STUDIES RELATED TO THE SYNTHESIS OF TETRACYCLINE

a thesis presented by

MOSHE NATHAN ROSENFELD

in partial fulfilment of the requirements

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OF THE

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

AUGUST, 1976.

בעהשי"ת

מה שהי' הוא שיהי' , ומה שנעשה הוא שיעשה
ואין כל חדש תחת השמש.
יש דבר שיאמר ראה זה חדש הוא כבר הי' לעולמים
אשר הי' מלפנינו.

(קהלת א, ט-י)

That which hath been, is that which shall be ,
And that which hath been done,is that which shall be done,
And there is nothing new under the sun .
Is there a thing, whereof it is said:'see this is new' ,
It hath been already in the ages, which were before us .

(Liber Ecclesiastae I,9-11)

ACKNOWLEDGEMENTS

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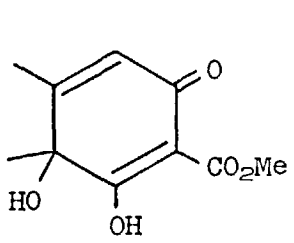
I wish to express my thanks to the Wellcome Trust for the award of a Fellowship for the period of this research.

Mosche N. Rosenfeld ,
Whiffen Laboratory,
July 1976.

ABSTRACT

Reviews of hydroxylation procedures for phenols and synthetic uses of organo-selenium compounds are presented.

The nature and chemical properties of diphenylseleninic anhydride are discussed. Diphenylseleninic anhydride has been used to oxidise simple and tetracycline model phenols; the products being hydroxydienones (e.g. 2-Carboxymethyl-3,4-dihydroxy-4,5-dimethylcyclohexa-2,5-dienone (A)), quinones (e.g. 2-Carboxymethyl-5,6-dimethyl-3-hydroxybenzoquinone (B)), and phenylseleno-substituted species (e.g. Methyl 2,6-dihydroxy-3,4-dimethyl-5-phenylselenobenzoate (C)).



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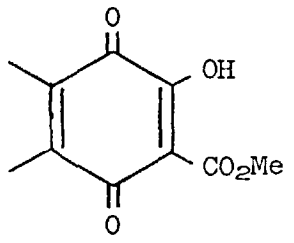

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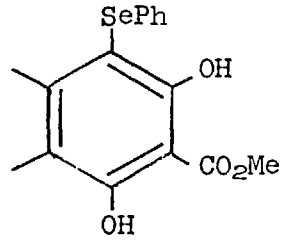
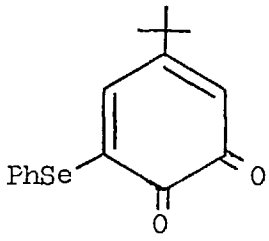


(C)

Prior formation of the phenolate anion, generally increased the yield of o-hydroxylation. The various mechanistic aspects of these transformations are discussed.

Overoxidation products (e.g. 3-t-butyl-5-phenylseleno-1,2-benzoquinone (D)) were sometimes encounted, if excess diphenylseleninic anhydride was used, or by inverse addition procedures.

The use of hexamethyldisilyl amide to generate the phenolate anions prior to treatment with diphenylseleninic anhydride, lead to the formation of novel selenoimines (e.g. 4,6-Dimethyl-1,2-benzoquinone monophenylseleno-2-imine (E)). The structures and mechanism of formation are presented.



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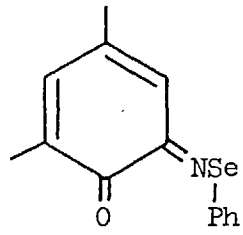
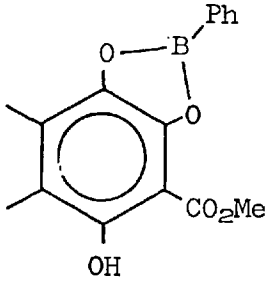


(E)

The tetracycline ring A model phenol series was extended with the synthesis of cyclic boronates (e.g. 2-Carbomethoxy-5,6-dimethyl-4-hydroxybenzene-1,2-phenylboronate (F)), diethylazo dicarboxylate and urazole derivatives (e.g. Methyl 5-diethylhydrazodicarboxyl-2,6-dihydroxy-3,4-dimethylbenzoate (G) and Methyl 2,6-dihydroxy-3,4-dimethyl-5-(4-phenylurazole)-benzoate (H)), and hydroxylation with diphenylseleninic anhydride was attempted.



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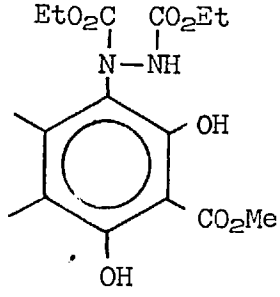

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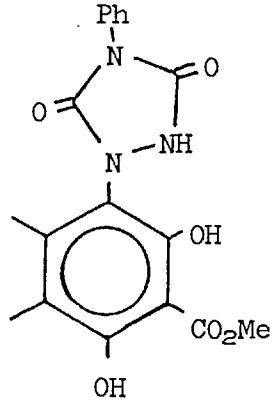

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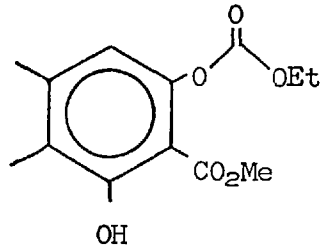


(I)

A synthesis of a number of model cathylate phenols (e.g. Methyl 3,4-dimethyl-2-hydroxy-6-(ethylcarbonate)-benzoate (I)) and their conversion to hydroxycyclohexadienones, using diphenylseleninic anhydride, has been developed.

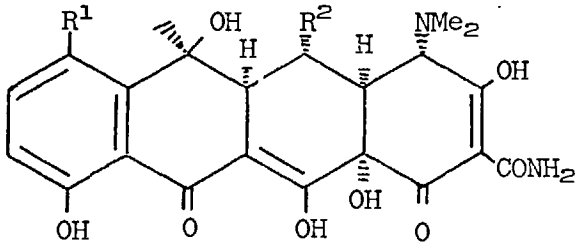
The synthesis of diphenyltellurinic anhydride and phenyltellurinyl chloride is presented, and reactions with phenols have been investigated.

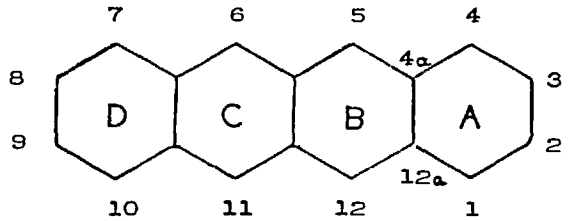
CONTENTS

INTRODUCTION

The most important antibiotics in modern therapy were discovered between 1940 and 1960. Since then, relatively few antibiotics of thoroughly novel structure and action have come into use. The advancements during the last decade have been achieved mainly by chemical modifications of the classical antibiotics .

The first tetracycline was aureomycin (1), isolated by Duggar[1] in 1948 from streptomyces aurefaciens, followed by terramycin (2) , which was obtained by Finlay et al.[2] in 1950 from streptomyces rimosus. Structural elucidation was achieved by Woodward and a research team at Chas-Pfizer and Co.[3] .





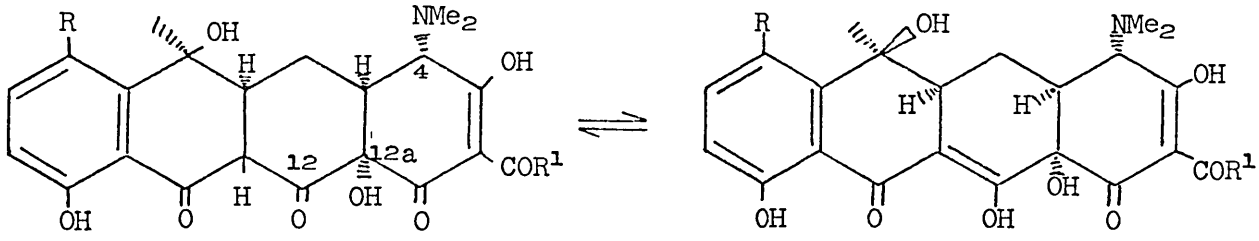
	R^1	R^2
I	Cl	H
II	H	OH

The chemistry of tetracyclines has been the subject of extensive reviews[4] and a number of Ph.D. theses at Imperial College[5].

(The numbering system, which will be used throughout this thesis with reference to the linear naphthacene skeleton, is shown in (1)).

HYDROXYLATION OF PHENOLS.

The synthetic route to the tetracyclines employed at Imperial College necessitates, at some stage, the introduction of the 12a- hydroxyl group into the aromatic ring A of a tetracyclic intermediate.

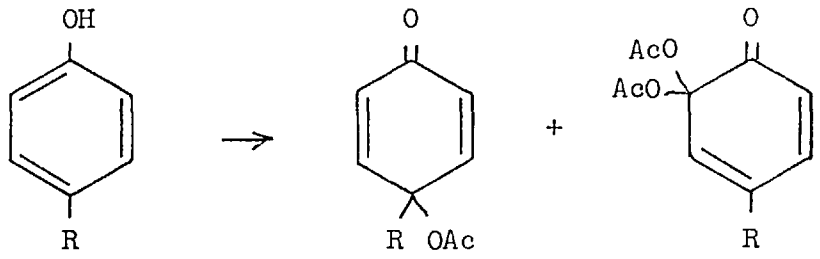


A large number of oxidation studies on model phenols have been undertaken with the objective of creating ortho-hydroxydienones. A summary of this work follows.

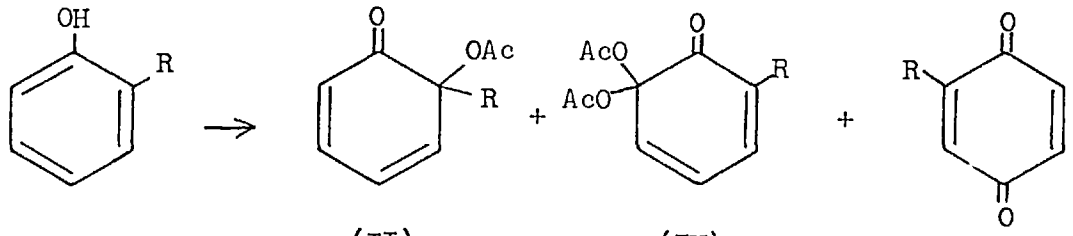
i.) Lead Tetra-acetate.

In 1950, Wessely[6] et al. examined lead tetra-acetate in acetic acid as a potential reagent to convert phenols into quinol acetates. It was shown, that para-substituted phenols form, in alcoholic solution, the corresponding para-quinol ethers[7]. Ortho-quinol derivatives could only be obtained from an ortho-substituted phenol. If, however, an ortho- and para-position can be attacked, the acetoxy group usually enters preferentially at the ortho-position. This position remains the reactive centre even when substituted with bulky groups such as methyl, ethyl, isopropyl, n-propyl or sec-butyl. However, a t-butyl substituent drastically reduces attack at the ortho position[8]. Phenols with an unoccupied ortho position give ortho-quinone diacetates (III and IV) in addition to, or instead of, the quinol acetates (I and II)[9]. Those phenols having a free para position can give

p-quinones as minor or in some cases major products[10] .

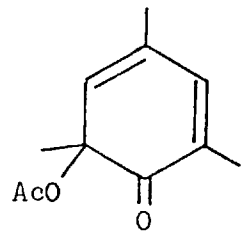


(I) (III)



(II) (IV)

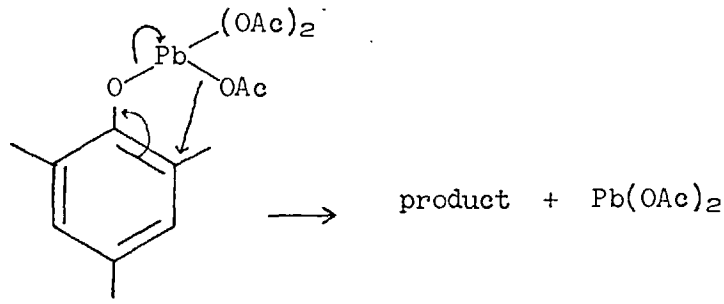
2,4,6-Trimethylphenol (mesitol), being a diortho aswell as para - substituted phenol, affords upon treatment with lead tetra-acetate, 2-acetoxy-2,4,6-trimethyl cyclohexadienone (V) .



(V)

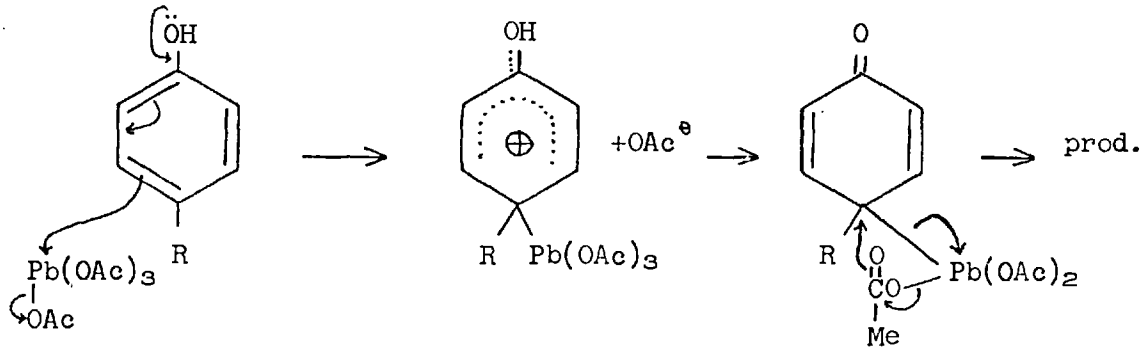
Similarly 2,4-dimethylphenol was converted to the corresponding dienone, which was isolated as its dimer.

The accepted mechanism for the Wessely acetoxylation involves an intramolecular reaction[11] .



'Intramolecular electrophilic mechanism for the Wessely acetoxylation'

Although the Wessely acetoxylation does not show a general preference for reaction at an ortho carbon with some substrates (such as mesitol), the proportion of ortho attack exceeds statistical predictions. The preference cannot be attributed to obvious steric or electronic factors in terms of intermolecular substitution[12] .



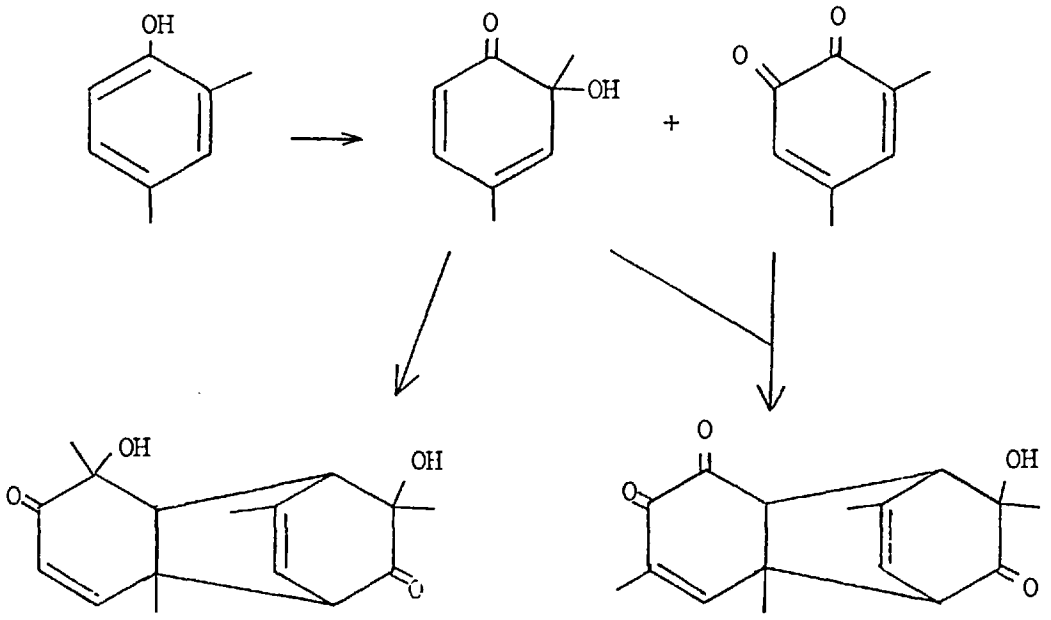
'Electrophilic mechanism for Wessely acetoxylation, involving plumbylation followed by intramolecular substitution '.

In summary, the evidence suggests, acetoxylation proceeds via intermolecular electrophilic attack, involving initial formation of a lead triacetate intermediate. Although there is no evidence clearly favouring initial C-plumbylation or direct acetoxylation of phenols by lead tetraacetate, there is no doubt, that the phenolic substrate is attacked elec-

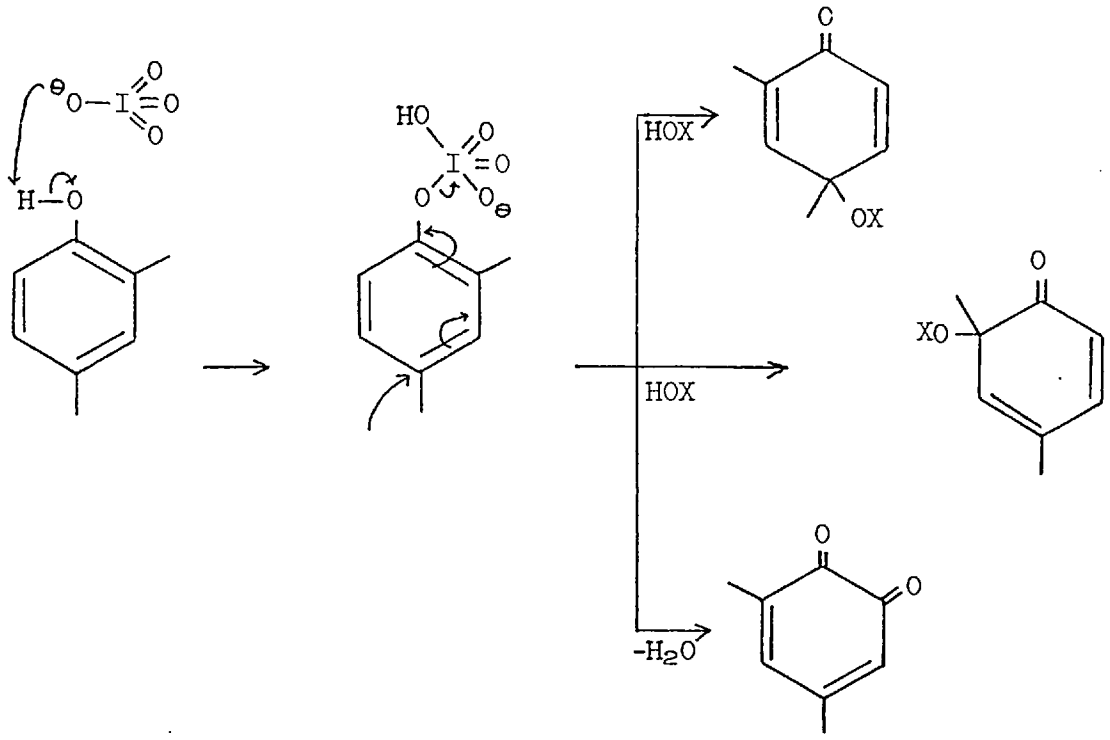
trophilically rather than either nucleophilically or homolytically[13] .

ii.) Sodium Periodate.

Adler[14] showed that 2,4-dimethylphenol with sodium periodate in aqueous or dilute acetic acid solution gave the corresponding o-quinol as its dimer, together with its Diels-Alder adduct with 3,5-dimethyl-o-benzoquinone.



Similar results were obtained with 2,6-dimethylphenol[15] . However, the para-quinol could be isolated as a minor component in the oxidation of 2,4-dimethylphenol and 2,4,6-trimethylphenol[14,16] . Adler et al. proposed a mechanism for the oxidation based on studies of the periodate-induced demethylation of catechol monoethers in O^{18}-labelled water[17] . In the reaction it could not be determined, whether the attack by solvent HOX takes place on the iodate ester by S_N 2' process, or whether the ester undergoes loss of iodate and hydroxylation by an S_N 1 process. An intramolecular ortho-attack via a cyclic diester is possible, but thought unlikely, as para-attack is equally rapid[10] .

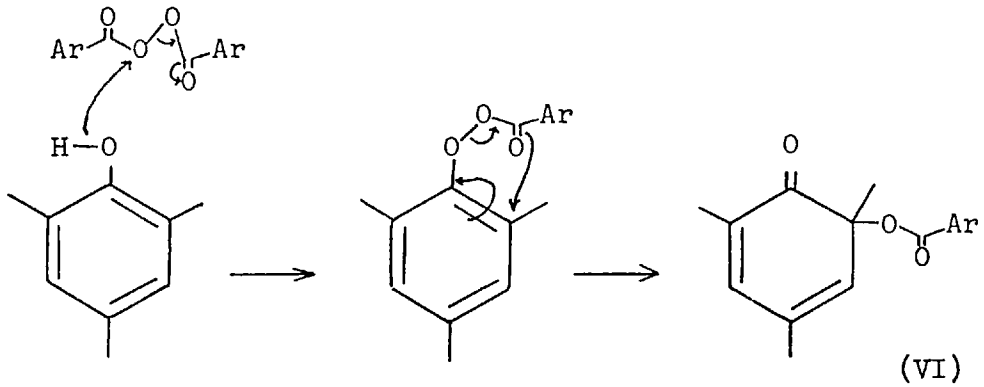


In conclusion, aqueous sodium periodate oxidises phenols, depending on the substitution pattern, to o- and p-quinones, aswell as o- and p-quinols. The solvent was shown to participate in the reaction, since $H_2{}^{18}O$ gave labelled o- and p-quinones. Recently it was shown, that the use of periodic acid, H_5IO_6, gave less pronouced para oxidation of phenols[18].

iii.) Acylperoxide and Peracetic Acid.

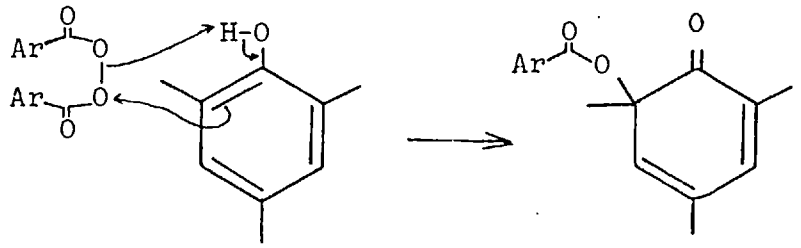
There is some confusion in the earlier literature on the reaction between phenols and diacyl peroxides[19]. As a result of work carried out in these laboratories[20], clarification of this oxidation was achieved. Thus treatment of sodium mesitate with benzoyl peroxide in ether at -20° yields the ortho-dienone (VI) as the major product. A certain amount of the para-dienone can be obtained upon heating (VI) to 120°. The rearrangement was explained in terms of a thermal sigmatropic (3,3) suprafacial[21] migration of the acyloxy group along the periphery of the cyclodienone

ring[20] . The initial step was thought to involve O-acyloxylation.

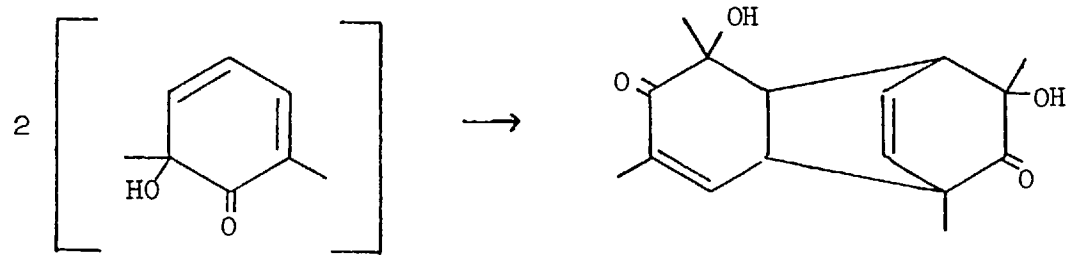


(VI)

Waring[11] alternatively postulates initial C-acyloxylation at the carbon atom ortho to the phenolic hydroxy group.



2,6-Dimethylphenol has been oxidised with trifluoroperacetic acid, giving the dimer (VII), undoubtedly formed via the ortho-hydroxydienone by Diels-Alder addition[22] .



(VII)

p-Methylphenol (p-cresol), however, yielded only para-hydroxydienone

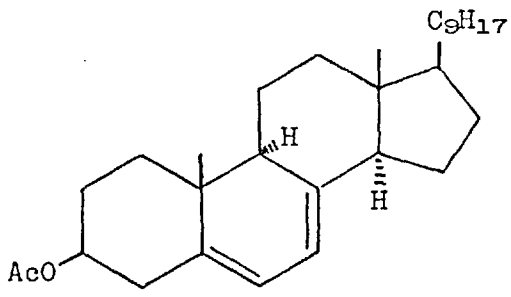
upon treatment with peroxyacetic acid[23] .

iv.) Cerium(IV) oxide / Hydrogen peroxide.

Transition metal ion/ hydrogen peroxide systems have been employed for oxidation of phenols. In the case of Ti^{IV}, Mo^{VI}, Co^{II}, Fe^{II}, Fe^{III}, Cu^{I} and Cu^{II} [24,25,26] para-hydroperoxydienones were formed. Workers in these laboratories[27] succeeded in converting phenols to their hydroperoxydienones, by using technical grade cerium(IV) oxide / hydrogen peroxide (30%) in t-butanol.

2,6-Di-t-butyl-4-methylphenol afforded under these conditions the light sensitive p-hydroperoxycyclohexadienone in good yield. Similarly mesitol and p-cresol were converted to their para-hydroperoxycyclohexadienones. Upon reduction with aqueous potassium hydroxide and potassium iodide the hydroperoxydienones gave the more stable hydroxydienone counterparts. The reduction could also be effected by dimethyl sulphide in tetrahydrofuran.

The reactive species in the above reactions appears to be singlet oxygen. This fact was proved by reacting ergosterol acetate (VIII) with technical cerium(IV) oxide / hydrogen peroxide (under nitrogen,no light).



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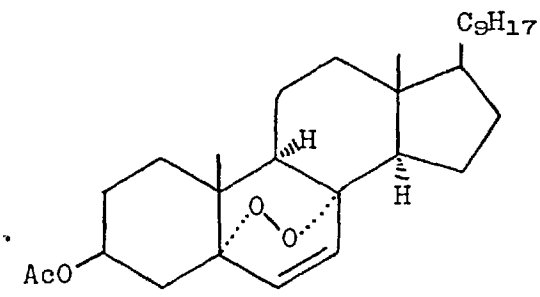

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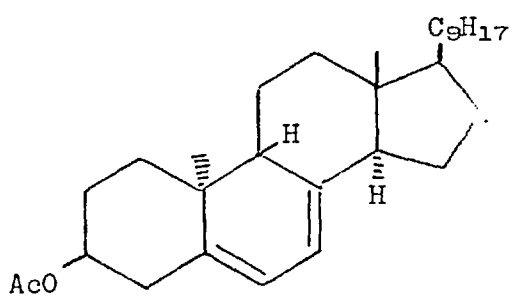

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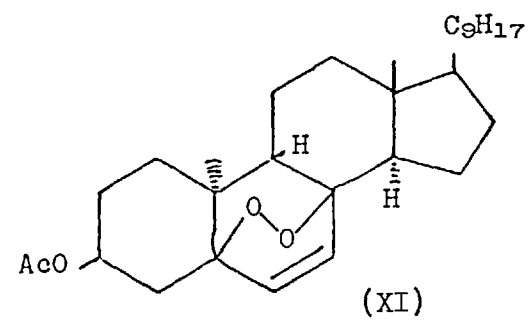


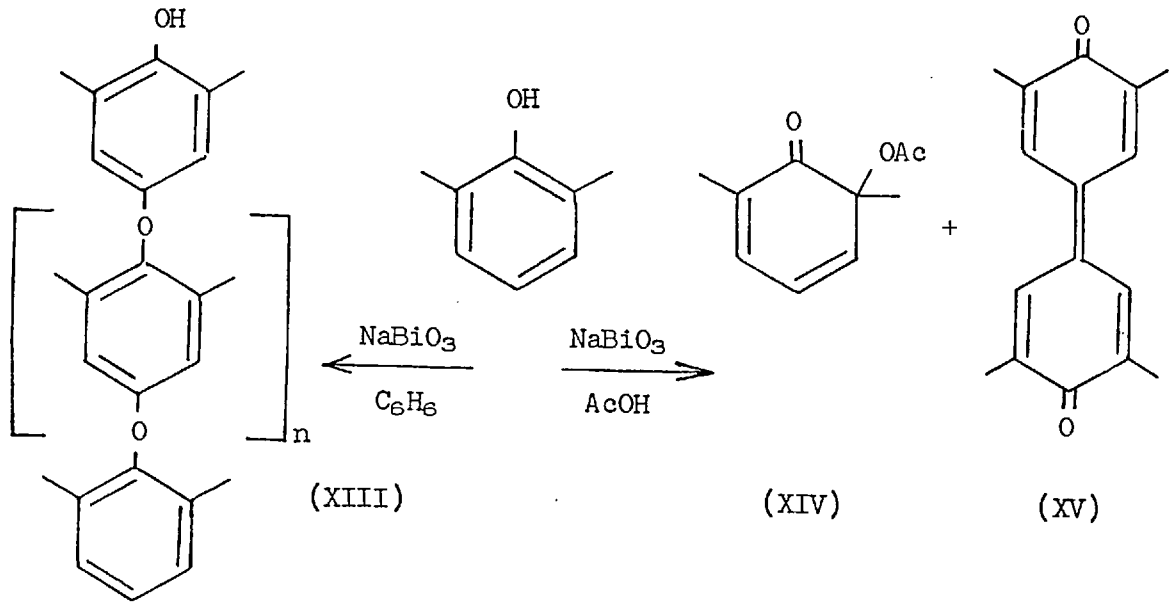
(XI)

The 5α,8α-peroxide (IX) was isolated in 38% yield. Similarly, lumisterol acetate (X) was converted into the corresponding 5β,8β-peroxide (XI) in 45% yield. A direct rate comparison, using equal amounts of the two dienes (VIII) and (X) in t-butanol under equivalent conditions yielded the peroxides (IX) and (XI) in the ratio 2.3 to 1, indicating that they are formed from singlet oxygen[28] .

These oxidations may be best regarded as occuring on the surface of the cerium dioxide with singlet oxygen, also generated at the surface; neither light nor oxygen was required for the reaction to take place. However, this method does not present a way of introducing a hydroxyl group specifically ortho with simpler phenols.

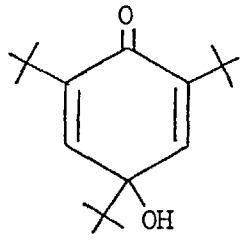
v.) Sodium Bismuthate.

Recently sodium bismuthate has gained some popularity as phenol oxidant[29] . Kon and McNelis[30] have shown that sodium bismuthate oxidised phenols in neutral aromatic solvents via a one-electron oxidation. The principal products were mostly the corresponding polyphenylene oxides (XIII).



(XIII) (XIV) (XV)

By changing the solvent to acetic acid, no polymers were detected. The oxidation products of 2,6-xylenol were 2-acetoxy-2,6-dimethylcyclohexadienone (XIV) and 3,3',5,5'-tetramethylbiphenylquinone (XV). A two-electron oxidation may be inferred from the acetoxy product. This observation was supported by the findings of a similar experiment involving mesitol, which produced acetoxylated cyclohexadienones[31], that is to say, similar to sodium periodate a known two-electron oxidant. Oxidation of 2,4,6-tri-t-butylphenol in such a manner, yielded 62% of para- and 22% ortho-acetoxylated cyclohexadienone. Kon proved that acidic bismuthate did not deliver a hydroxyl radical to a phenoxyl compound, giving intermediates such as 2,4,6-tri-t-butyl-4-hydroxycyclohexadienone (XVI), which might conceivably lead to the acetoxylated dienone.



(XVI)

vi.) Other Methods.

There are a number of other routes for the oxidation of phenols, mainly yielding para-hydroxylated substances. Thus thallium triacetate converts p-substituted phenols in alcoholic solutions to the corresponding p-quinol ethers[32].

Treatment of phenol with hydrogen peroxide in the presence of perphosphoric acid, $H_4P_2O_7$, over sulphur, phosphorous, or selenium for one hour at 75°, yielded a mixture of 55% catechol and 25% hydroquinone[33].

Merger et al.[34] found that phenolic carboxylic acids were hydroxy-

lated at room temperature in water by the action of ^{60}Co —rays. The hydroxylation, which can be carried out on a preparative scale, occurs with remarkable selectivity ortho to existing hydroxyl groups, and proceeds even more rapidly in the presence of oxygen. Nitrophenols are hydroxylated even faster than phenolic carboxylic acids and p-nitrophenol gives a 52% yield of 4-nitrocatechol after an irradiation time of 150 h . The postulated mechanism proceeds via the addition of a hydroxyl radical to the aromatic system, forming a cyclohexadienyl radical (XII), which either disproportionates or dehydrates[35] .

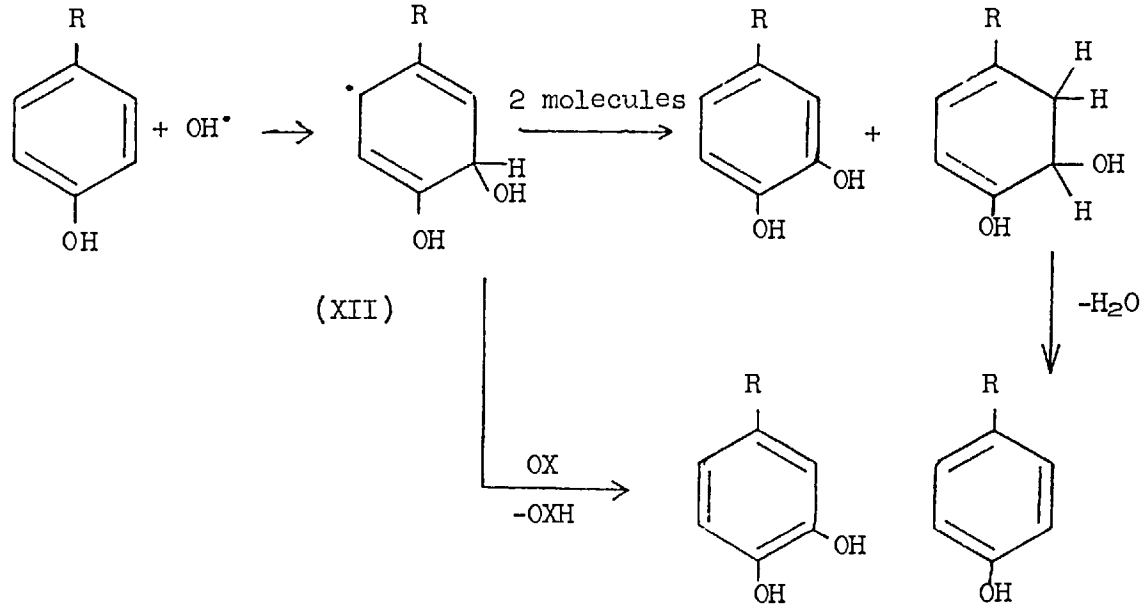
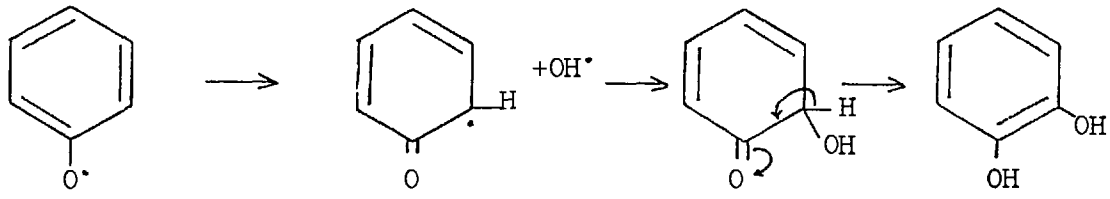


Photo-oxidation of phenols in aqueous solution[36] using light of 2537 Å, yields a fair amount of ortho-hydroxyphenols. The major disadvantage of this method is the possibility of radical dimerisation leading to by-products. In the presence of hydrogen peroxide, the yield of o-hydroxyphenol was somewhat increased, the best yields occuring with para-substituted phenols[37] . It was thought that the primary reaction was the fission of the oxygen-oxygen bond of hydrogen peroxide to form

two hydroxyl radicals, which initiate a chain decomposition. Abstracting a hydrogen atom from phenol generates a phenoxy radical, which in its canonical form combines with a hydroxy radical to give catechol.



Phenolic hydroxylations of modest interest to synthetic organic chemists, are enzymatic hydroxylations of phenols with molecular oxygen, a method developed by Ullrich[38] .

ORGANO-SELENIUM OXIDATIONS.

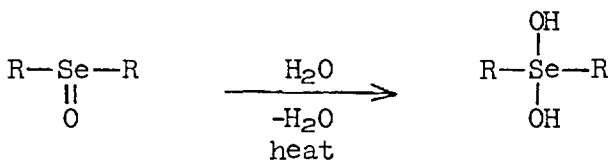
i.) The Importance of Selenium Reagents.

In 1920 the entire literature dealing with organoselenium chemistry consisted of a mere 200 papers. It is possible that the highly unplea - sant odour of some of these compounds, worse even than their sulphur analogues , discouraged many a capable chemist to investigate these highly interesting substances and their reactions. Like many other elements, selenium has been suspected of being a carcinogen, but without rigorous proof. Conversely, a number of its compounds have been tested as antitumor agents. Thus the organic chemistry of selenium has undergone major expansion during the past two decades, since it has increasingly gained importance in the field of biochemistry, physiology, toxicology, botany and,last not least- synthetic organic chemistry.

The following chapter presents a brief review of organo-selenium compounds, acting specifically as oxidants in organic syntheses.

ii.) Selenoxides and Selenones.

Selenoxides (I) may be prepared easily by hydrolysis of the corresponding diarylseleno dibromide or dichloride[39] in aqueous sodium hy - droxide or bicarbonate solution. The selenoxides are usually colourless, crystalline and non hygroscopic substances. In some cases hydrates may be generated, which have been formulated as the selenodihydroxide (II)[40],



(I) (II)

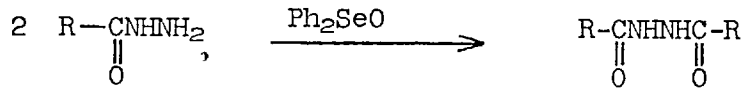
however these readily lose water upon drying in vacuum at elevated temperatures to regenerate the selenoxide.

Dialkyl selenoxides have also been produced by the oxidation of selenides with ozone[41] . Other methods for oxidising selenides to selenoxides include hydrogen peroxide, peracetic acid[42] , dinitrogen tetroxide[43] , sodium periodate[44] , iodobenzene dichloride[44] and Chloramine-T[45] .

The properties of the selenoxides differ significantly from selenides, since the Se atom is present in the tetravalent state. The co - valent character of the Se-O bond gives a certain polarity, which together with the lone pair of electrons remaining at selenium, facilitates adduct formation with many substances. This process may occur with acids[46] and metal salts such as perchlorates[47] or chlorides[48] . These complexes are quite stable.

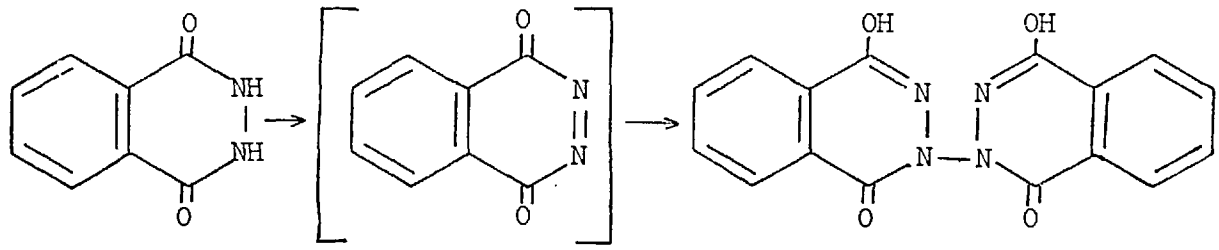
The use of selenoxides in organic syntheses is manifold. Barnard and Woodbridge[49] oxidised organic sulphides to sulphoxides using either dibenzyl selenoxide or diphenyl selenoxide.

Aryl or acyl hydrazides react with diphenyl selenoxide, giving pure sym-hydrazines (III) in very good yields[50] .



(III)

Cyclic hydrazides smoothly reacted with diphenyl selenoxide to form, initially, the azo species, which undergoes intermolecular reaction , yielding the dimer (IV)[51] . These findings were supported by the observation, that hydrazobenzene was easily dehydrogenated with diphenyl selenoxide to azobenzene[51] .



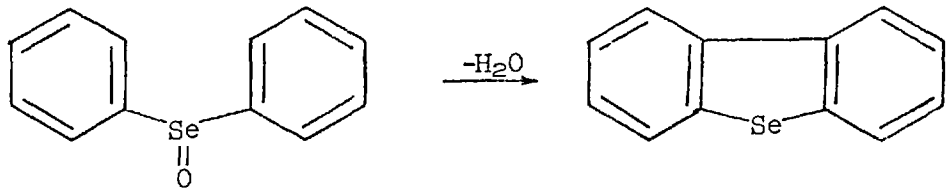
(IV)

Aryl-alkyl selenoxides are also well known and may be prepared easily by action of hydrogen peroxide on the relevant selenide[52] . An interesting rearrangement occurs on heating these selenoxides. Benzyl-phenyl selenoxide in a xylene solution heated to 110-130° for only 2-3 minutes yields 78% benzaldehyde. The corresponding sulphoxides require much higher temperatures. In such a manner a number of substituted benz-aldehydes were readily synthesised[53] and isolated as 2,4-dinitrophenyl-hydrazones.

$$ArCH_2\text{-}\underset{\underset{O}{\|}}{Se}\text{-}Ph \longrightarrow \left[ArCH_2\text{-}O\text{-}SePh\right] \longrightarrow Ar\text{-}CHO + \left[PhSeH\right]$$

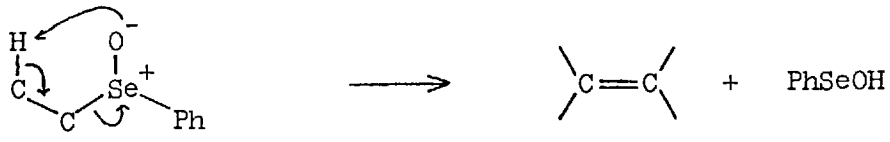
The mechanism of this reaction is not yet fully investigated, but preliminary experiments suggested the presence of radical intermedia - tes[53] .

A convenient method of synthesis of dibenzoselenophene (V) involves cyclodehydration of diphenyl selenoxide[54] . Selenophenes are widely used as high-temperature antioxidants for silicones, as extraction agents for the isolation and separation of metals, for analytical purpose and as physiologically active compounds[55] .

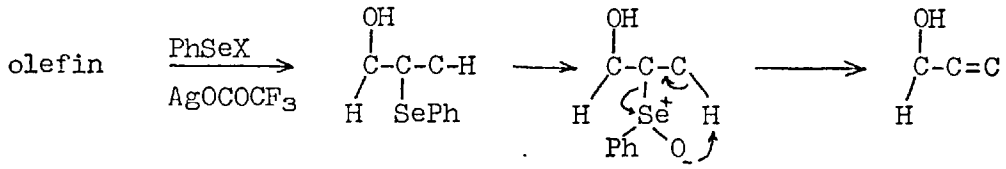


(V)

Possibly the most important contribution of selenoxides towards synthetic organic chemistry lies in the fact, that if the molecule containes a β-hydrogen atom, these species are inherently unstable and decompose to give olefins[56] .



In practice selenides are oxidised to selenoxides, which are not usually isolated, but readily yield expected olefins <u>via</u> a <u>syn</u> elimination[56c] . This idea has been carried further, and Clive[57] thus found a convenient method for the preparation of allylic alcohols. The general procedure involves forming a complex of a benzeneselenenyl halide with silver trifluoroacetate, which is sufficiently electrophilic to combine rapidly with an unactivated olefin at -10° . The trifluoro acetyl group was removed by mild hydrolysis ($NaHCO_3$, H_2O) and a high yield of a β-hydroxy selenide was obtained with <u>trans</u>-stereochemistry. These compounds are efficiently converted to allylic alcohols upon oxidation with hydrogen peroxide or ozone.

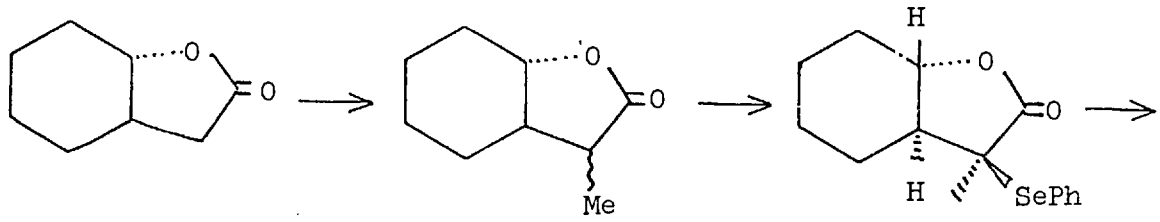


In the case of a terminal olefin, there was little regio selectivity, but for symmetrical olefins, this method offered a mild alternative to treatment of an epoxide with the strongly nucleophilic $PhSe^{\ominus}$ [56b], which was the previous route to β-hydroxyselenides. In a similar manner, Clive[56a] utilized the phenomenon of selenoxide fragmentation at, or below, room temperature to 'dehydrogenate' ketones to enones. Consequently the enol acetate of cyclohexanone was converted to 2-phenylselenocyclohexanone in good yield (with PhSeBr, $AgOCOCF_3$) and subsequent oxidation with $NaIO_4$, followed by <u>in situ</u> fragmentation of the selenoxide yielded 92% cyclohex-2-enone. Similar work was actively pursued by Reich and coworkers[58], who extended the reaction to include the preparation of β-dicarbonyl enones, cyclobutenones, and enone ketals. The α-phenylselenocarbonyl precursor can be prepared not only from ketones, but also from aldehydes, esters[59], enol acetates,[60] and acetylenes. It was recognised that the necessity for achieving a cyclic transition state in the selenoxide elimination, imposes conflicting conformational demands on cyclic systems. In fact, only a limited range of cyclic enones (five - and six-membered) could be prepared.

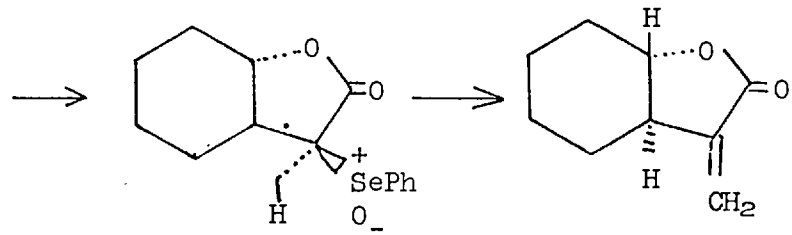
Proof for the cyclic nature of the elimination was obtained by an investigation of differences in elimination rates of diastereoisomeric steroidal selenoxides[61] and from the olefin stereochemistry in an acyc-

lic system[56c] . It was also established, that oxidation of the selenide to selenoxide, was sometimes carried out by treatment with ozone (in CH_2Cl_2) , since hydrogen peroxide caused rapid epoxide formation with some five- and six-membered cyclic ketones. It remains to be noted, that an important consequence of the mild reaction condition was that in all cases exclusively non enolised β-dicarbonyl enones (where applicable) were formed, even though a number of these systems were known to be significantly enolic at equilibrium[62] .

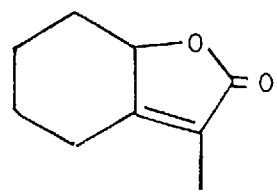
Grieco et al.[59] succeeded to apply this method to synthesise cis- and trans-fused lactones. In the case of the trans-fused γ-butyrolactone (VI), conversion to the trans-α-methylene-γ-butyrolactone (VII) was readily achieved with complete exclusion of the endocyclic isomer (VIII) .



(VI)



(VII)



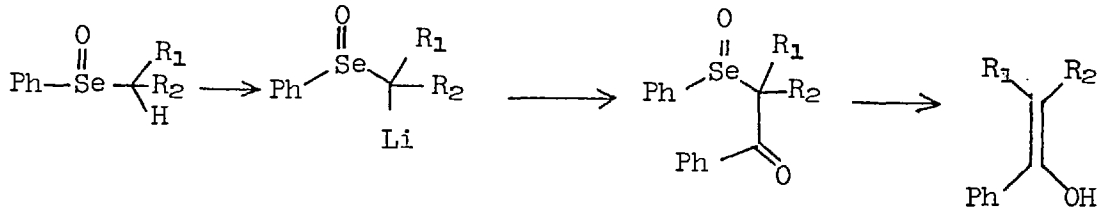
(VIII)

This result was thought to be due to a stereospecific alkylation of the lactone enolate, establishing the required anti relationship between the α-phenylseleno substituent and the adjacent methine proton. Syn-elimination must therefore lead to (VII) .

Sharpless[63] recently demonstrated, that electron withdrawing substituents on the aromatic ring increased both the rate of elimination and the final yield of olefin.

The pronounced advantage of these reactions over other methods, lies in their mildness, speed of reaction, and high yields due to 'one-pot' procedures.

Not all unsymmetrical selenoxides readily undergo elimination. Benzylphenyl[64] and methylphenyl selenoxides are quite stable due to the lacking β-hydrogen, and this property has been taken advantage of in a special way. These selenoxides are rapidly deprotonated at -78° by lithium diisopropylamide to form the anion (IX).



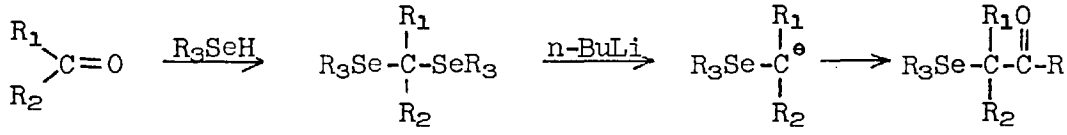
(IX) (X) (XI)

This species reacts readily with a ketone, aldehyde or alkyl halide at -78° to yield (X). After neutralisation, syn-elimination is achieved simply by heating in dichloro methane, and the product (XI) is obtained in good yield [65] .

A practical procedure would start with the oxidation of the selenide to selenoxide with ozone (if m-chloroperbenzoic acid were not applicable), followed by anion formation with lithium diisopropylamide. For-

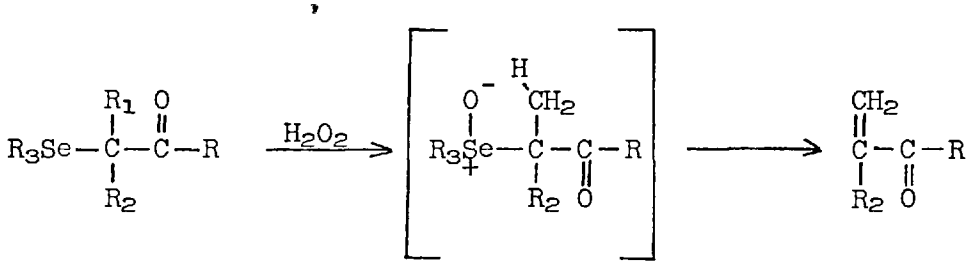
mation of the organo-lithium has also been successful, using lithium diethylamide or s-butyllithium/tetramethylethylenediamine (TMEDA) in hexane. In particular this method allows for easy transformation of an alkyl halide or alcohol to the functional equivalent of a vinyl anion in reactions with carbonyl compounds. Thus pronounced control of selenoxide eliminations away from hydroxy-, alkoxy- or acetoxy-substituted carbons has been achieved[66].

The use of α-selenoalkyl lithium[67] has allowed new synthetic routes to α-seleno(XII)-aldehydes(R=H), -ketones(R=alkyl or aryl), -esters(R=alkoxy or phenoxy) and -acids(R= OH)[68], using N,N-dimethylformamide, an acyl chloride, methyl chloroformate and carbon dioxide, respectively.



(XII)

Subsequent oxidation to selenoxide, followed by elimination afforded high yields of α,β-unsaturated carbonyl compounds (XIII).



(XII, $R_1=CH_3$) (XIII)

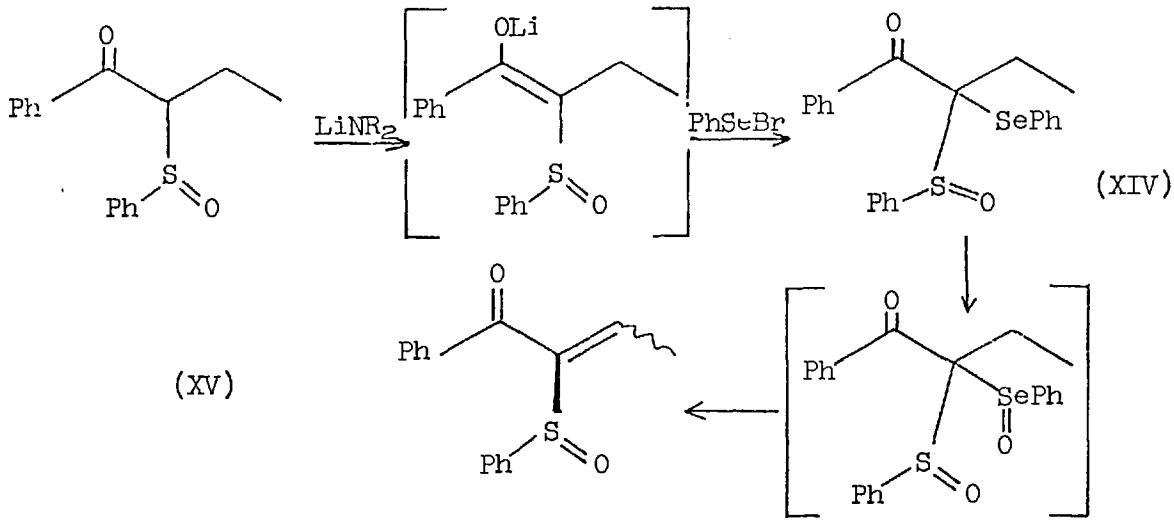
Reich's full paper[68] presents a good summary of ketone to enone conversions by syn selenoxide elimination. He examined the best procedures for initial selenylation (PhSeBr, PhSeH, $PhSeO_2CCF_3$) , and subsequent oxidation to selenoxide (ozone, hydrogen peroxide, sodium metaperiodate, m-chloroperbenzoic acid). He has revealed two types of side-reactions that may occur:

a.) Pummerer like transformations to α-diketones

b.) Interaction between enolate of α-phenylselenino ketones and a selenenylating species from disproportionation of benzeneseleninic acid.

The rate of selenoxide elimination was significantly accelerated by the carbonyl group, compared with simple alkylselenoxides. Furthermore, ethylene ketals of keto selenoxides undergo significantly slower elimination than the keto selenoxides themselves. The accelerating effect was even more pronouced for selenoxides, derived from β-dicarbonyl compounds.

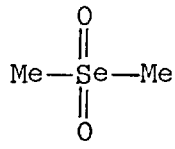
The selenoxide reactions are closely related to sulphoxide elimination procedures, developed by Trost and Salzmann[71] . The advantage of the selenoxide route, however, lies in the almost ideal stoichiometry of the selenenylation reaction and its unique mildness, and, of course, in the extreme mildness of the olefin forming step. Selenoxide elimination proceeds at ca. 80-100° lower temperatures, than the corresponding sulphoxide elimination[61] . Thus an α-phenylsulphino-α-phenylselenino ketone (XIV) undergoes selenoxide elimination exclusively, to give a vinyl sulphoxide (XV) , i.e., no sulphoxide elimination occurs.



Selenones.

Only a very limited number of dialkyl and diaryl selenones have so far been prepared and consequently their properties are not completely known. For this reason they have found only limited application in organic synthesis.

Paetzold et al.[70] claimed the synthesis of dimethyl selenone (XVI) by ozonolysis of the corresponding selenoxide. This result, however, contradicts statements by Ayrey et al.[41], who claimed that excess ozone in the oxidation of dimethylselenide, left the resulting selenoxide untouched.

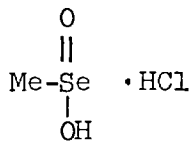


(XVI)

Aromatic selenones were reported by Rheinboldt and Giesbrecht[39] as a result of potassium permanganate oxidation of diphenyl selenoxide, which had previously been achieved by Krafft and Lyons[101], as early as

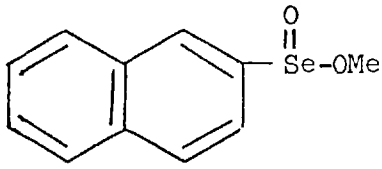
1896. Yagupol'skii and Voloshchuk[71] achieved the same effect, using trifluoroperacetic acid at -40° .

Selenones were found to be considerably less reactive than their selenoxide precursors. Dimethylselenone does not oxidise hydrochloric acid to chlorine[39] , but rather cleaves the molecule to form methyl chloride and the HCl- adduct of methaneseleninic acid (XVII) .

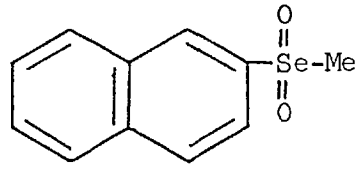


(XVII)

Loevenich et al.[72] report, that while the sodium salt of β-naphthylseleninic acid reacted with methyl chloroformate with evolution of CO_2 to yield the methyl ester (XVIII), the same salt reacted with methyl iodide, forming the naphthylmethyl selenone (XIX) .



(XVIII)



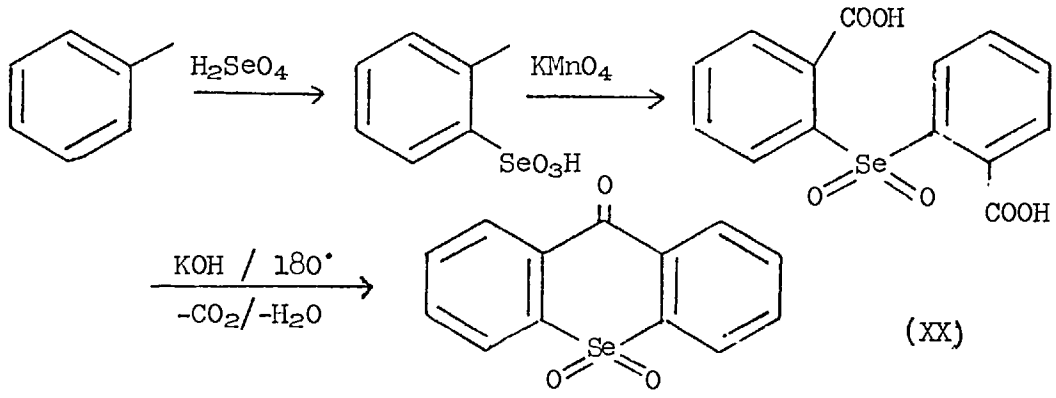
(XIX)

A similar observation has been reported in the synthesis of naphthylsulphones[73] . The silver salts of alkyl seleninic acids, however, reacted with alkyl iodides to form esters and not selenones[74] .

Physical studies have been carried out on selenones to some extent; for example, Paetzold et al.[70] examined the infra red properties of alkyl selenones and established the Se=O vibration at 890cm^{-1} . Bali

and Malhotra[75] studied the behaviour of alkyl selenones in sulphuric-acid and found them to be completely ionized. Diphenyl selenone, however, behaved as a weak electrolyte. The extent of protonation indicated, that selenones were stronger bases than the corresponding sulphones, but much weaker bases than their selenoxide equivalents.

Ris and Cerfontain[76] studied the selenonation of polyalkylbenzene with a mixture of H_2SeO_4 and acetic anhydride. In such a way, a number of arene selenonates could be prepared. This method had earlier been utilized to synthesise selenonexanthone (XX)[77].

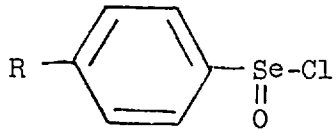


(XX)

It seems, that so far selenones have not been used as reagents in organic synthesis.

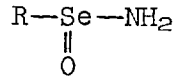
iii.) Seleninyl Halides.

The first member of this class of compounds was prepared by Pirisi and Sereli[78], who obtained p-nitrophenylseleninyl chloride (XXI, R = NO_2) by treatment of the relevant seleninic acid with thionyl chloride.



(XXI)

A better method for seleninyl chloride preparation was treatment of a selenenyl chloride with ozone[41] or nitrogen dioxide[79]. Seleninyl halides are very readily hydrolysed by water to the seleninic acid. Ammonia in aqueous solutions yields seleninamides[78, 80].



Sodium alkoxides on seleninyl halides yield the corresponding seleninic esters[41, 79]. In the infra red spectrum, seleninyl halides show ν (Se=O) at 930-1005 cm^{-1} [81].

Until recently, very little attention had been paid to the synthetic potential of seleninyl halides. Reich and co-workers[68] examined the utility of benzeneseleninyl chloride as seleninylating agent. Ketones and enolates were found to undergo C-seleninylation and subsequently yielded enones after fragmentation, but the method showed major handling disadvantages over the 'normal' selenoxide elimination reaction. Reich only recommends the use of seleninyl halide, when the other selenide oxidation procedures fail because of competing or preferential oxidation elsewhere in the molecule.

iv.) Seleninic and Selenonic Acids and Derivatives.

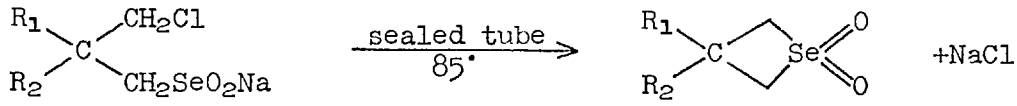
Seleninic acids may be considered as derivatives of selenious acid, $HOSeO_2H$; they are amphoteric and less acidic than carboxylic acids[82]. They may be prepared by oxidation of aliphatic[83, 84] or aromatic[85] selenols, diselenides[55] and diselenocycloalkanes[86]. Oxidations of selenocyanates, both aliphatic[87] and aromatic[88] are widely used. Aliphatic seleninic acids may also be prepared by a reaction of Grignard reagent with SeO_2, followed by acid hydrolysis of the complex[89].

$$RMgBr + SeO_2 \longrightarrow RSeO_2MgBr \xrightarrow[H_2O]{H^+} RSeO_2H$$

This method, however, fails for aromatic compounds[90].

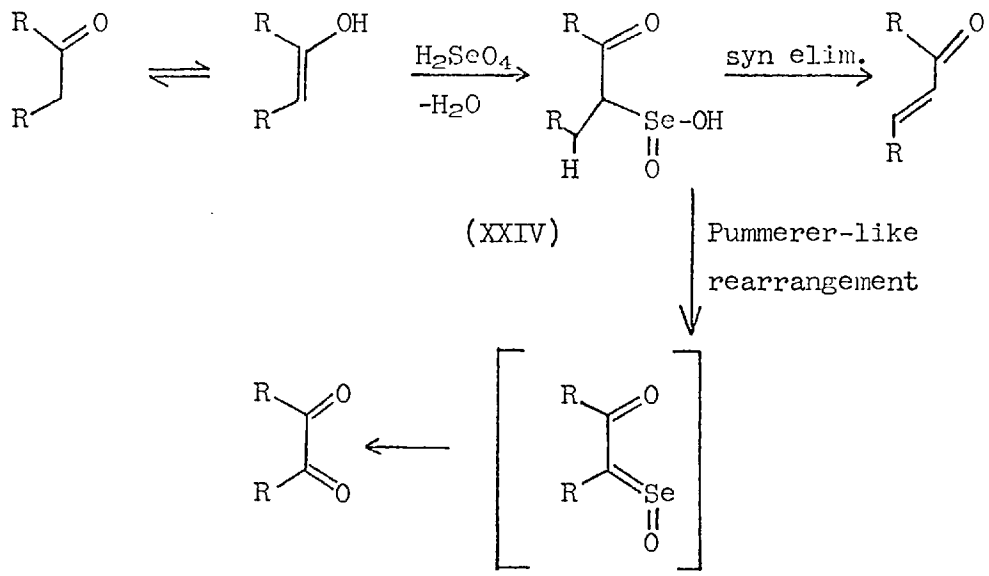
Thiophenol , mercaptans and p-thiocresol[91] have all been readily oxidised to disulphides, using seleninic acid, which becomes reduced to selenenic acid during the reaction.

Seleninic acid has also been utilised in several cyclization reactions. γ-Halosubstituted seleninic acid salts (XXII) undergo ring - closure to give the selenone (XXIII)[92] .



(XXIII)

Recently, Sharpless and Gordon[93] established, that selenium dioxide oxidations of ketones and aldehydes to α-diketones and glyoxals involved organoseleninic acid species. The proposed mechanism involved β-keto - seleninic acid (XXIV) as the key intermediate, which was formed by electrophilic attack of selenous acid on an enol. Although to date, it had not been possible to isolate the β-ketoseleninic acid, this species was generated <u>in situ</u> by the oxidation of α,α'-diketo diselenides[41] , which then proceeded to yield the same product .



Selenonic acids may be prepared in a number of ways. Dostal et al.[94] treated benzene with selenium trioxide in liquid sulphur dioxide to obtain an 85% yield of benzeneselenonic acid, m.p. 64° . The acid is amphoteric and forms a salt (XXV) with seleninic acid[95] .

$$\left[PhSe(OH)_2\right]^+ \left[PhSeO_3\right]^-$$

(XXV)

Strong oxidising agents, such as fuming nitric acid[97] , potassium permanganate[98] and chlorine/water[99] may oxidise diselenides to selenonic acids.

Being strong oxidising agents, selenonic acids can be easily reduced, however, because of their low stability, they have not so far been used in any synthetic application. Some selenonic acids, aswell

as their potassium salts are unstable to the point of being explosive when heated. o- and p-Nitrobenzeneselenonic acids have been found to be remarkably sensitive to sunlight[100] .

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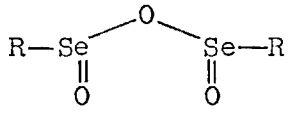
DISCUSSION

i) Discovery and Synthesis of Diphenylseleninic Anhydride.

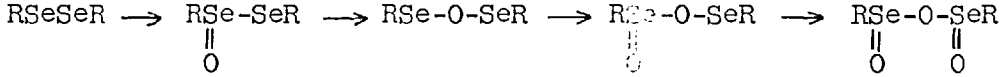
Seleninic Anhydrides (1) are colourless, hygroscopic solids which usually react readily with water.



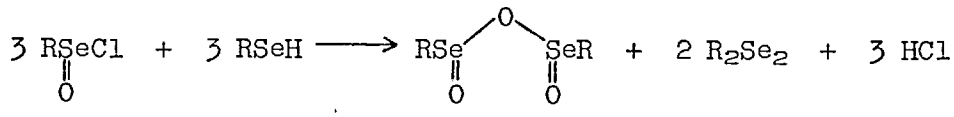
(1)

In 1909, Doughty[1] prepared benzeneselenonic acid by heating benzene and seleninic acid in a sealed tube at 110° for 100 hours. The selenonic acid, he reported, oxidised hydrochloric acid to chlorine, leaving him with phenylseleninic acid, m.p. 122° . Upon heating this acid he obtained a substance, m.p. 164°, which he correctly assumed to be diphenylseleninic anhydride (1, R= Ph). Lesser and Weis[2] prepared 2-carboxyphenylseleninic anhydride in 1913 in a very similar manner. The structural assignment for the anhydrides was based on the fact, that hydrolysis to the acid was readily achieved and continuous heating at 130° regenerated the anhydride.

It was not until 1962, that Ayrey,[3] during his investigations on the oxidation of diselenides by ozonolysis at low temperatures (-10° - -50°), obtained seleninic anhydrides in good yields. Their formation was explained *via* three plausible, but as yet undetected intermediates:

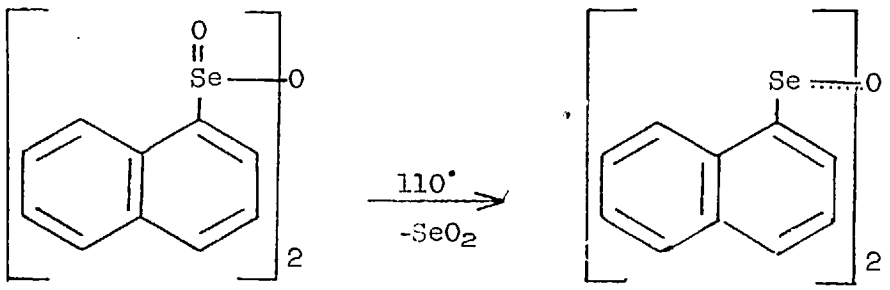


t-Butylhydroperoxide under anhydrous conditions also proved a successful oxidising reagent for diselenides[3, 4] . Aliphatic seleninic anhydrides were prepared for the first time by the oxidation of a suitable selenenyl halide with nitrogen dioxide in an argon stream[5,6] . The resulting seleninyl halide was reacted with selenophenol, under anhydrous conditions in the presence of a base (e.g. pyridine), to give seleninic anhydride and diselenide[3] :



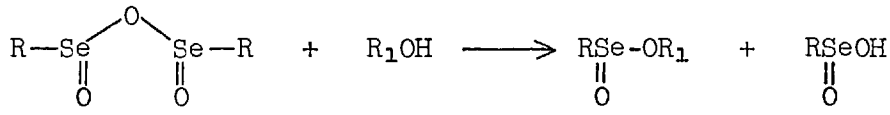
Properties

Generally speaking, seleninic anhydrides may be classified as stable compounds. For example, diphenylseleninic anhydride (1, R = Ph), when heated in vacuum at 160°, some sublimation occured, however, all the compound could be recovered unchanged. Kozlov et al.[7] , however, reported that α-naphthylseleninic anhydride was unstable and rearranged on heating to the selenoxide with elimination of SeO_2.



Diphenylseleninic anhydride could be recovered unchanged from benzene, nitrobenzene, sulpholane, dichloromethane, carbon tetrachloride,

acetonitrile, (in which the anhydride is insoluble), and DMA, DMF, THF, and chloroform (some solubility). Dimethylsulphoxide and HMPA reacted slowly with anhydride, turning yellow with the formation of diphenyl diselenide. Ethanol and methanol react immediately, forming the esters and seleninic acid :

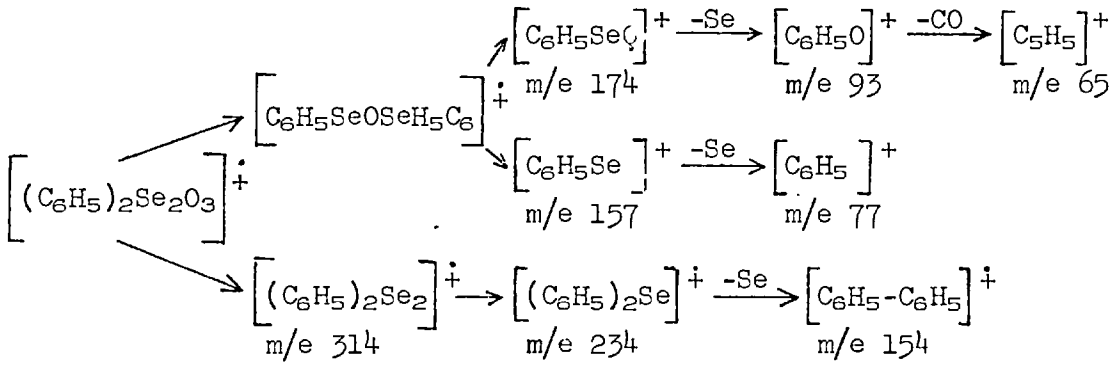


The esters were unstable to water and hydrolysed readily to give phenylseleninic acid. Thus, reactions with seleninic anhydride (1, R=Ph), may be carried out in a variety of solvents (thoroughly dried), that are not sensitive to oxidation or alternatively react with the anhydride.

Spectral Properties

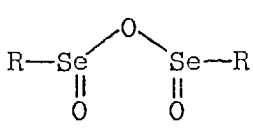
Diphenylseleninic anhydride has a molecular weight of 360.12 . The mass spectrum records the peaks 314 (38.7), 234 (37.1), 174 (42.0), 157 (85.5), 154 (75.8), 93 (27.4), 77 (100), and 65 (22.5).

This fragmentation pattern is similar to the aromatic selenoxide fragmentations investigated by Rebane[8] . The following scheme may be proposed :

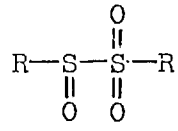


The selenium atom always shows up in the mass spectrum as a characteristic group of peaks, resulting from the typical distribution of the six major natural isotopes: ^{74}Se 0.87%; ^{76}Se 9.02%; ^{77}Se 7.58%; ^{78}Se 23.52%; ^{80}Se 49.82%.[9] The peak arising from the most abundant ^{80}Se isotope is in general chosen to represent a selenium-containing fragment.

The structure of diphenyl seleninic anhydride has been accepted as (1, R = Ph), i.e., a true anhydride. In contrast, the so-called sulphinic anhydrides (which are stable in water), are actually sulphinyl- sulphones (2)[10] .



(1)



(2)

In turn, true sulphinic anhydrides have never been observed in the oxidation of disulphides[11] .

The very extensive investigations of Paetzold[6, 12] and other workers[13] , have furnished much valuable information on Se-O vibrations in compounds such as selenoxides, seleninic acids and seleninic anhydrides. The following infra red absorption bands were assigned for seleninic anhydrides :

vibrational mode	wave number (cm^{-1})
ν_s (Se-O-Se)	500- 5[illegible]
ν_{as} (Se-O-Se)	600- [illegible]
δ (Se-O-Se)	170- 2[illegible]0

Although hydrolysis and alcoholysis reactions of seleninic anhydride indicate a Se-O-Se bridge structure, structural proof was obtained only by analysis of the vibrational spectra. Vibrational assignment was particularly easy for diphenylseleninic anhydride, but for the methyl and ethyl (i.e. aliphatic) analogues, complications occured due to coupled vibrations. The data of major interest concerning diphenylseleninic anhydride $Ph_2Se_2O_3$, as found by Paetzold et al.[6] , may be summarised as follows :

$(C_6H_5SeO)_2O$	Wave numbers (cm^{-1})	
ν Se-O ($+\gamma_2$)	859	vs
γ_1	746	vs
Ph-Se	687	vs
ν_{as} Se-O-Se	590	vs
ν_s Se-O-Se	557	m

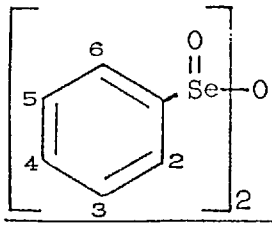
(ν = valency vibrations; γ = CH- out of plane vibrations; m= medium; vs= very strong).

Thus the Se-O-Se bridge may be deduced from the deformation vibration in the Raman spectra.

For further proof of the symmetric nature of diphenylseleninic anhydride, it was decided to carry out ^1H and ^{13}C nuclear magnetic resonance spectra, which could be obtained, using D^6MSO as a solvent.

^1H nmr showed the ortho-hydrogens of the phenyl groups at τ 2.167, para and meta hydrogens at τ 2.350 . The integration ratio as expected was 2:3 . Addition of D_2O caused a shift to τ 2.067 and τ 2.250, respectively, with corresponding formation of phenylseleninic acid.

The ^{13}C nmr data are tabulated on the following page :

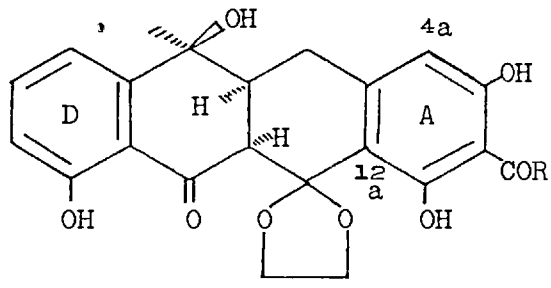


	Reference	
	D^6MSO (ppm)	TMS (ppm)
C_1	109.643	149.25
C_2 , C_6	86.309	125.91
C_3 , C_5	89.568	129.17
C_4	92.349	131.95

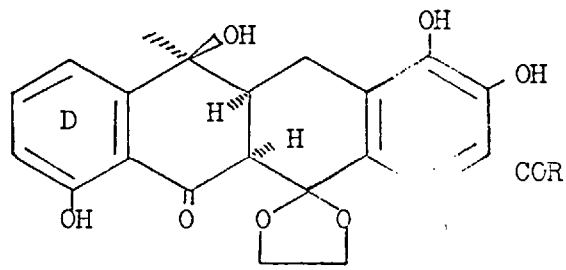
Had the molecule been unsymmetrical, two different phenyl groups would have been observed. No Se-C coupling was seen, since only 7.5% of selenium in natural abundance has spin (^{77}Se), and with ca. 1% ^{13}C present, the signal / noise ratio was too low, to show such a weak signal.

ii) '12a' Hydroxylation

The initial objective of the studies undertaken in the Tetracycline group, was the total synthesis of a 4a,12a-anhydro (3), or a 12a-anhydro (4) tetracycline, with an aromatic ring A.

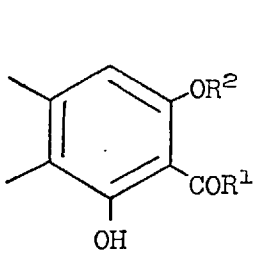


(3, R=OMe or NH_2)

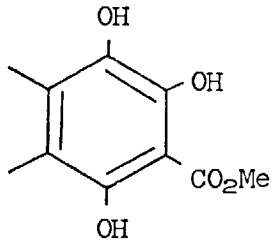


(4, R=OMe or NH_2)

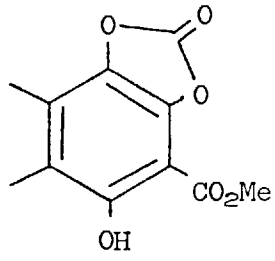
The work described in this thesis was directed towards finding a new 12a- hydroxylating procedure. With this objective in mind, phenols bearing substituents resembling those bonded to the ring A of the tetracyclic intermediates (3) and (4) had previously been synthesized[14, 15]. Such model phenols have the structures indicated below:



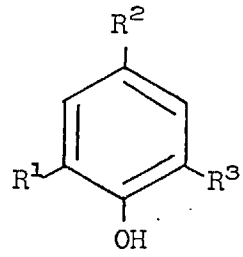
(5)



(6)



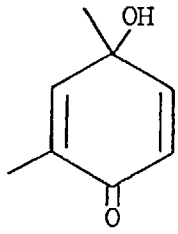
(7)



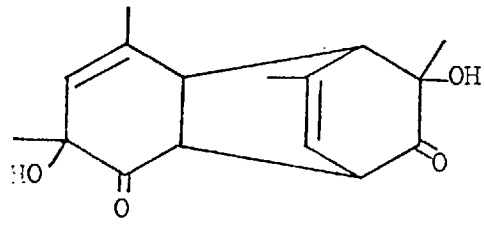
(8)

Before studying the effect of diphenylseleninic anhydride on these model phenols, with the goal of forming hydroxycyclohexadienones, a study was carried out using simpler phenols.

Treatment of 2,4-dimethylphenol (8, $R^1=R^2=Me$, $R^3=H$) with diphenylseleninic anhydride at room temperature in dichloromethane gave the p-hydroxydienone (9) (15% yield) and the dimer of the o-hydroxydienone (10), (40%)[16]. Although a two-fold excess of reagent had been used, not all the starting material was consumed.

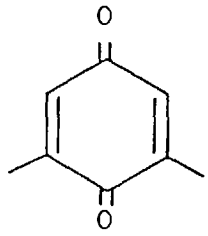


(9)

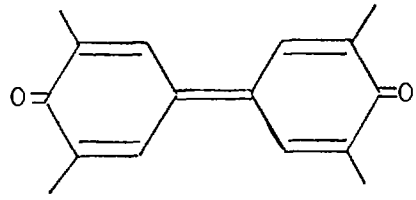


(10)

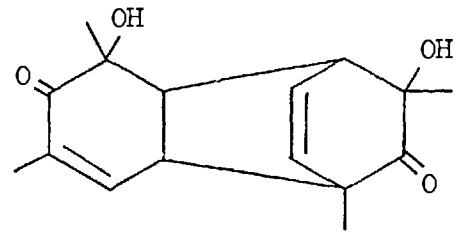
2,6-Dimethylphenol (8, R^1=R^3=Me, R^2=H) was treated with a 3-fold excess of anhydride, until no more starting phenol was apparent by thin layer chromatography (t.l.c.). Upon work up, p-quinone (11) (25%) and 3,3',5,5'-tetramethylbiphenylquinone (12)[17] (40%) were isolated, together with a small amount of o-hydroxydienone dimer (13).



(11)

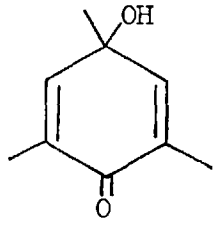


(12)

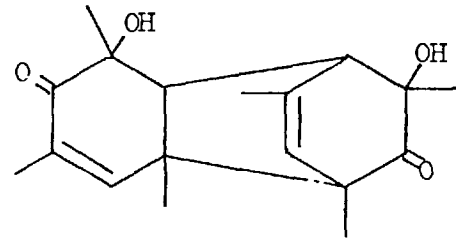


(13)

Treatment of 2,4,6-trimethylphenol (mesitol) (8, R^1=R^2=R^3=Me) with seleninic anhydride under equivalent conditions yielded p-hydroxydienone (14) (30%) and the dimer of the o-hydroxydienone (15)[18] (48%).



(14)



(15)

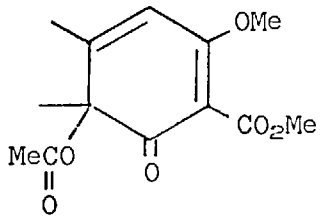
Evidently from these results, attack by the electrophilic reagent shows little ortho selectivity.

It was decided to test the reactivity of the reagent with more hindered phenols. 2,6-Di-t-butyl-4-methylphenol (8, R^1=t-butyl, R^2=Me) in dichloromethane reacted very slowly with seleninic anhydride. After 48 hours at room temperature, no major products could be isolated.

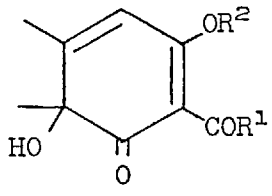
p-t-Butylphenol (8, R^1=R^3=H, R^2=t-butyl) did not react under similar conditions and could be recovered unchanged. The range of experiments was repeated using different solvents (pyridine, DMF), however, the only significant change seemed to be, that DMF favoured quinone formation in the case of 2,6-dimethylphenol, to give higher yields of biphenylquinone (12).

With these preliminary studies to hand, it now seemed worth attempting the conversion of the ring A models of type (5) to o-hydroxydienones, using the seleninic anhydride reagent.

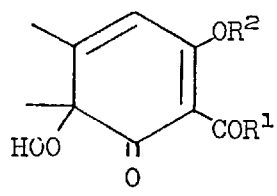
Bould[15] had previously succeeded in converting (5, R^1=R^2=OMe) into the o-acetoxycyclohexadienone (16) in 60% yield, using lead tetraacetate in methanol with boron trifluoride as catalyst. Preparation of the hydroxydienone (17, R^1=OMe, R^2=H) had been attempted by Davies[19], but met with failure. Quinney[20], using ceric oxide/ hydrogen peroxide, unsuccessfully tried to synthesise the hydroperoxydienone (18, R^1=OMe, R^2=H) from the phenol (5), however succeeded with the amide (18, R^1=NH_2, R^2=H), which was subsequently reduced to the known hydroxydienone (17, R^1=NH_2, R^2=H).



(16)



(17)

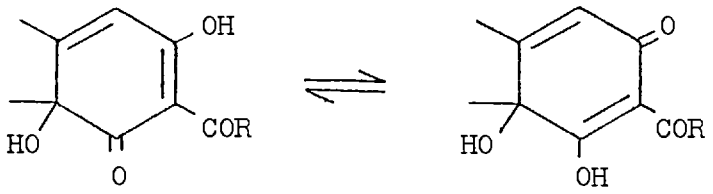


(18)

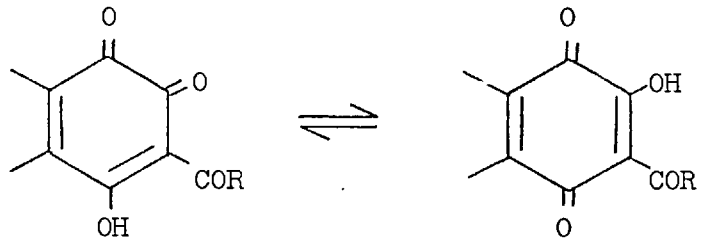
The major problem involves isolation of the ring A model hydroxydienones, as these products are strongly adsorbed on both silica gel and aluminium oxide, rendering their purification by standard chromatogra-

phic techniques very difficult.

In the reaction of seleninic anhydride with a ring A diphenol (5), two oxidation products (19 and 20), could in theory be produced :



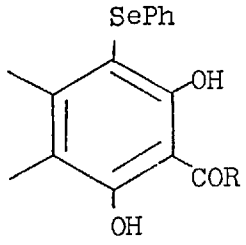
(19)



(20)

Phenol (5, R^1=OMe, R^2=H), when subjected to an equimolar quantity of diphenylseleninic anhydride, in dichloromethane at room temperature, a rapid reaction ensues, which consumes all the starting material. T.l.c. showed the appearance of two new compounds, apart from diphenyl diselenide, which is the degradation product of the anhydride. In order to extract any phenylseleninic acid formed, the reaction mixture was treated with aqueous bicarbonate solution. This layer, upon acidification and extraction yielded, however, not seleninic acid, but the desired and hitherto unknown o-hydroxydienone(19, R=OMe) in 35 % yield, which, being in its enolized form, was acidic enough for bicarbonate extraction. Thus a convenient way of isolating and purifying ring A hydroxydienones has been found, which overcomes chromatographic difficulties. Confirmation of the structure (19) was obtained by spectral data and elemental analy-

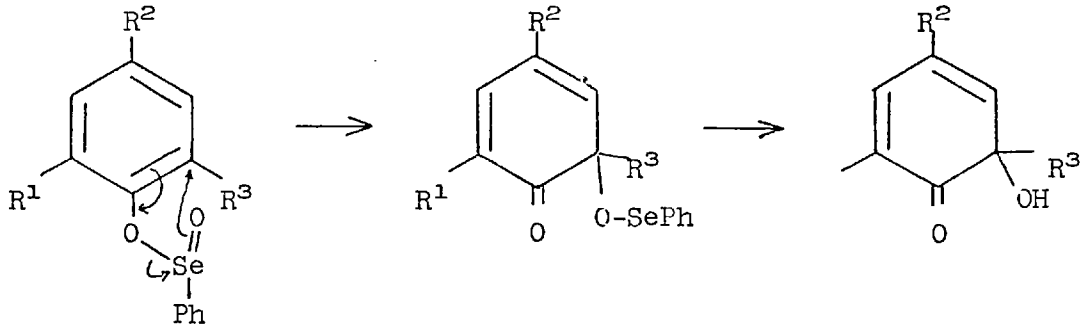
sis. Preparative layer chromatography (p.l.c.) of the remaining reaction mixture yielded 55% of the 5-selenated phenol (21, R=OMe) ; quinone (20, R=OMe) was not observed.



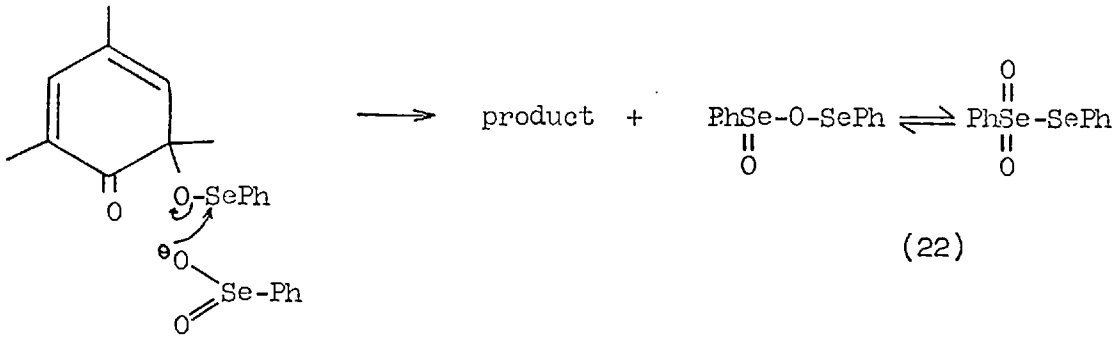
(21)

In the case of the ring A model amide (5, R^1=NH_2, R^2=H), using pyridine or chloroform as a solvent, 25% of the hydroxydienone (19,R=NH_2), 20% of the quinone (20, R=NH_2) and 45% of the selenated phenol (21, R=NH_2) were obtained.

The mechanism of this reaction possibly involves an electrophilic attack of Se on the oxygen atom of phenol, yielding a seleno ester and phenylseleninate anion. The seleno ester rearranges by intramolecular cyclisation followed by cleavage of the PhSe- unit to form diphenyl diselenide and the hydroxydienone :



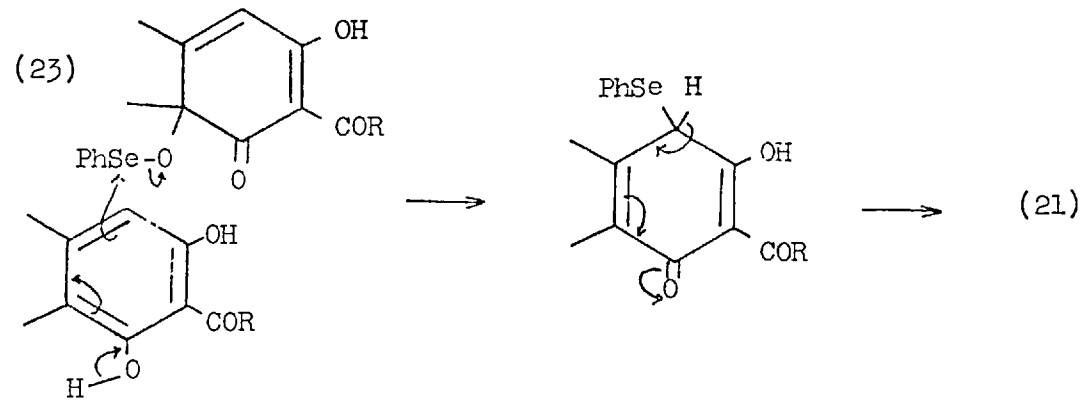
Analogous reaction mechanisms have been proposed for other phenolic hydroxylations, also $(PhSe)_2$ and $PhSeO_2H$ have been found as reaction products. In the reaction of the ring A model ester (5, R^1=OMe, R^2=H) with diphenylseleninic anhydride it was noticed that reaction went to completion with only one third of the molar amount of reagent, thus indicating that all three oxygen atoms of the anhydride take part in the oxidation process. Another alternative of the reaction pathway may be postulated:



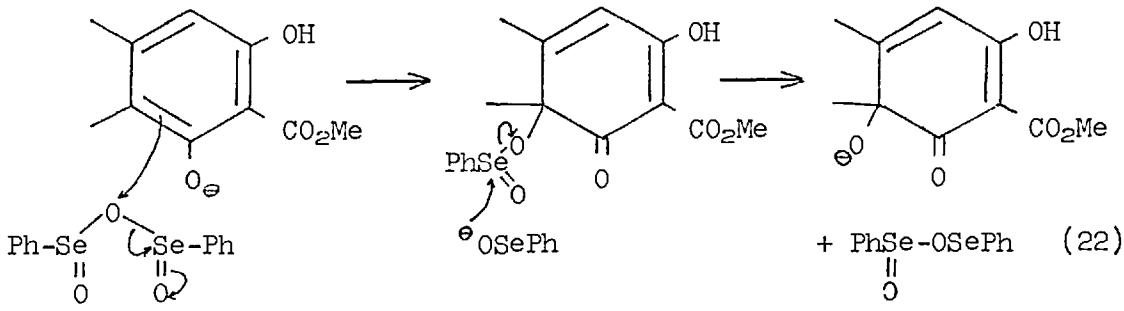
(22)

The formed 'phenylseleno-phenylseleninate' or 'selenone' (22) may attack another phenol molecule, as above, yielding a further molecule of hydroxydienone (19), with PhSeO·SePh as degradation product which ultimately completes the cycle for a third time forming diphenyldiselenide.

In order to rationalise the formation of selenated phenols (21), one can postulate nucleophilic attack of phenol on either the seleno - ester (23) or the selenoseleninate (22) as follows :

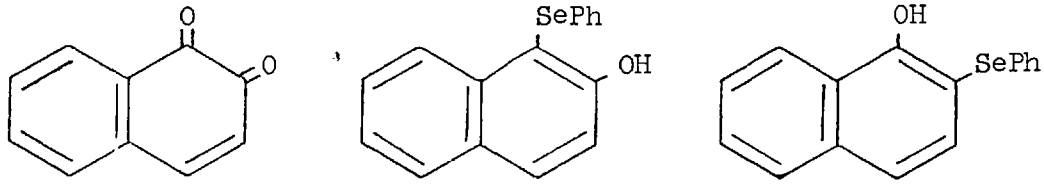


Alternatively the bridge oxygen of diphenylseleninic anhydride may be attacked, forming $PhSeO^{\ominus}$ as one of the reaction fragments . This fragment may then attack the unstable seleno ester to form selenoseleninate (22) and the anion of the hydroxydienone :



Compound (22) can then re-enter the oxidation cycle.
Diphenyl diselenide can be excluded as phenylselenating agent. Treatment of 2,4-dimethylphenol with $(PhSe)_2$ at room temperature for 24 hours, left the starting material untouched (t.l.c.) .

β-Naphthol, in tetrahydrofuran THF, reacted readily with an equimolar amount of diphenylseleninic anhydride giving two products, the ortho-quinone (24) (44%) and 1-phenylseleno-2-naphthol (25)[21] (43%);



(24) (25) (26)

a result consistent with the proposed mechanism. It was argued, that if β-naphthol was added to a solution or suspension of the anhydride, little chance of selenation should occur. In fact, dropwise addition of β-naph-

thol in minimal quantities of solvent (THF) to a slurry of anhydride in THF , resulted in almost exclusive quinone (24) formation (76% yield) . In order to exclude the possibility, that the seleno-seleninate (22) auto-oxidises in air to regenerate seleninic anhydride, the experiment was repeated under nitrogen gas, to give the same result .

α-Naphthol added to a suspension of diphenylseleninic anhydride reacted in a similar fashion. However, the reaction was more complicated and only a 55% yield of 1,2-naphthoquinone (24) and 23% of 2-phenyl-seleno-1-naphthol (26) could be isolated.

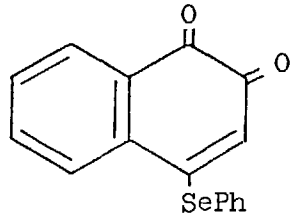
An attempt was made to synthesise the selenoseleninate (22) by the route outlined below :

$$\mathrm{Ph\text{-}Se(=O)\text{-}OM} + \mathrm{PhSeCl} \longrightarrow \mathrm{PhSe(=O)\text{-}OSePh}$$

(M= Na or Li) (22)

Equimolar amounts of phenylselenenyl chloride and the sodium salt of phenylseleninic acid were mixed in a suitable solvent (THF). A reaction took place, as judged by the colour change from orange-brown to yellow, but on work up only $PhSeO_2H$ and $(PhSe)_2$ were obtained. Similar attempts remained unsuccessful, when the lithium salt was used, although the reaction was carried out under nitrogen with careful exclusion of moisture. Owing to these observations, it was decided to prepare the reagent (22) in situ, and react it with β-naphthol to investigate its potential selenating properties. Indeed following this procedure yielded, after 2 hour reaction time, 67% of selenated naphthol (25). By allowing a similar reaction to proceed for 48 hours, further oxidation occured and only a 43% yield of phenylsel[illegible]-compound (25) was isolated. The

other by-product was identified as 1-chloro-2-naphthol (20%). A third isolated product had a deep violet colour and crystallised from ether as black plates, ν_{max} 1660-1680 cm^{-1} (shoulder), λ_{max} (ε) 272 (23,500), 325 (14,200) and 344 (16,300) nm. Mass spectral data, m/e 314, coupled with micro analytical data indicated the formation of a 4-phenylseleno-1,2-naphthoquinone (27), the first[22] known member of this class of compounds.

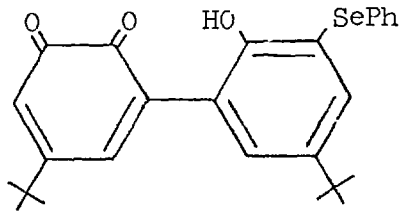


(27)

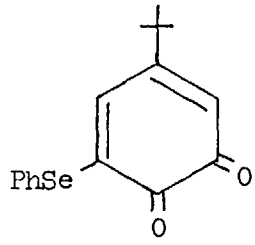
From these results it would appear, that there is a strict pattern in the sequence of reactions of diphenylseleninic anhydride with phenols, i.e., $Ph_2Se_2O_3$ acts as an oxidising agent (hydroxylating), $Ph_2Se_2O_2$ (22) as a selenating agent, and Ph_2Se_2O as an oxidising agent.

A reaction was carried out with 4-t-butylphenol, a compound that had previously shown very little tendency to react. When added to an equimolar amount of diphenylseleninic anhydride in THF, the solution was warmed to 45° for 30 minutes to initiate reaction, which was then allowed to proceed at ambient temperature for 24 hours. T.l.c. analysis showed the presence of an orange-red and a deep violet substance as main products. After isolation (p.l.c.), the red compound could be crystallised and purified from ethanol, melting between 210-215°. Infra red and ultra violet spectroscopy revealed a quinoid nature, and mass spectral evidence suggested structure (28). Micro analytical data were

in accord with this structure. The deep violet compound crystallised from ether as black plates, m.p. 120° . The molecular ion m/e 320 in the mass spectrum supported by elemental analysis indicated the formation of 3-t-butyl-5-phenylseleno-1,2-benzoquinone (29).



(28)



(29)

The yields for the isolated products (28) and (29) were 22% and 30% , respectively. It is worth noting that both substances are quite stable compounds in their crystalline forms, while the un-phenylselenosubstituted quinones are known to be rather unstable. The formation of the coupled quinone (28) may be explained in terms of initial oxidation, followed by coupling to the selenated phenol.

By converting the phenol to the phenolate ion, it was hoped that the increased nucleophilicity would promote o-hydroxylation at the expense of the side reactions. This conversion was achieved, using sodium hydride in glyme or THF under a nitrogen atmosphere[23] .

2,4-Dimethylphenol (8, R^1=R^2=Me, R^3=H) was dissolved in glyme, an equimolar quantity of NaH was added under N_2 at room temperature; after 10 minutes diphenylseleninic anhydride was introduced and allowed to react. Work up yielded 45% of the dimer of the o-hydroxydienone (10) , with no trace of the p-hydroxydienone present. 2,6-Dimethylphenol (8, R^1=R^3=Me, R^2=H) treated in a similar manner yielded 44% of the o-hydroxydienone dimer (13) and quinol oxidation products could only be detected

in trace amounts. Mesitol (8, $R^1=R^2=R^3=Me$) yielded,under these conditions,a 55% yield of o-hydroxydienone-dimer (15), with no para compound (14) detectable.

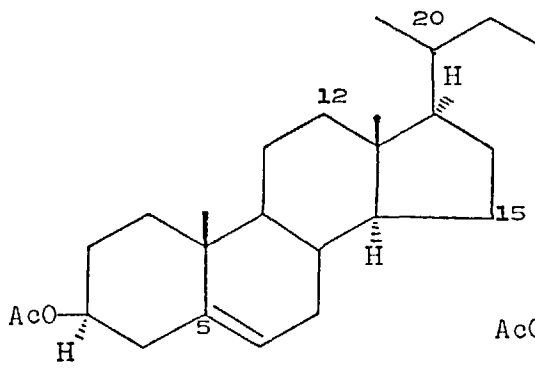
These encouraging results showed that a high degree of o-hydroxylation was possible. Extension of the reaction to the ring A models (5, $R^2=H$) should therefore provide higher yields of desired o-hydroxylated products. When the ester (5, $R^1=OMe$, $R^2=H$) was treated with NaH/ glyme under a nitrogen atmosphere, followed by oxidation with diphenylseleninic anhydride, the o-hydroxycyclohexadienone (17, $R^1=OMe$, $R^2=H$) could be isolated in a 75% yield. Selenated phenol (21, R=OMe) was also formed, albeit in only 17% yield. The ring A model amide (5, $R^1=NH_2$,$R^2=H$) was converted to the o-hydroxycyclohexadienone (17, $R^1=NH_2$, $R^2=H$) in 68% yield, with only trace amounts of quinone (20, $R=NH_2$) and selenated phenol (21, $R=NH_2$) being produced. Similar yields were obtained when these experiments were carried out in THF, or with potassium hydride replacing NaH. With naphthols, little improvement of the oxidation of anion versus the naphthol was achieved.

The α-naphtholate anion was formed from α-naphthol with NaH and treated with seleninic anhydride. Upon work up, three compounds were isolated, the selenated phenol (26) (38%), the 1,2-naphthoquinone (24) (36%) and a trace of 2-hydroxy-1,4-naphthoquinone, which was identified by m.p. 188-9° (189° , lit.[24]) and mass spectral data.

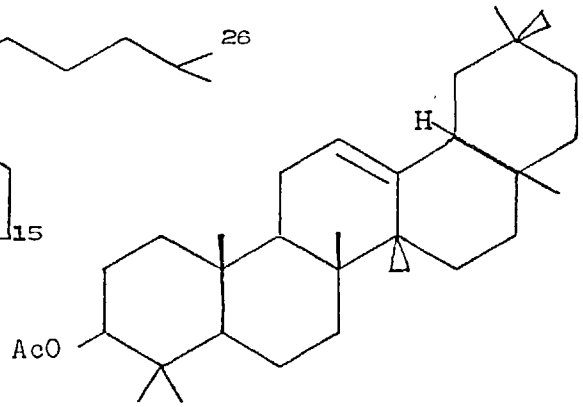
With β-naphtholate a much cleaner reaction occured with seleninic anhydride, and the selenated naphthol (25) was obtained in a 45% yield, together with 48% of 1,2-naphthoquinone (24).

Before continuing the studies of hydroxylation of phenols, it seemed important to investigate the reactivity of diphenylseleninic anhydride with unsaturated systems.

Cholesterol acetate (30a) was heated in benzene for 2 hours, after adding one molar equivalent of diphenylseleninic anhydride, without any reaction taking place. The same result was obtained using β-amyrin acetate (30b).



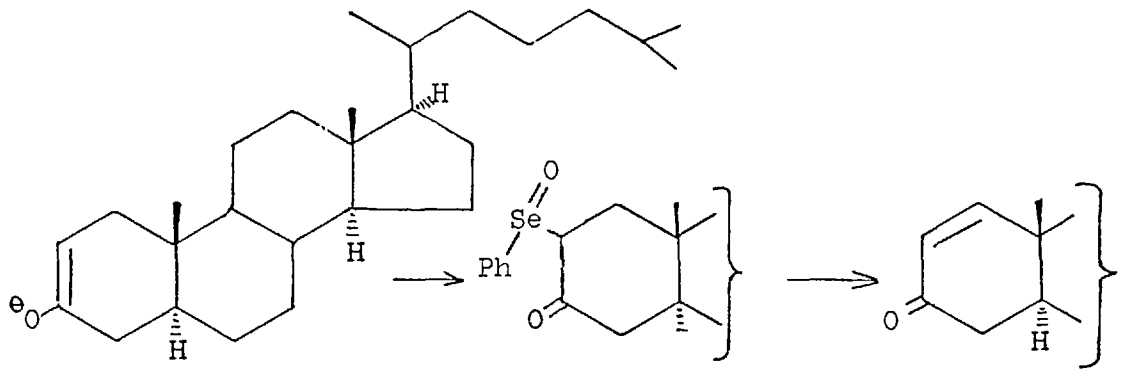
(30a)



(30b)

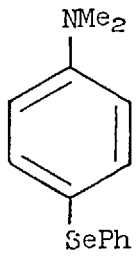
Acenaphthalene in dichloromethane or THF failed to react with the anhydride, even after boiling for 2 hours. Stilbene under equivalent conditions was recovered unchanged.

These results indicate that unsaturated systems are largely inert towards seleninic anhydride. Recently it has been shown[25], that cholestanone (31) can slowly be converted to cholestan-1-enone (32), using firstly lithium diisopropylamide, $LiN(^{i}Pr)_2$, followed by treatment with seleninic anhydride.

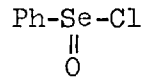


(31) (32)

N,N-Dimethylaniline only reacted with the reagent after reflux in THF, to give a modest yield of p-phenylselenenyl-N,N-dimethylaniline (33).(Pitombo[26] has prepared 1-N,N-dimethylamino-4-phenylselenenyl - naphthalene, using PhSeCl). Owing to the fact, that a selenium containing fragment, phenylseleninic acid, is produced as a by-product in these oxidation reactions, it was decided to investigate possible reactions of phenylseleninyl chloride, PhSeOCl, a compound described by Ayrey et al.[3] .

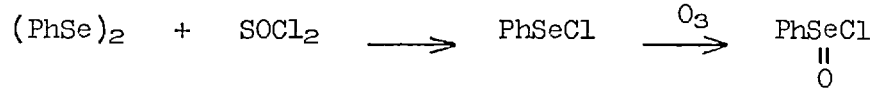


(33)



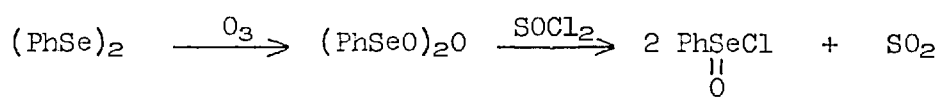
(34)

The literature[3] describes the preparation of (34) by ozonolysis of phenylselenenyl chloride :

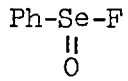


(34)

However, when this method was attempted, it failed to give the desired product. An alternative route was found, by treating diphenylseleninic anhydride with thionyl chloride, giving a quantitative yield of the desired compound (34).



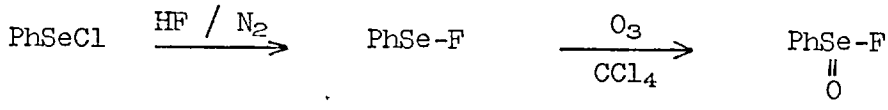
2,4-Dimethylphenol reacted very fast at room temperature with phenylseleninyl chloride to yield a number of selenated compounds. No major product could be isolated. Using phenylseleninyl chloride (34) for the ring A model ester (5, R^1=OMe, R^2=H) resulted in selenation, producing (21, R=OMe) in 55% yield. Only trace amounts of o-hydroxy-dienone (19, R=OMe) were produced as judged by nmr spectral analysis. Failure of the seleninyl chloride (34) as a hydroxylating agent prompted us to attempt the synthesis of the corresponding fluoride (35).



(35)

Early attempts[27] to prepare phenylselenenyl fluoride, PhSeF, had failed. Neither phenylselenenyl bromide on silverfluoride, nor diphenyl-diselenide subjected to a stream of fluorine gas yielded the desired compound. In every case an oil was obtained, which hydrolysed easily, failed to crystallise, and decomposed on distillation.

An alternative approach to its synthesis was therefore considered:

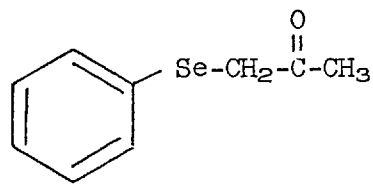


(35)

Hydrogenfluoride gas, in excess, was condensed with phenylselenenyl chloride at 0°, and allowed to react for 2 hours. Excess HF and HCl were driven off using a stream of dry nitrogen. The remaining brown oil was stirred with carbon tetrachloride, filtered and treated with ozone at

- 10°. As the reaction proceeded, a white precipitate was formed, which was filtered off at the end of the reaction, washed with a minimal quantity of acetone, and dried in vacuum. Mass spectral analysis of the product showed m/e 192, indicating the possible presence of the correct product. ^{19}F Nuclear magnetic resonance spectroscopy revealed a sharp singlet at 2030.0 Hz, 75.6 ppm to highfield of $CFCl_3$, which would be expected for the Se-F bond. A correct micro analytical analysis could not be obtained for this compound, which decomposed without melting at 138° .

The phenylseleninyl fluoride (35) was a highly reactive species and readily reacted with acetone, forming α-phenylseleno acetone(36)[26,28] an unstable oil, that easily decomposes to diphenyl diselenide and acetone.



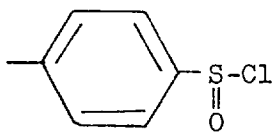
(36)

On reacting phenylseleninyl fluoride (35) with the phenolate of 2,4-dimethylphenol in benzene, two selenium containing derivatives of the phenol were obtained after extraction and preparative layer chromatography. These products were possibly the di- and tri-selenated 2,4-xylenol, but resisted all attempts at purification.

Clearly, from these results, phenylseleninyl fluoride (35) acts as a good selenating agent, but not as oxidising or fluorinating agent.

In order to verify the uniqueness of diphenylseleninic anhydride as a hydroxylating reagent, experiments were carried out with p-tolylsul-

phinyl chloride (37) and the sulphinyl sulphone (38)[10] .



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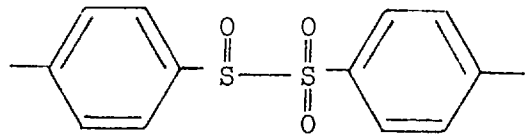
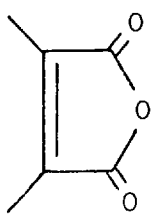


(38)

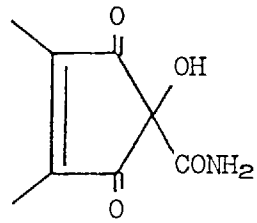
The sulphinyl chloride (37) was prepared according to the literature method[29] from sodium p-tolylsulphinate and thionyl chloride. The sulphinyl sulphone (38) was prepared according to the method of Knoevenagel[30] from the sulphinic acid.

Both sulphinyl compounds were reacted in turn with 2,4- and 2,6-xylenol, mesitol and the ring A model ester (5, R^1=OMe, R^2=H), after prior formation of the corresponding phenolates with NaH in glyme. Although the reaction mixtures were boiled for a length of time (up to six hours), the phenols were all recovered unchanged, together with degradation products such as di-(p-tolyl) disulphide, p-tolyldisulphoxide, and p-tolylsulphinic acid.

The selenium dioxide / hydrogen peroxide system, previously used by Davies[19], gave, upon reaction with the ring A model ester (5, R^1=OMe, R^2=H), mainly dimethylmaleic anhydride (39), a ring contraction product. A similar result was obtained using the amide (5, R^1=NH_2, R^2=H), although



(39)

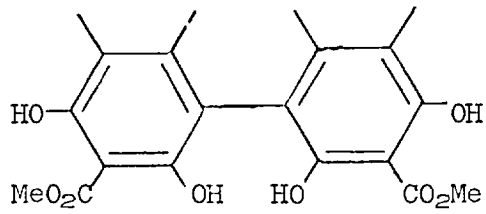


(40)

the pent-3-enone (40) was isolated in only 15% yield.

It remained to test the reactivity of selenium dioxide towards the phenolate of 2,4-xylenol, which after heating under reflux for 3 hours, gave only unreacted phenol upon work up.

Adler[31] has successfully o-hydroxylated certain phenols, using sodium metaperiodate inaqueous methanol. The ring A model ester (5, R^1= OMe, R^2=H) was subjected to $NaIO_4$ in aqueous methanol at room temperature for 18 hours, but no reaction occured (t.l.c., nmr). After warming the reaction mixture for 6 hours, 60% of starting material was recovered. However, a more polar compound had formed in modest yield, which, after mass spectral and nmr analysis showed it to be the dimer (41), the product of oxidative coupling.



(41)

Thus, $NaIO_4$ failed to give any ortho-hydroxylation of the ring A model.

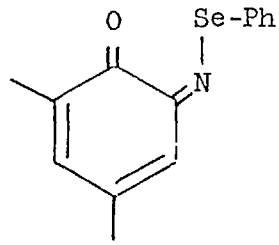
After establishing the uniqueness of the reagent for hydroxylating the tetracycline ring A models, we proceeded to investigate the use of different bases for phenolate formation, in order to optimise the formation of ortho-hydroxydienones.

In this respect, the sodium salt of hexamethyldisilazane (42), was prepared.

$$Na^+ \quad N^-(SiMe_3)_2 \qquad (42)$$

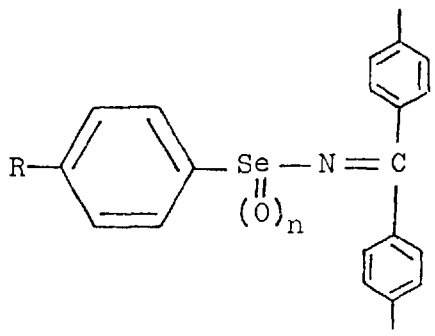
It readily reacts with phenols to form the corresponding phenolate anions[32] .

2,4-Dimethylphenol in anhydrous toluene was treated firstly with a molar equivalent of sodium bistrimethyl silylamide (42) under nitrogen, followed by diphenylseleninic anhydride after 10 minutes. An instantaneous reaction occured with the appearance of a deep red colour. Work up (p.l.c.) yielded a red compound in high yield, which was crystallised from ether at -78° . Mass spectral analysis revealed the incorporation of nitrogen into the molecule, m/e 291, and also showed the characteristic selenium pattern. ν_{max} 1615 cm^{-1} , λ_{max} 253,281,430, and 486 nm. These data showed a distinct similarity to the thioimines described by Barton et al.[33] . The compound was thus identified as the selenoimine (43). The micro analysis was in accord with this structure.



(43)

Tetravalent phenylselenoimines (44) have been described in the recent literature[34] , together with the divalent species (45) .

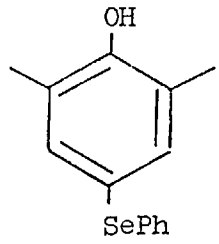


(44, n=1)

(45, n=0)

R= H, NO_2

2,6-Dimethylphenol, under above named conditions failed to yield the p-phenylselenoimine. Instead, 33% of the o-hydroxydienone dimer (13) could be isolated together with an oil, which was characterised as the p-phenylselenide (46) in 15% yield.

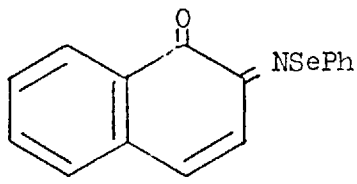


(46)

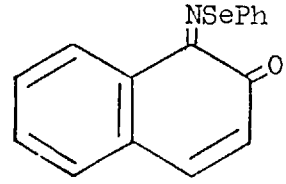
Compound (46) resisted all attempts at crystallisation and decomposed easily.

Mesitol, after reaction with $NaN(SiMe_3)_2$, followed by diphenylseleninic anhydride, yielded 42% of o-hydroxydienone dimer (15).

The anion of α-naphthol was formed with the lithium salt of hexamethyl disilazane, $LiN(SiMe_3)_2$, in THF, and after treatment with seleninic anhydride the 2-phenylselenoimine (47) was obtained in 42% yield, identified by the molecular ion at m/e 313, together with 12% of 2-phenylselenenyl-1-hydroxynaphthalene (26).



(47)



(48)

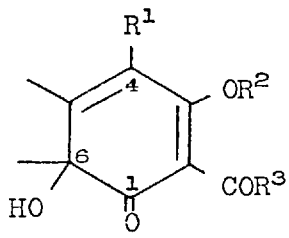
β-Naphthol yielded, in a similar manner, 20% of the imine (48) as a

red crystalline solid, m.p. 126-7° with the molecular ion at m/e 313 and the selenated naphthol (25) in 25% yield.

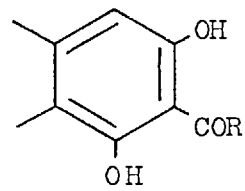
The selenoimines (47) and (48) were reductively acetylated with Zn/acetic anhydride/AcOH to yield the known N,O-diacetyl derivatives[33, 35]. Simple reduction (Zn/AcOH) afforded the o-aminonaphthols, thus giving a convenient method of synthesising o-aminophenols from phenols.

After succeeding in synthesising tetracyclic hydroxydienone models (49, $R^1=R^2=H$, $R^3=OMe$) and (49, $R^1=R^2=H$, $R^3=NH_2$), attempts were made to prepare C-4 substituted hydroxycyclohexadienones.

iii) 'C-4' - Functionality.

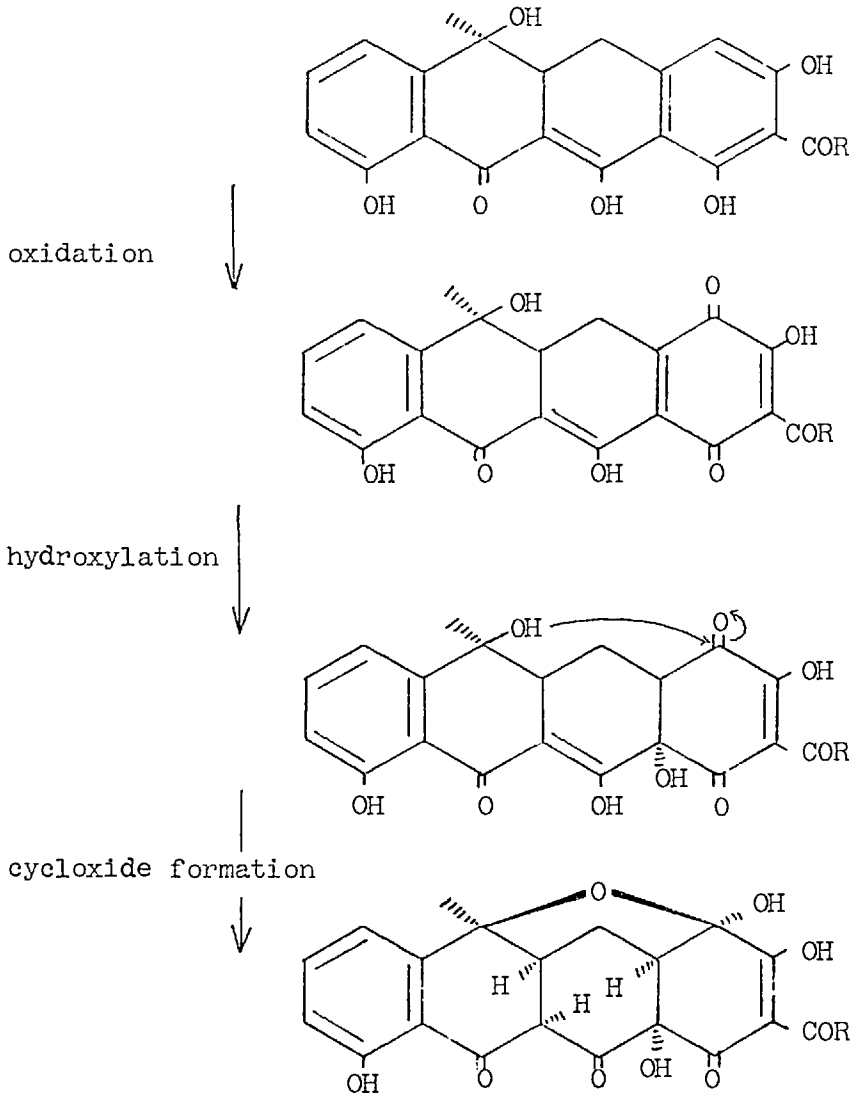


(49)



(50)

The species envisaged were derivatives with either N or O- substituents in the C-4 position. The route chosen to these species involved substitution of the diphenol (50), followed by hydroxylation. Extension to the corresponding tetracyclic compounds could lead to the cycloxide (51), which is regarded as a synthetic target in the Imperial College tetracycline synthesis.



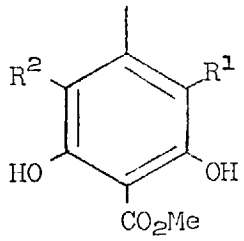
(51)

No attempts were made to C-4 substitute in hydroxydienones, since experiments in this direction have been met with failure[20] .

An 'ene'-type reaction between the model phenols and a suitable dienophile could be expected to yield a way of introducing functionality at C-4 .

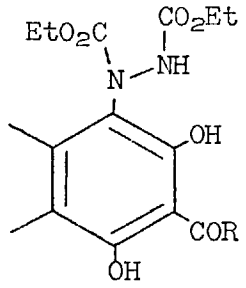
Diethylazo dicarboxylate (52) seemed a reasonable reagent. Reaction with the model methyl 2,6-dihydroxy-4-methylbenzoate (53, R^1=R^2=H) in dichloromethane, proceeds very cleanly to give 45% of the mono- (53, R^1 = H,R^2=$EtCO_2NHNCO_2Et$) and 48% of the di-substituted phenol (53, R^1=R^2= $EtCO_2NHNCO_2Et$) .

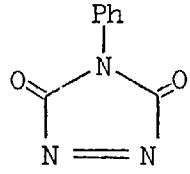
$EtCO_2N{=}NCO_2Et$



(52) (53)

Similarly, using the tetracyclic models (50, R=OMe and NH_2) gave 62% of the ester (54, R=OMe) and 64% of the amide (54, $R=NH_2$).



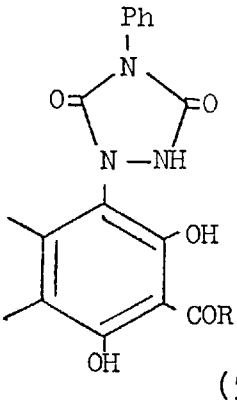


(54) (55)

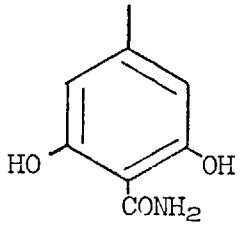
These substituted compounds could be obtained as crystalline substances and the structures were characterised by spectral and micro analytical data.

Cookson's reagent[36, 37], 4-phenyl-1,2,4-triazoline-3,5-dione (55), was readily available from its hydrazine precursor by oxidation with nitrogen dioxide. This reagent with the phenol (53, $R^1{=}R^2{=}H$) reacted at room temperature to yield two compounds, which after preparative layer chromatography could be isolated and identified as the mono- (53, $R^1{=}H$, R^2=N-4-phenylurazole) and di-substituted product (53, $R^1{=}R^2$=N-4-phenylurazole). The ring A model ester (50, R=OMe) reacted with Cookson's reagent to yield the hexasubstituted benzene (56, R=OMe) in high yield.

The amide (50, R=NH_2), however, showed very little tendency to react, even after forcing conditions (increased temperature) t.l.c. showed no major reaction product. The ester (56, R=OMe), however, could be readily converted to the amide (56, R=NH_2) in high yield, using standard ammonolysis conditions[38]. The amide (57) also failed to give either the mono or di-substituted product, when reacted with Cookson's reagent. Furthermore, all triazoline dione substituted phenols were very polar and isolation and purification by standard p.l.c. methods rarely succeeded .

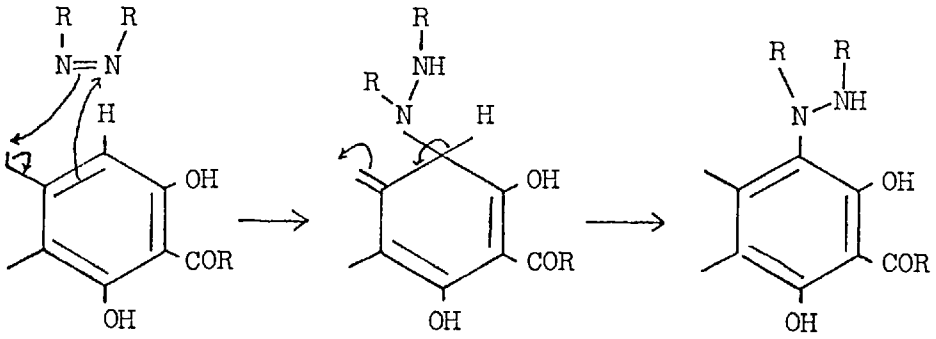


(56)



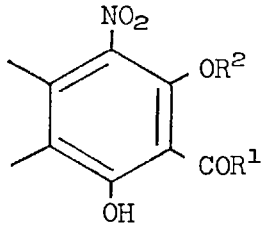
(57)

The mechanism for these C-4 substitutions may be postulated as initial ene reaction, followed by rearomatisation.

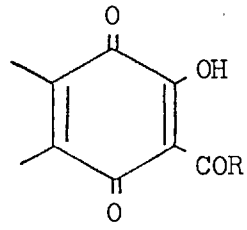


Yet another compound useful for extension of the model phenol series is the 4-nitrophenol (58, R^1=OMe, R^2=H). This compound was obtained by nitration of the diphenol (50, R=OMe) with nitrogen dioxide in dichloromethane, as yellow needles, m.p. 129° , from ethanol. As an oxidative

by-product, the quinone (59, R=OMe) was isolated in 35% yield. This quinone, in fact, is of importance in the preparation of the trihydroxy models.



(58)



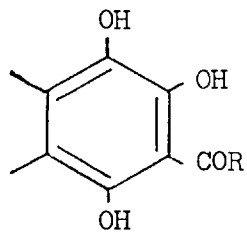
(59)

Bould[15] has obtained the quinone (59, R=OMe) by treatment of the phenol (50, R=OMe) with Fremy's salt, potassium nitrosodisulphonate (60)[39],

$$\cdot O-N-(SO_3K)_2$$

(60)

in 95% yield. Reduction of the quinone (59) to the triphenol (61, R=OMe) was readily achieved using $Pd/BaSO_4$ or by methanolic metabisulphite solution.

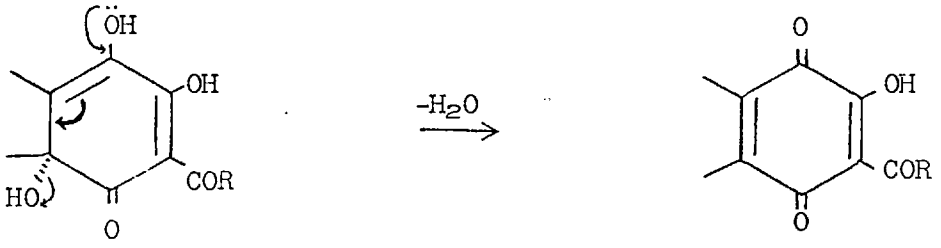


(61)

The quinoid amide (59, $R=NH_2$) was obtained in good yield by oxidation of the model amide (50, $R=NH_2$) with ammonium molybdate/hydrogen

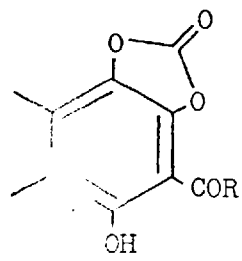
peroxide[20] . Hydrogenation in ethyl acetate over Pd/ $BaSO_4$ yielded a brownish solid, that was purified by sublimation (120°, 10^{-4} mm) . The yield of compound (61, R=NH_2) ranges between 90 and 95%. Although these trihydroxy compounds may be stored as solids under nitrogen for an indefinitive time, they quickly undergo oxidation in solution, to furnish the quinones (59).

Treatment of the triphenols (61) with diphenylseleninic anhydride rapidly produces the quinones (59). It was thought that the formation of the quinones may arise <u>via</u> dehydration of the initially formed hydroxydienone (62).



(62) (59)

Ways of eliminating this problem were investigated. A cyclic carbonate could be produced in high yields, by reacting the triphenol (61, R=OMe) in toluene with a trace of pyridine, with a stochiometric amount of phosgene at -5° under nitrogen.(63) was obtained as colourless crystals m.p. 167°, (167° ex lit.[15]).



(63)

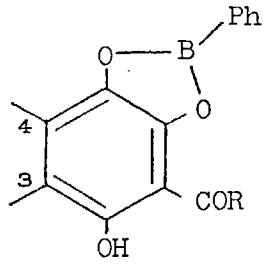
The amide (61, R=NH_2) under identical conditions partially dehydrates to give a mixture of a nitrile (ν_{max} 2150 cm^{-1}) and the desired carbonate (63, R=NH_2). The dehydration problem of the amide was readily overcome by using N,N'-carbonyldiimidazole in THF[40] , rather than phosgene. Work up with N/50 HCl to remove the imidazole, leaves the pale yellow product, m.p. 248° , ν_{max} 3400, 3250, 1765, 1675, and 1635 cm^{-1} . Micro analysis agrees with structure (63, R=NH_2).

In order to test, that the carbonates were inert to NaH/THF, they were treated with sodium hydride in THF for 1 hour under nitrogen, and after work up under acidic conditions (N/10 HCl), or aqueous potassium bisulphate, the unchanged carbonates (63) were returned.

Treatment of the phenolate of (63) (from carbonate (63) with sodium hydride) with $Ph_2Se_2O_3$, gave upon extraction the quinone (59). Using lithium hexamethylsilazane to preform the anion (63), did not alter the result. Forming the phenolate anion with sodium diisopropylamide, followed by seleninic anhydride addition, resulted eventually in the extraction of a pale yellow oil, which did not contain the characteristic infra red absorption for a cyclic carbonate. Spectral analysis showed m/e 256 , τ ($CDCl_3$) -1.0 (H), 5.95 (3H) and 7.9 (6H) (all singlets) and λ_{max} 274 (ε 9600) nm . From these data the compound clearly has a quinoid nature and a molecular formula of $C_{11}H_{12}O_7$. However, no reasonable structure could be proposed and micro analysis failed due to the instability of the compound.

Since seleninic anhydride seems to cause cleavage of the cyclic carbonate, another method of protecting the vicinal hydroxyl groups of the triphenol (61) was examined. Phenylboronic acid[41] has found extensive use in organic synthesis and the cyclic boronates may be cleaved easily to refurnish the diol[42] .

The ester (61, R=OMe), in ethanol, reacts readily to form the cyclic boronate (65, R=OMe). The infra-red spectrum reveals the characteristic B-O stretching at 1320 cm^{-1} and a strong absorption at 1440 cm^{-1} for the B-aryl bond[43].



(65)

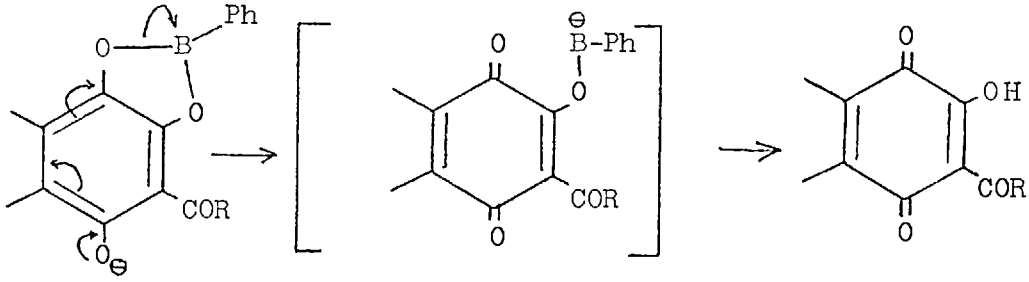
The nmr spectrum shows a broad signal for the 4-methyl group, as opposed to the sharp 3-methyl singlet, an effect which may well be due to a ^{11}B coupling.

The amide (65, R=NH_2) was prepared analogously. It seems, however, that the model amides in general incorporate solvent and correct micro analytical data may only be obtained after drying at elevated temperatures in vacuo. Purification of the boronates was achieved by recrystallisation.

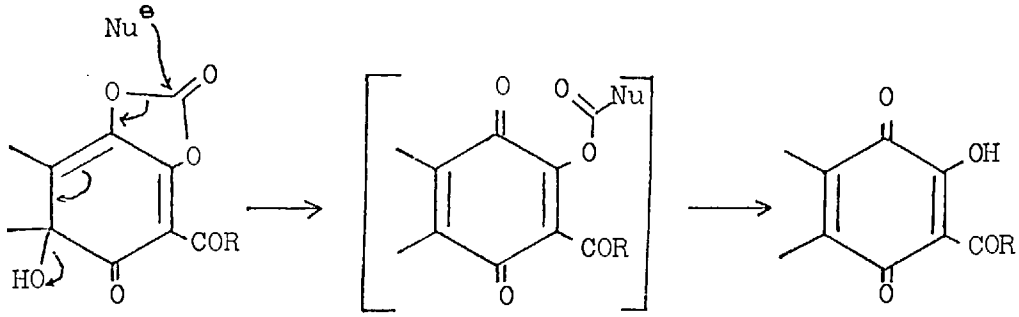
The model boronates (65) only proved stable towards sodium hydride in glyme or THF, when worked up with a buffer solution of potassium dihydrogen-phosphate. N/10 HCl caused decomposition of the compounds, similarly to basic or even neutral conditions.

Oxidation of the boronate (65) with diphenylseleninic anhydride seemed to proceed rapidly, as judged by the colour change to red-brown, and yielded a variety of products, of which the quinone (59) was identified by t.l.c. comparison. Owing to this result it appeared that the boronate model (65) was unsuitable for the synthesis of C-4 substituted

hydroxydienones (49). Indeed, failure was encountered with all C-4 substituted models, synthesised so far, with exception of the urazole-ester (56, R=OMe). The quinone formation may arise via the following pathway:

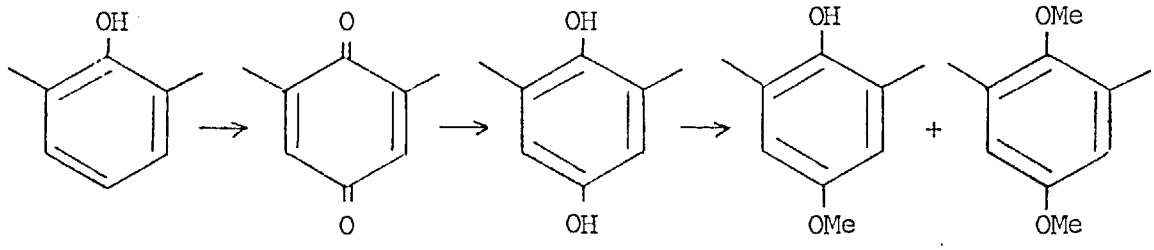


Alternatively, an attack by a nucleophile on the o-hydroxylated carbonate (63) , could also cause quinone formation:



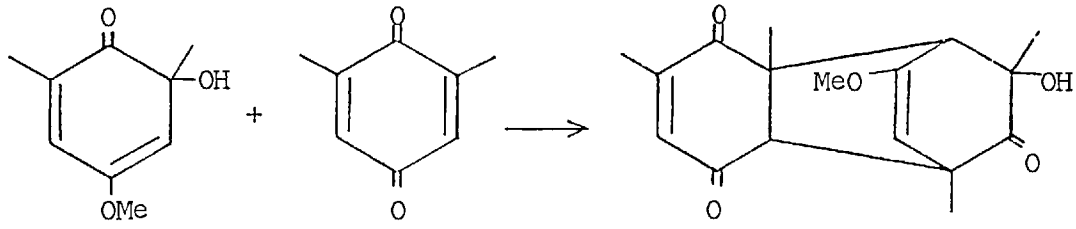
Other means of protecting the hydroxyl group in the C-4 position were also investigated. In this regard, the mono-methylether of 2,6-dimethyl-1,4-hydroquinone (66) seemed to be an appropriate model.

2,6-Xylenol was oxidised with selenium dioxide/hydrogenperoxide to the para-quinone and reduction by catalytic hydrogenation furnished the hydroquinone . This substance in acetone, was alkylated with dimethyl sulphate under reflux in the presence of potassium carbonate. P.l.c. yielded 62% of the desired product (66), m.p. 77° (77° ex lit.[44]), and a 31% yield of the dimethylether.



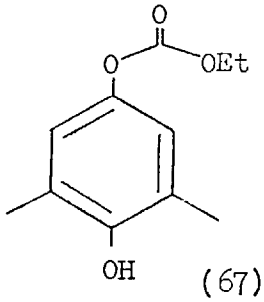
(66)

4-Methoxy-2,6-dimethylphenol (66), after reaction with sodium hydride in glyme, was treated with seleninic anhydride at temperatures ranging from 10° to -78° . Only formation of 2,6-dimethyl-1,4-quinone was observed. At low temperatures, a minor by-product could be isolated by p.l.c.. Mass spectral analysis of this product showed m/e 304, equivalent to $C_{17}H_{20}O_5$, suggesting the formation of the adduct of the o-hydroxydienone and quinone, i.e., by analogy with Adler's[31] results.



For many quinones, mass spectrum shows an M+2 peak, which is thought to arise from partial reduction by residual moisture, present in the inlet system and ionization chamber. The effect is more pronounced with o-quinones, since these possess a considerably higher redox potential than p-isomers, and has also been known to occur with quinoid dimers[45, 46] .

An alternative way of protecting the C-4 hydroxyl group via the ethyl carbonate derivative (cathylate) was considered. 2,6-Dimethyl-1,4-hydroquinone was reacted with a molar eqivalent of ethyl chloroformate in dichloro methane/pyridine. The desired mono-cathylate (67) was obtained in 60% yield, m.p. 87-8° . The dicathylate (68) and the mono-cathylate (69) were also isolated as crystalline by-products in 20% and 13% yield, respectively.



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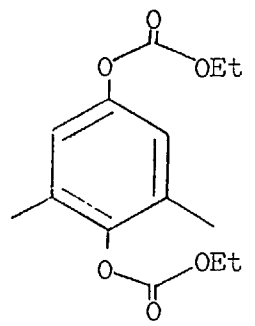
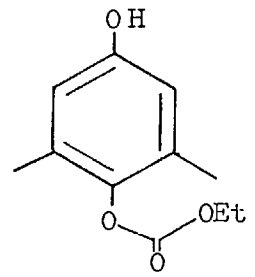


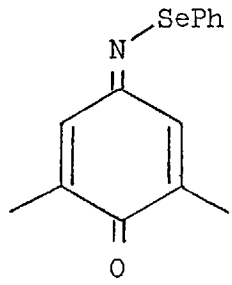
(68)



(69)

Cathylate (67) was treated with sodium hydride in glyme to form the phenolate anion, cooled to -78° and subsequently treated with diphenyl-seleninic anhydride. No reaction took place and starting material was recovered unchanged. Since no reaction occured even after raising the temperature to 25° , potassium hydride was used in the hope of achieving the anion more readily. Below 0° the phenolate was inert to oxidation, but above 0° all the starting material was immediately consumed with the resulting formation of a dark brown polymeric material, which was very polar (t.l.c.) and melted over a wide range. In another attempt to hydroxylate the phenol (67), the anion was formed using lithium hexamethyldisilazane. Immediately , upon addition of seleninic anhydride, a colour change to orange-red was observed, and after work up in the usual way , (KH_2PO_4), two major components could be detected by t.l.c. . The more polar substance was identified as the p-quinone (t.l.c., nmr, m.p.) ,

the other material could be crystallised from ether at -78° as orange-red needles, m.p. 140°. Mass spectral analysis indicated the presence of nitrogen in the molecule, m/e 291, as well as the characteristic selenium pattern. Other spectral properties were ν_{max} 1640 and 1620 cm^{-1}, λ_{max} 243, 261, 274, 356, and 448 nm (ε 13,400, 13,460, 12,600, 2650, and 10,900). These data, in conjunction with micro analytical analysis indicated the compound to be the para-selenoimine (70).



(70)

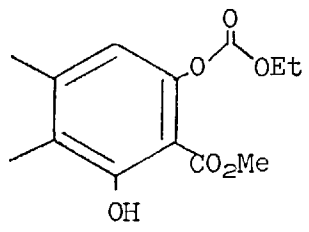
The data compared favourably with the corresponding thioimine, prepared by Barton[33].

The interesting chemistry of these new selenoimines is now being studied by other workers[47] in these laboratories, and mechanistic investigations are in process.

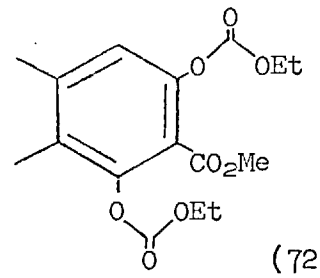
As a control experiment, the dicathylate (68) was treated with lithium hexamethyl-disilazane followed by seleninic anhydride, and was recovered unchanged. The use of the cathylate blocking group was investigated, using the tetracycline ring A models. In this regard it was of interest to synthesise the mono-cathylate (71), a derivative of the diphenol model (50, R=OMe).

Treatment of the ester (50, R=OMe) with a molar equivalent of ethylchloroformate in chloroform/pyridine, afforded only dicathylate (72) and starting material. Owing to this fact, it was decided to synthesise the

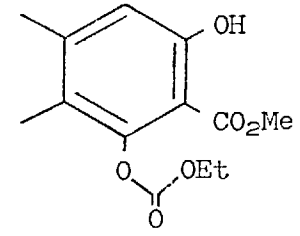
dicathylate (72), using excess ethylchloroformate, and then selectively hydrolyse one cathylate function, to yield the mono-cathylate (71).



(71)



(72)



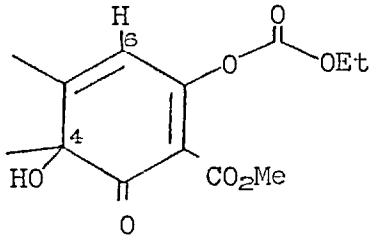
(73)

Dicathylate (72) was isolated by p.l.c. as a low melting colourless solid, m.p. 61° (light petroleum/ether). Nmr showed the presence of two ethyl groups and micro analysis confirmed the molecular formula $C_{16}H_{20}O_8$. Treating this dicathylate (72) with a calculated amount of sodium methoxide in methanol at 0° for five minutes, gave an excellent yield of mono-cathylate (71), m.p. 90° . No trace of the isomer (73) was seen (t.l.c.) . Supportive evidence for structure (71) will be presented later (see appendix), in the discussion on other ^{13}C nmr data of a series of cathylates.

At ambient temperature, cathylate (71) in dichloro methane did not react with diphenylseleninic anhydride. This is hardly surprising, since with the diphenol (50, R=OMe) hydrogen bonding forces to the methyl - ester are equally divided between both hydroxyl groups, whereas in the case of the mono-cathylate only the hydroxyl, that is expected to react with the anhydride, is available for bonding. A similar observation has been made by Marshall[48] .

Reaction of the phenolate anion (71), formed by sodiumhydride in THF under nitrogen, was still very slow with seleninic anhydride, and

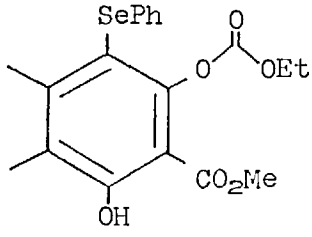
yielded 8% of the desired hydroxycyclohexadienone (74). Raising the reaction temperature to 55°, finally afforded 56% hydroxylated product (74) which could be extracted from a bicarbonate layer, after acidification with dilute, ice cold hydrochloric acid. The molecular ion was seen as peak at m/e 284, nmr spectrum clearly showed the quartet and triplet for the ethyl group, the upfield signal of the t-methyl group (C-4, τ 8.45), and the doublet for the vinylic proton (C-6) at τ 3.8 .



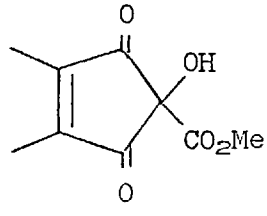
(74)

Micro analysis was in accord with structure (74).

Addition of the mono-cathylate (71) to seleninic anhydride in THF under reflux, yielded 45% of the hydroxydienone (74). The other product isolated after p.l.c. of the organic phase, was the selenated cathylate (75), which ran at the same R_f as starting material and could not be separated, even after multiple elution techniques. Nevertheless, the nmr spectrum clearly shows the presence of the PhSe- group and a molecul

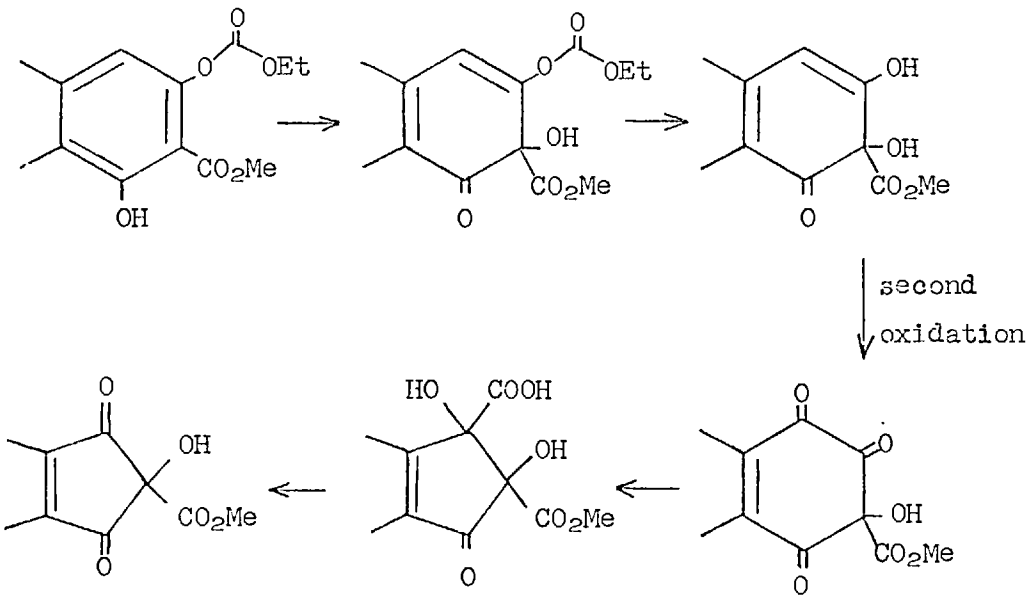


(75)



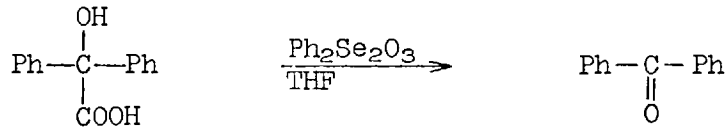
(76)

ion m/e 424 was seen in the mass spectrum. A minor by-product was isolated and purified by crystallisation. Nmr spectrum of which shows a singlet (6H) at τ 7.9 and a singlet (3H) at τ 6.3 . The ultraviolet spectrum with λ_{max} 255nm and an absorption of ν_{max} 1660-80 cm^{-1} in the infra red spectrum suggested a quinoid structure. With m/e 200 (M+2) and micro analysis fitting for a molecular formula $C_9H_{10}O_5$, the product was identified as the ring-contracted cyclopentene-dione (76), 10% yield. A mechanism for its formation may be postulated as follows:



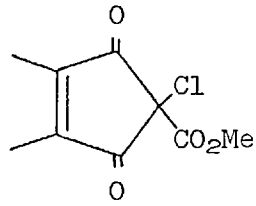
(76)

To test the final oxidation step of this mechanism, an α-hydroxy acid (benzilic acid (77)) was refluxed in THF with diphenylseleninic anhydride to give benzophenone (78) in 65% yield.



(77) (78)

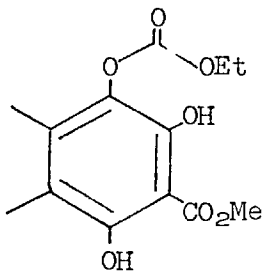
A similar ring-contraction of the ring A model quinones was reported by Bould[15] , who obtained the 2-chlorocyclopentendione ester (79) with N-chlorosuccinimide, NCS .



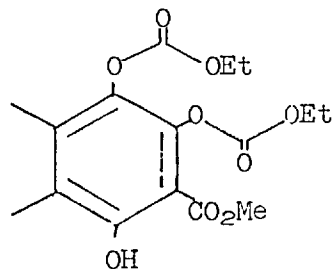
(79)

Thus seleninic anhydride can be used for converting α-hydroxy-acids to ketones.

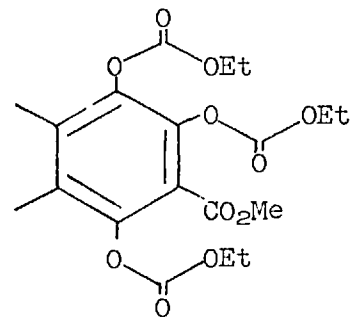
Attempts were made to synthesise the model cathylate (80).



(80)



(81)

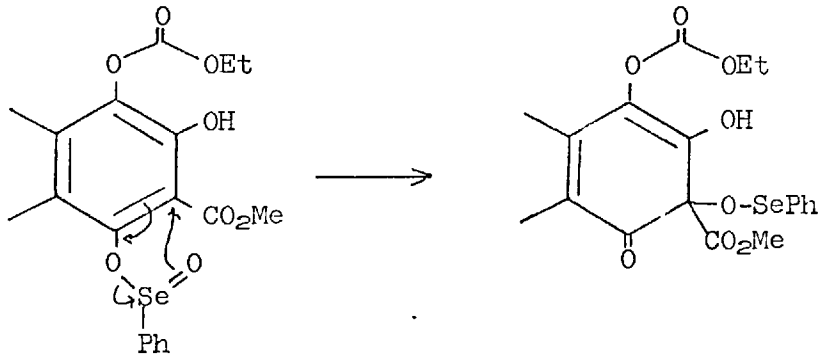


(82)

The triphenol (61, R=OMe) was reacted with ethyl chloroformate , (one third molar equivalent), at 0° in chloroform/pyridine. P.l.c. gave a 82% yield of the mono-cathylate (80); the nmr spectrum clearly showed the disappearance of the 3-hydroxyl group, which in the triphenol (61, R=OMe) showed up at τ 4.8; the 2- and 6-hydroxyl functions resonate at τ 0.6 and 0.0 . Further spectroscopic evidence for the structure (80) will be presented in the later discussion of the ^{13}C nmr data of model cathylates (appendix). Also formed in the reaction of the triphenol (61,

R=OMe) with ethyl chloroformate were 8% of the dicathylate (81), m.p. 88°, and 11% of the tricathylate (82). Both compounds were characterised by spectral and analytical data.

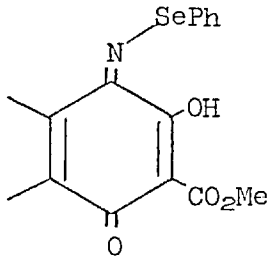
The mono-cathylate (80) was treated with sodium hydride in THF under nitrogen to form the phenolate anion. Subsequent treatment with diphenylseleninic anhydride resulted in the formation of a dienone, but there was evidence, that the oxidation had taken place in the wrong position and cleavage of the seleno-ester had not occured.



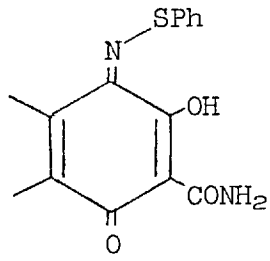
The cathylate function as well as the carbomethoxy ester and the ring carbonyl group were seen in the infra red spectrum at 1760, 1680 and 1645 cm^{-1}, respectively. The presence of selenium in the molecule was revealed by application of $PdCl_2/H_2SO_4$ spray on the t.l.c.-plate. This compound resisted all efforts of crystallisation and decomposed slowly, even when kept at low temperatures. Reduction, using alcoholic potassium metabisulphite solution yielded the triphenol (61, R=OMe).

By using hexamethyldisilyl amide, $HN(SiMe_3)_2$, a result, analogous to the 2,6-xylenol-4-cathylate reaction (67), was obtained. Seleninic anhydride caused immediate reaction and an orange compound was formed. P.l.c. resulted in the isolation of orange crystals, m.p. 132°. The molecular ion in the mass spectrum was seen at m/e 365, thus indicating both nitrogen and selenium present in the molecule. The structure

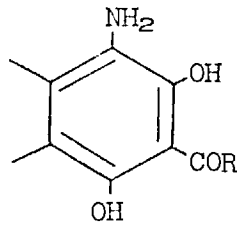
(83) was assigned on the basis of micro analytical data and comparison with similar compounds (84) and (85).



(83)



(84)

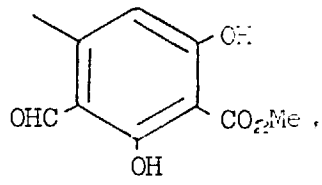


(85)

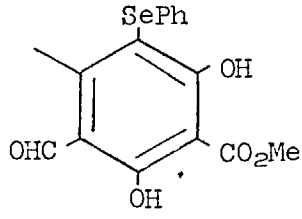
As opposed to Bateson[49], who had prepared the thioimine (84) of the amide, which could not be converted to the corresponding amino - phenol (85, R=NH_2), reduction of the selenoimine (83) proceeded with ease (Zn,AcOH) to the amine (85, R=OMe), m/e 227 (M^+).

Extension of this reaction sequence to the tetracyclic series, may present a useful pathway of introducing a C-4 dimethylamino group.

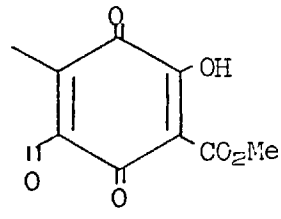
Attempted hydroxylation of related ring A model esters were briefly studied. Aldehyde (86) was readily available in these laboratories[15].



(86)



(87)



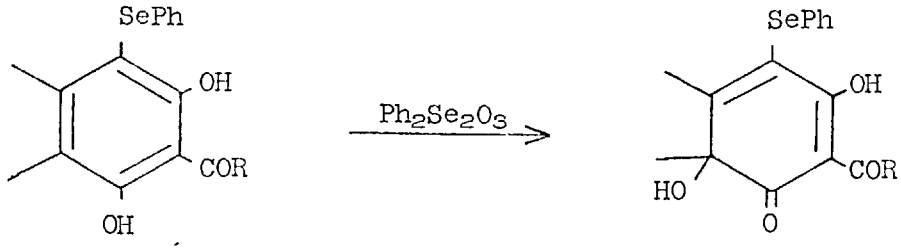
(88)

Treatment of the aldehyde-ester (86) with diphenylseleninic anhydride in dichloro methane gave a slightly more polar compound, which was isolated by p.l.c. . This product showed 5 aromatic protons in the nmr spectrum, and the incorporation of selenium could be seen on t.l.c. ($PdCl_2$

spray) and also by the characteristic pattern in the mass spectrum, m/e 366 . Recrystallisation from ethanol yielded pale yellow needles, m.p. 137° . Micro analysis supported structure (87), a compound obtained in 70% yield. A second, very polar compound could be isolated as a red oil, λ_{max} 272 nm, and seemed to be a product of quinoid nature. Nmr spectrum showed τ 7.55 (3H,s), 5.85 (3H,s), and -0.5 (H,s), which coincided with structure (88), a compound which had previously been synthesised by Bould[15] .

Repetition of this experiment with the phenolate anion of (86) , (formed from the phenol (86), using NaH in THF), yielded 72% of the selenide (87) and ca. 17% of impure quinone (88). Further studies of the aldehyde model (86) were abandoned.

It was now attempted to 'overoxidise' the selenide (21, R=OMe), to obtain the hydroxycyclohexadienone (89).



(21) (89)

Carrying this reaction out in the usual way, using NaH as base, starting material was only consumed after using excess reagent and warming to 50° . An oil was obtained after work up, which showed in the nmr the characteristic highfield (τ 8.45) peak for the tertiary methyl group of hydroxydienone (89). However, a strong singlet (6H) was noted at τ 7.85 which indicated two equivalent methyl groups on a double bond, i.e., the presence of quinone (59, R=OMe). This was supported by mass spectral data

showing a molecular ion at m/e 368 (hydroxydienone (39)) and m/e 210 (quinone (59, R=OMe)). Ultraviolet spectrum indicated λ_{max} 221, 238, 257, 272, 288, and 328 nm, clearly a mixture of both compounds. Owing to the high polarity, p.l.c. separation was impossible. Extraction with bicarbonate solution failed due to the acidic character of both pro - ducts.

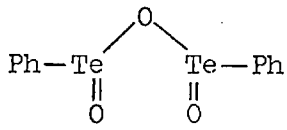
Extension of diphenylseleninic anhydride hydroxylations to tetracycline models, is the subject of intensive research currently pursued at Imperial College[49, 50].

Recently, diphenylseleninic anhydride has been applied to convert amines to ketones or aldehydes[51] . Diphenylseleninic anhydride promises to be of synthetic importance in the future.

iv) Synthesis of Diphenyltellurinic Anhydride.

The organic chemistry of tellurium compounds is still largely unexplored, although a number of reviews[52-58] have been published. Many tellurium containing substances reported in the literature are poorly characterised and many contradicting statements have been published, concerning the reactions of these compounds.

Our interest in diphenylseleninic anhydride prompted an attempt to synthesise the tellurium analogue (90).

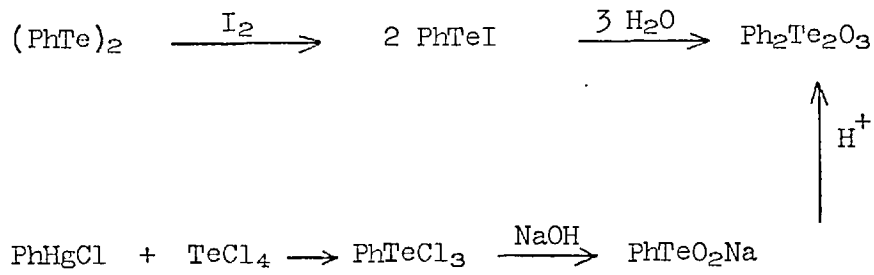


(90)

Compound (90) had been previously described by Petragnani[59] , although it was poorly characterised and none of its reactions have been

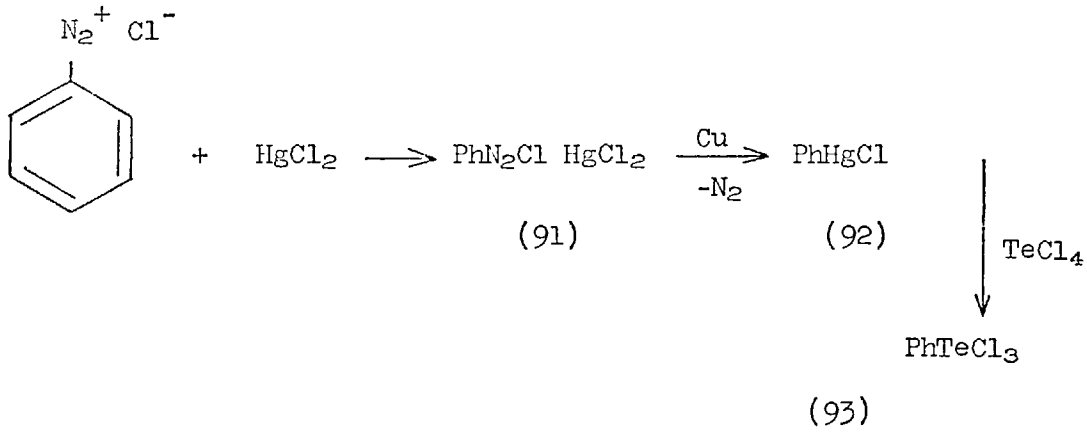
reported.

Preparation can be achieved either via the iodide upon hydrolysis[60] or via hydrolysis of the trihalide with alkali or bicarbonate[59] .



Both methods make one important point quite clear. The tellurinic anhydride can be obtained under aqueous conditions, i.e., no dehydration of an intermediate tellurinic acid was needed. Owing to this fact, the existence of phenyltellurinic acid is doubtful, although Lederer reports[61] its synthesis. The author's attempts to repeat Lederer's work, failed.

The anhydride (90) was prepared using the trihalide-hydrolysis method. Diazotised aniline was reacted with mercuric chloride, forming the complex (91), which was decomposed with copper powder at low temperatures[62] to give a high yield of phenylmercuric chloride (92), m.p. 250-2° . The chloride (92) in dioxan (distilled from sodium) was treated with an equimolar quantity of tellurium tetrachloride under reflux for one hour[63] . After cooling the solution, the mercuric chloride/dioxan complex could be filtered off. The remaining solution was concentrated to yield a solid, recrystallised from benzene, m.p. 216-8°, (lit. 215-8°)[64] , which was shown to be identical with phenyltelluro trichloride (93) 70% yield.



The trichloride (93) was hydrolysed with caustic soda, acidified, and the precipitated white powder (90) collected, m.p. 225-230° . Micro analysis and volumetric titration of this powder agreed with the values expected for the anhydride (90).

A number of control experiments disclosed, that tellurinic anhydride was much less reactive than its selenium equivalent. Ring A model ester (5) in THF was left untouched by the anhydride, and the sodium hydride/glyme method only yielded starting material after work up. Mesitol under a variety of conditions proved equally inert to the reagent.

An attempted oxidation of diphenyl disulphide to sulphoxide or sulphone, did not yield any new products. Neither cholesterol nor N,N'-dimethylaniline in boiling THF were affected by tellurinic anhydride. The reagent remained unchanged in ethanol under reflux.

Diphenyltellurinic anhydride (90) could be reduced with aqueous potassium metabisulphite to give diphenyl ditelluride (94), which was in accordance with the literature[65] . Ozonolysis of the ditelluride (94) by analogy with the literature preparation[3] of diphenylseleninic anhydride, yielded a white substance, which was proved to be identical with the tellurinic anhydride (90) by spectral data (infra red) and mixed melting point.

Oxidation of the ditelluride (94) with concentrated nitric acid, afforded a white solid, m.p. 225-238° . Micro analytical data revealed the presence of nitrogen, and a molecular formula $C_{24}H_{21}NO_7Te_4$ could be assigned. A possible structure is the nitric acid adduct (95).

PhTe—TePh

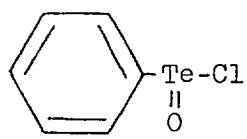
(94)

$2\ [PhTe(=O)OTePh] \cdot [HNO_3]$

(95)

Lederer[63] reports to have obtained phenyltellurinic acid, $PhTeO_2H$ under these conditions.

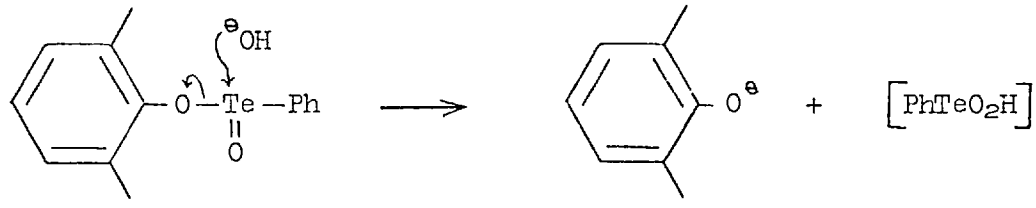
Since the anhydride (90) was so unreactive towards phenolic and unsaturated systems, reactions of the more reactive phenyltellurinyl chloride (96) were investigated. Phenyltelluro trichloride (93) was heated to reflux with distilled water as a solvent. After 15 minutes, the milky white solution gave phenyltellurinyl chloride (96), which was isolated in good yield, m.p. 250° (dec.)[59] . Micro analysis was in agreement with structure (96).



(96)

The stability of this compound is remarkable, since it remained unreacted in hot water, as opposed to phenylseleninyl chloride (34), which hydrolyses rapidly on contact with moisture.

Again the model ester (5) was recovered unchanged after addition of the chloride (96) in boiling THF. However, the phenolate of 2,6-xylenol in glyme seemed to react, as the chloride (96) was consumed. After work up (aqueous KH_2PO_4), the unchanged phenol and a quantitative amount of tellurinic anhydride (90) was obtained. This result can be explained in terms of initial ester formation (97), followed by hydrolysis to yield phenyltellurinic acid, which rapidly dehydrates to give the anhydride (90). Attempts to hydrolyse the anhydride to the acid failed . Rather remarkably the tellurinic anhydride may be recrystallised from hot water.

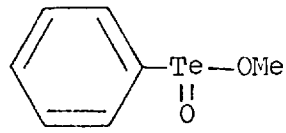


(97)

The sodium salt, $PhTeO_2Na$, may be formed easily by treating the anhydride with calculated amounts of NaOH, followed by precipitation with acetone. This sodium salt proved inert to refluxing ethyl chloroformate, which in the corresponding selenium case readily yields the ethyl ester.

Another attempt to prepare a tellurinic ester, $PhTeO_2Me$, using phenyltellurinyl chloride (96) and sodium methoxide was not very successful. After evaporation of the solution to dryness and evacuation for 5 hours, the nmr spectrum showed τ ($CDCl_3$) 1.9-2.35 (2H) and 2.4-2.8 (3H)

for the PhTe- group and 6.6 (3H,bs) for the Me- function., i.e., data consistent with structure (98) .



(98)

Isolation attempts, however, failed, giving phenyltellurinic anhydride (90) as the only characterisable product.

APPENDIX *

In the course of hydroxylation studies of tetracycline ring A model phenols, two important phenolethylcarbonates (71) and (80) (see page 79 and 82, as well as compound (4) and (5) of the table on the following page), have been synthesised from their phenolic precursors.

To verify their structures unambigeously, simpler model cathylates were synthesised, which allowed the assignement of the ring (aromatic) and side-chain (aliphatic) carbon atoms by ^{13}C nmr spectroscopy.

The 4-fluoromethylsalicylate (2) helped to identify all 6 ring carbon atoms by means of C-F coupling constants, which are characteristic for ortho, meta and para positions.

The structural proof for compound (4) is strongly supported by the fact, that C-4 and C-6 (meta to cathylate) differs, as expected, very little from the diphenol precursor, whereas the isomer with the cathylate function in the C-4 position would have shown significant shifts for these carbon atoms.

The chemical shift values for compound (5) were predicted on the basis of additivity tables[82] . All carbon atoms could be assigned for this compound, except for C-6 and C-7, which could not be differentiated.

It is worth noting the remarkable shift of the cathylate carbonyl group (C-7), which moves by 20ppm upfield, when in the vicinity of a carbomethoxy group (C-10 and C-11).

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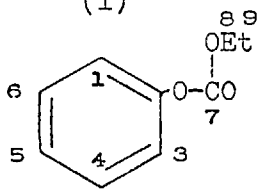
* Thanks are due to Dr. P.J.Mitchell, who assisted in compiling the ^{13}C nmr data.

^{13}C - NMR DATA OF MODEL CATHYLATES

(1)



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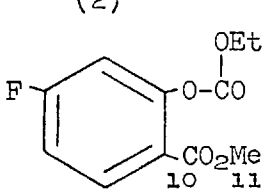
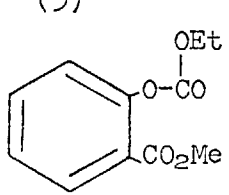
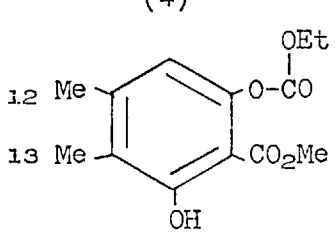


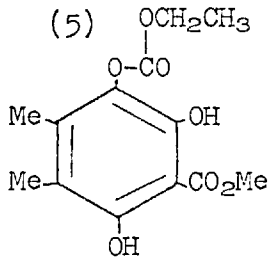
(3)



(4)



(5)



C

	observed	observed	J_{CF} [Hz]	predicted from (2) - effects of substituent F	observed	predicted from (3) + effects of substituents	observed	predicted	observed
1		34.40	25.20	47.30	46.26	40.60	39.83	59.21	53.46
2		75.32	12.0	73.92	73.64	72.32	70.93	67.17	62.17
3		42.58	4.40	47.08	46.02	31.38	27.11	21.10	20.98
4		56.67	10.5	55.27	56.80	82.77	83.40	72.88	72.10
5		36.48	22.0	49.38	49.12	46.28	44.10	38.98	38.31
6		88.28	255.9	53.88	54.67	64.88	69.07	56.48	78.72
7	95.50				76.25		76.00		76.45
8	-16.03				-12.09		-12.18		-12.04
9	-63.06				-62.63		-62.69		-62.83
10					87.76		92.70		92.80
11					-24.91		-24.48		-24.13
12							-56.23		-63.67
13							-65.49		-65.94

(Shifts are ppm from $CDCl_3$, 76.9ppm downfield tms, and negative values indicate upfield $CDCl_3$)

Experimental

Unless otherwise stated, the following data apply to experiments described in this thesis.

Melting points were measured on a Kofler Block and are uncorrected. Infra red spectra were taken on Unicam S.P. 200 or Perkin Elmer P.E. 157 spectrometers as liquid films or nujol mulls for solid samples. Nmr spectra were measured in deuterochloroform with Varian T 60 or XL 100 instruments, using tetramethylsilane as the internal standard. Ultraviolet spectra were recorded for ethanol solutions, using a Unicam S.P. 1800 spectrometer; s refers to a shoulder absorption. Mass spectra were obtained with an A.E.1 MS 9 at 70 eV.

Solvents were dried, when necessary, by standard techniques. Organic solutions from extractions were dried over sodium sulphate. Light petroleum refers to the fraction b.p. 60-80° . Silica gel used for chromatography (t.l.c. and p.l.c.) was Merck GF_{254} . Products from p.l.c. were isolated in order of decreasing R_f values. The abbreviation DPSA refers to diphenylseleninic anhydride.

The following abbreviations apply to nmr data:

s.....singlet

d.....doublet

t.....triplet

q.....quartet

bs.....broad singlet

m.....multiplet

Diphenyldiselenide

Prepared by the reaction of potassium selenocyanate, KSeCN, with diazotised aniline to yield phenylselenocyanate, PhSeCN, which was hydrolysed with ammonia gas in refluxing methanol. Method of Behagel and Seibert[66], m.p. 60-1°, 83% overall yield.

Diphenylseleninic anhydride, DPSA, (1).

a) Prepared by ozonolysis of diphenyldiselenide in carbon tetrachloride at -10° according to the method of Ayrey et al.[3], m.p. 164-5°, (lit. 165°).

b) Diphenyldiselenide was oxidised with concentrated nitric acid to yield the nitric ester of phenylseleninic acid, $PhSe(O)ONO_2$. Basification with caustic soda to pH 7 precipitates the free acid, m.p. 122° (lit. 122-4°)[67], which when heated to 120° *in vacuo* for 1 h yields the anhydride, m.p. 164°, 78% overall yield.

Phenylseleninyl chloride (34).

Freshly prepared diphenylseleninic anhydride (1) (100mg, 0.28mmol) in anhydrous ether (5ml) was cooled to -78° and thionyl chloride (600mg, 5.5mmol) was added dropwise over 15 min. The reaction mixture was allowed to warm to room temperature and finally was heated gently to boiling (35°). Solvent and excess thionyl chloride were removed under reduced pressure to afford pure phenylseleninyl chloride (34) (110mg,95%), m.p. 74-5° (lit. 72-5°)[3]. The compound was very sensitive to moisture and required manipulation in a dry box.

Reaction of 2,4-dimethylphenol with DPSA

2,4-Dimethylphenol (100mg, 0.82mmol) in dimethylformamide (2ml), was treated with seleninic anhydride (286mg, 0.8mmol) for 2 h at ambient temperature. The solution turned yellow due to formation of diphenyldiselenide. Isolation of the products by p.l.c. (silica, light pet-

roleum, ethyl acetate 30%) gave i) diphenyldiselenide (115mg), ii) recovered starting material (23mg), iii) the dimer of the o-hydroxydienone (10) (46mg, 40%), m.p. 236° (lit. 237-8°)[16], m/e 276 (M^+), and iv) p-hydroxydienone (9) (17mg, 15%) as colourless prisms, m.p. 73° (lit. 73-4°)[16], τ 2.7-3.8 (3H,m), 7.6 (H, bs), 7.9 (3H, d), and 8.2 (3H, s); m/e 138 (M^+).

Reaction of 2,6-dimethylphenol with DPSA

2,6-Dimethylphenol (105mg, 0.86mmol) in DMF (2ml) was treated with seleninic anhydride (292mg, 0.81mmol) for 2 h at room temperature. Chromatography on silica (light petroleum/ ethyl acetate 30%) afforded i) quinone (11) as red needles from light petroleum (30mg, 25%), m.p. 72°, (lit. 73°)[69], ν_{max} 1655 cm^{-1}, τ 3.3 (2H, s) and 7.75 (6H, s), ii) the tetramethylbiphenylquinone (12) as deep red solid (42mg, 40%), m.p. 211-14° from AcOH, (lit. 212-15°)[17], λ_{max} 254, 269(s), and 415 nm (ε 18,500 for 415nm), and iii) the o-hydroxydienone dimer (13) (12mg, 5%), a white crystalline substance, m.p. 183°, identical to an authentic sample[16].

Reaction of 2,4,6-trimethylphenol with DPSA

Mesitol (100mg, 0.73mmol) in dry dichloromethane (5ml) was treated with seleninic anhydride (180mg, 0.5mmol) with stirring at ambient temperature for 2 h. Chromatography on silica gel (light petroleum/ ethyl acetate 10%) afforded i) p-hydroxydienone (14) as colourless crystals (33mg, 30%), m.p. 123° (lit. 123-4°)[18b], m/e 152 (M^+) and ii) the dimer of the o-hydroxydienone (15) (54mg, 48%), m.p. 181° (lit. 181-3°)[70], m/e 304 (M^+).

2,6-Di-t-butyl-4-methylphenol with DPSA

2,6-Di-t-butyl-4-methylphenol (108mg, 0.49mmol) in dichloromethane (3ml) was stirred with seleninic anhydride (165mg, 0.46mmol) at room temperature. After 48 h, only 50% of starting phenol was consumed, to-

gether with no obvious major product (t.l.c.) .

p-t-Butylphenol with DPSA

p-t-Butylphenol (112mg, 0.75mmol) in dichloromethane (4ml) was treated with seleninic anhydride (174mg, 0.48mmol) at room temperature. T.l.c. indicated no reaction taking place.

Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (5, R^1=OMe, R^2=H).

Prepared by hydrogenation of methyl 2-formyl-p-orsellinate in glacial acetic acid over palladium on carbon catalyst by the method of Bould [15] , m.p. 108-9° (lit. 108°)[71] .

Reaction of Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (5) with DPSA.

Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (5, R^1=OMe, R^2=H) (100mg, 0.5mmol) in dry dichloromethane (5ml) was treated with diphenylseleninic anhydride (195mg, 0.54mmol) and stirred at room temperature. After 15 min the reaction was quenched with aqueous sodium bicarbonate (10ml, 10%) and extracted with dichloromethane (3 x 25ml). The dried extracts were evaporated under reduced pressure and the residue chromatographed on silica gel (light petroleum/ ethyl acetate 30%) to afford i) diphenyldiselenide (146mg, 86% based on DPSA) and ii) methyl 2,6-dihydroxy-3,4-dimethyl-5-phenylselenobenzoate (21, R=OMe) (99mg, 55%) as a pale yellow oil, which was triturated with methanol, m.p. 118-9° , ν_{max} 3450, 1690, and 1620 cm^{-1} , τ 7.9 (3H, s), 7.5(3H, s), 5.9 (3H, s), 2.8 (5H, m), and 0.3 and -0.6 (H, s, both exchanged by D_2O); λ_{max} 221, 238, 258, 270(s), and 338 nm (ε 21,500 , 17,560 , 18,720 , 12,650 , and 3600). (Found: C,54.35; H,4.49%. m/e 352 . $C_{16}H_{16}O_4Se$ requires C,54.64; H,4.59%; M,352).

The bicarbonate layer was acidified with N/10 hydrochloric acid and extracted with dichloromethane (3 x 25ml). The dried extracts were evaporated under reduced pressure and gave 2-carboxymethyl-3,4-dihydroxy-

4,5-dimethylcyclohexa-2,5-dienone (19, R=OMe) (38mg, 35%) , m.p. 111° (from ether/petroleum at 0°), ν_{max} 3450 and 1680(s) cm^{-1} , τ 8.6(3H, s), 7.8 (3H, d, J=1.6Hz), 6.1 (3H, s), and 4.0 (H, d, J=1.6Hz); λ_{max} 224, 278, and 284 nm (ε 11,200 , 2450, and 2000). (Found: C,56.9; H,5.79%; m/e 212. $C_{10}H_{12}O_5$ requires C,56.6; H,5.7%; M,212).

The bicarbonate-acidification-extraction method will be refered to as 'standard work up' in future experimental descriptions.

2,6-Dihydroxy-3,4-dimethylbenzamide with DPSA.

2,6-Dihydroxy-3,4-dimethylbenzamide (5, $R^1=NH_2$, $R^2=H$) (115mg, 0.64 mmol) in chloroform (4ml) was treated with diphenylseleninic anhydride (200mg, 0.55mmol) with stirring at room temperature. After 35 min the reaction was worked up in the standard way. The organic layer yielded after p.l.c. (silica, chloroform) i) diphenyldiselenide (152mg) , ii) 2,6-dihydroxy-3,4-dimethyl-5-phenylselenobenzamide (21, R=NH_2) (96mg, 45%), m.p. 175° (from ethanol); ν_{max} 3380, 3200, 1635, and 1595 cm^{-1}; τ 7.85 (3H, s), 7.55 (3H, s), and 2.8 (5H, m); λ_{max} 222,245, and 322 nm (ε 23,380 , 19,700 , and 3490). (Found: C,53.56; H,4.25; N,4.17%; m/e 337. $C_{15}H_{15}NO_3Se$ requires C,53.58; H,4.5; N,4.17%; M,337), and iii) 2-carbamoyl-3-hydroxy-5,6-dimethylbenzoquinone (20, R=NH_2) (25mg, 20%), m.p. 165-6° [20] , ν_{max} 3400, 3310, and 1650 cm^{-1}; λ_{max} 272 and 412 nm (ε 21,800 and 770); m/e 195 (M^+).

The bicarbonate layer upon acidification yielded 2-carbamoyl-3,4-dihydroxy-4,5-dimethylcyclohexa-2,5-dienone (19, R=NH_2) as pale yellow solid (32mg, 25%), m.p. 146-7° (lit. 146°)[20] , ν_{max} 3450, 3380, 3200, and 1685 cm^{-1} ; m/e 197 (M^+).

2-Hydroxynaphthalene with DPSA

2-Hydroxynaphthalene (144mg, 1mmol) in tetrahydrofuran (4ml) was treated with diphenylseleninic anhydride (360mg, 1mmol) at ambient tem-

perature. After 4 h reaction time, preparative layer chromatography (silica, light petroleum/ ether 35%) gave i) diphenyldiselenide (280mg), ii) 1-phenylseleno-2-hydroxynaphthalene (25) (132mg, 44%), m.p. 77-8°, (from methanol), ν_{max} 3450 cm^{-1} ; τ 1.7-3.2 (m); λ_{max} 225, 245, 276, 288(s), 322, and 335 (ε 25,500 , 27,000 , 18,350 , 16,200 , 8150, and 11,900). (Found: C,64.14; H,4.33%; m/e 300. $C_{16}H_{12}OSe$ requires C,64.22; H,4.43%; M,300), and iii) the 1,2-naphthoquinone (24) as yellow-orange crystals from ether (68mg, 43%), m.p. 146° (lit. 145-7°)[72] ; λ_{max} 250, 340, and 405 nm (ε 20,000 , 2350, and 2400); m/e 158 (M^+).

Addition of 2-Hydroxynaphthalene to DPSA.

To a stirred suspension of diphenylseleninic anhydride (360mg, 1mmol) in THF (5ml) at ambient temperature was added a solution of 2-hydroxy - naphthalene (144mg, 1mmol) in THF (2ml) over 20 min . The reaction mixture rapidly turned orange, and after a further 10 min, filtration (removal of DPSA and phenylseleninic acid) leaves a clear orange solution, which was evaporated under reduced pressure. Addition of ether (3ml) , triturated the quinone (24), which was removed by filtration (120mg, 76%), m.p. 145-6° (mixed m.p. 146°). The etherial mother liquors showed traces of selenated naphthol and diphenyldiselenide (t.l.c.) .

Repetition of this experiment under a nitrogen atmosphere, did not change the yields.

Addition of 1-Hydroxynaphthalene to DPSA.

To a stirred suspension of diphenylseleninic anhydride (360mg , 1mmol) in THF (3ml) at room temperature was added a solution of 1-hydroxy . .thalene(144mg, 1mmol) in THF (1ml) over 15 min . The yellow reaction mixture was worked up in the previously described manner and gave i) 1-hydroxy-2-phenylselenonaphthalene (26), sublimed at (2mm) as pale yellow nuggets (69mg, 23%), m.p. 61-2°, ν_{max} 3450 cm^{-1} ; λ_{max} 224,245,

259(s), 304, 317(s), and 322nm (ε 28,000 , 32,150 , 18,050 , 7000, 5200, and 4150). (Found: C,64.2; H,4.2%; m/e 300. $C_{16}H_{12}OSe$ requires C,64.22; H,4.43%; M,300), and ii) the 1,2-naphthoquinone (24) as yellow-orange solid (87mg, 55%), m.p. 145-6° (mixed m.p. 144°).

Sodium Phenylseleninate

Phenylseleninic acid (190mg, 1mmol) was dissolved in a solution of sodium hydroxide (44mg, 1.1mmol in 2ml water) and acetone (10ml) was added after 5 min. The reaction mixture was cooled to -10° for 10 min, and the precipitated sodium salt (202mg, 90.5%) was isolated by filtration, washed with acetone and dried in vacuo.

Lithium Phenylseleninate

Phenylseleninic acid (190mg, 1mmol) was added to a solution of lithium hydroxide (24mg, 1.1mmol) and water (2ml). After 10 min , solvent was removed under reduced pressure and the remaining lithium phenylseleninate (182mg, 92%) was washed with ether (3 x 5ml) and dried in vacuo.

Phenylselenenyl chloride, PhSeCl.

Diphenyldiselenide (300mg, 0.96mmol) in ether (25ml) was cooled to 0° and sulphuryl chloride (130mg, 0.96mmol) added slowly. The reaction mixture was allowed to warm to room temperature, filtered (to remove insoluble $PhSeCl_3$), and after removal of the solvent under reduced pressure gave the chloride (340mg, 93%), m.p. 60° (lit. 60-1°)[3] , from petroleum.

Diphenylselenoseleninate (22).

Phenylselenenyl chloride (191mg, 1mmol) in THF (5ml) was added to sodium phenylseleninate (213mg, 1mmol), with careful exclusion of moisture. The initial orange-brown colour quickly turned yellow, however , after filtration to remove NaCl, only diphenyldiselenide and phenylse-

leninic acid (m.p. 122°) could be detected. A similar attempt with the more soluble lithium salt failed, even when glyme or dioxan were substituted for THF. Further reactions with the reagent (22) were therefore carried out without isolation, i.e., in situ.

2-Hydroxynaphthalene with phenylseleninate (22).

2-Hydroxynaphthalene (144mg, 1mmol) in THF (2ml) was added to phenylselenoseleninate (22) (350mg, 1.02mmol), prepared in situ, under anhydrous conditions. After 2 h, chromatography on silica gel (light petroleum/ ether 35%), yielded 1-phenylseleno-2-hydroxynaphthalene (25) (200 mg, 67%), m.p. 77° (mixed m.p. 77°).

Repeating this reaction for longer periods of time (48 h), gave after chromatography on silica gel (light petroleum/ ether 35%) i) the 1-phenylseleno-2-hydroxynaphthalene (25) (130mg, 43%), m.p. 77°, ii) 1-chloro-2-hydroxynaphthalene (36mg, 20%), m.p. 70° (from aqueous MeOH), (lit. m.p. 70°)[73], m/e 180,178 (M^+), and iii) 4-phenylseleno-1,2-naphthoquinone (27) as black plates from ether (102mg, 23%), m.p. 172°(dec), ν_{max} 1660-80 cm^{-1} ; λ_{max} 272, 325, and 344 nm (ε 23,500 , 14,200 , and 16,300); τ 3.2 (H, d) and 2.85-1.95 (9H, m). (Found: C,61.36; H,3.4% ; m/e 314. $C_{16}H_{10}O_2Se$ requires C,61.35; H,3.22%; M,314).

p-t-Butylphenol with DPSA.

p-t-Butylphenol (150mg, 1mmol) in THF (2ml) was added to a stirred suspension of diphenylseleninic anhydride (360mg, 1mmol) in THF (2ml) . The reaction mixture was initially warmed to 45° for 30 min, then left to react at ambient temperature for 24 h. Chromatography (silica, light petroleum/ ether 25%) gave i) 4-t-butyl-6-(1-hydroxy-2-phenylseleno-4-t-butylbenzene)-1,2-benzoquinone (28) as red needles from ethanol (49mg, 22%), m.p. 210-15° , ν_{max} 1660(s) cm^{-1} ; λ_{max} 227, 254, 288(s), and 378 nm (ε 21,320 , 24,340 , 13,450 , and 1120); τ 8.85 (18H, m), 4.32

(H, d, J=1.1Hz), 4.28 (H, d, J=1.1Hz), and 3.85-3.35 (7H, m). (Found: C,66.66; H,5.98%; m/e 468. $C_{26}H_{28}O_2Se$ requires C,66.8; H,6.04%; M,468), and ii) 4-t-butyl-6-phenylseleno-1,2-benzoquinone (29) (96mg, 30%), m.p. 120° (from ether) as deep red violet crystals, ν_{max} 1665(s) cm^{-1}; λ_{max} 246 and 372 (ε 26,150 and 1420); τ 9.18 (9H, s), 4.8 (H, d, J=1.2Hz), 4.55 (H, d, J=1.2Hz). (Found: C,59.99; H,4.98%; m/e 322 (M+2); $C_{16}H_{16}O_2Se$ requires C,60.19; H,5.05%).

General Method for Phenolate Formation.

The formation of phenolate anions used for future experiments was achieved by the following method. The phenol (100-200mg) was dissolved in glyme or THF (distilled from CaH_2, 5ml) under nitrogen at room temperature, and sodium hydride (80% in a suspension of oil, one molar equivalent), previously washed with dry solvent, was added with continuous stirring. The reaction was allowed to proceed for 15 min before oxidising the phenolate in situ with diphenylseleninic anhydride.

2,4-Dimethylphenolate with DPSA.

Sodium 2,4-dimethylphenolate (from 2,4-xylenol (106mg, 0.87mmol), NaH (25mg, 80%)) in benzene (10ml) was treated with diphenylseleninic anhydride (350mg, 0.97mmol) at room temperature in a nitrogen atmosphere. After 2 h, the reaction mixture was quenched with aqueous potassium dihydrogen-phosphate (5ml, 10%), extracted with chloroform (3 x 25ml) and evaporated under reduced pressure. The resulting oil was chromatographed (silica, light petroleum/ ether 25%) to yield i) diphenyldiselenide (280mg) and ii) the dimer of o-hydroxydienone (10) as colourless crystals (53mg, 45%), m.p. 235-7°(lit. 237-8°)[16] , λ_{max} 225, 270, and 315 nm.

2,6-Dimethylphenolate with DPSA.

Sodium 2,6-dimethylphenolate (from 2,6-xylenol (122mg, 1mmol), NaH

(31mg, 80%)) in THF (6ml) was treated with seleninic anhydride (360mg, 1mmol) at room temperature under a nitrogen atmosphere. After 2 h the reaction mixture wasquenched with aqueous potassium dihydrogenphosphate (5ml, 10%) and extracted with chloroform (3 x 25ml). The dried organic extracts (Na_2SO_4) were evaporated under reduced pressure and the resulting oil yielded after silica chromatography (light petroleum/ ether 35%), the dimer of the o-hydroxydienone (13) as white prisms (61mg, 44%), m.p. 183° (lit. 183-4°)[16] .

2,4,6-Trimethylphenolate with DPSA.

Sodium 2,4,6-trimethylphenolate (from mesitol (136mg, 1mmol), NaH (32mg, 80%)) in THF (5ml) was treated with diphenylseleninic anhydride (365mg, 1.03mmol) at room temperature under nitrogen. After 2 h, the reaction was quenched with aqueous potassium dihydrogenphosphate (8ml, 10%), extracted with chloroform (3 x 25ml) and evaporated under reduced pressure. The resulting oil was purified by chromatography (silica, light petroleum/ ether 25%) and gave i) diphenyldiselenide (291mg) and ii) the dimer of o-hydroxydienone (15) as white crystals (84mg, 55%), m.p. 182° (lit. 181-3°)[70] , mixed m.p. 182° .

Ring A model phenolate ester with DPSA.

Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (5, R^1=OMe, R^2=H) (147mg, 0.75mmol) in glyme (5ml) was treated with sodium hydride (24mg, 80%, one equivalent) to form the mono-anion, under a nitrogen atmosphere at room temperature. DPSA (280mg, 0.93mmol) was added after 10 min and the reaction was quenched after stirring for a further 30 min (aqueous KH_2PO_4, 10ml, 10%), extracted with chloroform (3 x 25ml) and worked up by the bicarbonate method. The organic layer was chromatographed after evaporation of solvents (silica, light petroleum/ ether 35%), giving i) diphenyldiselenide (215mg) and ii) the phenylseleno-derivative (21, R=OMe)

as pale yellow needles (46mg, 17%), m.p. 118°, mixed m.p. 118° . The bicarbonate layer was acidified, extracted with chloroform and finally evaporated under reduced pressure to yield 2-carbomethoxy-3,4-dihydroxy-4,5-dimethylcyclohexa-2,5-dienone (19, R=OMe) as colourless crystals (119mg, 75%), m.p. 111° , mixed m.p. 111° ; τ 8.6 (3H, s), 7.8 (3H, d, J=1.6Hz), 6.1 (3H, s), and 4.0 (H, d, J=1.6Hz).

Ring A model phenolate amide with DPSA.

2,6-Dihydroxy-3,4-dimethylbenzamide (5, $R^1=NH_2$, $R^2=H$) (108mg, 0.6 mmol) in glyme (5ml) was treated with sodium hydride (18mg, 80%, one molar equivalent) to form the mono-anion, at room temperature under nitrogen. Diphenylseleninic anhydride (216mg, 0.6mmol) was added after 10 min and after further 12 h the reaction mixture was quenched with KH_2PO_4 (10ml, 10%), extracted with chloroform (3 x 30ml) and worked up in the usual way. The organic layer was evaporated under reduced pressure and showed only trace amounts of selenated phenol (21, $R=NH_2$) and quinone (20, $R=NH_2$) (t.l.c. and nmr). The bicarbonate layer,after work up, afforded the o-hydroxydienone (19, $R=NH_2$) as pink crystals (81mg, 68%), m.p. 146-7° (lit. 146°)[20] , mixed m.p. 145-7° .

1-Naphtholate with DPSA.

Sodium 1-naphtholate (from 1-hydroxynaphthalene (101mg, 0.7mmol) and NaH (21mg, 80%)) in THF (4ml) was reacted with diphenylseleninic anhydride (252mg, 0.7mmol) for 2 h under nitrogen. After work up in the usual way, chromatography on silica gel (light petroleum/ ether 35%) yielded i) the selenated naphthol (26) as pale yellow needles (76mg, 38%), m.p. 61° , mixed m.p. 61° , ii) 1,2-naphthoquinone (24) as orange crystals (38mg, 36%), m.p. 146°, mixed m.p. 145-6°, and iii) 2-hydroxy-1,4-naphthoquinone (5mg, 4%), a yellow substance, m.p. 188-9° (lit. 189°)[24] , m/e 174 (M^+).

2-Naphtholate with DPSA.

Sodium 2-naphtholate (from 2-hydroxynaphthalene (115mg, 0.8mmol) and NaH (24mg, 80%)) in tetrahydrofuran (5ml) was reacted with diphenylseleninic anhydride (298mg, 0.83mmol) for 2 h under nitrogen at room temperature. Work up in the usual way, followed by chromatography on silica gel (light petroleum/ ether 35%) yielded i) 1-phenylseleno-2-naphthol (25) as yellowish crystals (101mg, 42%), m.p. 77-8° , mixed m.p. 77° , and ii) 1,2-naphthoquinone (24) as orange crystals (63mg, 48%), m.p. 145° , mixed m.p. 145° .

Cholestrerol acetate and DPSA.

When cholesterol acetate (30) (120mg, 0.28mmol) in benzene (3ml) was reacted with diphenylseleninic anhydride (110mg, 0.3mmol) for 2 h under reflux, no reaction was observed (t.l.c.) .

β-Amyrin acetate and DPSA.

When β-amyrin acetate (129mg, 0.28mmol) in benzene (4ml) was treated with diphenylseleninic anhydride (120mg, 0.33mmol) for 2 h under reflux, no reaction occured (t.l.c.) .

Acenaphthalene with DPSA.

Acenaphthalene (139mg, 0.91mmol) in dichloromethane (4ml) was treated with diphenylseleninic anhydride (300mg, 0.85mmol) and after 2 h no reaction was seen by t.l.c. .

trans-Stilbene with DPSA.

trans-Stilbene (145mg, 0.8mmol) in THF (4ml) was heated with seleninic anhydride (350mg, 0.97mmol) for 2 h under reflux; by t.l.c. no reaction had occured.

N,N'-Dimethylaniline with DPSA.

N,N'-Dimethylaniline (121mg, 1mmol) in tetrahydrofuran (4ml) was heated with diphenylseleninic anhydride (360mg, 1mmol) to boiling.

After 6 h, chromatography on silica gel (light petroleum/ ether 25%) showed large amounts of starting material and a new substance at similar R_f . 4-Phenylseleno-N,N'-dimethylaniline (33) was isolated as yellow oil (60mg, 22%), λ_{max} 213 and 274 nm (ε 18,000 and 21,300); τ 2.4-3.5 (9H, m) and 7.1 (6H,s); m/e 277 (M^+). The oil resisted all attempts at crystallisation and slowly decomposed to N,N'-dimethylaniline and diphenyldiselenide.

2,4-Dimethylphenol with phenylseleninyl chloride (34).

2,4-Xylenol (125mg, 1.02mmol) in tetrahydrofuran (3ml) was treated with freshly prepared phenylseleninyl chloride (34) (210mg, 1.01mmol) . A fast reaction occured at room temperature, to yield a number of selenated products (t.l.c., $PdCl_2$-spray). No major product could be isolated.

Ring A model ester with phenylseleninyl chloride.

Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (5, R^1=OMe, R^2=H) (150mg, 0.75mmol) in dichloromethane (5ml) was treated with phenylseleninyl chloride (34) (165mg, 0.8mmol) at room temperature. A fast reaction took place to yield, upon work up in the usual way, followed by chromatography on silica gel (light petroleum/ ether 35%), the 5-phenylseleno-derivative (21, R=OMe) as pale yellow crystals (146mg, 55%), m.p. 118° , mixed m.p. 118° . The o-hydroxydienone (19, R=OMe) was only observed in trace amounts in the nmr spectrum of the total reaction mixture.

Phenylseleninyl fluoride (35).

Phenylselenenyl chloride (500mg, 2.62mmol), in a polyethylene container, was cooled to -5° and a stream of hydrogen fluoride gas was condensed on it for 15 min with strict exclusion of moisture. After the gas inlet tube was removed, the reaction was allowed to proceed for another 105 min . The reaction mixture was then flushed with a strong stream of dry nitrogen gas, to remove excess hydrogen fluoride and any hydrogen

chloride formed. The remaining brown oil (425mg) was taken up in carbon tetrachloride (25ml), filtered, and treated with ozone at -10° for 6 h. A white precipitate which formed was removed by filtration, washed with cold acetone (3 x 2ml), and dried *in vacuo* at 80° . Phenylseleninyl - fluoride (35) was obtained as a white powder (310mg, 62% overall yield), m.p. 138°(dec.), ^{19}F nmr showed the selenium-fluorine bond as a sharp singlet at 2030.0 Hz, 75.6 ppm to highfield of $CFCl_3$. (Found: C,35.78; H,2.66; F,9.56%; m/e 192. C_6H_5FOSe requires C,37.72; H,2.64; F,9.94%; M,192).

α-Phenylselenoacetone (36).[26,28]

Phenylseleninyl fluoride (35) (100mg, 0.52mmol) was heated with acetone (10ml) under reflux. T.l.c. indicated the formation of a new product, α-phenylselenoacetone (36), which was isolated by chromatography on silica gel (light petroleum/ benzene 20%) as a pale yellow oil (66mg, 60%), ν_{max} 1720 cm^{-1} , τ 7.75 (3H, s), 6.5 (2H, s), and 2.6 (5H, s); m/e 214 (M^+).

2,4-Dimethylphenolate with phenylseleninyl fluoride.

Sodium 2,4-dimethylphenolate (from 2,4-xylenol (122mg, 1mmol) and sodium hydride (24mg, 80%)) in benzene (5ml) was treated with phenylseleninyl chloride (35) (195mg, 1.1mmol) for 2 h. Work up in the usual way followed by preparative layer chromatography on silica gel, yielded two compounds containing selenium ($PdCl_2$-spray). The first substance showed a ratio aliphatic:aromatic protons 6:11 in the nmr, indicating the introduction of two PhSe- groups; the second compound had a ratio aliphatic to aromatic protons 6:17, indicating three PhSe- groups. However, the substances could not be crystallised and were not characterised further.

p-Tolylsulphinyl chloride (37).

Prepared from sodium p-tolylsulphinate and thionyl chloride according to the method of Arcus et al.[29] .

Di-p-tolylsulphinyl sulphone (38).

Prepared from p-tolylsulphinic acid by the method of Knoevenagel[30] , m.p. 75° .

2,4-Dimethylphenol with SeO_2.

Sodium 2,4-dimethylphenolate (from 2,4-xylenol (128mg, 1.05mmol) and sodium hydride (33mg, 80%)) in THF (4ml) was heated with SeO_2 (500 mg) under reflux for 3 h. Nmr spectral analysis and t.l.c. showed only 2,4-xylenol after work up.

Ring A model ester with SeO_2/H_2O_2.

Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (5, R^1=OMe, R^2=H) (150mg, 0.75mmol) in t-butanol (5ml) was treated with hydrogen peroxide (90% , 0.2ml) and selenium dioxide (200mg) under exclusion of light. The solution was stirred at 35° for 12 h, poured into ice water (15ml), and extracted with dichloromethane (3 x 70ml). Evaporation of the dried CH_2Cl_2 layer gave a yellow oil, which upon chromatography on silica gel (light petroleum/ ethyl acetate 30%) yielded, as a major product, dimethyl maleic anhydride (39) as white crystals (32mg, 31%), m.p. 91° , (mixed m.p. with authentic sample 91-2°), ν_{max} 1740-60 cm^{-1} , τ 7.9(s).

2,6-Dihydroxy-3,4-dimethylbenzamide with SeO_2/H_2O_2.

Phenol (5, R^1=NH_2, R^2=H) (181mg, 1mmol) in t-butanol (6ml) was treated with hydrogen peroxide (90%, 0.2ml) and selenium dioxide (200mg) under exclusion of light. The solution was stirred at 35° for 12 h, poured into ice water (25ml), and extracted with dichloromethane (3 x 60ml). Evaporation of the dried CH_2Cl_2 layer gave an oil, which after chromatography on silica gel (chloroform/ methanol 10%) afforded 1-carbamoyl-

3,4-dimethyl-2,5-dioxo-1-hydroxypent-3-ene (40) (27mg, 15%), m.p. 238°, ν_{max} 3330, 3220, 1690, 1650, and 1600 cm^{-1} ; τ 7.85 (s); m/e 183 (M^+).

Ring A model ester with sodium metaperiodate.

Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (5, R^1=OMe, R^2=H) (196mg, 1mmol) in methanol/water (15ml) was treated with $NaIO_4$ (300mg) in water (2ml) and the reaction mixture was warmed on a steam bath for 6 h. Extraction of the cooled mixture with dichloromethane (3 x 50ml) afforded a pale yellow oil, which after chromatography on silica gel (light petroleum/ ethyl acetate 30%) gave i) starting material (118mg, 60%) and ii) 3,3'-dicarbomethoxy-2,2',4,4',-tetrahydroxy-5,5',6,6'-tetramethylbiphenyl (41) (12mg, 12%), m.p. 214-5° ; ν_{max} 3400, 1660(s), and 1630 cm^{-1} ; τ 7.95 (6H, s), 7.75 (6H, s), 5.95 (6H, s), 0.9 (2H, s), and -0.8 (2H, s, both exchanged with D_2O). (Found: C,61.28; H,5.88%; m/e 390 . $C_{20}H_{22}O_8$ requires C,61.53; H,5.68%; M, 390).

Sodium bis-trimethylsilylamide (42).

Prepared according to the method of Wannagat and Niederprüm[32], in quantitative yield.

4,6-Dimethyl-1,2-benzoquinone-monophenylseleno-2-imine (43).

2,4-Xylenol (98mg, 0.8mmol) in toluene (5ml) was treated with sodium bis-trimethylsilylamide (42) (300mg, excess) at room temperature under a nitrogen atmosphere. After 15 min, diphenylseleninic anhydride (300mg, 0.83mmol) was added to the stirred mixture. The solution immediately turned red and after 30 min was quenched with water (10ml), extracted with chloroform (3 x 25ml), and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a red oil, which was purified by column chromatography (alumina, benzene), giving i) diphenyldiselenide and ii) the selenoimine (43) as deep red needles (206mg, 91%), m.p. 120-1° (from ether at -78°), ν_{max} [illegible] cm^{-1} ; τ (CCl_4) 7.85 (6H, s),

3.2-2.2 (2H, m), and 2.8-2.5 (5H, m); $\lambda_{max}(CCl_4)$ 253, 281(s), 430(s), and 486 nm (ε 9450, 5200, 6820, and 14,170) . (Found: C,57.63; H,4.53; N,4.81%; m/e 291. $C_{14}H_{13}NOSe$ requires C,57.92; H,4.51; N,4.85%; M, 291).

2,6-Dimethylphenol and sodium bistrimethylsilylamide/ DPSA.

2,6-Xylenol (108mg, 0.88mmol) in toluene (10ml) was treated with sodium bis-trimethylsilylamide (42) (250mg, excess) under nitrogen at ambient temperature with constant stirring. Diphenylseleninic anhydride (300mg, 0.83mmol) was added in small portions and allowed to react for 30 min. The reaction mixture was quenched with water (10ml), extracted with chloroform (3 x 30ml), and after evaporation of the solvent, chromatography on silica (light petroleum/ ethyl acetate 30%) yielded the o-hydroxydienone dimer (13) as colourless crystals (19mg, 33%), m.p. 193°, ν_{max} 1740, 1730, and 1695 cm^{-1} ; m/e 276 (M^+), and 2,6-dimethyl-4-phenylselenophenol (46) , isolated as a pale yellow oil (37mg, 15%), ν_{max} 3450 cm^{-1} ; τ (CCl_4) 7.6 (6H, s), 5.3 (H, s), 3.1 (2H ,s),and 2.7 (5H, m); m/e 278 (M^+). Compound (46) resisted all attempts of crystallisation and decomposed slowly at room temperature.

2,4,6-Trimethylphenol with sodium bis-trimethylsilylamide/ DPSA.

Mesitol (136mg, 1mmol) in toluene (8ml) was treated with sodium bis-trimethylsilylamide (42) (350mg, excess) under nitrogen. Diphenylseleninic anhydride (365mg, 1.04mmol) was added and the reaction was stirred for a further 30 min, quenched with water (10ml), and extracted with chloroform (3 x 25ml). The dried extracts were evaporated under reduced pressure and chromatographed on silica (light petroleum/ ether), affording the dimer of o-hydroxydienone (15) (64mg, 42%), m.p. 182° (mixed m.p. 181-3°). Numerous by-products were also formed in low yield, which were not isolated.

1,2-Naphthoquinone-monophenylseleno-2-imine (47).

1-Hydroxynaphthalene (136mg, 0.95mmol) in THF (3ml) was treated with lithium bis-trimethylsilylamide (167mg, 1mmol) at ambient temperature for 10 min under nitrogen. Diphenylseleninic anhydride (120mg, 0.33mmol) was added and the reaction mixture was stirred for a further 1 h. Work up in the usual way gave after chromatography (silica, light petroleum/ chloroform), i) diphenyldiselenide (10mg), m.p. 60° , ii) 1-hydroxy - 2-phenylselenonaphthalene(26)(43mg,12%), m.p. 61° , mixed m.p. 60-2° , and iii) the selenoimine (47) as red plates (122mg, 42%), m.p. 164° , ν_{max} 1660 cm^{-1} ; m/e 313 (M^+) .

Treatment of the selenoimine (47) (100mg, 0.32mmol) with zinc (200 mg) in acetic acid/ acetic anhydride (5ml) for 15 min afforded, after work up, 2-amino-1-hydroxynaphthalene-N,O-diacetate as pale yellow prisms (69mg, 89%), m.p. 129° (lit. 129-30°)[35] .

1,2-Naphthoquinone-monophenylseleno-1-imine (48).

2-Hydroxynaphthalene (172mg, 1.2mmol) in glyme (3ml) was treated with lithium bis-trimethylsilylamide (180mg, 1.2mmol) at room temperature under nitrogen. After 10 min, diphenylseleninic anhydride (460mg, 1.28 mmol) was added. After 60 min, work up in the usual manner gave upon chromatography on silica (light petroleum/ chloroform), i) diphenyldiselenide (45mg), ii) 2-hydroxy-1-phenylselenonaphthalene (25) as yellow needles (87mg, 25%) , m.p. 76-7° (from ethanol), mixed m.p. 77° , and iii) the selenoimine (48) as red crystaline solid (65mg, 20%), m.p. 126-7° , ν_{max} 1660 cm^{-1} ; λ_{max} 228, 264, 277, 286, 320, 332, and 456 nm (ε 28,000 , 11,000 , 12,500 , 7580, 8200, and 2200); m/e 313 (M^+).

The selenoimine (48) (65mg, 0.2mmol) was treated with zinc powder (200mg) in acetic acid/ acetic anhydride (5ml) for 15 min to yield the 2-amino-1-hydroxynaphthalene-N,O- acetate (46mg, 91%), m.p. 205-6° ,

(lit. 206°)[35].

Treatment of the imine (48) with zinc and acetic acid under a nitrogen atmosphere, yielded 2-amino-1-hydroxynaphthalene in good yield (90%), m.p. 150°(lit. 150-1°)[74], ν_{max} 3450, 3330, 1635, and 1610 cm^{-1}. m/e 159 (M^+).

Diethyl azodicarboxylate (52).

Prepared from the hydrazo-precursor by oxidation with chlorine[75], b.p. 109°, 13mm, in 83% yield.

Methyl 2,6-dihydroxy-4-methyl-3-(N-hydrazodicarboxydiethyl ester)-benzoate (43, R^1=H, R^2= $EtCO_2NHNCO_2Et$).

Methyl orsellinate (100mg, 0.55mmol) in dichloromethane (5ml) was stirred with diethyl dicarboxylate (52) (170mg, 0.98mmol) for 3 days while heating under reflux. Preparative layer chromatography on silica (light petroleum/ ethyl acetate) gave i) the mono-hydrazodicarboxylate (53, R^1=H, R^1=$EtCO_2NHNCO_2Et$) as colourless crystals (88mg, 45%), m.p. 158-9°, ν_{max} 3350(b), 1780, and 1710 cm^{-1}; τ 8.4-8.0 (6H, m), 7.85 (3H, s), 6.1 (3H, s), 6.0-5.5 (4H, m), and 3.1 (H, s); λ_{max} 218, 223, 255, 263(s), and 319nm (ε 12,590 , 13,200 , 6650, 4600, and 1500). (Found: C,50.67; H,5.44; N,7.68%; m/e 356. $C_{15}H_{20}N_2O_8$ requires C,50.56; H,5.66; N,7.86%; M, 356), and ii) the dihydrazodicarboxylate (53, R^1=R^2=$EtCO_2NH$-NCO_2Et) as white prisms (140mg, 48%), m.p. 209-10° (from ether), ν_{max} 3400, 3280, 3190, 1735, 1710-1700, and 1625 cm^{-1}; λ_{max} 222, 253, 263, (s), and 318nm (ε 25,300 , 9050, 7180, and 3000); τ 8.4-8.0 (12H, m), 7.9 (3H, s), 6.15 (3H, s), and 6.0-5.4 (8H, m). (Found : C,47.42; H,5.71; N,10.53%; m/e 530. $C_{21}H_{30}N_4O_{12}$ requires C,47.56; H,5.7; N,10.56%; M, 530).

2,6-Dihydroxy-3,4-dimethyl-5-(N-hydrazodicarboxydiethyl ester)-methyl-benzoate (54, R=OMe).

The ester (50, R=OMe) (104mg, 0.73mmol) in dichloromethane (10ml) was treated with diethyl azodicarboxylate (52) (120mg, 0.68mmol) at reflux for 6 h. Chromatography on silica (light petroleum/ ethyl acetate 30%) afforded the hydrazo ester (54, R=OMe) as white crystals (122mg, 62%), m.p. 146° (from methanol), ν_{max} 3400, 3250, 1725, 1700, 1665, and 1630 cm^{-1} ; λ_{max} 226,259,267(s),and 332 nm (ε 19,950 , 11,700 , 9650, and 3800); τ 8.7 (6H, t, J=3.7Hz), 7.9 (3H, s), 7.6 (3H, s), 5.95 (3H, s), 5.8-5.5 (4H, q, J=3.7Hz), and 2.7 (H, s). (Found: C,51.65; H,5.98, N, 7.58%; m/e 370. $C_{16}H_{22}N_2O_8$ requires C,51.89; H,5.99; N,7.56%; M, 370).

2,6-Dihydroxy-3,4-dimethyl-5-(N-hydrazodicarboxydiethyl ester)-benzamide (54, R=NH_2).

Amide (50, R=NH_2) (101mg, 0.55mmol) in methanol (10ml) was treated with diethyldiazocarboxylate (52) (103mg, 0.59mmol) at room temperature for 1 h with constant stirring. The hydrazo ester (54, R=NH_2) crystallised from the reaction and was removed by filtration as yellow-orange needles (127mg, 64%), m.p. 247-8° , ν_{max} 3460, 3340, 3200, 1715(b), 1695, and 1635 cm^{-1} ; λ_{max} 228, 256, 264(s), and 322 nm (ε18,400 , 9940, 7630, and 4790); τ (D^6MSO) 8.7 (6H ,m), 7.9 (3H, s), 7.5 (3H, s), 5.9 (4H, m), and 2.7 (H, s). (Found: C,50.78; H,5.87; N,11.93%; m/e 355. $C_{15}H_{21}N_3O_7$ requires C,50.7; H,5.96; N,11.83%; M, 355).

N-4-Phenyl-1,2,4-triazoline-3,5-dione (55), Cookson's Reagent.

Prepared from 4-phenylurazole by oxidation with $...O_4$, by the method of Stickler et al.[76] , m.p. 160-80° (dec.) .

Methyl 2,6-dihydroxy-4-methyl-3-(N-4-phenylurazole)-...nzoate (53, R^1=H, R^2=4-phenylurazole).

The diphenol (..., $R^1=R^2$=H) (182mg, 1mmol) in dic...romethane (10ml) was treated with Cookson's Reagent (55) (200mg, 1.14mm...l) at room temperature for 6 h. P.l.c. on silica gel (light petroleum/ ethy... acetate 30%)

yielded the mono-urazole (53, R^1=H, R^2=4-phenylurazole) as yellowish plates (314mg, 88%), m.p. 237-8° ; ν_{max} 3430, 3190, 1765, 1700(s), and 1645 cm^{-1} , λ_{max} 224, 256, 266(s), and 332 nm (ε 26,150 , 12,000 , 9680, and 4760); τ 7.85 (3H, s), 6.05 (3H, s), 5.15 (H, s), and 2.9-2.5 (5H, m). (Found C,57.02; H,4.3; N,11.75%; m/e 357. $C_{17}H_{15}N_3O_6$ requires C,57.14; H,4.23; N,11.76%; M, 357).

Methyl 2,6-dihydroxy-3,4-dimethyl-5-(N-4-phenylurazole)-benzoate (56, R=OMe).

The ring A ester (50, R=OMe) (110mg, 0.56mmol) in dichloromethane (15ml) was treated under reflux together with Cookson's Reagent (55) (84mg, 0.48mmol) for 30 min. On cooling the reaction mixture in ice, the urazole (56, R=OMe) was obtained as white long needles (146mg, 70%), m.p. 248° (from acetone/methanol); ν_{max} 3460, 3230, 1780, 1720, 1685, and 1645 cm^{-1} ; λ_{max} 227(s), 258, 267(s), and 333 nm (ε 26,000 , 12,150 , 9685, and 4390). (Found: C,57.97; H,4.67; N,11.35%; m/e 371. $C_{18}H_{17}N_3O_6$ requires C,58.22; H,4.61; N,11.32%; M, 371).

2,6-Dihydroxy-3,4-dimethyl-5-(N-4-phenylurazole)-benzamide (56, R=NH_2).

The urazole-ester (56, R=OMe) (100mg, 0.27mmol) was added to THF (2ml.), saturated with ammonia gas. Ammonia solution (0.88, 2ml) was added and the reaction mixture was stirred at room temperature for 24 h, under an atmosphere of NH_3 . Evaporation to dryness yielded the urazole-amide (56, R=NH_2), as light brown solid (95mg, 99%), m.p. 234-5° (acetone/methanol); ν_{max} 3420, 3250, 1720, 1670, and 1630 cm^{-1} ; τ (D^6MSO) 8.0 (6H, s), 2.6 (5H, s), and 1.8 (2H, s); λ_{max} 226(s), 255(s), 260(s), and 319 nm (ε 28,900 , 9500, 7130, and 4000). (Found: C,57.32; H,4.77; N, 15.42%; m/e 356. $C_{17}H_{16}N_4O_5$ requires C,57.3; H,4.53; N,15.72%; M, 356). Correct micro analysis could only be obtained after drying at 130° for 3 days in vacuo.

2,6-Dihydroxy-4-methylbenzamide (57) with Cookson's Reagent (55).

The benzamide (57) (160mg, 0.96mmol) in THF (25ml) was treated with Cookson's Reagent (55) (177mg, 1.1mmol) under reflux for 5 h. The solution was evaporated under reduced pressure and the residue revealed a number of products as shown by t.l.c. . Chromatography (silica, ethyl acetate/ chloroform 35%) gave as the most polar band a brown gum (10mg, 5%), which exhibited a peak m/e 342 in the mass spectrum corresponding to $C_{16}H_{14}N_4O_5$, the mono urazole. Purification of this compound could not be achieved by standard techniques.

Methyl 2,6-dihydroxy-3,4-dimethyl-5-nitrobenzoate (58).

The ester (50, R=OMe) (105mg, 0.54mmol) in dichloromethane (25ml) with anhydrous Na_2SO_4 (10g) was cooled to -10° and a slow stream of N_2O_4 was passed through the solution. When all the starting material was consumed (1 h), p.l.c. yielded i) the nitro-ester (58) as deep yellow needles (72mg, 59%), m.p. 129° (from ethanol), ν_{max} 3450, 1680, and 1650 cm^{-1} ; τ 7.9 (3H, s), 7.7 (3H, s), and 5.9 (3H,s); λ_{max} 256, 266(s), and 331 nm (ε 10,200 , 7300, and 2700). (Found: C,50.04; H,4.6; N,5.57%; m/e 241. $C_{10}H_{11}NO_6$ requires C,49.8; H,4.6; N,5.81%; M, 241), and ii) the quinone (59, R=OMe) as red plates (40mg, 35%), m.p. 67-8° (mixed m.p. with authentic sample 67°), ν_{max} 1680, 1660, and 1645 cm^{-1}.

Fremy's Salt (60)[39].

Prepared by the method of Bould[15], orange needles, % yield.

4-Carbomethoxy-3-hydroxy-6-methyl-2,5-toluquinone (59, R=OMe).

Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (50, R=OMe) (335mg, 1.7 mmol) in ethanol (50ml) was added to a solution of Fremy's salt (60) (8g, excess) in water (120ml),containing sodium acetate (m, 10ml). After stirring for 18 h, the solution was acidified with dilute hydrochloric acid (N/10, 35ml), extracted with chloroform (3 x 50ml), and evaporated und

reduced pressure to yield quinone (59, R=OMe) as an orange oil, which was triturated with light petroleum (338mg, 96%), m.p. 68° (lit. 68°)[15], ν_{max} 1680, 1660, and 1645 cm^{-1} .

Methyl 2,3,6-trihydroxy-4,5-dimethylbenzoate (61, R=OMe).

a) 4-Carbomethoxy-3-hydroxy-6-methyl-2,5-toluquinone (59, R=OMe) (195mg, 0.93mmol) was dissolved in dry benzene (3ml) and hydrogenated over 10% palladium on barium sulphate until uptake of hydrogen ceased. Removal of the catalyst, followed by evaporation of the solvent yielded a pale yellow solid, sublimed at 80°, 10^{-4}mm Hg, as nuggets (193mg, 91%), m.p. 133-4° (lit. 134°)[15] , ν_{max} 3450 and 1675 cm^{-1} , τ 7.85 (3H, s), 7.7 (3H, s), 5.95 (3H, s), 4.8 (H, s), 0.7 (H, s), and 0.3 (H, s, all three exchanged by D_2O) .

b)Stirring the toluquinone (59, R=OMe) with methanol/water, yielded upon addition of aqueous sodium metabisulphite, followed by normal work up procedures after 30 min, the triphenol (61, R=OMe) in excellent yield (97%).

2-Carbamoyl-3-hydroxy-5,6-dimethylbenzoquinone (59, R=NH_2).

The benzamide (50, R=NH_2) (181mg, 1mmol) in t-butanol (10ml) was treated with ammonium molybdate (25mg) and hydrogen peroxide (30%, 10ml). After 30 min, the orange solution was diluted with water (50ml) and extracted with chloroform (3 x 50ml). Evaporation of the solvent, followed by recrystallisation from benzene, afforded the quinone (59, R=NH_2) as red prisms (183mg, 94%), m.p. 165° (lit. 164-6°)[20] , ν_{max} 3400, 3320, and 1650 cm^{-1} , λ_{max} 270 and 414 nm (ε 21,300 and 790).

4,5-Dimethyl-2,3,6-trihydroxybenzamide (61, R=NH_2).

The quinoid amide (59, R=NH_2) (195mg, 1mmol) was dissolved in ethyl acetate (5ml) and hydrogenated over 10% palladium on barium sulphate , until uptake of hydrogen ceased. Removal of the catalyst, followed by

evaporation of the solvent under reduced pressure, yielded the trihydroxyamide (61, R=NH_2) as a yellowish-green solid, sublimed at 120°, 10^{-4}mm Hg, (183 mg, 93%), m.p. 110°(dec.); ν_{max} 3450, 3250, 1680, and 1630 cm^{-1}; τ 7.85 (bs);(Found: C,54.82; H,5.48; N,6.9%; m/e 197. $C_9H_{11}NO_4$ requires C,54.82; H,5.62; N,7.1%; M, 197).

Triphenol (61, R=OMe) with DPSA.

The triphenol (61, R=OMe) (110mg, 0.52mmol) was treated under nitrogen with diphenylseleninic anhydride (180mg, 0.5mmol). After 10 min the reaction was queched with water (10ml), extracted with dichloromethane (3 x 20ml), and evaporated to yield red prisms from light petroleum, (105mg, 98%), m.p. 68°, identical with an authentic sample of the quinone (59, R=OMe) by m.p. .

Triphenol (61, R=NH_2) with DPSA.

The trihydroxyamide (61, R=NH_2) (125mg, 0.63mmol) in THF (5ml) was treated with diphenylseleninic anhydride (185mg, 0.52mmol) under a nitrogen atmosphere. After 10 min, the reaction was quenched with water (10ml) and work up in the usual manner gave the quinoid amide (59, R=NH_2) (112mg, 85%), m.p. 165° (mixed m.p. 165-6°).

Methyl 4,5-dimethyl-2,3,6-trihydroxybenzoate (61, R=OMe) with phosgene.

The triphenol (61, R=OMe) (500mg, 2.34mmol) in toluene (15ml) and dry pyridine (3ml) were cooled to 0° under a nitrogen atmosphere. A toluene solution of phosgene (5%, 6ml) was added and stirred for 10 min. The reaction mixture was poured into ice cold hydrochloric acid (N/10, 25ml) and the organic material was extracted with ether (3 x 75ml). Evaporation of the solvent afforded a colourless solid, which was recrystallised from benzene giving the cyclic carbonate (63, R=OMe) (530mg, 89%), m.p. 167° (lit. 167-8°); ν_{max} 3200, 1835, and 1680 cm^{-1}.

N,N'-Carbonyldiimidazole

Prepared from phosgene and imidazole in tetrahydrofuran by the

method of Staab and Wendel[40].

4,5-Dimethyl-2,3,6-trihydroxybenzamide-2,3-carbonate (63, R=NH_2).

The trihydroxyamide (61, R=NH_2) (82mg, 0.42mmol) in THF (5ml) was treated with N,N'-carbonyldiimidazole (80mg, 0.48mmol) in tetrahydrofuran (2ml) at 0° for 1 h. The reaction mixture was quenched with dilute, ice cold hydrochloric acid (N/50, 15ml) and extracted with chloroform, (3 x 50ml), to yield after solvent evaporation the cyclic carbonate (63, R=NH_2) as light yellow solid (72mg, 80%), m.p. 248° (from CH_2Cl_2/$CHCl_3$), ν_{max} 3400, 3250, 1810, 1675, and 1635 cm^{-1} ; τ 7.9 (6H, s), and 1.9 (H, s, exchanged with D_2O). λ_{max} 233, 268, and 344 nm (ε 22,300 , 21,200 , and 6800). (Found C,53.76; H,4.08; N,6.16%; m/e 223. $C_{10}H_9NO_5$ requires C,53.82; H,4.06; N,6.28%; M, 223).

Carbonate (63, R=OMe) with NaH/glyme.

Carbonate ester (63, R=OMe) (123mg, 0.52mmol) in glyme (5ml) was treated with sodium hydride (24mg, 80%) under nitrogen. After 15 min , the reaction was quenched with aqueous potassium bisulphate (10%, 15ml) and extracted with chloroform (3 x 50ml) to afford the carbonate (63, R=OMe) unchanged (115mg, 93%), m.p. 167° (mixed m.p. 167°) .

Carbonate (63, R=NH_2) with NaH/glyme.

Carbonate amide (63, R=NH_2) (141mg, 0.63mmol) in glyme (5ml) was treated with sodium hydride (28mg, 80%) under nitrogen. After 15 min , the reaction was quenched with aqueous potassium bisulphite (10%, 15ml) and extracted with chloroform (3 x 50ml) to afford the carbonate (63, R=NH_2) (121mg, 94%) unchanged, m.p. 248° (mixed m.p. 246-8°).

Reaction of Carbonate (63, R=OMe) anion with DPSA.

a) The carbonate (63, R=OMe) (103mg, 0.43mmol) in glyme (5ml) was treated with sodium hydride (20mg, 80%) under nitrogen at ambient temperature. After 15 min, diphenylseleninic anhydride (180mg, 0.5mmol) was

added. Work up in the usual way afforded quinone (59, R=OMe) (63mg, 78%), m.p. 68° .

b) The carbonate (63, R=OMe) (75mg, 0.31mmol) in tetrahydrofuran (5ml) was treated with sodium diisopropylamide (53mg), followed by diphenylselenine anhydride (120mg, 0.33mmol). After 2 h, work up in the usual manner resulted in a pale yellow oil (64mg), ν_{max} 1720 and 1675 cm^{-1} ; τ 7.9 (6H, s), 5.95 (3H, s), and -1.0 (H, s); λ_{max} 274 nm (ε 9600). The molecular ion appeared at m/e 256 corresponding to $C_{11}H_{12}O_7$.

4,5-Dimethyl-2,3,6-trihydroxymethylbenzoate-2,3-phenylboronate (65).

Methyl 4,5-dimethyl-2,3,6-trihydroxybenzoate (61, R=OMe) (60mg, 0.28 mmol) in ethanol (5ml) was treated with phenylboronic acid, $PhB(OH)_2$ (34mg, 0.28mmol) and stirred for 2 h at room temperature. Removal of the solvent afforded a pale yellow solid, the boronate (65, R=OMe) (59mg , 71%), recrystallised from dichloromethane, m.p. 135-6°, ν_{max} 3180, 1675, 1650,1440, and 1320 cm^{-1} ; τ 7.9 (3H, s), 7.75 (3H, bs), 5.95 (3H, s), 2.7 (5H, s) and 0.6 (H, s). (Found: C,64.35; H,5.14%; m/e 298. $C_{16}H_{15}BO_5$ requires C,64.46; H,5.07%; M, 298).

4,5-Dimethyl-2,3-6-trihydroxybenzamide-2,3-phenylboronate (65, R=NH_2).

4,5-Dimethyl-2,3,6-trihydroxybenzamide (61, R=NH_2) (100mg, 0.51mmol) in ethanol (5ml) was treated with phenylboronic acid (62mg, 0.51mmol) , for 2 h under constant stirring. The boronate (65, R=NH_2) crystallised from the reaction mixture and was removed by filtration as white needles (97mg, 67%), washed with ethanol , m.p. 266-8° (benzene), ν_{max} 3300, 3150, 1730, 1440, and 1320 cm^{-1} ; τ 7.9 (6H, s), 2.65 (5H, m), and 1.9 (H, s, exchanged with D_2O); λ_{max} 220, 272, and 405 nm (ε 13,000 , 17,000 , and 800). (Found: C,63.66; H,5.1; N,4.75%; m/e 283. $C_{15}H_{14}BNO_4$ requires C,63.6; H,4.98; N,4.95%; M, 283). Micro analytical data were only correct after drying the sample at 135° for 5 days in vacuo.

Boronate (65) with NaH/glyme.

The boronate (65 (115mg, 0.41mmol) in glyme (3ml) was treated with sodium hydride (24mg, 80%) under nitrogen. Work up with either water or N/10 hydrochloric acid caused decomposition of the starting material (65) and only work up with aqueous KH_2PO_4 buffer (10%) allowed recovery of the boronate (73%).

Boronate (65, R=OMe) anion with DPSA.

The boronate ester (65, R=OMe) (95mg, 0.34mmol) in glyme (3ml) was treated with sodium hydride (15mg, 80%) under nitrogen at room temperature to form the phenolate anion. After 15 min, diphenylseleninic anhydride (160mg, 0.44mmol) was added and the reaction turned red in colour after 25 min. Work up in the usual manner gave the quinone (59, R=OMe) as red plates (63mg, 88%), m.p. 68° (mixed m.p. 66-8°).Other minor products were seen by t.l.c., but not isolated.

Nitrobenzoate (58) with DPSA.

Methyl 2,6-dihydroxy-3,4-dimethyl-5-nitrobenzoate (58) (112mg, 0.46 mmol) in dimethylformamide (2ml) was treated with diphenylseleninic anhydride (120mg, 0.33mmol) at room temperature . After 30 min DMF was removed under reduced pressure. Extraction with sodium bicarbonate solution (10%, 15ml) yielded phenylseleninic acid (160mg), m.p. 121-2° (mixed m.p. 121°). The organic layer contained no major compounds (t.l.c.).

Urazole ester (56, R=OMe) with DPSA.

Methyl 2,6-dihydroxy-3,4-dimethyl-5-(N-4-phenylurazole)benzoate (56, R=OMe) (110mg, 0.3mmol) in pyridine (2ml) was treated with seleninic anhydride (135mg, 0.37mmol) at ambient temperature. After 1 h pyridine was removed under reduced pressure. The resulting solid was washed with benzene, which removed all diphenyldiselenide (81mg). The remaining material was recrystallised from methanol to yield brown crystals (95mg, 85%), m.p.

194-6° , ν_{max} 3450, 1760, 1710-1700, and 1630 cm^{-1} ; λ_{max} 220, 257, 266(s), 321(s) nm (not quant.); m/e 387 (M^+) corresponds to the hydroxydienone $C_{18}H_{17}N_3O_7$, however, the compound could not be obtained in a pure state for analysis.

2,6-Dimethyl-1,4-benzoquinone.

2,6-Xylenol (5.3g, 43.44mmol) in t-butanol (20ml) was treated with selenium dioxide (500mg) and hydrogen peroxide (30%, 3ml) for 18 h. Extraction with chloroform (3 x 150ml) gave the benzoquinone (5.4g, 91%) as yellow needles, m.p. 72° (from benzene/light petroleum), (lit. 71-2°)[77] , ν_{max} 1660 and 1630 cm^{-1}, τ 7.9 (6H, s) and 3.4 (2H, s).

2,6-Dimethyl-1,4-hydroquinone.

2,6-Dimethyl-1,4-benzoquinone (5g, 36.23mmol) in ethyl acetate (85 ml) was hydrogenated with 10% palladium on barium sulphate as catalyst. When hydrogen uptake ceased, the catalyst was removed and the solvent evaporated under reduced pressure. The hydroquinone was isolated as pale yellow plates (4.7g, 93%), m.p. 150° (from chloroform),(lit.149-150°)[78] , ν_{max} 3360 and 1620 cm^{-1} .

2,6-Dimethyl-4-methoxyphenol (66).

Prepared from 2,6-dimethyl-1,4-hydroquinone with potassium carbonate and dimethyl sulphate, according to the method of Magnus[79] , m.p. 77° (lit. 77°)[44] , ν_{max} 3350 and 1625 cm^{-1} , 62% yield.

2,6-Dimethyl-4-methoxyphenol anion (66) with DPSA.

The methoxyphenol (66) (152mg, 1mmol) in glyme (3ml) was treated with sodium hydride (29mg, 80%) under nitrogen, and diphenylseleninic anhydride (360mg, 1mmol) was added after 10 min , when the reaction mixture had been cooled to 0° (ice). Work up in the usual manner afforded after 30 min 2,6-dimethyl-1,4-benzoquinone (70.4mg, 51%), m.p. 71-2°, (mixed m.p. 71°). At lower temperatures (-20°) a minor [illegible]-product (3mg)

was isolated, λ_{max} 253 nm (ε 28,000); m/e 304 (M^+). This compound was possibly the adduct between quinone and o-hydroxydienone, $C_{17}H_{20}O_5$.

2,6-Dimethyl-4-(ethylcarbonate)phenol (67).

2,6-Dimethyl-1,4-hydroquinone (300mg, 2.17mmol) in dichloromethane (10ml) was treated with ethylchloroformate (310mg, 2.85mmol) and pyridine (1ml) at room temperature for 25 min. Chromatography on silica gel (light petroleum/ ether 40%) gave i) the mono-cathylate (67) as macro crystals (274mg, 60%), m.p. 87-8° (from light petroleum), ν_{max} 3490 and 1750 cm^{-1} ; λ_{max} 218 and 279 nm (ε 7535 and 2230); τ 8.6 (3H, t, J=7.5Hz), 7.85 (6H,s), 5.6 (2H, q, J=7.5Hz), 5.15 (H, s, exchanged with D_2O), and 3.3 (2H, s). (Found: C,62.65; H,6.58%; m/e 210. $C_{11}H_{14}O_4$ requires C,62.85; H,6.71%; M, 210), ii) the dicathylate (68) as rhombic crystals (122mg, 20%), m.p. 43-4° (light petroleum); ν_{max} 1760-50 cm^{-1}; λ_{max} 264 nm (ε 365); τ 8.65 (6H, t, J=7.2Hz), 7.85 (6H, s), 5.75 (4H, q, J=7.2Hz), and 3.2 (2H, s), (Found C,59.55; H,6.37%; m/e 282. $C_{14}H_{18}O_6$ requires C,59.57; H,6.43%; M, 282), and iii) the 3,5-dimethylmono-cathylate (69), colourless crystals from light petroleum (68mg, 15%), m.p.74°, ν_{max} 3400 and 1760 cm^{-1} ; τ 8.65 (3H, t, J=7.4Hz), 7.85 (6H, s), 5.7 (2H, q, J=7.4Hz), 4.75 (H, s, exchanged with D_2O), and 3.3 (2H, s); λ_{max} 218 and 279 nm (ε 7300 and 2380). (Found: C,62.72; H,6.64%; m/e 210 . $C_{11}H_{14}O_4$ requires C,62.85; H,6.71%; M, 210).

Cathylate (67) with NaH/ DPSA.

Cathylate (67) (135mg, 0.64mmol) in glyme (5ml) was reacted with sodium hydride (22mg, 80%) and subsequently treated with seleninic anhydride (230mg, 0.64mmol) at a temperature range from -78° to 25° . Removal of small aliquots, worked up with aqueous $KHSO_4$ and extracted with chloroform, showed only unreacted starting material (t.l.c.) .

Replacement of sodium hydride with potassium hydride, caused upon reaction with diphenylseleninic anhydride extensive decomposition.

Cathylate (67) with lithium bis-trimethylsilylamide/ DPSA.

Cathylate (67) (93mg, 0.44mmol) in tetrahydrofuran (3ml) was treated with lithium bis-trimethylsilylamide (85mg) under nitrogen at room temperature. After 10 min the mixture was cooled to 0° and diphenylseleninic anhydride (185mg, 0.51mmol) was added to the stirred mixture. After 20 min the orange-red solution was quenched with aqueous KH_2PO_4 (10%, 15ml), extracted with chloroform (3 x 50ml), and evaporated to dryness. Chromatography on silica (light petroleum/ ether 25%) yielded i) diphenyldiselenide (78mg) and ii) 2,6-dimethyl-1,4-benzoquinone-monophenylseleno-4-imine (70) as orange-red needles (110mg, 85%); m.p. 140-1° (from ether at -78°); ν_{max} 1635 cm^{-1} ; λ_{max} 243, 261, 274(s), 356, and 448 nm (ε 13,400 , 13,460 , 12,600 , 2650, and 10,900); τ 8.0 (3H, d), 3.0 (2H, m), and 2.8-2.2 (5H, m). (Found: C,57.69; H,4.42; N,4.88%; m/e 291. $C_{14}H_{13}NOSe$ requires C,57.92; H,4.51; N,4.85%; M, 291).

Dicathylate (68) with lithium bis-trimethylsilylamide / DPSA.

The dicathylate (68) (120mg, 0.43mmol) in tetrahydrofuran (3ml) was treated with lithium bis-trimethylsilylamide (60mg) followed by diphenylseleninic anhydride (150mg, 0.42mmol). Work up after 2 h yielded starting material (68) (115mg, 95%), m.p. 43° (mixed m.p. 43-4°).

Ring A model ester (50, R=OMe) with ethylchloroformate.

Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (50, R=OMe) (392mg, 2mmol) in chloroform (10ml, passed through alumina column) and pyridine (1ml) was treated with ethylchloroformate (434mg, 4mmol) at room temperature. After 1 h the reaction mixture was quenched with cold hydrochloric acid (N/10, 15ml), extracted with dichloromethane (2 x 50ml), and evaporated to dryness. The resulting oil crystallised from light petroleum/ ether

at -5° . The dicathylate (72) was obtained as colourless prisms (612mg, 89%), m.p. 61°, ν_{max} 1775, 1735, and 1635 cm^{-1}; λ_{max} 215, 256, and 316 nm (ε 27,200 , 7,620 , and 4200); τ 8.7-8.4 (6H, t, J=7.6Hz), 7.85 (3H, s), 7.65 (3H, s), 6.15 (3H, s), 5.85-5.4 (4H, q, J=7.6Hz), and 3.0 (H, s). (Found: C,56.68; H,5.84%; m/e 340. $C_{16}H_{20}O_8$ requires C,56.47; H,5.92%; M, 340).

Dicathylate (72) with sodium methoxide.

Sodium metal (11mg, 0.48mmol) was dissolved in methanol (3ml) at 0° under a nitrogen atmosphere. A solution of dicathylate (72) (258mg, 0.96 mmol) in methanol (9ml) was added and reaction was allowed to proceed for 5 min. After work up with hydrochloric acid (N/10, 15ml) and extraction with dichloromethane (3 x 25ml) gave methyl 3,4-dimethyl-6-(ethyl-carbonate)-2-hydroxybenzoate (71) as large rhombic crystals (192mg, 96%) m.p. 90° (from light petroleum / ether, 0°); ν_{max} 3300, 1765, 1675, and 1630 cm^{-1} ; λ_{max} 213, 254, and 312 nm (ε 27,800 , 7850, and 4220); τ 8.7-8.5 (3H, t, J=7Hz), 7.95 (3H,s), 7.8 (3H, s), 6.05 (3H, s), 5.85-5.45 (2H, q, J=7Hz), 3.25 (H, s), and -1.0 (H, s, exchanged with D_2O) . (Found: C,58.18; H,6.06%; m/e 268. $C_{13}H_{16}O_6$ requires C,58.2; H,6.01%; M, 268). (For ^{13}C data see appendix).

Monocathylate (71) with DPSA.

The monocathylate (71) (117mg, 0.44mmol) in dichloromethane (3ml) was treated with diphenylseleninic anhydride (180mg, 0.5mmol) at ambient temperature for 3 h. No reaction was detected by t.l.c. .

Monocathylate (71) with NaH/ DPSA.

The monocathylate (71) (107mg, 0.4mmol) in tetrahydrofuran (2ml) was treated with sodium hydride (10mg, 80%) under a nitrogen atmosphere. After 10 min diphenylseleninic anhydride (160mg, 0.45mmol) was added and the temperature raised to 55° for 2 h. Work up in the usual manner,

afforded from the organic layer after chromatography, i) diphenyldiselenide (83mg) and ii) a mixture of starting material (71) and selenated cathylate (75), which could not be separated, even after multiple elution techniques. The mass spectrum shows the base peak relevant for both compounds at m/e 268 and m/e 424 (with the characteristic selenium pattern).

The bicarbonate layer yielded upon acidification, extraction and evaporation a pale yellow oil, which slowly crystallised from light petroleum to give 2-carbomethoxy-5,6-dimethyl-3-(ethylcarbonate)-6-hydroxycyclohexadienone (74) (30mg, 55%, based on starting material consumed), m.p. 98° ; ν_{max} 3450, 1770, 1680, and 1630 cm^{-1} ; λ_{max} 226, 276, 283, and 314 nm (ε 11,350 , 2600, 2180, and 4490); τ 8.8-8.55 (3H, t, J=7.4Hz), 8.45 (3H, s), 7.8 (3H, m), 6.05 (3H, s), 6.0-5.55 (2H, q, J=7.4Hz), and 3.8 (H, d). (Found: C,54.92; H,5.73%; m/e 284. $C_{13}H_{16}O_7$ requires C,54.93; H,5.67%; M, 284).

Cathylate (71) with DPSA (no base) under boiling conditions.

Monocathylate (71) (139mg, 0.52mmol) in THF (5ml) was heated to boiling with diphenylseleninic anhydride (180mg, 0.5mmol) for 3 h. Work up in the usual manner afforded the o-hydroxydienone (74) (66mg, 45%). The organic layer yielded a mixture of i) starting material (71) and ii) selenated cathylate (75),as well as iii) a new product (10mg, 10%) , 2-carbomethoxy-4,5-dimethyl-2-hydroxycyclopent-4,5-en-1,3-dione (76), m.p. 126-7°; ν_{max} 1660-80 cm^{-1} ; τ 7.9 (6H, s) and 6.3 (3H, s). λ_{max} 255 nm (ε 22,000). (Found: C,54.33; H,5.08%; m/e 200 (M+2). $C_9H_{10}O_5$ requires C,54.55; H,5.09%; M, 198).

Benzilic acid with DPSA.

Benzilic acid (77) (228mg, 1mmol) in tetrahydrofuran (5ml) was treated with diphenylseleninic anhydride (360mg, 1mmol) under reflux

for 18 h. Chromatography on silica gel (ether/ light petroleum) yielded benzophenone (78) (118mg, 65%), m.p. 47° from water (mixed m.p. 46-7°), m/e 182 (M^+).

3-Carbomethoxy-2,4-dihydroxy-5,6-dimethylcyclohexaethylcarbonate (80).

Methyl 3,4-dimethyl-2,3,6-trihydroxybenzoate (61, R=OMe) (200mg , 0.94mmol) in chloroform (5ml) and pyridine (1ml) were treated with ethyl-chloroformate (103mg, 0.95mmol) at 0° for 1 h. Work up with hydrochloric acid (N/10, 15ml) and extraction with dichloromethane (3 x 50ml), resulted in an oil, which precipitates colourless crystals, the monocathylate (80). After filtration, the mother liquors yielded upon chromatography on silica (light petroleum/ ether 30%) i) more monocathylate (220mg, 82% total yield), m.p. 98-9° ; ν_{max} 3400, 1760, and 1665 cm^{-1} ; λ_{max} 218, 258, 266(s), and 336 nm (ε 14,750 , 12,500 , 10,200 , and 3890). τ 8.7-8.45 (3H, t, J=6.8Hz), 7.85 (3H, s), 7.8 (3H, s), 5.95 (3H, s), 5.9-5.5 (2H, q, J=6.8Hz), 0.6 (H, s), and 0.0 (H, s, both exchanged with D_2O). (Found: C,54.72; H,5.56%; m/e 284. $C_{13}H_{16}O_7$ requires C,54.93; H,5.67%; M, 284), ii) the dicathylate (81) (27mg, 8%), m.p. 88° ; ν_{max} 3400, 1770, and 1635 cm^{-1} ; τ 8.7-8.4 (6H, t, J=6.5Hz), 7.85 (3H, s), 7.75 (3H, s), 6.0 (3H, s), 5.95-5.55 (4H, q, J=6.5Hz), and -0.3 (H, s, exchanged with D_2O). (Found C,53.86; H,5.58%; m/e 356. $C_{16}H_{20}O_9$ requires C,53.93; H, 5.66%; M, 356), and iii) the tricathylate (82) as a yellow oil (44mg, 11%), which resisted all crystallisation attempts. ν_{max} 1785, 1730, and 1630 cm^{-1}; λ_{max} 233(s) and 282 nm. τ 8.75-8.5 (9H, t, J=7.3Hz), 7.9 (3H, s), 7.8 (3H, s), 6.0 (3H, s), and 5.85-5.4 (6H, q, J=7.3Hz). (Found: C,53.01; H,5.65%; m/e 428. $C_{19}H_{24}O_{11}$ requires C,53.27; H,5.65%; M, 428).

Cathylate (80) with NaH/ DPSA.

The monocathylate (80) (142mg, 0.5mmol) in tetrahydrofuran (4ml) was treated with sodium hydride (15mg, 80%) under nitrogen. When the

phenolate anion had formed, diphenylseleninic anhydride (180mg, 0.5mmol) was added and the reaction mixture was stirred for 2 h. Work up in the usual way afforded a pale yellow oil (121mg), which resisted all attempts at crystallisation. ν_{max} 1760, 1680, and 1645 cm^{-1} ; τ 8.9-8.4 (3H, t), 7.95 (3H, s), 7.85 (3H, s), 6.1 (3H, s), 6.0-5.5 (2H, q), 2.9-2.1 (5H, m), and -0.65 (H, s, exchanged with D_2O); λ_{max} 216, 254, 273, and 318 nm (ε 15,000 , 9850, 11,500 , and 3560). Treatment of this oil with $KHSO_3$ (5g) in water (3ml) and methanol (3ml) for 1 h, yielded upon extraction with chloroform (3 x 25ml) a pale yellow solid, which was washed with light petroleum (3 x 10ml) to remove diphenyldiselenide (12mg). The remaining methyl 3,4-dimethyl-2,3,6-trihydroxybenzoate (61, R=OMe) (63mg, 59%) was sublimed at 80°, 10^{-4}mm Hg, m.p. 133° (mixed m.p. 133°).

Cathylate (80) with hexamethyldisilazane, $HN(SiMe_3)_2$, /DPSA.

The monocathylate (80) (115mg, 0.4mmol) in tetrahydrofuran (5ml) was treated with hexamethyldisilazane base (2ml) under nitrogen and after 10min , diphenylseleninic anhydride (160mg, 0.4mmol) was added. The solution immediately turned orange. Work up in the usual manner, followed by preparative layer chromatography on silica (light petroleum / ethyl acetate 35%) gave 2-carbomethoxy-5,6-dimethyl-3-hydroxy-1,4-benzoquinone-monophenylseleno-4-imine (83) as orange prisms (106mg, 72%), m.p. 132° (from chloroform); ν_{max} 1680-1660 cm^{-1} ; τ 7.95 (3H, s), 7.9 (3H, s), 6.05 (3H, s), 2.7-2.2 (5H, m), and -0.85 (H, s, exchanged with D_2O); λ_{max} 263 and 412 nm (ε 17,150 and 21,390). (Found: C,52.89; H, 4.17; N,3.69%; m/e 365. $C_{16}H_{15}NO_4Se$ requires C,52.75; H,4.15; N,3.85%; M, 365).

Reduction of the selenoimine (83) with zinc/ acetic acid yielded upon work up 5-amino-2,6-dihydroxy-3,4-dimethylbenzoate (85), m/e 227 (M^+).

Methyl 2,6-dihydroxy-3-formyl-4-methyl-5-phenylselenobenzoate (87).

Methyl 2,6-dihydroxy-3-formyl-4-methylbenzoate (86) (120mg, 0.61 mmol) in tetrahydrofuran (2ml) was treated with sodium hydride (12mg, 80%) under a nitrogen atmosphere. After 10 min, diphenylseleninic anhydride (220mg, 0.61 mmol) was added to the stirred reaction mixture . After 2 h the solution was quenched with aqueous KH_2PO_4 (10ml, 10%) , and extracted with chloroform (2 x 25ml). Preparative layer chromatography on silica (light petroleum/ ethyl acetate 30%) gave i) diphenyldiselenide (130mg), ii) the seleno-aldehyde (87) as pale yellow needles (145mg, 70%) from ethanol, m.p. 137° ; ν_{max} 3450, 2700, 1680, and 1630 cm^{-1} ; λ_{max} 230(s), 244, 252, 266(s), and 342 nm (ε 16,900 , 23,150 , 22,580 , 14,000 , and 8250); τ 7.2 (3H, s), 5.95 (3H, s), 2.7 (5H, bs), and -0.25 (H, s). (Found: C,52.61; H,3.86%; m/e 366. $C_{16}H_{14}O_5Se$ requires C,52.75; H,3.87%; M, 366), and iii) 4-carbomethoxy-6-formyl-3-hydroxy-2,5-toluquinone (88)[15] , λ_{max} 272 nm (ε 12,300); τ 7.55 (3H, s), 5.85 (3H, s), and -0.5 (H, s).

Repeating this experiment with the aldehyde phenolate (from aldehyde (78) (135mg, 0.68mmol) and sodium hydride (14mg, 80%)) in glyme (5ml), treatment with diphenylseleninic anhydride (285mg, 0.75mmol) , afforded after work up the selenated aldehyde (87) (169mg, 72%) and the quinone (88) (23mg, 17%), m.p. 141-4°(lit. 145°)[15] .

Seleno-ester (21, R=OMe) with NaH/DPSA.

Methyl 2,6-dihydroxy-3,4-dimethyl-5-phenylselenobenzoate (21, R=OMe) (140mg, 0.4mmol) in THF (5ml) was treated with sodium hydride (12mg, 80%) under nitrogen. After warming the reaction mixture to 50° , diphenylseleninic anhydride (144mg, 0.4mmol) was added. Work up after 2 hours gave a pale yellow oil from the bicarbonate extract. Nmr spectrum exhibited τ 8.4 (3H, s), 7.65 (3H, s), 6.0 (3H, s), and 2.65 (5H, m), consistent

with the o-hydroxydienone (89) , but clearly other peaks τ 7.85 (6H, s) and 5.95 (3H, s) showed the presence of quinone (59, R=OMe). Separation of the mixture of both compounds could be achieved neither by extraction, nor by chromatographic methods. The mass spectrum exhibited both molecular ions, m/e 268 (89) and m/e 210 (59, R=OMe). λ_{max} 221, 238, 257, 288, and 328 nm for the hydroxylated selenophenol (89) was superimposed by a strong absorption λ_{max} 272 for the quinone (59, R=OMe).

Phenylmercuric chloride (92).

Aniline (31g, 0.33mol) in conc. hydrochloric acid (150ml) with water (200ml) was cooled with ice (200g). Sodium nitrite (23g) was added with stirring and more ice (200g) was introduced, keeping the temperature below 5° .To this solution of the diazonium salt, $HgCl_2$ (90g) in HCl (100ml) and ice (100g) was added slowly. The addition compound $PhN_2Cl \cdot HgCl_2$ precipitated and was removed by filtration, washed with water (150ml) and acetone (100ml). A stirred suspension of this addition complex (91) in acetone was treated with copper powder (13g) with the evolution of nitrogen. After 15 h, the resulting precipitate was removed by filtration and recrystallised from benzene, to yield the chloride (92) (85.4g, 82%) , m.p. 251-2° (lit. 250-2°)[80] .

Phenyltellurinyl trichloride (93).

Phenylmercuric chloride (92) (3.5g, 11mmol) in dioxan (50ml) was treated with tellurium tetrachloride (3g, 11mmol) and the reaction mixture was heated to reflux for 1 h. After cooling, $HgCl_2$·dioxan adduct was removed by filtration as large plates. The filtrate was evaporated to dryness and the resulting phenyltellurinyl trichloride (93) was recrystallised from benzene (2.4g, 70%), m.p. 215-7° (lit. 215-8°)[63] .

Diphenyltellurinic anhydride (90).

Phenyltellurinyl trichloride (93) (3.2g, 10mmol) in sodium hydroxide (10%, 20ml) was heated to reflux for 1 h and the cooled mixture was acidified with acetic acid (10%) to pH 7. The white precipitate was isolated by filtration. The anhydride (90) (2.2g, 93%) was recrystallised from hot water, m.p. 226-30° (lit. 220-225°)[59] . (Found: C,31.26; H,2.43 ; $C_{12}H_{10}O_3Te_2$ requires C,31.51; H,2.2%) m/e 207 corresponds to the PhTe-moiety .

Phenyltellurinyl chloride , PhTeOCl (96).

Phenyltellurinyl trichloride (93) (2g, 6.5mmol) in water (25ml) was heated on a steam bath for one hour. On cooling the solution, a precipitate formed, which was isolated by filtration, washed with water,and recrystallised from hot water to yield phenyltellurinyl chloride (96) (1.64g, 100%), m.p. 250° . (Found C,28.04; H,1.9; Cl,13.85 ; C_6H_5ClOTe requires C,28.13; H,1.97; Cl,13.84%) m/e 242 (base peak M-16) .

Diphenyltellurinic anhydride (90) in ethanol.

Diphenyltellurinic anhydride (90) (114mg, 0.25mmol) in absolute ethanol (25ml) was heated to reflux for 18 h. Evaporation of the solvent under reduced pressure, afforded the anhydride (90) unchanged (113mg), m.p. 226-229° . (Diphenylseleninic anhydride yielded under these conditions ethyl phenylseleninate and phenylseleninic acid)[3] .

Ring A model ester (5) with diphenyltellurinic anhydride.

Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (5) (98mg, 0.5mmol) in glyme (3ml) was treated with sodium hydride (15mg, 80%) under nitrogen. Diphenyltellurinic anhydride (90) (229mg, 0.5mmol) was added and the reaction mixture was heated to reflux for 1 h. Work up in the usual manner afforded the phenol (5) unchanged, m.p. 108° (mixed m.p. 107-8°) (92mg, 94%).

Diphenylditelluride (94).

Diphenyltellurinic anhydride (90) (457mg, 1mmol) was added to a solution of potassium metabisulphite (5g) in water (20ml). The reaction mixture turned red upon heating for one hour at 50° in a nitrogen atmosphere. Extraction with chloroform (3 x 50ml) gave diphenylditelluride (94) as red plates (380mg, 93%), m.p. 66-7° (lit. 67°)[58, 63] ; λ_{max} ($CHCl_3$) 255 and 407 nm (ε 25,000 and 985).

Diphenylditelluride with ozone.

Diphenylditelluride (94) (410mg, 1mmol) in carbon tetrachloride (85ml) was cooled to -10° and a steady stream of ozone was passed through the solution. A white precipitate formed, which was isolated by filtration after 1 h., washed with chloroform to yield diphenyltellurinic anhydride (90) (412mg, 90%), m.p. 226-230° (mixed m.p. 224-228°).

Diphenylditelluride with nitric acid.

Diphenylditelluride (94) (205mg, 0.5mmol) in water (2ml) was treated with conc. nitric acid (5ml), according to the method of Lederer[64] . Evaporation of the solvent under reduced pressure left a solid, the nitrotellurinate adduct (95) , recrystallised from water,(200mg), m.p. 225-238° . (Found: C,30.6%; H,2.15; N,1.48 ; $C_{24}H_{21}NO_7Te_4$ requires C, 30.48; H,2.24; N,1.48%).

2,6-Dimethylphenol with NaH/ phenyltellurinyl chloride.

2,6-Xylenol (122mg, 1mmol) in glyme (5ml) was treated with sodium hydride (30mg, 80%) under nitrogen. After 10 min , phenyltellurinyl chloride (96) (256mg, 1mmol) was added and the solution heated under reflux. After 2 h, work up afforded 2,6-xylenol (112mg, 92%) and diphenyltellurinic anhydride (226mg, 100%), m.p. 226-230° (mixed m.p. 224-231°).

Sodium phenyltellurinate, $PhTeO_2Na$.

The anhydride (90) (458mg, 1mmol) was dissolved in aqueous sodium hydroxide (80mg, 2mmol, 2ml water). Acetone (20ml) was added and the solution was cooled to 0° . After 24 h the crystalline sodium phenyltellurinate was separated by filtration (476mg, 92%) and was dried *in vacuo* at 100° .

Sodium phenyltellurinate and ethylchloroformate.

Sodium phenyltellurinate (183mg, 0.7mmol) was added to ethylchloroformate (6ml) and heated under reflux for 6 h. The sodium salt was recovered unchanged (171mg) after isolation.

Phenyltellurinyl chloride and sodium methoxide.

Phenyl tellurinyl chloride (96) (256mg, 1mmol) in methanol (3ml) was added to a solution of sodium methoxide (23mg sodium in 3 ml methanol) . The clear solution was evaporated to dryness and the nuclear magnetic resonance spectrum showed τ 1.9-2.35 (2H, *o*-protons), 2.4-2.8 (3H, *m*- and *p*-protons), and 6.6 (3H, bs, Me-), i.e., consistent with methyl phenyltellurinate (98). Attempts to isolate this compound resulted in formation of diphenyltellurinic anhydride (90) (110mg, 48%).

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