O) bond, the resultant 5a-hydroxylated compound was an unsuitable substrate for further structural elaboration.



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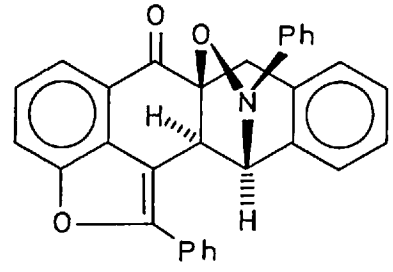

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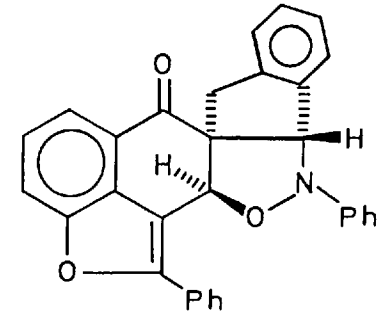
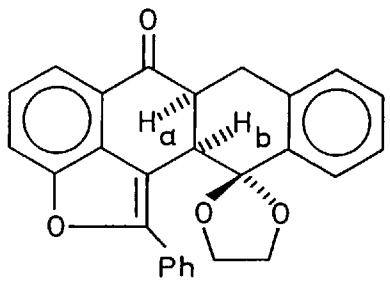


(72)

A successful approach to cyclised products was realised *via* C-12 stabilised radical intermediates [79]. Photolysis of the 1,3-dioxolane derived from the tricyclic aldehyde gave, by the action of heat and in the presence of a catalyst, the tetracyclic acetal (73), whose linear *cis*-fused structure was established by N.M.R., which showed a vicinal *cis*-coupling constant J_{ab}= 5.5 Hz., consistent with (73) yet inconsitent with the alternative spiro isomer (74).



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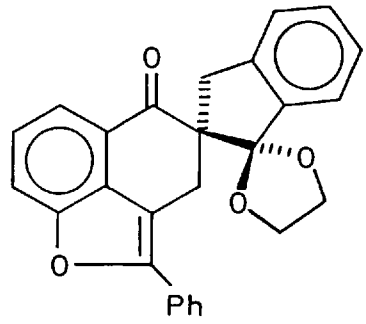
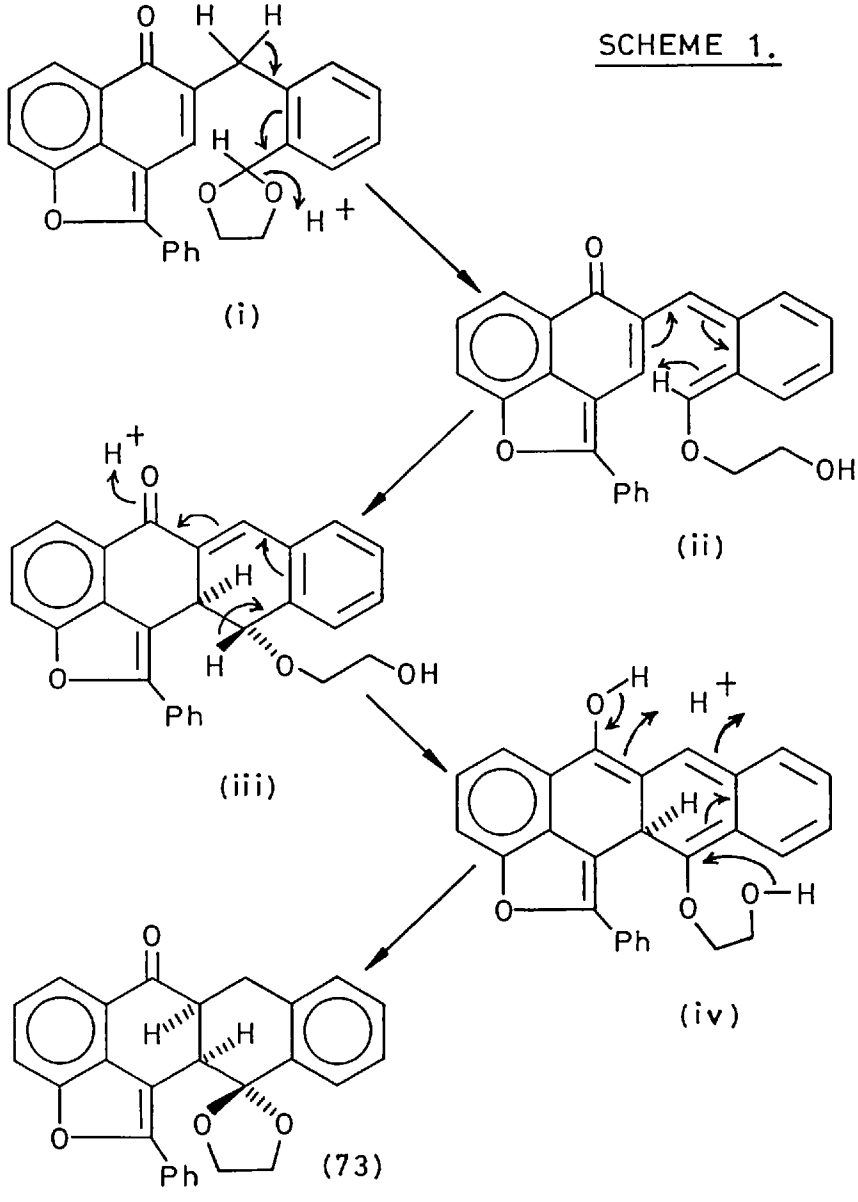


(74)

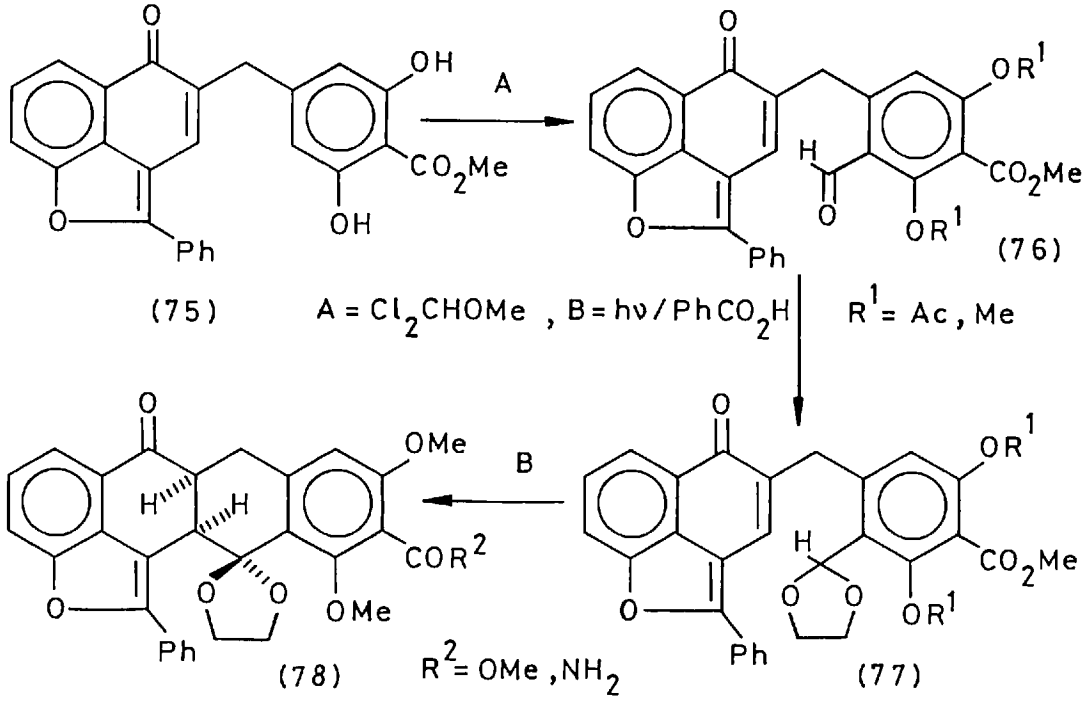
Although dibenzoyl peroxide was the original catalyst chosen, later a careful analysis of its many thermal decomposition products, revealed that the active component was benzoic acid. Deliberate addition of benzoic acid during photolysis gave more reproducible yields (78%, over 25h). The originally proposed mechanism for this reaction is shown in Scheme 1. below.

SCHEME 1.

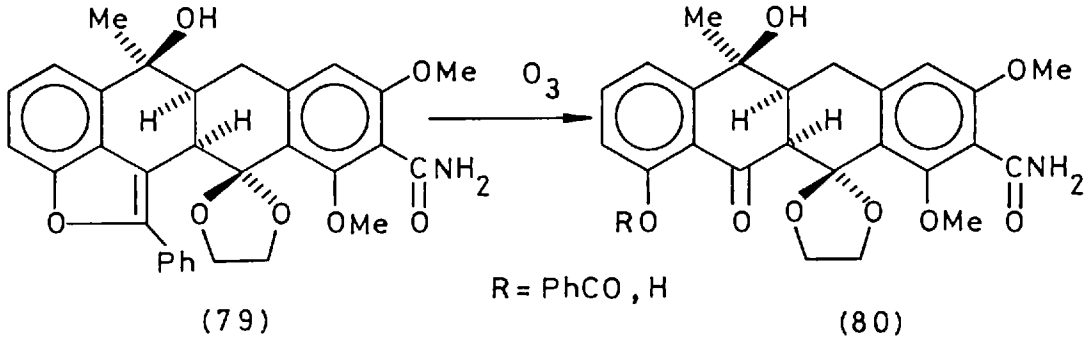


Following the acid catalysed ring opening of the 1,3-dioxolane (i), photolytic excitation and conrotatory ring closure of the triene (ii) gives the stereospecific product (iii). Enolisation and reclosure of the acetal (iv) then gives the observed product (73). This photocyclisation is also catalysed by non-nucleophilic bases, and modifications of the above mechanism to account for this will be discussed later.

Formylation of the ring-A substituted compound (75) with dichloromethyl methyl ether was the best route to the tricyclic aldehyde (76) [80]. The aldehyde-diphenol (76, R^1=H) gave only traces of the unstable 1,3-dioxolane (77, R^1=H) with ethylene glycol/acid, or by transacetalisation with the ethylene acetal of butan-2-one/ boron trifluoride etherate, and generally deformylation occurred. An improved procedure, involving acetalisation with ethyleneorthocarbonate [81], gave high yields of (77, R^1=H), but photocyclisation of the free diphenol does not occur cleanly with acid-catalysis [82]. The diacetate (76, R^1=Ac) and the dimethyl ether (76, R^1=Me) both gave good yields of their corresponding 1,3-dioxolanes under standard conditions, however, photocyclisation of (77, R^1=Ac) was unsatisfactory due to competing photo-Fries rearrangement reactions. This left the more stable dimethyl ether (77, R^1=Me) as the only useful substrate for cyclisation to (78, R^2=OMe).



Stepwise conversion of the ester to the amide (78, R^2= NH_2) and treatment with methyllithium, gave a small quantity of the masked carbinol (79). Ozonolysis and reduction of the ozonide with dimethyl-sulphide gave the keto-benzoate (80, R= PhCO) which provided the keto-phenol (80, R= H) upon treatment with base. Finally, demethylation and deacetalisation of (80, R=H) was required under mild conditions to afford the tetracyclic diphenol (65).However, no suitable conditions were found, and only hydrogen iodide in boiling phenol cleaved the methyl ethers which, with concomitant deacetalisation, dehydration and aromatisation, gave the biogenetic intermediate 6-methylpretetramid (10).



(79) (80)

The deprotection of masked tetracyclic intermediates has remained a central problem in this synthetic approach to Tetracycline, and futher work in this area is presented in this thesis.

B. MODERN ORGANOSELENIUM CHEMISTRY.

Prior to 1973, the organic chemistry of selenium reagents has been limited mainly to the use of the element, to effect dehydrogenations and the isomerisation of alkenes, and to the allylic hydroxylation and oxidation reactions of the dioxide [83]. Since this time, several new organic transformations have been effected by novel selenium reagents. Comprehensive reviews of the more contemporary literature are now available, by Klayman and Günther [84] and more recently by Clive [85], in addition to those appearing in other theses from this laboratory [86,87,88]. A brief discussion of the use of organoselenium reagents in modern organic synthesis, with particular attention to reduction/oxidation reactions, will comprise the basis of this review.

B.1. Selenols and Derivatives in Reduction Reactions.

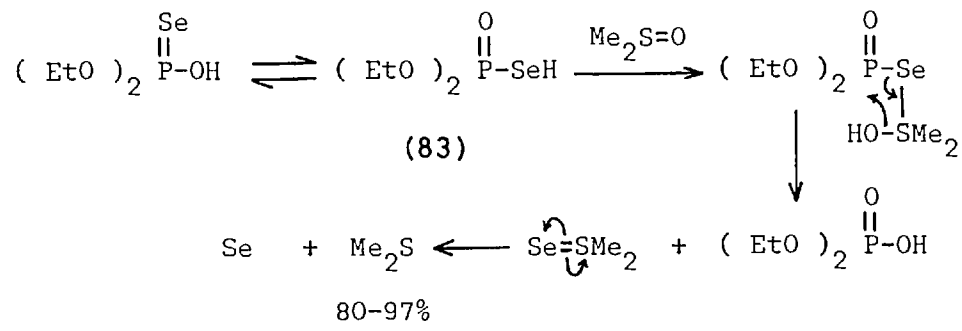
The reduction of aryldiazonium salts to arylhydrazines is commonly achieved by treatment with sodium sulphite, stannous chloride[89], or triphenylphosphine [90]. Recently Perkins *et al.* [91] demonstrated that benzeneselenol (PhSeH) efficiently reduces aryldiazonium fluoroborates (81) to hydrazines (82) in CH_2Cl_2, (PhSH is ineffective) as shown below.

$$\underset{(81)}{ArN_2^+\ BF_4^-} + 4\ PhSeH \xrightarrow[CH_2Cl_2\ /\ \Delta]{} \underset{(82)}{\{\ ArN_2H_4\ \}^+\ BF_4^-}\ {}^{80\%} + 2\ Ph_2Se_2$$

The addition of 5-10% acetone alters the electron donor properties of the selenol and results in the generation of N_2 and aryl--phenylseleno products, presumably *via* a radical pathway.

Although selenium reagents have been employed to effect the deoxygenation of epoxides (oxiranes) [92,93], the use of selenols in deoxygenations has been limited to the preparation of sulphides from sulphoxides, *via* 2-*N*-dimethylaminoethane selenol/H_3PO_3 [94], or *O,O*-diethylhydrogenphosphoroselenoate (83) [95] for which Mikołajczyk

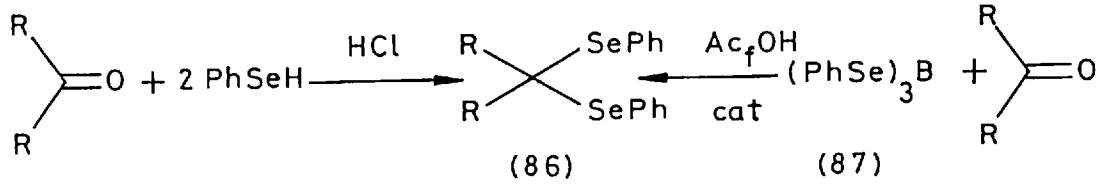
proposes the mechanism:



The intermediacy of the diselenide (84) in this reaction has been suggested by Clive [96], who has also evaluated the stoichiometric and catalytic conversion of terminal epoxides to alkenes (70-92% yield) *via* the tellurium analogue (85) of the reagent (83) [97].

(84) (85)

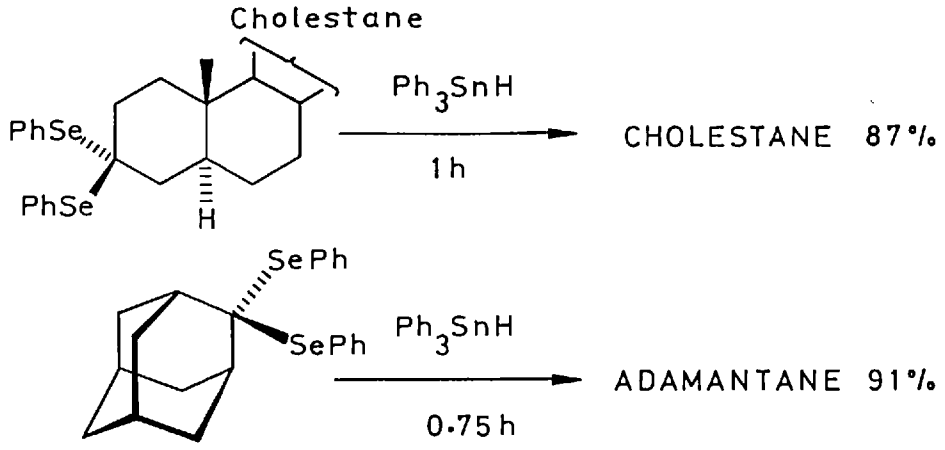
Bis-selenoacetals (86) are prepared classically from PhSeH and the ketone with dry HCl [98]. By analogy to the corresponding RS-carrier [99], the crystalline borane (87) [100] has been shown to afford selenoacetals in good yield [101], avoiding the very oxygen-sensitive and noxious selenol.



(86) (87)

The treatment of (86) with base affords promising nucleophilic, stabilised-carbanion synthons [85], which with ketones and aldehydes give β-hydroxyselenides, ultimately convertible to alkenes [102] or allylic alcohols [103]. However, reduction with tin hydrides (e.g. Ph_3SnH, Ph_3SnD, n-Bu_3SnH), lithium/ethylamine, or Raney nickel produces alkanes in good yield [104]. The use of triphenylstannane (Ph_3SnH) is compatible with the presence of sulphides and the method constitutes the mild

reduction of a ketone to an alkane, especially useful where the presence of other functionalities preclude alternative reduction methods.

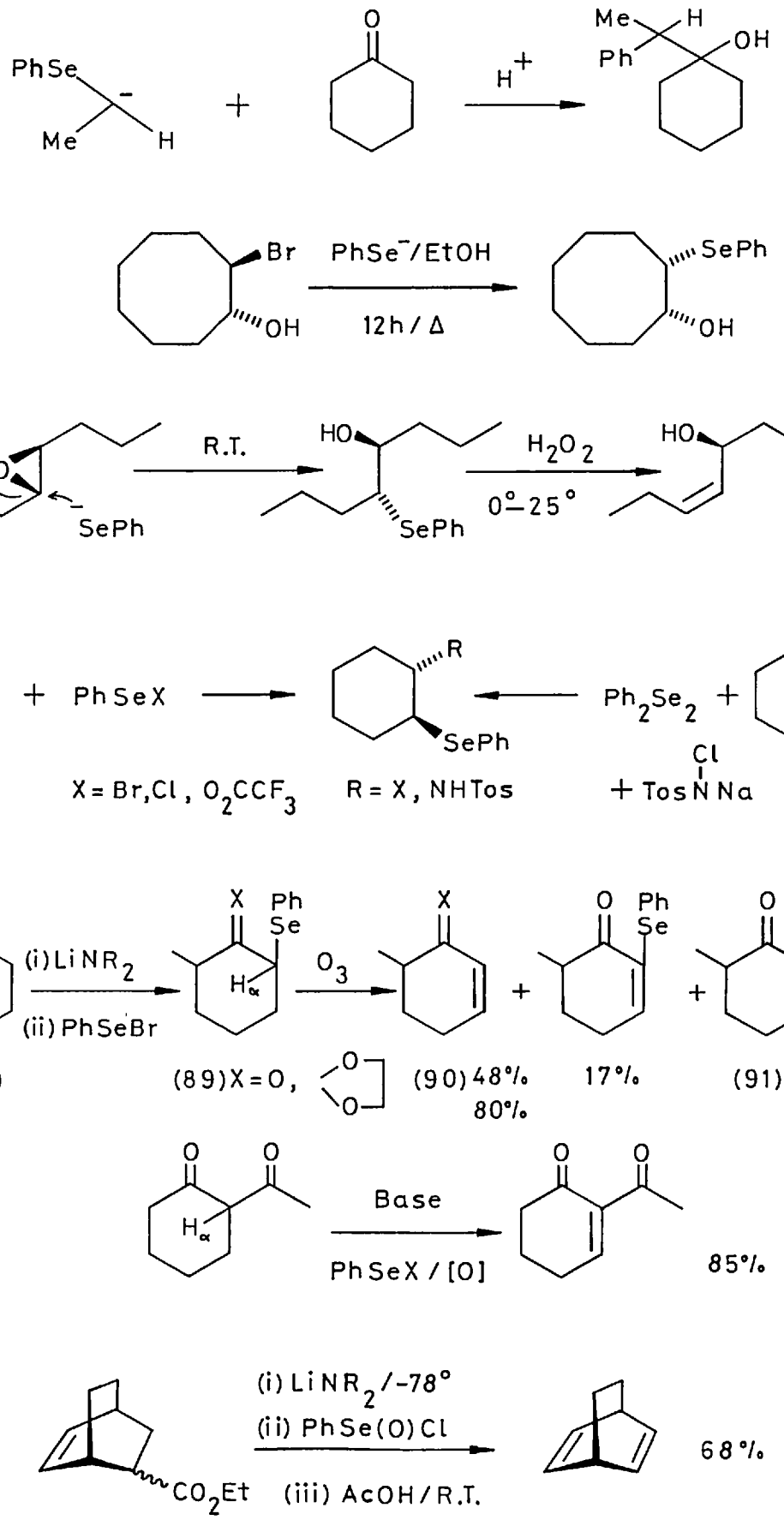


B.2. Selenoxides in Oxidation Reactions.

Arylseleno groups can be incorporated into organic molecules in a number of ways: by formation of β-hydroxyselenides as above [85] or *via* nucleophilic attack of the benzeneselenolate anion ($PhSe^-$) on an epoxide [103] or alkyl halide [105]; the electrophilic addition of benzeneselenenyl halides or acetates [106,107], or of diphenyldiselenide/anhydrous Chloramine-T [108] to alkenes; and by the treatment of enol-acetates (AgO_2CCF_3 catalysed) [109] or ketone enolates ($LiN(i\text{-}Pr)_2$, etc.) [110] with PhSeX (X=Br, Cl). Subsequent oxidation of the selenide (by ozone, hydrogen peroxide, sodium metaperiodate, metachloroperbenzoic acid) affords the benzeneseleninyl derivative (selenoxide), also obtainable directly, in lower yield, using benzeneseleninyl chloride (PhSe(=O)Cl) in the above displacement reactions [110]. Some examples of such transformations are shown in Scheme 2.

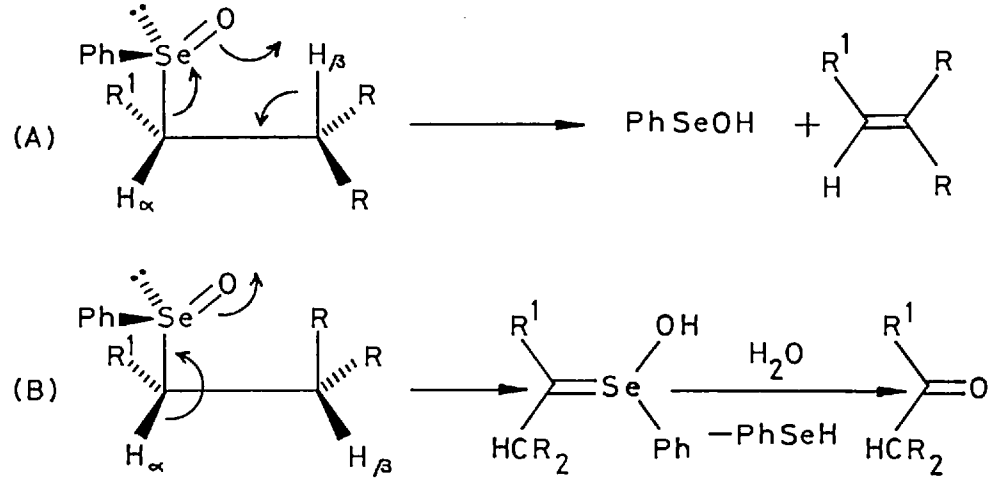
The facile elimination of benzeneselenenic acid (PhSeOH) from selenoxides containing a β-hydrogen is now well known. The reaction usually occurs at or below room temperature and was first observed by Jones [111], who deduced that a *syn*-elimination process occurred in the steroidal selenoxides which he studied,(path A) in the example below. Configurations which preclude the availability of *cis*-β-hydrogens usually

SCHEME 2.


PhSe
Me
H
Me
H
Ph
OH
H+
Br
OH
PhSe⁻/EtOH
12h / Δ
SePh
OH
R.T.
HO
SePh
H2O2
0°–25°
HO
PhSeX
X = Br, Cl, O2CCF3
R = X, NHTos
Ph2Se2
+ TosNNa
Cl
(i) LiNR2
(ii) PhSeBr
Hα
O3
(88)
(89) X = O,
(90) 48%
80%
17%
(91) 9%
Base
PhSeX / [O]
85%
(i) LiNR2 / -78°
(ii) PhSe(O)Cl
(iii) AcOH / R.T.
CO2Et
68%

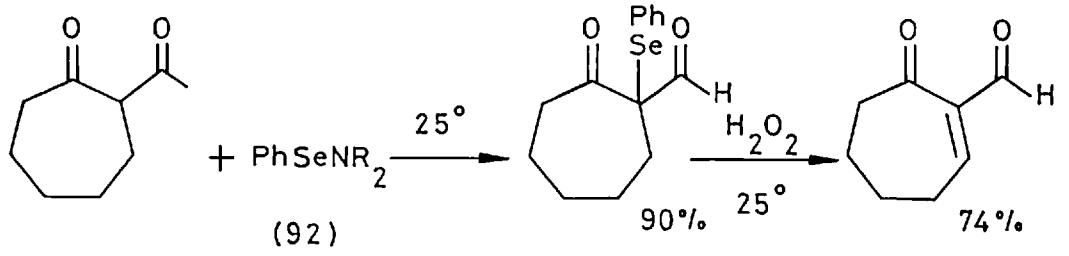
lead to stable selenoxides, as do examples where conformational constraints hinder the achievement of a cyclic transition state [112] .

Alternatively, Pummerer-type rearrangement products (path B) can also be observed, particularly in these latter cases, which is enhanced by the presence of a more acidic H_α (e.g. if R^1=carbonyl).

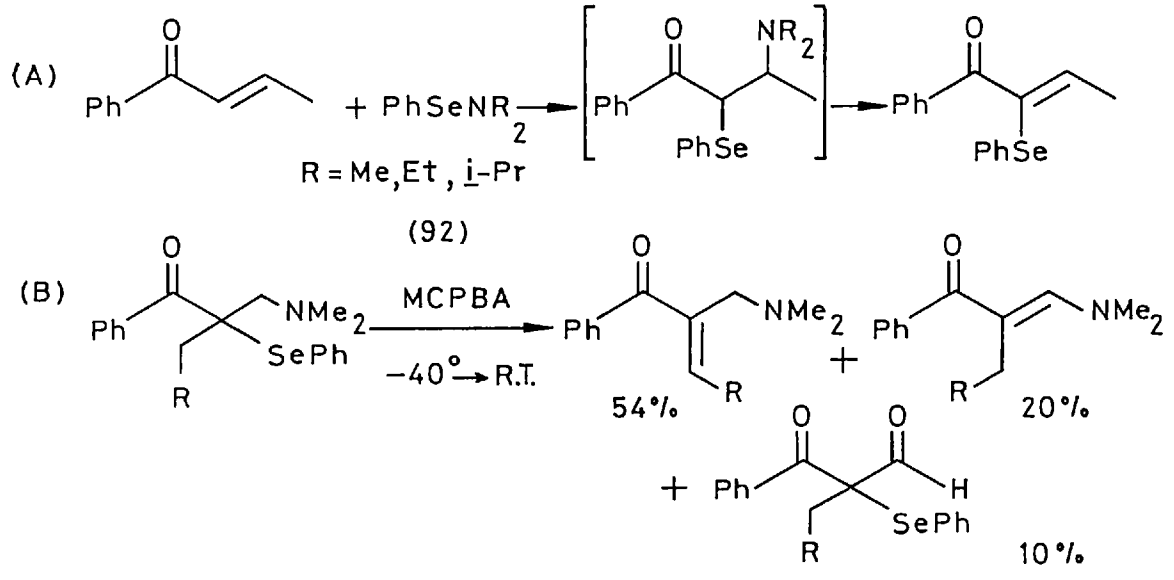


This divergent mechanism thus accounts for the production of the α-diketone by-product (91) from (88) (Scheme 2.); the ethylene acetal of (89) has a less acidic H_α , therefore an analogous reaction gives (90) as the only product.

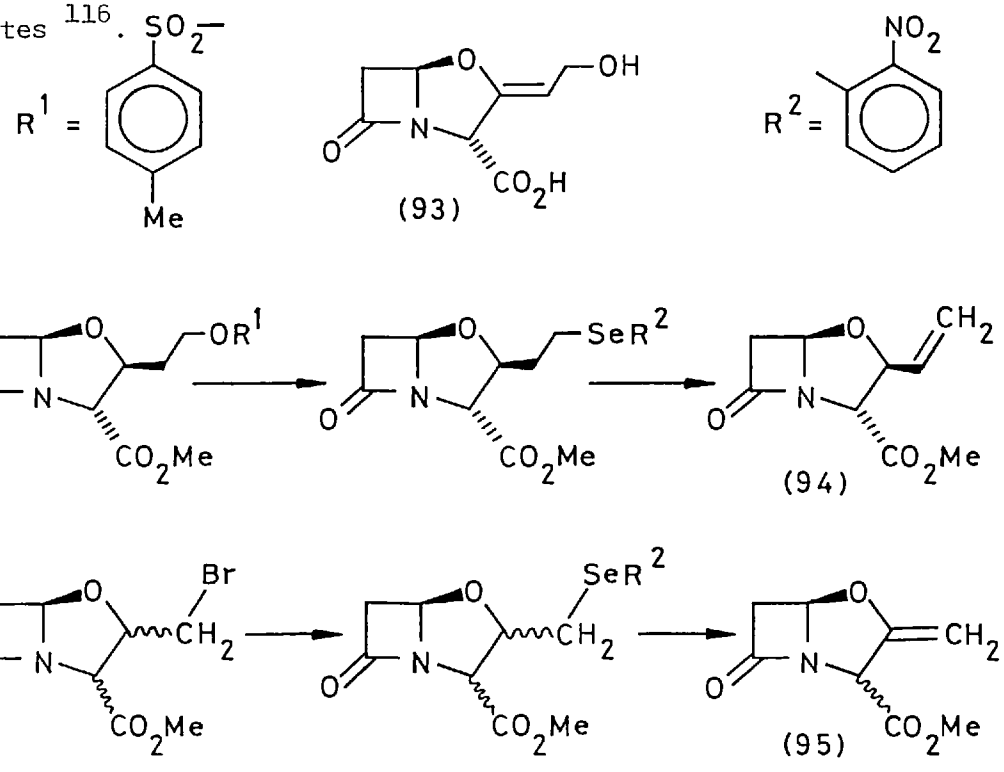
Reich [113] has demonstrated the complementary use of benzeneselenenamides (prepared from secondary amines and PhSeX) (92) as phenylselenating species. The dimethylamine derivative (92, R=Me) is more susceptible to hydrolysis than (92, R=Et, *i*-Pr) and an example of their use is given below.



Advantageously, (92) reacts with electron-deficient alkenes. e.g. reaction (A) below, although the regioselectivity of the derived selenoxide elimination is less rigid than normal [103,106] e.g. reaction(B).

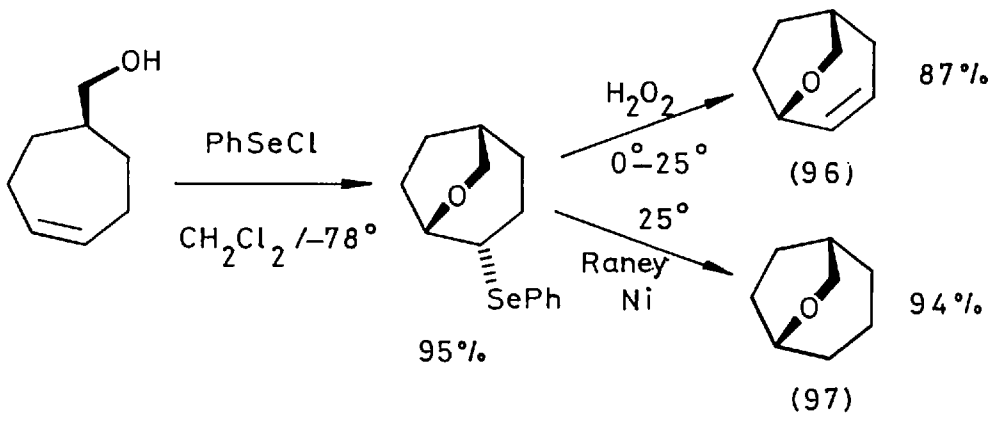


In all these cases, the formation of an enone (or ketone *via* Pummerer) represents a formal oxidation by the organoselenium species. (For a review of oxidations mediated by selenoxides *per-se*, see Refs. 85 and 86). A contemporary example of the use of selenoxides in natural product chemistry, is the preparation of two analogues (94) and (95)[114] of the novel β-lactam Clavulanic acid (93) [115], *via ortho*-nitroselenide intermediates [116].



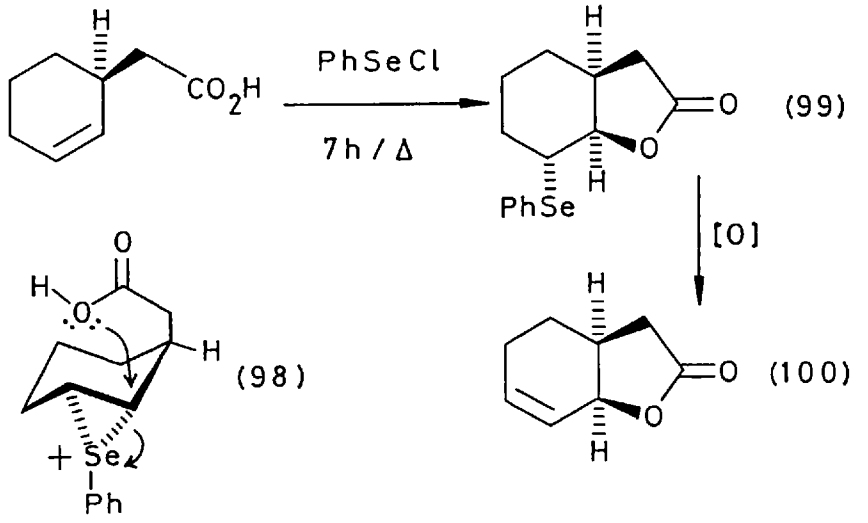
B.3. Cyclofunctionalisation.

The preparation of cyclic ethers from ene-alcohols and benzeneselenenyl chloride has been demonstrated by Nicolaou [117] to proceed in high yield, e.g. (96) and (97).

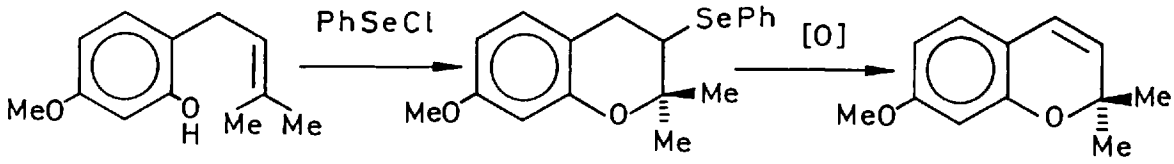


Although Nicolaou has extended this synthetic approach to several heterocycles [118], further examples in this field have been widely studied by Clive *et al.*, who has coined the phrase "cyclofunctionalisation" to describe this set of reactions.

Such ring closures are believed to proceed *via* the episelenide species (98) in an *exo-tet* mode [77] favoured for 3-7 atom rings. An example is the preparation of the bicyclic lactone (99) [119,120]. The *cis*-fused ring junction in (99) was confirmed by oxidation to the known compound (100) [121].

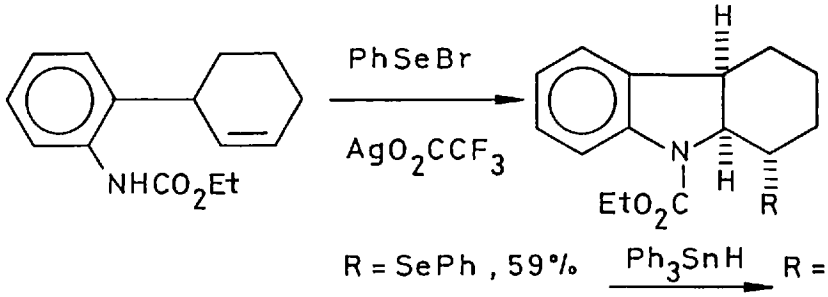


Extension of this reaction to the cyclisation of *ortho*-alkenyl phenols [122], has furnished the natural insecticide Precocene I (101) [123].



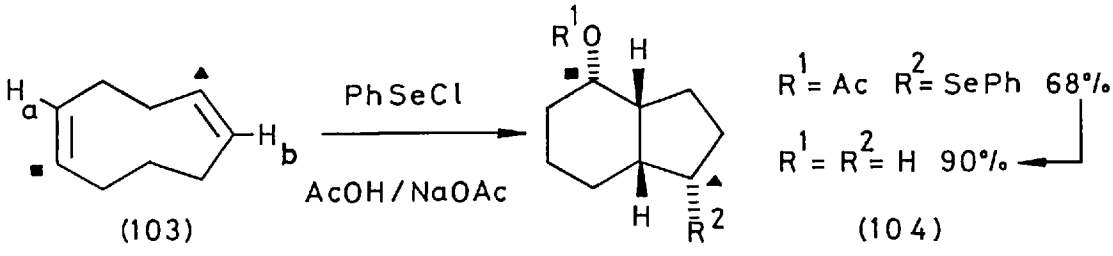
(101)

Because arylselenenyl halides attack primary amines at nitrogen [84,113], the analogous cyclisations of *ortho*-alkenylanilines is unsuccessful. However, conversion of the aniline to its urethane derivative (with ethylchloroformate) has proved efficacious, as treatment with benzeneselenenyl bromide then gives cleanly the required *N*-heterocycle, e.g. (102) [124].



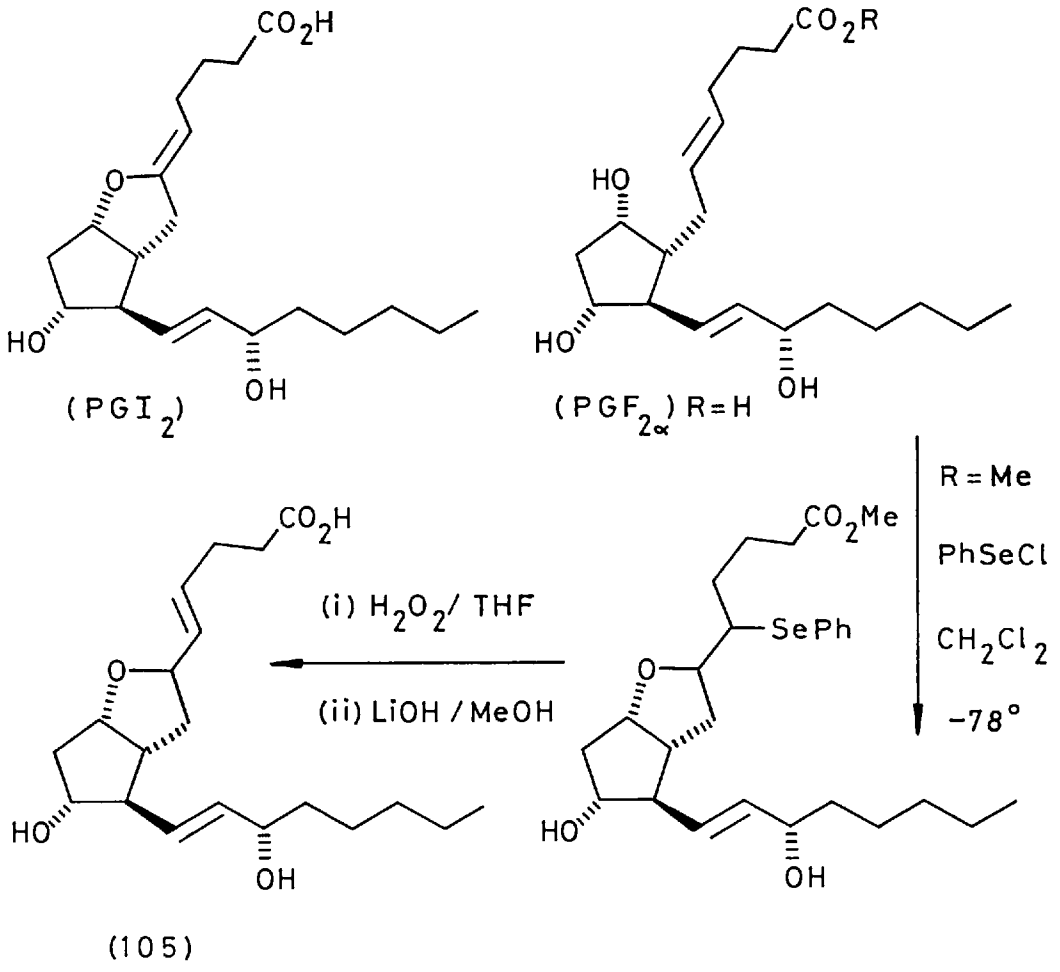
(102)

Recently Clive has extended the field even further by producing a transannular cyclofunctionalisation of (Z,Z)-cyclonona-1,5-diene (103) to the hydrindan (104) [125].



(103) (104)

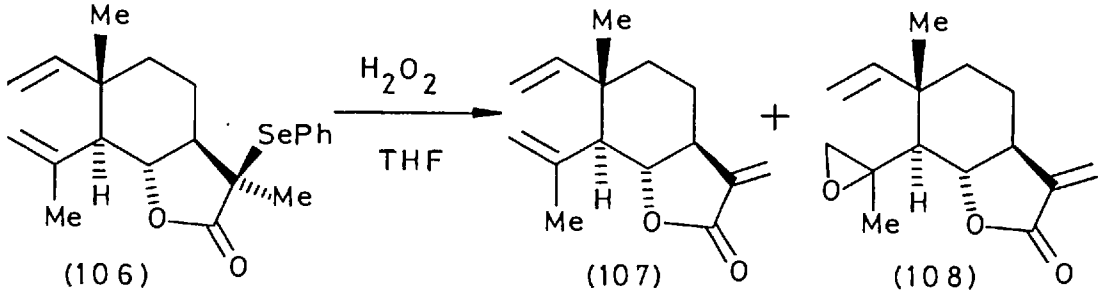
The most noteable application of the above techniques to natural product synthesis, is the preparation of analogues (105) of Prostacyclin (PGI_2) from the prostaglandin ($PGF_{2\alpha}$) by Nicolaou [126], whose useful contributions to this field are sustained [127,128].


CO2H
O
HO
OH
(PGI2)
CO2R
HO
HO
OH
(PGF2α) R=H
R = Me
PhSeCl
CH2Cl2
-78°
CO2Me
SePh
O
HO
OH
(i) H2O2/ THF
(ii) LiOH / MeOH
CO2H
O
HO
OH
(105)

B.4. Benzeneseleninic Acid and Anhydride Oxidations.

Benzeneseleninic acid ($PhSeO_2H$) can be prepared from benzeneselenol [129] or selenocyanate [130], and diphenyldiselenide (Ph_2Se_2) [84,131] by a variety of oxidants. Use of the acid alone in synthesis has remained relatively unexplored, although recently Sharpless [132] and Reich [133] have reported its use, by comproportionation with Ph_2Se_2 to generate benzeneselenenic acid (PhSeOH) *in-situ*, and its subsequent reaction with alkenes to afford β-hydroxyselenides. Grieco has used the acid to generate peroxybenzeneseleninic acid (PhSe(O)OOH) *in-situ*, which he has shown effects epoxidations, as detailed below.

Based upon earlier work [134], it was anticipated that the α-methyl-α-phenylseleno-γ-lactone (106) would be smoothly converted to the dehydrosaussurea lactone (107) by treatment with hydrogen peroxide, *via* the selenoxide [135].

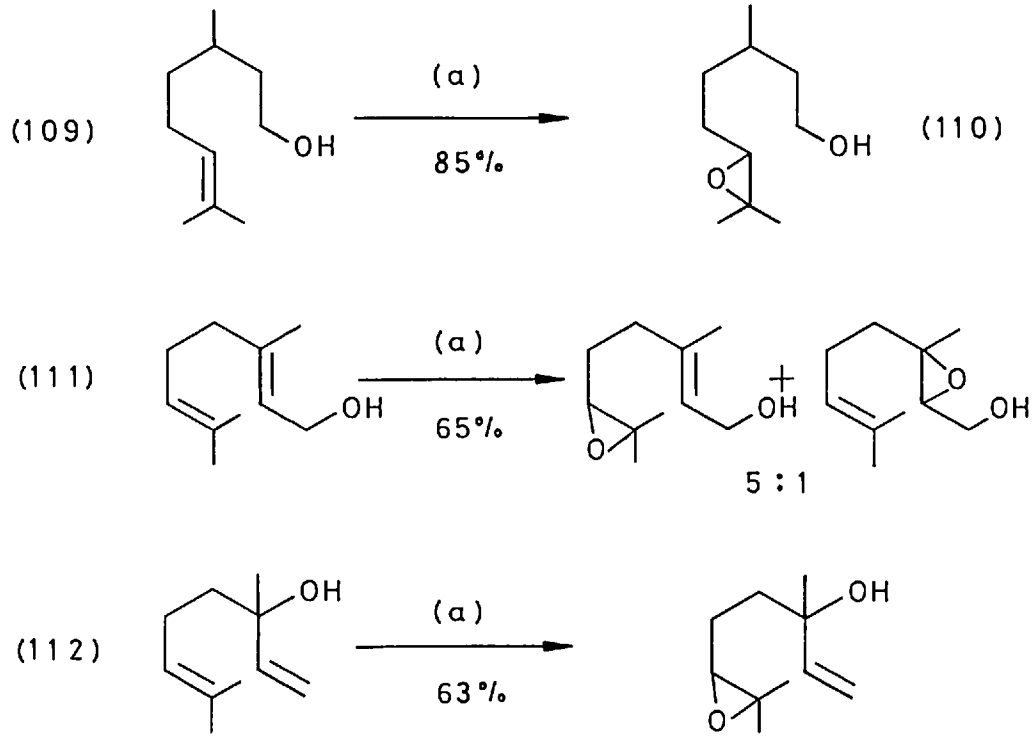


H_2O_2	8 equiv.	18%	30%
	2 equiv.	93%	0%

However, with an excess of H_2O_2 the major product was the monoepoxide (108). Since only 2 equivalents of H_2O_2 gave none of the by-product (108), it was reasoned that excess peroxide reacts further with PhSeOH (generated in the *syn*-elimination step) to give $PhSeO_2H$ and PhSe(O)OOH ; the latter behaving as an efficient epoxidising species, as suspected earlier by Reich [110].

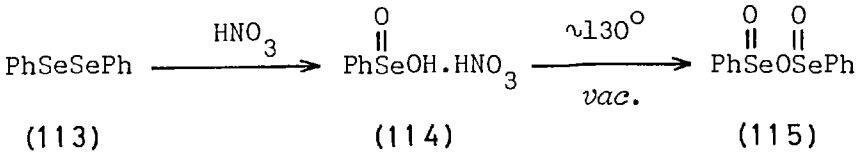
Thus, the treatment of citronellol (109) with the reagent generated from $PhSeO_2H$/50% (aq) H_2O_2/pH 7 phosphate buffer (a), gave the epoxide (110) in good yield. The stereoselectivity of the epoxidation

is equivalent to that obtained from transition metal/hydroperoxide systems [136], and is regioselective for the most substituted (C=C) bond, as exemplified by geraniol (111) and linalool (112).

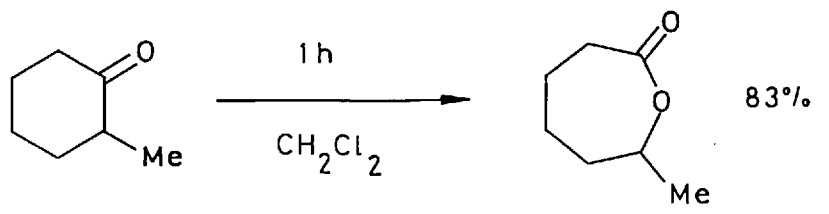


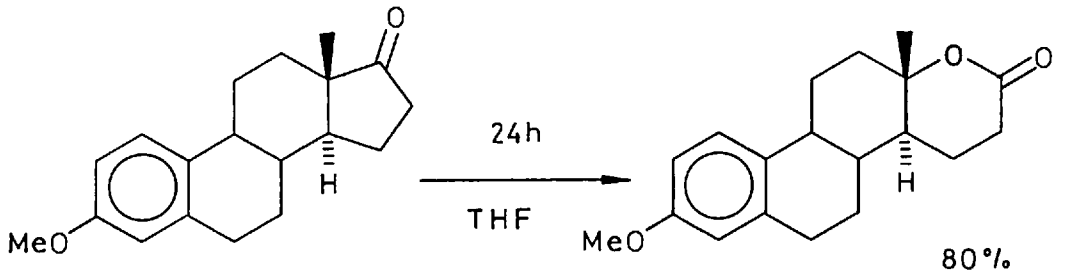
A further example of the application of the $PhSeO_2H/H_2O_2$ system is the conversion of ketones into lactones, analogous to the Baeyer-Villiger reaction, useful in cases where the usual reagents (MCPBA, *anhydrous* CH_3CO_3H) have previously failed [137]. Some examples of this reaction are shown in Scheme 3.

Benzeneseleninic anhydride(115) has been known since 1909 [138] and can be prepared by ozonolysis of Ph_2Se_2 (113) [139]. Preparation on a large scale is conveniently achieved by oxidation of Ph_2Se_2 with conc. nitric acid and subsequent dehydration of the nitrate complex (114) *in-vacuo* at $\sim 130^{\circ}$ for several hours, to yield (115) quantitatively: m.p.= 164°. Other physical properties of the anhydride have been reviewed elsewhere [86,87].

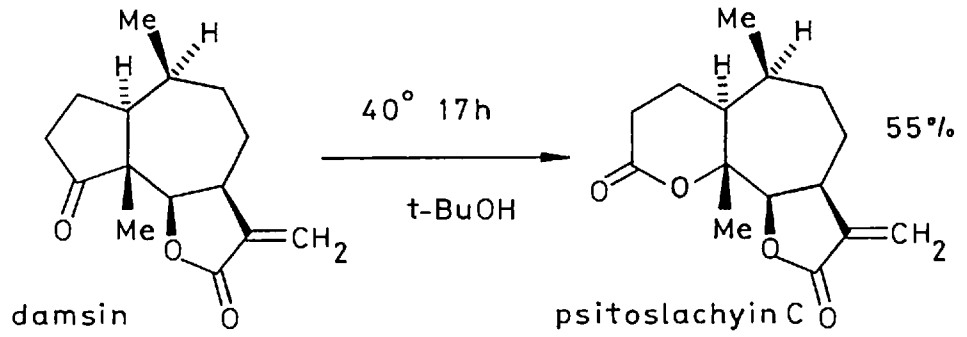


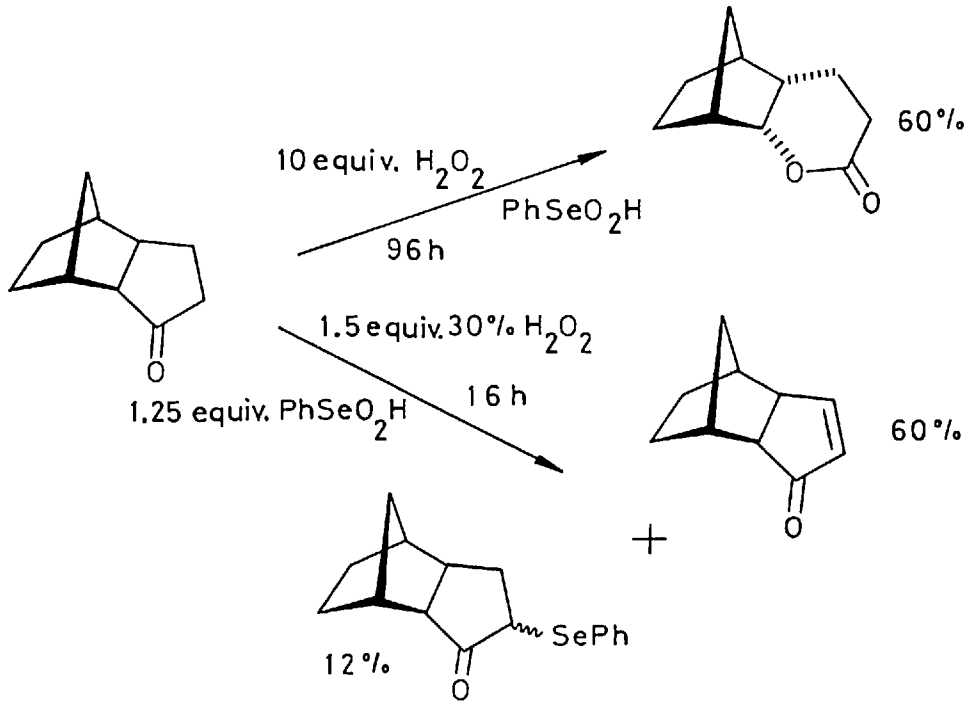
SCHEME 3.



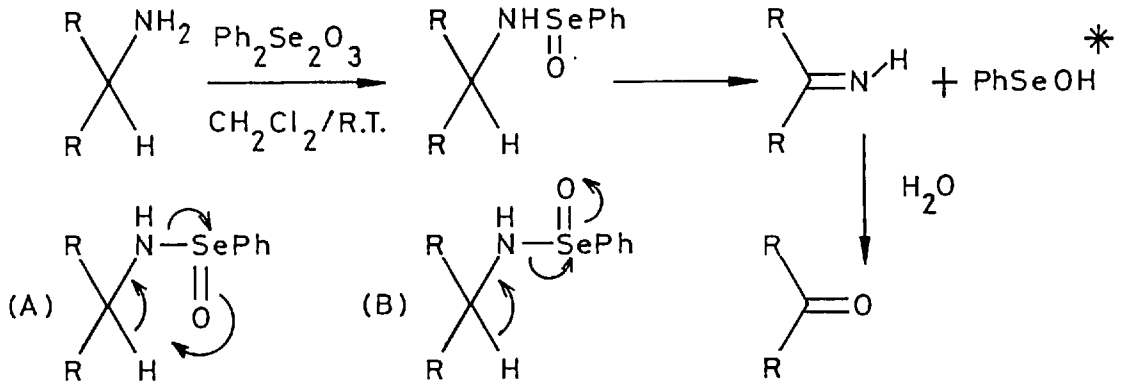


oestrone methyl ether



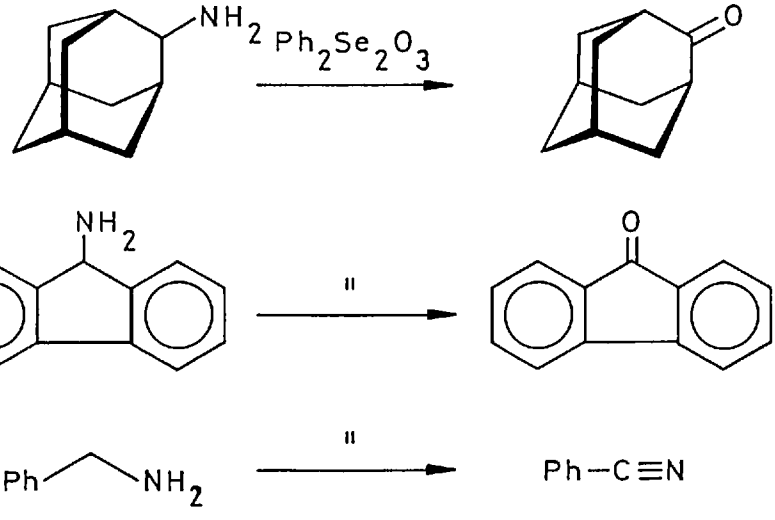


Czarny has shown [140] that $Ph_2Se_2O_3$ reacts with primary amines to give seleninamides which subsequently rearrange (by β-elimination, path (A), or by 1,2-elimination [85], path (B)) to imines, which are susceptible to hydrolysis to ketones upon work-up, or even under the reaction conditions (see ✳).



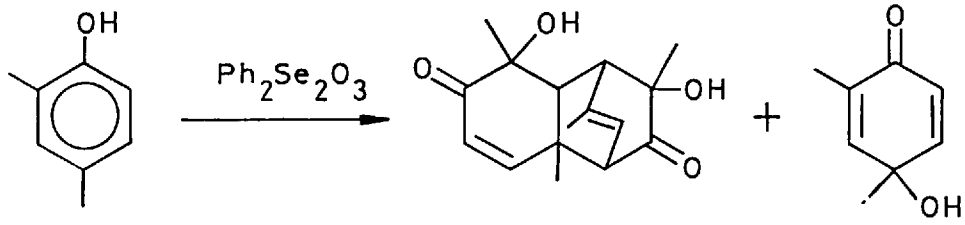
(✳ 3 PhSeOH ⟶ $PhSeO_2H$ + Ph_2Se_2 + H_2O) [110,132,133]

The method has been limited to the preparation of non-enolisable ketones (97-98%) from primary amines. Benzylamine appears to react anomalously to yield benzonitrile (85%).[141]



Rosenfeld [86] discovered that treatment of certain phenols with benzeneseleninic anhydride in CH_2Cl_2 , produced a range of *ortho*-hydroxydienones, *para*-hydroxydienones and *para*-quinones; the relative yields depend upon the substitution pattern of the phenol.

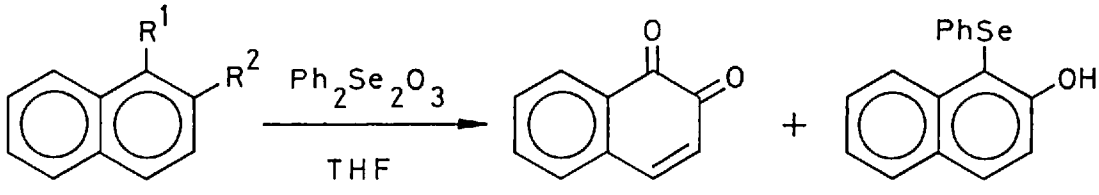
2,4-Dimethylphenol (116) gave an *ortho*-hydroxydienone [52], obtained as the dimer (117) *via* Diels-Alder addition, in comparable yield (40%) to the more common procedures (e.g. $NaIO_4$ [142]), and a trace (15%) of the *para*-isomer (118).



(116) (117) (118)

This, and other examples [52], led to an evaluation of the technique to incorporate the C-12a- hydroxyl group into Tetracycline ring-A model compounds, as discussed earlier in this review.

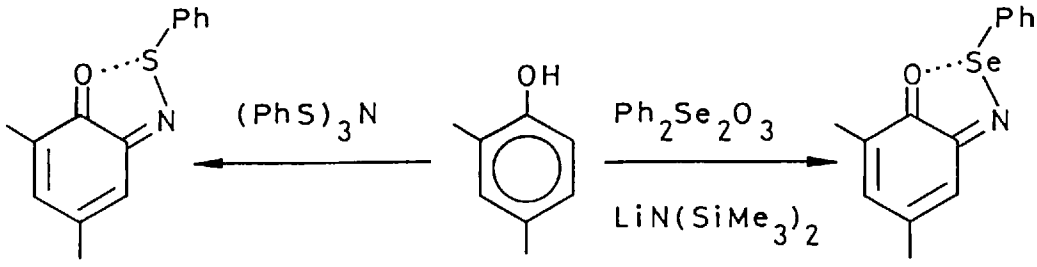
The treatment of phenols unblocked at a potential *ortho*-hydroxylation site with $Ph_2Se_2O_3$, generally results in the formation of *ortho*-quinones [143] and phenylselenenylated by-products. The reaction is slow at R.T. , yet at 50° it is rapid and favours the production of the *ortho*-quinone at the expense of the PhSe-derivative, as in the example shown below.



R^1= OH , R^2= H, 62 % R.T., 28 %

R^1= H , R^2= OH, 63 % 50°, 0 %

Following the observation that phenolate anions (from 1 equiv. NaH) exhibited greater *ortho*-selectivity towards hydroxylation by $Ph_2Se_2O_3$ than did the free phenol [52], the effect of generating the anion by a different base, sodium or lithium hexamethyldisilazane (120), was investigated. This surprising reaction led to the production of selenoimines, e.g. (121) [144], analogous to the thioimine (119) prepared from the phenol and tribenzenesulphenamide, as shown below.

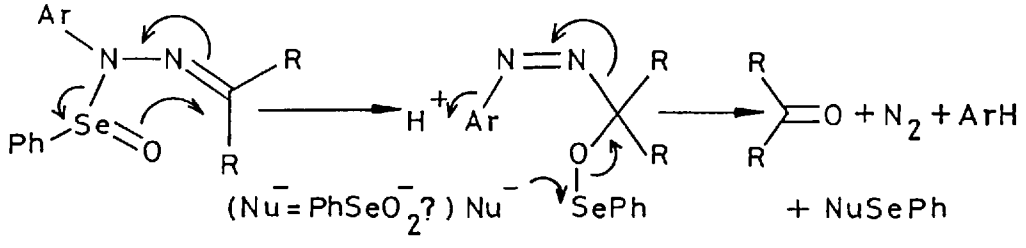


(119) (120) (121)

Reductive acetylation (Zn/Ac_2O) or the action of benzenethiol concludes a mild *ortho*-amination procedure for phenols, which may yet find application in the introduction of the C-4- dimethylamino group during Tetracycline syntheses.

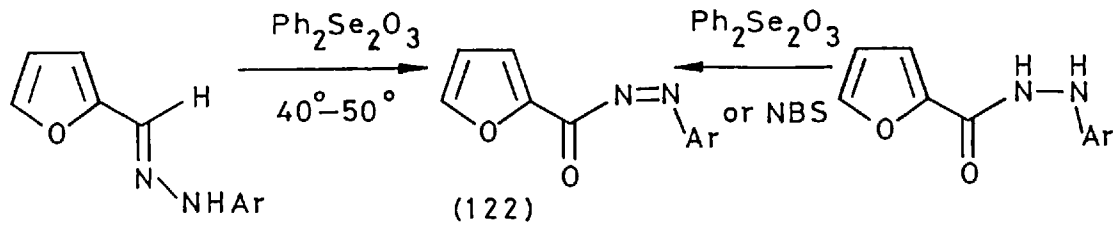
The aminyl base (120) appears unique in this reaction. Attempts to determine the nature of the possible intermediate resulting from (120) and $Ph_2Se_2O_3$ have so far proved fruitless [87]. The possibility of radical intermediates in this reaction have not yet been disregarded; recent studies on the aminyl radical [145] may prove helpful in this connection.

Benzeneseleninic anhydride regenerates ketones from their aryl- and tosyl-hydrazones, oximes and semicarbazones, in THF at 50-60° in good yield [88,146]. Compatible with the evidence that 2,6-dimethyl-phenylhydrazones react *ca.* 10 times slower than the unsubstituted cases, that *N,N*-dimethylhydrazones and *N*-methoxyoximes do not react at all, and that nitrobenzene is a by-product (96%) from *para*-nitrophenylhydrazones, the following mechanism has been proposed.



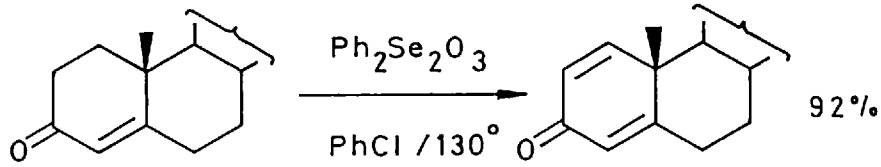
Similarly, aliphatic aldehyde tosylhydrazones and oximes afford the parent aldehyde (68-92%) with $Ph_2Se_2O_3$. However, the corresponding phenyl- or *para*-nitrophenyl-hydrazones give acylazo-derivatives, e.g. (122) [147]. These latter compounds can also be prepared from the acyl-

hydrazide with $Ph_2Se_2O_3$ or with *N*-bromosuccinimide [148].



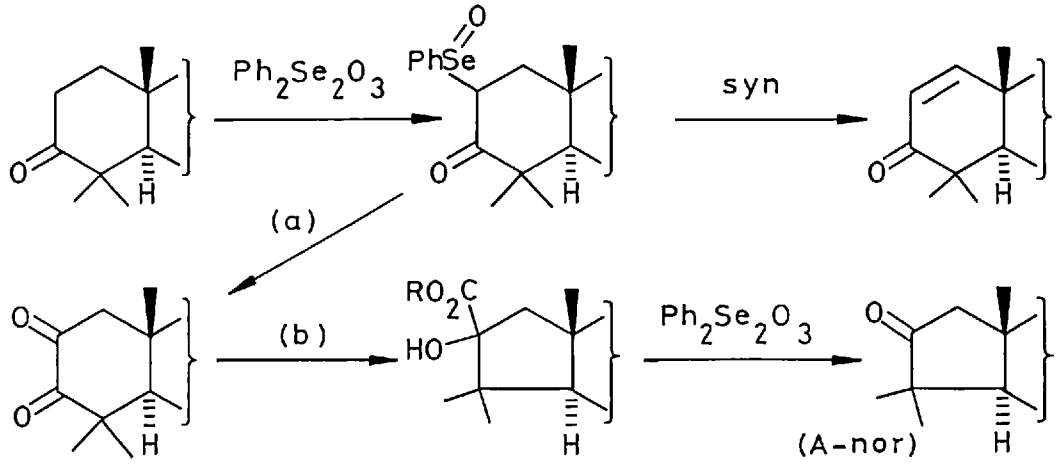
The oxidation of hydroxylamines to nitroso compounds (NB. not nitro) and hydrazines to azo compounds (not azines) can also be effected with $Ph_2Se_2O_3$ [147]; this latter result has been confirmed independently by Back [149], who also was able to generate the powerful reductant, diimide, from hydrazine hydrate and $Ph_2Se_2O_3$ or $PhSeO_2H$.

Finally, benzeneseleninic anhydride in hot chlorobenzene dehydrogenates steroidal ketones and enones, into enones and dienones respectively [150], in improved yields over existing methods [151], e.g. 1-cholestene into cholesta-1,4-diene-3-one (123).

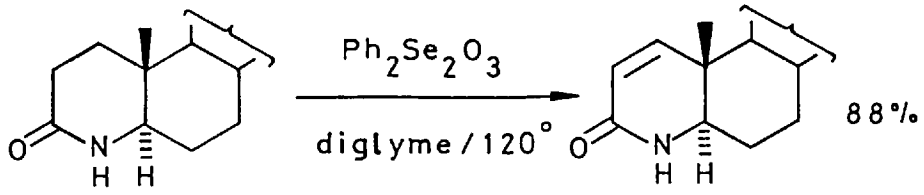


(123)

By-products of this reaction include phenylselenated species and, in some cases, A-*nor*-ketones, probably *via* Pummerer-type (a) and benzilic acid-type (b) rearrangements.



By the application of the above dehydrogenation procedure to 4-azacholestan-3-one (124) [152], Back has prepared the novel 4-azacholest-1-ene-3-one (125) [149].



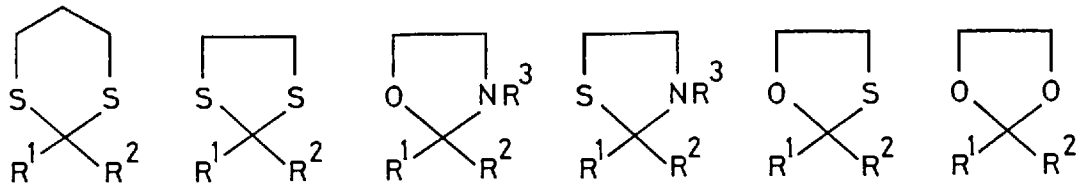
(124) (125)

C. SULPHUR CHEMISTRY.

The reactions of organic sulphur compounds constitute an integral part of modern chemistry [153]. The role of sulphur in heterocyclic chemistry extends from the established reactions of thiophene [154] to the more exotic thio-sugars [155] of current interest. Within this range lies the sulphur heterocycles derived to mask carbonyl group functionality, whose use as protecting groups against adverse reaction conditions and as acyl-anion equivalents, is now well known [156,157] and will be discussed below. In addition, the sulphur analogue of the carbonyl group, the thione, continues to attract attention and some specific examples, together with some reactions of selenocarbonyls, selones, will also be mentioned.

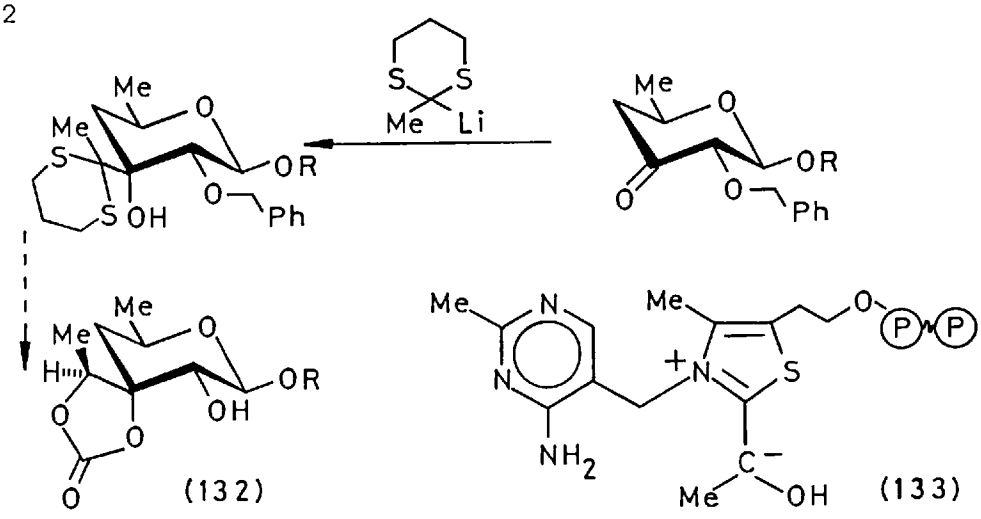
C.1. Sulphur Heterocycles in Organic Synthesis.

The saturated heterocyclic systems: 1,3-dithiane (126) [156,157], 1,3-dithiolane (127) [156,157], 1,3-oxazolidine (128) [158a], 1,3-thiazolidine (129) [158b], 1,3-oxathiolane (130) [159], and 1,3-dioxolane (131) [158c], represent heterocyclic masked forms of their derived carbonyl compounds, prepared by treatment with the appropriate dithiol, diol, or aminothiol/alcohol, under standard conditions. The acyclic equivalents of (126), (127), (130), and (131) are widely known, but confer no special



(126) (127) (128) (129) (130) (131)

advantages. The employment of (126) and (127) in organic synthesis has been extensively reviewed again by Seebach [160], with particular attention to the use of 2-lithio-derivatives of (126) as nucleophilic acylating species, for which Seebach has coined the term "umpolung" to describe this inversion of normal carbonyl group reactivity. An interesting synthesis [161] of the branched monosaccharide aldgaroside B (132) serves to illustrate the value of this technique and, coincidentally, to compare the chemist's approach to (132) with that of the natural nucleophilic acylating species (133), the so-called "active aldehyde" thiamine derivative, known to achieve the two carbon chain elongation *in-vivo*.[162]



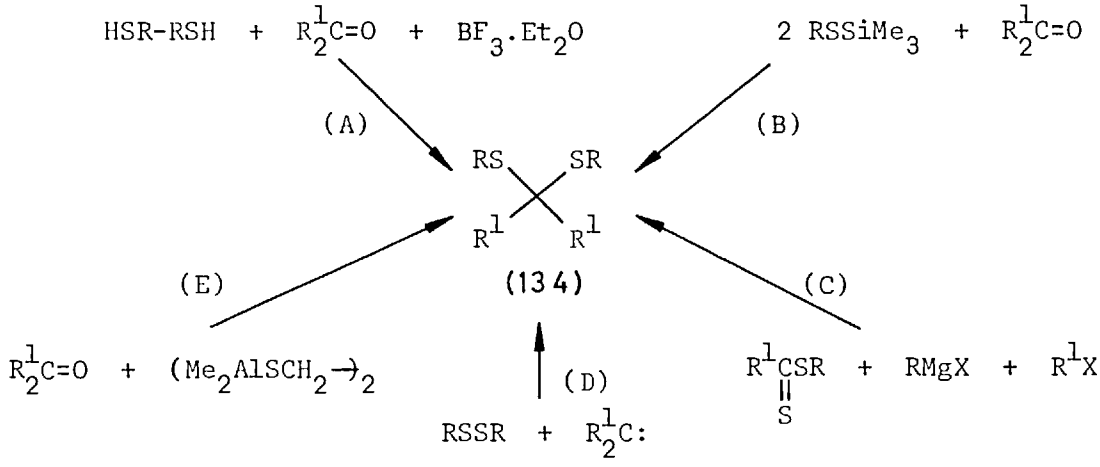
(132) (133)

The use of the 1,3-dithiolane (127) in such reactions is prohibited by the inherent instability of the anion at C-2 (127, R^1=H), due to the facile elimination of ethylene [156] (which does not occur in 126) and thus general decomposition. However, 1,3-dithiolanes continue to be used to protect aldehydes and ketones, even if only on economic grounds [163]! Also, whilst the electrophilic addition of substrates to 2-lithio-derivatives of the unsaturated 2-oxazolines has been widely

exploited by Meyers [164], the corresponding reactions of 1,3-oxazolidines (128, R^3=H, alkyl) are unknown, as are those of (129) and (130), although Fuji *et al.* [165] has reported the use of 2-lithio-1,3-oxathianes. Derivatives (128) to (131) will not be discussed further here, instead attention will be focused upon the chemistry of (126) and (127).

Dithioacetals (134, R-R linked in cyclic derivatives) are prepared classically by the method of Fieser [166], from the carbonyl and a dithiol (thiol for acyclic derivatives) in the presence of a Lewis-acid catalyst , e.g. borontrifluoride etherate (A). Other more recent routes [167] to (134) (Scheme 4.) involve reaction of: carbonyls with alkylthiotrimethylsilane under neutral conditions (B); thiocarbonyls with Grignard reagents (C); the insertion of carbenes into disulphides (D); and esters or lactones with *bis*(dimethylaluminium)1,2-ethane-dithiolate (E) [168].

SCHEME 4.



The equilibrium between the substrate (134) and its hydrolysis products lies strongly towards the dithioacetal [160], therefore cleavage is best effected by the irreversible removal of the thiol products, by evaporation of volatile thiols, such as MeSH, by complex-ation with metal ions, or by transacetalisation [169].

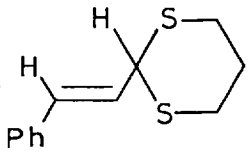
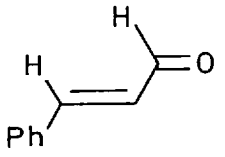
The formation of transition metal thiolates (e.g. of Hg, Ag, Cd, etc.) can lead to acidic reaction conditions [170], therefore the use of excess mercuric chloride to effect dethioacetalisation is usually [171] accompanied by a base (e.g. K_2CO_3). However, excess mercury reagents can be detrimental to aromatic or olefinic compounds, although the use of mercuric oxide/borontrifluoride etherate has been employed successfully with more sensitive substrates.[172]

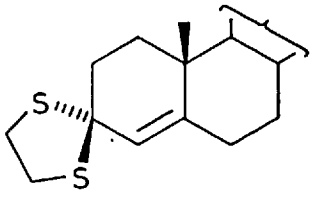
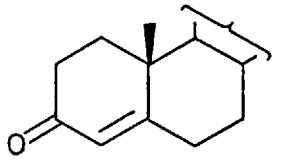
Many reagents for dethioacetalisation rely upon alkylation at sulphur, followed by hydrolysis to regenerate the carbonyl compound. Methyl iodide [173], methylfluorosulphonate ($MeOFSO_2$, Magic Methyl$^{(R)}$) [173,174], and triethyloxoniumtetrafluoroborate [175] have all been employed for this purpose. The related aminating reagents *N*-chloro-*N*-sodio-4-methylbenzenesulphonamide (Chloramine-T $^{(R)}$) [176] and *O*-mesitylenesulphonylhydroxylamine (MSH) [177] also give good yields of carbonyl products, although excess reagent can diminish the yield, which appears to be optimum with stoichiometric amounts.

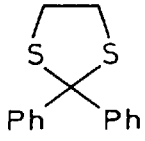
Oxidative techniques [160] involving halogens, *N*-bromo- and *N*-chlorosuccinimide, dibenzoylperoxide, and lead tetraacetate have been indicated for use in this reaction. Whilst the novel reagent thallium-*tris*(trifluoroacetate) [178] also performs dethioacetalisations, cerium-ammonium nitrate [179] remains the one-electron oxidant of general choice, although in a recent example [180] an unexpected competitive oxidation product was obtained from a 1,3-dithiolane/Ce^{4+} reaction.

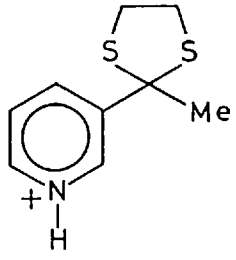
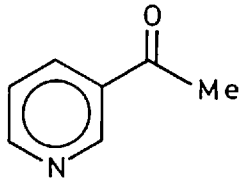
Formally oxidised 1,3-dithianes have been studied in relation to their conformational mobility [181] and stereoselective formation and addition of electrophiles [182]. Also, the lithiation and subsequent synthetic reactions of cyclic [183] and acyclic [184] dithioacetal-*S*-oxides have been studied, together with their mechanism of hydrolysis [160]. The *in-situ* generation and hydrolysis of such *S*-oxides has been reported

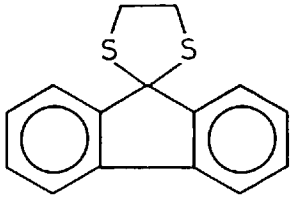
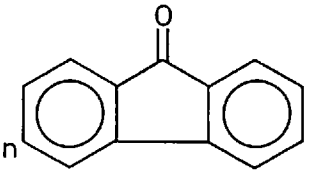
SCHEME 5.

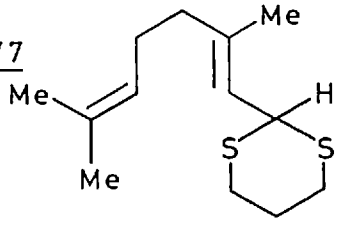
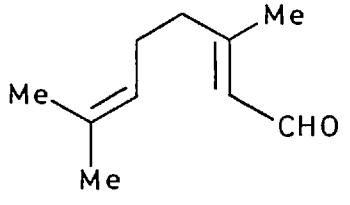
Ref. 172  $HgO/BF_3.Et_2O$, THF/H_2O  86 %

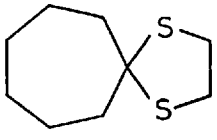
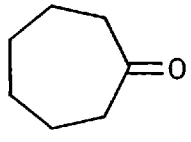
Ref. 173  MeI / MeOH, H_2O / 20h  60 %

Ref. 174  (i) $MeOFSO_2$, (ii) (aq) NaOH $Ph_2C=O$ 90 %

Ref. 175  (i) $Et_3^+O\,BF_4^-$ / 4d, (ii) $CuSO_4$ / NH_3  95 %

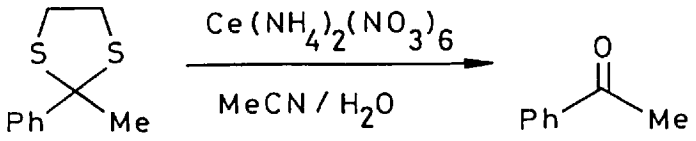
Ref. 176  TosNClNa, MeOH/H_2O/15min  84 %

Ref. 177  MSH / R.T., CH_2Cl_2  74 %

Ref. 178  (i) $Tl(O_2CCF_3)_3$, THF / R.T., (ii) H_2O  80 %

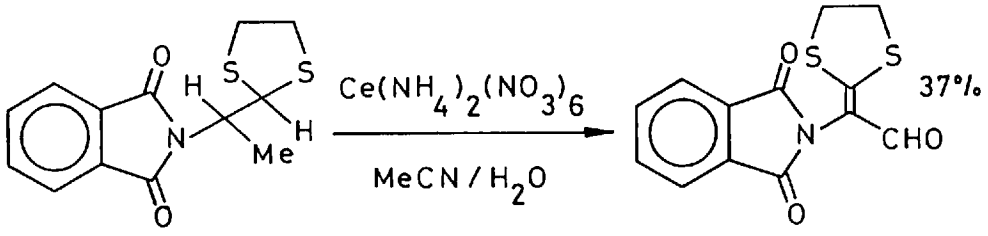
SCHEME 5. contd.

Ref.179



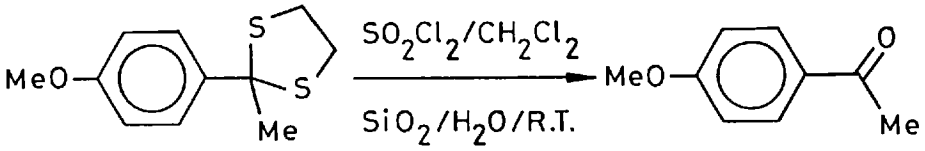
80 %

Ref.180



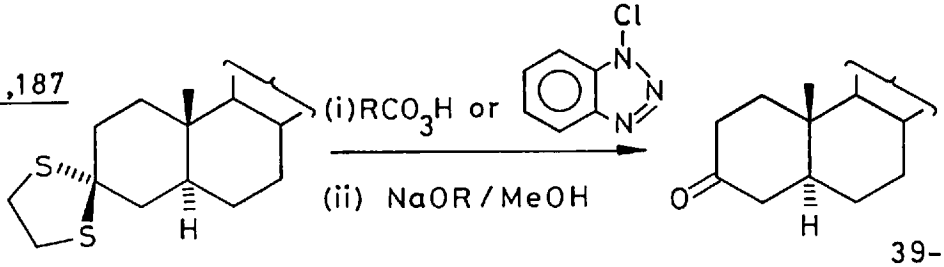
37%

Ref.185



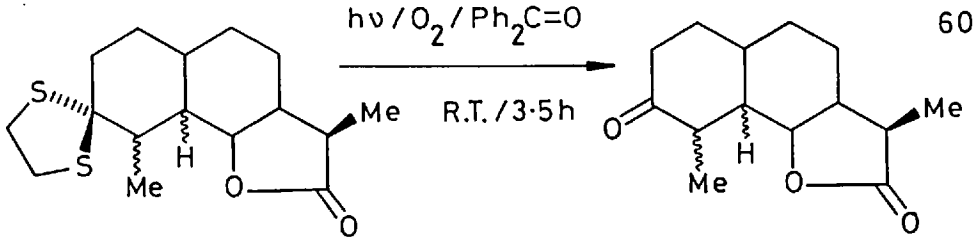
77%

Refs.186,187



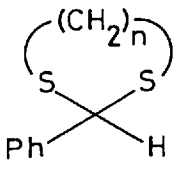
39-50%

Ref.188



60%

Ref.190



Ag-AgI electrode / H_2O

MeCN / 0·03 Acm^{-2} / 1·5 V

PhCHO

n = 3 : 58-77 %

n = 2 : 5 %

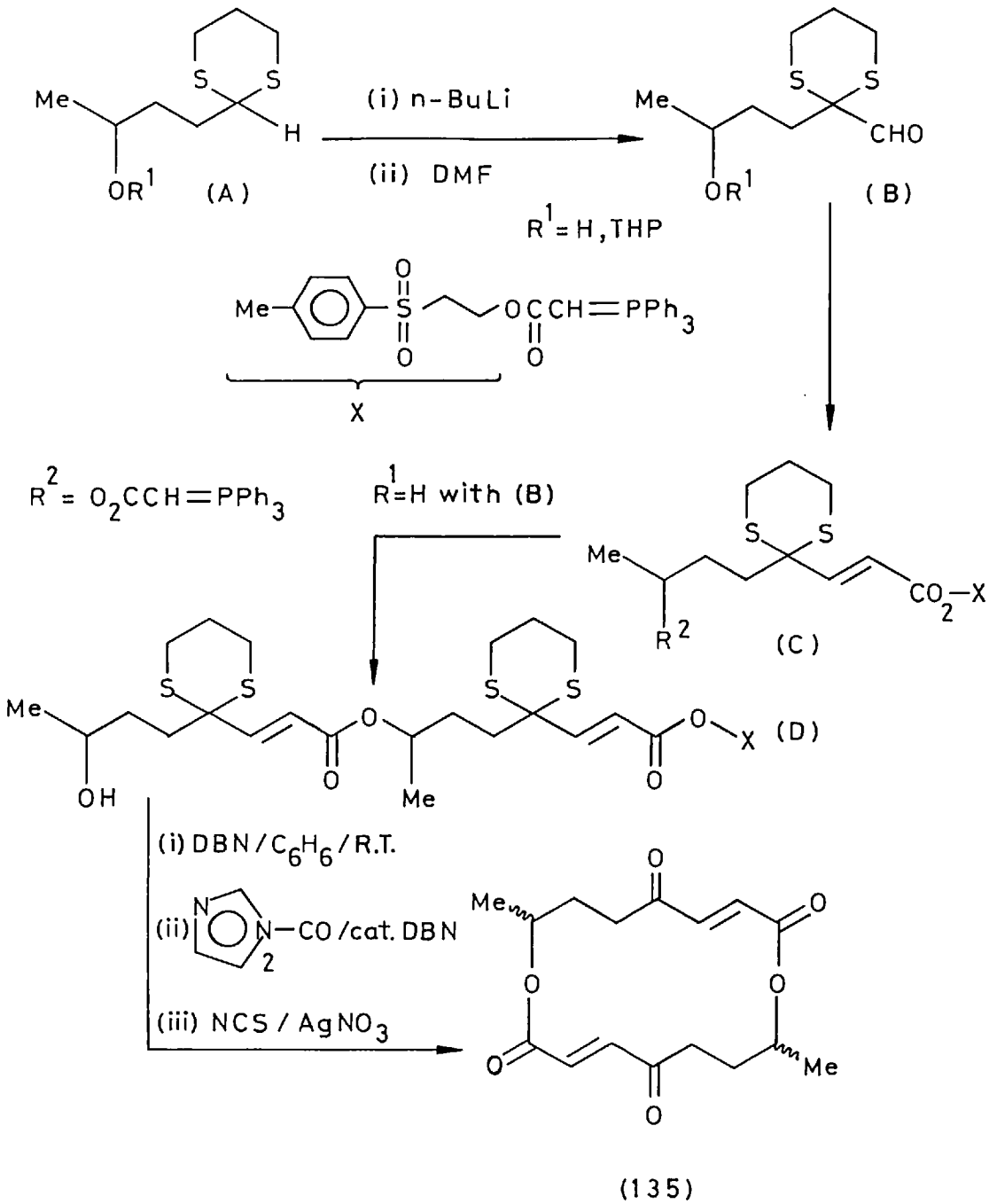
with sulphuryl chloride (SO_2Cl_2) [185], and the method claimed to give no over-oxidised or chlorinated by-products. Oxidation of steroidal 1,3-dithiolanes with monoperphthalic acid or *meta*-chloroperbenzoic acid gives the corresponding *bis*-sulphone [186] or *bis*-sulphoxide [187] respectively. Both are labile to base and regenerate the parent ketone in moderate yield. Direct reaction with 1-chlorobenzotriazole [187] followed by base also proceeds to the ketone *via* the *bis*-sulphoxide.

Photolysis (high pressure Hg lamp) in the presence of a benzophenone photosensitiser in a stream of oxygen, is applicable to the deprotection of several ketones[188] and in particular to a tetrahydrosantonine derivative, which was formerly incompatible with most of the techniques already listed above.

The electrochemical removal of dithioacetal groups was first observed during the anodic oxidation of geminal disulphides, which led to (C-S) bond cleavage and the formation of carbonyl compounds [189]. This method of dethioacetalisation has been developed by Utley on a preparative scale for 1,3-dithianes [190], but shown to be incompatible with the corresponding 1,3-dithiolane derivatives.

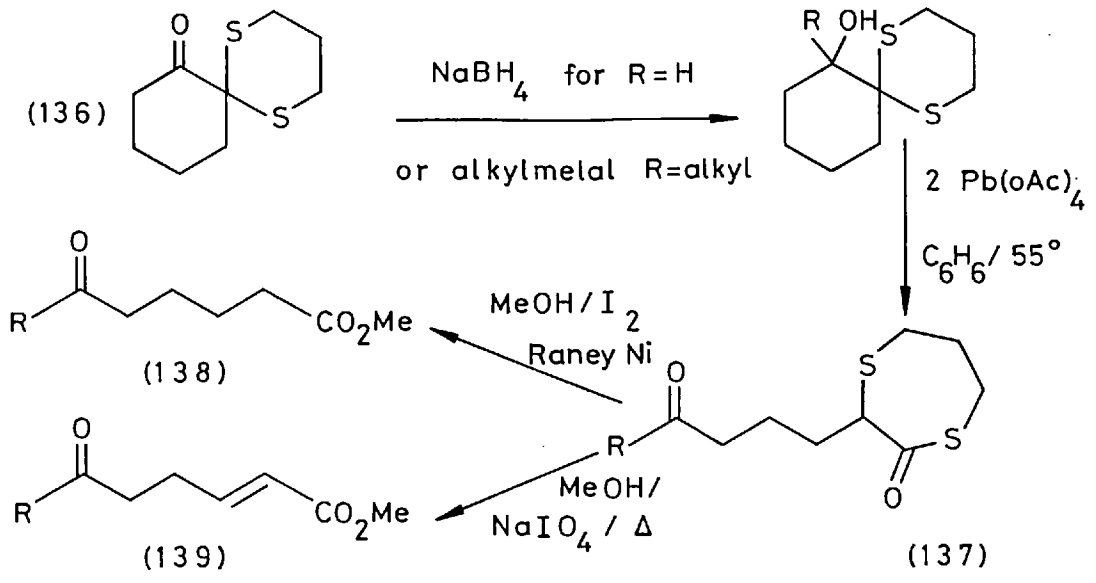
Examples of many of the above reactions are illustrated in Scheme 5.

An outstanding achievement in organic synthesis, which incorporates the useful features of the 1,3-dithiane group, is the synthesis by Raphael *et al.*[191] of the macrocyclic antibiotic (±) Pyrenophorin (135). Although the final deprotection step of the 1,3-dithiane proceeds in only *ca.* 10% yield, the synthesis also demonstrates the utility of the 2(*para*-tolylsulphonyl)ethyl ester, as a selectively removable carboxylic acid protecting group, and the use of diimidazol-1-yl ketone, as a lactonising agent, as partially detailed below.

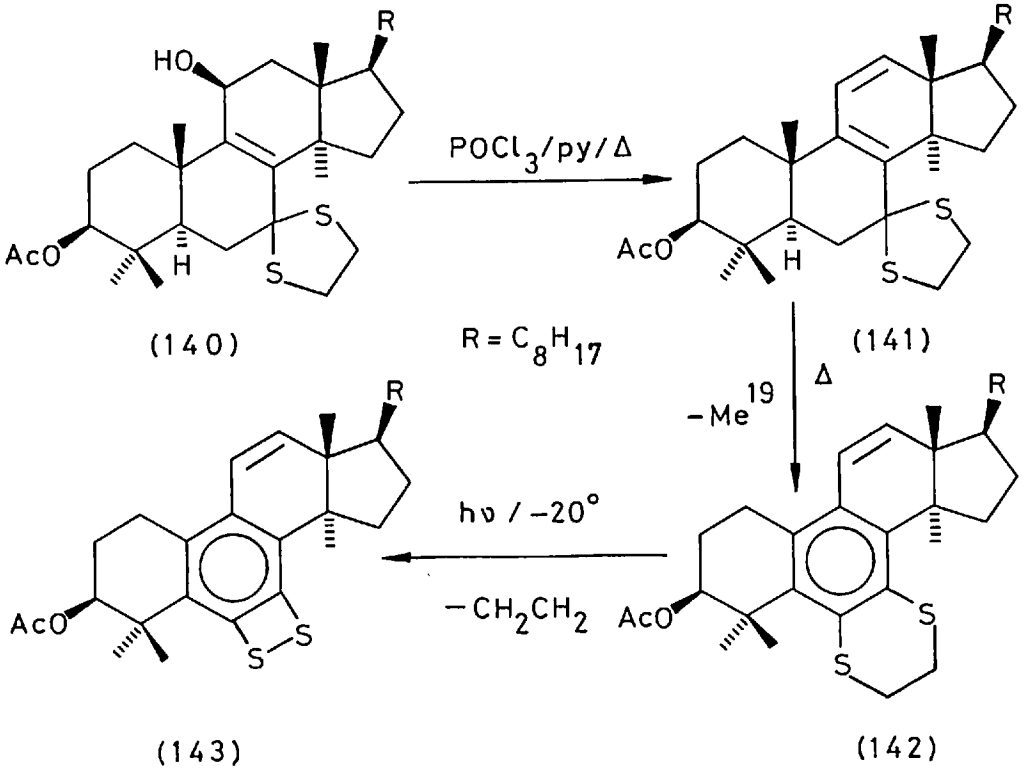


(135)

Finally, some useful rearrangement reactions of 1,3-dithianes and 1,3-dithiolanes should be mentioned. Trost [192] has utilised an oxidative *seco*-rearrangement of α-keto-1,3-dithianes to effect selective functionalisation of cycloalkanones. Thus, (136) is converted by a redox process to the α-thio-thiolester (137), which can be reductively or oxidatively cleaved to the saturated and unsaturated keto-esters (138) and (139) respectively.

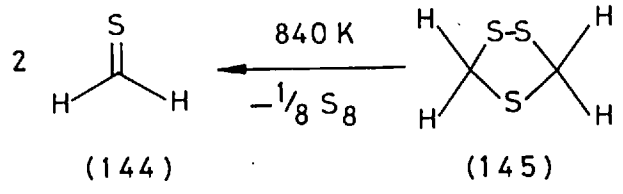


Although the ring expansion of 1,3-dithiolanes to dihydro--1,4-dithiines is known to be mediated by *N*-halourethanes [193], a similar expansion has been shown by Barton *et al.* [194] to occur thermally under certain conditions. Accordingly, the 1,3-dithiolane (140) was dehydrated to (141), which rearranged thermally to the ring-B aromatic steroid (142). Photolysis then eliminated ethylene to generate the dithiete (143), whose unusual stability is ascribed to the steric protection afforded by the host molecule. The structure of (143) was confirmed by X-ray analysis.

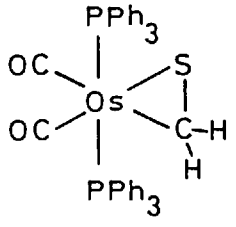


C.2. Thiocarbonyl (and Selenocarbonyl) Compounds.

Whilst much is now known of the chemistry of thioketones (thiones), thioaldehydes remain relatively unknown, and in particular the simpler homologues, thioacetaldehyde [195] and thioformaldehyde (144) are difficult to prepare. Evidence suggests that (144) exists within the interstellar medium [196], although at closer hand it has only been briefly observed in the gas phase [197], by pyrolysis of 1,2,4-trithiolane (145). However, more recently a stable osmium complex of (144) has been prepared (146) [198].

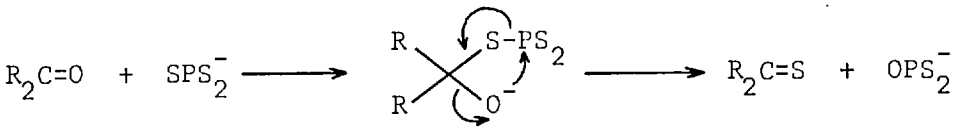


(144) (145)

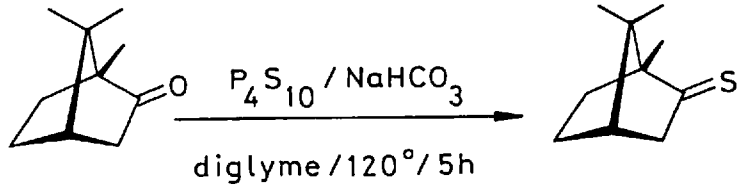


(146)

The most common general procedure for the preparation of thiones, is to react the corresponding ketone with tetraphosphorus decasulphide (P_4S_{10}) [199] in non-polar or polar solvents, the latter being enhanced by the addition of one equivalent of sodium sulphide or sodium hydrogen carbonate [200]. The active species by this method is believed to be SPS_2^-, as shown in the example below.



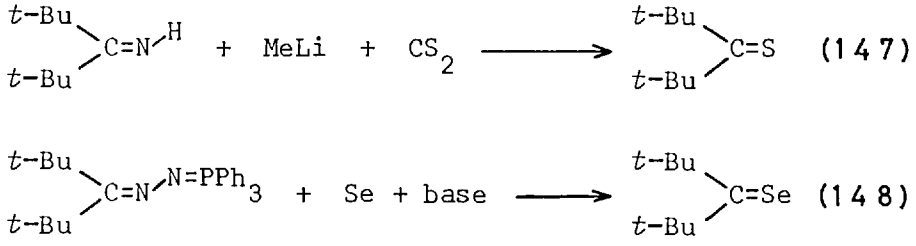
e.g.



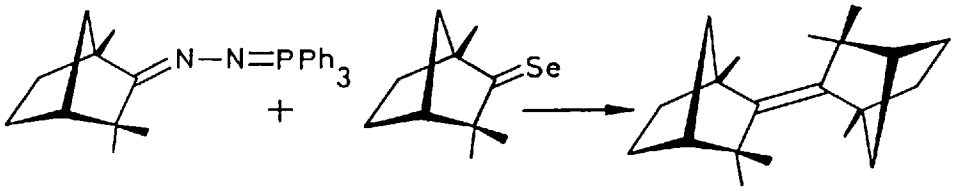
70%

The treatment of ketones with hydrogen sulphide/hydrogen chloride, silicon sulphide, boron sulphide, and *bis*(diethylaluminium) sulphide also result in conversion to the corresponding thione [201].

The sterically hindered di-*tert*-butylthione (147) was prepared by Barton *et al.*[202] by the treatment of pivalone-imine with methyl-lithium and carbon disulphide. The analogous selenoketone (selone)(148) was prepared from the phosphoranylidene hydrazone and selenium in the presence of a base.

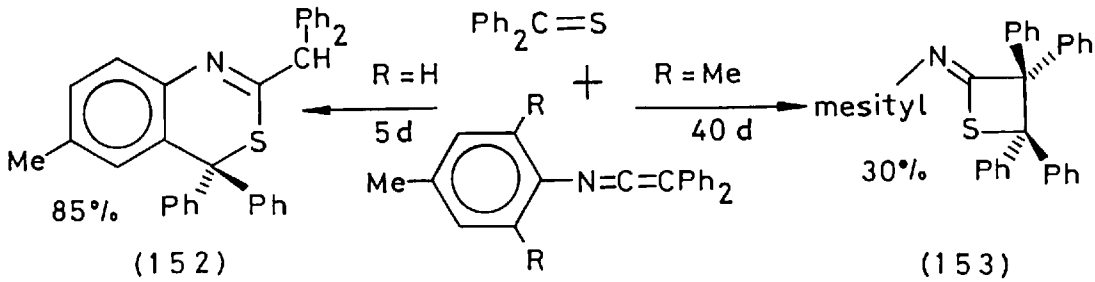


Similarly, the fenchylidene derivative (149) affords the selone (150), although by deliberately reacting (149) and (150) together, Barton *et al.*[203] were able to prepare hexamethyl-2,2'-binorbornylidene (151), presumably *via* loss of N_2 then extrusion of selenium from an episelenide intermediate, which is the most sterically hindered alkene yet prepared.

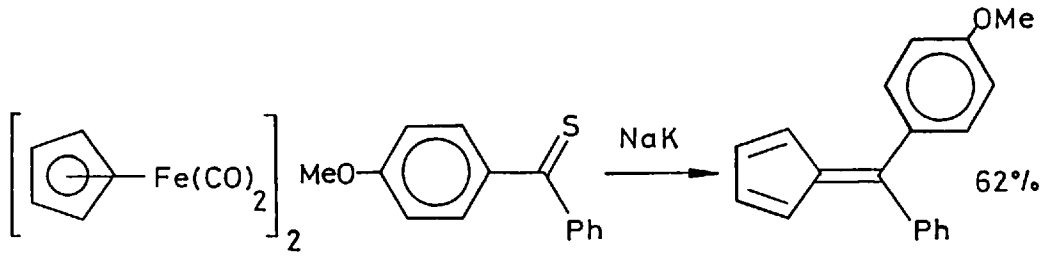


(149) (150) (151)

Other contemporary examples of the use of thiones in synthesis include the reaction of ketenimines with thiobenzophenone, to afford either 4(H)-3,1-benzothiazines (152) or 2-iminothietanes (153) [204], and the preparation of the highly coloured fulvene (154) from a thione with dicarbonylcyclopentadienyliron anion [205].

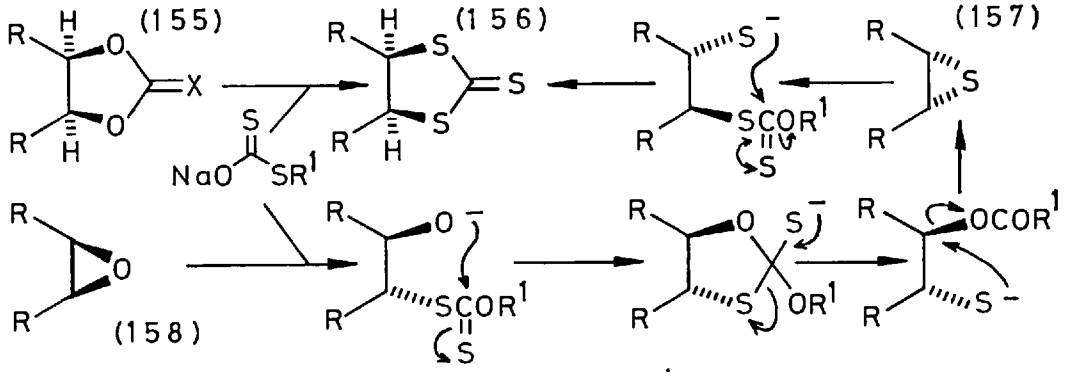


(152) (153)



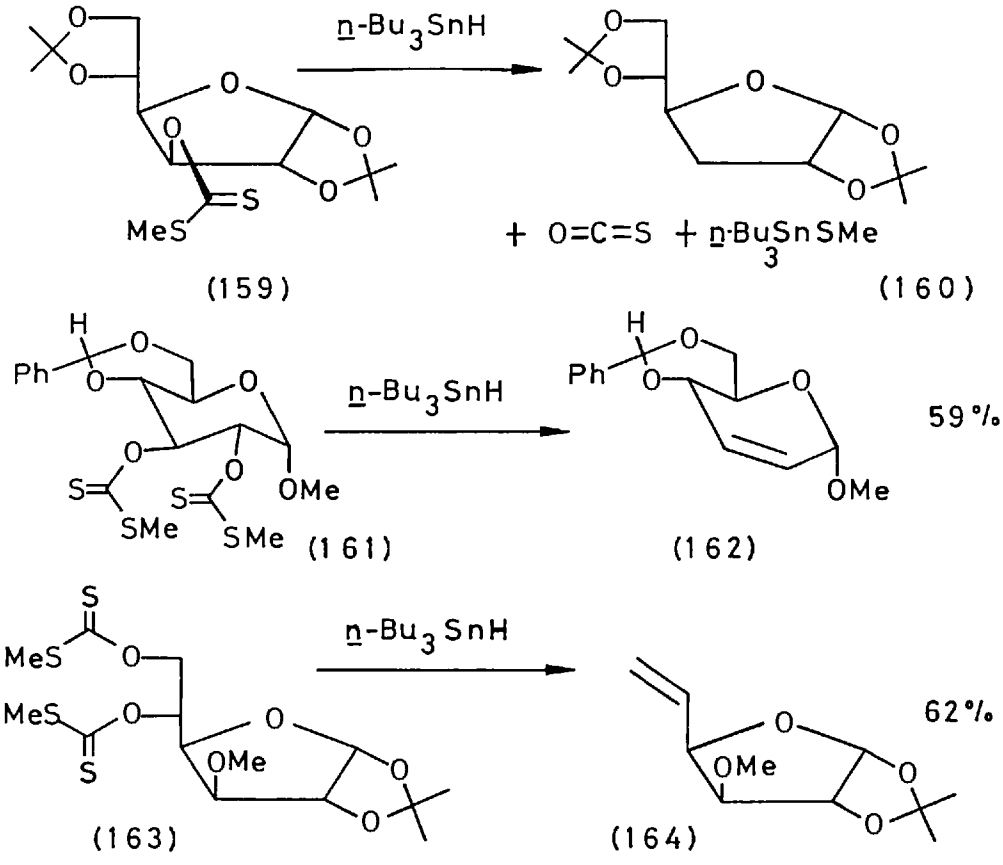
(154)

Cyclic trithiocarbonates (156) are useful derivatives in carbohydrate chemistry, and are prepared from either carbonates (155, X=O), thioncarbonates (155, X=S), or epoxides (158) *via* episulphides (157) with sodium (or potassium) *O*-alkylxanthate [206].

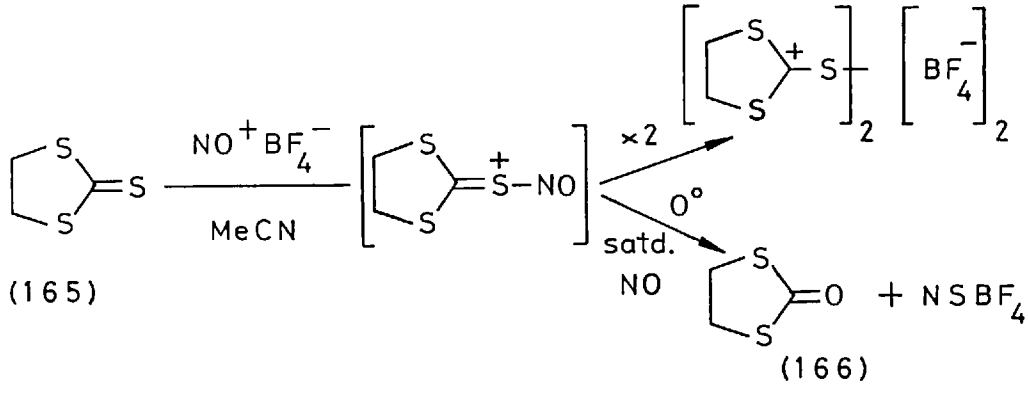


Related compounds of interest are the acyclic *mono*- and *bis*-dithiocarbonates (xanthates). They are prepared from the corresponding alcohol and a base (routinely: sodium hydride, imidazole, or, in these laboratories, tetramethylguanidine) with carbon disulphide and an alkyl halide. Barton has shown [207] that tri-*n*-butylstannane (n-Bu_3SnH) smoothly converts the xanthate derivatives of secondary alcohols to alkanes; in the case of (159) to the corresponding deoxysugar (160). Stick [208] has recently employed the analogous deuteride (n-Bu_3SnD) to follow the stereochemical course of the reduction by ^1H N.M.R. *Bis*-xanthates of vicinal diols react even further under these mild conditions to yield alkenes [209], e.g. (161) and (163) give (162) and (164) respectively.

Early interest in the oxidation of thiocarbonates [210] and thioureas [211] has been extended to several thione systems. Barton *et al.* have reported [212] that whilst the treatment of di-*tert*-butylthione (147)

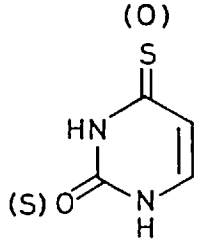


with peroxyacids led to the stable sulphine (C=S=O), under the same conditions the selone (148) expelled elemental selenium and gave the parent ketone. Doyle has reported [213] that during the dimerisation of 1,3-dithiolan-2-thione (165) with nitrosonium salts, excess reagent gives the corresponding ketone (dithiocarbonate) (166).

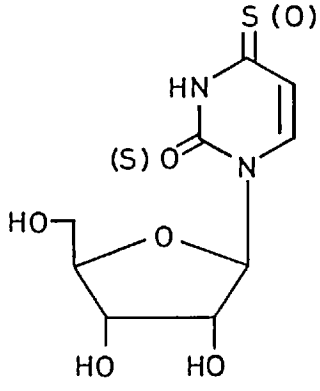


Other reagents which effect the transformation of thiones into ketones (particularly reported for thioureas) include: nitric acid [214], mercuric acetate [215], selenium dioxide [216], potassium permanganate [217], manganese dioxide [218], alkyl nitrites [219], mesitylenenitrile oxide [220],

and iodine/dimethylsulphoxide [221]. The latter reagent (I_2/DMSO) (also conditions which convert 1,3,5-trithianes to aldehydes [222]) has been used to transform thioureas, and their important cyclic analogues— thiopyrimidines (167)— to their *oxo*-derivatives [223]. Since the discovery that 4-thiouridines occur naturally as minor components of the *t*-RNA in *E. coli* [224], their structural or conformational role [225] and their selective oxidation [226] have been investigated. Dimethylsulphoxide smoothly converts thionucleosides (168) to nucleosides [227] without degradation of the sugar moiety. Although the use of strong acid catalysts (e.g. H_2SO_4) seriously limits this method, catalysis with iodine [223] is now preferred.



(167)



(168)

The conversion of thio- and selenophosphoryl compounds to their oxygen analogues has also been studied, for which I_2/DMSO [223], nitric acid or potassium permanganate [228], and dimethyl selenoxide [229] are reported to effect the transformation, the latter proceeding stereospecifically at chiral phosphorus. Other alkyl and arylselenoxides [230] are known to smoothly convert thiones to ketones, and the analogous aryltelluroxides (Ar_2TeO) are similarly being evaluated for this purpose in these laboratories [231].

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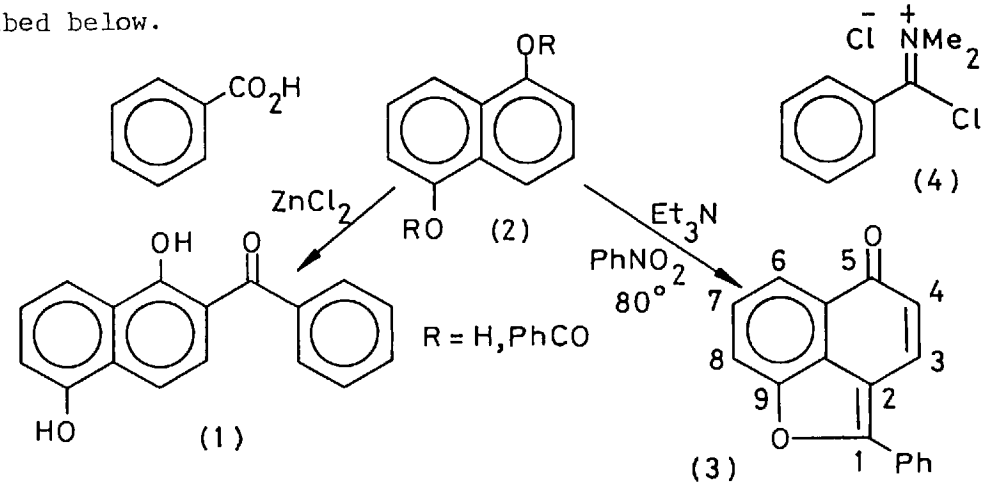
RESULTS and DISCUSSION

1. Preparation of ACD-Tricyclic Intermediates.

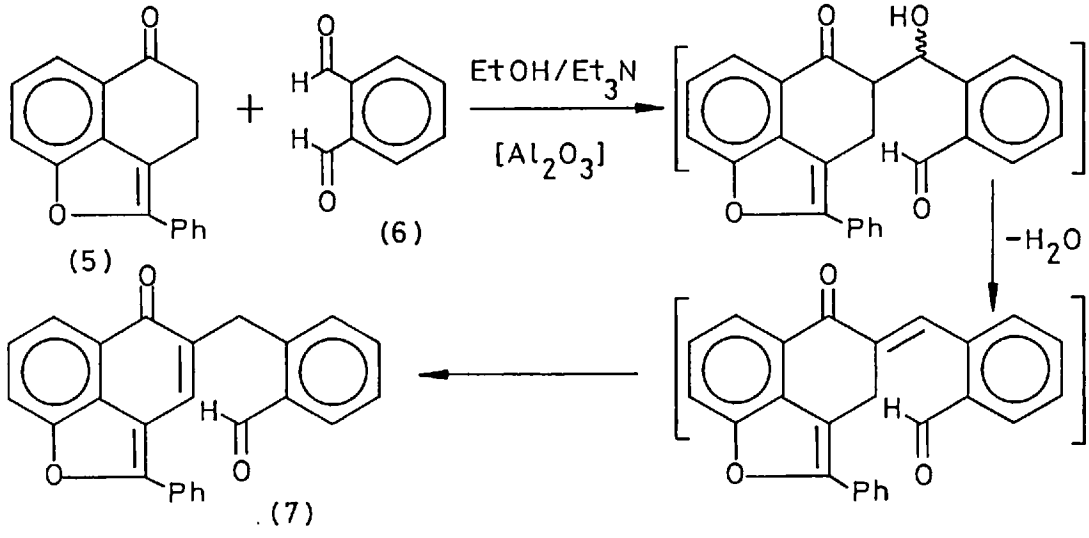
At the outset of the Imperial College approach to tetracycline synthesis, the desired potential ACD-tricyclic intermediate was *2-benzoyl-1,5-dihydroxynaphthalene* (1), prepared by the zinc chloride - catalysed Friedel Crafts acylation of benzoic acid with 1,5-dihydroxynaphthalene (2, R=H). During this reaction small amounts (*ca.* 10%) of the potentially more useful *peri*-naphthofuran (3) were isolated. Until recently, this reaction remained the only preparative route to (3) [1], but an alternative approach, pioneered by Dawes [2] and Cardoso [3], is now preferred [4], as described below.



Treatment of *N,N*-dimethylbenzamide with phosgene gave the extremely hygroscopic Vilsmeier salt (4) [5]. After addition of the diol (2, R=H) to (4) in the molar ratio 1:2.5, the reaction proceeds in nitrobenzene/triethylamine at 80° to afford (3) [6], 43% on a large scale (50 g, 2, R=H). Attempts were made to perform this reaction in other solvents [7], namely 1,4-dioxan and carbon disulphide, as the presence of the high boiling nitrobenzene restricted the yield of (3) by direct crystallisation from the reaction mixture. However, by comparison with earlier attempts [2,4] using benzene, chlorobenzene, toluene, diglyme, dimethylformamide, and pyridine, the yields of (3) were low and usually

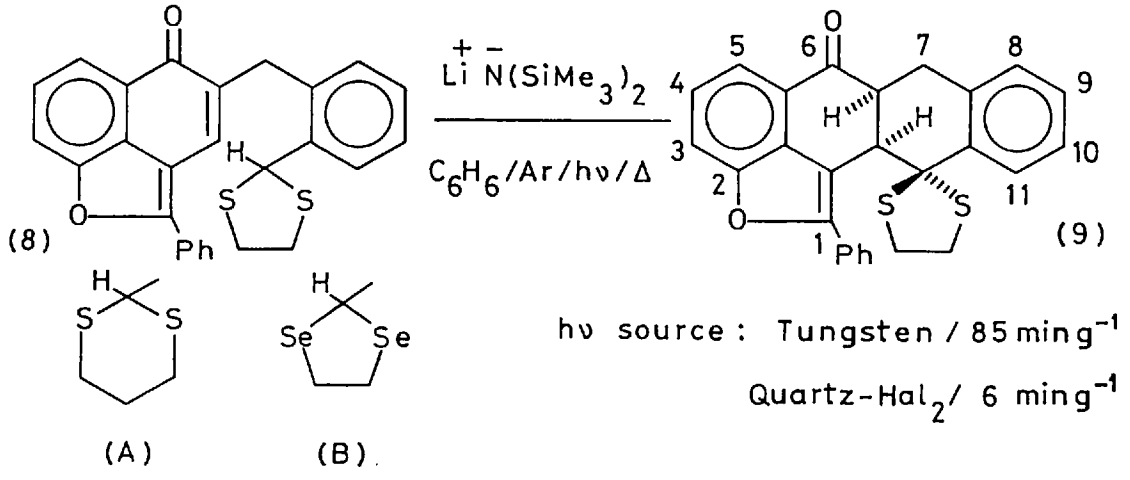
only the by-product of direct *O*-benzoylation (2, R=PhCO) [8] was isolated, thus confirming nitrobenzene as the most suitable solvent for this reaction.

Hydrogenation of (3) to the 3,4-dihydro-*peri*-naphthofuran (5) [1], in the presence of W-2 grade Raney nickel catalyst [9], was routinely performed in toluene to afford (5) in 70% yield. Condensation of (5) with *ortho*-phthaldialdehyde (6) on a small scale resulted in only 62% yield of the tricyclic aldehyde (7) [10]. However, continuous drying of the ethanol solvent, by refluxing over activated alumina in a Soxhlet apparatus, increased the yield to 80%, and the presence of triethylamine ensured rapid isomerisation of the exocyclic enone intermediate to the endocyclic enone product (7).



The precedents for a suitable masked equivalent to the aldehyde function in (7), and their use to effect cyclisation of ring-B, have been described in the review section of this thesis. At the inception of the work discussed here, the 1,3-dithiane derivative (8, A) [2] and the *bis*-selenoacetal (8, B) [3] had already been evaluated in transformations to tetracyclic compounds. The former (8, A) was deemed unsuitable, as it led to no effective enhancement in the yield and because the tetracyclic products were not crystalline and were difficult to handle, which is exceptional since 1,3-dithiane derivatives are renowned for their

crystallinity [11]. The latter (8, B) was both difficult to prepare and unstable in solution and so too had to be abandoned. Since the 1,3-dithiolane derivative had shown promise in the preliminary studies on ring-A substituted intermediates [3], it was accordingly prepared in the case of (8), from the aldehyde (7) and 1,2-ethanedithiol under Fieser's conditions [12]. Whilst the derivative (8) was protected from light during normal handling, its sensitivity to day-light was not as extreme as that reported earlier [13].



2. Photocyclisation to Tetracyclic Products.

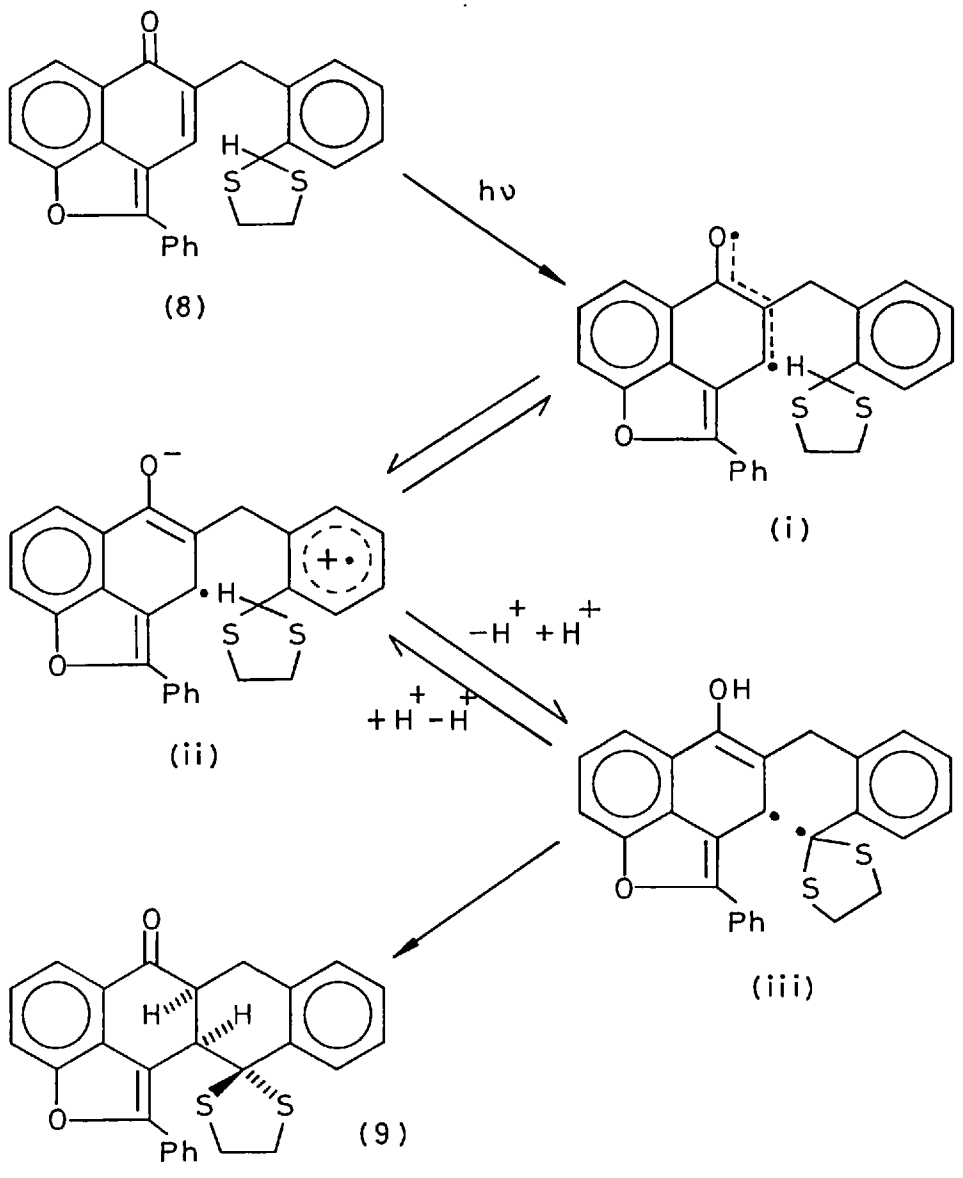
The photocyclisation reaction of type (8) to (9) has been studied in some detail in these laboratories by Dawes [2], Cardoso [3], Clive [13], Bateson [14], and others. Combined with a tungsten filament light source, a number of catalysts e.g. dibenzoylperoxide, benzoic acid, potassium-*tert*-butoxide, and sodium hydride, have been shown to facilitate this transformation. However, the most superior catalyst found to date is the lithium salt of 1,1,1,3,3,3-hexamethyldisilazane. In the case studied, optimum yields of (9) were obtained in the presence of < 0.25 mole - equivalents of the non-nucleophilic base; typically 0.16 equiv. were used. The reactions were performed in deoxygenated benzene at reflux temperature (no reaction occurred below 80°) under dry N_2 or Argon, and followed

routinely by t.l.c. and U.V. spectroscopy. Irradiation with three 250 W tungsten lamps provided 73-80% (9) at a rate of 85 ming^{-1}, whereas a single 650 W tungsten/quartz-halogen lamp gave 75-85% (9) in only 6 ming^{-1}! In this way improvements in both the yield and reaction times were effected over existing methods.

The mechanism for the photocyclisation reaction proposed by Barton [15](see review) for the acid catalysed closure of ring-B is adequate in the case of ACD 1,3-dioxolanes, but does not account for the observed sensitivity of the reaction to traces of oxygen, and the ring-opening and closure of the acetal is incompatible with the observed reactivity of the corresponding sulphur analogues [3]. Ample evidence exists to support the intermediacy of ketyl-radicals [16], the reactions of which are sensitive to oxygen [17]. The intermolecular photochemical addition of such radicals to simple conjugated enones, in the presence of a sensitizer (e.g. benzophenone), has been demonstrated [18] to occur in good yield. These precedents support the conclusion that, in the observed base-catalysed photocyclisation of ACD 1,3-dithiolanes, radical intermediates may be involved. An analogous example of a revised mechanism published by Barton [19], is presented in Scheme 1.

After light-induced excitation of (8) to the 1,4-diradical (i) (the thermal constraint on this reaction casts uncertainty on the state, triplet or singlet, of the diradical) an electron transfer [20] from ring-A would give the radical cation - radical anion intermediate (ii). A base (or acid) catalysed {1,7} proton shift would generate the diradical (iii) which could couple conventionally, and rearrangement of the enol would then lead to the thermodynamically most stable form of the cyclised product (9). The observed ^{1}H-5a,11a coupling constant, J=3-5Hz., supports the assigned *cis*-fused ring junction.

SCHEME 1.

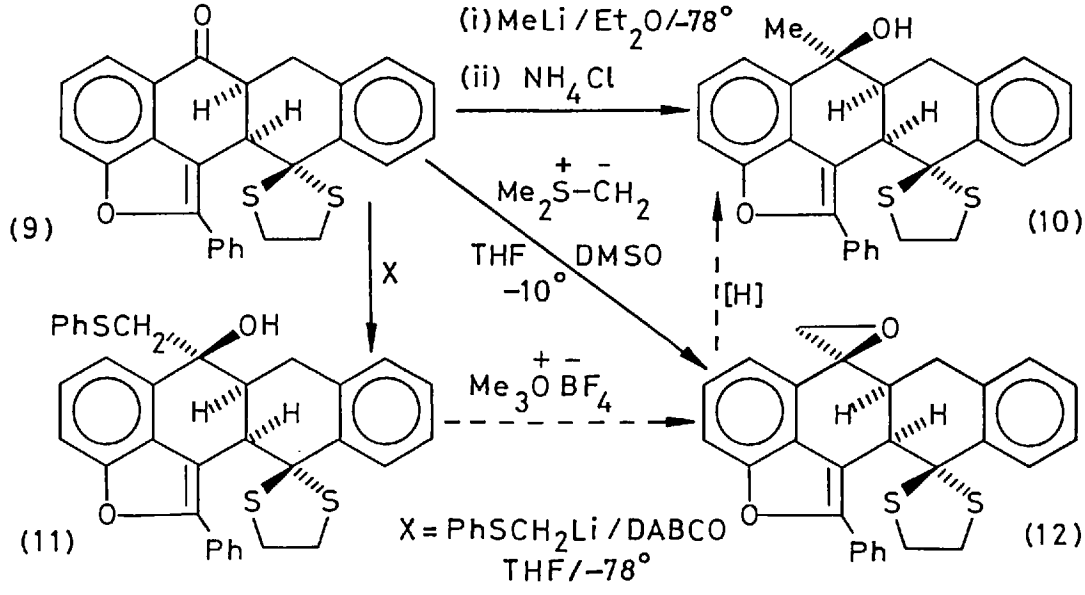


In an endeavour to observe direct evidence for the radical intermediates proposed above, the photocyclisation reaction was studied by electron-spin resonance (E.S.R.) spectroscopy. A solution of the substrate (8) in deoxygenated benzene under N_2 was irradiated directly in the heated cavity (87°) of a Varian E9 E.S.R. instrument, and the field scanned (± 200 G) from a field set of 3 300 G at a microwave frequency of 9.164 GHz. Upon optimisation of the observational parameters, transient signals were recorded in the range g=1.9956 - 2.0281 following the initial addition of $LiN(SiMe_3)_2$, although no significant, persistent, signals could be seen during the course of the brief photolysis (*ca.* 1 min) either in the presence or absence of radical spin-traps. It is concluded

therefore, that the initial interaction of the ACD-tricyclic acetal and the base may generate some form of charge-transfer complex (as suggested by the immediate change in colour from light to dark yellow upon the addition of the base) whose subsequent reaction may be difficult to observe by E.S.R. spectroscopy, due possibly to the short half-life or low concentration (observable limit is $\sim 10^{-7}$M) of the radical intermediates.

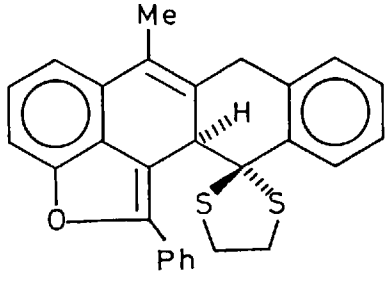
3. Routes to C-6 Carbinol Derivatives.

The reduction of the C-6 ketone of tetracyclic C-12 - masked compounds with sodium borohydride and subsequent acetylation, has been employed to prepare crystalline 6-demethyl derivatives suitable for X-ray analysis [15]. However, the desired functionality at C-6 require the addition of the elements of Me,H to the ketone. The unsuitability of the Grignard reagent, methylmagnesium iodide, for this transformation, had previously been demonstrated for the ring-A substituted tetracyclic 1,3-dithiolane [3] and 1,3-dioxolane [14].The treatment of (9) with standardised [21] 1.8M ethereal methyllithium gave a low yield of the carbinol (10) and much unchanged (9), even with a 10-20 fold excess of MeLi. This limitation is probably due to competitive anion formation (i.e. enolate) by the nucleophilic base, as suggested earlier [15].

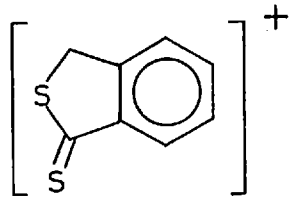


An alternative approach to (10) was attempted by the addition of the phenylthiomethyllithium/DABCO complex [22] (generated *in-situ* from thioanisole and *n*-butyllithium in the presence of 1,4-diazabicyclo - {2.2.2}octane (DABCO)) to the ketone (9) in THF at -78°. The reagent is reported [23] to add smoothly to both sterically hindered or readily enolised ketones and, by the application of a suitable alkylating agent (e.g. Meerwein's reagent [24]) , to afford the corresponding oxirane. In this case, only 13% of the β-hydroxy sulphide (11) was detected (N.M.R.) therefore its conversion to (12) and hence reduction to (10) was not attempted. A second approach to the oxirane (12) was evaluated, by the reaction of dimethylsulphonium methylide [25] (prepared *in-situ* from trimethylsulphonium iodide and the methylsulphinyl carbanion from sodium hydride and dimethylsulphoxide) with (9). However, the product, showing correct *m/e* 454 M^+, and a cyclic ($-CH_2-O-$) group at δ 3.0, was obtained in only 5% yield, so this approach was also discontinued.

Continuance with the methyllithium method afforded yields of 50-60% (10) by multiple treatment (*ca.* 5 times) and work-up procedures applied to the (9)-(10) mixture. The ready dehydration of (10) to (13) was apparent during handling, and exemplified by the lack of a strong molecular ion (456 M^+) in its mass spectrum (which showed *m/e* 438 M^+-H_2O, and 166 attibutable to the fragment ion (14)) and from the changes in its U.V. spectrum (310 nm (ε 15 800) → 344, 354, and 368 nm (ε 14 500, 15 400, and 10 800) with isobestic points at 295 and 326 nm)with dil.acid.



(13)

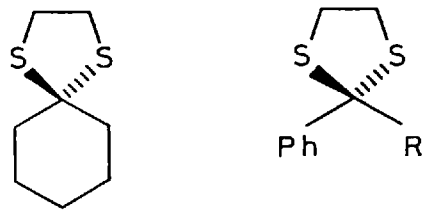


m/e = 166

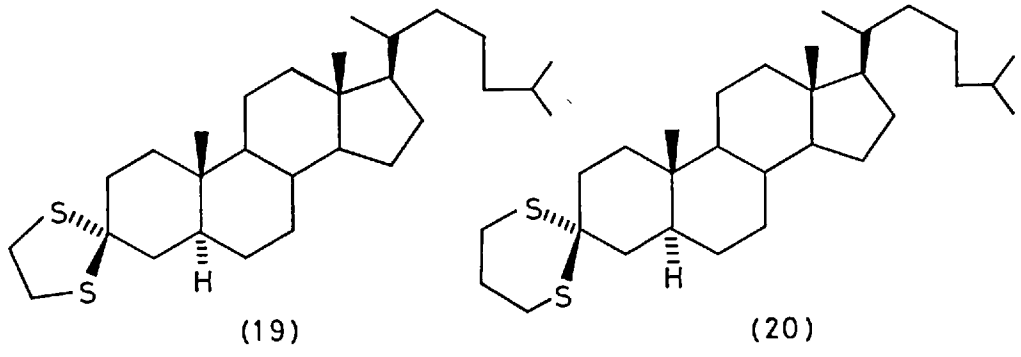
(14)

4. Deprotection of Thioacetals to their Parent Carbonyl Compounds.

To aid the study of the required deprotection reactions of (9) and (10), a number of simple 1,3-dithiolanes (15)-(19) and a 1,3-dithiane (20) were prepared [12,26,27].

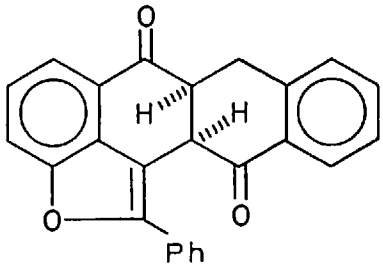


(15) (16) R = H; (17) R = Ph (18)

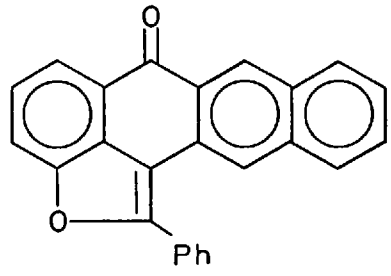


(19) (20)

Preliminary studies revealed that, together with the results of others [3,4], whilst many of the standard and newer methods for the conversion of thioacetals to their parent ketones or aldehydes (see review) were suitable for compounds (15)-(20), they were incompatible with the more sensitive tetracyclic substrates (9) and (10). Alkylation with methyl iodide [28] followed by hydrolytic work-up seemed the most promising of the milder procedures, although long reaction times and low yields of the derived ketone were observed with the models (18) and(19), and accordingly (9) gave none of the diketone (21) [10], even after 2 weeks at reflux temperatures. Whilst the more vigorous (and *DANGEROUS* [29a]) reagent methylfluorosulphonate ($MeOFSO_2$, Magic Methyl (R)) [29b] reacted well with (18) and (19), reaction with (9) gave only the undesired ring-B aromatic product (22) [10] in 37% yield.



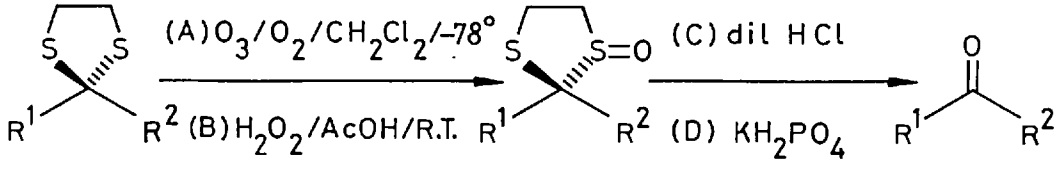
(21)



(22)

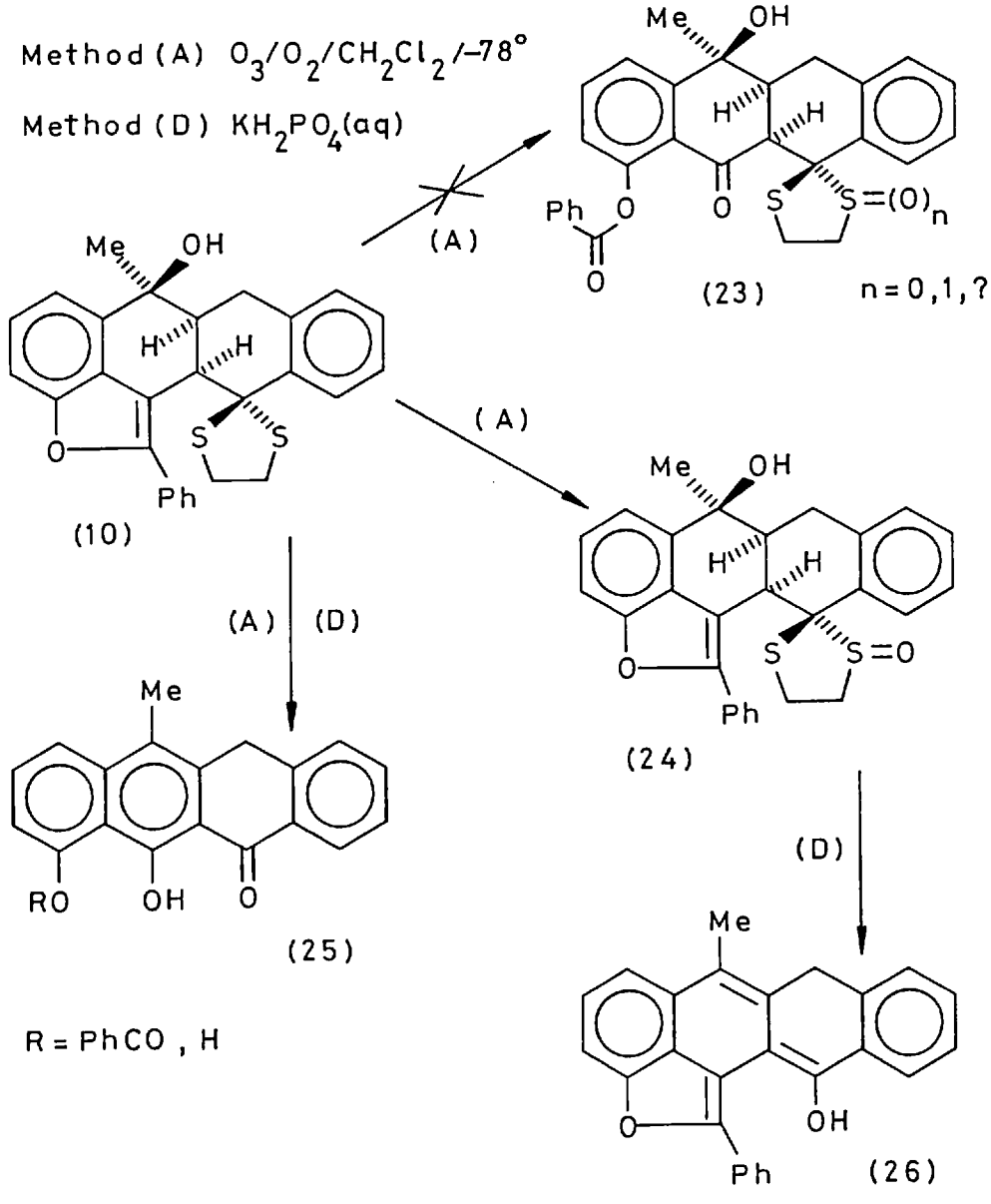
Having exhausted many alkylation and metal-ion catalysed deprotection procedures, attention was turned towards oxidative methods. In contrast to its normal versatility [30], selenium dioxide proved to be an unsuitable oxidant in this case, e.g. (18) and $SeO_2/AcOH/C_6H_6/H_2O$ afforded only 1% α-tetralone, the major products being viscous oils of high molecular weight.

Whilst oxidation of 1,3-dithiolanes to their corresponding *bis*-sulphones [31] and *bis*-sulphoxides [32] then subsequent cleavage with base, has been shown to yield the parent carbonyl compounds, preliminary investigations with (9) and (10) suggested that the attainment of the desired oxidation level was both difficult (probably on steric grounds) and accompanied general oxidative degradation of the substrate. However, selective oxidation to the monosulphoxide alone has been reported [33,34] to enhance the lability of the 1,3-dithiolane group towards acid-catalysed hydrolysis. This was verified by the mono-*S*-oxidation of (15)-(18), (Method(A) [35], Method(B) [33]) and the subsequent dilute aqueous acid hydrolysis (Method(C), and over longer periods Method(D)) to the corresponding parent carbonyl compounds in good yield (53-85%).



Method (A): (15), (16) and (18) Method (B): (17)

Application of the ozonolysis procedure (Method (A) [35]) to the carbinol (10) under anhydrous conditions, gave the desired monosulphoxide (24) in 38% yield, free from the alternative product(s) (23, n=0,1,?). However, mild acid hydrolysis of (24) was disappointing, generating many products of which one probably had the structure (26), since ozonolysis of (10) in the presence of (aq) KH_2PO_4 gave the keto-benzoate (25,R=PHCO) with *m/e* 394 M^+ and whose U.V. spectrum ($\lambda_{max.}$ 300, 384, and 402 (sh) nm (ε 14 500, 16 300, and 15 200)was unchanged by the addition of acid, but with NaOMe/MeOH showed an immediate bathochromic shift of 14 nm,presumably due to the formation of the monoanion of the keto-phenol, and later a new absorption appeared at $\lambda_{max.}$ 342 nm (ε 14 500) with an isobestic point at 353 nm, due to the dianion of the keto-diphenol (25, R=H). Accordingly, this approach to C-12 - keto tetracyclines was abandoned.

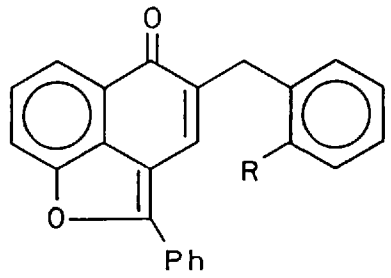


5. Oxazolidine and Thiazolidine Tetracyclic Compounds.

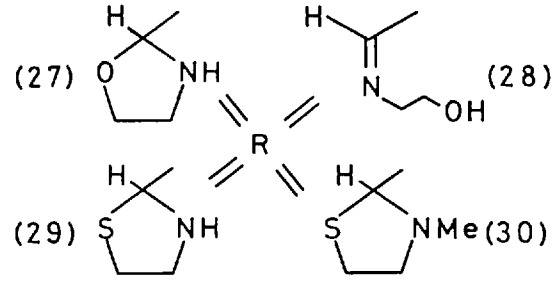
By analogy to the 1,3-dioxolane and 1,3-oxathiolane derivatives of the model tetracyclic systems studied earlier [10,15], the corresponding 1,3-oxazolidine and 1,3-thiazolidine compounds also offered compatability with the photocyclisation step, stability to methyllithium, and the possibility of ready removal under mild conditions from the tetracyclic products, and were thus evaluated.

All attempts at condensation of the aldehyde (7) with 2-aminoethanol failed under normal conditions to give the cyclic oxazolidine (27). It is reported [36a] that unsubstituted cyclic oxazolidines may be unstable and that the acyclic Schiff's base (28) is the predominant form. This was unsuitable for our purposes, so attention was turned to the thiazolidine derivatives [36b].

The treatment of (7) with 2-aminoethanethiol gave 98% yield of the (NH) thiazolidine (29). Similarly the (NMe) thiazolidine (30) was obtained in 73% yield, for which the *N*-methyl-2-aminoethanethiol precursor (34) was prepared as follows. The hydrochloride (31) reacted with aqueous formaldehyde to afford thiazolidine hydrochloride (32) [37], from which the free base could be liberated with (aq) potassium carbonate. Reduction of either (32) or the free base (33) with lithium aluminium hydride in THF resulted in a low yield (*ca.* 7%) of the desired monomethylated aminethiol (34) [38]. By following standard work-up procedures [39,40] or by treatment of the alumina complex with both ethylenediaminetetraacetic acid (EDTA) or Rochelle's salt [41], even with careful handling under N_2 to minimise the facile oxidation of (34) to its disulphide, the yield could not be improved. However, an alternative method, involving the addition of (32) to a blue solution of sodium in liquid ammonia, afforded (34) in 41% yield, free from the alternative reduction product: 2-methylthioethylamine [42]. Literature methods for the preparation of (34) rely upon the reaction of *N*-methylaziridine with hydrogen sulphide [43] (66%). However, the precursor



(7) R = CHO



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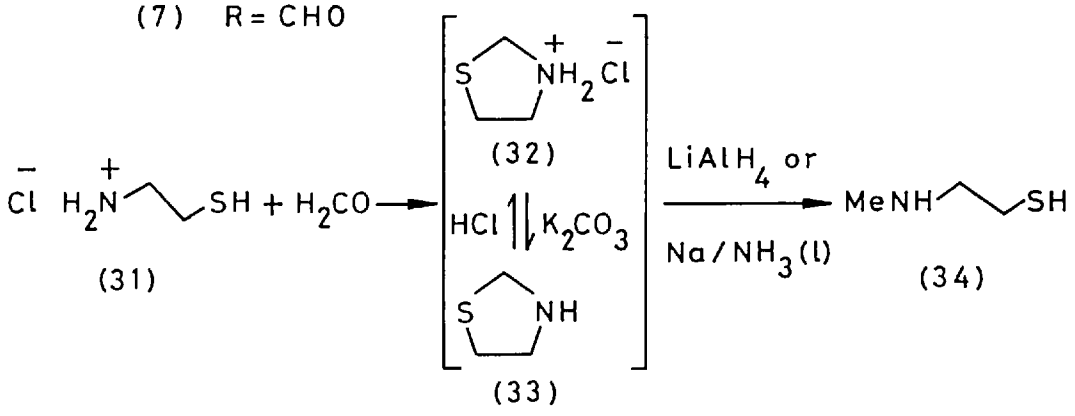


(31) (32) (33) (34)

for this route is 2-chloroethanol which is treated with phosgene (80%) [44], methylamine and subsequent alkaline hydrolysis (72%) [44,45], and conc. sulphuric acid [46] or chlorosulphonic acid [47] (47%), to give the aziridine, and hence to (34) in only 18% overall yield. Thus, the simple Na/NH_3 (l) method constitutes a significant improvement to the preparation of (34).

Photocyclisation of (29) with either the tungsten or quartz/halogen lamps, under the usual conditions, gave 19-20% of the cyclised product (35) as a single epimer. The low yield was probably due to the lability of the (N-H) bond to attack by the catalytic base, resulting in competitive radical anion formation. In contrast, (30) gave a higher yield, 58-65%, of a 1:1 mixture of α-thio-β-aza and α-aza-β-thio epimers (36), analogous to that of the 1,3-oxathiolanes observed before [15], presumably due to the closer equivalence in size of the (NMe) and (S) moieties, unlike in the (NH) case of (35).

A number of attempts at the preparation of the diketone (21) from (35) and (36) are detailed in the experimental section, and some of the more successful results are summarised in Table 1. below. Under neutral or basic (NH_3) conditions, silver nitrate [11] gave little or none

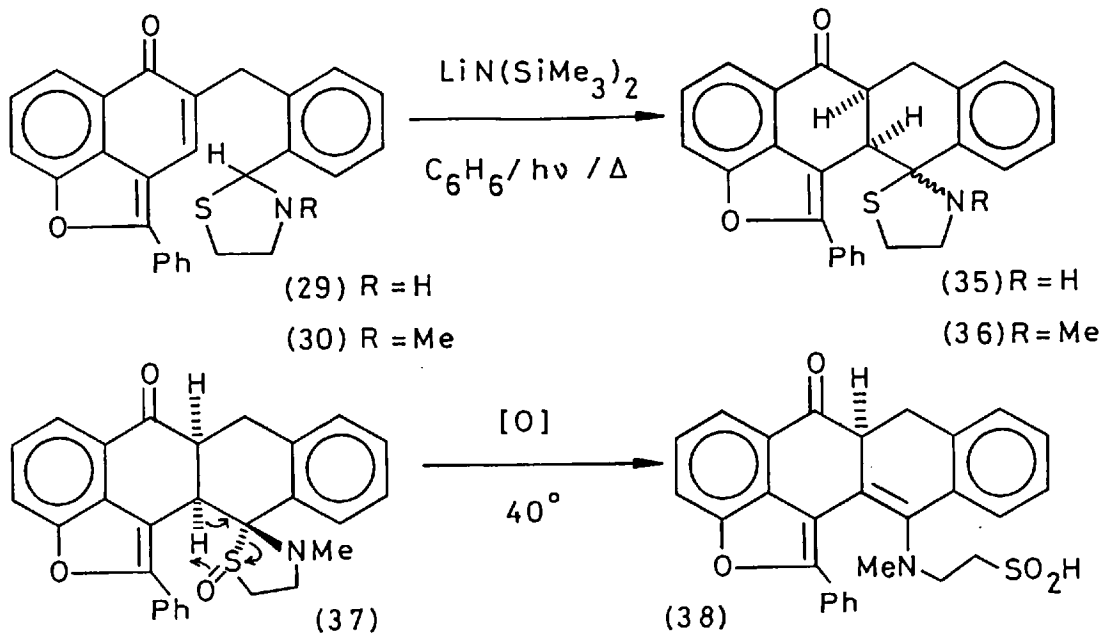


Table 1.

Thiazolidine	Reagents (at R.T.)	Ref.	Yield (21)
(35)	$AgNO_3$, HNO_3, 30 min	11	64%
(36)	$AgNO_3$, HNO_3, 1 day	11	15%
(36)	$HgCl_2$, $CaCO_3$, MeCN, 72h	48	32%
(36)	HgO, $BF_3.Et_2O$, 72h	49	39%
(36)	NBS, (aq) Me_2CO, 72h	11	17%
(36)	$NaIO_4$, (aq) 1,4-dioxan, 12h	50	none
(36)	MCPBA, THF, -78°to 40°, HCl	-	44%

of the diketone (21) from either of the thiazolidines. With the addition of acetic or nitric acids, up to 64% of (21) was produced, however this method would not have been applicable to C-6 carbinol derivatives. The mercuric chloride [48] and mercuric oxide [49] reagents formed polar complexes which liberated up to 39% of (21). Although oxidation with *N*-bromosuccinimide (NBS) [11] and sodium metaperiodate [50] proved unsuccessful, *meta*-chloroperbenzoic acid (MCPBA) afforded the tertiary enamine-sulphinic acid (38), presumably *via* rearrangement [51] of the sulphoxide (37) at the relatively low temperature of 40°. The sulphinic acid residue in (38)

could arise due to excess MCPBA or by disproportionation of the intermediate sulphenic acid, and its structure is supported by strong I.R. absorptions at $\nu_{max.}$ 1 250 and 1 160 cm^{-1}, *m/e* 469 M^+; the low field (NMe) resonance at δ 2.2 , absence of the 12a-H doublet (δ 4-5), and a characteristic absorption at $\nu_{max.}$ 1 660 cm^{-1} is consistent with the assigned enamine moiety. Subsequent hydrolysis of (38) *in-situ* with dil. HCl afforded (21) in 44% yield; estimated in the presence of unconverted (36) by an N.M.R. technique, as detailed in the Appendix. This yield (44%) approaches the probable maximum of 50% by this method, since the α-aza-β-thio epimer of (36) could not be expected to undergo the same *syn*-elimination as in (37), due to configurational constraints.

Further work with the thiazolidine compounds was not pursued and efforts directed again towards the deprotection of the tetracyclic 1,3-dithiolanes, since contemporary evidence [3] suggested that these were the derivatives of choice for the ring-A substituted analogues.

6. Benzenesulphenyl Chloride, Benzeneselenenyl Chloride and Benzeneseleninic Anhydride reactions with 1,3-Dithiolanes.

Benzenesulphenyl chloride (PhSCl) [52] and benzneselenenyl chloride (PhSeCl) [53] are readily prepared from the corresponding disulphide and diselenide with one equivalent of sulphuryl chloride (SO_2Cl_2). It was found that two equiv. of either PhSCl or PhSeCl, after hydrolytic work-up, regenerated ketones and aldehydes from their 1,3-dithiolanes in moderate yield (see Table 2. below). However, the application of these "soft - electrophiles" to the tetracyclic derivatives (9) and (10) was disappointing , as with other examples under study [4]. An alternative reagent found to effect this transformation was the versatile and novel oxidant: benzeneseleninic anhydride ($Ph_2Se_2O_3$ - see review,section B) [53]. The reaction occurred under (apparently) neutral conditions, in THF or CH_2Cl_2, and did not require hydrolytic work-up, and the main by-product, diphenyldiselenide

(Ph_2Se_2) could easily be separated by p.l.c. or by fractional crystallisation and reoxidised back to $Ph_2Se_2O_3$, thus making the reaction economically sound. The yields of regenerated carbonyl compounds with the anhydride were generally good; Table 2. Noteably, the yield of 5α-cholestan-3-one from (19) and (20) by this method, exceeds many reported yields for this transformation[29b,31,32,54].

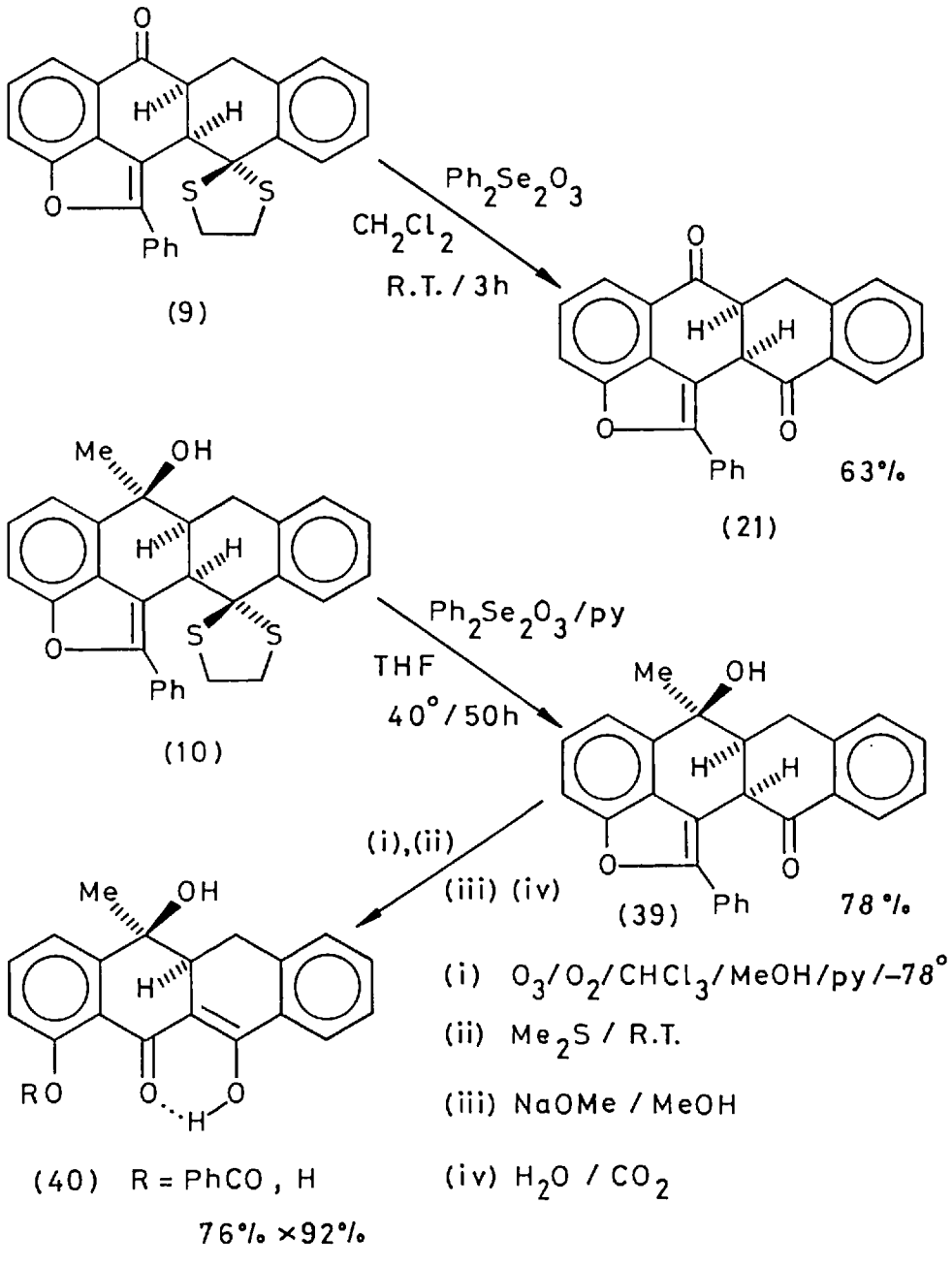
Table 2.

Dithioacetal	Yield of Parent Aldehyde or Ketone with:		
	PhSCl	PhSeCl	$Ph_2Se_2O_3$
(15)	-	-	59%(a)
(16)	54%(b)	38%(b)	78%(b),92%(a)
(17)	-	-	93%(c)
(18)	74%(b)	32%(b)	65%(b),70%(a)
(19)	32%(c)	-	72%(c)
(20)	-	-	73%(c)

(a) estimated by G.L.C.
(b) isolated as the 2,4-dinitrophenylhydrazone derivative
(c) isolated by p.l.c.

In this manner, the tetracyclic keto-dithiolane (9) was converted to the diketone (21) in 63% yield. Previous routes to (21) have involved: (a) cleavage of the 1,3-dioxolane with HCl (10%) [15] or (b) with trityl tetrafluoroborate (65%) [55]; (c) direct photocyclisation of the aldehyde (7) (29%) [13]; (d) the action of alumina on the tetracyclic cyanohydrin (76%) [10]; and (e) the cleavage of the 1,3-oxathiolane with mercuric acetate (70%) [15]. However, based upon the overall yield from the aldehyde (7) these yields reduce to: (a) 6%; (b) 40%; (c) 29%; (d) 22%; and (e) 24% , compared to the favourable overall yield here of 50% of (21), employing $Ph_2Se_2O_3$.

Repetition of an earlier attempt [56] proved that the selective addition of methyllithium to the C-6 ketone of (21) did not occur, and was thus not a feasible route to the 12-keto-6-carbinol (39). However, by a slight modification of the general procedure, $Ph_2Se_2O_3$ reacted smoothly with (10) to give (39) in 78% yield. Ozonolysis of (39) at -78° followed by decomposition of the ozonide with dimethylsulphide, gave the benzoate (40, R=PhCO) in 76% yield. Alkaline solvolysis and careful reacidification with carbon dioxide, then afforded the fully deprotected ring-A unsubstituted Tetracycline (40, R=H).

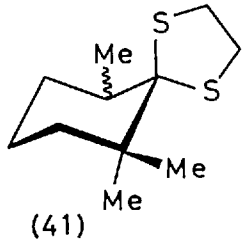


7. Studies of the Benzeneseleninic Anhydride / Thioacetal Reaction.

The general deprotection reaction proceeds smoothly in many solvents, namely: tetrahydrofuran, dichloro-; trichloro-; and tetrachloromethane, benzene, and chlorobenzene, and whilst the reagent is compatible with pyridine, other common nitrogen-containing solvents give less satisfactory results.

The assumption that the initial reaction between benzeneseleninic anhydride ($Ph_2Se_2O_3$) and a 1,3-dithiolane generates a formally oxidised (S=O) intermediate, was discredited by the inertness of *2,2-diphenyl-1,3-dithiolane-1-oxide* , and others, towards the anhydride. Confirmation that $Ph_2Se_2O_3$ does not transfer oxygen to sulphides and selenides to form oxides was obtained by the lack of reaction of diphenylsulphide [57] , diphenylselenide [58] and dibenzylsulphide under a variety of conditions, although the latter did react at 120° over 1.5h to yield benzaldehyde (94%). Correspondingly, diphenylsulphoxide and dibenzylsulphoxide [59] were inert towards $Ph_2Se_2O_3$, suggesting that the formation of benzaldehyde from dibenzylsulphide proceeds *via* an alternative mechanism to the known acid-catalysed rearrangement of the sulphoxide [60].

The sterically hindered 1,3-dithiolanes (41) and (42) reacted well with $Ph_2Se_2O_3$ to afford trimethylcyclohexanone and fenchone in good yield (see Table 3.).



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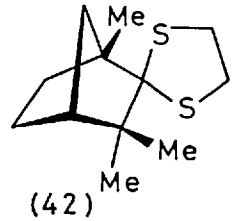
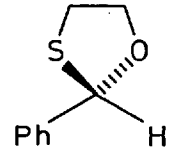
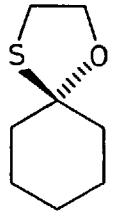


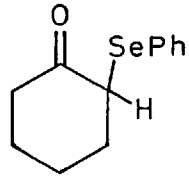
(42)



(43)



(44)



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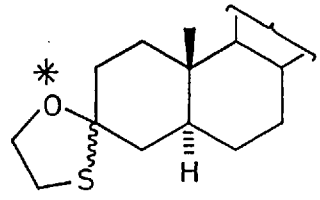

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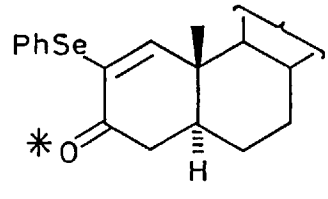


(47)

The anhydride was also found to react with 1,3-oxathiolanes, e.g. (43), (44), and (46) to regenerate the parent carbonyl compounds; see Table 3. However, whilst the reaction with (43) was straightforward and analogous to that of the 1,3-dithiolane (16), the reactions of (44) and (46) were complicated by the formation of phenylselenenylated by-products, namely (45) and (47), together with 1-cholesten-3-one in the case of (46), which lowered the yield of the desired ketone.

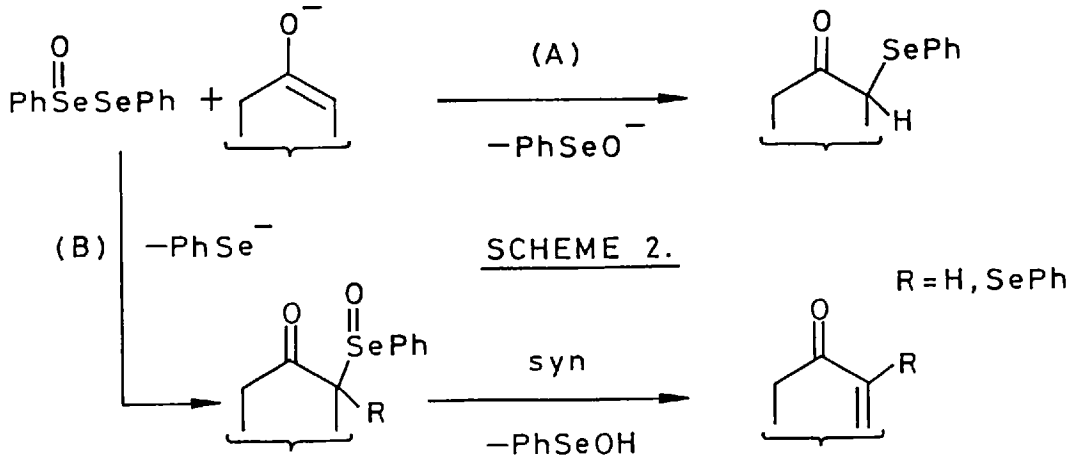
Table 3.

Substrate	Conditions with $Ph_2Se_2O_3$	Carbonyl Product Yield
(41)	THF, 50°, 18h	63%(a)
(42)	THF, 50°, 18h	78%(a)
(43)	THF, R.T., 7.5h	95%(a)
(44)	THF, R.T., 7.5h	55%(a), (45) 40%(b)
(46)	THF, R.T., 23h	20%(b), (47) 36%(b)

(a) estimated by G.L.C.

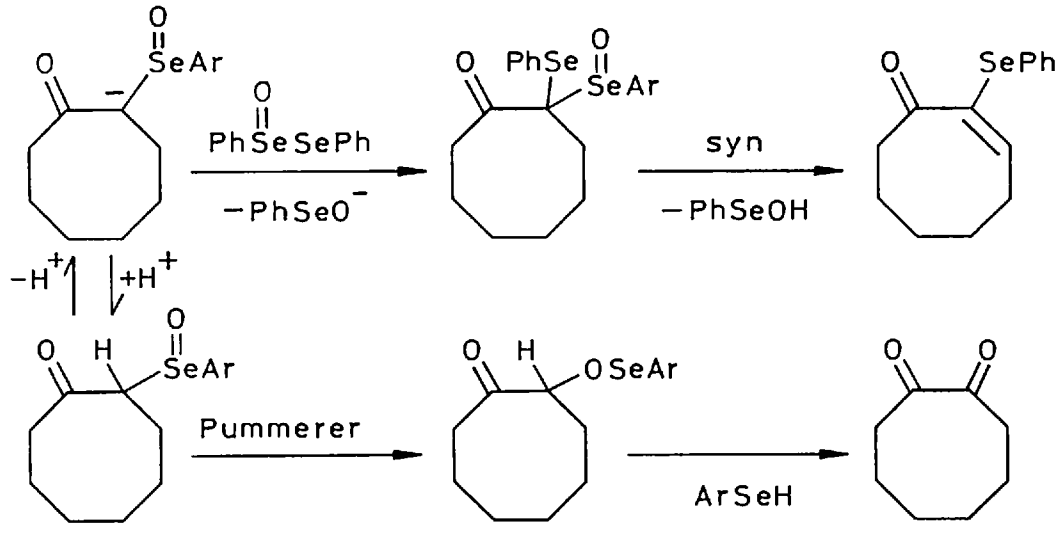
(b) isolated by p.l.c.

The existence of a (C-O) bond at the spiro carbon atom in the 1,3-oxathiolanes, probably facilitates the formation of an intermediate enolate (or enol) and the carbonyl oxygen of the product may derive from the oxathiolane rather than from the benzeneseleninic anhydride (e.g. O* in (46) and (47)). Such an enolate could react with the, as yet, hypothetical [53] intermediate PhSe(O)-SePh,as proposed in Scheme 2, in either of two ways, (A) or (B), where R=H or SePh.



SCHEME 2.

Precedents for this process exist from contemporary examples [53] and from those of Reich [61], who postulates the same scheme to account for the observed product mixture from the 2-arylseleninocyclooctanone (48). The pathway leading to the Pummerer-type α-diketone product (49) will be discussed later.



(48) (49)

Benzeneseleninic anhydride dissolves in water to yield two mole equivalents of benzeneseleninic acid ($PhSeO_2H$) which, having the same combined oxidising capacity {O} as the anhydride, can be reduced to diphenyldiselenide (Ph_2Se_2) by a suitable reductant, e.g. iodide ion. Application of the ubiquitous sodium thiosulphate ($Na_2S_2O_3$)/starch titration technique [53b], with the overall stoichiometry shown in Scheme 3 below, allowed the oxidising capacity of the remaining $Ph_2Se_2O_3$ to be followed.

SCHEME 3.

(i) $Ph_2Se_2O_3 + H_2O \longrightarrow 2\ PhSeO_2H$

(ii) $2\ PhSeO_2H + 6H^+ + 6e^- \longrightarrow Ph_2Se_2 + 4H_2O$

(iii) $2\ I^- \longrightarrow I_2 + 2e^-$

(iv) $I_2 + 2\ S_2O_3^{2-} \longrightarrow 2\ I^- + S_4O_3^{2-}$

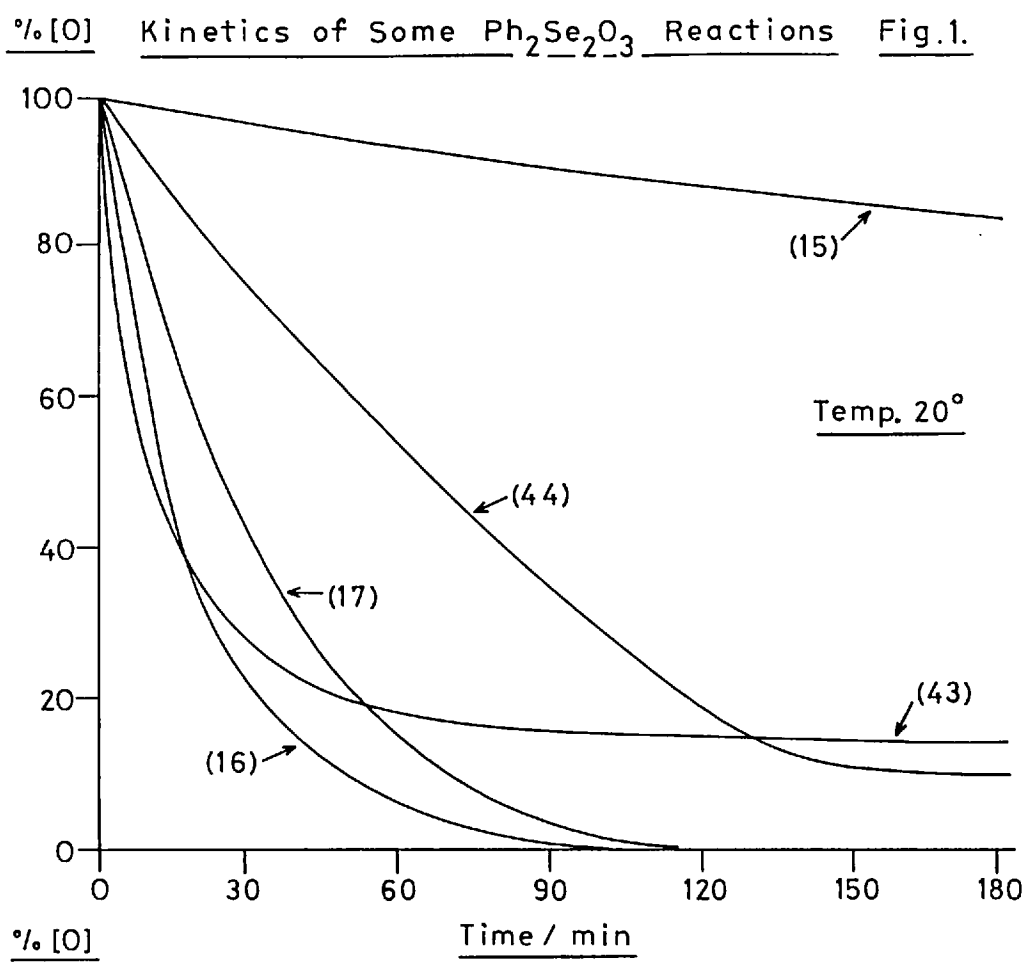
Thus: $Ph_2Se_2O_3 \equiv 3\ I_2 \equiv 6\ Na_2S_2O_3 \equiv 3\ \{O\}$

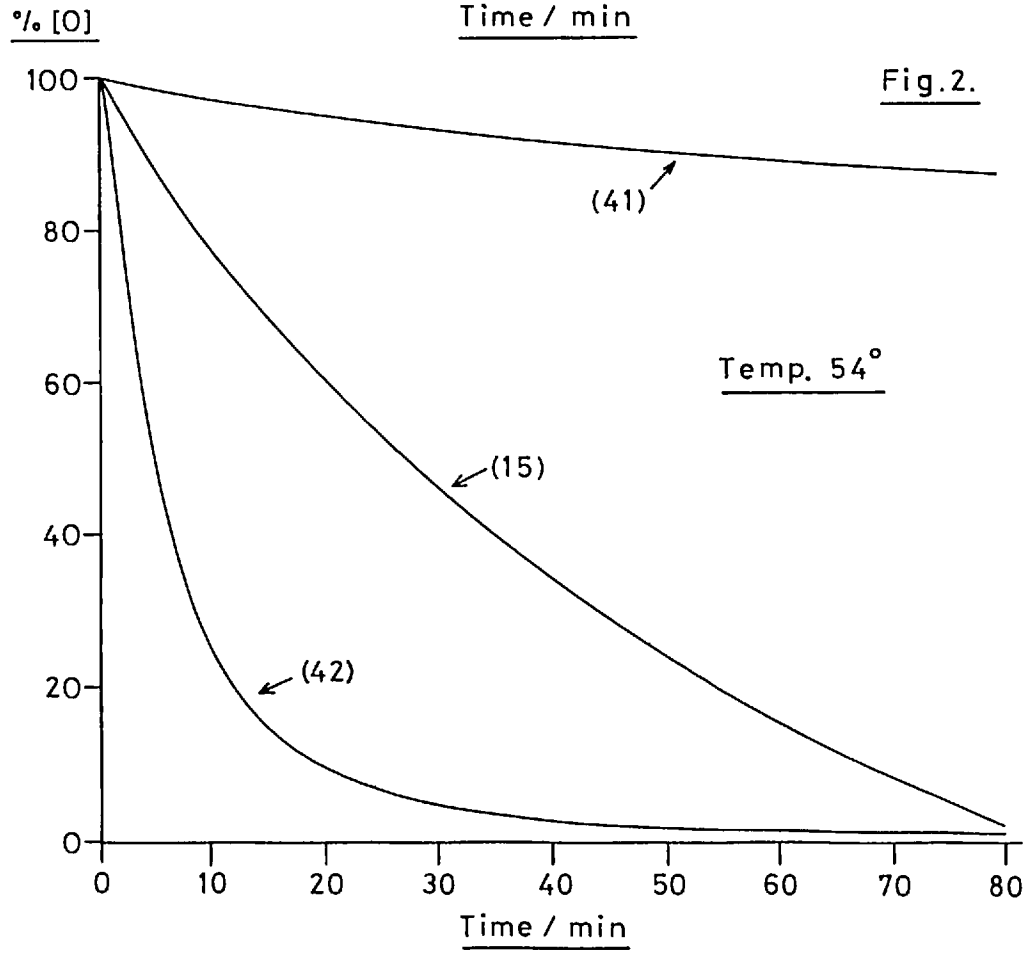
i.e. $Ph_2Se_2O_3$ (90.0 mg, 0.25 mmol) ≡ $Na_2S_2O_3$ (15 ml, 0.1M)

Reactions were performed in dry tetrahydrofuran (THF) at room temperature (R.T.)($\sim 20^{o}$) and {O} values were calculated as a percentage of those determined for a control reaction mixture lacking the thioacetal. The results for (15), (16), (17), (43), and (44) are presented graphically below (Fig. 1.). Generally, 1,3-dithiolanes consume all the oxidising capacity of the anhydride, whereas with the 1,3-oxathiolanes some 10-18% {O} remained after the normal reaction period. This is consistent with the hypothesis that some of the spiro-oxygen is found in the carbonyl products. The cycloaliphatic derivative (15) reacts slowly at R.T. with a "half-life" $t_{\frac{1}{2}}$ = 9h, whilst the benzylic derivatives (16) and (17) showed $t_{\frac{1}{2}}$ = 17.5 min and 25.5 min respectively; the monosubstituted compound reacting predictably faster than the disubstituted. The analogous 1,3-oxathiolane (43) showed $t_{\frac{1}{2}}$ = 9 min and, correspondingly, (44) reacted much faster than (15) with $t_{\frac{1}{2}}$ = 76 min.

The generation of Ph_2Se_2 always mirrored the decline in {O}, reaching quantitative limits, except with (44) and (46) where the phenylselenenylated products (45) and (47) accounted for the remaining selenium. Hydrolytic work-up prior to the isolation of products was not essential.

The sterically hindered 1,3-dithiolanes (41) and (42) gave unexpected results (Fig. 2). Whilst (41) showed a predictable decrease in reaction rate towards $Ph_2Se_2O_3$ relative to (15), the fenchone derivative (42) showed an accelerated rate; the initial rate ratios of (42) : (15) : (41) were 20 : 5 : 1 at 54^{o} and 72 : 26 : 1 at 20^{o}. This anomalous behaviour may result from the faster ejection of products from (42) due to enhanced steric compression in the transition state, or, due to the 7-methylene bridge in (42) effectively "tying back" the α-methyl groups relative to their conformation in (41), the spiro centre at C-2 being less hindered in (42) than in (41). The former explanation would require an unreasonably high entropy of activation to reach the


% [O]
Kinetics of Some $Ph_2Se_2O_3$ Reactions
Fig.1.
100
80
60
40
20
0
(15)
Temp. 20°
(44)
(17)
(43)
(16)
0
30
60
90
120
150
180
Time / min

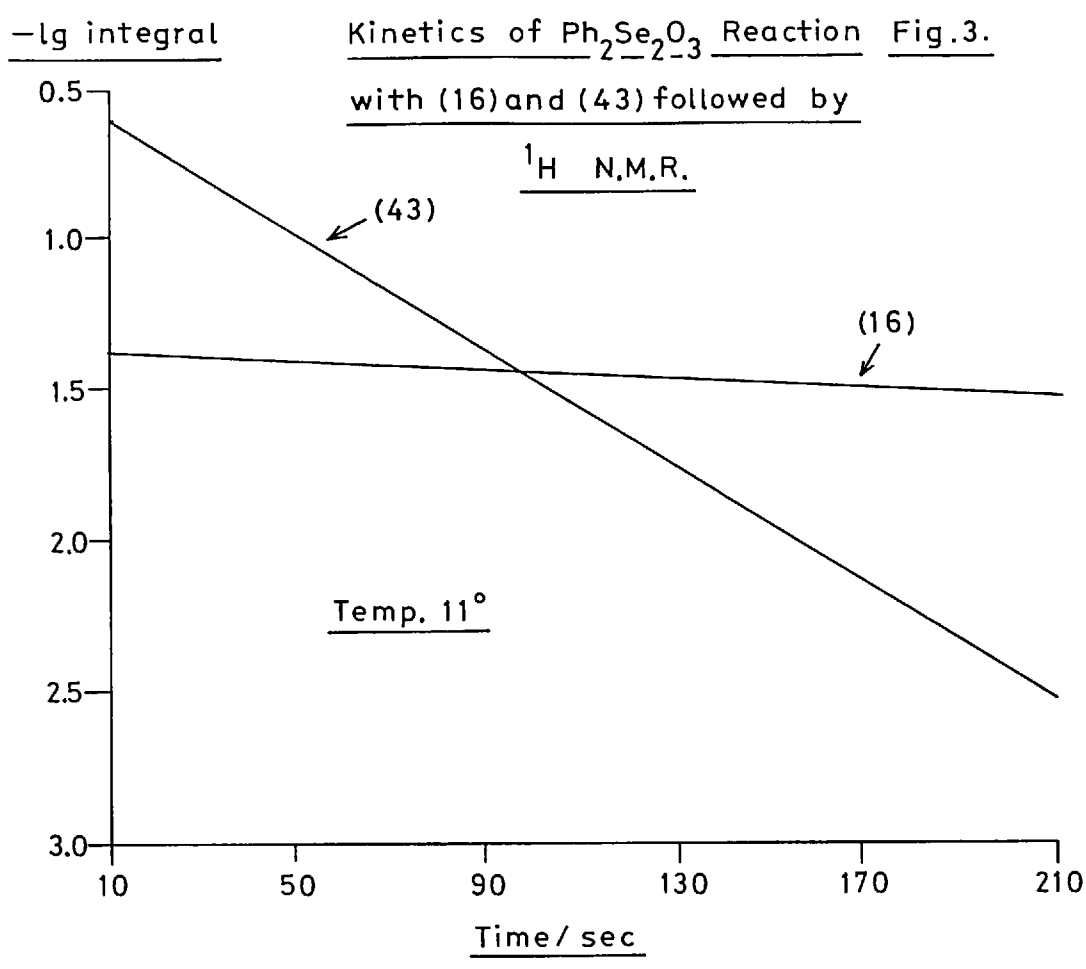

% [O]
Fig.2.
100
80
60
40
20
0
(41)
Temp. 54°
(15)
(42)
0
10
20
30
40
50
60
70
80
Time / min

transition state in the first place, and the latter is improbable since the preparation time of (42) from the ketone was twice that for (41) at the same temperature (t.l.c. control). Thus, a satisfactory explanation is not apparent.

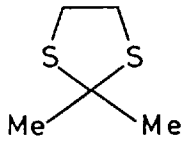
The formation of carbonyl products was rapid when followed by I.R. or N.M.R. spectroscopy and maximum concentrations of product were approached faster than at the rate expected from the above titration results. This suggests that the rate limiting step is not the generation of carbonyl products, but the subsequent rearrangement of the selenium--oxygen-sulphur intermediate to form diphenyldiselenide and an oxygenated sulphur moiety (see below). Therefore a more direct estimation of the relative reaction rates of 1,3-dithiolane *versus* 1,3-oxathiolane was obtained by an N.M.R. technique, which followed the competitive disappearance of each substrate.

The benzylic protons of (16) and (43) resonate at δ 5.60 and δ 5.88 respectively. An equimolar solution of (16), (43), and $Ph_2Se_2O_3$ in deuteriochloroform was observed at 100 MHz. (XL 100) at 11°. By employing a modified [62] Varian FT/16D program, T_1 values could be monitored automatically and individual peak integrals measured at predetermined values of the total elapsed time (10 s, then every 40 s). The result, presented graphically in Fig. 3, suggests that (43) is consumed approximately 10 times faster than (16); c.f. 2 times estimated by iodometric titration. Based upon a simple collision theory, (43) should experience only half the effective collisions by the reagent at sulphur than should (16), therefore,if sulphur (and not oxygen) *is* the site of initial reaction, this highlights the additional increased reactivity of (43) relative to (16).

Since less than stoichiometric amounts of $Ph_2Se_2O_3$ lead to less than optimum yields, the "excess" oxidising capacity (2 {O}) must be consumed by the departing sulphur moiety. This component was isolated



directly from the reaction mixture of the anhydride with (50) and indirectly from (17). Elemental analysis showed this insoluble, apparently polymeric, material to have an empirical molecular formula between $C_2H_4S_2O$ and $C_2H_4S_2O_2$, although the latter is probably the more accurate, due to the difficulty in purification of the polymer. ^1H N.M.R. at 100 MHz. showed only complex methylene resonances at δ (d^5-py) 3.209-2.789, and absorptions at $\nu_{max.}$ 1 320 (SO_2, symm.) and 1 125 (SO_2, asymm.) cm^{-1} are consistent with the thiol-sulphone structure (51) for this polymer, which had similar properties to the peracid oxidation product of *poly*(ethylenedisulphide) (52) [63]. Unfortunately, the corresponding product could not be isolated from any of the 1,3-oxathiolane reaction mixtures, therefore, the fate of the sulphur moiety in these cases remains uncertain.



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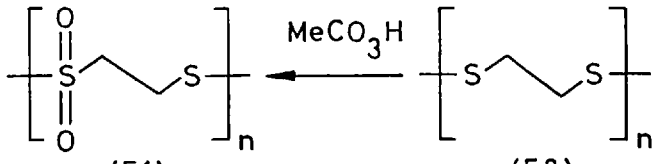
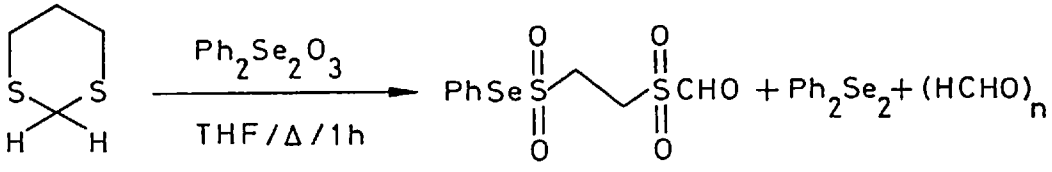


(51) (52)

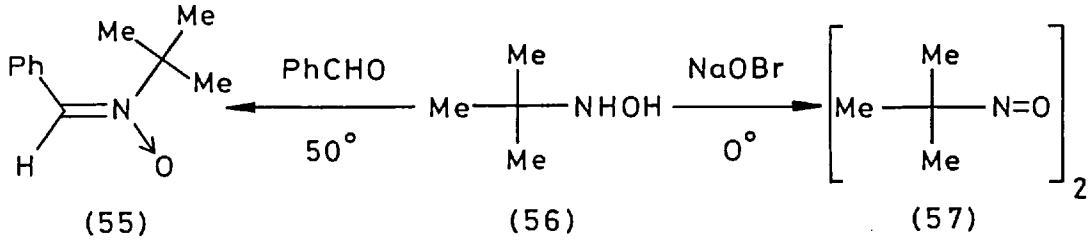
The 1,3-dithiane (53) [64] reacted with $Ph_2Se_2O_3$ to afford paraformaldehyde [65], Ph_2Se_2, and an unstable, monomeric compound which was characterised as the *bis*-sulphone (54), rather than as the analogous polymer to (51). However, this is not a direct comparison, since the spiro-H_2 compound(53) may be a special case and unfortunately the corresponding spiro-Me_2 derivative was not tested.



(53) (54)

Before proposing an overall mechanism for the 1,3-dithiolane deprotection reaction, the possibility of a radical pathway was first investigated by E.S.R. spectroscopy. The heterogeneous nature of the initial $Ph_2Se_2O_3$/1,3-dithiolane mixture can be tolerated for E.S.R. measurements. Whilst polar solvents of relatively high dielectric constant (e.g. THF) would have been preferred for this study (especially with spin-traps which add more efficiently in polar solvents [66]) they necessitated the use of thin, flat cells, which proved less convenient than the normal cylindrical, anaerobic tubes, which are only compatible with non-polar solvents. Thus, reactions were performed in anhydrous, deoxygenated benzene under N_2 at room temperature and below. Under optimal observational conditions, no radicals were detected in the absence of spin-trapping agents. The use of such agents, to produce persistent adducts from short-lived radical intermediates, is now widespread in E.S.R. spectroscopy [67]. Accordingly, *N-tert*-butylphenyl-

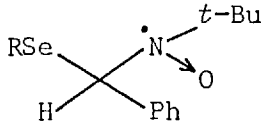
nitrone (PBN) (55) [68] and the colourless 2-methyl-2-nitrosopropane dimer (57) [69] were prepared from *N-tert*-butylhydroxylamine (56) and evaluated as described below.



(55) (56) (57)

If radicals were to be found in the deprotection reaction, they would probably be centred at carbon, sulphur, or selenium; the latter being most interesting, since the study of organoselenium radicals appears to be a relatively neglected field. Ingold [70] has recently reported the photolysis of dimethyldiselenide (Me_2Se_2) and the detection of its radical adduct to the nitrone (55). This work was successfully repeated by irradiation of Me_2Se_2 [71] in benzene (high pressure Hg lamp) for 55 min at R.T. then cooled to -50° and the E.S.R. spectrum of the adduct (58, **R**=Me) recorded, which consisted of a distorted triplet of double doublets, having the parameters listed below:

R=Me



(58)

$g = 2.0091$; $a_N = 14.0$ G; $a_H = 5.0$ G; $a_{3H} = 0.5$-1.0 G.

(lit.,[70]: $g = 2.0097$; $a_N = 13.5$ G; $a_H = 2.1$ G; $a_{3H} = 0.85$ G.)

The "g-values" were calculated from the resonant condition:

$g = \frac{h\nu}{\beta B}$, where h = Plank's constant; 6.625×10^{-27} erg.s

β = Bohr magneton; 9.273×10^{-21} ergG.$^{-1}$

ν = R.T. operating frequency; $\sim 9 \times 10^{9}$ Hz.

B = Field strength; $\sim$ 3 300 G.

The relatively high g-value (2.0091) and the broad and distorted signal is indicative of a radical centred upon a high atomic weight, spin-orbit coupled atom, e.g. selenium.

Since the phenylseleno radical (PhSe·) was an anticipated intermediate in the deprotection reaction, attempts were made to observe the analogous adduct (58, R=Ph). The known thermochromism of Ph_2Se_2 [72] and its obsreved [73] catalytic isomerisation of Calciferol, have been interpreted as evidence for the existence of PhSe· radicals in solution. The irradiation of Ph_2Se_2 at R.T. [74] and at -196° [75] has been claimed to generate PhSe· species, although this latter work has been reported as unreproducible [76].

During the irradiation of yellow Ph_2Se_2 in the solid and in benzene solution,at R.T. and at -160°, with low and high pressure mercury and tungsten lamps, no radicals were detected. PBN (55) is less efficient at trapping primary alkyl [66] or aryl [67] radicals than other (nitroso) traps, and accordingly no radicals showing significantly high g-values were detected in its presence; only species of low g-value, resulting from the photolytic cleavage of (55) [77] were observed. However, irradiation of Ph_2Se_2 in benzene for 15 hours in the presence of the dissociated, pale blue coloured, *tert*-butylnitroso monomer [78] from (57), gave rise to a complex E.S.R. signal consisting of three overlapping triplets (all a_N = 15 G.) and a singlet centred at: g = 2.0106; g = 2.0099; g = 2.0088; and g = 2.0046, respectively (see Fig. 4.). Whilst several of these absorptions have relatively high g-values, many could be reproduced by a control irradiation of (57) in the absence of Ph_2Se_2 , therefore they fail to convincingly confirm the the existence of arylselenium radicals during this method of photolysis of Ph_2Se_2. Similarly, 1,1-diphenylethylene [79] and pure anthracene (which gave adducts of g = 2.0039-59 when heated with azo-*iso*-butyronitrile (AZBN)) also failed to trap any PhSe· species.

Fig. 4.

E.S.R. Spectrum of Ph_2Se_2+t-BuNO / hν / 15 h

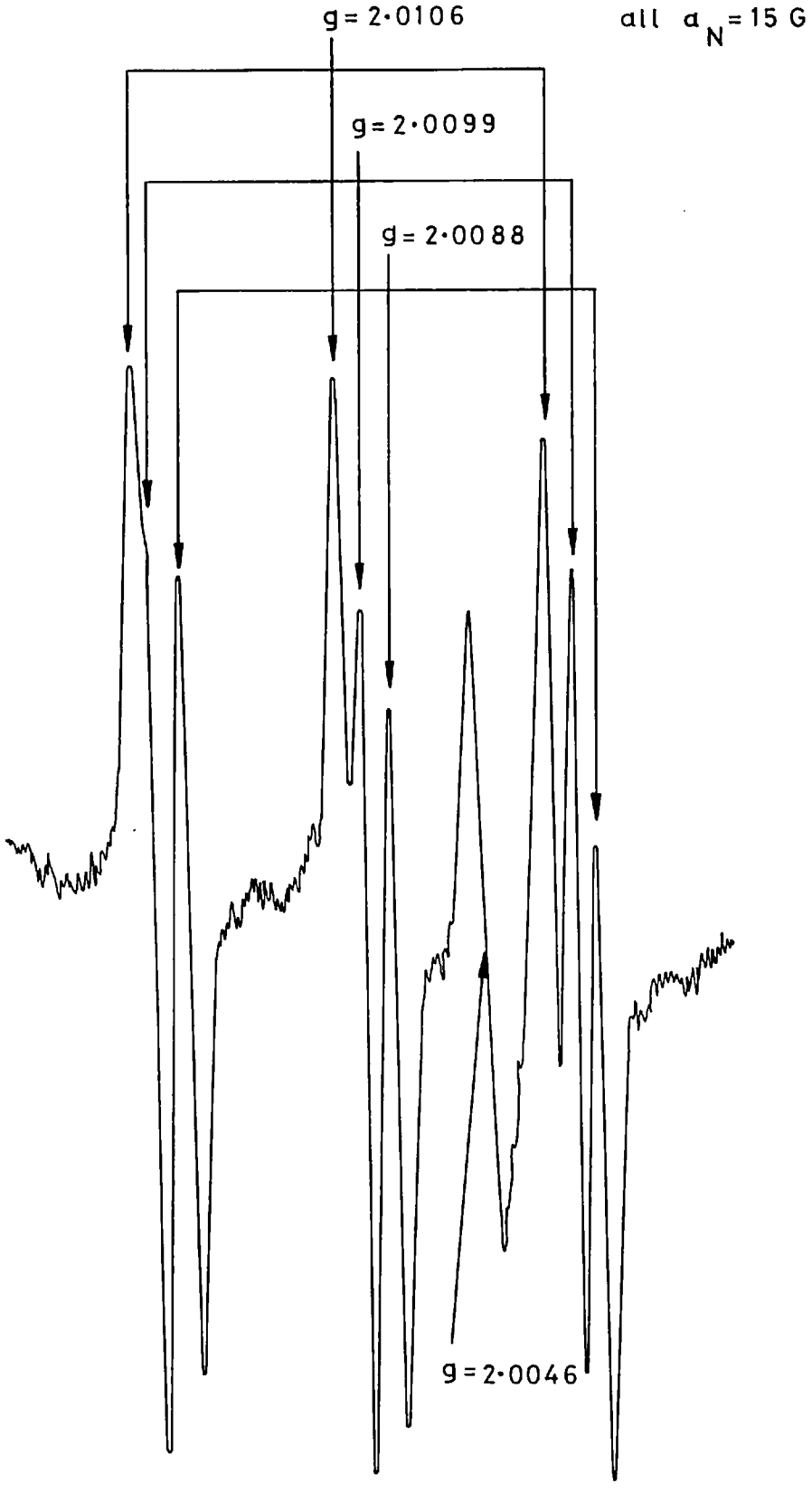
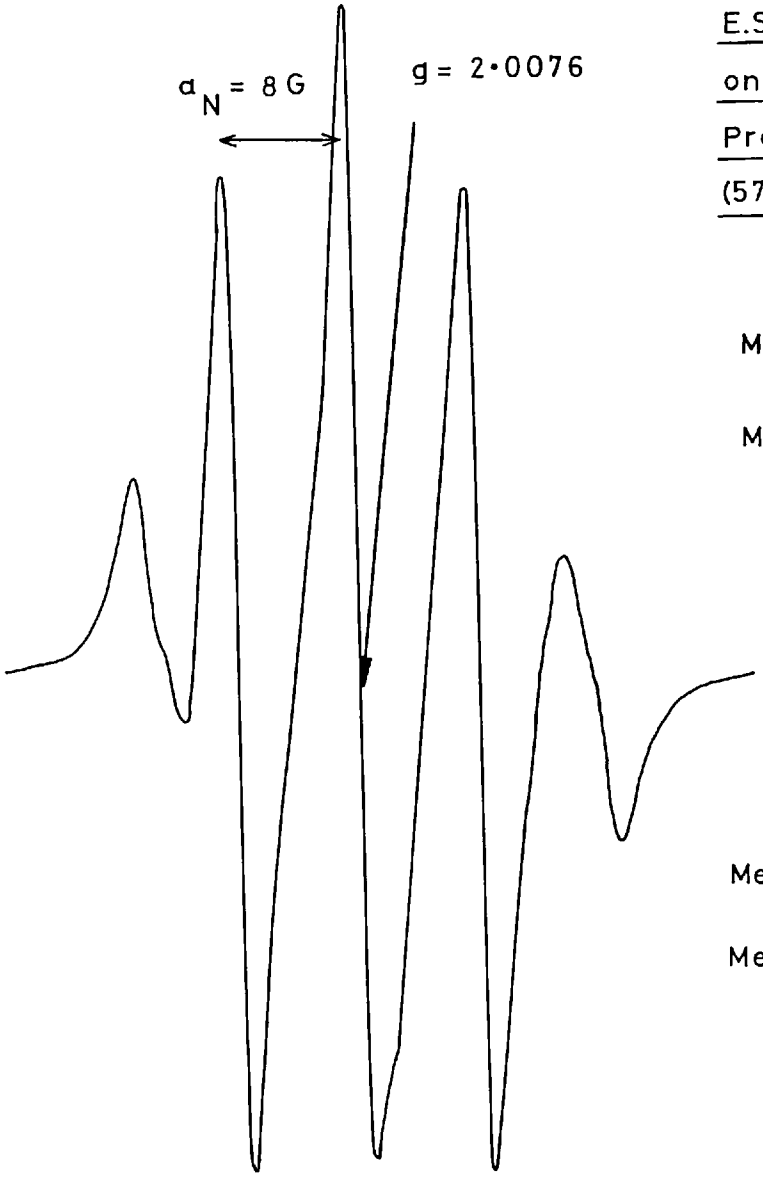
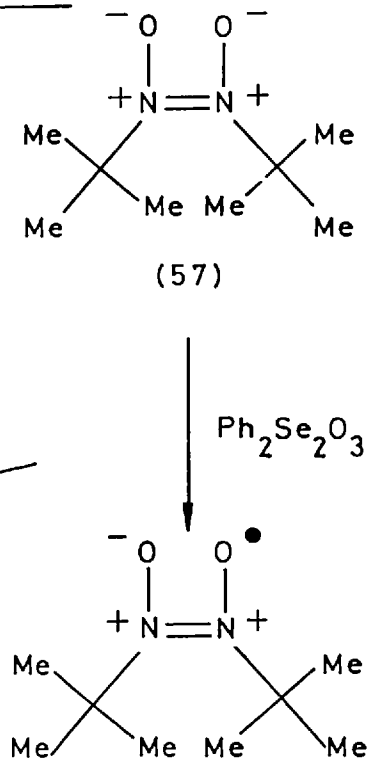


Fig.5.



E.S.R. Spectrum of the one-electron Oxidation Product from $Ph_2Se_2O_3$ + (57).



(57)

When the nitrone (55) was added to a $Ph_2Se_2O_3$/2-phenyl-1,3-dithiolane (16) reaction mixture at R.T., a broad singlet, g = 2.0012, was observed. Upon standing (*ca.* 2h) a triplet, g = 2.0105; a_N = 12.5 G., and a quintet, g = 2.0076; a_N = 8 G., developed and the solution became pale green in colour (yellow + blue) suggesting that Ph_2Se_2 had been produced as normal, and that the nitrone had decomposed. A control reaction of $Ph_2Se_2O_3$ and (55) in benzene at R.T. gave 90% benzaldehyde (p.l.c. isolation) and the monomer of (57). (N.B. $Ph_2Se_2O_3$ + (56) → the monomer of (57) and not the nitro compound [53c].). A mixture of (16) and

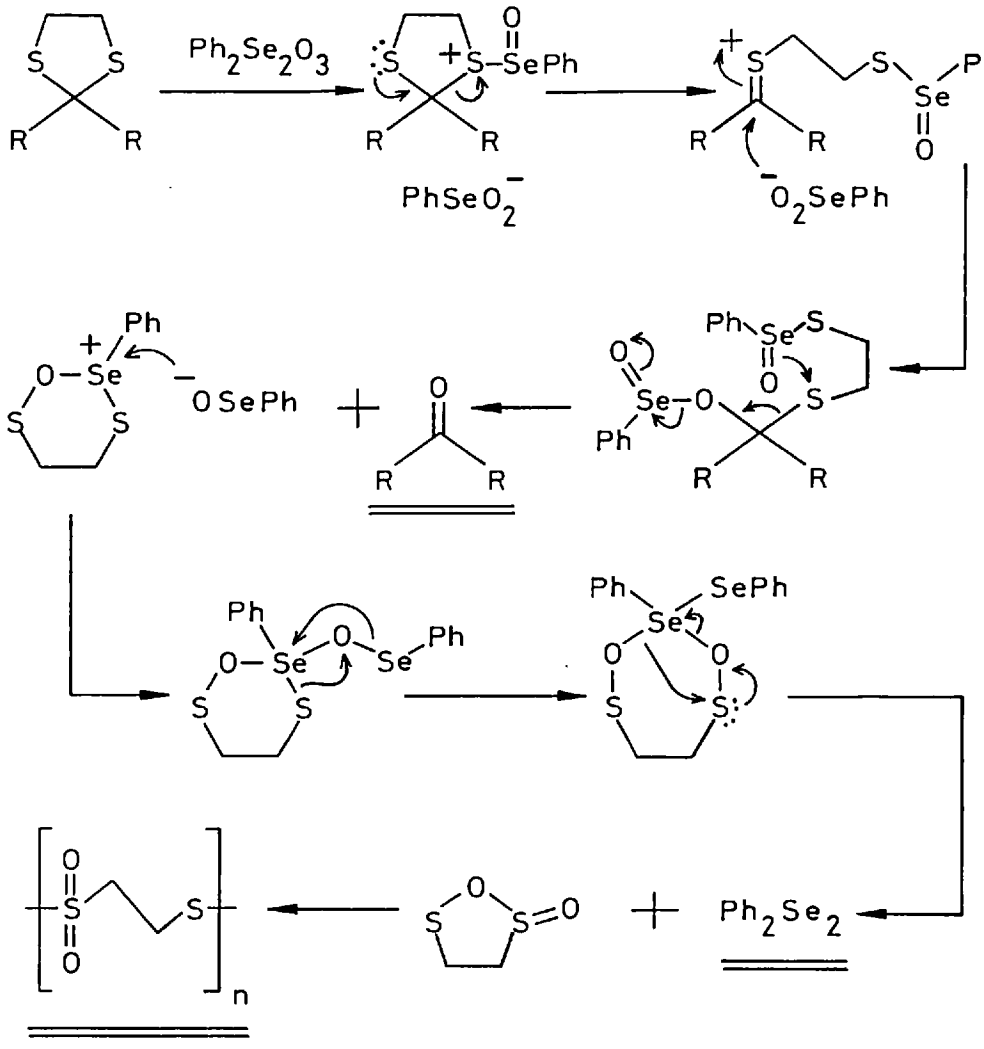
(57) alone in benzene, also gave rise to a triplet, g = 2.0105; with a_N = 12.5 G. (the intensity of which was enhanced by exposure to day-light), identical to the signal observed above and similar to those reported [16] for adducts of 1,3-dioxolanes. The quintet, g = 2.0076; with a_N = 8 G. (Fig. 5.) was reproduced by mixing $Ph_2Se_2O_3$ with (57) in benzene. A one-electron oxidation of the dimer (57) could produce a species in which the unpaired electron would be distributed between the two magnetically equivalent, coupled nitrogen atoms (n=1+1: leads to the multiplicity 2n + 1 = 5) so giving rise to the quintet signal, Fig. 5.

In the absence of spin-traps, no radicals could be detected during the general deprotection reaction, and since that in their presence the extraneous radical species can be accounted for, it appears that no radical intermediates, including the elusive PhSe· radical, are present during this reaction, within the bounds of experimental sensitivity ($\sim 10^{-7}$ molar concentration limit) and over the operational time scale of the E.S.R. instrument.

1,3-Dithiolanes and 1,3-oxathiolanes do not react with benzeneseleninic acid ($PhSeO_2H$) or its sodium salt; indeed the addition of either to a normal deprotection reaction mixture virtually quenches further reaction. Similarly, one mole-equivalent of water renders the $Ph_2Se_2O_3$ inactive, suggesting that the novel behaviour of the anhydride is a function of the intact reagent. Therefore, from all the above evidence, the following ionic mechanism (Scheme 4.) is proposed [80].

The initial reaction is considered the ring opening of the 1,3-dithiolane,by the attack of selenium at sulphur followed by the expulsion and subsequent nucleophilic attack of the benzeneseleninate anion at the spiro-carbon. This gives, after intramolecular rearrangement, the early formation of the carbonyl product, benzeneselenenate anion, and a cyclic selenium-sulphur-oxygen cation. The rate determining step

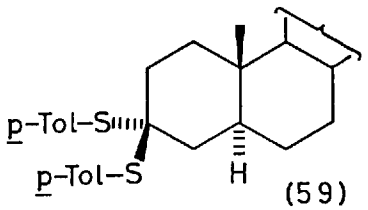
SCHEME 4.



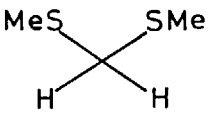
may then be the subsequent sigmatropic rearrangements of the selenium-sulphur-oxygen species, which finally generates diphenyldiselenide and the observed polymer, probably *via* the cyclic monomer, as shown above.

Acyclic dithioacetals also react with benzeneseleninic anhydride; e.g. (59) affords 5α-cholestan-3-one in 52% yield. However, the yield of Ph_2Se_2 in this reaction can be as low as 20%, since the departed oxidised sulphur moiety contains a phenylselenenyl residue. Thus, *bis*(methylthio)methane (60) reacts to give the colourless product (62); with *m/e* 236 M^+ (determined from the most abundant line (^{80}Se) of the selenium isotope pattern ^{81}). *Bis*(*para*-tolylthio)methane (61) reacts with $Ph_2Se_2O_3$ to afford a pale yellow, water soluble, product, whose

spectroscopic data (particularly I.R.) are consistent with either structure (63) or (64); the latter possibility would have been an interesting example of a sulphinic acid/selenenic acid anhydride.



(59)



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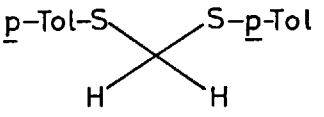

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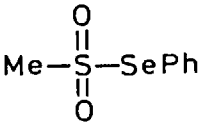
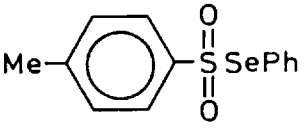
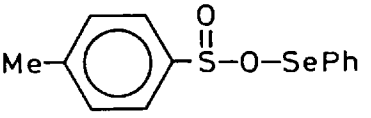


(62)



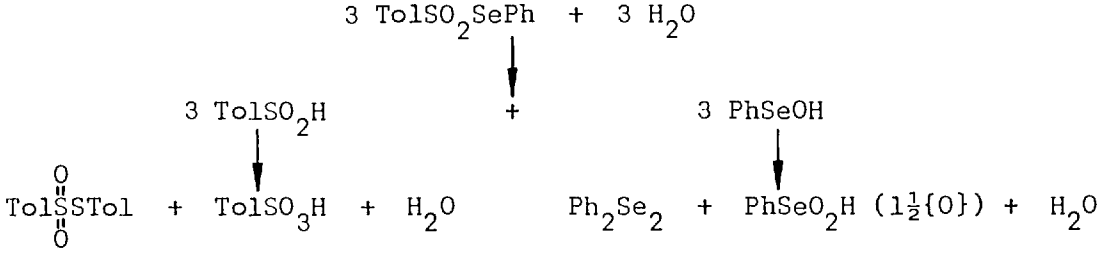
(63)



(64)

Iodometric titration of (63)/(64) indicated that it was an oxidant, with an oxidising capacity of $\frac{1}{2}$ {O} per molecule, which is in accordance with the dissociation and disproportionation (Scheme 5.) as shown below.

SCHEME 5.



Comparison of the ^{13}C-N.M.R. spectrum of (62) and the spectrum of (63)/(64) with that of diphenylselenide (A, Table 4.), suggests that the PhSe- residue is unoxidised (since the quaternary carbons in $Ph_2Se_2O_3$ (D) [53a] appear at much lower field). However, the predicted chemical shifts for toluenesulphonyl chloride (B) (obtained by summation of the substituent chemical shifts (SCS values) of toluene and benzenesulphonyl chloride [82] relative to benzene) and those measured for toluenesulphinic acid (C), still do not provide a clear distinction between

Table 4.

Compound	^{13}C - Chemical Shift [a] Relative to Tetramethylsilane [b].					Me
(62) [c]	136.78,	131.01,	129.87,		127.54 [q],	51.10
(A) [c]	132.72,	130.98 [q],	129.07,		127.04 .	—
(63)/(64) [c]	(144.42)[q],(142.49)[q],	136.98,	130.67,	129.33,(129.08),	127.82[q],(126.79),	20.44
(B) [d]	(144.10)[q],	(140.70)[q],			(126.30),(126.20),	21.20
(C) [c]	(143.17)[q],	(142.18)[q],		(129.41),	(124.65).	21.18
(D) [e]	149.25 [q],	131.95,	129.17,		125.91 .	—

(A) PhSePh (B) TolSCl (C) $Tol\overset{O}{\overset{\|}{S}}-OH$ (D) $Ph_2Se_2O_3$.

a : Parenthesis indicates a carbon nucleus directly bonded to sulphur.

b : Measured relative to the solvent then calculated relative to TMS.

c : Determined in deuteriochloroform solution.

d : Predicted from summation of SCS values for toluene and $PhSO_2Cl$ [82]; C_6H_6 resonates at δ 128.90 from TMS.

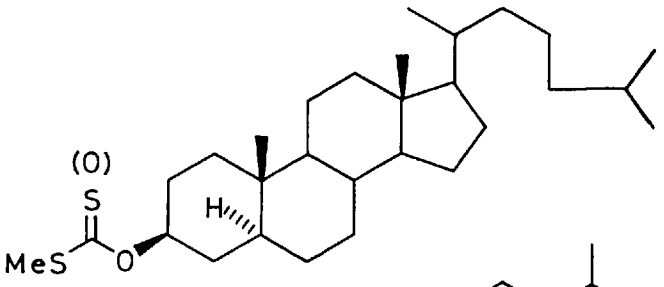
e : Determined in hexadeuteriodimethylsulphoxide solution.

structures (63) and (64). The problem was finally resolved chemically, as an authentic sample of compound (63) was prepared independently by the method of Britten-Kelly [83], from Ph_2Se_2 and Chloramine-T(R), and shown to have identical melting point, mixed melting point, and spectroscopic properties to the product from the reaction of $Ph_2Se_2O_3$ with (61).

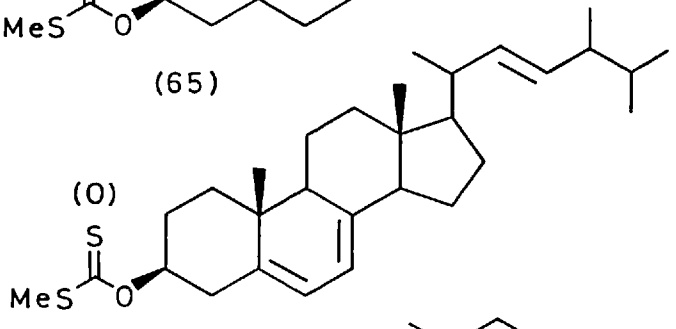
Because the study of the acyclic dithioacetals was far less comprehensive than that of the cyclic analogues, and since the observed products probably arise *via* a more complex intermolecular process, a corresponding reaction mechanism is not conjectured.

8. Conversion of Thiocarbonyl Compounds into Their Corresponding *Oxo*- Derivatives using Benzeneseleninic Anhydride.

Consideration of the 1,3-dithiolane deprotection mechanism (Scheme 4.) suggested that thiocarbonyl compounds should also be reactive towards $Ph_2Se_2O_3$. A number of readily available thiocarbonyl compounds were treated with the anhydride and found generally to afford their corresponding *oxo*- derivatives in good yield. For example, the methylthiothioncarbonate (xanthate) (65) [84] reacted with $Ph_2Se_2O_3$ at R.T. over 12 hours to yield 67% of the methylthiocarbonate (65*). This general transformation was selective for (C=S) into (C=O) even in the presence of other sulphur moieties, and was also found to be compatible with thionbenzoates, selenobenzoates, thioureas, trithiocarbonates, and non-enethiolisable thioketones. Several examples derived from both simple substates and more complex natural product derivatives are presented below, (65)-(80) [84-93], and the yields and properties of their corresponding *oxo*- products (65 *)-(80 *), are described in the experimental section.



(65)



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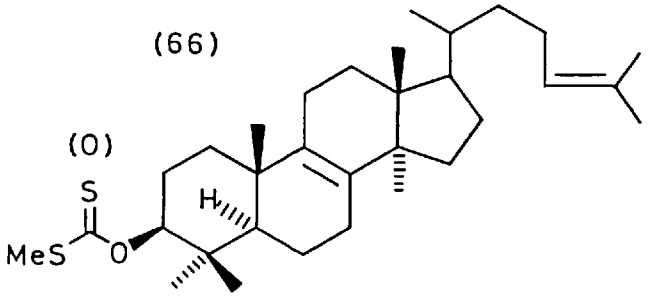

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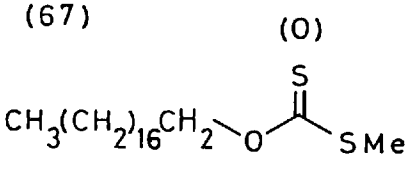

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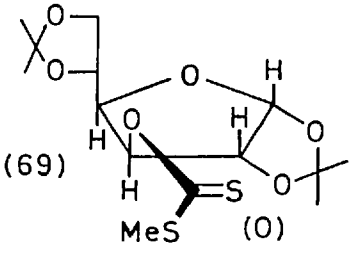

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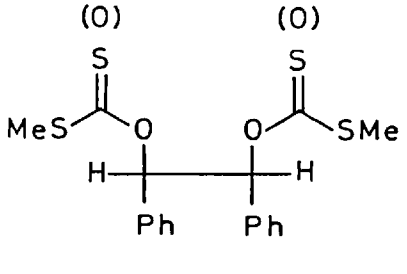

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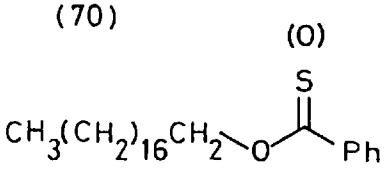
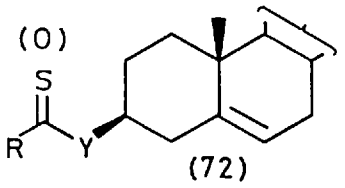


(71)

Cholestane

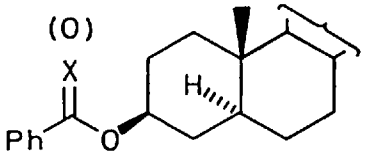


(72)

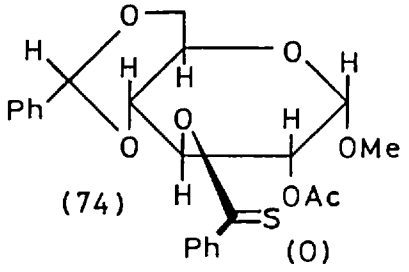
R = H, Y = O ; R = Me, Y = O

R = Ph, Y = O; R = Ph, Y = S

Cholestane



X = S, Se (73)



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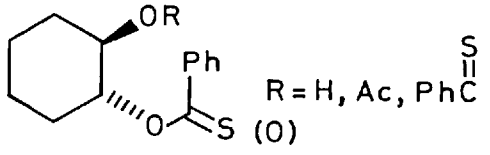


(75)

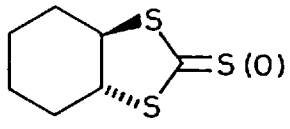
R = H, Ac, PhC(=S)

$(p\text{-Cl-PhO})_2C{=}S$ (O)

(76)

$(RNH)_2C{=}S$ (O)

R = H, Ph (77)



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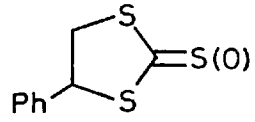
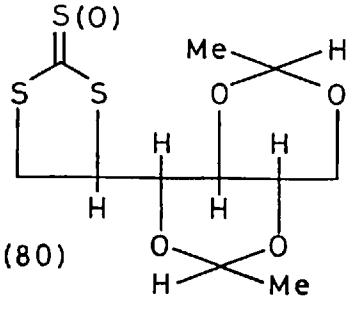


(79)

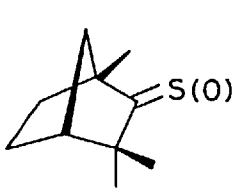


(80)

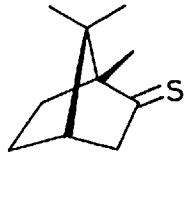
Many of the published methods for the conversion of thiones into their *oxo*- derivatives have been discussed in the review section of this thesis. In contrast to benzeneseleninic anhydride, which constitutes a mild reagent for this process, many of the literature methods are quite vigorous (e.g. $KMnO_4$, HNO_3, etc.) and may thus be incompatible with more sensitive functionalities present in the substrates.

The reactivity of selenium dioxide was compared with $Ph_2Se_2O_3$ towards several of the above substrates,and found either not to react at all, or give mixtures of many intractable products. One notable exception is the selenobenzoate (73, X=Se) which reacted with SeO_2 over 3 days to afford elemental selenium and the benzoate (73 *, X=O) in 97% yield. However, the selenium-selenium interaction which occurs here must be regarded as a special case, and not generally applicable to the thiones. Minor limitations observed with the thione/anhydride reaction are that the yield of ureas from thioureas is somewhat uncompetitive with some of the literature methods, and that occasionally phenylselenenylated or phenylseleninylated by-products may be produced (usually not more than 10%).

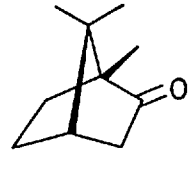
Whereas the non-enethiolisable compound thiofenchone (81) [94] reacted well with $Ph_2Se_2O_3$ to yield 89% fenchone (81 *),thiocamphor (82)[94] only afforded 9% camphor (83), the major products being 3-*endo*-phenylseleninylcamphor (84)(36%) and camphor quinone (85)(54%).



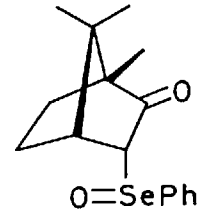
(81)



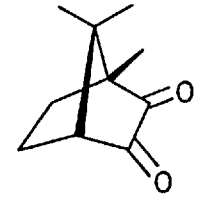
(82)



(83)



(84)



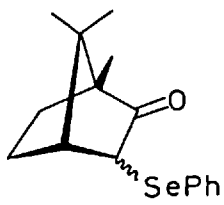
(85)

The by-product (84) probably arises *via* the mechanism outlined earlier (Scheme 2) and whilst being configurationally stable towards the *syn*-elimination of PhSeOH to form an enone, (84) is susceptible to

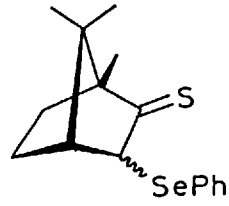
Pummerer-type rearrangement, as in the earlier example, (48) → (49), noted by Reich [61]. Accordingly, (84) was unstable at R.T. and gave the α-diketone, camphor quinone (85) and Ph_2Se_2 upon standing.

An authentic sample of the unoxidised 3-phenylselenenylcamphor (86) was eventually prepared as a 4:1 mixture of *endo : exo* epimers, from the enolate of camphor ((83) + $LiN(SiMe_3)_2$) and phenylselenenyl chloride. The mixture resisted all attempts at base catalysed epimerisation to a single, thermodynamically most stable, epimer and resolution of the mixture (p.l.c. or fractional crystallisation) was without success. However, although (86) was inert towards $Ph_2Se_2O_3$ and sodium metaperiodate, oxidation of the least hindered (*endo*) epimer occurred smoothly with *meta*-chloroperbenzoic acid at 0^o, and warming to R.T. gave only camphor quinone (85) and Ph_2Se_2 , presumably *via* a Pummerer-type rearrangement of the intermediate selenoxide (84).

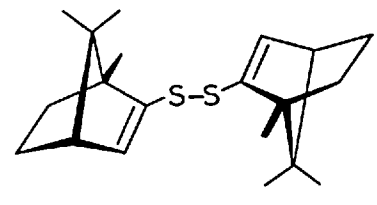
An attempt was made to prepare the analogous 3-phenylselenenyl thiocamphor (87), from racemic thiocamphor (82) and PhSeCl . However, probably due to the preference of the "soft" electrophilic selenenyl cation for the "soft" nucleophilic thiolate anion (rather than for the relatively "hard" C-3 centre), only oxidation of the thiolate occurred. This gave Ph_2Se_2 and apparently the coupled product (*bis*-vinyldisulphide) as a diastereomeric mixture (88), known to be the products from the treatment of the thiolate of (82) with iodine [95], or from (82) directly with Choramine-T (R) [96].



(86)



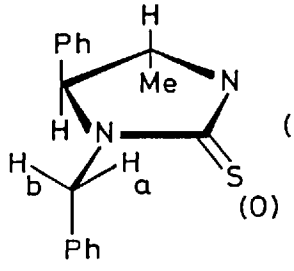
(87)

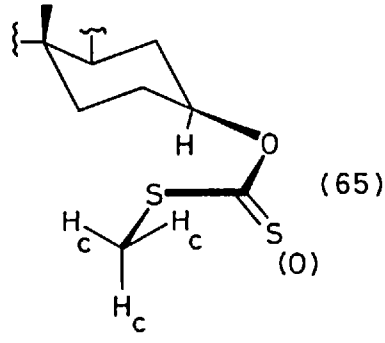


(±) (88) (±)

Returning to the steroidal xanthates, when their reaction with $Ph_2Se_2O_3$ was followed by I.R. or N.M.R. spectroscopy, as with the

1,3-dithiolanes earlier, rapid formation of the *oxo*- products was observed. By the latter technique it was interesting to note that the (SMe) ^{1}H resonance of the *oxo*- product, e.g. (65 *), appeared at somewhat higher field, δ 2.28 (MeSCOO), than in the starting material, e.g. (65), δ 2.53 (MeSCSO). This difference is a function of the relative magnitudes of the aniostropic deshielding effects of the carbonyl *versus* thiocarbonyl groups; the latter being known to be more strongly deshielding [97], as evidenced by the difference in chemical shift (Δδ) measured between the methylene protons of the cyclic thiourea (89) and the analogous cyclic urea (89 *) [98]. A suitable conformer of the xanthate (65) is shown alongside (89) below, to illustrate the similarities between the two systems.





Δδ : H_a ; 0.55-0.69 ppm

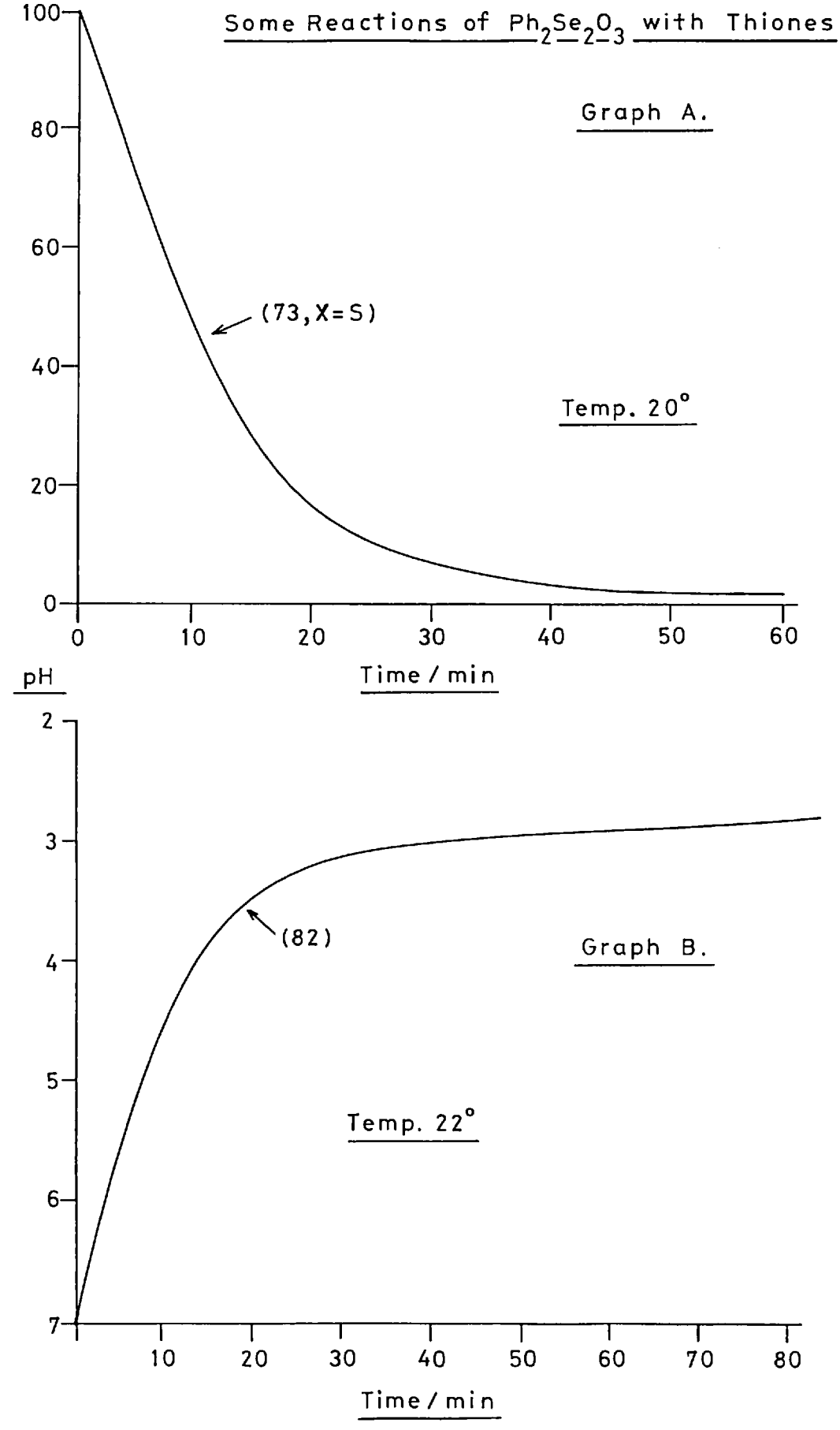
Δδ : H_b ; 0.12-0.13 ppm

Δδ : H_c ; 0.25 ppm

The following explanation is offered for the above effect. The relative magnitude of the anisotropic deshielding effect of (C=O) *versus* (C=S), which arises due to the circulation of (C=X) bonding π-electrons, is consistent with the observed bathochromic shift in the U.V. spectrum from (C=O) to (C=S) [99], due to an increase in the energy of the respective $n \rightarrow \pi^*$ transitions. This suggests that the non-bonded electrons (n) are of lower energy in the ground state of the (C=S) group, therefore contributions from the (C=S) antibonding modes (π^*) are less likely to reduce the internuclear bonding electron density. This would then lead to less suppression of the (N.M.R.) deshielding activity of the circulating, bonding (π) electrons of the (C=S) group *versus* (C=O).

Fig. 6.

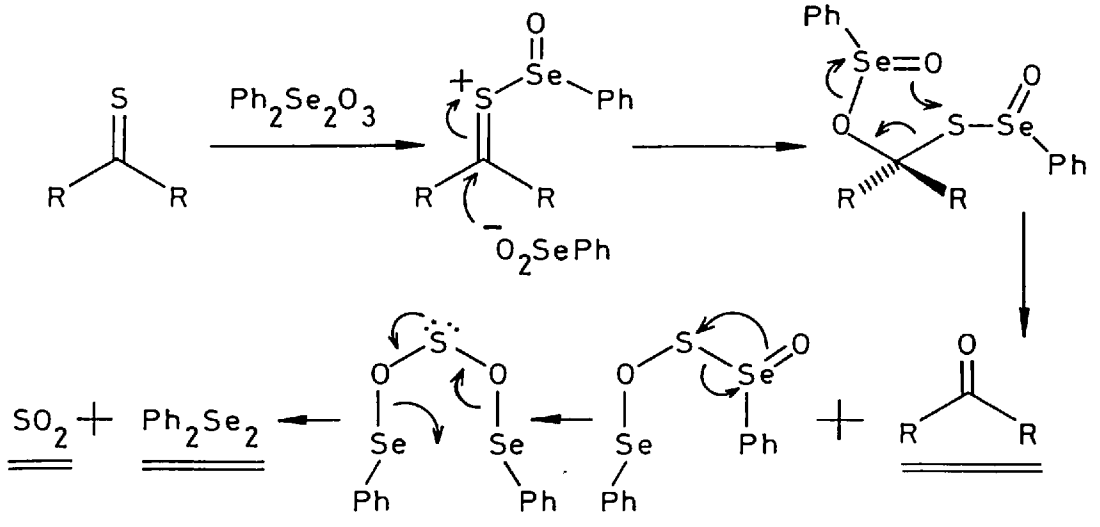
Some Reactions of $Ph_2Se_2O_3$ with Thiones



Following the thione/$Ph_2Se_2O_3$ reaction by iodometric titration revealed that all of the oxidising capacity (100% {O}) of the anhydride was consumed; indeed, with excess reagent (2 equiv.) up to 33% {O} extra capacity could also be consumed in the examples studied (65) and (71). A typical result from a time-course experiment with (73, X=S) is presented graphically in Fig. 6, graph A.

Upon displacement of the atmosphere above a thione/$Ph_2Se_2O_3$ reaction mixture with dry N_2 ($CaCl_2$/NaOH desiccant only), analysis of the effluent gases revealed that a volatile, acidic by-product (not found in control mixtures) was produced. A large scale reaction of thiocamphor (82) and $Ph_2Se_2O_3$ was analysed by passing the effluent gases with the N_2 carrier into water and the resultant pH of the water monitored with a digital pH meter. The result is presented in Fig. 6, graph B and shows an exponential fall in pH with time. Also, the effluent gases caused a slight darkening of a nickel hydroxide impregnated test paper [100] which is consistent with the hypothesis that the sulphur moiety departs as sulphur dioxide. Therefore, from the above evidence, and the fact that no radicals were detected by E.S.R. spectroscopy, the following ionic mechanism (Scheme 6.) is tentatively proposed for this transformation.[101]

SCHEME 6.



The initial electrophilic attack of $Ph_2Se_2O_3$ at the thione sulphur, then expulsion and subsequent nucleophilic attack of the benzeneseleninate anion, is followed by intramolecular rearrangement through a 5-membered transition state. This leads to the formation of the carbonyl product and a linear sulphur moiety which, after the requisite Pummerer-type and sigmatropic rearrangements, afford diphenyldiselenide and sulphur dioxide.

Finally, two miscellaneous reactions of benzeneseleninic anhydride should be mentioned.

(i) The anhydride reacts with thiols to give disulphides, e.g. benzenethiol gives diphenyldisulphide (82%); the corresponding *ortho*-hydroxydienethione was not observed. Since water is produced during the course of this reaction, the use of $Ph_2Se_2O_3$ confers no advantages and is equivalent to the reaction already known[102] between thiols and several free arylseleninic acids ($ArSeO_2H$), as generalised below.

$$2\ ArSeO_2H + 6\ RSH \longrightarrow Ar_2Se_2 + 3\ R_2S_2 + 4\ H_2O$$

and

$$ArSeO_2H + 2\ RSH \longrightarrow ArSeOH + R_2S_2 + H_2O$$

where Ar = *ortho*-nitrophenyl, this gives stable arylselenenic acids.

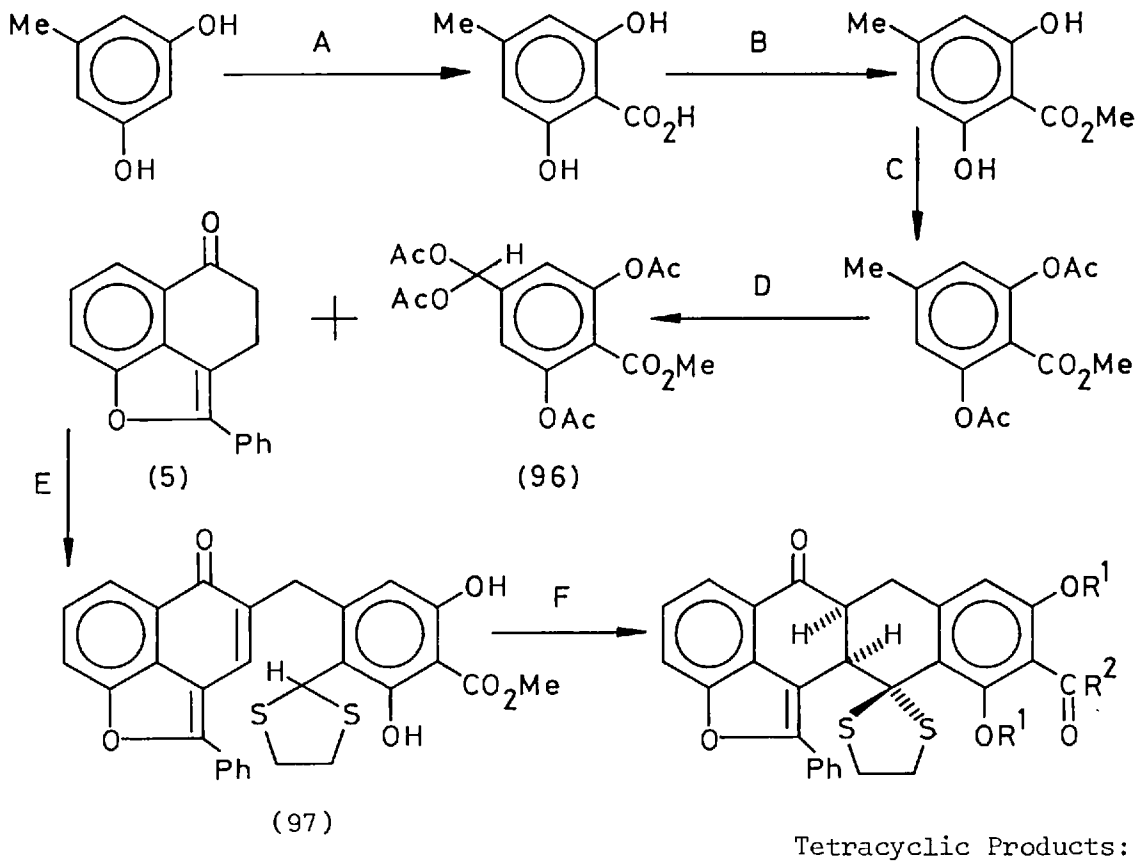
(ii) Phosphines, phosphine sulphides, phosphine selenides; e.g.(90), (91), (92); and thiophosphates; e.g.(95), react with $Ph_2Se_2O_3$ to give moderate yields (43-59%) of the corresponding phosphine oxide (93) and phosphate (94). However, coupled with the problems of clean separation of the Ph_2Se_2 by-product and the difficulty of purification of the products, this transformation proceeds in lower yield than existing literature procedures, notably the iodine/dimethylsulphoxide method[103].

$$\{\ Ph_3P\ ;\ Ph_3P{=}S\ ;\ Ph_3P{=}Se\ \} \rightarrow Ph_3P{=}O \qquad (PhO)_3P{=}O \leftarrow (PhO)_3P{=}S$$

(90) (91) (92) (93) (94) (95)

9. Preparation of Ring-A Substituted Tetracyclic Compounds and Their Reactions with Benzeneseleninic Anhydride.

The functionalised ring-A substituted precursor (96) has been routinely prepared in these laboratories by the well established method outlined below. Condensation of (96) with 3,4-dihydro-*peri*-naphthofuran (5) under acidic conditions and subsequent hydrolysis of the acetate groups, followed by formylation with dichloromethylmethyl ether and thioacetalisation [12], affords the ACD-tricyclic precursor (97). Photocyclisation under the normal conditions gave the tetracyclic 1,3-dithiolane-ester (98) [3], which was smoothly converted to the corresponding amide (99) with tetrahydrofuran/(aq) ammonia at R.T.



A. $KHCO_3/HOCH_2CH_2OH/120^o$

B. $Me_2SO_4/NaHCO_3/Me_2CO$

C. $Ac_2O/NaOAc/100^o$

D. $Ac_2O/AcOH/CrO_3/MnSO_4$

E. (i) H^+/(ii) Cl_2CHOMe/(iii) $HSCH_2CH_2SH$

F. $LiN(SiMe_3)_2/h\nu$ /Δ

Tetracyclic Products:

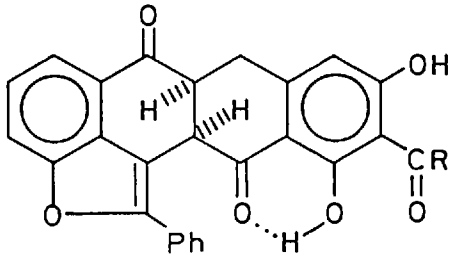
(98) R^1= H, R^2= OMe

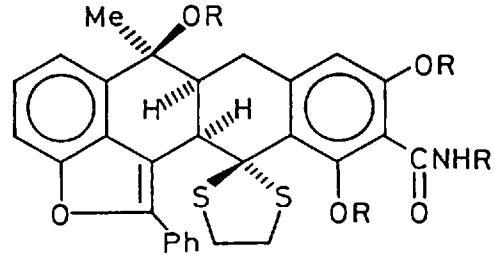
(99) R^1= R^3= H, R^2=NHR^3

(100) R^1= R^3= $SiMe_3$, R^2= NHR^3

For the purposes of the work described below, the above preparation of (98) was routinely performed in these laboratories by Ms. M. Bielska, whose invaluable assistance is gratefully acknowledged.

Prior to the amidation of (98) , it was encouraging to discover that benzeneseleninic anhydride reacted smoothly as desired with the free diphenolic form of the ester (98), to afford the highly fluorescent tetracyclic 6,12-diketone-ester (101) in 64% yield. Unfortunately, the analogous deprotection reaction with the amide (99) was completely unsuccessful under the same conditions, and at this stage the 6,12-diketone-amide (102) proved an elusive product.





(101) R = OMe

(102) R = NH_2

(103) R = H

(104) R = $SiMe_3$

Since the ester functionality in (98) appeared to provide a significant (yet not understood) protective role during the $Ph_2Se_2O_3$ reaction, before proceeding to studies of the C-6 carbinol compounds, e.g. (103), interconversion of the diketone-ester (101) and the diketone-amide (102) was attempted. Any such method of hydrolysis and subsequent amidation of (101) had also to be compatible with the very acid-labile carbinol substrate (103), therefore basic reaction conditions were chosen. Direct reaction of (101) with THF/(aq) NH_3 at R.T. or below, only resulted in degradation of the 1,4-diketone moiety, as did alcoholic alkali (KOH/MeOH) and many other bases (e.g. imidazole, tetramethyl-guanidine), therefore this approach was discontinued.

Trimethylsilyl iodide (Me_3SiI = TMS-I) has been claimed [104] to effect the mild cleavage of esters (and 1,3-dioxolanes, but *not* 1,3-dithiolanes [105]) to carboxylic acids under neutral, non-aqueous conditions. The reagent is easily prepared from the more readily available TMS-chloride *via* the disiloxane, as shown below.

$$2\ Me_3SiCl + H_2O \longrightarrow (Me_3Si)_2O \xrightarrow[60^\circ \rightarrow 140^\circ]{I_2\ /\ Al} 2\ Me_3SiI$$

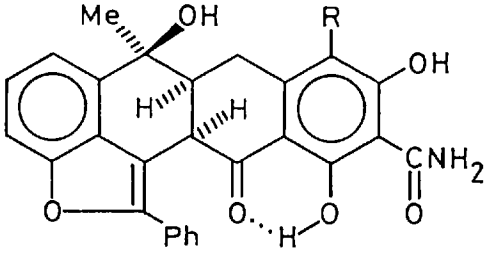
However, the reagent proved too vigorous for the diketone-ester (101) and, even in the presence of pyridine and with or without quenching with water or ammonia, only afforded many decomposition products. Therefore, this approach to (102) was also abandoned.

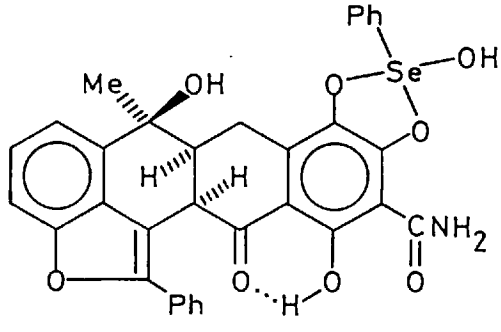
It was suspected that the presence of the free diphenolic groups of the amide (99) contributed towards its undesired behaviour with $Ph_2Se_2O_3$, as known for simpler, analogous systems [106]. Therefore, protection of the phenolic hydroxyl groups was investigated. In this connection, Cardoso [3] had already evaluated the acetyl and ethyl-carbonate (cathylate) derivatives of (99) without success. Preliminary tests now, showed that the *O*-formyl and the methoxyethoxymethyl ether (MEM) [107] derivatives were also unsuitable, mainly due to the difficulty of their preparation and their tendency to afford only *mono*-, rather than *bis*-, substituted derivatives. However, some success was achieved with the trimethylsilyl (TMS) derivatives, as detailed below.

The treatment of the amide (99) with *bis*(trimethylsilyl)-acetamide [108] was disappointing, as little or no conversion to the *tris*-TMS derivative (100) occurred. Also, since this reagent is known to degrade C-2 carboxamido tetracyclines to the corresponding nitrile under certain conditions [109], an alternative reagent was sought. Hassall and Thomas [110] have reported many TMS derivatives of tetracyclines prepared from TMS-chloride in the presence of pyridine and hexamethyldisilazane.

Accordingly, the amide (99) gave the *tris*-TMS derivative (100) quantitatively by this method; the presence of three TMS substituents could be clearly resolved by facile ^{1}H N.M.R. analysis of the non-polar derivative in carbontetrachloride solution. (Normally, Fourier transform N.M.R. spectroscopy of a dilute d^{6}-DMSO or d^{3}-MeCN solution is necessary due to the pronounced insolubility of these tetracyclic compounds.). The subsequent reaction of (100) with $Ph_2Se_2O_3$ in CCl_4, followed by *in-situ* work-up with ammonium fluoride to remove the TMS groups, gave a low yield (*ca.* 24%) of the 6,12-diketone-amide (102), characterised by U.V. and mass spectroscopy.

Whilst earlier reactions of the amide (99) with methyllithium had been frustrated by their irreproducibility [3], under the conditions employed here the carbinol (103) was prepared consistently in 80% yield. Trimethylsilylation of (103) as above gave cleanly the *tetrakis*-TMS derivative (104) (by N.M.R.). However, upon reaction with $Ph_2Se_2O_3$ at R.T. or at 0°, (104) was decomposed to many products, none of which had the properties expected of the desired keto-carbinol (105).





(105) R = H (106) R = $PhSe(O)_2$ (107)

Direct reaction of the free diphenol-carbinol (103) with $Ph_2Se_2O_3$ at 0° proceeded cleanly during the initial stages and (by tlc) to afford a bright blue-fluorescent product of lower polarity than the starting material. The reaction proceeded even better at -23° (CO_2/CCl_4 cold bath), although reaction times were long (*ca.* 48h) and during which time the temperature of the coolant was not allowed to rise above -20°.

This reaction afforded a low yield (*ca.* 23%) of a colourless, crystalline material which, by elemental microanalysis, appeared to contain a $PhSe(O)_2$ unit, and the absence of a C-8 proton (by N.M.R.) and other spectroscopic data is consistent with the structure (106), proposed above.

The relative R_f values of (106) and (103) can be explained by the anomalously low polarity of the regenerated C-12 ketone and the neighbouring C-11 hydroxyl group, due to mutual hydrogen bonding. This effect was also observed with the diketone-ester (101) and the diketone-amide (102). Also. the unexpected thermal stability of (106) (i.e. the formation of a ring-A quinone was not observed) and the absence of a selenoxide (Se=O) absorption in its I.R. spectrum, suggests that (106) may occur predominantly as the cyclic tautomer (107), for which some literature precedents exist [111]. Unfortunately, the lack of further time prohibited the extension of this work beyond this stage.

In conclusion, it is believed that this work has slightly extended an established approach to Tetracycline synthesis. Through the discovery of a new dithioacetal deprotection technique, and other reactions of the novel oxidant benzeneseleninic anhydride, it is hoped that a useful contribution has been made towards the field of organic chemistry.

EXPERIMENTAL

Melting points were determined using a Kofler block apparatus and are uncorrected.

Infra-red spectra were recorded on a Perkin Elmer 157 spectrometer against a polystyrene 1 603 cm^{-1} reference; (s) and (vs) refer to strong and very strong absorptions, respectively.

Ultra-violet and visible spectra were recorded using a Unicam S.P. 800 spectrophotometer; (sh) refers to a shoulder absorption.

Proton nuclear magnetic resonance spectra were obtained at 60 MHz on a Varian T-60 and an E.M. 360A instrument and proton and carbon-13 Fourier transform spectra (at 100 MHz and 25.16 MHz respectively) on a Varian XL 100 instrument, for solutions generally in carbon tetrachloride or deuteriochloroform with tetramethylsilane as internal standard. The following abbreviations apply to N.M.R. data: (s)-singlet, (d)-doublet, (t)-triplet, (q)-quartet, (quin)-quintet, (brd)-broad singlet, (m)-multiplet, and (env)-envelope.

Mass spetra were recorded at 70 eV. on both A.E.I. MS9 and V.G. Micromass 7070 instruments; *m/e* of fragments containing selenium were determined from the most abundant (^{80}Se) line of the isotope pattern [81].

Organic solvents were purified and dried by standard proceures [7]. Petr. ether, refers to light petroleum ether b.p. 40-60°, unless otherwise specified.

Chromatographic silica gel employed was grade MerckGF_{254} (for t.l.c. and p.l.c.) and Hopkin and Williams 100 mesh (for columns).

1. Preparation of *N,N*-Dimethylbenzamide.

Benzoyl chloride (536 ml, 4.61 mole) and CH_2Cl_2 (400 ml) were mixed in a 5l. flask and cooled to $\sim 0^{\circ}$ in an ice-salt bath. Aqueous dimethylamine solution (2 l. 26% w/v, 11.53 mole) was added slowly over 2h and the mixture efficiently stired and kept $<30^{\circ}$. After a further 1h stirring, the organic layer was separated and, with the addition of NaCl ($\sim$20g), the (aq) layer was extracted (CH_2Cl_2, 2X100 ml). The combined extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. Distillation gave a clear distillate, b.p.$_{1\ mmHg}$ 113°, which upon seeding with an authentic sample [4] yielded rosettes of the benzamide (615.1 g, 89.5%), m.p. 39-43° (lit.,[5] 41°), $\lambda_{max.}$ 220 nm (ε 5 600), $\nu_{max.}$ 1 620, 1 500, 1 410, 1 260, 1 210, 1 090, 1 070, 1 030, 810, 750, and 710 cm^{-1}, $\delta(CDCl_3)$ 7.35 (5H) and 3.0 (6H).

2. Preparation of the Vilsmeier Salt (4).

Dichloromethane (200 ml) was cooled in an acetone/CO_2 bath under a stream of dry N_2. Phosgene (160 g, 1.62 mole) was added dropwise by condensation onto a cold finger. CH_2Cl_2 (200 ml) was added to the cold soln. with the *N,N*-dimethylbenzamide soln. (120 g, 0.81 mole in dry CH_2Cl_2, 100 ml). The mixture was allowed to warm to R.T. then left to stand under a stream of dry N_2 for 24h.

Excess phosgene and solvent were removed at the high vacuum pump over 6h. The Vilsmeier salt was ground to a fine powder under N_2 and subjected to a high vacuum for a further 18h. This yielded the *α-chlorobenzaldehydo-N,N-dimethylimidinium chloride* (4)(160 g, 0.8 mole) which showed $\delta(CDCl_3$ under Argon) 8.1-7.6 (5H, m) and 4.2 (6H, s). A signal at δ 3.0 showed the presence of only 1.6% unreacted benzamide.

3. Preparation of *Peri*-Naphthofuran (3).

To the ground salt (4)(160 g, 0.8 mole) was added commercial 1,5-dihydroxynaphthalene (2, R=H)(51.2 g, 0.32 mole) and the mixture efficiently stirred under dry N_2. Nitrobenzene (120 ml) and triethylamine (220 ml) were mixed together and added to the reactants. When intimately mixed, the reaction vessel was lowered into an oil bath maintained strictly at 80° and stirring continued until complete by t.l.c. (40 min).

After cooling to R.T. in ice, ice-water (250 ml) was added and the mixture extracted ($CHCl_3$, 600 ml total) until only by-products remained in the (aq) phase. Evaporation of the solvent under reduced pressure (at $<30^{\circ}$) afforded a dark oil which, upon brief cooling and

trituration with ethanol (~200 ml) and standing in the cold for 12h, fractionally crystallised the desired product from the reaction mixture. Filtration, washing with cold EtOH and Petr. ether gave yellow needles of *2-phenylnaphtho{1,8-bc}furan-5-one* (3)(34 g, 43%), m.p. 137° (MeOH), (lit.,[6] 137-137.5°), $\lambda_{max.}$ 205, 250 (sh), 265, and 398 nm (ε 20 000, 8 000, 17 000, and 25 000), $\nu_{max.}$ (Nujol) 1 645, 1 590, 1 560, 1 295, 1 270, 1 170, 1 080, 1 065, 820, 780, and 700 cm^{-1}, δ($CDCl_3$) 8.0 (4H, m), 7.5 (5H, m), and 6.7 (1H, d, J=9Hz.).

4. Investigation of some Solvent Effects upon the Production of (3).

To the powdered Vilsmeier salt (4)(3.2 g, 16 mmol) from Expt.2 above, was added the diol (2, R=H)(1 g, 6.3 mmol) with intimate mixing. Triethylamine (5 ml) was added with the solvent under the conditions below:

(i) Nitrobenzene (10 ml) at 80° for 30 min. The mixture became yellow → orange → brown and became quite viscous; product (3) was seen by t.l.c. The reaction was quenched with water (50 ml), extracted ($CHCl_3$) and column chromatography of the residue over silica/C_6H_6 yielded (3) (552 mg, 35%), m.p. 135°.

(ii) 1,4-Dioxan (30 ml) at 40° for 3.5h. The mixture became yellow → light brown and only a trace of (3) was detected by t.l.c. Quenching with water (50 ml) and extraction ($CHCl_3$) recovered no (3); only a cream coloured material (562 mg) was isolated which, after washing (EtOH) showed m.p. 236-8°, c.f. lit.,[8] 242.5° for *1,5-dibenzoyloxynaphthalene* (2, R=PhCO), $_{max.}$ (Nujol) 1 730, 1 590, 1 270, 1 235, and 1 090 cm^{-1}, and ^1H N.M.R. showed mainly aromatic protons: δ 7.3-8.3.

A sample of (2, R=PhCO) was refluxed with 2M NaOH, acidified (conc.HCl), extracted (Et_2O), dried (Na_2SO_4) and upon evaporation the residue was subjected to t.l.c. analysis giving positive correlations against references of (2, R=H) and benzoic acid.

(iii) 1,4-Dioxan (30 ml) at 80° for 75 min. The mixture became yellow → brown and t.l.c. showed only a trace of (3); the major product at this higher temp. was (2, R=PhCO) again.

(iv) Carbon disulphide (30 ml) at reflux (47°) for 45 min. Of the small amount of (2, R=H) which reacted,only (2, R=PhCO) was produced. No attempt was made to work-up the reaction mixture.

5. Preparation of W2 Grade Raney Nickel [9].

Raney's alloy (Ni/Al_2, 300 g) was added in small portions to a rapidly stirred soln. of NaOH (380 g, in 1.5 l H_2O) in a 4 l beaker cooled in an ice-salt bath. The temp. was maintained <25° in order to moderate H_2 evolution (over 5h). After standing at R.T. overnight the mixture was then heated on a steam bath with stirring for 12h.

Upon cooling, the soln. was decanted and a fresh soln. of NaOH (100 g, in 2 l H_2O) was added with stirring and brief heating. The black mass of Raney nickel then settled readily and by a process of decantation and washing with water (30 times) all the alkali was removed (to pH 7, paper). The metal was washed with 95% EtOH (10 times) then absolute EtOH (5 times) and finally transferred to a bottle and stored under abs. EtOH. The activity of the catalyst was demonstrated by its pyrophoric nature upon drying.

6. Preparation of 3,4-Dihydro-*peri*-naphthofuran (5).

Perinaphthofuran (3)(10 g, 40 mmol) was dissolved in dry toluene (800 ml) and briefly heated to effect solution. The soln. was filtered (Celite) into a 2 l. conical hydrogenation vessel and alcohol-free Raney nickel (∿5 g) was added. Up to 1/3 of the theoretical amount of H_2 was then absorbed (100 mlg^{-1}) after which the spent catalyst was filtered off (Celite, with destruction in HNO_3- *CARE !*), fresh catalyst added and the whole process repeated twice more. Before the final catalyst addition, the volume of solvent was reduced to ∿300ml by evaporation under reduced pressure.

After complete reaction (t.l.c. silica/$CHCl_3$/MeOH 20:1) the catalyst and toluene were removed and the residue recrystallised from MeOH to afford *3,4-dihydro-2-phenylnaphtho{1,8-bc}furan-5-one* (5)(7 g, 70%), m.p. 113-4° (lit.,[1] 113-4°), $\lambda_{max.}$ 275 and 360 nm (ε 20 000 and 12 500), $\nu_{max.}$ (Nujol) 1 680, 1 285, 1 255, 1 220, 1 100, 1 145, 795, 775, 760, 745, and 700 cm^{-1}, δ($CDCl_2$) 7.9-7.2 (8H, m), 3.47 (2H, t, J=7Hz.), and 2.97 (2H, t, J=7Hz.).

7. Preparation of the Model Tricyclic Aldehyde (7).

3,4-Dihydro-*peri*-naphthofuran (5)(5 g, 20 mmol) and *ortho*-phthaldialdehyde (6)(3.75 g, 28 mmol) were mixed together in a 250 ml 3-neck flask fitted with a Soxhlet apparatus containing thimbles of

activated alumina. Abs. EtOH (100 ml) and Et_3N (20 ml) were added and the mixture refluxed for 8h under N_2 (the Al_2O_3 was changed every 2h and Et_3N (2 ml) added).

Upon cooling to R.T. and standing for 14h, the crystallised product was filtered off and recrystallised (CH_2Cl_2/Me_2CO) to yield *4(2-formylbenzyl)-2-phenylnaphtho{1,8-bc}furan-5-one* (7)(5.87 g, 80%), m.p. 140-2° (lit.,[10] 142-4°), $\lambda_{max.}$(EtOH) 257 and 402 nm (ε 20 000 and 30 000), $\nu_{max.}$ (Nujol) 1 685, 1 630, 1 260, 1 195, 1 060, 1 020, 870, 800, 780, and 760 cm^{-1}, δ($CDCl_3$) 10.35 (1H, s), 8.07-7.33 (13H,m), and 4.42 (2H, s).

8. Preparation of the 1,3-Dithiolane derivative of the Aldehyde (7).

The aldehyde (7)(1 g, 2.7 mmol) was added to dry benzene (40ml), AcOH (50 ml), 1,2-ethanedithiol (2 ml), and $BF_3.Et_2O$ (1 ml, dropwise) with stirring in the dark. The reaction was complete in 75 min (t.l.c., silica/C_6H_6/EtOAc 4:1) and the reagents quenched by pouring into satd. (aq) $NaHCO_3$ (300 ml). Extraction (CH_2Cl_2), drying (Na_2SO_4) and evaporation to dryness gave a bright yellow residue which, after column chromatog. (silica/C_6H_6/C_6H_6-EtOAc 10:1 → 5:1) and recrystallisation (EtOH), gave *4(2,2'(1',3'-dithiolanyl)benzyl)-2-phenylnaphtho{1,8-bc}furan-5-one* (8)(1.12 g, 93%), m.p. 184-7° (lit.,[13] 185-7.5°), $\lambda_{max.}$($CHCl_3$) 267 and 395 nm (ε 16 000 and 28 400), $\nu_{max.}$(Nujol) 1 636, 1 560, 1 260, 1 060, 1 025, 765, and 690 cm^{-1}, δ($CDCl_3$) 8.0-7.17 (13H,m), 5.93 (1H, s), 4.13 (2H, d, J=2Hz.), and 3.4 (4H, m).

9. Photocyclisation of the Dithioacetal (8) to (9).

The dithioacetal (8)(1 g, 2.3 mmol) was added to dry deoxygenated benzene (600 ml) under N_2. The catalytic base $LiN(SiMe_3)_2$ (61 mg, 0.16 equiv.)-prepared from *n*-butyllithium (1.5M, 2 ml) and 1,1,1,3,3,3-hexamethyldisilazane (1 ml) in dry THF (10 ml) over 1h, and dried under vac. for 4h- was added quickly to the reaction soln. and the mixture irradiated with three 250 Watt tungsten lamps for 85 min. The reaction was followed by t.l.c. (silica/C_6H_6/$CHCl_3$ 5:2) and by U.V. spectroscopy (395 → 354 nm).

The benzene soln. was washed with satd. (aq) KH_2PO_4 (100 ml) and water (100 ml), after which drying ($MgSO_4$), evaporation under reduced pressure, and recrystallisation of the residue (CH_2Cl_2/MeOH, with Et_2O washing) yielded *12-ethylenedithiaspiro-6aα,7,12,12aα-tetrahydro-1-phenyl(6H)naphthaceno{1,12-bc}furan-6-one* (9)(752 mg, 75%), m.p.226-9°

(lit.,[13] 221-8°), $\lambda_{max.}$($CHCl_3$) 276 and 354 nm (ε 21 000 and 10 500), $\nu_{max.}$(Nujol) 1 690, 1 255, 1 070, 760, and 700 cm^{-1}, δ($CDCl_3$) 8.0-7.17 (12H, m), 4.75 (1H, d, J=3Hz.; *cis*-coupling), and 4.0-2.7 (7H, m).

Photolysis of the above reaction mixture with a quartz/halogen lamp (Atlas Al-233, 650 Watt) permitted routine preparation of the cyclised product (9) on a larger scale (2 g, 85%) over shorter irradiation times (30 min).

10. Preparation of the Carbinol (10) with Methyl Lithium.

The tetracyclic ketone (9)(150 mg, 0.34 mmol) was added to dry, deoxygenated THF (15 ml) under N_2 , cooled to -78° and the soln. stirred rapidly. Methyllithium (1.8M, Et_2O: 1 ml) [21] was added dropwise and after 30 min this was repeated.

The reaction was quenched by the addition of solid NH_4Cl (2 g) at -78° then water (2 ml), followed by extraction (CH_2Cl_2), drying (Na_2SO_4), evaporation of the solvent and recrystallisation of the residue (CH_2Cl_2/MeOH) gave a mixture of (9) and the carbinol (10), (150 mg). After drying the mixture *in-vacuo* overnight, the above process was repeated three more times and at each intermediate stage the yields of the mixture of (9) and (10) were: (130 mg) and (93 mg). Finally, p.l.c. (silica/C_6H_6/EtOAc 10:1) gave the crystalline tetracyclic product *12-ethylenedithiaspiro-6aα,7,12,12aα-tetrahydro-6α-methyl-1-phenyl(6H) naphthaceno{1,12-bc}furan-6β-ol* (10)(54 mg, 35%),m.p. 218-20° , $\lambda_{max.}$(CH_2Cl_2) 310 nm (ε 15 800), c.f. $\lambda_{max.}$ 305 nm (ε 17 990) for the corresponding 6-hydroxy-6-demethyl case (ref. 13), $\nu_{max.}$(CH_2Cl_2) 3 400 cm^{-1}, δ($CDCl_3$) F.T. 7.85-7.02 (12H, m), 4.27 (1H, brd), 3.32-2.72 (7H, m), 1.76 (1H, s), and 1.52 (3H, s), *m/e* 456 M^+ (very weak), 441, 438, meta-stable 421 (calc. 420.7), and base peak 166.

11. Attempted Preparation of the 6,2' - Oxirane (12).

Sodium hydride (120 mg, 5 mmol) as an 80% dispersion in oil (150 mg) was washed three times with Petr. ether, the soln. decanted and the residue dried *in-vacuo*. Dimethylsulphoxide (5 ml) was added and the mixture heated to 60° for 1h, after which H_2 evolution ceased. The methylsulphinyl carbanion soln. was cooled to R.T. and dry THF (8 ml) added, then the mixture cooled to -10° in an ice-salt bath.

Trimethylsulphonium iodide (1.02 g, 4.3 mmol) in DMSO (6 ml) and THF (2 ml) was added slowly over 3 min to the stirred soln. The tetracyclic ketone (9)(100 mg, 0.23 mmol) in DMSO (2 ml) was added

quickly, and stirring continued at -10° for 30 min, then with the cold bath removed until R.T. was attained. (N.B. the ylide decomposes at temps. >0°) [25]. Ice-water (100 ml) was added and the mixture extracted ($CHCl_3$) and subsequently p.l.c. gave *12-ethylenedithiaspiro-6aα,7,12,12aα-tetrahydro-1-phenyl(6H)naphthaceno{1,12-bc}furan-6,2'-oxirane* (12) as an impure brown powder (5 mg, 5%), δ($CDCl_3$) 3.0, *m/e* 454 M^+.

12. Preparation of the Dithioacetal (15).

Cyclohexanone (5 g, 51 mmol) was added to benzene (20 ml), AcOH (20 ml), 1,2-ethanedithiol (4.5 ml, 54 mmol), and $BF_3.Et_2O$ (46 ml, 153 mmol) and the mixture stirred for 1h; complete by t.l.c. (silica/C_6H_6/EtOAc 4:1). The mixture was poured into satd. (aq) $NaHCO_3$ (300 ml), extracted (CH_2Cl_2), dried (Na_2SO_4), evaporated to dryness and the oily residue distilled under reduced pressure to yield *spiro{2,1'-cyclohexane-1,3-dithiolane}* (15)(5.18 g, 58%), b.p.$_{0.1mmHg}$ 100-10°, (lit.,[26] b.p.$_{6mmHg}$ 114-5°), $\nu_{max.}$ (film) 2 900, 2 850, 1 440, 1 275, 1 130, 1 020, and 780 cm^{-1}, δ(neat) 3.23 (4H, s) and 2.0-1.4 (10H,env).

13. Preparation of the Dithioacetal (16).

Method [12] as in Expt 12 above with the following quantities: benzaldehyde (5 g, 47 mmol), 1,2-ethanedithiol (4.2 ml, 50 mmol), $BF_3.Et_2O$ (42 ml, 141 mmol) and 1h reaction time. Work-up as before gave *2-phenyl-1,3-dithiolane* (16)(6.58 g, 77%), b.p.$_{0.1mmHg}$ 100-4°, (lit.,[27] b.p.$_{0.7mmHg}$ 109°), $\nu_{max.}$(film) 3 000, 2 900, (2 000-1 660: overtone and combination band fine structure), 1 600, 1 495, 1 450, 1 420, 1 280, 1 088, 1 035, 880, and 710 cm^{-1}, δ(neat) 7.6-7.0 (5H, m), 5.6 (1H, s), and 3.08 (4H, m).

14. Preparation of the Dithioacetal (17).

Method [12] as in Expt. 12 above with the following quantities: benzophenone (3.479 g, 19.1 mmol), 1,2-ethanedithiol (1.6 ml, 19.2 mmol, 1 equiv.), $BF_3.Et_2O$ (10 ml, ~4 equiv.), and 3 days reaction time at R.T. Work-up as above , followed by crystallisation, column chromatog.(silica/C_6H_6) and recrystallisation (C_6H_6) afforded *2,2-diphenyl-1,3-dithiolane* (17)(4.77 g, 96%), m.p. 105-6°, $\nu_{max.}$ ($CHCl_3$) 3 040, 2 950, (2 200, 1 960, 1 910, 1 815), 1 600, 1 490, 1 450, 1 115, 1 280, 1 080, and 1 040 cm^{-1}, δ($CDCl_3$) 7.7-7.1 (10H, m) and 3.33 (4H, s), *m/e* 258 M^+, 230, 229, and meta-stable 205, calc. 205.04.

15. Preparation of the Dithioacetal (18).

Method [12] as in Expt. 12 above with the following quantities: α-tetralone (5 g, 34 mmol), 1,2-ethanedithiol (3.2 ml, 38 mmol), $BF_3.Et_2O$ (31 ml, 102 mmol), and 4h reaction time. Work-up as before yielded *3',4'-dihydrospiro{1,3-dithiolane-2,1'(2'H)naphthalene}* (18) (5.1 g, 67%), m.p. 50-3°, b.p. $_{0.1mmHg}$ 110-115°, $\nu_{max.}$ (Nujol) 1 275, 1 155, 1 065, 943, and 755 cm^{-1}, δ ($CDCl_3$) 7.9-7.1 (4H, m), 3.47 (4H,m), 2.77 (2H, t, J=6Hz.), 2.3 (2H, env), and 2.0 (2H, env).

16. Preparation of the Dithioacetal (19).

Method[12] as in Expt. 12 above with the following quantities: 5α-cholestan-3-one (346 mg, 0.89 mmol), 1,2-ethanedithiol (0.1 ml, 1.2 mmol), BF_3Et_2O (1 ml, ∿5 equiv.), and 30 min reaction time. Work-up as before, followed by recrystallisation (Petr. ether) gave needles of *spiro{2,3'-cholestane-1,3-dithiolane}* (19)(372 mg, 90%), m.p. 143-4°, (lit.,[12] 142-4°).

17. Preparation of the Dithioacetal (20).

Method [12] as in Expt. 12 above with the following quantities: 5α-cholestan-3-one (2.001 g, 5.18 mmol), 1,3-propanedithiol (0.57 ml, 5.7 mmol, 1.1 equiv.), $BF_3.Et_2O$ (3 ml, ∿4.6 equiv.), and reaction time 3.5h at R.T. Work-up as before , followed by recrystallisation (Petr. ether) gave *spiro{2,3'-cholestane-1,3-dithiane}* (20)(2.05 g, 83%), m.p. 137-8° , *m/e* 476 M^+, 402, 401, 369, and 247 , meta-stables: 338-9 and 286, calc. 476 → 402: 339.5; 476 → 401: 337.8; 476 → 369: 286.0 .

18. Deprotection of 1,3-Dithiolanes *via* Methylation Reagents.

A. Methyl Iodide.

Using the conditions of Fetizon and Jurion [28], the substrates were refluxed with methyl iodide in aqueous acetone containing Na_2CO_3 as a buffer. Work-up was by evaporation of the solvent and excess MeI followed by p.l.c. to isolate the regenerated ketone.

(i) α-Tetralone. The parent 1,3-dithiolane (18)(508.8 mg, 2.29 mmol) and MeI (1.4 ml, 10 equiv.), after heating at reflux for 2 weeks gave the ketone (110.2 mg, 33%).

(ii) 5α-Cholestan-3-one. The parent 1,3-dithiolane (19)(37.5 mg, 81 μmol), and MeI (0.1 ml, 21 equiv.), after heating at reflux for 2 weeks gave the ketone (6.5 mg, 21%).

(iii) Model Tetracyclic Diketone (21). The parent 1,3-dithiolane (9)(47.1 mg, 0.1 mmol) and MeI (0.1 ml, 15 equiv.), after heating at reflux for 2 weeks gave no diketone (21).

B. Magic Methyl$^{(R)}$ ($MeOFSO_2$).

The reagent was used in dry benzene at R.T. under N_2 according to the method of Ho and Wong [29]. Work-up was by the addition of 2M NaOH to pH 7, extraction (C_6H_6), followed by p.l.c. to isolate the regenerated ketone.

(i) α-Tetralone. The parent 1,3-dithiolane (18)(448.4 mg, 2.2 mmol) and $MeOFSO_2$ (1.6 ml, 10 equiv.), after 3h gave the ketone (149.2 mg,45%).

(ii) 5α-cholestan-3-one . The parent 1,3-dithiolane (34.2 mg, 74 μmol) and $MeOFSO_2$ (0.1 ml, 17 equiv.), after 2.5h gave the ketone (25.8 mg,90%).

(iii) Model Tetracyclic Diketone (21). The parent 1,3-dithiolane (9) (52.5 mg, 0.12 mmol) and $MeOFSO_2$ (0.1 ml, 10 equiv.) were reacted together over 22h. T.l.c. (silica/C_6H_6 x 2) showed a clean yellow product with a strong yellow fluorescence (366 nm) of similar R_f to (21), yet clearly not the desired diketone.The following data is consistent with the product being the known [10] aromatic ketone *1-phenyl(6H)naphthaceno{1,12-bc}furan-6-one* (22)(15.2 mg, 37%), m.p. 248-8.5° , (lit.,[10] 245°), $\lambda_{max.}$ (MeOH) 222 (sh), 250, 312, 332, 400 (sh), and 422 nm (ε 24 600, 50 600, 18 300, 16 000, 6 200, and 7 800), $\nu_{max.}$ ($CHCl_3$) 1 650 cm^{-1}, δ($CDCl_3$) F.T. showed only aromatic protons, *m/e* 346 M^+.

19. Reaction of the Dithioacetal (18) with Selenium Dioxide.

The dithioacetal (18)(1.22 g, 5.5 mmol), and SeO_2 (690 mg, 6.2 mmol) were stirred together in a mixture of benzene (25 ml) and AcOH (1 ml). Water (1 drop) was added and the mixture heated at reflux for 3h, after which t.l.c. detected some α-tetralone together with many other products. Separation by p.l.c. yielded <1% α-tetralone.

20. Preparation of the Mono-*S*-oxide of (15).

The dithioacetal (15)(163 mg, 0.94 mmol) was dissolved in dry CH_2Cl_2 (40 ml) and cooled to -78° . Ozone-rich oxygen was bubbled through the soln. for 2h and the oxidation followed by t.l.c. (silica/ $C_6H_6/CHCl_3$ 10:1) and by solution phase I.R. (CH_2Cl_2). Argon was then passed through the cold mixture for 1h to displace excess O_3 , dimethylsulphide (2 ml) added with stirring over 45 min, then the soln. was

warmed and the solvent evaporated. Upon standing overnight in the cold, the product crystallised. Recrystallisation (Petr. ether 30-40°) gave *spiro{2,1'-cyclohexane-1,3-dithiolane-1-oxide}* (44.6 mg), m.p. 84-5°, $\nu_{max.}$ (CH_2Cl_2) 1 060 cm^{-1}, $\delta(CDCl_3)$ 3.3 (4H, m) and 2.0-1.7 (10H, env), *m/e* 190 M^+ and base peak 81.

21. Preparation of the Mono-*S*-oxide of (16).

Method as in Expt. 20 above with the following quantities: the thioacetal (16)(214 mg, 1.2 mmol) with ozone for 3h gave, after recrystallisation (C_6H_6) *2-phenyl-1,3-dithiolane-1-oxide* (171 mg), m.p. 57-8°, $\nu_{max.}$(CH_2Cl_2) 1 060 cm^{-1}, *m/e* 198 M^+ and base peaks 122 and 121.

22. Preparation of the Mono-*S*-oxide of (17).

The dithioacetal (17)(1.112 g, 4.31 mmol) in AcOH (30 ml) was treated with H_2O_2 (32%, (aq), 0.5 ml, 1.1 equiv.) at R.T. for 24h. After pouring the soln. carefully into satd. (aq) $NaHCO_3$ (300 ml) the (aq) layer was extracted ($CHCl_3$), dried (Na_2SO_4), and upon evaporation of the solvent, recrystallisation of the residue (C_6H_6/Petr. ether) gave *2,2-diphenyl-1,3-dithiolane-1-oxide* (1.05 g, 89%), m.p. 124-6°, (lit.,[33] 131-2°), $\nu_{max.}$($CHCl_3$) 1 060 cm^{-1}, $\delta(CDCl_3)$ 7.7-7.2 (10H, m) and 3.3-3.0 (4H, complex, m), *m/e* 274 M^+, 258, 198, and 165, meta-stable 137.5, calc. 198 → 165: 137.5 .

23. Preparation of the Mono-*S*-oxide of (18).

Method as in Expt. 20 above with the following quantities: the dithioacetal (18)(221 mg, 0.99 mmol) with ozone for 6.5h gave a mixture of products containing α-tetralone (15 mg, 8%) and the monoxide as an oil, which upon standing in the cold crystallised to afford *3',4'-dihydrospiro{1,3-dithiolane-2,1'(2'H)naphthalene-1-oxide}* (126mg), m.p. <20°, $\nu_{max.}$(CH_2Cl_2) 1 060 cm^{-1}, *m/e* 238 M^+.

24. Acid Catalysed Hydrolysis of the 1,3-Dithiolane-*S*-oxides.

The corresponding monosulphoxides of each of the 1,3-dithiolanes (15)-(18) were treated at R.T. with either dil. HCl (0.1M) or satd. (aq) KH_2PO_4 to afford the derived carbonyl compounds as shown in the table below:

Mono-*S*-oxide of:	HCl; Time	Yield	KH_2PO_4; Time	Yield
(15)	21h	53%	-	-
(16)	5h	77%	2d	61%
(17)	5h	85%	3d	70%
(18)	4h	81%	2d	55%

25. Ozonolysis of the Carbinol (10).

The carbinol (10)(37.2 mg, 81.5 μmol) was dissolved in dry CH_2Cl_2 (4 ml) and O_3 rich O_2 was passed through the soln. for 4h at -78° until no (10) remained by t.l.c. Dry N_2 was passed to dispell excess O_3 at -78° for 45 min and the ozonide was decomposed with Me_2S (1 ml) with stirring at -78° over 30 min and gradual warming to R.T.

Partial evaporation of the solvent precipitated a product which, after recrystallisation (EtOH) gave *12-ethylenedithiaspiro-6aα,7,12,12aα-tetrahydro-6α-methyl-1-phenyl(6H)naphthaceno{1,12-bc}furan-6β-ol-mono-S-oxide* (24)(14.7 mg, 38%), m.p. 146-7°, $\nu_{max.}$ (CH_2Cl_2) 1 040 cm^{-1}, $\lambda_{max.}$ 310 nm (ε 14 900), *m/e* 454 M^+-18.

Repetition of this procedure with the addition of satd.(aq) KH_2PO_4 (0.5 ml) during work-up, gave after p.l.c. (silica/$CHCl_3$/EtOAc 1:1) a blue-fluorescent product *6-methyl-5,11,11a,12-tetrahydro-11,12-dioxonaphthacene-10-yl-benzoate* (25, R=PhCO)(800 μg, 3%), m.p. (EtOH) 204-6°, $\lambda_{max.}$ 300, 384, and 402 (sh) nm (ε 14 500, 16 300, and 15 200), *m/e* 394 M^+ , 105, and 77.

26. Attempted Condensation of (7) with 2-Aminoethanol.

The model tricyclic aldehyde (7)(500 mg, 1.37 mmol) and 2-aminoethanol (0.1 ml, 95%, 92 mg, 1.1 equiv.) were heated together in boiling benzene (40 ml) under N_2 in the dark. Water was azeotropically separated from the reaction using a Dean-Stark apparatus. After 22h no depletion of (7) was seen, so more 2-aminoethanol (1 ml, 11 equiv.) was added. After 7h the mixture was very dark in colour and only decomposition products were observed by t.l.c. This reaction was abandoned and not pursued further.

27. Condensation of (7) with 2-Aminoethanethiol.

The aldehyde (7)(300 mg, 0.82 mmol) and 2-aminoethanethiol (72 mg, 1.1 equiv.- previously liberated from the stock hydrochloride with MeONa/MeOH) were heated together in boiling benzene (40 ml) under

N_2 in the dark for 12h, with the separation of water as above. T.l.c (silica/C_6H_6/EtOAc 4:1) indicated the formation of a new product of lower R_f than (7). Evaporation of the solvent, p.l.c. (silica/$CHCl_3$), drying *in-vacuo* afforded a yellow solid, yet unrecrystallisable "glass", of the (NH) thiazolidine derivative *4(2,2'(1',3'-thiazolidinyl)benzyl)-2-phenylnaphtho{1,8-bc}furan-5-one* (29)(343 mg, 98%), $\lambda_{max.}$ 249, 266, and 402 nm (ε 14 800, 17 000, and 25 200), $\nu_{max.}$(Nujol) 3 500, 1 645, 1 590, 1 575, and 695 cm^{-1}, δ ($CDCl_3$) 8.0-7.3 (12H, m), 5.8(1H,s), 4.2 (2H, s), 3.1 (4H, s), and 2.2 (NH, brd), *m/e* 423 M^+ and 362.

28. Preparation of *N*-Methyl-2-aminoethanethiol (34).

2-Aminoethanethiol hydrochloride (31)(25.95 g, 0.23 mole) and (aq) formaldehyde (40%, 17 ml, 1 equiv.) were stirred together in water (40 ml) under N_2 at R.T. for 24h (CaO tube fitted to prevent CO_2 absorption). Removal of the water under reduced pressure afforded after recrystallisation (EtOH) long needles of *thiazolidine hydrochloride* (32) (24 g, 83%), m.p. 180°(dec.) (lit.,[37] 180°(dec.)). The free base could be liberated with (aq) K_2CO_3 to give *1,3-thiazolidine* (33) b.p.$_{0.2mmHg}$ 25°, n_D^{21} 1.550 (lit.,[37] n_D^{30} 1.551), $\nu_{max.}$(neat) 3 300, 2 980, and 850 cm^{-1}, δ(neat+TMS) 4.1 (2H, s), 3.2-2.6 (4H, m), and 2.3 (1H, s).

Thiazolidine hydrochloride (32)(13.55 g, 107 mmol) was added slowly to a stirred suspension of $LiAlH_4$ (9.5 g, 250 mmol, 2.34 equiv.), in dry THF (400 ml) under dry N_2 at R.T. By t.l.c. (silica/EtOAc) all (32) was consumed after 25 min. The reaction mixture was worked-up by a standard procedure [39,40], involving cooling in an ice-bath, addition of ice-water (9 ml), 10% NH_4Cl (aq)(9 ml), followed by more water (27 ml). The alumina precipitate was filtered off under N_2 (N.B. the oxidation of the product (34) to the disulphide was found to be very facile in air), washed with dry Et_2O, the combined filtrates partially evaporated, dried (Na_2SO_4), and finally evaporated to dryness.

The crystalline residue was resublimed under high vacuum at R.T. (CO_2/acetone cold finger) to yield *N-methyl-2-aminoethanethiol* (34) (646 mg, 7%), m.p. 40-45° (lit.,[38] 48-54°) , $\nu_{max.}$($CHCl_3$) 3 350, 2 900, and 2 500 cm^{-1}, δ ($CDCl_3$) 2.73 (4H, m), 2.43 (3H, s), and 1.70 (2H, s, exch. D_2O, i.e. SH and NH are coincident). The sample appeared to be free from the other possible reduction product; *2-methylthioethylamine*[42], by N.M.R.

29. Repeat $LiAlH_4$ Reduction of (32) with EDTA and Rochelle Salt Work-Up.

Thiazolidine hydrochloride (32)(11.86 g, 94.5 mmol) was reduced by $LiAlH_4$ (3.35 equiv.) as in Expt. 28 above. After normal work-up and filtration, the THF/Et_2O filtrate gave (34) in similar yield as before. The alumina cake was divided roughly into two halves, still under N_2, and each half treated as follows:

(a) EDTA disodium salt.$2H_2O$ (28 g) was dissolved in the minimum of water (600 ml) and mixed with the alumina.

(b) Rochelle's salt [41] (27 g) was dissolved in the minimum of water (150 ml) and mixed with the alumina.

In both cases none of the adsorbed, water soluble, product(34) could be extracted (Et_2O, $CHCl_3$, CH_2Cl_2, etc.) so therefore complexation of the alumina did not improve the overall yield.

30. Non-Aqueous Reduction of (32) by Sodium in Liquid Ammonia.

Thiazolidine hydrochloride (32)(2 g, 15.9 mmol) was added slowly under dry N_2 to a blue solution of sodium (800 mg, 34.7 mmol, 2.18 equiv.) in liquid NH_3 (∿150 ml, condensed from a stock cylinder) at -78°. The deep blue colour of the soln. was discharged after 90% of (32) had been added therefore, after introducing the remainder, small pieces of sodium were added until a pale blue colour persisted.

The mixture was stirred at -78° for 1.5h, then solid NH_4Cl (∿2 g) was added and the soln. allowed to warm to R.T. with evaporation of the NH_3 over 3h. The colourless residue was extracted (Et_2O),filtered, and dried (Na_2SO_4) under N_2, and evaporation of the Et_2O afforded colourless crystals of (34) which, after resublimation yielded (600 mg, 41%), with identical properties as above (Expt. 28).

31. Condensation of the Aldehyde (7) with (34).

Method as for Expt. 27 above, with the following quantities: the aldehyde (7)(300 mg, 0.82 mmol) and (34)(101 mg, 1.11 mmol, 1.35 equiv.) in benzene for 4 days (t.l.c. control). Work-up, followed by p.l.c. (silica/$CHCl_3$) and drying *in-vacuo* afforded a yellow solid, yet unrecrystallisable "glass", of the (NMe) thiazolidine derivative *4(2,2'(3'-methyl-1',3'- thiazolidinyl)benzyl)-2-phenylnaphtho{1,8-bc} furan-5-one* (30)(262 mg, 73%), $\lambda_{max.}$ 250, 267, and 402 nm (ε 12 500, 17 600, and 26 300), $\nu_{max.}$(Nujol) 1 650, 1 600, and 1 580 cm^{-1},

δ ($CDCl_3$) 8.0-7.1 (12H, m), 5.06 (1H, s), 4.06 (2H, brd), 3.3-2.6 (4H,m), and 2.18 (3H, s), *m/e* 437 M^+, 377, and 362.

32. Photocyclisation of the (NH) Thiazolidine (29).

To (Na)-dry benzene (750 ml), previously deoxygenated by N_2 at reflux over 1h, was added the (NH) thiazolidine (29)(200 mg, 0.47mmol), and some of the benzene distilled from the soln. to azeotropically remove any remaining water. The catalytic base $LiN(SiMe_3)_2$ (20 mg, 0.25 equiv.) was added and the mixture irradiated with three 250 Watt tungsten lamps over 3h (t.l.c. and U.V. control). Upon cooling, work-up was by the addition of satd. (aq) KH_2PO_4 (to pH 7, paper), extraction (C_6H_6/$CHCl_3$), drying (Na_2SO_4), evaporation under reduced pressure, and column chromatog. (silica/C_6H_6/$CHCl_3$) gave apparently only one epimeric form of the colourless tetracyclic derivative *12-ethyleneazathiospiro-6aα,7,12,12aα-tetrahydro-1-phenyl(6H)naphthaceno{1,12-bc}furan-6-one* (35) (37 mg, 19%), m.p. ($CHCl_3$/EtOH) 175-6°(dec.), $\lambda_{max.}$(EtOH) 275, 295(sh), 307(sh), and 350 nm (ε 20 350, 13 500, 9 900, and 13 500), $\nu_{max.}$($CHCl_3$) 1 700 cm^{-1}, δ ($CDCl_3$) 8.0-7.2 (12H, m), 4.38 (1H, d, J=5Hz.), and 4.2-2.6 (7H, m), *m/e* 423 M^+, 422, 421, and 407. (Found: C, 76.65; H, 4.95; N, 3.2; S, 8.0 . $C_{27}H_{21}O_2NS$ requires C, 76.6; H, 4.9; N, 3.3; S,7.55%).

33. Repeat Photolysis of (29) with a Quartz/Halogen Lamp.

Photolysis of (29)(254 mg, 0.6 mmol) with base (17.9 mg,0.2equ) in C_6H_6 (1.5 l) with an Atlas Al-233 , 650 Watt quartz/halogen lamp gave the cyclised product after only 6 min (U.V. control). Yield (35)(53.2 mg, 20%).

34. Photocyclisation of the (NMe) Thiazolidine (30).

Method as for Expt. 32 above with the following quantities: (30)(132 mg, 0.3 mmol), base (13 mg, 0.26 equiv.), C_6H_6 (1.0 l), with tungsten lamp irradiation for 1h. Work-up as above gave a colourless mixture of α-aza-β-thio and α-thio-β-aza isomers in the approximate ratio 1:1 (by N.M.R. integration of the two N-Me signals). All attempts to separate these epimers by p.l.c. were unsuccessful. The mixture of epimers of *N-methyl-12-ethyleneazathiospiro-6aα,7,12,12aα-tetrahydro-1-phenyl(6H)naphthaceno{1,12-bc}furan-6-one* (36) showed yield (77 mg, 58%), m.p. ($CHCl_3$/EtOH) 192-4° (dec.), $\lambda_{max.}$(EtOH) 278 and 354 nm ,

(ε 23 500 and 11 600), $\nu_{max.}$ (Nujol) 1 700 cm^{-1}, δ($CDCl_3$) 8.0-7.2 (Ar,m), 4.46 (1H, d relative to NMe^1, J=6Hz.), 4.0-2.4 (complex), 2.08 (NMe^1), and 1.63 (NMe^2), *m/e* 437 M^+, and 375. (Found: C, 76.7; H, 5.15; N, 3.1. $C_{28}H_{23}O_2NS$ requires C, 76.9; H, 5.25; N, 3.2 %).

35. Repeat Photolysis of (30) with a Quartz/Halogen Lamp.

Photolysis of(30)(130 mg, 0.29 mmol) with base (13 mg, 0.25 equ) in C_6H_6 (1.5 l) with an Atlas Al-233, 650 Watt lamp gave the cyclised product after only 5 min (U.V. control. Yield (36) (84 mg, 65%).

Deprotection of Tetracyclic Model Compounds.

36. (NH) and (NMe) Thiazolidine-masked Compounds.

Preliminary attempts were made on a small scale at the cleavage of the thiazolidine moiety in the tetracyclic derivatives with H^+, MeO^-, $Ph_2Se_2O_3$ and MeI without success. However, more successful attempts include:

(All reactions were performed in (aq) THF under N_2 and at R.T. in the light, unless otherwise stated).

A. $AgNO_3$

(i) (35)(6.9 mg) and $AgNO_3$ (excess) were reacted under neutral conditions over 4 days. Only a trace of the diketone (21) was observed.

(ii) (35)(several mg), $AgNO_3$ (excess) and AcOH (added to pH 4) were reacted over 2h. The mixture was bright yellow, gave no precipitate and gradually became darker. A trace of the diketone (21) was observed.

(iii)(35)(11.8 mg), $AgNO_3$ (excess) and HNO_3 (added to pH 3) were reacted over 30 min. A yellow precipitate formed and became darker. Yield of diketone isolated by p.l.c. (21)(6.5 mg, 64%).

(iv) (35)(several mg), $AgNO_3$ (excess) and sufficient NH_3 to dissolve the precipitate, were reacted over 2h. Only base-line material (t.l.c.) was produced and neutralisation did not liberate any diketone (21).

(v) (36)(11.6 mg), $AgNO_3$ (excess) at pH 7 over 4 days. Gave a trace (21).

(vi) (36)(several mg), $AgNO_3$ (excess) and AcOH (pH 4) over 2h. Gave only dark base-line material and a purple coloured product, not the diketone.

(vii)(36)(23 mg), $AgNO_3$ (excess), HNO_3 (pH 3) over 1 day. A yellow ppt. formed upon mixing. Yield of diketone (21)(2.8 mg, 15%).

(viii) (36)(several mg), $AgNO_3$ (excess) and sufficient NH_3 to dissolve the ppt. Immediate decomposition upon mixing.

B. HgO and $HgCl_2$

(i) (35)(8.3 mg) with $HgCl_2$ (8.5 mg, 1.6 equiv.) and $CaCO_3$ (excess) in (aq) MeCN. No reaction after 6 days at R.T.

(ii) (36)(16.5 mg) with $HgCl_2$ (11 mg, 1.06 equiv.) and $CaCO_3$ (excess) in (aq) MeCN. A brown ppt. formed,after 72h filtration and p.l.c. twice of the filtrate gave the diketone (21)(4.4 mg, 32%).

(iii) (36)(20.1 mg), HgO (red, 13.7 mg, 1.37 equiv.) and $BF_3.Et_2O$ (two drops). A brown ppt. formed, and after 72h filtration and p.l.c. twice of the filtrate gave the diketone (21)(6.5 mg, 39%).

C. *N*-Bromosuccinimide (NBS).

(36)(32.4 mg) and NBS (14.5 mg, 1.16 equiv.) were reacted in (aq) acetone over 72h. Many products were observed by t.l.c. although some diketone was resolved. Filtration and p.l.c. twice of the filtrate gave the diketone (21)(4.6 mg, 17%).

D. $NaIO_4$.

(36)(154.8 mg, 0.354 mmol) was stirred in dioxan (10 ml) and H_2O (2 ml) at 0° the a soln. of $NaIO_4$ (78.4 mg, 0.366 mmol, 1.03 equiv.) in H_2O (0.75 ml, 0.5M) was added dropwise, stirred for 3h then allowed to warm to R.T. overnight. The orange soln. was filtered to remove $NaIO_3$ and the filtrate dried (Na_2SO_4) and subjected to p.l.c. (silica/$CHCl_3$). The product was unstable to p.l.c. and no diketone (21) was isolated.

E. *Meta*-Chloroperbenzoic Acid (MCPBA).

(i) (36)(152.5 mg, 0.349 mmol) was dissolved in CH_2Cl_2 (7 ml) and the soln. cooled to -78°. A soln. of MCPBA (96%, 74.9 mg, 0.434 mmol, 1.24 equiv.) in CH_2Cl_2 (3 ml) was added slowly with stirring. After 3h a ppt. formed which redissolved upon warming to R.T. during which the yellow soln. became orange. Washing with satd. (aq) $NaHCO_3$, drying (Na_2SO_4) and evaporation of the solvent gave an orange residue which was purified by reprecipitation from MeOH (not p.l.c., c.f. Expt. 36 D above).

The following data is consistent with this product being the tertiary enamine-sulphinic acid *12(2-sulphinylethyl)-N-methylamino-6a,*

7-dihydro-1-phenyl(6H)naphthaceno{1,12-bc}furan-6-one (38)(57.2 mg, 35%), m.p. 170° (dec.), $\lambda_{max.}$(EtOH) 247, 315, and 337nm (ε 29 400, 17 300, and 13 500), $\nu_{max.}$ ($CHCl_3$)1 700, 1 660, 1 250, 1 160, 1 055, and 1 035 cm^{-1}, δ($CDCl_3$) 8.0-7.0 (Ar, m), no signals in the range 5.0-4.0 (i.e. 12a-doublet is absent), 3.8-3.0 (-CH_2-, m), and 2.2 (brd, NMe), *m/e* 469 M^+ for $C_{28}H_{23}O_4NS$.

Before the above data were correctly assigned, the following experiments (all in THF at R.T. under N_2) were attempted in order to cleave the expected sulphoxide (37):

(a) Treatment with $Ph_2Se_2O_3$; apparently no reaction.

(b) Treatment with (aq) MeI; apparently no reaction.

(c) Treatment with (aq) $AgNO_3/NH_3$; became dark green and showed no diketone (21).

(d) Treatment with (aq) $AgNO_3/HNO_3$; mixture became red and showed a trace of the diketone (21) after several hours.

(ii) (36)(111.7 mg, 0.255 mmol) was treated with MCPBA (96%, 59.9mg, 0.333mmol, 1.3 equiv.) in dry THF (8 ml) at -78° for 1h. Warming to R.T. over 1h then heating to 40° for 2h generated the enamine (38) as before which, without isolation, was hydrolysed with dil. HCl (1.0M, 2 ml) over 2h (t.l.c. control). The product was isolated by washing with satd. (aq) $NaHCO_3$, extraction ($CHCl_3$), drying (Na_2SO_4), and evaporation of the solvent. Since the diketone (21) isolated was contaminated with some starting material (unlike the cases where Ag^+ and Hg^{2+} complexed with (36) and slowly exuded product) the yield of (21)(34.6 mg, 44%) was estimated by an N.M.R. technique, detailed in the Appendix.

37. Reaction of the Dithioacetal (16) with Benzenesulphenyl Chloride[52].

2-Phenyl-1,3-dithiolane (16)(82.7 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (3 ml) and added to a soln. of PhSCl (88.2 mg, 0.61 mmol, 1.4 equiv.) and stirred under N_2 at R.T. The yellow colour of the reagent was discharged immediately upon addition of the substrate, but even after 30 min t.l.c. showed some (16) remained. More PhSCl (81.2 mg, 0.56 mmol, 1.25 equiv.) in CH_2Cl_2 (1 ml) was added, and after a further 15 min no (16) remained and only Ph_2S_2 and benzaldehyde were detected.

Satd. (aq) $NaHCO_3$ (0.5 ml) was added to quench the reaction and excess reagent. (A control reaction with PhSCl + 2,4-DNPH gave a complex mixture of products). 2,4-Dinitrophenylhydrazine soln. (0.14M, 4 ml) was added and the DNP derivative isolated by filtration, drying

of the filtrate (Na_2SO_4), evaporation of the solvent and recrystallisation (CH_2Cl_2/EtOH). The hydrazone showed identical R_f, m.p., mixed m.p., and I.R. spectrum to an authentic sample; yield (70.2 mg, 54%).

38. Reaction of the Dithioacetal (18) with PhSCl.

Method as for Expt. 37 above with following quantities: 3',4'-dihydrospiro{1,3-dithiolane-2,1'(2'H)naphthalene} (18)(97.7 mg, 0.44 mmol) and PhSCl (79.7 mg, 0.53 mmol, 1.2 equiv.) and after 30 min a further (72.2 mg, 0.5 mmol, 1.1 equiv.) in CH_2Cl_2 (2.5 ml) under N_2 at R.T. for a total of 40 min. Work-up as above afforded the 2,4-DNP of α-tetralone (106.8 mg, 74%) identical to an authentic sample.

39. Reaction of the Dithioacetal (19) with PhSCl.

Method as for Expt. 37 above with the following quantities: spiro{2,3'-cholestane-1,3-dithiolane} (19)(66.7 mg, 0.144 mmol) and freshly prepared PhSCl (84.7 mg, 0.58 mmol, 4 equiv.) in CH_2Cl_2 (3.5 ml) for 3h, during which time no product formed. Warming to 40° for 3h then at R.T. for 3.5 days gave, after work-up as above and p.l.c. (silica/C_6H_6) *5α-cholestan-3-one* (17.9 mg, 32%), identical to an authentic sample.

40. Preparation of Benzeneselenenyl Chloride (PhSeCl) [53].

To a solution of diphenyldiselenide (1 g, 3.2 mmol) in dry CCl_4 (2 ml) was added with stirring a soln. of sulphuryl chloride (SO_2Cl_2, 0.43 g, 3.2 mmol, 1.0 equiv.) in one portion at R.T. After 30 min the dark soln. was filtered (dry Celite), to remove any insoluble $PhSeCl_3$ by-product, and evaporation of the solvent and recrystallisation (C_6H_6/Petr. ether) gave *benzeneselenenyl chloride* (1.14 g, 93%), identical to an authentic sample [53].

41. Reaction of the Dithioacetal (16) with Benzeneselenenyl Chloride.

2-Phenyl-1,3-dithiolane (16)(80 mg, 0.44 mmol) in THF (3 ml) was treated with PhSeCl (92 mg, 0.48 mmol, 1.1 equiv.) at 50° for 1h, then overnight at R.T. Addition of a few drops of satd. (aq) $NaHCO_3$ followed by the calculated amount of 2,4-DNPH soln. (0.14M, 4 ml) gave the hydrazone of benzaldehyde (48 mg, 38%).

42. Reaction of the Dithioacetal (18) with PhSeCl.

Method as for Expt. 41 above with the following quantities: (18)(81.6 mg, 0.37 mmol), PhSeCl (77.3 mg, 0.4 mmol, 1.1 equiv.) in THF (3 ml) for 1h (t.l.c. control). Work-up as above gave the 2,4-DNP of α-tetralone (38.5 mg, 32%).

43. Preparation of Benzeneseleninic Anhydride ($Ph_2Se_2O_3$).

To a stirred suspension of diphenyldiselenide (10 g, 32 mmol) in water (10 ml) at R.T. was cautiously added conc. nitric acid (10 ml) dropwise. After the evolution of nitrogen oxides had ceased, water and excess HNO_3 were removed at the high vacuum pump. The colourless residue ($PhSeO_2H.HNO_3$ complex) was heated *in-vacuo* at 120° for *ca.* 24h, during which some benzeneseleninic acid and unconverted Ph_2Se_2 sublimed onto the upper surface of the flask. The residue was pulverised in dry air to yield *benzeneseleninic anhydride* ($Ph_2Se_2O_3$)(10.97 g, 95%), m.p. 164° (lit.,[53] 165°).

44. Reaction of the Dithioacetal (16) with $Ph_2Se_2O_3$.

The dithiolane (16)(80 mg, 0.44 mmol) was dissolved in dry (CaH_2) THF (3 ml) and $Ph_2Se_2O_3$ (174 mg, 0.48 mmol, 1.1 equiv.) added in one portion to the stirred soln. at R.T. under Argon, for 40 min. Work-up of the reaction mixture afforded benzaldehyde (three separate runs):

(a)	p.l.c. isolation	34%
(b)	2,4-DNP isolation	78%
(c)	G.L.C. estimation	92%

45.A. Reaction of the Dithioacetal (17) with $Ph_2Se_2O_3$.

Method as in Expt. 44 above with the following quantities: (17)(152.6 mg, 0.59 mmol), $Ph_2Se_2O_3$ (234.4 mg, 0.65 mmol, 1.1 equiv.), THF (15 ml) under N_2 for 2h. Isolation by p.l.c. (silica/Petr. ether/C_6H_6) and recrystallisation (EtOH) afforded benzophenone (99.9 mg, 93%).

B. As above with (17)(327.1 mg, 1.26 mmol), $Ph_2Se_2O_3$ (152.0 mg, 0.42 mmol, 0.33 equiv.), THF (8 ml) for 3h yielded benzophenone only (109.5 mg, 47%).

46. Reaction of the Dithioacetal (18) with $Ph_2Se_2O_3$.

Method as for Expt. 44 above with the following quantities: (18)(81.8 mg, 0.37 mmol), $Ph_2Se_2O_3$ (146 mg, 0.41 mmol, 1.1 equiv.),

THF (3 ml) and stirred under Argon for 30 min. Work-up of the reaction mixture afforded α-tetralone (three separate runs):

(a)	p.l.c. isolation	25%
(b)	2,4-DNP isolation	65%
(c)	G.L.C. estimation	70%

47. Reaction of the Dithioacetal (19) with $Ph_2Se_2O_3$.

The dithiolane (19)(115 mg, 0.25 mmol) and $Ph_2Se_2O_3$ (98.2 mg, 0.27 mmol, 1.1 equiv.) were stirred together in dry ($CaCl_2$) CH_2Cl_2 (3ml) at R.T. under N_2 for 1h (t.l.c. control). Isolation by p.l.c. (silica/C_6H_6) afforded 5α-cholestan-3-one (69.1 mg, 72%), m.p. 128°.

48. Reaction of the Dithioacetal (20) with $Ph_2Se_2O_3$.

Spiro{2,3'-cholestane-1,3-dithiane} (20)(255 mg, 0.536 mmol) and $Ph_2Se_2O_3$ (213 mg, 0.589 mmol, 1.1 equiv.)were stirred together in dry THF (7 ml) at R.T. under N_2 for 16h. Isolation by p.l.c. as above, afforded 5α-cholestan-3-one (150.6 mg, 73%), m.p. 128°.

49. Reaction of the Tetracyclic Dithioacetal (9) with $Ph_2Se_2O_3$.

The tetracyclic thioacetal-ketone (9)(63.3 mg, 0.144 mmol) and $Ph_2Se_2O_3$ (60 mg, 0.167 mmol, 1.15 equiv.) were stirred together in dry CH_2Cl_2 (2 ml)(N.B. THF found less suitable for this reaction) at R.T. under N_2 . The suspension reacted slowly with the formation of Ph_2Se_2 and the mixture became homogeneous after 3h. T.l.c. (silica/C_6H_6 x3 for max. resolution) showed the disappearance of (9) and the formation of a number of products, of which the diketone (21) was the most abundant after 3.5h.

Work-up by the addition of satd. (aq) $NaHCO_3$ (1 ml)(to remove any $PhSeO_2H$ rather than hydrolytic decomposition of any intermediates), extraction (CH_2Cl_2), drying (Na_2SO_4) and the addition of MeOH permitted fractional crystallisation of the desired product which, after washing (Petr. ether) and drying *in-vacuo* gave the tetracyclic model diketone *cis-6aα,7,12,12aα-tetrahydro-1-phenyl(6H)naphthaceno{1,12-bc}furan-6,12-dione* (21)(32 mg, 63%), m.p. 205-210° (slow heating); m.p. 225° (dec.) (rapid heating to 200°) (lit.,[10] 234-5°), $\lambda_{max.}$($CHCl_3$) 260, 275 (sh), 280 (sh), 295, 305 (sh), and 360 nm (ε 42 300, 29 600, 26 100, 24 200, 20 500, and 17 800), $\nu_{max.}$ 1 700 cm^{-1}, δ ($CDCl_3$) 8.0-7.2 (12H, m),

4.78 (1H, d, J=7Hz.), and 4.1-3.1 (3H, m), *m/e* 364 M^+. The product (21) was identical to an authentic sample prepared earlier by direct photocyclisation, in low yield, of the aldehyde (7). The above method of preparation was repeated routinely on a large scale (1 g).

50. Reaction of the Tetracyclic Diketone (21) with Methyl Lithium.

The model diketone above (21)(134 mg, 0.368 mmol) was dissolved in dry THF (6 ml) under N_2 and treated with ethereal methyllithium (1.5M, 1 ml, 4 equiv.) at -78° over 40 min. Addition of solid NH_4Cl (1g) at -78°, then water (1 ml), filtration through Celite/Na_2SO_4 and then evaporation of the solvent afforded only a very dark residue. T.l.c. analysis (silica/C_6H_6 x4) revealed some diketone (21) together with 8 products of greater polarity, some of which exhibited strong blue fluorescence under U.V. stimulation. Resolution of the product mixture by p.l.c. (silica/C_6H_6/$CHCl_3$) failed to provide a suitable derivative and the preparation of the keto-carbinol (39) by this approach was abandoned, as before [56].

51. Reaction of the Dithioacetal-Carbinol (10) with $Ph_2Se_2O_3$.

The tetracyclic thioketal-carbinol (10)(17.5 mg, 38 µmol) was stirred with a suspension of $Ph_2Se_2O_3$ (17.6 mg, 49 µmol, 1.3 equiv.) in dry CH_2Cl_2 (1 ml, previously shaken with satd. (aq) $NaHCO_3$ soln. and dried (Na_2SO_4)) containing dry pyridine (3 drops) under N_2 at R.T. (A control mixture of the anhydride and pyridine showed no reaction at R.T. over 8h). After 5h t.l.c. (silica/C_6H_6/EtOAc 5:1) showed that some (10) still remained, whereupon the addition of more $Ph_2Se_2O_3$ (6.4 mg, 0.36 equiv.) completed the deprotection reaction over a further 3h.

Work-up with satd. (aq) $NaHCO_3$ soln. (1 ml), extraction(CH_2Cl_2), drying (Na_2SO_4) and p.l.c. (as above) afforded the colourless keto-carbinol *cis-6aα,7,12,12aα-tetrahydro-6α-methyl-1-phenyl(6H)naphthaceno{1,12-bc}furan-6β-ol-12-one* (39)(7.4 mg, 51%), m.p. (C_6H_6/Petr.ether/MeOH) 180-2°,(lit.,[56] 180-3°), $\lambda_{max.}$($CHCl_3$) 245, 298 (sh), 311, and 325 (sh) nm (ε 23 300, 25 900, 28 200, and 16 300), $\nu_{max.}$(Nujol) 3 400, and 1 680 cm^{-1}, δ ($CDCl_3$) 8.0-7.2 (12H, m), 4.42 (1H, d, J=5Hz.), 3.4-3.2 (2H, m), 2.8 (1H, m), and 1.75 (3H, s), *m/e* 380 M^+, 362, metastable 345 (calc. 344.8), 319, 245, 244, and 215.

By exhaustive treatment of (9) with MeLi/THF more (10) was prepared, of which (60.6 mg, 0.133 mmol) were treated with with portions of $Ph_2Se_2O_3$ (107.6 mg, 0.299 mmol, 2.25 equiv.) in THF/py at R.T. → 40°

under N_2 over 50h. Isolation by p.l.c. gave further quantities of (39) (39.7 mg, 78%) with properties as above.

52. Ozonolysis of (39) to the Model Tetracyclic Benzoate (40, R=PhCO).

The keto-carbinol (39)(30.8 mg, 80 μmol) was dissolved in dry $CHCl_3$/50% MeOH (10 ml) containing pyridine (0.5 ml) and ozone-rich O_2 passed through the soln. at -78° for 3h. Excess O_3 was displaced by N_2 over 45 min and Me_2S (1 ml) added at -78° to decompose the ozonide, then slow warming to R.T. overnight.

After evaporation of the solvent, the residue was subjected to p.l.c. (silica/$CHCl_3$/EtOAc 3:2), the blue fluorescent material eluted and recrystallisation (C_6H_6/Petr. ether) gave the crude diketo-benzoate *6β-hydroxy-6α-methyl-5,5aα,6,11,11a,12-hexahydro-11,12-dioxo-naphthacene-10-yl-benzoate* (40, R=PhCO)(25.6 mg, 76%), which after rechromatog. (short dry silica column/$CHCl_3$/EtOAc 3:2) and recrystallisation(C_6H_6/ Petr. ether) gave the pure diketo-benzoate; m.p.187-90°, $\lambda_{max.}$(MeOH) 228, 257 (sh), 309, 381, and 400 (sh) nm (ε 22 400, 17 500, 14 500, 19 600, and 15 400), $\nu_{max.}$($CHCl_3$) 3 500, 1 730, 1 680, 1 603, 1 270, and 1 230 cm^{-1}, δ($CDCl_3$) 8.4-7.2 (Ar H), 3.5 (1H), 3.1 (1H), and 1.7 (3H, s), *m/e* 412 M^+, 411, 410, 394, 105, and 77. (Found: C, 75.6; H, 4.8; $C_{26}H_{20}O_5$ requires C, 75.75; H, 4.85 %).

53. Solvolysis of (40, R=PhCO) to the Ring-A Unsubstituted Tetracycline.

The diketo-benzoate (40, R=PHCO)(6.7 mg, 16.2 μmol) was dissolved in dry MeOH (2 ml) and the yellow soln. treated with freshly prepared NaOMe/MeOH (1 ml, containing 60 μmol of base; HCl standardisation) and rapidly stirred under N_2 for 100 min (t.l.c. control). To the red coloured soln. was added water (2 ml), $CHCl_3$ (10 ml) and sufficient solid CO_2 to restore the original yellow colour. The organic layer was separated, dried (Na_2SO_4) and after evaporation of the solvent the residue was chromatographed (silica column/$CHCl_3$/EtOAc 4:1) and the first yellow fraction collected under N_2. Evaporation of the solvent at low temp. and recrystallisation of the residue (C_6H_6/Petr. ether) gave the ring-A unsubstituted Tetracycline *6β,10-dihydroxy-6α-methyl-5,5a--6,11,11a,12-hexahydronaphthacene-11,12-dione* (40, R=H)(4.6 mg, 92%) m.p. 150-5° (dec.), $\lambda_{max.}$(MeOH) 220, 239, 285, 305, 388, and 406 nm (ε 12 200, 8 750, 4 200, 3 900, 14 500, and 12 800), $\nu_{max.}$($CHCl_3$)

1 680 and 1 610 cm^{-1}, δ ($CDCl_3$) 12.3 (1H, s, OH), 7.48-7.0 (Ar H), 3.23 (1H, s, OH), 3.15 (1H, t, J=3.5 Hz.), 1.78 (2H, d, J=3.5 Hz.), 1.54 (3H, s), and 1.26 (1H, s, OH), *m/e* 308 M^+, 307, 306, 290, 256, 247, and 163. (Found: C, 73.85; H, 5.2; $C_{19}H_{16}O_4$ requires C, 74.0; H, 5.2 %).

54. $Ph_2Se_2O_3$/1,3-Dithiolane Reactions Followed by Iodometric Titration.

The general procedure [53b] was applied as follows. Freshly activated $Ph_2Se_2O_3$ (360 $gmol^{-1}$, 90.0 mg, 0.25 mmol) portions were weighed accurately into a series of dry R.B. flasks (10 ml) and sealed by septum caps. The 1,3-dithiolane (2.5 mmol) was dissolved in dry THF (50 ml). For each reaction (at R.T. under an N_2 balloon) the THF soln. (5 ml, 0.25 mmol. 1.0 equiv.) was transferred by syringe to the appropriate flask and magnetically stirred.

After the desired reaction time, the unused reagent was quenched by the addition of dil. H_2SO_4 (*ca.* 5 ml), the mixture stirred for 1 min, Ph_2Se_2 extracted (Et_2O) and the (aq) and ethereal layers separated.

The ether layer was dried (Na_2SO_4) and evaporated to dryness in the presence of chromatographic silica gel. The silica "plug" and adsorbed Ph_2Se_2 was transferred to a silica column and eluted with Petr. ether/Petr. ether + trace Et_2O, and after evaporation of the ether the recovered Ph_2Se_2 was crystallised and weighed.

To the (aq) layer was added EtOH (10 ml), starch soln. (few drops) and solid potassium iodide (*ca.* 5 fold excess) and the mixture shaken and allowed to stand for 1 min before titration to the end-point (black/brown → yellow) with 0.1M $Na_2S_2O_3$ soln. The stoichiometry (see text) shows that 0.25 mmol $Ph_2Se_2O_3$ is equivalent to 15 ml 0.1M $Na_2S_2O_3$ soln. All results quoting "% oxidising power remaining ≡ {O} " are derived from the titre/ml as a percentage of 15.

55. Preparation of Dibenzylsulphoxide.

Dibenzylsulphide (1.777 g, 8.3 mmol) in AcOH (30 ml) was treated with H_2O_2 (32% (aq), 1.0 ml, 1.13 equiv.) at R.T. over 24h. Work-up by pouring into excess satd. (aq) $NaHCO_3$, extraction ($CHCl_3$), washing (H_2O), and drying (Na_2SO_4) gave, after partial evaporation of the solvent, colourless crystals of dibenzylsulphoxide (1.695 g, 89%), m.p. 136-7° (lit.,[59] 133°), $\nu_{max.}$ ($CHCl_3$) 1 060 cm^{-1}, δ ($CDCl_3$) 7.3

(1OH, brd) and 3.87 (4H, s), *m/e* 230 M^+, 214, 182, 181, 180, and meta-stable 141 (calc. 230 → 180; 140.87).

56. Preparation of Diphenylsulphide.

Diphenylsulphoxide (6.93 g, 34 mmol) in dry CH_2Cl_2 (40 ml) was treated with acetyl chloride (5 ml, 70 mmol, 2.06 equiv.) dissolved in CH_2Cl_2 (15 ml) by dropwise addition with stirring at R.T. After 24h the solvent was evaporated and the residue extracted (C_6H_6), washed (satd. (aq) $NaHCO_3$), dried (Na_2SO_4) and the product fractionally distilled to afford diphenylsulphide (4.33 g, 68%), b.p. $_{23mmHg}$ 178-82° (lit.,[57] b.p. $_{16.5mmHg}$ 157-8°), *m/e* 186 M^+, 185, 184, 109, 108, and 92.

57. Preparation of Diphenylselenide.

To the Grignard reagent PhMgBr, from Mg (850 mg, 35.42 mmol) and bromobenzene (5.56 g, 35.41 mmol, 1 equiv.) in dry Et_2O (40 ml) under dry N_2, was added slowly a soln. of Ph_2Se_2 (9.997 g, 32.04 mmol, 0.9 equiv.) in Et_2O (80 ml), whereupon the yellow colour of the diselenide was discharged.

After cooling in an ice-bath and the addition of cold, satd. (aq) NH_4Cl (150 ml), the ether layer was immediately separated and washed (NaOH, 2M, 150 ml x3, to remove PhSeH), separated, dried (Na_2SO_4) and the ether evaporated. The product residue was distilled twice under reduced pressure, to yield diphenylselenide (4.944 g, 66%), b.p.$_{0.1}$ 100-4° (lit.,[58] b.p.$_{2mmHg}$ 103-32°) . Neutralisation of the alkaline extracts (dil. HCl) and oxidation with I_2 gave recovered Ph_2Se_2 (4.99 g, 89% of the theoretical amount). Data Ph_2Se: *m/e* 234 M^+, 154, and 77, ^{13}C: ($CDCl_3$) 132.72, 130.98 (q), 129.07, and 127.04 .

58. Reactivity of $Ph_2Se_2O_3$ towards Sulphides, Selenides and Sulphoxides.

A. $Ph_2Se_2O_3$ + Sulphides and Selenides.

The anhydride (1 equiv.) failed to react with Ph_2S, Ph_2Se, and $(PhCH_2)_2S$ in dry THF over several days at R.T. or at reflux for 24h. In chlorobenzene at reflux for 24h Ph_2S and Ph_2Se did not react, although some Ph_2Se_2 was generated and $PhSeO_2H$ precipitated; $(PhCH_2)_2S$ (264.2 mg, 1.23 mmol) did react in boiling PhCl over 1.5h and column chromatog. (silica/Petr. ether/C_6H_6/Et_2O) afforded Ph_2Se_2 (363 mg, 94%) and benzaldehyde (101.6 mg, 78% if 1 mole $(PhCH_2)_2S$ → 1 mole PhCHO). The corresponding sulphoxides or sulphones were not detected (t.l.c., I.R.).

B. $Ph_2Se_2O_3$ + Sulphoxides.

Diphenylsulphoxide and dibenzylsulphoxide were both inert towards $Ph_2Se_2O_3$ in THF at R.T. or prolonged reflux.

C. $Ph_2Se_2O_3$ + 1,3-Dithiolane-1-oxides.

Two 1,3-dithiolane-1-oxides failed to react with the anhydride under normal deprotection conditions, at R.T. over several days. Upon heating to reflux in THF some Ph_2Se_2 was formed, but little or no carbonyl compounds were detected:

(i) 2-Phenyl-1,3-dithiolane-1-oxide (45.0 mg, 0.23 mmol) in THF (5 ml) with $Ph_2Se_2O_3$ (90 mg, 0.25 mmol, 1.1 equiv.) at R.T. for 23h. After dil. H_2SO_4 work-up, the (aq) layer required 7.65 ml, 0.1M, $Na_2S_2O_3$ to end - point. Thus, 51% oxidising power remained.

(ii) 2,2-Diphenyl-1,3-dithiolane-1-oxide (62 mg, 0.23 mmol) in THF (5ml) with $Ph_2Se_2O_3$ (90 mg, 0.25 mmol, 1.1 equiv.) at R.T. for 23h. As above, the titre (14.25 ml) showed 95% {O} remained.

59. Preparation of the Dithioacetal (41).

2,2,6-Trimethylcyclohexanone (6.43 g, 45.95 mmol) was dissolved in C_6H_6 (30 ml) and AcOH (30 ml) and 1,2-ethanedithiol (8 ml, 91.67mmol, 2 equiv.) added. $BF_3.Et_2O$ (11.5 ml, 2 equiv.) was added dropwise and the mixture stirred under N_2 at 40-45° for 2 days (t.l.c. control).

Normal base work-up, with additionally washing with 1M NaOH (200 ml x5) followed by distillation under reduced pressure gave the colourless product *spiro{1,3-dithiolane-2,1'(2',2',6'-trimethylcyclohexane)}* (41)(8.68 g, 88%), b.p. $_{0.9mmHg}$ 104-8° (semi-solid at R.T.), $\nu_{max.}$(Nujol) 1 280, 1 242, 1 208, 1 082, 980, 915, 882, and 795 cm^{-1}, δ ($CDCl_3$) 3.35-3.0 (4H, m), 1.8-1.4 (7H, m), 1.18 (3H, s), 1.17 (3H,s), and 1.05 (3H, s), *m/e* 216 M^+, 202, 188, 173, 145, 123, and 105; meta-stable 164 (calc. 216 → 188: 163.6).

60. Preparation of the Dithioacetal (42).

Fenchone (6.14 g, 40.4 mmol) was dissolved in C_6H_6 (30 ml), AcOH (30 ml) to which was added 1,2-ethanedithiol (7.1 ml, 81.4 mmol) and $BF_3.Et_2O$ (10 ml) and the mixture stirred at R.T. for 17.5h then at 40-45° for 4 days (t.l.c. control). Work-up as in Expt.59 above, gave *spiro{1,3-dithiolane-2,2'(1',3',3'-trimethylbicyclo{2.2.1}heptane)}* (42)(7.79 g, 85%), b.p. $_{0.7mmHg}$ 110-12°, $\nu_{max.}$(Nujol) 1 275, 1 100,

970, and 840 cm^{-1}, δ($CDCl_3$) 3.27-2.9 (4H, m), 1.8-1.3 (7H, m), 1.27 (3H, s), and 1.17 (6H, s), *m/e* 228 M^+, 200, 145, 123, 105, and 81; meta-stable 175.5 (calc. 228 → 200: 175.4).

61. Preparation of the Hemithioacetal (43).

Benzaldehyde (10.9 g, 102.8 mmol) was dissolved in dry C_6H_6 (80 ml) to which was added 2-hydroxyethanethiol (7.9 ml, 113.4 mmol, 1.1 equiv.) and *para*-toluenesulphonic acid (47 mg) and the mixture heated to reflux , with the separation of water in a Dean-Stark apparatus over 19h. Upon cooling , the soln. was washed with satd. (aq) $NaHCO_3$ (50 ml x2), water (50 ml x2), dried (Na_2SO_4) and after removal of the solvent, the residue was distilled under reduced pressure to afford *2-phenyl-1,3-oxathiolane* (43)(15.5 g, 91%), b.p. $_{3mmHg}$ 90-92°, $\nu_{max.}$(film) 3 000, 2 900, 2 850, 1 495, 1 450, 1 230, 1 065, and 715 cm^{-1}; δ (neat + TMS) 7.43-7.0 (5H, m), 5.88 (1H, s), 4.27-3.97 (1H, m), 3.72-3.33 (1H, m), and 3.1-2.7 (2H, m), *m/e* 166 M^+, 133, 121, 107, 106, 105, 91, 90, 89, 79, 78, 77, 61, 60, 59, 51, 45, and 32.

62. Preparation of the Hemithioacetal (44).

Cyclohexanone (12.27 g, 125.2 mmol), 2-hydroxyethanethiol (9.6 ml, 137.8 mmol, 1.1 equiv.), and TosOH (44 mg) were refluxed in C_6H_6 (80 ml) over 5h, with separation of water and work-up as in Expt.61 above, to afford *spiro{2,1'-cyclohexane-1,3-oxathiolane}* (44)(16.39 g, 83%), b.p. $_{0.7mmHg}$ 48-50° , $\nu_{max.}$(film) 2 800, 2 700, 1 445, 1 350, 1 265, 1 240, 1 145, 1 080, 1 070, and 895 cm^{-1}, δ (neat+TMS) 4.08 (2H, t, J=6Hz.), 2.93 (2H, t, J=6Hz.), and 1.8-1.2 (10H, env), *m/e* 158 M^+, 130, 115, 99, 98, 60, 55, and 32.

63. Reaction of the Dithiolanes (15), (41), and (42), and the Oxathiolanes (43) and (44) with $Ph_2Se_2O_3$.

All the following reactions were performed in THF and the yields of the corresponding carbonyl products estimated by G.L.C. (Column: 10% carbowax on chromosorb W, naphthalene as internal standard and sequentially diluted reference samples were used to calibrate the Perkin Elmer F 11, FID instrument). The quantities and yields were as follows:

(i) (15)(182.1 mg), $Ph_2Se_2O_3$ (378 mg), R.T., 18h, yielded cyclohexanone (59%).

(ii) (41)(54.6 mg) , $Ph_2Se_2O_3$ (91 mg) , 50° , 18h, yielded 2,2,6-trimethylcyclohexanone (63%).

(iii) (42)(57 mg), $Ph_2Se_2O_3$ (90 mg), 50°, 18h, yielded fenchone (78%).

(iv) (43)(164.2 mg), $Ph_2Se_2O_3$ (356 mg), R.T., 7.5h, yielded benzaldehyde (95%).

(v) (44)(159.7 mg), $Ph_2Se_2O_3$ (364 mg), R.T., 7.5h, yielded cyclohexanone (55%).

64. Relative Deprotection Rates with $Ph_2Se_2O_3$.

Using the technique of iodometric titration (Expt. 54) the relative rates of consumption of the oxidising power of the anhydride was determined for the simple substrates above. Also, by employing a modified [62] Varian FT/16D program the relative rate of reaction of (16) and (43) was determined directly. Each set of these results is presented graphically and discussed in the main text.

65. Large Scale Reaction of the Oxathiolane (44) with $Ph_2Se_2O_3$.

The oxathiolane (44)(532 mg, 3.37 mmol) and $Ph_2Se_2O_3$ (1.224 g, 3.4 mmol, 1.01 equiv.) were reacted together in dry THF (8 ml) at R.T., under a stream of N_2 to remove cyclohexanone, over 1h. Column chromatog. (silica/C_6H_6) afforded recovered Ph_2Se_2 532.5 mg, 50%) and an oily, polar product, characterised as *2-phenylseleniocyclohexanone* (45)(340mg, 40%), $\nu_{max.}$(film) 1 700 cm^{-1}, δ ($CDCl_3$) 7.67-7.13 (5H, m), 3.9 (1H, t, J=5Hz.), and 2.7-1.5 (8H, env), *m/e* 254 M^+, 158, and 97.

No stable product containing the departed sulphur moiety could be isolated from the most polar product fraction.

66. Preparation of the Steroidal Oxathiolane (46).

To a soln. of 5α-cholestan-3-one (1 g, 2.59 mmol) in C_6H_6(50ml) was added 2-hydroxyethanethiol (1 ml, 14.35 mmol, 5.5 equiv.) and TosOH (40 mg) and the mixture heated to reflux with the separation of water over 3h. Upon cooling, the C_6H_6 soln. was washed with satd. (aq)$NaHCO_3$ (50 ml x2), water (50 ml x2), dried (Na_2SO_4) and evaporated to dryness. The residue was recrystallised (Me_2CO/MeOH) to yield *spiro{2,3'- cholestane-1,3-oxathiolane}* (46)(1.086 g, 94%), as a mixture of two epimers (by t.l.c. and N.M.R.), m.p. 127-31°, for the epimeric mixture (p.l.c. (silica/C_6H_6) partially resolved the two components: m.p. (less polar) 144-5°; m.p. (more polar) 113-4°), $\nu_{max.}$($CHCl_3$) 2 900, 2 850, 1 440, and 1 060 cm^{-1}, δ ($CDCl_3$) 4.2 ($\frac{1}{2}$ x 2H, t, J=6Hz.), 4.13 ($\frac{1}{2}$ x 2H, t,

J=6Hz.), 3.02 (2H, brd, t, J=6Hz.), and 2.0-0.6 (complex), *m/e* 446 M^+, 386, and meta-stable 334 (calc. 446 → 386: 344.07), $\{\alpha\}_D$ + 22.7° , $\{\alpha\}_{Hg}$ + 22.6° .

67. Reaction of (46) with $Ph_2Se_2O_3$.

To a soln. of the oxathiolane (46)(282.8 mg, 0.63 mmol) in dry THF (5 ml) was added $Ph_2Se_2O_3$ (251.3 mg, 0.7 mmol, 1.1 equiv.) and the mixture stirred at R.T. under N_2 for 23h. The solvent was partially evaporated prior to p.l.c. (silica/C_6H_6) and two major product bands were isolated:

(i) the more polar fraction (30.4 mg) m.p. 106-9° (EtOH/Petr. ether), $\lambda_{max.}$(EtOH) 229 and 270 nm (ε (based upon MW 385 $gmol^{-1}$) 4 500 and 540), $\nu_{max.}$($CHCl_3$) 2 900, 1 710, 1 680, 1 450, 1 410, 1 360, 1 275, 1 230, and 1 030 cm^{-1}, δ ($CDCl_3$) 7.1 (1H, d, J=10Hz.), 5.8 (1H, d,J=10Hz.), 2.3-2.0 (-CH_2CO, group), and 2.0-0.6 (complex), *m/e* 386, 384 (and other groups differing by 2 mass units). The data is consistent with this product being (an inseparable) mixture of *5α-cholestan-3-one* and *1-cholesten-3-one*.

(ii) the less polar fraction *2-phenylselenenyl-1-cholesten-3-one* (47) (69.8 mg) m.p. (Petr. ether) 128-9°, $\lambda_{max.}$(EtOH) 215, 235 (sh), 265, and 320 nm (ε 9 550, 4 070, 2 300, and 750), $\nu_{max.}$($CHCl_3$) 2 900, 2 850, 1 665, 1 590, 1 440, and 1 030 cm^{-1}, δ($CDCl_3$) 7.6-7.1 (5H, m), 6.7 (1H, s), 2.5-2.35 (-CH_2CO, group), 2.0-0.6 (complex), *m/e* 540 M^+, 383, and meta-stable 272 (calc. 540 → 383: 271.65), $\{\alpha\}_D$ - 5.5°, $\{\alpha\}_{Hg}$ - 5.9°. (Found: C, 73.1; H, 9.15; $C_{33}H_{48}SeO$ requires C, 73.4; H, 9.0%).

The addition of pyridine (1 rquiv.) to the above reaction mixture, slightly enhances the yield of the PhSe- derivative (47)(36%) over the ketone-enone (20%), and recovered Ph_2Se_2 (82%) accounts for 82% + ($\frac{1}{2}$ x 36%) = 100% of the selenium, suggesting that (47) is derived *via* an enolate intermediate, as reported for similar examples [53,61].

68. Preparation of the Dithioacetal (50).

By Fieser's method [12], acetone (10.1 g, 174.1 mmol) and 1,2-ethanedithiol (14 ml, 167.3 mmol, 0.96 equiv.) were mixed together in C_6H_6 (30 ml), and AcOH (30 ml) and cooled to 0°. $BF_3.Et_2O$ (5 ml, 39.8 mmol, 0.23 equiv.) was added dropwise over 25 min. After 1.5h at R.T. the mixture was poured into satd. (aq) $NaHCO_3$ (200 ml), extracted (CH_2Cl_2), separated and washed (H_2O to pH 7), dried (Na_2SO_4) and after

evaporation of the solvents, the residue was distilled under reduced pressure to afford *2,2-dimethyl-1,3-dithiolane* (50)(8.89 g, 40%), b.p. $_{2mmHg}$ 52°, δ (CCl_4) 3.3 (4H, s) and 1.76 (6H, s), *m/e* 134 M^+, 119, 106, and 74.

69. Reaction of the Dithioacetals (17) and (50) with $Ph_2Se_2O_3$.

The reaction between (50)(533.2 mg, 3.98 mmol) and $Ph_2Se_2O_3$ (1.435 g, 3.99 mmol, 1 equiv.) in THF (6 ml) at R.T. under N_2 was complete after 45 min (t.l.c. control). Evaporation of the solvent (and acetone product) under reduced pressure at R.T. gave a dark oil which, upon treatment with Et_2O/Petr. ether, was resolved into a yellow soln., from which Ph_2Se_2 (1.154 g, 93%, m.p. 61-2°) was isolated, and an insoluble grey powder (319 mg, 65%) characterised as the polymer (51) $\nu_{max.}$(KBr disc) 1 320 (SO_2, symm) and 1 125 (SO_2, asymm) cm^{-1}, 100 MHz. ^1H, FT, δ(d^5-pyridine) 3.209-2.789 (complex $-CH_2-$ resonances).

From an analogous reaction of (17), as in Expt. 45.A above, the most volatile fraction was isolated directly from the reaction mixture by distillation under reduced pressure. This fraction, of b.p. $_{1.5-2mmHg}$ 134-50°, consisted mainly of Ph_2Se_2 and presumably some of the monomer or oligomers of (51), since trituration (Et_2O/Petr. ether) precipitated the polymer (51), showing similar I.R. active $-SO_2$ functionality.

70. Preparation of the Polymer (52).

1,2-Ethanedithiol (4 ml, 47.8 mmol) in CH_2Cl_2 (25 ml) was cooled to -30° to -25° and treated with sulphuryl chloride (SO_2Cl_2, 3.9 ml, 47.8 mmol, 1 equiv.) by addition over 10 min, then the mixture warmed to 0° for 30 min and finally allowed to attain R.T. After pouring into ice-water (300 ml) the colourless ppt. was washed with water (50 ml x 2), satd. (aq) $NaHCO_3$ (50 ml x 2), water (50 ml x 2), and finally rinsed with acetone and dried *in-vacuo* to yield *poly(ethylenedisulphide)* (52)(4.18 g, 95%), m.p. 148-51° (lit.,[63a] 145-50° and lit.,[63b] 132-45°), $\nu_{max.}$(Nujol) featureless, very insoluble in all solvents.

71. Peracid Oxidation of the Polymer (52) to Polymer (51).

The polymer (52)(329 mg, 3.58 mmol, based upon repeating unit) was suspended in AcOH (25 ml) and H_2O_2 (32%, (aq), 0.8 ml, 7.53 mmol, 2.1 equiv.) was added with stirring at R.T. for 3 days. Treatment with base, washing with hot water, boiling in acetone, filtration and drying

in-vacuo, afforded the polymer (51) with the following characteristics: very insoluble in all solvents yet sparingly soluble in pyridine, δ (d^5-pyridine) 4.5-3.4 (complex, m), $\nu_{max.}$ (Nujol) 1 410, 1 320, 1 220, 1 130, 1 040 (v. weak), and 740 cm^{-1}.

72. Preparation of 1,3-Dithiane (53).

Freshly prepared methylal (b.p. $_{1\ atm.}$ 41-2°, 6.8 ml, 78 mmol) and 1,3-propanedithiol (7 ml, 70 mmol) were mixed together in $CHCl_3$ (100 ml) and the soln. added dropwise to a boiling mixture of $CHCl_3$ (30 ml), AcOH (16 ml), and freshly distilled $BF_3.Et_2O$ (8.5 ml) over 3h under N_2. After cooling, the mixture was poured into satd. (aq) $NaHCO_3$ (200 ml), the organic layer separated, washed with water (50 ml x 2), with base (5%, (aq) KOH, 100 ml x 2), and water to pH 7. After drying (Na_2SO_4) and evaporation of the solvent , the residue crystallised. Recrystallisation (MeOH) afforded *1,3-dithiane* (53)(3.44 g, 41%, first crop), m.p. 52-4° (lit.,[64] 53-4°), δ ($CDCl_3$) 3.76 (2H, s), 2.82 (4H, t, J=5Hz.), and 1.9 (2H, m).

73. Reaction of 1,3-Dithiane with $Ph_2Se_2O_3$.

To a soln. of the dithiane (53)(365 mg, 3.04 mmol) in THF (6 ml) was added $Ph_2Se_2O_3$ (1.101 g, 3.06 mmol, 1 equiv.) and the mixture stirred at R.T. for 6h then heated to reflux for 1h under N_2. Paraformaldehyde polymer, m.p. 120° (lit.,[65] 121-3°, c.f. anhydrous polymer m.p. 170-2°) was detected as a sublimate on the inner surface of the reflux condenser.

Column chromatog. (silica/C_6H_6/$CHCl_3$) of the reaction soln. gave recovered Ph_2Se_2 (630.3 mg, 66%), and a polar yellow oil (326 mg). Rechromatography (short dry silica column) produced a cleaner compound (54) which proved unstable at R.T. and generated Ph_2Se_2 upon standing. This product showed: $\nu_{max.}$ ($CDCl_3$) 1 700 (brd), 1 575, 1 435, 1 400, 1 320 (SO_2, symm), 1 120 (SO_2, asymm), 1 020, and 1 000 cm^{-1}, δ ($CDCl_3$) 10.03 (1H, s), 7.90-7.10 (5H, m), 3.68 (2H, t, J=6.5Hz.), 3.38 (2H, t, J=6.5Hz.), and 2.45 (2H, quin, J=6.5Hz.), *m/e* 356 M^+, 279, 263, 237, 199, 171, 157, 91, 77, and 64 (SO_2), meta-stable 111 (calc. 356 → 199: 111.2).

74. Preparation of 2-Methyl-2-nitropropane.

Tert-butylamine (143 ml, 100 g, 1.37 mole) was added over 15 min to a stirred soln. of $KMnO_4$ (646 g, 4.08 mole) in water (3 l), the temp. raised to 55° over 1.5h and maintained for 3h. The product was extracted by steam distillation, the organic phase was extracted (Et_2O, 250 ml), washed with dil. HCl (2M, 50 ml x 2), water (50 ml x 2), dried (Na_2SO_4) and after removal of the solvent, the residue distilled at atmospheric pressure to yield *2-methyl-2-nitropropane* (97.7 g, 70%), b.p. $_{1\ atm}$ 125-6° (lit.,[69] 127-8°, f.p. 25-6°), δ($CDCl_3$) 1.6 (s), *m/e* no M^+, base peak 57 (Me_3C^+).

75. Preparation of the Hydroxylamine (56).

Aluminium foil (30 g, 1.1mole , 5 x 25 cm strips rolled into cylinders and activated by dipping into a soln. of $HgCl_2$ (8 g) in water (400 ml) for 15 sec then washed (EtOH,Et_2O)) was added to Et_2O (1.5 l) containing water (16 ml). 2-Methyl-2-nitropropane (60.4 g, 586 mmol)was added dropwise over 1h with stirring,to maintain vigorous reflux. After 45 min the ethereal soln. was decanted from the alumina, filtered under N_2 (the product is very air sensitive in soln.), washed with (aq) NaOH (2M, 250 ml x 2), dried (Na_2SO_4) and the resultant pale blue soln. evaporated under reduced pressure (the blue nitroso oxidation product co-distilled with the ether) to yield a colourless residue of *N-tert-butylhydroxylamine* (56)(5.15 g, 10%), m.p. 59-60° (lit.,[69] 59-65°), δ ($CDCl_3$) 6.07 (2H, brd, coincident NH and OH) and 1.12 (9H, s), *m/e* 89 M^+, 74, 58, 57, and 56.

76. Preparation of the Nitrone (55).

The hydroxylamine (56)(2.02 g, 22.7 mmol) was mixed with freshly purified and N_2-distilled benzaldehyde (2.4 g, 22.6 mmol, 1 equ) and, with no solvent, the components were stirred under N_2 at 45° until the mixture was colourless and homogeneous, and then heated further to 50-60° for 4h (t.l.c. control). Upon cooling to R.T. the mixture was extracted (CH_2Cl_2), washed (H_2O), dried (Na_2SO_4), and after removal of the solvent, the residue was recrystallised twice (Petr. ether) to give *N-tert-butylphenylnitrone* (55)(2.29 g, 57%), m.p. 74-5° (lit.,[68] 75-6°), δ ($CDCl_3$) 8.37-8.17 (2H, m), 7.5 (1H, s), 7.4-7.3 (3H, m), and 1.58 (9H, s), *m/e* 177 M^+, 146, 131, 130, 122, 121, 120, and 104.

77. Preparation of the Nitroso Dimer (57).

To a cool, stirred soln. of NaOH (2.74 g, 68.5 mmol) in water (20 ml) was added dropwise Br_2 (1.4 ml, 27.2 mmol) from a syringe, and the resultant yellow soln. was cooled to -10° and the hydroxylamine (56) (2.02 g, 22.7 mmol) added in large portions whilst the temp. was kept $<0^{\circ}$. The mixture was then cooled to -32° for 1h then allowed to attain R.T. over 4h, whereupon the colourless ppt. was collected, washed (cold H_2O), air-dried, then pulverised and stored in a vacuum desiccator, to yield *2-methyl-2-nitrosopropane dimer* (57)(1.68 g, 85%), which behaved in soln. according to literature reports [69,78].

78. Preparation of 1,1-Diphenylethylene.

To the Grignard reagent PhMgBr (from Mg (9 g, 0.375 mmol) and PhBr (60 g, 0.382 mmol) in Et_2O (150 ml)) cooled in an ice-bath, was added AnalaR EtOAc (14.5 g, 0.165 mmol, 0.44 equiv.) in Et_2O (50 ml). After warming to R.T. then cooling again, a soln. of NH_4Cl (30 g) in water (50 ml) was added, the ether layer decanted, the (aq) layer extracted (Et_2O) and the combined Et_2O solns. evaporated . The residue was heated in boiling 20% H_2SO_4 (100 ml) for 2h to effect dehydration, and upon cooling the upper organic layer was separated, dried ($MgSO_4$) and fractionally distilled under reduced pressure to yield *1,1-diphenylethylene* (18.2 g, 61%), b.p. $_{20mmHg}$ 147-9° (lit.,[79] b.p.$_{25mmHg}$ 156°), $\nu_{max.}$($CDCl_3$) 3 040, 2 930, 1 605, 1 575, 1 490, 1 445, 1 330, 1 245, 1 075, 1 070, 1 033, and 840 cm^{-1}, δ($CDCl_3$) 7.4-7.1 (10H, m) and 5.33 (2H, s).

79. Preparation of the Dithioacetal (59).

5α-Cholestan-3-one (2.005 g, 5.19 mmol) and *para*-tolylthiol (1.383 g, 11.15 mmol, 2.15 equiv.) were stirred together in C_6H_6 (30 ml), AcOH (10 ml), and $BF_3.Et_2O$ (0.7 ml), over 2h at R.T. Aqueous work-up and extraction (C_6H_6) afforded an oil, crystallisable from *i*-PrOH/Petr. ether 60-80°, to afford *3,3-bis(para-tolylthio)-5α-cholestane* (59) (1.918 g, 60%, first crop), m.p. 103-4°, δ ($CDCl_3$) 7.52-6.97 (8H, m), 2.35 (3H, s), 2.3 (3H, s), and 1.9-0.5 (steroidal CH, CH_2, and Me). (Found: C, 80.05; H, 9.95; $C_{41}H_{60}S_2$ requires C, 79.8 ; H, 9.8 %).

80. Preparation of the Dithioacetal (60).

To a stirred suspension of $NaBH_4$ (12 g) in absolute EtOH (100ml) at 0^o was added slowly dimethyldisulphide (30 ml, 334 mmol, 1 equiv.). After warming to R.T. over 1h and cooling again, 2M HCl was added dropwise to liberate the methanethiol from its salt. The MeSH vapour was led, *via* a $CaCl_2$ tube, to a flask, fitted with a CO_2/acetone condenser, which contained methylal (25 ml, 282 mmol) to which was then added $BF_3.Et_2O$ (10 ml) and the mixture stirred without solvent for 3h with warming to R.T. Following transferrence under N_2 *via* a catheter to satd. (aq) $NaHCO_3$ (100 ml), the organic layer was separated, washed (1M, (aq) KOH, 50 ml x 2), then with brine (to pH 7), dried (Na_2SO_4) and the resultant oil distilled under reduced pressure to afford *bis(methylthio)methane* (60)(22.24 g, 73%), $\nu_{max.}$(film) 2 870, 1 420, 1 300, 1 080, 1 040, and 955 cm^{-1}, δ ($CDCl_3$) 3.32 (2H, s) and 2.42 (6H, s).

81. Preparation of the Dithioacetal (61).

As above, *para*-tolylthiol (5.07 g, 40.89 mmol) and methylal (3.15 g, 41.45 mmol, 1 fold excess) mixed in dry $CHCl_3$ (30 ml) was added dropwise to a boiling mixture of $BF_3.Et_2O$ (5 ml), AcOH (10 ml), and $CHCl_3$ (60 ml) under a strong stream of N_2 (to avoid aerial oxidation to the disulphide). Cooling after 1h and the addition of water (50 ml) gave a colourless organic layer which was separated, washed with satd. (aq) $NaHCO_3$ then H_2O, dried (Na_2SO_4) and after evaporation of the solvent, the yellow oil was distilled under reduced pressure to afford pure *bis(para-tolylthio)methane* (61)(3.724 g, 70%), crystallises $<20^o$, $\nu_{max.}$(film) 3 000-2 850, 1 490, 1 190, 1 085, 1 015, and 800 cm^{-1}, δ (CCl_4) 7.21 (4H, d, J=7Hz.), 6.96 (4H, d, J=7Hz.), 4.13 (2H, s), and 2.33 (6H, s).

82. Reaction of the Dithioacetal (59) with $Ph_2Se_2O_3$.

To a soln. of (59)(258 mg, 0.419 mmol) in THF (10 ml) was added $Ph_2Se_2O_3$ (161.5 mg, 0.448 mmol, 1.07 equiv.) with stirring for 2h at R.T. (no reaction), then at 40^o for 18.5h. T.l.c. showed 5α-cholestan-3-one, Ph_2Se_2, and a product of intermediate R_f (later shown to be (63) below). P.l.c. (silica/C_6H_6) gave 5α-cholestan-3-one (161 mg, 52%), m.p. 128^o.

83. Reaction of the Dithioacetal (60) with $Ph_2Se_2O_3$.

To a soln. of (60)(338.2 mg, 3.131 mmol) in THF (6 ml) was added $Ph_2Se_2O_3$ (933.5 mg, 2.593 mmol, 0.83 equiv.) with stirring under N_2

at R.T. for 17h (t.l.c. control). Column chromatog. (silica/C_6H_6) isolated the water-soluble oxidant *methylphenylselenenylsulphone* (62) (573.5 mg, 78% crude) and after recrystallisation (C_6H_6/Petr. ether) (325 mg, first crop), m.p. 84-5° , $\nu_{max.}$ (KBr disc) 1 470, 1 435, 1 400, 1 300 (vs), 1 180, 1 120 (vs), 1 060, 1 020, 1 000, 955, 915, 750, 740, 700, and 665 cm^{-1}, ^1H: δ($CDCl_3$) 7.9-7.68 (2H, m), 7.57-7.33 (3H, m), and 3.27 (3H, s), ^{13}C: δ($CDCl_3$) 136.78, 131.01, 129.87, 127.54 (q), and 51.1 (Me), *m/e* 236 M^+, 173, 171, 157, 155, 117, 115, 77, and 64. (Found: C, 35.75; H, 3.4; $C_7H_8SSeO_2$ requires C, 35.75; H, 3.4 %).

84. Reaction of the Dithioacetal (61) with $Ph_2Se_2O_3$.

To a soln. of (61)(2.178 g, 8.38 mmol) in THF (10 ml) was added $Ph_2Se_2O_3$ (3.033 g, 8.43 mmol, 1.01 equiv.) and the mixture stirred under N_2 at 55° for 16.5h. After cooling and partial evaporation of the solvent column chromatog. (silica/Petr. ether/C_6H_6/$CHCl_3$) afforded a less polar fraction containing Ph_2Se_2 and some unused (61), followed by a more polar fraction which upon evaporation gave a pale yellow residue, which was recrystallised (C_6H_6/Petr. ether) to afford (1.428 g, 55%), for which structures (63) and (64) are consistent with the following data: m.p. 78-9°, $\nu_{max.}$ (KBr disc) no (C=O), 1 590, 1 080, and 1 135 cm^{-1}, ^1H: δ($CDCl_3$) 7.5-7.0 (9H, m) and 2.32 (3H, s), ^{13}C: δ($CDCl_3$) 144.42 (q), 142.49 (q), 136.98, 130.67, 129.33, 129.08, 127.82 (q), 126.79, and 20.44 (Me), *m/e* 312 M^+, 247, 232, 157, 139, and 91. (Found: C, 50.4; H, 3.8; S, 11.6; $C_{13}H_{12}SSeO_2$ requires C, 50.15; H, 3.9; S, 10.3 %).

The compound is soluble in cold water, and iodometric titration showed that (81.8 mg, 0.263 mmol), with excess KI/H^+, required $Na_2S_2O_3$ (0.05M, 5.0 ml) to end-point ≡ ½ {O} oxidising capacity per molecule. Decomposition occurs upon warming (50-80° for 3-4days) to give Ph_2Se_2 and a complex mixture of selenated products.

An authentic sample of (63) was prepared according to the method of Britten-Kelly [83], by the addition of portions of *anhydrous* Chloramine -T (456 mg, 2.004 mmol, 2.0 equiv.) to a stirred soln. of Ph_2Se_2 (312 mg, 1.0 mmol) in dry CH_2Cl_2 (5 ml) over 10 min at R.T. After 1h, p.l.c. (silica/C_6H_6) gave recovered Ph_2Se_2 (163.1 mg, 52%), and the product *para-tolylphenylselenenylsulphone* (63)(95.5 mg, 32%). Note: a repeat preparation of (63) using 4 equiv. of Chloramine-T left only a trace of Ph_2Se_2 unconsumed, but still only 29% of (63) was recoverable. Data: m.p. 77-8°, with the above reaction product m.p. 77-8°, IR & NMR identical.

Thiocarbonyl Compounds.

Most of the substrates used in the following reactions with benzeneseleninic anhydride were already available, therefore no preparations are described. The sources of provided materials are acknowledged where appropriate.

In general, all reactions were performed at room temperature (R.T.) under dry N_2 (balloon) in dry tetrahydrofuran (THF), freshly distilled from calcium hydride, using between 3-10 ml of solvent for between 50-300 mg of the thiocarbonyl substrate; approximately 1 equiv. of $Ph_2Se_2O_3$ was used. Reaction mixtures were concentrated by partial evaporation of the ether and (except where stated) subjected to p.l.c. (silica) prior to the isolation of the products; no aqueous work-up was usually necessary. The product yields (all of recrystallised material), spectroscopic and other properties are listed below.(* = *oxo*).

85. Oxidation of the Methyl Xanthate (65).[84]

(65)(302.5 mg, 0.633 mmol), $Ph_2Se_2O_3$ (260 mg, 0.722 mmol, 1.14 equiv.), 12h, p.l.c. (Petr. ether) gave *5α-cholestanyl-3β-ol-methylthio carbonate* (65 *)(195 mg, 67%), m.p. (Petr. ether) 117° , $\nu_{max.}(CDCl_3)$ 2 800, 2 760, 1 700 (brd), 1 442, 1 422, 1 245, 1 160 (brd), 1 000, and 840 cm^{-1}, δ ($CDCl_3$) 2.28 (3H, s), *m/e* 462 M^+, 447, 418, 384, 371, 355, and 215, meta-stable 433 (calc. 462 → 447: 432.5), $\{\alpha\}_D$ + 16° (c.f. parent (65) $\{\alpha\}_D$ + 4.9°) . (Found: C, 75.35; H, 11.0; S, 6.95; $C_{29}H_{50}SO_2$ requires C, 75.3; H, 10.9; S, 6.9 %).

86. Comparison Reaction of (65) with Selenium Dioxide.

(65)(156.5 mg, 0.327 mmol), SeO_2 (79 mg, 0.712 mmol, 2.18equiv.) R.T., 3 days, t.l.c. analysis showed much starting material remained together with an intractable mixture of products.

87. Reaction of (65) with $Ph_2Se_2O_3$ followed by I.R. and N.M.R.

The ^1H N.M.R. spectrum of the xanthate (65)(43.4 mg, 90.7 μmol) dissolved in $CDCl_3$ (0.5 ml, with 1% TMS) was recorded (∿28°). Finely powdered $Ph_2Se_2O_3$ (1 equiv.) was added and the TMS-locked N.M.R. spectrum recorded after 1 min and 10 min. Even after 1 min no resonance at δ2.53 (MeSCSO) was detected; a new resonance appeared at higher field, δ2.28 (MeSCOO), as above (Expt. 85).

Similarly the I.R. spectrum of aliquots from a separate reaction

mixture showed, after 1 min and 10 min, a substantial absorption at 1 700 cm^{-1}.

88. Oxidation of the Methyl Xanthate (66) [85].

(66)(161.3 mg, 0.332 mmol), $Ph_2Se_2O_3$ (132.2 mg, 0.367 mmol, 1.11 equiv.), 2h, p.l.c. (Petr. ether x 2, Petr.ether/C_6H_6 2:1) gave *ergosteryl-3β-ol-methylthiocarbonate* (66 *)(110.8 mg, 71%), m.p.(Petr. ether) 125°, $\nu_{max.}(CDCl_3)$ 1 700 cm^{-1}, δ ($CDCl_3$) 2.32 (3H,s), *m/e* 470 M^+, 468, 426, 424, 378, 376, 363, 337, 253, and 251. (Found: C, 76.4; H, 9.85; S, 6.95; $C_{30}H_{46}SO_2$ requires C, 76.55; H, 9.85; S, 6.8 %).

89. Oxidation of the Methyl Xanthate (67) [85].

(67)(215.3 mg, 0.417 mmol), $Ph_2Se_2O_3$ (168.7 mg, 0.469 mmol, 1.12 equiv.), 5h, at R.T. showed no reaction; reflux (THF), 1h, then p.l.c. (Petr. ether x 2), gave *lanosteryl-3β-ol-methylthiocarbonate* (67 *)(131.2 mg, 63%), non-crystalline to date.

90. Oxidation of the Methyl Xanthate (68) [85].

(68)(218.1 mg, 0.606 mmol), $Ph_2Se_2O_3$ (241 mg, 0.669 mmol, 1.1 equiv.), 24h, p.l.c. (Petr. ether x 2), gave *n-octadecylmethylthiocarbonate* (68 *)(133.4 mg, 64%), non-crystalline to date.

91. Oxidation of the Methyl Xanthate (69) [86].

(69)(301.9 mg, 0.86 mmol), $Ph_2Se_2O_3$ (311 mg, 0.86 mmol, 1 equiv.) 2h, p.l.c. (Petr. ether/C_6H_6 1:1), gave *1,2,5,6-di-O-isopropylidene-α-D-glucofuranose-3-ol-methylthiocarbonate* (69 *)(216 mg, 75%), m.p. (Petr. ether/C_6H_6) 54-6°, $\nu_{max.}(CCl_4)$ 2 900, 1 720, 1 380, 1 375, 1 208, 1 120, 1 080, and 1 030 cm^{-1}, δ (CCl_4) 5.75 (1H, d, J=4Hz.), 5.25 (1H, d, J=2Hz.), 4.43 (1H, d, J=4Hz.), 3.98 (4H, m, contains J=2Hz.), 2.33 (3H, s), 1.47 (3H, s), 1.37 (3H, s), and 1.27 (6H, s), *m/e* 334 M^+, 319, 279, 261, 233, 201 ,175, 127, 113, 101, 75, 59, and 43, meta-stable 213.5 (calc. 319 → 261: 213.5).

92. Oxidation of the *Bis*(Methyl Xanthate) (70) [87].

(70)(186.2 mg, 0.427 mmol), $Ph_2Se_2O_3$ (343 mg, 0.952 mmol, 2.02 equiv.), 5h, p.l.c. (Petr. ether x 1, C_6H_6 x 1) resolved the products into two components: (a) less polar; *dihydrobenzoin-bis(methylthio - carbonate)* (70 *)(159 mg, 92%), δ ($CDCl_3$) 7.6-7.1 (10H, Ar), 6.12

(2H, d, non-equivalence of benzylic protons, with J=0Hz., due to conformational effects ?), and 2.25 (6H, s), *m/e* 270 M^+-92 i.e. less (MeSCOOH), 227, 181 M^{2+}, and 153. (b) more polar; (11 mg, 8% max.) ($CDCl_3$) 7.9-7.2 (8H, m) and 3.27 (3H, s).

93. Oxidation of the Thionbenzoate (71) [85].

(71)(252.3 mg, 0.647 mmol), $Ph_2Se_2O_3$ (234.2 mg, 0.65 mmol, 1 equiv.), 6h, p.l.c. (Petr. ether x 2), and recrystallisation (EtOAc) gave *n-octadecylbenzoate* (71 *)(183 mg, 76%), m.p. 42°.

94. Oxidation of the Thionformate (72, R=H, Y=0) [88].

(72, R=H, Y=0)(207.5 mg, 0.483 mmol), $Ph_2Se_2O_3$ (175.9 mg, 0.489 mmol, 1.01 equiv.), 4h, p.l.c. (Petr. ether/C_6H_6 1:1), afforded *4-cholesten-3β-ol-formate* (72 *, R=H, Y=0)(70 mg, 35%), m.p. 93-5°. (lit.,[65b] 96°).

95. Oxidation of the Thionacetate (72, R=Me, Y=0) [89].

(72, R=Me, Y=0)(185.6 mg, 0.418 mmol), $Ph_2Se_2O_3$ (161 mg, 0.447 mmol, 1.07 equiv.), 4h, p.l.c. (Petr. ether/C_6H_6 1:1), afforded *4-cholesten-3β-ol-acetate* (72 *, R=Me, Y=0)(105 mg, 59%), m.p. 110-112° (lit.,[65b] 114-5°).

96. Oxidation of the Thionbenzoate (72, R=Ph, Y=0) [90].

(72, R=Ph, Y=0)(224.9 mg, 0.444mmol), $Ph_2Se_2O_3$ (176 mg, 0.489 mmol, 1.1 equiv.), 24h, p.l.c. (Petr. ether), afforded *4-cholesten-3β-ol-benzoate* (72 *, R=Ph, Y=0)(157.3 mg, 73%), m.p. 148° (lit.,[65b] 150-1°), $\nu_{max.}$(CCl_4) 1 722, 1 600, and 1 270 cm^{-1}.

97. Comparison Reaction of (72, R=Ph, Y=0) [90] with Selenium Dioxide.

(72, R=Ph, Y=0)(185.7 mg, 0.367 mmol), SeO_2 (85 mg, 0.766 mmol, 2.09 equiv.), R.T. 10 days. T.l.c. analysis showed only a trace of the desired benzoate together with many less polar products.

98. Oxidation of the Dithionbenzoate (72, R=Ph, Y=S) [85].

(72, R=Ph, Y=S)(203.7 mg, 0.39 mmol), $Ph_2Se_2O_3$ (141.2 mg, 0.39 mmol, 1 equiv.), 24h, p.l.c. (Petr. ether/C_6H_6 1:1) gave *4-cholesten-3β-thiol-benzoate* (72 *, R=Ph, Y=S)(99 mg, 50%), m.p. 167°, $\nu_{max.}$(CCl_4) 2 800, 2 750, 1 670, 1 550, 1 250, 1 210, 1 180, 920, 865, 810-740 (brd),

& 700 cm^{-1}, *m/e* 506 M^+, 504, 401, 369, and 353, meta-stable 339 (calc. 401 369: 339.5). (Found: C, 80.6; H, 10.05; S, 6.35; $C_{34}H_{50}SO$ requires C, 80.6; H, 9.95; S, 6.3 %).

99. Oxidation of the Thionbenzoate (73, X=S) [87].

(73, X=S)(228.5 mg, 0.45 mmol), $Ph_2Se_2O_3$ (165.1 mg, 0.46 mmol, 1.02 equiv.), 3.5h, p.l.c. (Petr.ether x 2), gave *5α-cholestan-3β-ol-benzoate* (73 *, X=O)(152.3 mg, 69%), m.p. 136-7° (lit.,[65b] 136-7°).

100. Oxidation of the Selenobenzoate (73, X=Se) [91].

(73, X=Se)(205 mg, 0.369 mmol), $Ph_2Se_2O_3$ (133 mg, 0.369 mmol, 1 equiv.), 40 min, p.l.c. (Petr. ether x 2), gave *5α-cholestan-3β-ol-benzoate* (73 *, X=O)(150 mg, 83%), m.p. 137° (lit.,[65b] 136-7°).

101. Comparison Reaction of (73, X=Se) [91] with Selenium Dioxide.

(73, X=Se)(182 mg, 0.328 mmol), SeO_2 (74.8 mg, 0.674 mmol, 2.05 equiv.), R.T., 3 days, the red soln. became colourless. A deposit of red selenium was filtered off, and after evaporation of the filtrate and recrystallisation of the residue (EtOAc) gave *5α-cholestan-3β-ol-benzoate* (73 *, X=O)(145.9 mg, 97%), m.p. 136-7° (lit.,[65b] 136-7°).

102. Oxidation of the Thionbenzoate (74) [87].

(74)(252.4 mg, 0.568 mmol), $Ph_2Se_2O_3$ (205 mg, 0.569 mmol, 1 equiv.), 6h, p.l.c. (Petr. ether x1, C_6H_6 x1) and elution (Et_2O/EtOAc) afforded the crude product (140 mg, 58%); recrystallisation (C_6H_6/Petr. ether) gave *2-O-acetyl-4,6-benzylidene-1α-O-methylglucopyranose-3-ol-benzoate* (74 *)(130 mg, 54%), m.p. 144-5°, $\nu_{max.}$(Nujol) 1 745, 1 720, and 1 600 cm^{-1}, *m/e* 428 M^+, 427, 397, 351, 306, 279, 246, 219, 149, and 105. (Found: C, 64.45; H, 5.6; $C_{23}H_{24}O_8$ requires C, 64.5; H, 5.6%).

103. Oxidation of the Thionbenzoate (75) [85].

(75, R=H)(222.6 mg, 0.94 mmol), $Ph_2Se_2O_3$ (342 mg, 0.95 mmol, 1.01 equiv.), 2.5h, p.l.c. (Petr. ether x1, C_6H_6 x1, $CHCl_3$ x2), gave *cyclohexan-1,2-trans-diolmonobenzoate* (75 *, R=H)(97.5 mg, 47%), m.p. 91-2° (lit.,[65c] 92-3°), $\nu_{max.}$(CCl_4) 3 450 and 1 710 cm^{-1}, *m/e* 221 M^++1 (due to chemically induced ionisation by H^+ abstraction in the relatively high pressure of the MS9 ion source i.e. 10^{-4} torr used for this sample; c.f. 10^{-7} torr generally employed), 203, 105, and meta-stable 186.5 (calc. 221 → 203: 186.5). Work-up of the above

reaction mixture with Ac_2O/pyridine prior to p.l.c., gave the acetate-benzoate (75 *, R=Ac)(62%).

104. Oxidation of the *Bis*(Thionbenzoate) (75, R=PhC=S).[85]

(75, R=PhCS)(208.4 mg, 0.585 mmol), $Ph_2Se_2O_3$ (426.8 mg, 1.186 mmol, 2.03 equiv.), 2h, p.l.c. (C_6H_6), gave cleanly *cyclohexan-trans-1,2-dioldibenzoate* (75 *, R=PhCO)(166.4 mg, 88%), m.p. 94-5° (lit.,[65c] 94.5°), $\nu_{max.}(CCl_4)$ 1 715 cm^{-1}.

105. Oxidation of the Thioncarbonate (76) [85].

(76)(299 mg, 1 mmol), $Ph_2Se_2O_3$ (360.8 mg, 1 mmol, 1 equiv.), 4h, the polar product was isolated by treatment of the concentrated, red soln. with Petr. ether, to remove Ph_2Se_2, and after filtering and recrystallisation of the residue (C_6H_6/Petr. ether) this gave *bis(para-chlorophenyl)carbonate* (76 *)(195.7 mg, 70%), m.p. 154°, $\nu_{max.}(CCl_4)$ 1 780 and 1 485 cm^{-1}, *m/e* 284-282 M^+ (due to Cl isotopes), 240, 238, 176, 174, 113, and 111.

106. Oxidation of Thiourea (77, R=H) [92].

(77, R=H)(221.7 mg, 2.92 mmol), $Ph_2Se_2O_3$ (1.052 g, 2.92 mmol, 1 equiv.), 3h, after filtration the residue was dissolved in water, treated with (aq) $Na_2S_2O_5$, partitioned with Et_2O, to remove Ph_2Se_2, and the (aq) layer evaporated at R.T. under reduced pressure. Recrystallisation (EtOH) gave *urea* (77 *, R=H)(120.7 mg, 69%), $\nu_{max.}$(Nujol) 1 660 (brd) cm^{-1}.

107. Oxidation of the Thiourea (77, R=Ph) [92].

(77, R=Ph)(297.1 mg, 1.303 mmol), $Ph_2Se_2O_3$ (470.7 mg, 1.308 mmol, 1 equiv.), 5h, work-up as above, afforded *N,N-diphenylurea* (77 *, R=Ph)(106.5 mg, 39%).

108. Oxidation of the Trithiocarbonate (78) [93].

(78)(220 mg, 1.158 mmol), $Ph_2Se_2O_3$ (417 mg, 1.158 mmol, 1 equiv.) for 1h, p.l.c. (C_6H_6/Petr.ether 1:1) gave *cyclohexan-1,2-trans-diyl-dithiocarbonate* (78 *)(117.3 mg, 58%), m.p. 109-10° (lit.,[93] 109-10°), $\nu_{max.}(CHCl_3)$ 1 730 and 1 640 (brd, C-S overtone) cm^{-1}, *m/e* 174 M^+, 146, 114, 99, 81, and 80; and a more polar PhSe- derivative (by N.M.R.), (52 mg, 14%), $\nu_{max.}(CHCl_3)$ 1 710-1 730 (brd) cm^{-1}.

109. Oxidation of the Trithiocarbonate (79) [93].

(79)(157.8 mg, 0.74 mmol), $Ph_2Se_2O_3$ (268 mg, 0.74 mmol, 1 equ) for 3h, p.l.c. (C_6H_6/Petr. ether 1:1) afforded *phenylethan-1,2-diyl-dithiocarbonate* (79 *)(145.9 mg, 84%), (no trace of a PhSe- deriv.), δ (CCl_4) 7.33 (5H, m), 5.13 (1H, t, J=8Hz.), and 3.63 (2H, d, J=8Hz.), c.f. the starting material: 7.42 (5H, m), 5.57 (1H, d of d, J=7, 8.8Hz.), and 4.05 (2H, overlapping d x 2, J=7, 8.8Hz.).

When the trithiocarbonate (79)(162.5 mg, 0.767 mmol) and $Ph_2Se_2O_3$ (553 mg, 1.536 mmol, 2 equiv.) were heated together in boiling THF (6 ml) for 18h, only the single product (79 *) was obtained. Furthermore, iodometric titration of the cooled reaction mixture required (aq) $Na_2S_2O_3$ (0.1M, 46 ml), i.e. 49% {O} capacity remained.

110. Oxidation of the Trithiocarbonate (80) [86].

(80)(84.7 mg, 0.275 mmol), $Ph_2Se_2O_3$ (102.1 mg, 0.284 mmol, 1.03 equiv.), 5h, p.l.c. (C_6H_6/Petr. ether 1:1), gave *diethylidene-5,6-anhydro-L-mannitol-dithiocarbonate* (80 *)(51 mg, 64%), m.p. 148-50°, *m/e* 292 M^+, 291, 277, 258, 232, 199, 176, 173, 129, 87, 85, and 83.

111. Oxidation of Thiofenchone (81) [94].

(81)(100.8 mg, 0.6 mmol), $Ph_2Se_2O_3$ (216 mg, 0.6 mmol, 1 equiv.) for 2h, G.L.C. (column: fluorosilicone oil on chromosorb W) showed retention times: naphthalene (internal standard) 6.5 min, thiofenchone 5.9 min, and *fenchone* (81 *) 5.2 min (89%).

112. Oxidation of Thiocamphor (82) [94].

(82)(193.6 mg, 1.15 mmol), $Ph_2Se_2O_3$ (415 mg, 1.15 mmol, 1 equ) for 3h, p.l.c. (C_6H_6/Petr. ether 1:1) gave *camphor* (83)(9%); *3-endo-phenylseleninocamphor* (84)(36%), δ ($CDCl_3$) 7.75-7.22 (5H, m), 6.38 (1H, d, J=4Hz.), 2.4 (1H, t, J=4Hz.), 2.1-1.4 (4H, m), 1.23 (3H,s), and 0.78 (6H, s); and *camphor quinone* (85)(54%), $\nu_{max.}$ (CCl_4) 1 780 and 1 760 cm^{-1}, δ (CCl_4) 2.5-1.2 (5H, m), 1.03 (6H, s), and 0.9 (3H, s), m.p. (sealed tube) 196-7° (lit.,[65d] 199°), *m/e* 166 M^+, 138, 123, 110, 95, 83, 69, 55, and 41, meta-stables: 115, 109.5, and 87.5 (calc. 166 → 138: 114.7; calc. 138 → 123: 109.6; calc. 138 → 110: 87.7).

113. Preparation and Oxidation of Phenylselenocamphor (86).

Preliminary attempts to generate a satisfactory enolate of camphor with the bases NaH, *n*-BuLi, and $LiN(i\text{-}Pr)_2$ (followed by N.M.R. with D_2O or MeI quenching) were unsuccessful. Satisfactory results were obtained using $LiN(SiMe_3)_2$.

To $LiN(SiMe_3)_2$ (1.307 g, 7.83 mmol) in THF (6 ml), cooled to 0^o under N_2, was added camphor (83)(1.16 g, 7.63 mmol, 0.98 equiv.) in THF (3 ml) *via* a syringe. After 5 min, the stirred enolate soln. was warmed to R.T. then cooled to 0^o again before the addition of PhSeCl (1.5 g, 7.83 mmol, 1 equiv.) in THF (3 ml) over 20 min, then warmed to R.T. The product was isolated by dilution with Et_2O, washing (dil. HCl, to pH 7), separation, drying ($MgSO_4$), evaporation of the ether and column chromatog. of the residue (silica/Petr. ether/C_6H_6 1:1/$CHCl_3$). A polar fraction afforded *3-phenylselenenylcamphor* (86)(1.413 g, 60%), c.f.17% with $LiN(i\text{-}Pr)_2$ as base, as an uncrystallisable 4:1 mixture of *endo : exo* epimers, c.f. 2:1 with $LiN(i\text{-}Pr)_2$, $\nu_{max.}$($CDCl_3$) 3 040, 2 900, 2 850, 1 575, 1 440, 1 360, 1 295, 1 275, 1 250, 1 015, 840, and 830 cm^{-1}, δ ($CDCl_3$) 7.7-7.1 (5H, m), 4.5 and 4.13 (integral ratio 1:4, 1H combined, d x 2, J=5Hz. each), 2.2-1.0 (5H, env), 1.1 (3H, s), 1.05 (3H, s), and 0.98 (3H, s), *m/e* 308 M^+, 306, 197, 186, 151, 143, 123, and 83.

The product (86) was inert towards oxidation by $Ph_2Se_2O_3$ (1 equiv., R.T., 5 days); (aq) $NaIO_4$ (1 equiv., 0^o, 50 min, R.T., 4h); however, MCPBA (1.12 equiv., $0^o \rightarrow$ R.T., 2h) consumed the least hindered epimer (i.e. *endo*- with H_α at δ4.13) to afford Ph_2Se_2 and camphorquinone (85)(by t.l.c.), presumably *via* a Pummerer-type rearrangement of the intermediate selenoxide.

114. Attempted Preparation of Phenylselenothiocamphor (87).

$LiN(SiMe_3)_2$ was prepared *in-situ* from $HN(SiMe_3)_2$ (2.12 g, 13.17 mmol) and *n*-BuLi (1.05M, 12.5 ml, 13.17 mmol, 1 equiv.) in THF (0^o) (4 ml) over 15 min. To this soln. was added (±) thiocamphor (82)(1.1 g, 6.55 mmol, 0.49 equiv. to base) in THF (3 ml) dropwise over 15 min. The orange colour of (82)was discharged upon formation of the thiolate, to which was added PhSeCl (1.26 g, 6.56 mmol, 0.5 equiv. to base) in THF (4 ml) at 0^o for 1h. After warming to R.T. and acidic work-up, the yellow soln. gave after p.l.c. Ph_2Se_2 and a mixture of non-polar products whose properties are consistent with them being a diastereomeric mixture of *bis*-vinyldisulphides (88) [95,96], δ ($CDCl_3$) 5.82 and 5.23 (integral

ratio 1:1, 2H combined, d x 2, J=3Hz. each), 2.58-1.0 (10H, env), and 0.95-0.6 (18H, m), *m/e* 336 M^++2, 301, 200, and 137.

115. Iodometric Titrations for some Thione / $Ph_2Se_2O_3$ Reactions at 20°.

(a) 5α-Cholestanyl-3β-ol-methylthioxanthate (65); after 5h, at 20° in THF consumed 100% {O} of the anhydride.

(b) *n*-Octadecylthionbenzoate (71); as (a) above.

(c) 5α-Cholestanyl-3β-ol-thionbenzoate (73, X=S); the remaining {O} capacity of the anhydride was followed to completion of the reaction, see Fig. 6, graph A.

For cases (a) and (b) above, when 2 equiv. $Ph_2Se_2O_3$ was employed an extra 33% {O} capacity was also consumed.

116. Detection of Acidic, Gaseous By-Products from Thione Reactions.

(a) To a soln. of the xanthate (65)(412.4 mg, 0.863 mmol) in THF (10ml) was added $Ph_2Se_2O_3$ (323.4 mg, 0.898 mmol, 1.04 equiv.) and the mixture stirred at R.T. under a bubbled stream of $CaCl_2$/NaOH-dried N_2. The effluent gases were conducted through (aq) NaOH (0.1M, 50 ml), during which time the mixture was slowly heated to reflux. Iodometric titration of the final alkaline soln. against (aq) HCl (0.5M, required 10.35 ml) indicated the consumption of 0.53 mmol base (blank, 9.30 ml, 0.5M, HCl) eqivalent to 31% capture of SO_2.

(b) Under similar conditions, thiocamphor (82)(427.1 mg, 2.54 mmol) was treated with $Ph_2Se_2O_3$ (915 mg, 2.54 mmol, 1 equiv.) in THF (10 ml). The effluent gases were bubbled through water at 22° (initially at pH 7.3) and the exponential decrease in pH to 2.78 over 74 min monitored with a digital pH meter. The results are presented in Fig. 6, graph B.

(c) A nickel hydroxide-impregnated test paper (from filter paper + soln. $NiSO_4.6H_2O$ (1 g) in 0.880 NH_3 (3 ml), dried at 110° then treated with a soln. of NaOH (500 mg) and Na_2CO_3 (200 mg) in water (10 ml) for 5 min, then dried at 110° 100) was slightly darkened upon exposure to the effluent gases above.

117. Reaction of Benzenethiol with $Ph_2Se_2O_3$.

A soln. of benzenethiol (0.2 ml, 1.94 mmol) in dry THF (5 ml) was added slowly to a suspension of $Ph_2Se_2O_3$ (701 mg, 1.95 mmol,1 equiv.) in dry THF (5 ml) cooled to 0°. After warming to R.T. over 1h, the soln. was filtered to recover $PhSeO_2H$ (380 mg, 52%) and evaporation of the

filtrate and p.l.c. (silica/Petr. ether x 4) afforded a colourless sample of *diphenyldisulphide* (174 mg, 82%).

118. Preparation of Triphenylphosphine Sulphide (91) and Selenide (92).

To dry, degassed benzene (100 ml) under N_2 was added triphenylphosphine (7.43 g, 28 mmol) and, in portions, elemental sulphur (900mg, 28 mmol, 1 equiv.) at R.T. followed by slow warming to reflux, then maintained for 1h (t.l.c. control). After cooling and evaporation of the C_6H_6, the colourless residue was recrystallised (EtOH) to afford long needles of the *IRRITANT* product *triphenylphosphine sulphide* (91) (7.14 g, 85%), m.p. 163-4°, *m/e* 294 M^+, 262, 185, 183, 139, 108, 107, and 77.

The above method, employing Ph_3P (7.25 g, 27.6 mmol)and elemental selenium (2.18 g, 27.6 mmol, 1 equiv.) afforded the *IRRITANT* product *triphenylphosphine selenide* (92)(7.64 g, 81%), m.p. 187-9°, *m/e* 342 M^+, 262, 185, 183, 108, 107, and 77.

119. Reaction of the Phosphorus Compounds (90),(91),(92),&(95)/$Ph_2Se_2O_3$.

(a) Triphenylphosphine (90)(300.6 mg, 1.15 mmol), $Ph_2Se_2O_3$ (138.6mg, 0.385 mmol, 0.33 equiv.), THF (5 ml), R.T., 40 min, afforded *triphenylphosphine oxide* (93) (137 mg, 43%), m.p. 152°.

(b) (91)(464 mg, 1.58 mmol), $Ph_2Se_2O_3$ (568 mg, 1.58 mmol, 1 equiv.) in boiling THF (10 ml), 1h, afforded (93)(259 mg, 59%), m.p. 151°.

(c) (92)(300 mg, 0.88 mmol), $Ph_2Se_2O_3$ (349.3 mg, 0.97 mmol, 1.1 equiv.), 0° for 15 min, R.T. for 40 min, afforded rapidly (93)(136.5 mg, 56%), m.p. 151°, and elemental selenium (red allotrope)(24.7 mg, 36%).

(d) (95)(204 mg, 0.6 mmol), $Ph_2Se_2O_3$ (215 mg, 0.6 mmol, 1 equiv.), R.T., 16h, afforded *tri-O-phenylphosphate* (94)(101 mg, 52%), m.p. 48-9°.

120. Preparation of the Tetracyclic Ester (98).[3]

The tricyclic 1,3-dithiolane (97)(510 mg, 0.96 mmol) was irradiated (quartz/halogen lamp) in boiling benzene (2 l) in the presence of $LiN(SiMe_3)_2$ (35.9 mg, 0.22 mmol, 0.23 equiv.) over 15 min (t.l.c. and U.V. control). The usual work-up procedure then afforded the crystalline tetracyclic ester *methyl, 12-ethylenedithiaspiro-6aα,7,12,12aα-tetrahydro-9,11-dihydroxy-6-oxo-1-phenyl(6H)naphthaceno{1,12-bc}furan-10-carboxylate* (98)(252 mg, 49%), m.p. 241 (dec.), $\lambda_{max.}(CHCl_3)$ 243, 266,

and 349 nm (ε 26 000, 23 500, and 17 000), δ ($CDCl_3$) 11.1 (1H, s), 9.33 (1H, s), 7.99-7.26 (8H, m), 6.44 (1H, s), 4.73 (1H, d, J=5Hz.), 4.03 (3H, s), 3.9-2.8 (6H, m), and 2.0-1.7 (1H, m), *m/e* 530 M^+, 470, 438, 256, 247, and 224, $\nu_{max.}$ ($CHCl_3$) 1 670 and 1 630 cm^{-1}

121. Preparation of the Tetracyclic Amide (99).[3]

To a suspension of the ester (98)(500 mg, 0.94 mmol) in THF (7 ml) was added 0.880 NH_3 (5 ml) and the mixture stirred at R.T. for 22h. Acidic work-up and repeated reprecipitation, afforded, *12-ethylenedithiaspiro-6aα,7,12,12aα-tetrahydro-9,11-dihydroxy-6-oxo-1-phenyl(6H)naphthaceno{1,12-bc}furan-10-carboxamide* (99)(363 mg, 75%), m.p. 211° (dec.), $\lambda_{max.}$ ($CHCl_3$) 243, 266, and 349 nm (ε 26 000, 23 500, and 17 000), $\nu_{max.}$ (Nujol) 3 400, 3 300-3 100, 1 680, 1 655, and 1 620 cm^{-1}, δ ($CDCl_3$), 10.1 (1H, s), 8.7 (1H, s), 8.01-7.29 (8H, m), 6.54 (1H, s), 4.91 (1H, d, J=5Hz.), 4.15-2.89 (9H, m), and 1.98-1.8 (1H, m), *m/e* 515 M^+, 455, 438, 247, 241, and 224.

122. Preparation of the Tetracyclic Carbinol (103).[3]

To a soln. of the keto-amide (99)(279.6 mg, 0.54 mmol) in THF (20 ml) at -78° under N_2, was added ethereal methyllithium (1.5M, 9 ml, 25 equiv.) and the mixture stirred for 40 min (t.l.c. control). Work-up by the addition of NH_4Cl at -78°, warming to 0°, addition of water, then at R.T. drying of the ethereal soln. (Na_2SO_4). Partial evaporation of the solvent and the addition of MeOH, fractionally crystallised the product *12-ethylenedithiaspiro-6aα,7,12,12aα-tetrahydro-6β,9,11-trihydroxy-6α-methyl-1-phenyl(6H)naphthaceno{1,12-bc}furan-10-carboxamide* (103)(223.7 mg, 78%), m.p. 198°(dec.), $\lambda_{max.}$ (CH_2Cl_2) 250, 296, 312, and 324 nm (ε 14 500, 14 500, 14 000, and 14 000), $\nu_{max.}$ (KBr disc) 3 450, 3 350-2 900, 1 695, 1 655, 1 605, 1 415, 1 280, 1 260, 1 085, 1 045, 775, and 760 cm^{-1}, δ ($CDCl_3$) 13.3 (1H, s), 10.0 (1H, s), 8.0-7.38 (8H, m), 6.52 (1H, s), 4.87 (1H, d, J=5Hz.), 4.06-2.7 (7H, m), and 1.58 (3H, s), *m/e* 513 M^+-18, 453, 436, 241, and 224.

123. Reaction of the Tetracyclic Ester (98) with $Ph_2Se_2O_3$.

The ester (98)(120 mg, 0.23 mmol) and $Ph_2Se_2O_3$ (81.5 mg, 0.23 mmol, 1 equiv.) were stirred together in dry CH_2Cl_2 (3 ml) at R.T. for 7h. After a further 16h in the cold, the precipitated crude product was filtered off, washed (Et_2O) to remove Ph_2Se_2, and recrystallised (MeOH) to afford the dimethanolate of *methyl, cis-6aα,7,12,12aα-tetra—*

hydro-9,11-dihydroxy-6,12-dioxo-1-phenyl(6H)naphthaceno{1,12-bc}furan--10-carboxylate (101)(65.4 mg, 64%), m.p. 252°(dec.), $\lambda_{max.}$ ($CHCl_3$) 260, 275 (sh), 294, 337, and 358 nm (ε 23 800, 22 500, 21 000, 17 200, and 13 600), $\nu_{max.}$ (KBr disc) 3 550-3 300, 3 050, 2 800, 1 685, 1 665, 1 620, 1 580, 1 440, 1 240, and 760 cm^{-1}, δ ($CDCl_3$) 8.06-7.28 (8H, m), 6.58 (1H, s), 5.87 (1H, s), 4.85 (1H, d, J=5Hz.), 4.01-3.09 (3H, m), 3.95 (3H, s), and 1.53 (2 MeOH), *m/e* 454 M^+, 437, 423, 422, 405, 394, 376, 366, 349, 337, 247, 208, and 176. (Found: C, 67.1; H, 4.9; $C_{27}H_{18}O_7.2MeOH$ requires C, 67.2; H, 5.0 %).

124. Preparation of Trimethylsilyl Iodide [104] and Reaction with (101).

Trimethylsilyl chloride (15 ml, 118 mmol) was added carefully to water (100 ml) and the mixture vigorously stirred for 1h at R.T. The resultant disiloxane was separated, washed (H_2O), dried (Na_2SO_4 for 3h), then filtered and (7.36 g, 45.4 mmol) added to powdered aluminium metal (2.54 g, 90.7 mmol, 2 equiv.) and the mixture warmed to 60° under N_2. Iodine (23.13 g, 91.1 mmol, 2 equiv.) was added slowly from a Newman tube. After 1h at reflux, the refluxant was colourless and the apparatus was quickly modified to distill the product, under N_2, directly from the reaction mixture, to yield *trimethylsilyl iodide* (Me_3SiI)(18.79 g, 80%).

Reaction of Me_3SiI with the diketone-ester (101) produced many by-products and, in common with other attempted methods (e.g. KOH/MeOH, (aq) NH_3, imidazole/60% (aq) MeOH, tetramethylguanidine/60% (aq) MeOH) gave none of the free C-10 carboxylate or derivatives suitable for subsequent amidation.

125. Preparation of the Diketone-Amide (102) *via* the *Tris*-TMS Cpd. (100).

Whilst *bis*(trimethylsilyl)acetamide [108] failed to react effectively, the treatment of the amide (99)(100 mg, 0.19 mmol) in pyridine (5 ml) with $HN(SiMe_3)_2$ (1 ml) and Me_3SiCl (1 ml) under N_2 at R.T. over 40 min, gave quantitatively the *tris*-TMS derivative (100) (by N.M.R.; δ(CCl_4/CH_2Cl_2 internal reference) 0.5, 0.4, and 0.2, 3 Me_3Si-). After removal of the excess reagents *in-vacuo*, $Ph_2Se_2O_3$ (70 mg, 0.19 mmol, 1 equiv.) was added to the substrate in CCl_4/CH_2Cl_2 (5 ml), and the mixture stirred at RT for 16h. Work-up with NH_4F , followed by repeated reprecipitation of the separated product afforded *cis-6aα,7,12,12aα-tetrahydro-9,11-dihydroxy-6,12-dioxo-1-phenyl(6H)naphthaceno{1,12-bc}furan-10-carboxamide* (102)(20 mg, 24%), $\lambda_{max.}$ ($CHCl_3$) 248, 275 (sh), 280, 295, 305 (sh), 330, and 354 nm (ε 30 000, 18 700, 17 700, 17 600,

16 100, 12 900, and 10 900), *m/e* 439 M^+, 422 $M^+ - NH_3$, and 394 $M^+ - HCONH_2$.

126. Direct Reaction of the Carbinol (103) with $Ph_2Se_2O_3$.

The tetracyclic carbinol (103)(212.5 mg, 0.4 mmol) was suspended in THF (10 ml) containing pyridine (2 drops) and cooled to -23° (CO_2/CCl_4 cold bath) under N_2, then treated with $Ph_2Se_2O_3$ (288 mg, 0.8 mmol, 2 equiv.) over 20.5h (N.B. the use of only 1 equiv. of the anhydride usually left large quantities of starting material unreacted). Work-up by the addition of satd. (aq) $NaHCO_3$, extraction ($CHCl_3$), drying (Na_2SO_4) and p.l.c. (silica/$CHCl_3$/EtOAc 1:1) gave, after recrystallisation ($CHCl_3$/MeOH) the monomethanolate of *cis-6aα,7,12,12aα-tetrahydro-6β,9,11-trihydroxy-6α-methyl-12-oxo-8-phenylseleninoyl-1-phenyl(6H)naphthaceno{1,12-bc}furan-10-carboxamide* (106/7)(59.7 mg, 23%), $\lambda_{max.}$ ($CHCl_3$) 278, 330, and 350nm (ε 21 900, 13 000, and 12 400), $\nu_{max.}$ (KBr disc) 3 500-3 200, 2 850, 1 680, 1 650, 1 590, 1 450, 1 250, 770, 760, 740 and 700 cm^{-1}, δ ($CDCl_3$) 18.17 (1H, s), 11.65 (1H, s), 8.0-7.9 (2H, m), 7.7-7.6 (2H, m), 7.5-7.3 (9H, m), 4.55 (1H, d, J=5Hz.), 3.65-3.4 (1H, m), 3.15-2.8 (2H, m), and 1.5 (3H, s).

(Found: C, 60.3; H, 3.7; N, 2.1; $C_{33}H_{25}O_8SeN.MeOH$ requires ; C, 60.4; H, 4.3; N, 2.1 %).

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APPENDIX.

N.M.R. Technique, Experiment 36.E.(ii).

Estimation of the yield of the diketone (21) in a mixture containing starting material (36) by N.M.R. was made as follows:

Let the starting material (36) be represented by (SM) and the diketone product (21) by (DK).

Before reaction with MCPBA (SM mg) = 111.7 mg (which in theory gives (DK) 93.0 mg).

(DK mg) + (SM mg) mixture isolated = 51.2 mg .

A. (SM) N.M.R. spectrum shows 12a-H resonance at 4.46 and 4.36 ppm.
B. (DK) N.M.R. spectrum shows 12a-H resonance at 4.78 ppm.

$$\text{Integral ratio A/B} = \frac{\text{(SM moles)}}{\text{(DK moles)}} = 1/2.5$$

$$\text{Thus, } 2.5 = \frac{\text{(DK mg)}/364\,000}{\text{(SM mg)}/437\,000} = \frac{437}{364} \times \frac{\text{(DK mg)}}{\text{(SM mg)}} = 1.2 \times \frac{\text{(DK mg)}}{\text{(SM mg)}}$$

$$\text{Therefore, (SM mg)} = \frac{1.2}{2.5} \times \text{(DK mg)} = 0.48 \times \text{(DK mg)}$$

From total mixture isolated (DK mg) + 0.48 x (DK mg) = 51.2 mg

Thus, (DK mg) = $\frac{51.2}{1.48}$ mg

i.e. weight of diketone (21) produced (DK mg) = 34.6 mg

By substitution, unused starting material (SM mg) = 16.6 mg

Hence, weight of starting material consumed (SM) = 111.7-16.6

(SM) = 95.1 mg

which should afford, in theory, product (DK) = 79.2 mg

Therefore, the yield of (DK) based upon recovered (SM) is:

$$\text{(DK) Yield (21)} = \frac{34.6}{79.2} \times 100 = 44\%$$

Removal of 1,3-Dithiolan Protecting Groups by Benzeneseleninic Anhydride

By Derek H. R. Barton,* Nigel J. Cussans, and Steven V. Ley
(*Chemistry Department, Imperial College, London* SW7 2AY)

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Removal of 1,3-Dithiolan Protecting Groups by Benzeneseleninic Anhydride

By DEREK H. R. BARTON,* NIGEL J. CUSSANS, and STEVEN V. LEY
(*Chemistry Department, Imperial College, London* SW7 2AY)

Summary Benzeneseleninic anhydride smoothly regenerates ketones and aldehydes from their 1,3-dithiolan derivatives at room temperature in tetrahydrofuran (or CH_2Cl_2) in good yield and, in particular cases, where all other common procedures have failed.

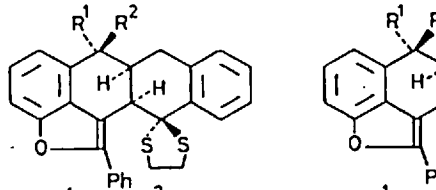
WE report here a new procedure for the reformation of ketones (and aldehydes) from their corresponding dithioacetals using benzeneseleninic anhydride,[1] ($Ph_2Se_2O_3$) which shows advantages over existing methods.[2]

In a typical experiment the tetracyclic carbinol (**1**), which contains a sterically hindered 1,3-dithiolan unit, was treated with benzeneseleninic anhydride at room temperature in dry tetrahydrofuran (THF) to afford the deprotected carbinol (**2**) in high yield (Table). Under similar conditions the ketone (**3**) could be smoothly converted into the diketone (**4**).

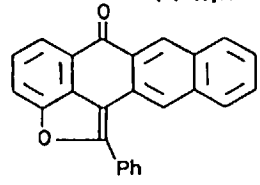
TABLE. Reactions of dithiolan derivatives with $Ph_2Se_2O_3$ to give the parent carbonyl compound.[a]

1,3-Dithiolan	Time	% Yield[b]
(**1**)[c]	50 h	78 [of (**2**)]
(**3**)[d]	3·5 h	63 [of (**4**)]
(**6**)	3 h	21 (59 by g.l.c.)
(**7**)	40 min	78 (DNP) (92 by g.l.c.)
(**8**)	1 h	93
(**9**)	30 min	65 (DNP) (70 by g.l.c.)
(**10**)	1 h	72
(**11**)[e]	18 h	(63 by g.l.c.)
(**12**)[f]	2 h	(78 by g.l.c.)

[a] In THF at room temperature unless otherwise noted. [b] Isolated yield of carbonyl compound [or 2,4-dinitrophenylhydrazone (DNP)] unless noted. [c] In THF–pyridine at 40 °C. [d] In CH_2Cl_2 at room temperature. [e] In refluxing THF. [f] In THF at 55 °C.



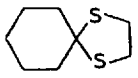
(1) R^1 = Me; R^2 = OH
(3) R^1,R^2 = O
(2) R^1 = Me; R^2 = OH
(4) R^1,R^2 = O



(5)

In comparison, attempted deprotection of compound (**3**) with standard reagents [HgO, $HgCl_2$, $Hg(OAc)_2$, $AgNO_3$, MeI–H_2O, or $MeOSO_2F$]) gave none, or only small quantities, of the desired ketone (**4**). Indeed, the major product from

the reaction of compound (3) with $MeOSO_2F$ was shown to be the tetracyclic ketone (5).[3] Other more vigorous conditions (particularly low pH) had to be avoided during the deprotection of the carbinol (1) owing to the easy loss of the hydroxy group by dehydration.



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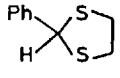

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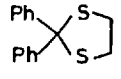

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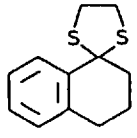

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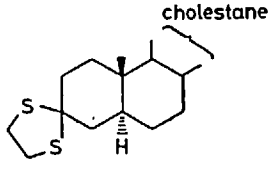
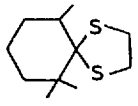


(10)



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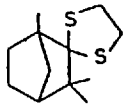


(12)

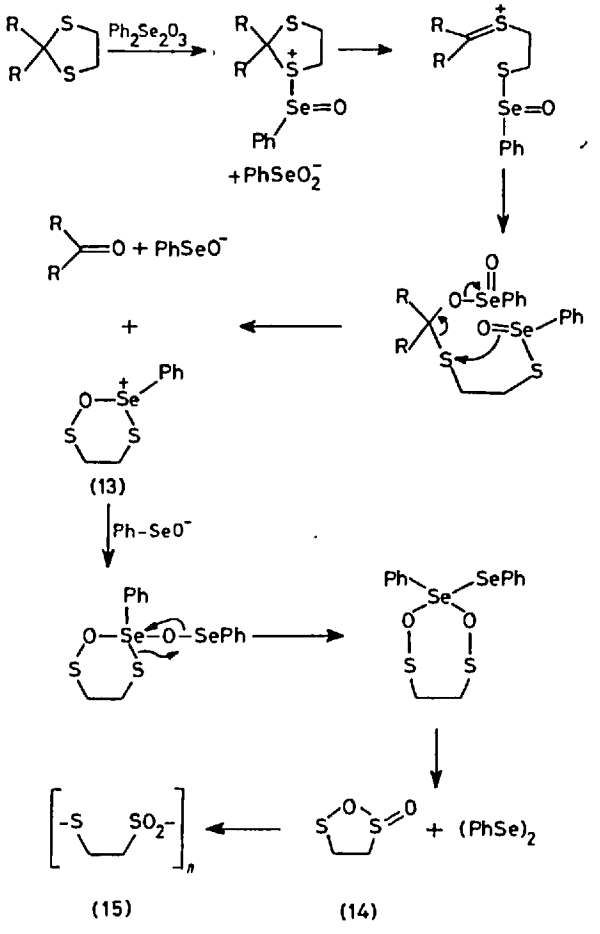
The 1,3-dithiolan analogues of cyclohexanone (6), 2,2,6-trimethylcyclohexanone (11), fenchone (12), benzaldehyde (7), benzophenone (8), α-tetralone (9), and 5α-cholestan-3-one (10) all reacted with the anhydride giving the parent carbonyl compounds in good yield (Table). Noticeably (10) was recovered in 72% yield from its ethylene dithioacetal. This yield equals or exceeds those for other reported procedures for this transformation.[4]†

1,3-Dithian derivatives can also be deprotected by the use of the anhydride. For example, the 1,3-dithian derivative of the cholestane system gave cholestanone in 73% yield after 16 h at room temperature.

In all the reactions studied, diphenyl diselenide was formed quantitatively and all three oxygen atoms of the reagent were consumed. Also, if the reactions were followed by n.m.r. or i.r. spectroscopy, rapid formation of the carbonyl products was observed even under scrupulously dry conditions. Hydrolytic work-up was not essential. Whilst the monosulphoxides of 1,3-dithiolans have been shown to enhance reconversion into ketones[5] the monosulphoxides of each dithioacetal in this study did not react with benzeneseleninic anhydride under normal conditions. In addition, attempts to generate diphenyl sulphoxide and dibenzyl sulphoxide from their sulphides with the anhydride failed (even after heating in THF for several days). We conclude that oxidation to a sulphoxide (and subsequent reaction) is not an intermediate step in the reaction.

Selenium dioxide reacts with dithioacetals at room temperature to give a complex mixture of products.

A possible mechanism for the reaction is summarised in the Scheme; there are, of course, plausible alternatives which we will discuss in more detail in a full paper. Apart from the carbonyl compound and $(PhSe)_2$, the other product was a polymer (15). This was identified by composition and by comparison with the per-acid oxidation product of polyethylene disulphide.[6] We tentatively consider it to be formed from (13) through the monomer (14).



SCHEME

No radicals could be detected by e.s.r. spectroscopy.

We thank the S.R.C. for a Studentship (to N.J.C.), and Dr. J. F. Gibson for use of the e.s.r. (Varian E9) instrument.

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† Use of MeI/H_2O and 'Magic Methyl' give the ketone in 21 and 90% yield, respectively.

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(*Department of Chemistry, Imperial College, London* SW7 2AY)

Summary A number of xanthates, thioesters, thiocarbonates, thioamides, and thiones have been converted into the parent oxo carbonyl derivatives in high yield by treatment with benzeneseleninic anhydride at room temperature in tetrahydrofuran.

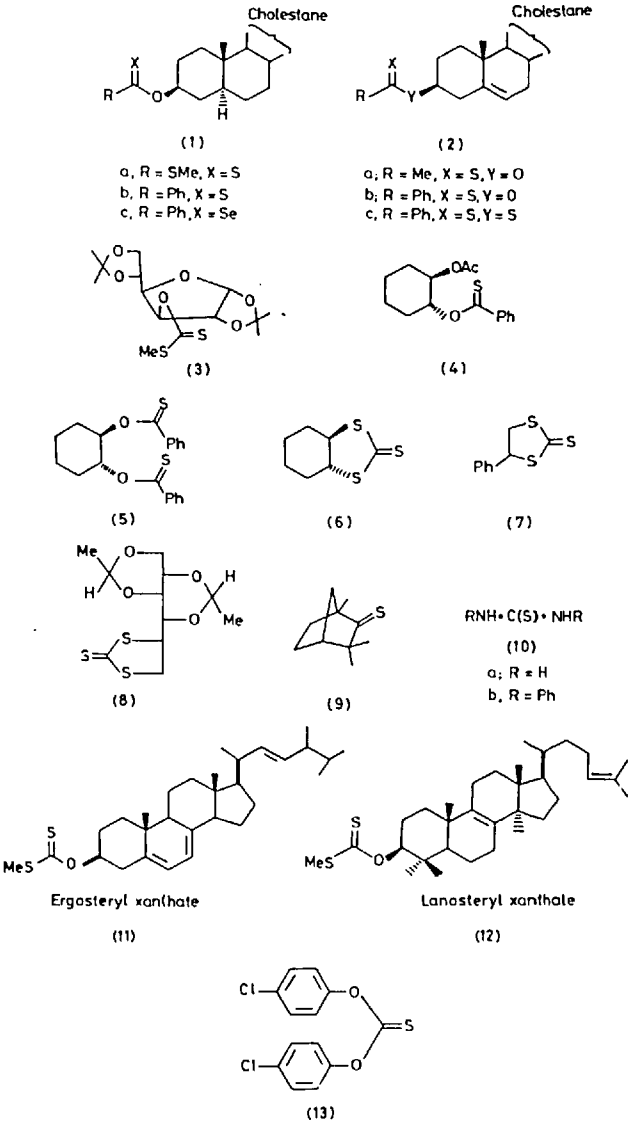
RECENTLY benzeneseleninic anhydride, $(PhSeO)_2O$, has been shown to be a mild and versatile reagent for oxidation of organic substrates.[1] Here we report its use in the conversion of thiocarbonyl compounds into oxo derivatives, a reaction which has not received much attention in the literature.[2]

A variety of xanthates, thiocarbonates, thioamides, and thiones, (**1**)—(**13**), (Table), were treated at room temperature in tetrahydrofuran with 1 equiv. of benzeneseleninic anhydride. The reaction was routinely followed by t.l.c. and the products isolated by p.l.c. after disappearance of the starting material from the reaction mixture. In the

TABLE[a]

Comp.	Reaction time/h	Yield of oxo-derivative /%[b]	Comp.	Reaction time/h	Yield of oxo-derivative /%[b]
(**1a**)	12	67	(**6**)	1	58
(**1b**)	3·5	69	(**7**)	3	84
(**1c**)	0·6	83	(**8**)	5	64
(**2a**)	4	59	(**9**)	2	89[c]
(**2b**)	24	73	(**10a**)	3	60
(**2c**)	24	51	(**10b**)	5	39
(**3**)	2	75	(**11**)	2	71
(**4**)	2·5	62	(**12**)	1[d]	63
(**5**)	2	88	(**13**)	4	70[e]

[a] Reactions were carried out with 1 equiv. of $(PhSeO)_2O$ in tetrahydrofuran at room temperature unless stated otherwise. [b] Yields of products isolated by preparative layer chromatography unless stated otherwise. [c] Estimated by g.l.c. [d] Reaction carried out at reflux. [e] Isolated by precipitation and recrystallisation.



majority of examples the yields of carbonyl compounds were good. The major byproduct of the reaction was diphenyl diselenide which could be readily isolated and reoxidised to the anhydride. The examples were chosen to illustrate not only use in simple transformations but also in more complex natural products.

In several reactions we have compared the use of selenium dioxide as an alternative reagent for oxidation;[3] however, only mixtures of products or very long reaction times were observed. The best of these reactions gave a 97% yield of benzoate after treatment of cholestan-3β-ol seleno-benzoate with SeO_2 for 3 days. We regard this result as a special case as generally the yields were much lower.

The fact that thiofenchone rapidly affords the oxo derivative is a good indication that reaction proceeds well even when there are considerable steric restrictions. Thiocamphor, on the other hand, gave three products on reaction with the anhydride which were characterised as camphor (9%), camphor quinone (54%), and 3-*endo*-phenylselenino-camphor (36%) which rapidly decomposes to camphor-quinone on standing at room temperature. In accord with this result, oxidation of an authentic sample of 3-phenyl seleno-camphor by *m*-chloroperbenzoic acid also afforded camphor-quinone at room temperature. Generally therefore, thiocarbonyl compounds which also contain an enolisable methylene group are expected to lead to more complex reaction mixtures on oxidation by the anhydride.

The precise mechanistic details of these reactions are not known although it is clear by n.m.r. spectroscopy that the oxo derivative is formed during the reaction even with strict exclusion of water and oxygen. Apart from diphenyl-diselenide as a reaction byproduct, we have also detected sulphur dioxide in the effluent gases.

The above reactions constitute a mild and effective method for the conversion of thiocarbonyl compounds into the corresponding oxo species.

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