STUDIES RELATED TO THE TOTAL SYNTHESIS OF TETRACYCLINE

a thesis presented by

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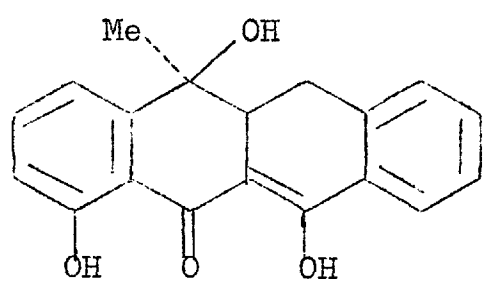
ABSTRACT.

The first section of this thesis describes three aspects of tetracycline chemistry:

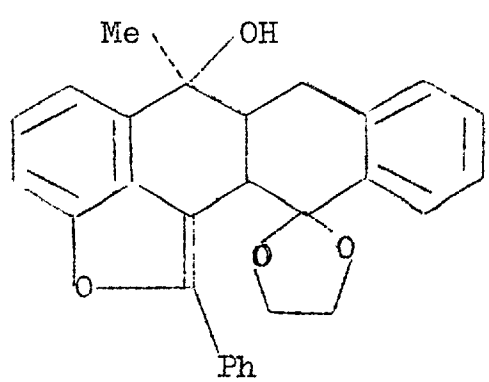
1) Some important reactions of the tetracyclines.
2) Recent progress in the synthesis of tetracyclines.
3) A summary of the results obtained in these laboratories towards the synthesis of tetracycline.

A discussion of the author's work on this project is contained in the second section.

1. The synthesis of the model tetracycline (A) from the alcohol (B) is described.

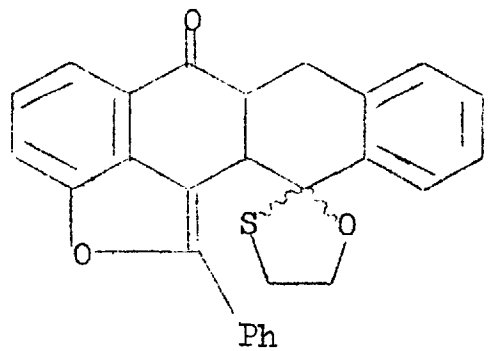


(A)



(B)

The use of the hemithio ketal (C) has been examined and the alcohol (D) prepared from (C).



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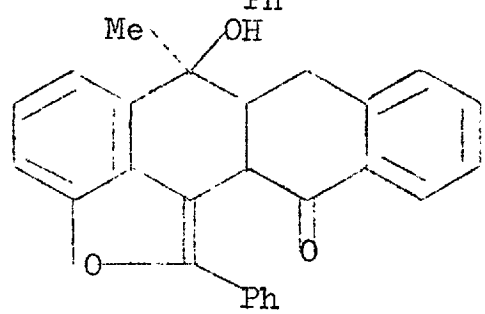
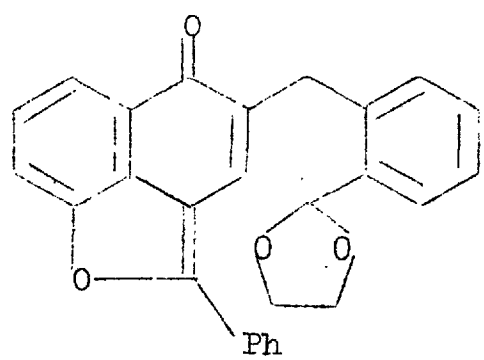
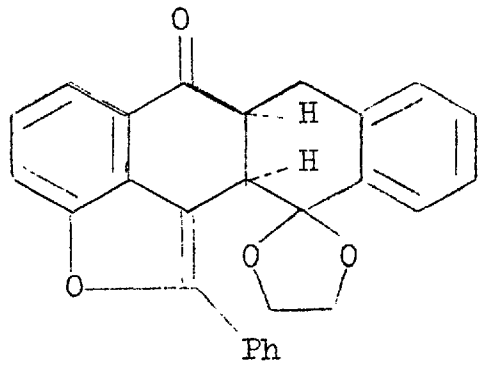


(D)

2. The photolysis of the acetal (E) to give the tetracyclic ketal (F) has been investigated. This reaction was found to be acid catalysed and not free radical. A possible mechanism is discussed.

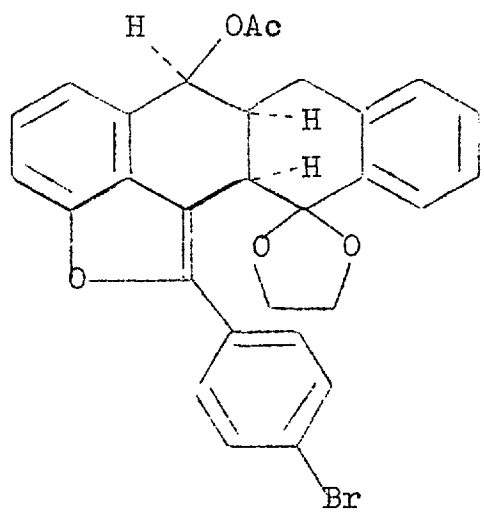


(E)



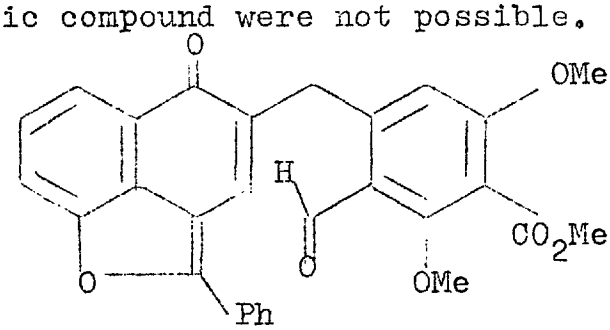
(F)

3. The bromo-acetate (G) has been prepared and a X-ray crystallographic study carried out. This confirms the assigned stereochemistry.

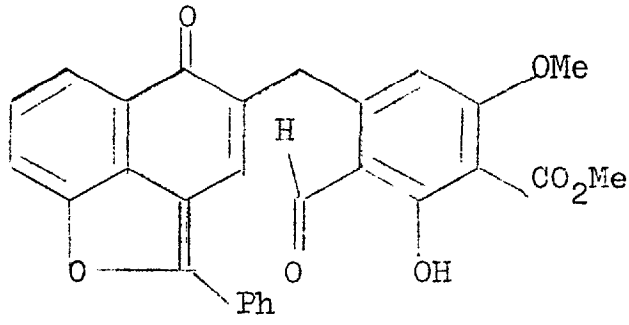


(G)

4. The aldehyde (H) has been selectively demethylated to give the phenol (I) but further transformations to a tetracyclic compound were not possible.

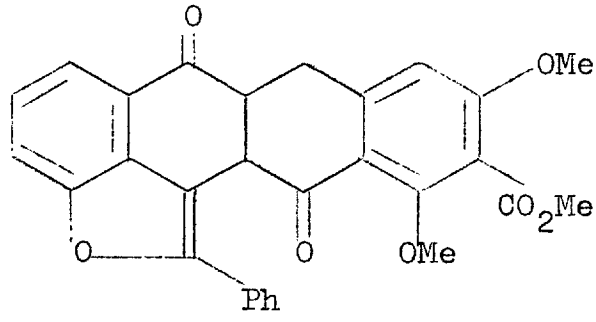


(H)



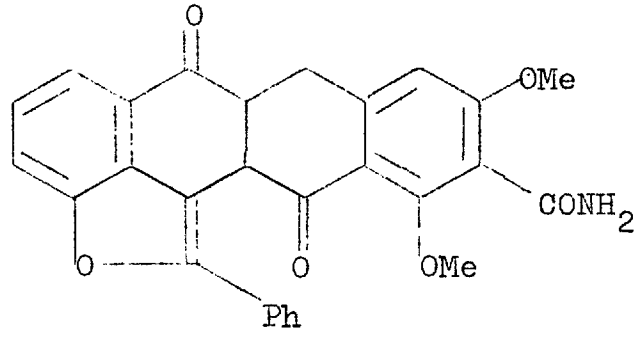
(I)

The photolysis of the aldehyde (H) to the diketone (J) is described, along with attempts to selectively demethylate the ortho methoxyl group and reduce the 6-carbonyl function.



(J)

5. The use of novel Lewis acids to prepare the diketone (K) is discussed. Attempts on the selective demethylation and reduction reactions are described.



(K)

6. The extension of the use of the Lewis acids described in part 5 to steroidal ketals and related compounds is described. The mechanism of their action has been examined.

ACKNOWLEDGEMENTS.

I wish to thank Professor D.H.R. Barton, F.R.S., for his guidance and encouragement during this research. I also wish to thank Dr. P.D. Magnus, Dr. L. Bould, Dr. T. Hase and Dr. M.J. Pearson for their helpful advice and friendship.

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Whiffen Laboratory
August, 1969.

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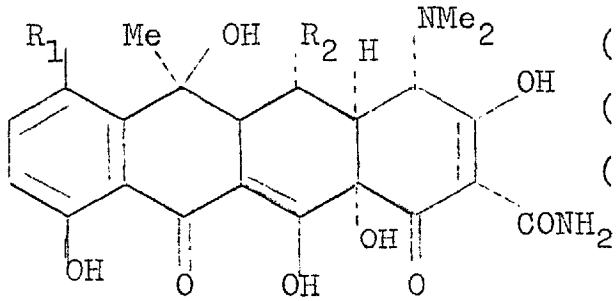
Introduction.

The tetracyclines are a group of powerful antibiotics produced by various strains of Streptomyces, which are active against a wide range of human and animal pathogens[1,2].

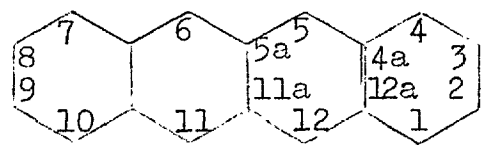
The first of these antibiotics to be found was isolated from Streptomyces aureofaciens as an orange yellow hydrochloride and was named aureomycin (1)[3,4]. Degradative studies[5,6] showed its structural similarities to terramycin (2), an antibiotic discovered in 1950 as a metabolite of Streptomyces rimosus[7]. The structure and probable stereochemistry of terramycin was elucidated by Woodward and his co-workers at the laboratories of Chas. Pfizer and Co.[8].

The parent member of this group of antibiotics is tetracycline itself (3) which was obtained from the hydrogenolysis of aureomycin[9,10]. It was then shown that this product was identical to a metabolite isolated previously from Streptomyces albo-niger[11]. Thus aureomycin and terramycin are 7-chloro-tetracycline and 5-hydroxy-tetracycline respectively using the numbering

system shown below.



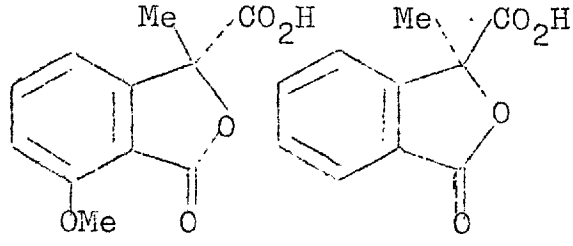
(1) R_1=Cl R_2=H
(2) R_1=H R_2=OH
(3) R_1=R_2=H



Several other tetracyclines have been isolated, among them 7-bromo[12,13], 6-demethyl[14,15] and 7-chloro-6-demethyl derivatives[14, 15], a number of 2-acetyl-2-decarboxamido tetracyclines[16,17] and several dehydro compounds[18]. The labile 7-chloro-5-hydroxy tetracycline has also been isolated[19].

X-ray analysis of aureomycin[20] and terramycin[21] has confirmed the structures and established the stereochemistry of the five common asymmetric centres. The configuration of the C-5 hydroxyl group of terramycin was determined by n.m.r. spectroscopy[22] and by a re-examination of the earlier X-ray data[23].

The absolute configuration at C-6 of aureomycin has been determined[24] by a comparison of the O.R.D. curves of a degradation product, 3(R)-7-methoxy-3-methylphthalide-3-carboxylic acid (4) with 3(S)-3-methylphthalide-3-carboxylic acid (5) related to S(+)-atrolactinic acid (6).



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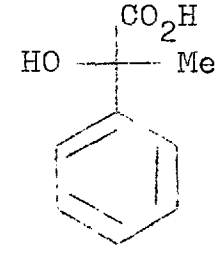
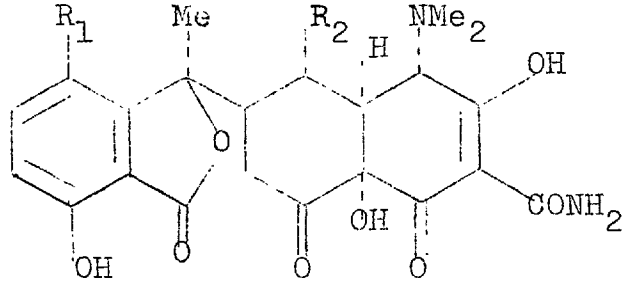


(6)

The Chemistry of Tetracycline.

The chemistry of tetracycline has been reviewed extensively both in the literature and by workers in these laboratories[25]. The latest published review covers the literature up to 1968[26]. This short survey is intended to cover the reactions pertinent to a synthetic route to a naturally occurring tetracycline.

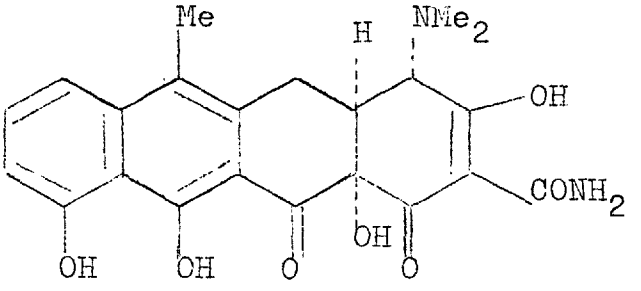
The C-6 hydroxyl group of the tetracyclines together with the remaining oxygenation pattern renders them susceptible to both acid and base attack. The initial products from reaction in basic media are the isotetracyclines (7)[27].



(7)

The C-6 hydroxyl group bears a *trans* relationship to the adjacent proton and hence is favourably set up for dehydration; moreover the aromatisation of ring C provides an extra driving force for the reaction. The

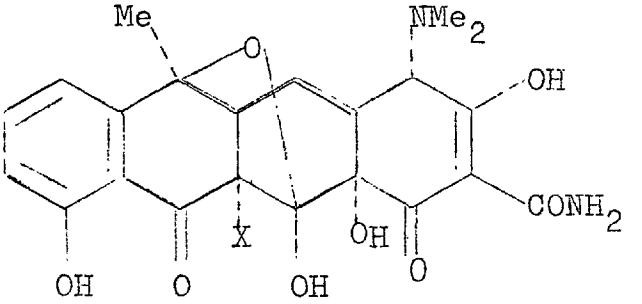
products from the acid treatment of tetracyclines are the 5a,6 anhydrotetracyclines (8)[28].



(8)

In the presence of buffered solutions of pH 2-6 the C-4 dimethylamino group is readily epimerised to give approximately equal amounts of each epimer[29,30,31,32]. This epimerisation is reversible and so the configuration at C-4 will present no problem during synthesis.

The C-6 hydroxyl group permits the formation of 6,12 and 6,4 hemiketals. When amphoteric tetracycline is treated with perchloryl fluoride in the presence of base the 11α-fluoro-6,12,-hemiketal (9) is formed[33, 34, 35].



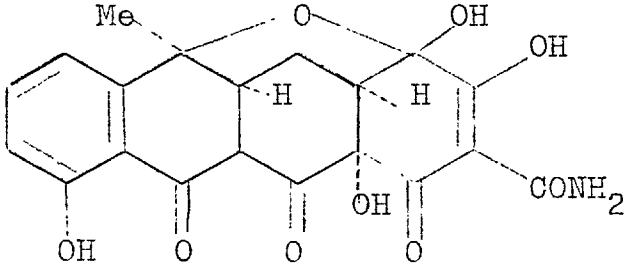
(9) X=F

(10) X=Cl

Tetracycline can be regenerated by hydrogenolysis[36] or by metallic reducing agents[37].

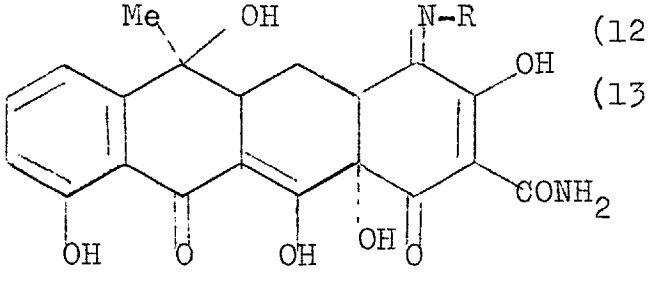
The corresponding chloro compound (10) is obtained by the reaction of tetracycline with N-chlorosuccinimide in glyme[35].

In contrast to these reactions when tetracycline hydrochloride is treated with N-chlorosuccinimide in water then 4-oxo-4-dedimethylaminotetracycline-4,6-hemiketal (11) is precipitated[38].



(11)

The tetracycloxide (11) provides a means of introducing nitrogen into the molecule at C-4 since it reacts with hydrazine and hydroxylamine to form the hydrazone (12) and oxime (13) respectively[38].



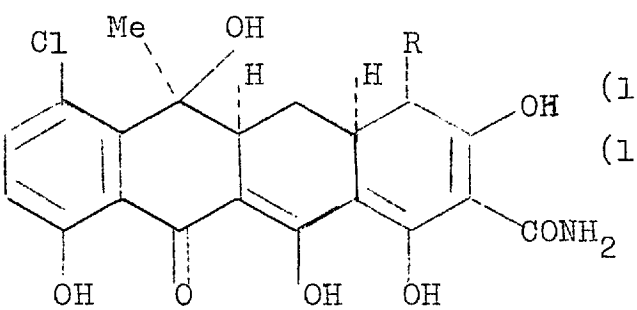
(12) R=NH_2

(13) R=OH

Both the hydrazone and the oxime can be converted to 4-epi-tetracycline[38]. The tetracycloxide can also be hydrogenated in dimethylformamide containing ammonium hydroxide and magnesium chloride to the 4-epi-amino-tetracycline[38].

The tetracycloxide (11) could, therefore, be used as a relay compound in a synthetic route.

A reaction of considerable interest to any synthetic route is the introduction of a hydroxyl function in the 12a position of the 12a deoxytetracyclines. The latter (14) and (15) can be oxidised to tetracyclines by the use of sodium nitrite-oxygen or enzymatically with curvularia lunata[39].



(14) R=NMe_2

(15) R=H

12a-anhydrotetracycline can be oxidised to anhydro-tetracycline with perbenzoic acid[22,40]. The use of metals, in elemental form or as salts, together with gaseous

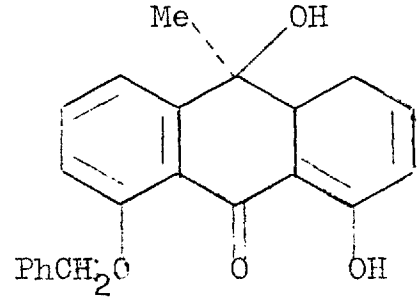
oxygen has been used to oxidise 12a-anhydro-tetracyclines[27,41,42,43].

The 5a,6 anhydrotetracyclines can be photo-oxidised[44] under sensitised conditions[45] to 6-peroxy-5a,11a-dehydro-tetracyclines. Hydrogenation then gives a mixture of tetracyclines and 5a-epi tetracyclines.

The synthesis of tetracyclines.

The total synthesis of a naturally occurring tetracycline has been the goal of several groups of organic chemists. Their work has been the subject of several reviews[46,47,48]. The culmination of this vast amount of work is the synthesis of tetracycline itself by Shemyakin[49] and of terramycin by Muxfeldt[50].

The starting point of Shemyakin's synthesis was the dienediolone (16), prepared in six stages from juglone[51]. This was condensed with the triethylammonium salt of ethylnitroacetate to give a mixture of the epimeric adducts (17).



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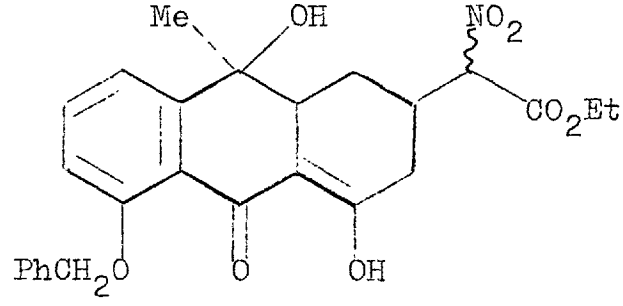
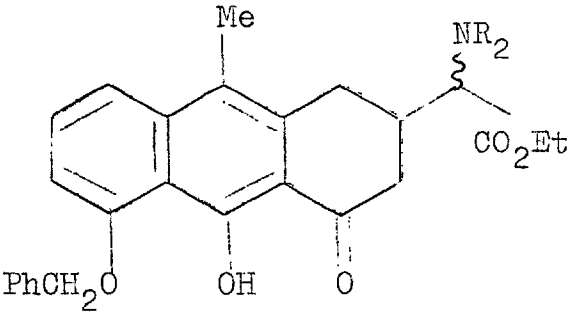


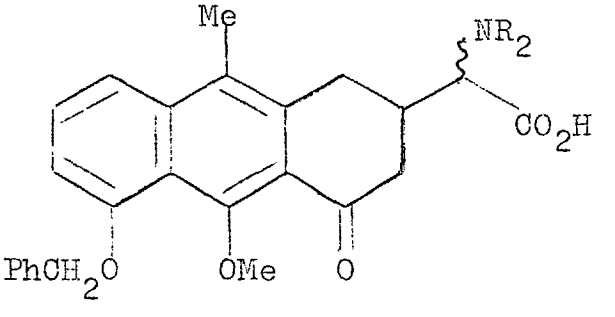
(17)

Dehydration of the tertiary alcohol with methanolic hydrochloric acid at 80°C gave the nitro compound (18), which was reduced with zinc dust in acetic acid to the amine (19).



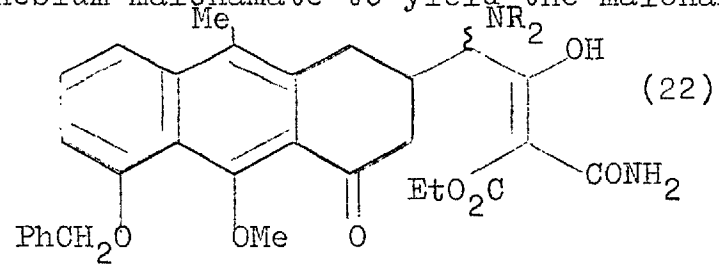
(18) R=O
(19) R=H
(20) R_2=Phthal.

The amine was methylated with methyl iodide-silver oxide and the ester group then saponified. Attempts were made to condense this acid as the chloride, isopropyl carbonate or isobutyl carbonate with ethyl ethoxymagnesium malonamate but without success. Consequently the amine (19) was acylated with carboethoxy-phthalimide to furnish the phthaloyl derivative (20). This was then methylated and saponified to give, after recyclisation of the phthalimido group, the acid (21).



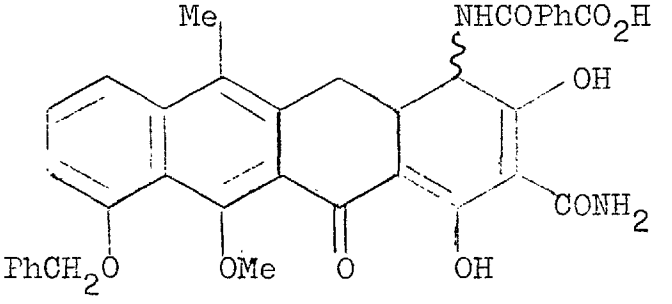
(21) R_2=Phthal.

The acid (19) was then converted to its chloride on treatment with phosphorous pentachlorde in dimethyl-formamide, which was then condensed with ethyl ethoxy-magnesium malonamate to yield the malonamate (22).



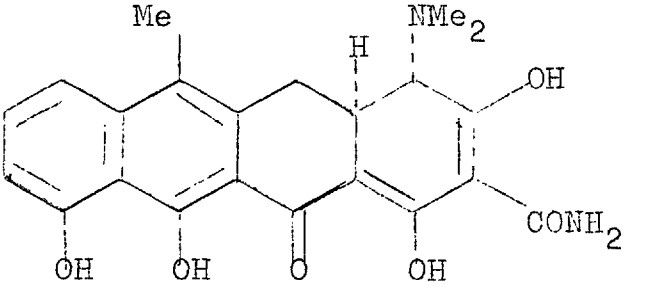
(22) R_2= Phthal.

The hydronaphthacene (23) was then obtained by cyclising the ester (22) with sodium methylsulfinyl-methide in dimethylsulphoxide.



(23)

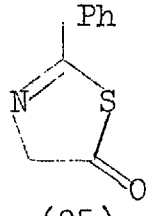
Hydrolysis with hydrogen bromide in acetic acid and methylation with methyliodide in tetrahydrofuran gave (±)-12a-deoxy-5a,6-anhydrotetracycline (24).



(24)

The (-) component of this racemate (24) had previously been converted into 5a,6 anhydrotetracycline[52] which in turn had been transformed to tetracycline by Schach von Wittenau[45].

Muxfeldt's synthesis of terramycin[50] was based on three basic units; the thiazolone (25)[53], methyl-3-oxo-glutaramate (26) and the aldehyde (27).



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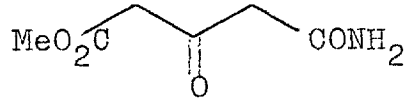

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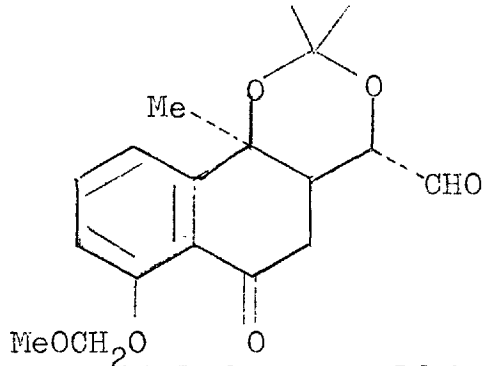
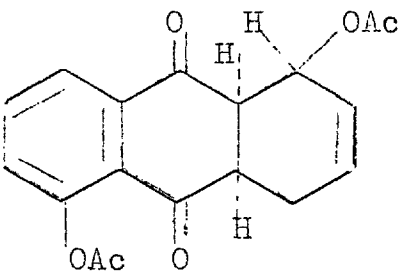
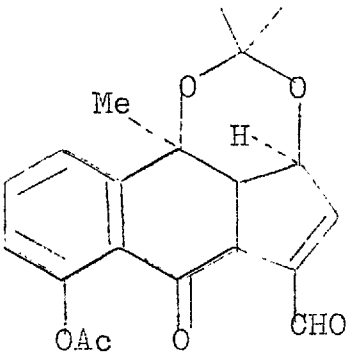


(27)

The starting material for the aldehyde (27) was the adduct (28) of juglone acetate and 1-acetoxybutadiene, which was converted to the aldehyde (29) in seven steps.

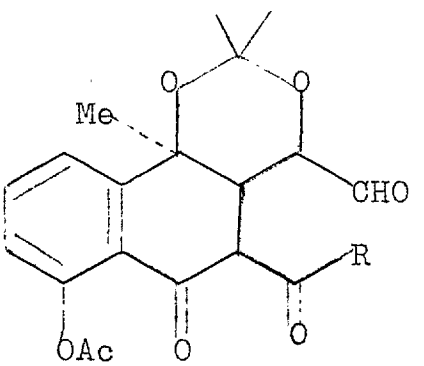


(28)



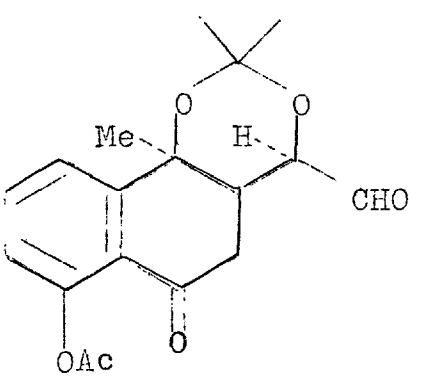
(29)

Ozonolysis and hydrolysis of (29) gave a mixture of the di-aldehyde (30) and the aldehyde-acid (31) which was converted to a mixture of the aldehydes (32) and (33) with aqueous sodium carbonate.



(30) R=CHO

(31) R=CO_2H



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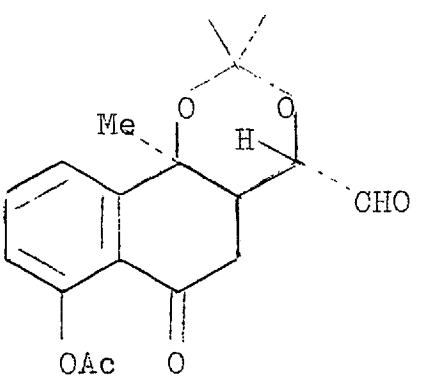
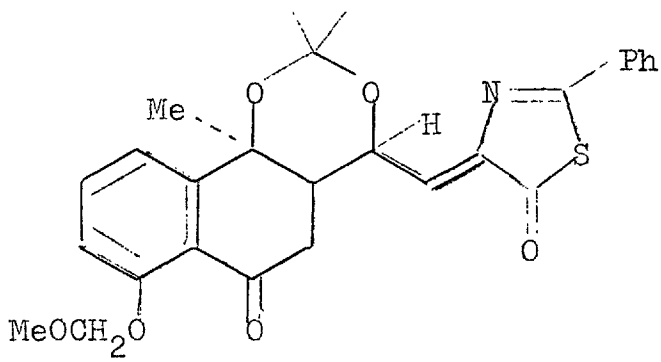


(33)

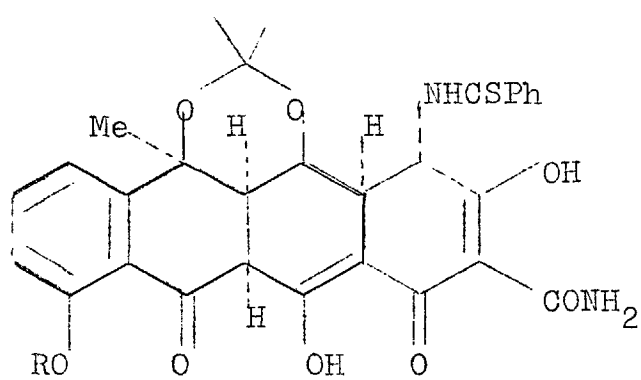
The mixture of (32) and (33) was then converted to the required aldehyde (27) in three steps involving enamine formation with piperidine in benzene, methoxy methylation of the resulting phenol and hydrolysis of the enamine function on deactivated silica gel.

The aldehyde (27) was condensed with the thiazolone (25) in the presence of basic lead acetate in tetrahydrofuran to give the thiazolone (34).



(34)

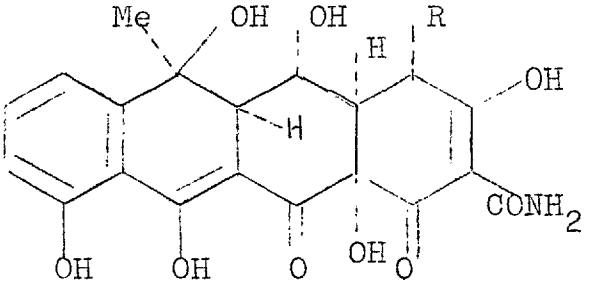
Condensation of the lithium salt of methyl-3-oxoglutaramate (26) with (34), in the presence of butyl lithium and potassium tert-butoxide, led to the tetracyclic compound (35).



(35) R=CH_2OMe

(36) R=H

The methoxymethyl ether protecting group was then removed with acetic acid to furnish the phenol (36) which was 12a hydroxylated with molecular oxygen in a basic media. The acetonide grouping was removed under mild acidic conditions (0.01 N methanolic hydrochloric acid) to give the free alcohol (37).



(37) R= NHCSPh

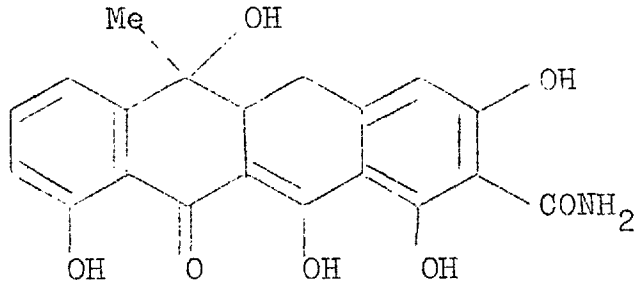
(38) R= $\overset{+}{N}H=C(SMe)-Ph$ I^-

(39) R= $NH_3Cl^{(+)(-)}$

The final stages to (±) terramycin involved methylation to the thioimino salt (38), hydrolysis to (39) and finally alkylation with dimethyl sulphate and Hunig's base in tetrahydrofuran.

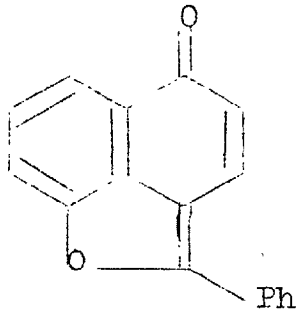
Synopsis of Previous Work[55].

In contrast to the published syntheses of tetracyclines the basic idea of the Imperial College group was to condense a suitably substituted aromatic ring A onto a CD unit and then to form ring B by cyclisation. It was also decided to have as many of the functional groups present as possible before the cyclisation in order to minimise the number of manipulations necessary on the labile tetracyclic materials. The intermediate aim was the synthesis of 4a,12a-anhydro-4-dedimethylamino tetracycline (40). The synthesis of tetracycline would then be completed by dearomatisation of ring A, introduction of a dimethylamino group at C-4 and the hydroxylation at C-12a.

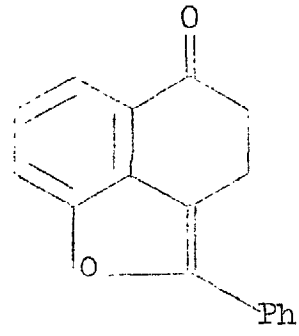


(40)

The CD unit (41) was formed by a Friedel Crafts reaction between 1,5 dihydroxynaphthalene and benzoic acid. This was hydrogenated over Raney nickel to give the dihydro-compound (42).

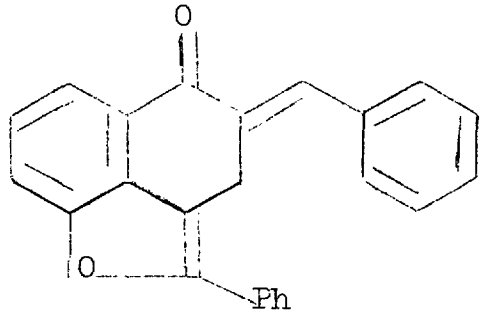


(41)



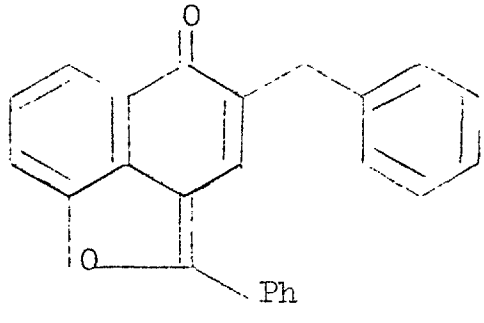
(42)

The dihydroperinaphthofuran (42) contains an active methylene group which provides entry into the ACD tricyclic series of compounds. The feasibility of this reaction was shown by the formation of the benzylidene derivative (43) by condensation with benzaldehyde under acidic conditions.



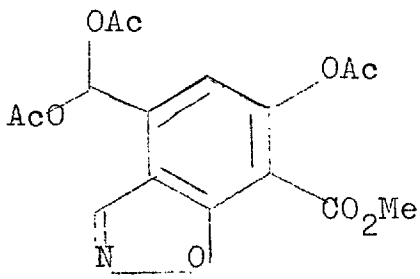
(43)

Condensation under basic conditions gives the endocyclic double bond compound (44), which is also formed by refluxing the exo compound (43) in triethylamine.

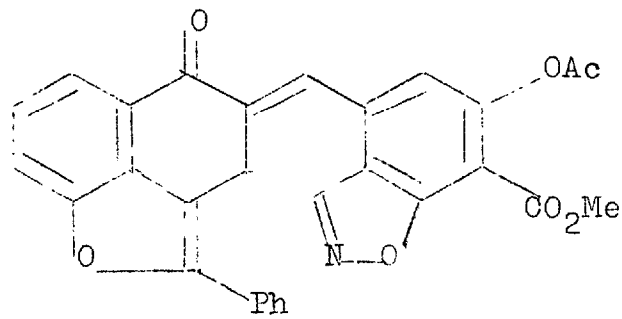


(44)

The substituted ring A isoxazole (45) was then synthesised from orcinol and condensed with dihydro-perinaphthofuran to give the benzylidene compound (46).

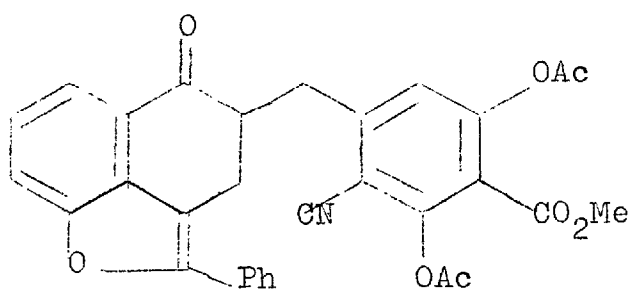


(45)



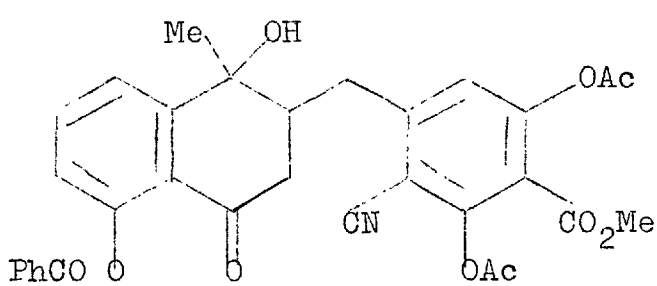
(46)

The exo-double bond was reduced by hydrogen iodide in acetic acid and dehydration with acetic anhydride in pyridine gave the nitrile (47).



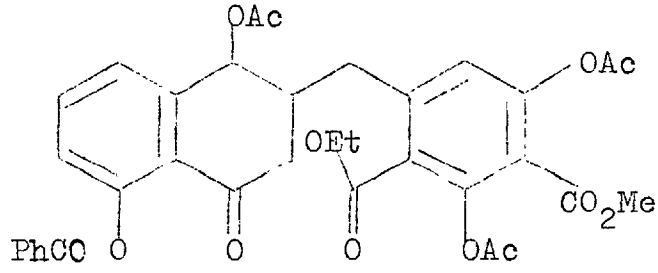
(47)

Reaction with methyl magnesium iodide followed by ozonolysis yielded the tetralone (48). This, however, failed to cyclise under a variety of basic conditions.



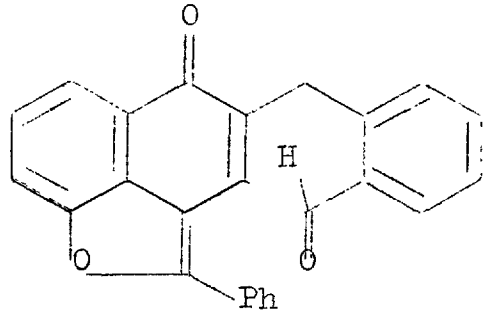
(48)

The ester derivative (49) was then synthesised but again this failed to cyclise.



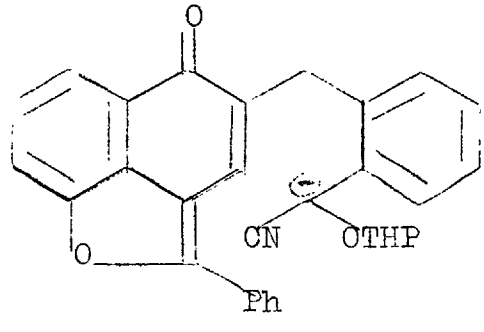
(49)

In order to study possible cyclisation reactions in more detail the model aldehyde (50) was prepared from dihydroperinaphthofuran and o-phthalaldehyde under basic conditions.

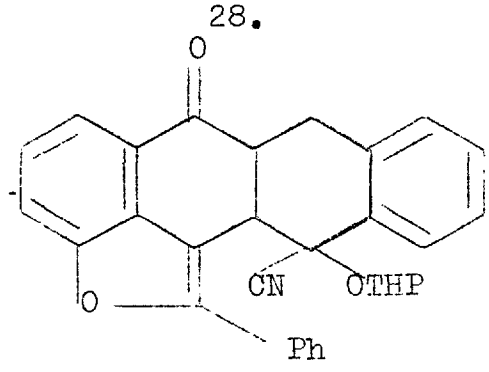


(50)

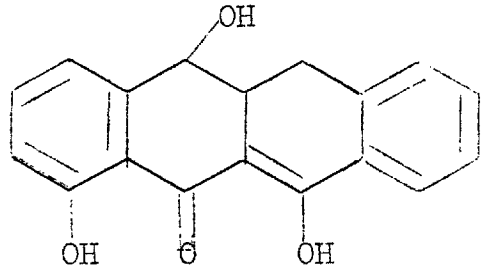
Michael addition of the benzylic anion (51) gave the tetracyclic compound (52). This was then transformed to the model tetracycline (53) in six stages, but in only poor yield.



(51)

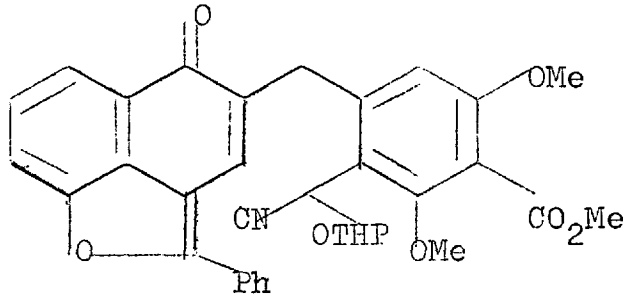


(52)



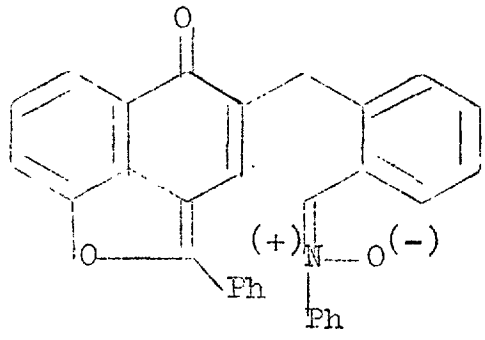
(53)

When this reaction was extended to the substituted compound (54), however, no cyclisation was observed.

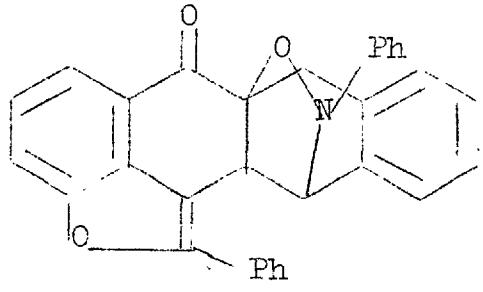


(54)

An alternative method of cyclisation was found using a 1,3 dipolar addition reaction. The nitrone (55) was prepared from the aldehyde (50) by the action of phenylhydroxylamine, and this spontaneously cyclised to the isoxazolidene (56).

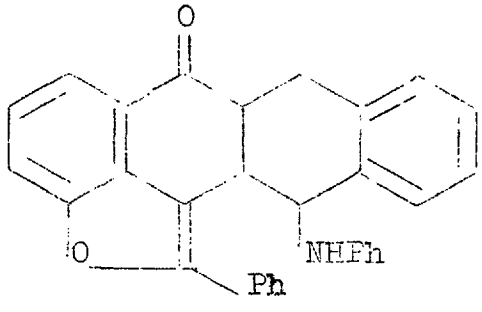


(55)



(56)

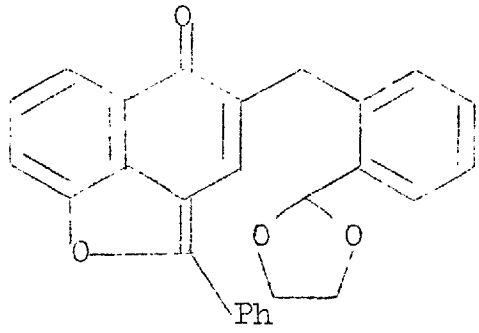
This reaction was successfully extended to the substituted ring A series. The isoxazolidene (56) was readily converted to the 12-phenylamino compound (57) but further transformation to the 12-keto compound could not be effected.



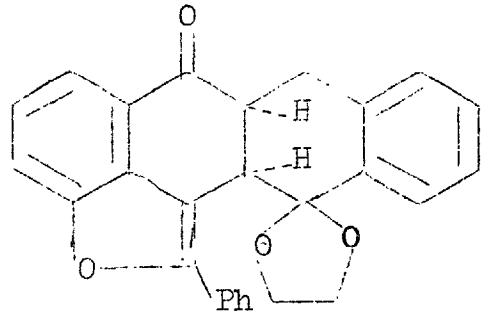
(57)

An ideal ring B cyclisation reaction that enabled manipulations at C-12 to be carried out was the photo-cyclisation of the acetal (58), in the presence of

benzoyl peroxide, to the tetracyclic ketal (59).

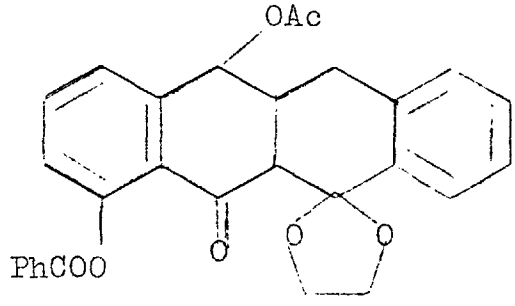


(58)



(59)

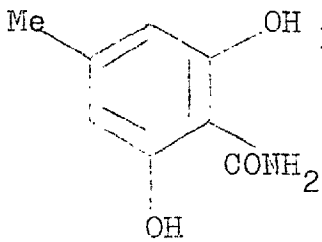
The naphthofuran protecting group could be removed, after reduction and acetylation at C-6, by ozonolysis to give the ketobenzoate (60).



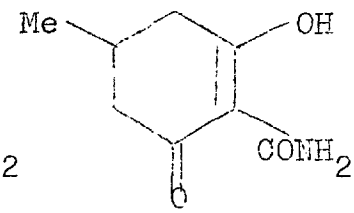
(60)

Once a tetracyclic molecule had been prepared there remained the problem of obtaining the correct oxidation level and substitution pattern in ring A.

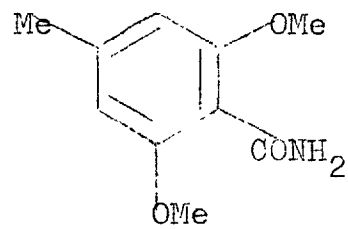
The model resorcinol (61) was catalytically reduced to the β diketone (62) but the tetracyclic compound (40) could not be so reduced. The diketone (62) was also obtained by a Birch reduction of the dimethyl ether (63), followed by acid hydrolysis.



(61)



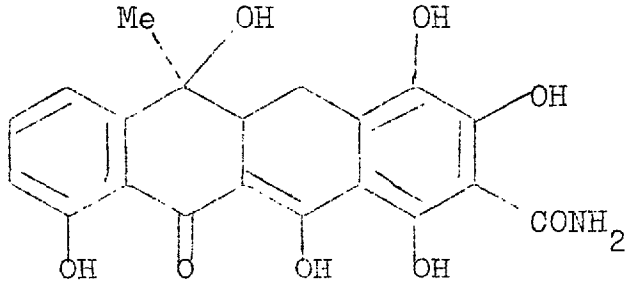
(62)



(63)

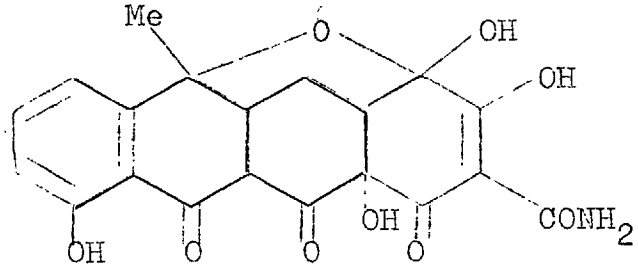
When a dimethylamino group was introduced, however, no useful product could be isolated from the reduction. Methods were then sought for inserting nitrogen into the double bond of an enol ether but these met with no success.

Due to the difficulty of the reduction of ring A after the introduction of nitrogen at C-4, or of amination after reduction of the aromatic ring the objective was modified to 4a,12a-anhydro-4-hydroxy-4-dedimethylaminotetracycline (64).



(64)

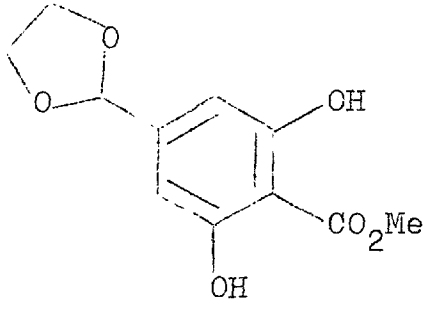
By oxidative hydroxylation and dearomatisation of ring A nitrogen can be introduced at C-4 via the tetracycloxide (65).



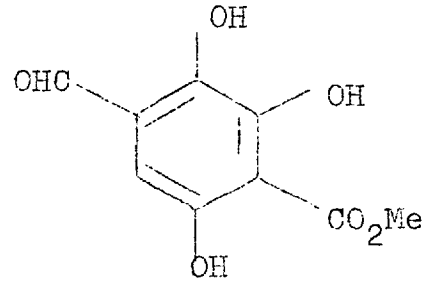
(65)

Model work showed that Fremy's salt was a suitable reagent for the introduction of the extra oxygen atom by oxidation to a quinone and reduction to the phenol.

The ethylene ketal (66) was oxidised by Fremy's salt and then catalytically reduced to furnish, after acid treatment, the trihydroxy aldehyde (67).

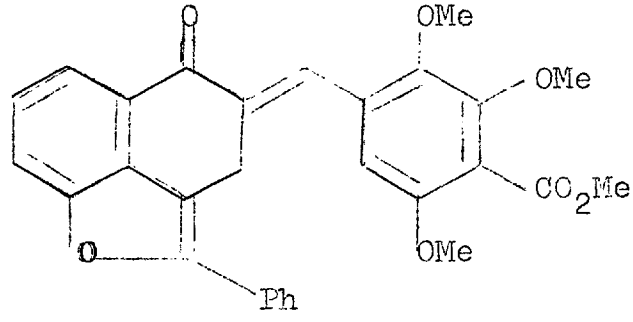


(66)



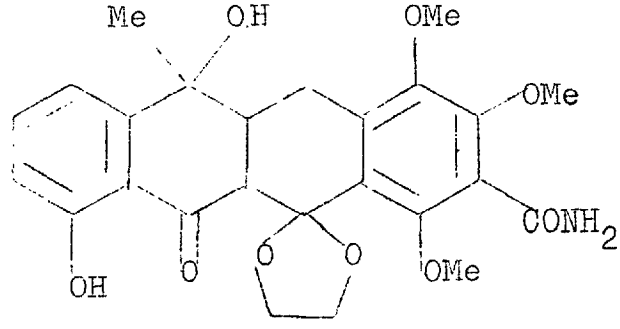
(67)

The aldehyde (67) was methylated and then condensed with dihydroperinaphthofuran to give the ACD compound (68).



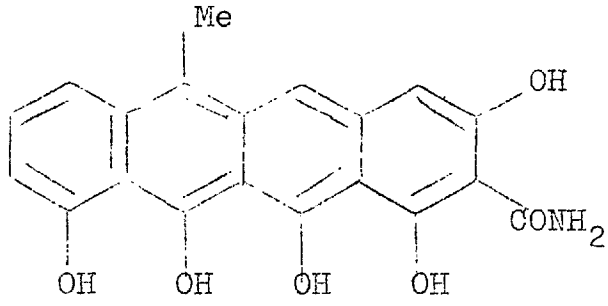
(68)

The important tricyclic compound was converted, in 9 steps, to the intermediate (69).



(69)

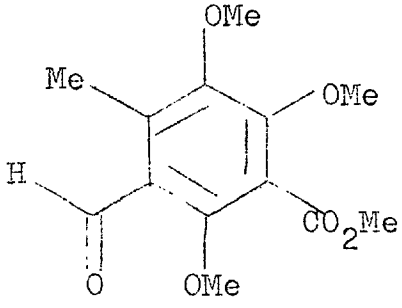
Conversion of (69) to 6-methyl pretetramid (70) was accomplished by refluxing it with hydrogen iodide in phenol.



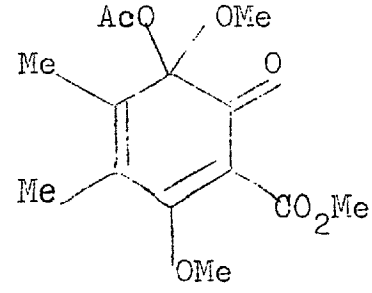
(70)

To obtain a tetracycline from the intermediate (69) requires removal of the ketal group, dearomatisation of ring A, hydroxylation at C-12a and demethylation of ring A.

The model trimethoxy aldehyde (71) was prepared and converted to the dienone (72) by treatment with boron trichloride, hydrogenation and lead tetra-acetate oxidation. This shows a possible means of dearomatisation and ether cleavage.



(71)



(72)

A variety of methods for introducing the 12a-hydroxyl group have been tried and are reviewed elsewhere[56].

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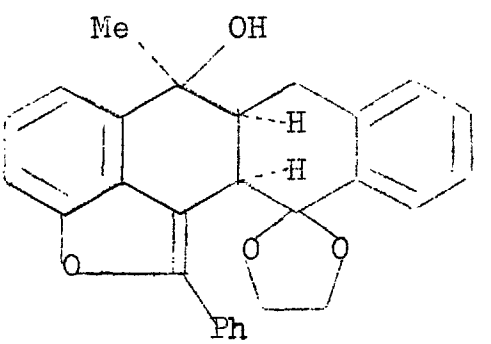
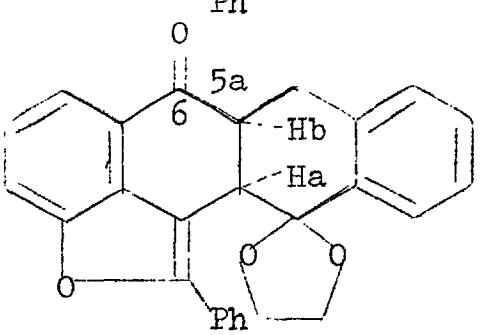
DISCUSSION

1. Studies leading to the 6,10,11,12 oxygenation pattern of tetracycline.

When the present work was started the model tertiary alcohol (1) had been prepared[1] by the reaction of ethereal methyl lithium on the tetracyclic ketone (2). The yield, however, was only in the range 50-60%, due to the enolization of the starting ketone. Furthermore the presence of unreacted starting material created problems in purifying the alcohol. In an effort to obtain complete reaction, without enolization interferring, the addition of methyl lithium was carried out in the presence of acetylacetone and cyclopentadiene. It was hoped that transfer of the enolate anion would occur, but no improvement in the yield was obtained.



(1)



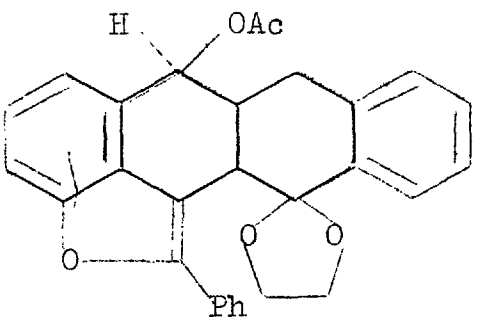
(2)

In the ketone (2) the 5a proton is on the α face and hence is readily attacked by strong bases. If the ring junction were trans then the 5a proton would be relatively inaccessible to the attacking base. In an attempt to epimerise the 5a position the cis ketone (2) was reacted with potassium tert-butoxide in tert-butanol in the absence of oxygen. This treatment led to the slow formation of a new product with λ_{max} 292,305, 320, 342, 425 n.m. which suggested that oxidation of the enol had taken place with subsequent aromatisation of ring B, at the expense of a reduction elsewhere in the molecule. This epimerisation was then abandoned.

It was found that the best method of preparing the alcohol (1) was to add a large excess (20-30 equivalents) of methyl lithium to an ether-benzene solution of the ketone at room temperature. Using this procedure it was found that all the starting material could be reacted and the alcohol (1) isolated in 50-60% yield by preparative thin layer chromatography.

The alcohol (1) was then ozonised under the conditions developed for the 6-acetate (3), using triphenyl phosphine[2] to reduce the ozonide. This led to a mixture of products in which ring B was aromatic.

To study the ozonolysis reaction in more detail the model tertiary alcohol (4) was prepared by the action of methyl magnesium iodide on dihydroperinaphthofuran.



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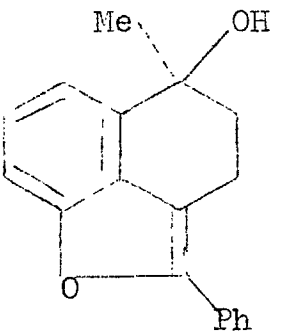


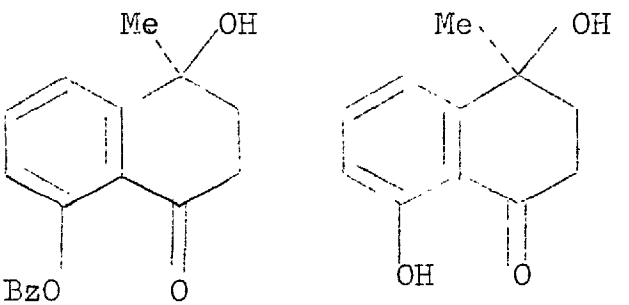
(4)

This was ozonised in chloroform/methanol at -30° until the u.v. spectrum showed 95% reaction. Reduction of the ozonide with triphenyl phosphine gave the keto-benzoate (5), contaminated with triphenyl phosphine oxide. Purification could not be effected by chromatography or fractional crystallization.

The reaction was repeated using dimethyl sulphide[3] as the reducing agent and after thin layer chromatography the keto-benzoate (5) was isolated in 75% yield.

The keto-benzoate was then saponified with sodium methoxide in anhydrous methanol at room temperature to give (6) in 85% yield. The mass spectrum of (6) gave a molecular ion at m/e 192, consistent with the anticipated structure. The n.m.r. spectrum showed the methyl group

as a sharp singlet at 8.40τ and the phenolic hydroxyl as a singlet at -2.50τ, (exchangeable with D_2O).



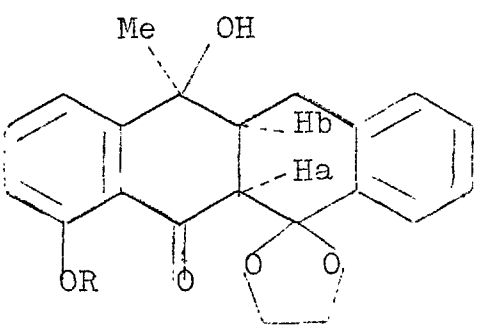
(5) (6)

The tetracyclic alcohol (1) was then ozonised at -76° in chloroform/methanol containing a trace of pyridine. This led to a much cleaner reaction than before and on working up with dimethyl sulphide the keto-benzoate (7a, R=-COPh) was obtained in 76% yield, λ_{max} 3440, 1735, 1675, 1603 cm^{-1}, λ_{max} 234 n.m. (ε 24,200), 286 n.m. (ε 4,300). The n.m.r. spectrum showed Ha as a doublet at 6.07τ (J_{ab}=4 cps), the tertiary methyl group at 8.30τ and the benzylic hydroxyl group at 8.20τ.

The benzoate group was saponified by treatment with sodium methoxide in anhydrous methanol and the product (7b,R=H) was isolated in 70% yield. The phenolic hydroxyl group is strongly hydrogen bonded to the carbonyl group as shown by its very low position in the n.m.r. spectrum at -2.02τ and by the carbonyl frequency

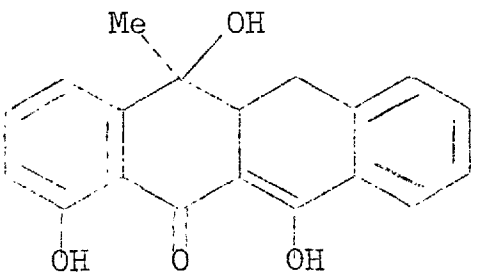
in the i.r. spectrum at 1645 cm^{-1}.

The final transformation to be achieved in this series of experiments was the removal of the ketal grouping, without dehydration of the 6-alcohol. The use of aqueous oxalic acid solution in a two phase system produced no reaction and the starting material was recovered unchanged. The hydrolysis was successfully achieved using dilute hydrochloric acid in acetone and the product (8) isolated in 50% yield. It appeared to be rather unstable and decomposition occurred if further purification was attempted. The structure was assigned on the basis of the n.m.r. spectrum which showed the 10 and 12 hydroxyl groups at -2.24τ and -5.64τ respectively. The tertiary methyl group appeared at 8.25τ and the benzylic hydroxyl at C_6 at 8.33τ while the protons at C_5 and C_{5a} appeared as a multiplet at 6.50-7.10τ.



(7a) R=COPh

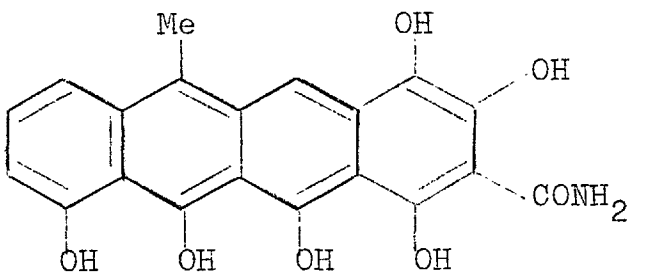
(7b) R=H



(8)

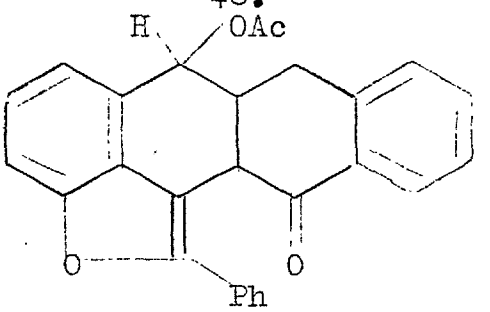
The product (8) has the required structure reputed to be necessary for antibiotic activity[4].

The procedure developed for the ozonolysis and saponification has been used successfully by other workers in these laboratories[5] for the preparation of 4-hydroxy-6-methyl pretetramid (9).



(9)

The last stage in the sequence, the hydrolysis of the ketal protecting group, could be avoided if the 12-keto group was present before ozonolysis. Since the keto-acetate (10) was available[6] it was ozonised under the usual conditions and the 11,12 diketone (11a,R=-COPh) isolated in 34% yield. The spectral and analytical data were consistent with the assigned structure. The free phenol (11b,R=H) had previously been obtained from the keto-acetate (10), but in only 6% yield[6].



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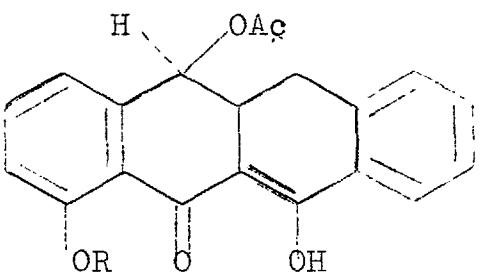
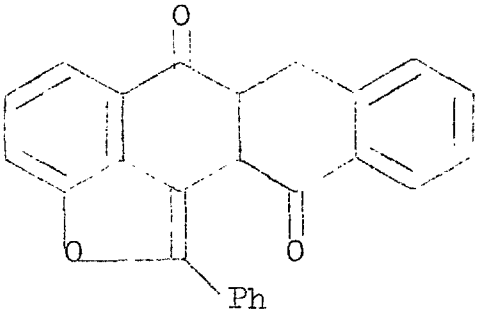


(11a) R=-COPh

(11b) R=H

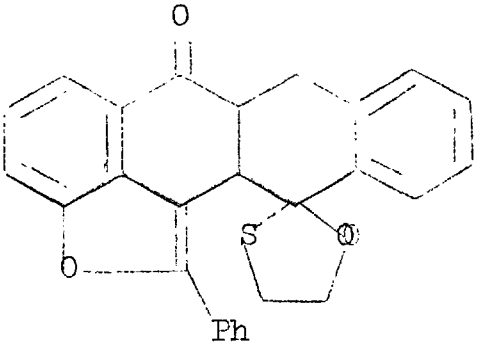
Having shown the feasibility of ozonolysis in the presence of the 12-keto group we then turned to investigating methods of hydrolysing the ketal group before ozonolysis. The tetracyclic ketal (2) was treated with p-toluenesulphonic acid in refluxing toluene. This led to general degradation of the molecule and little of the required diketone (12) was formed (as judged by t.l.c.). The use of dilute hydrochloric acid in dioxane gave the diketone (12), but in only 10% yield. It was then suggested that the use of a Lewis acid might lead to the required diketone. Boron trichloride in dichloromethane at -76° led to an equilibrium mixture of the starting material and diketone in a ratio of 1:1, as judged by t.l.c. Benzaldehyde was added to the reaction in an attempt to capture the ethylene glycol and force the equilibrium over by transketalisation, but no improvement

in the proportion of diketone was noticed.

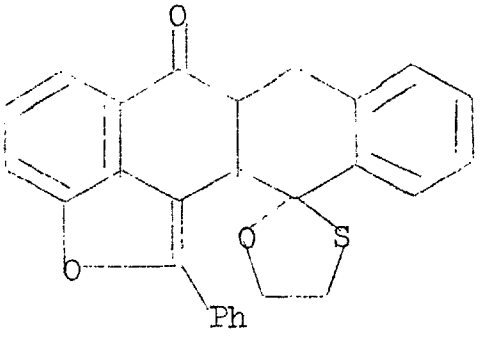


(12)

Since the removal of the ketal group was an obviously inefficient process our attention turned to the use of hemithioketals since it is known[7] that these can be removed by the use of mercuric acetate. A mixture of the diastereoisomeric ketals (13) and (14), in glacial acetic acid, was treated with mercuric acetate and potassium acetate. After 24 hours the reaction was worked up and the diketone (12) isolated in 70% yield.

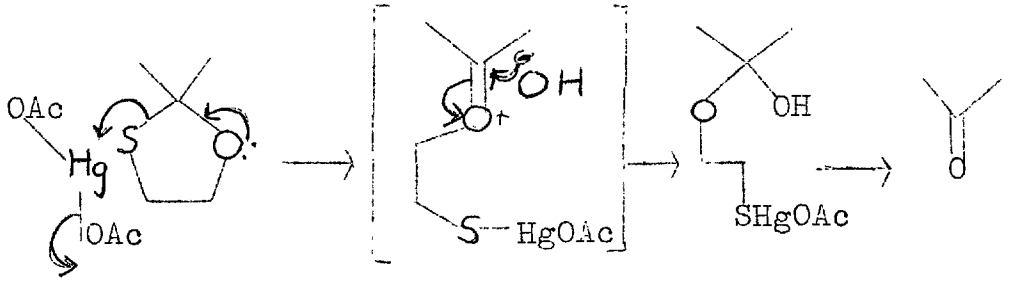


(13)



(14)

It is interesting to note that the isomer with the sulphur atom α reacts more rapidly than the β isomer. The probable mechanism for the reaction is:-



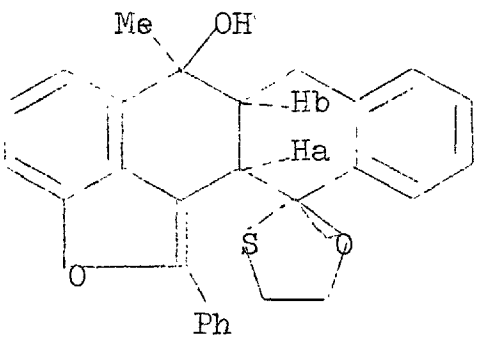
(A)

The intermediate (A) has the C_{12} sp^2 hydridised and consequently will be the same whether derived from (13) or (14). This implies that the rate determining step must be the initial complexing with the mercuric acetate to form (A). Hence the isomer with the sulphur atom on the more accessible face, i.e. α, will react faster.

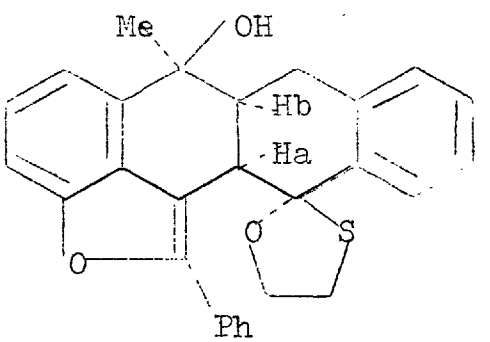
The diketone (12) was then treated with methyl lithium in the usual manner and the product isolated by preparative thin layer chromatography. The n.m.r. spectrum showed that it was a mixture of isomers since two methyl signals were present at 8.55τ and 8.27τ. This mixture

was not examined further.

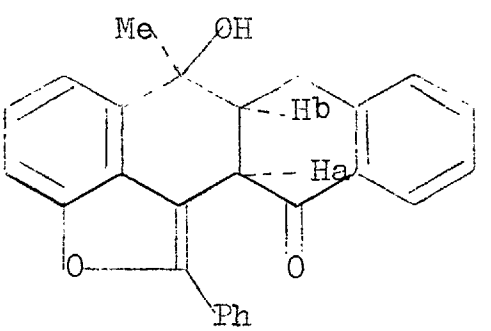
A mixture of the isomers (13) and (14) was reacted with methyl lithium solution to give a mixture of the 6 methyl alcohols (15) and (16), which upon treatment with mercuric acetate and aqueous sodium hydroxide in ethanol/ dimethyl formamide gave the keto-alcohol (17) in 77%yield.



(15)



(16)



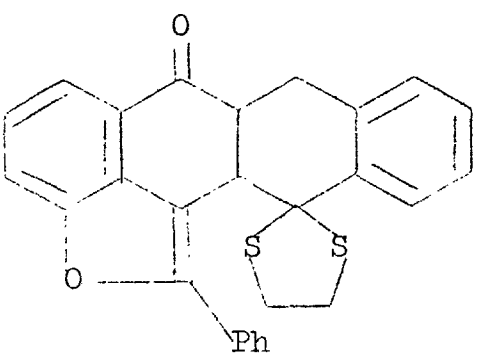
(17)

The isomers (13) and (14) were separated by preparative thin layer chromatography and each treated with methyl lithium to give the alcohols (15) and (16) respectively. In (15) Ha is at 5.74τ (J_{ab}=4.5cps) and the tertiary methyl group at 8.32τ, whilst in (16) Ha is at 5.61τ (J_{ab}=5cps) and the tertiary methyl group at 8.28τ.

Having obtained the alcohol (17) the next step to attempt was the ozonolysis. However, it was felt that the general inconvenience of some of these reactions and the difficulty of purification made the use of hemithioketals unsuitable for synthetic use. Furthermore, work in the main series of compounds with ring A substituted showed that the photo-cyclisation of hemithioacetals went in very low yield and would be of no synthetic use[8].

Stereochemistry of the hemithioketals.

The stereochemistries of the hemithioketals (13) and (14) were assigned by Clive[9] on the basis of the u.v. spectra of the two compounds. The u.v. spectrum of (13) showed λ_{max} 276, 292, 304, 346 n.m. which is similar to the oxygen ketal analogue (2) which shows λ_{max} 279, 296, 308, 352 n.m. The other isomer (14), however, shows λ_{max} 279, 353 n.m. which is similar to the dithioketal analogue (18) which shows λ_{max} 278, 352 n.m.



(18)

The lack of fine structure in the u.v. spectrum of (18) was described as being due to the orbital interactions of the sulphur atom with the 6-carbonyl group to give a "smoothed out" u.v. spectrum.. If this reasoning is correct then the isomer with no fine structure in its u.v. spectrum has the sulphur atom on the β face where it can interact with the 6-carbonyl function as shown in fig.A.

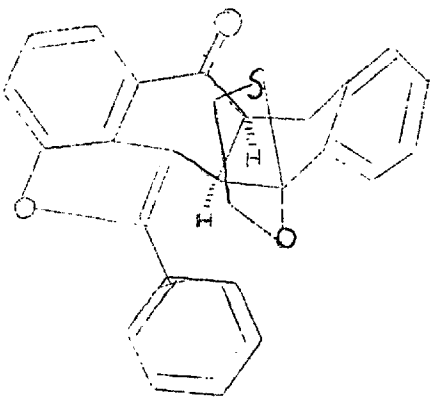
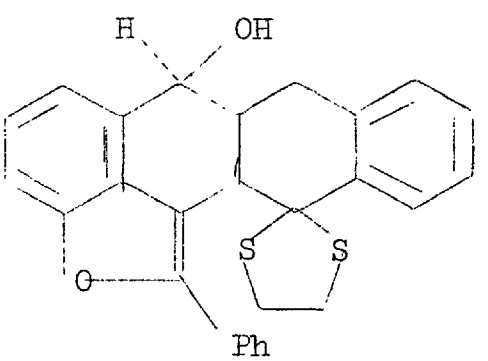
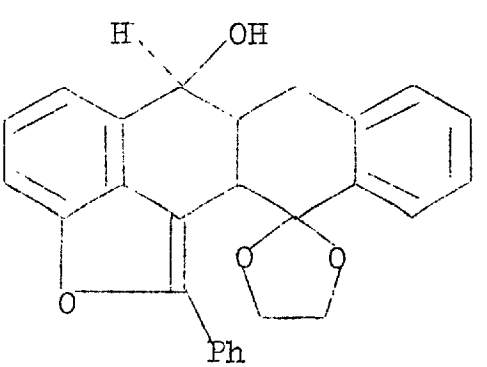


Fig. A.

An interesting difference between the dithioketal and the dioxy-analogue is in the ease of acetylation of the respective 6-alcohols. The dithio alcohol (19) is acetylated at room temperature whereas the oxygen analogue (20) requires heating on the steam bath.

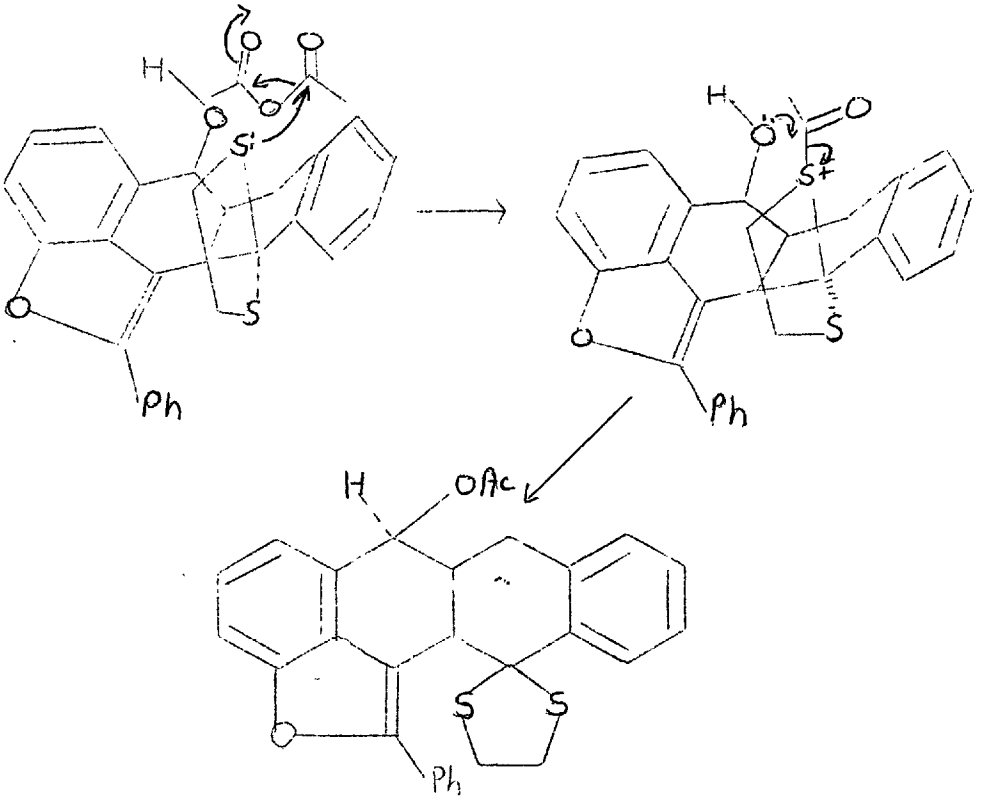


(19)

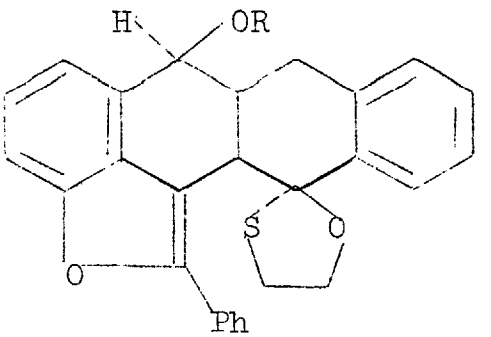


(20)

A possible explanation for this difference is the anchimeric assistance provided by the thioketal group as shown below.

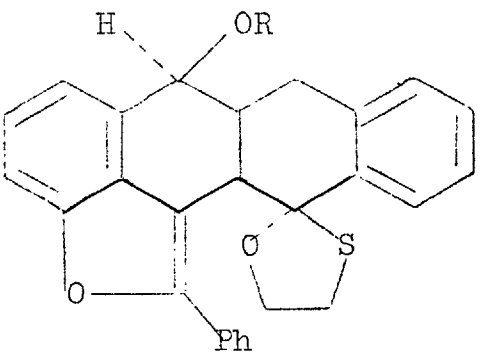


It was hoped that this difference in the rates of acetylation between the sulphur and oxygen analogues would give a method of proving the assigned stereochemistries of (13) and (14). The two isomers (13) and (14) were reduced by sodium borohydride to the alcohols (21a. R=H) and (22a, R=H). The n.m.r. spectrum in conjunction with infra red evidence suggested that the alcohol with the 12-β-oxygen substituent (21a, R=H) was more hydrogen bonded than the 12-β-sulphur epimer.



(21a) R=H

(21b) R=-$COCH_3$

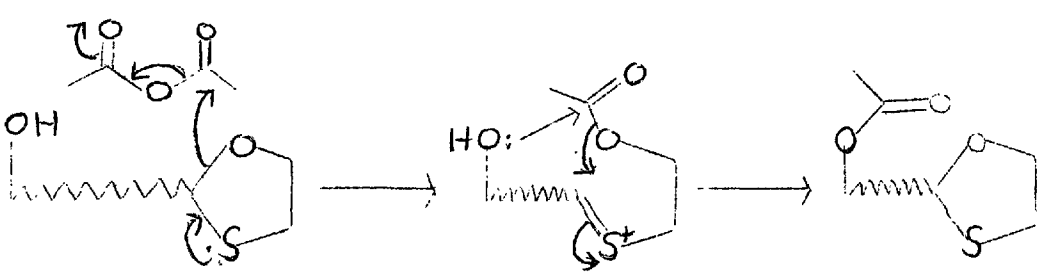


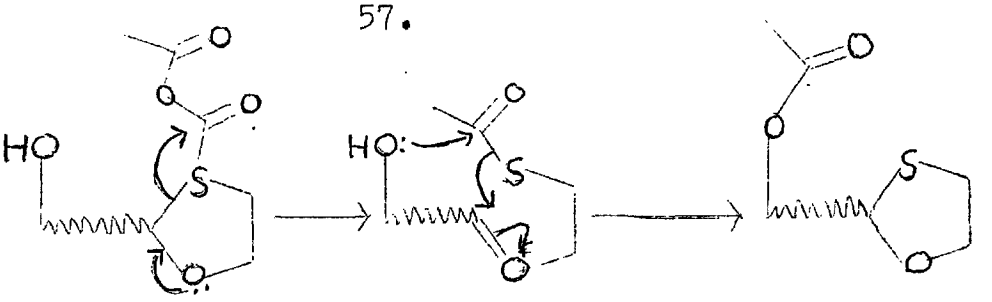
(22a) R=H

(22b) R=-$COCH_3$

Both epimers were acetylated with acetic anhydride-pyridine at room temperature to give the acetates (21b, 22b). However, the 12-β-oxy-6-β-alcohol had a half reaction time of 1 hour whereas the 12-β-thio-6β-alcohol had a half reaction time of 3 hours. This result was surprising since the opposite was expected. To explain this result the following mechanism is proposed:-

A



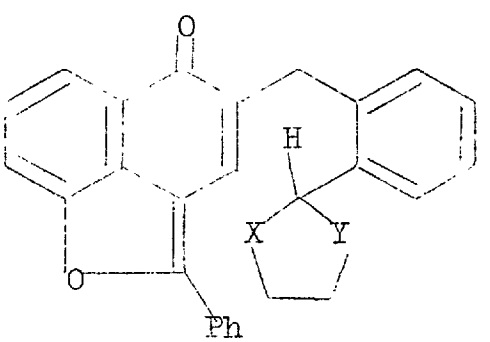
B 

The enhanced rate in A is due to the sulphonium ion. If this is true the ethylenedioxy alcohol should acetylate at room temperature through an oxonium ion intermediate. The reason it does not is due to the fact that a C–O bond (ca.84 kcal $mole^{-1}$) is some 22 kcal $mole^{-1}$ stronger than a C–S bond (ca.62 kcal $mole^{-1}$), and also being symmetrical in electron density does not induce polarisation shown in B.

Although the assigned stereochemistries have not been proved chemically the n.m.r. evidence on the epimeric pairs (13,14), (15,16), (21,22) lends weight to the original assignments (13) and (14).

2. Studies on the photocyclisation reaction

From previous work[9] on the formation of the tetracyclic ketal (2) it was found that by using a tungsten lamp, and benzoyl peroxide as an initiator, the reaction could be carried out in refluxing benzene to give a yield of 50-70%. The main disadvantage of the reaction was that to process any amount of the acetal required quite lengthy periods of irradiation. This was overcome by the use of the hemithio and dithioacetals (24) and (25), which required a much shorter reaction period.



(23) X=Y=O

(24) X=O, Y=S

(25) X=Y=S.

To establish that the reaction was indeed a photochemical one the acetal (23) was refluxed, in benzene, first with benzoyl peroxide, and secondly with azobisbutyronitrile, in the absence of light. No reaction could be observed and the acetal was recovered unchanged. The cyclisation was attempted under more vigorous conditions by heating the acetal, in a sealed

tube , at 210° for one hour and at 305° for three hours. Neither of these experiments gave any of the cyclised material.

The stereochemistry of the cyclised product has been assigned as a cis fusion of the B and C rings (see next section for details). It is possible that the product formed is the trans isomer which is converted to the cis isomer on the alumina used for its purification. To investigate this possibility the product formed in the photolysis was directly reduced to the 6-alcohol with sodium borohydride. This was purified and shown to be identical in all respects to the alcohol produced by reduction of the cis ketone (2).

The effects of various solvents on the reaction were examined and the results obtained are summarised in Table 1.

TABLE 1

Solvent	Additive	Yield %	Reaction Time (hrs.)
Benzene	Benzoyl peroxide	54	39
Acetone	" "	8	24
Ethanol	" "	36	19
Dioxan	" "	42	47
"	A.B.I.	52	24
"	None	69	19
"	None, nitrogen specially purified	27	66
"	None, air bubbled through solution	10	19

It can be seen that with benzoyl peroxide as the additive benzene is the best solvent. Interesting results were obtained when dioxan was used as the solvent since it was possible to carry out the reaction without any additive being present. This, it was thought, was due to dioxanyl radicals being produced by the presence of oxygen in the nitrogen used. When all of the oxygen had been removed with an activated catalyst[10] the yield diminished to 27%. However, when air was bubbled through the solution the yield fell even further to 10%.

We thought that the purpose of the benzoyl peroxide might be to remove trace impurities in the benzene, which inhibited the reaction, and was not a true initiator or catalyst. To test this hypothesis the purified benzene normally used in the photolysis experiments was refluxed in the presence of benzoyl peroxide. After 72 hours of refluxing the benzene was distilled out and used in a photolysis without any benzoyl peroxide being present. The yield obtained was 11%, the same as that using the untreated benzene.

The residue obtained after destroying benzoyl peroxide by refluxing in benzene was then used as the additive in the photolyses. The results obtained are shown in Table 2.

TABLE 2

Amount of residue (mg/100mg of acetal)	Yield %	Reaction Time (hrs)
7	24	66
80	46.5	50
150	67	46
300	73	50
600	75	30

Hence fairly large amounts of destroyed benzoyl peroxide are more efficient than benzoyl peroxide itself

in the photolysis reaction.

The next step was to isolate the compound, present in the destroyed benzoyl peroxide, which is responsible for the enhanced rate and yield in the cyclisation reaction. The thermal and photochemical decomposition of benzoyl peroxide has been extensively studied and a large number of the products isolated[11]. The first of these decomposition products to be tested was biphenyl, which gave a yield of 10% when used as an additive. Phenyl benzoate, another decomposition product, gave a yield of 23%. The residue obtained from the thermal destruction of the benzoyl peroxide was chromatographed on an alumina column eluting with 10% benzene/petrol. This gave two fractions, the first of which was a mixture of biphenyl and dihydrobiphenyl (identified by i.r.), and the second a mixture of tetrahydroquaterphenyls. On washing the column with ether a further fraction was collected. When the photolysis was carried out in the presence of the tetrahydroquaterphenyl fraction yields of 20% and 44% were obtained with 13mg. and 180mg. of additive per 100mg. of acetal. The ether washings from the column gave a yield of 44% on photolysis. These experiments are summarised in Table 3.

TABLE 3

Additive (mg/100mg of acetal)	Yield %	Reaction Time (hrs.)
Biphenyl (12)	10	68
Phenylbenzoate (7)	23	43
Tetrahydroquaterphenyls (13)	20	96
" " " (180)	44	96
Washings from column (180)	44	80

It is apparent that none of these fractions is the true 'catalyst' since the yields obtained do not approach that obtained from using destroyed benzoyl peroxide.

In another attempt to separate the active component the residue was distilled at 100° at 5×10^{-4}mm.Hg. The first fraction, collected in a liquid nitrogen trap, was identified as a mixture of benzoic acid and biphenyl. The second fraction was a mixture of benzoic acid, 1,4 dihydrobiphenyl and biphenyl, while the involatile residue was rich in esters. Photolysis of the acetal in the presence of the first fraction gave a 57% yield of the cyclised material while the residue gave a yield of only 28%. The second fraction also gave a yield of 57%. After removal of the acidic material, the first

fraction gave a yield of 18% and the acidic material produced a yield of 78%. It, therefore, appears that the true catalyst for the cyclisation is benzoic acid. When an equivalent weight of benzoic acid was used a yield of 78% was again produced, while the use of two equivalents gave no increase in the yield but increased the rate of reaction. Use of less than one equivalent of benzoic acid led to a decrease in the yield of cyclised material.

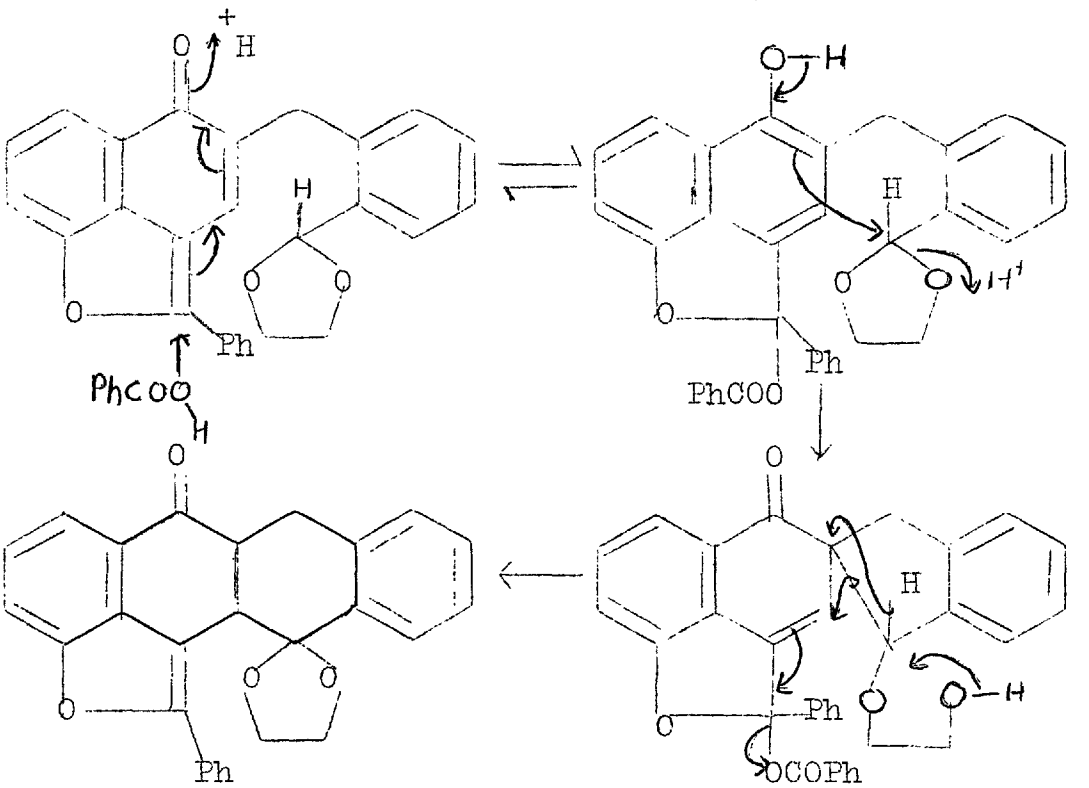
To examine the effect of different acids on the cyclisation glacial acetic, p-nitrobenzoic and p-methoxybenzoic acids were used and gave yields of 62%, 57% and 75% respectively, as shown in Table 4.

TABLE 4

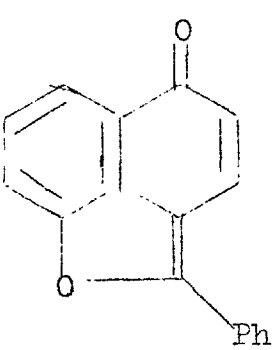
Acid Used	Yield %
Benzoic	78
Acetic	62
p-Nitrobenzoic	57
p-Methoxybenzoic	75

Having established that the photocyclisation was dependant on the presence of an acid our attention

turned to elucidating the mechanism of this unusual reaction. The first idea was that the benzoic acid was adding to the perinaphthofuran chromophore and the cyclisation proceeded by the following mechanism:-

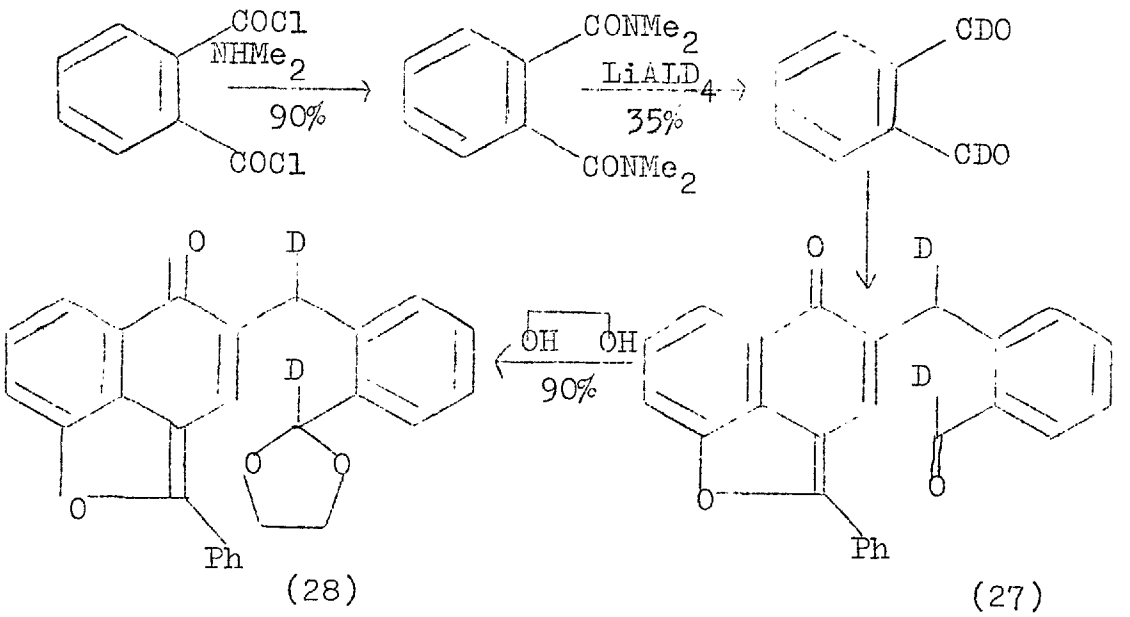


To test the first step of this mechanism perinaphthofuran (26) was photolysed, in benzene, in the presence of one equivalent of benzoic acid but no reaction occurred.



(26)

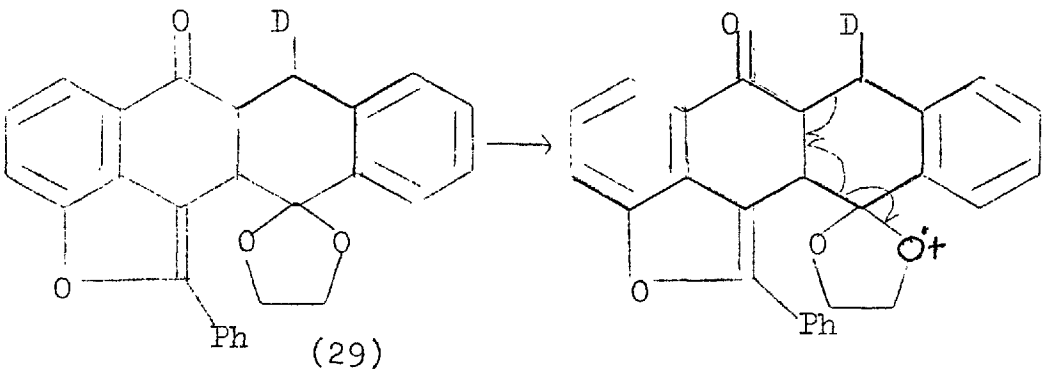
It was thought that the use of a labelled acetal would be helpful in elucidating the mechanism. The dideuteroacetal (28) was synthesised by the following route.



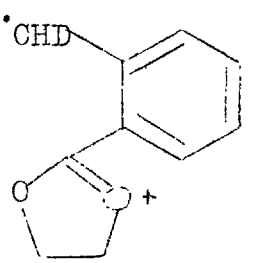
It is interesting to note that both deuterium atoms in the phthalaldehyde were retained in the ACD tricyclic aldehyde (27). This implies that the base catalysed rearrangement of the exo double bond to the endo position, which occurs during the reaction is irreversible.

The deuteroacetal was then photolysed in the presence of benzoic acid and mass spectrometry showed that the product (29) contained only one deuterium atom.

The n.m.r. spectrum still showed a sharp doublet for Ha and, therefore, the deuterium atom must be in the methylene bridge. This was confirmed by the base peak of the mass spectrum at m/e 163 due to the following fragmentation.

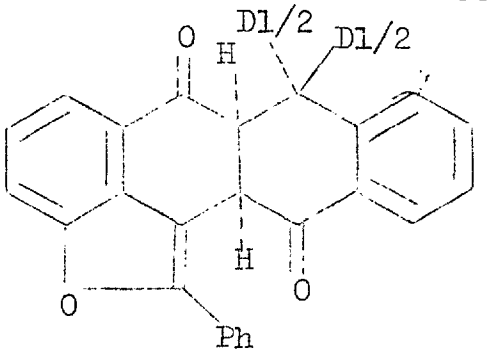


(29)

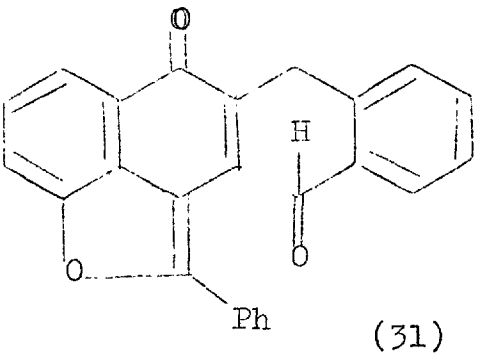


m/e 163.

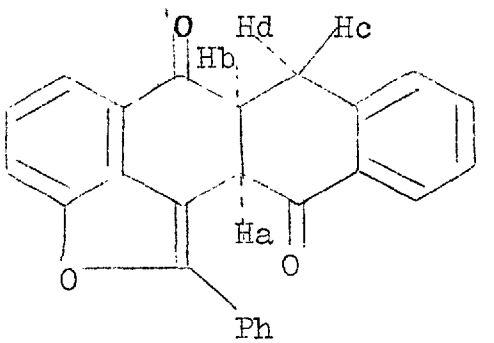
The stereochemistry of the deuterium atom could not be found from the n.m.r. spectrum due to the complexity introduced by the ketal protons. To overcome this the deuteroaldehyde (27) was photolysed in the usual way to give the deuterodiketone (30) in 36% yield. As a means of checking the coupling constants for the deuterodiketone the aldehyde (31) was cyclised to the diketone (32) and the coupling constants determined by spin decoupling.



(30)



(31)



(32)

J_{ab} = 6.5 cps

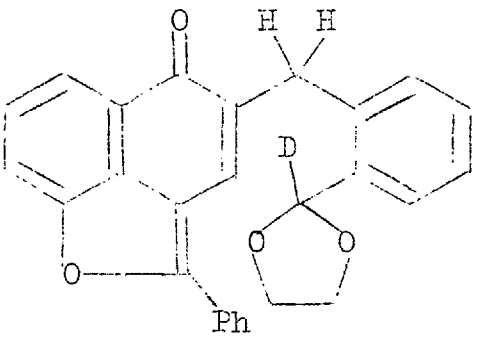
J_{bc} = 5 cps

J_{bd} = 2.5 cps

J_{dc} = 16 cps

The n.m.r. of the deuterodiketone (30) showed that the deuterium atom was evenly distributed between the α and β positions.

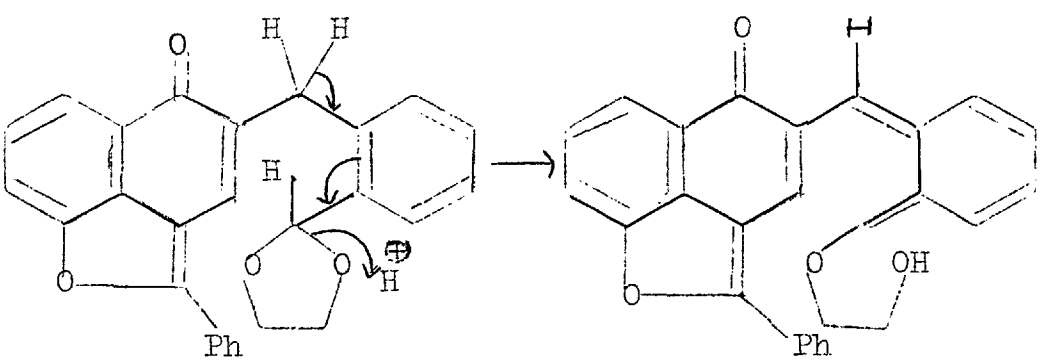
It was impossible to decide whether the deuterium atom in the cyclised material was derived from that originally in the methylene bridge or in the acetal portion. To answer this question we hoped to prepare the mono deuterated acetal (33) by base exchange on the di-deuterated acetal (27). The use of potassium tert-butoxide in tert-butanol or of sodamide in liquid ammonia failed to exchange the deuterium atom in the methylene bridge.



(33)

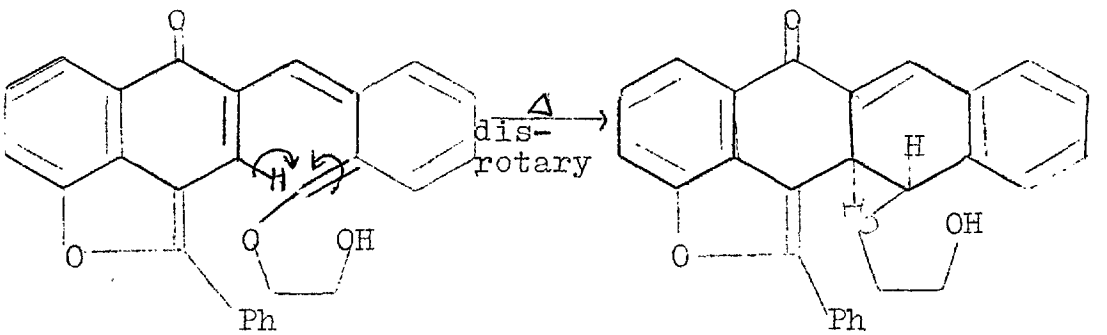
We then decided to find out if any of the protons derived from the acid used were incorporated into the cyclised material. Deuterobenzoic acid was prepared from benzoyl chloride and deuterium oxide. When this was used in the photolysis n.m.r. showed that no deuterium had been incorporated into the cyclised material.

A mechanism has been put forward[12] to explain the photocyclisation and is shown below. The first step is a reversible acid catalysed 1,5 hydrogen shift[13] to the triene (34).

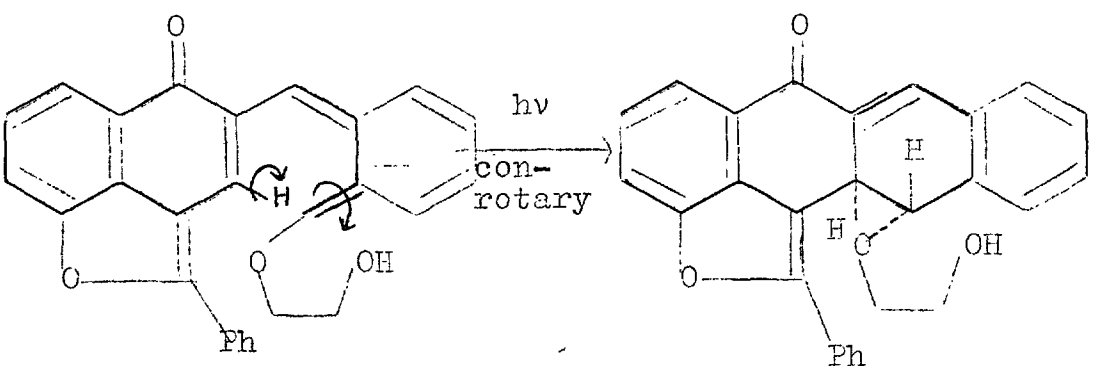


(34)

The triene then undergoes an electrocyclic cyclisation, governed by the Woodward-Hoffmann rules[14]. This process can be either thermal or photochemical to give the cyclised materials (35) or (36) respectively.

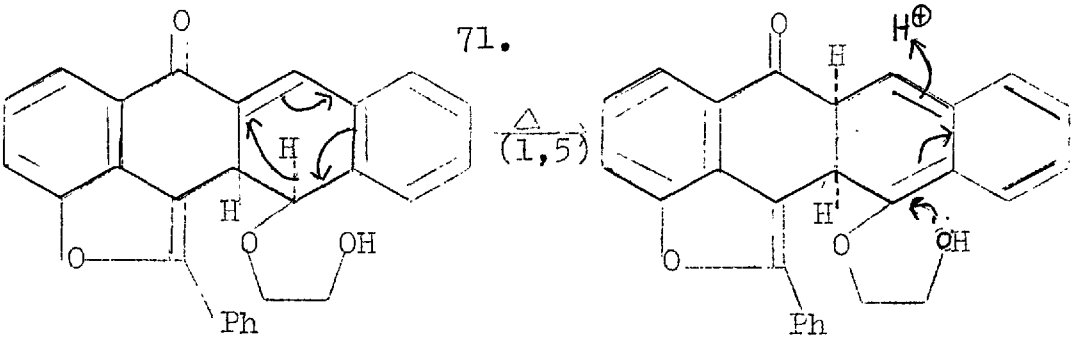


(35)



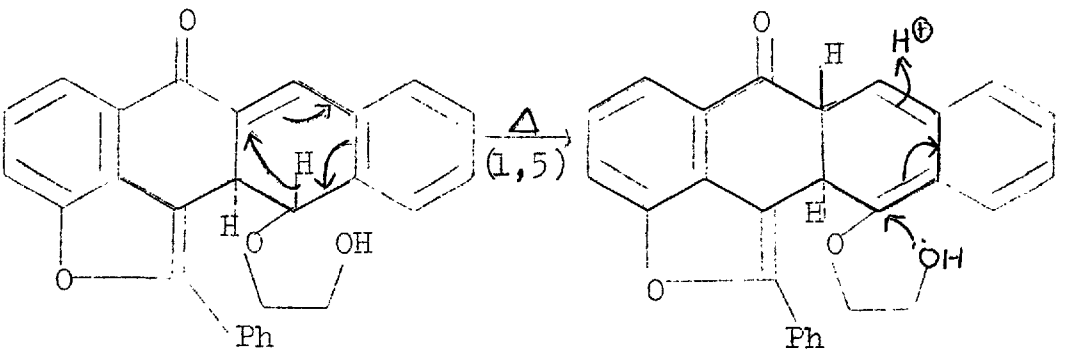
(36)

The next step is a 1,5 sigmatropic rearrangement which must be suprafacial and hence a thermal process[15].

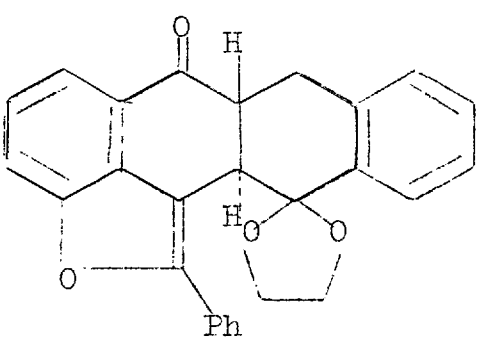


(35)

(2)



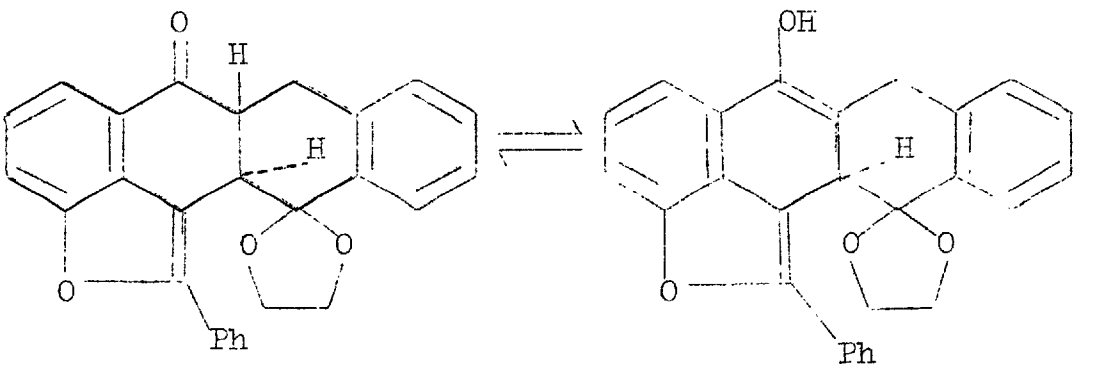
(36)



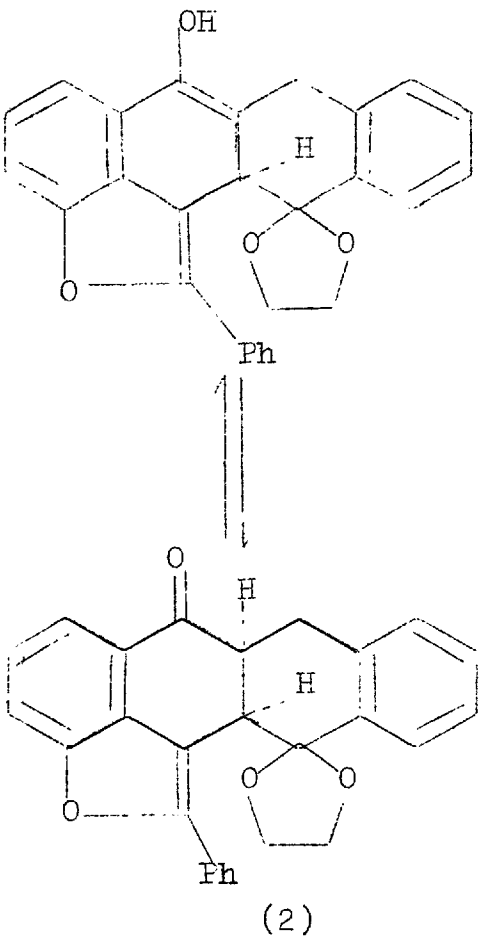
(37)

The photochemical cyclisation is the more likely route since the alternative route has no photochemical

steps and it has been shown that light is necessary for the reaction. This route, however, predicts a trans fused product (37), whereas a cis fused product (2) is isolated. This means that the trans fused product (37) must have equilibrated to the more stable cis product (2) under the reaction conditions.



(37)



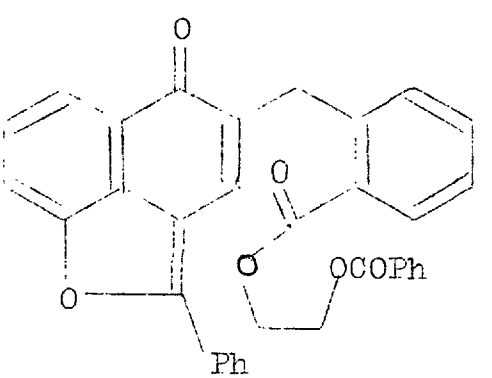
(2)

This would explain why the deuterium atom on the acetal is not found in the 5a positon of the product.

The rate of cyclisation must be faster than the rate of enolisation since when the reaction was carried out in the presence of deuterobenzoic acid and the starting material recovered no deuterium had been incorporated into it.

Attempts were made to trap the triene (34) with dimethyl acetylene dicarboxylate and tetracyanoethylene but these were unsuccessful.

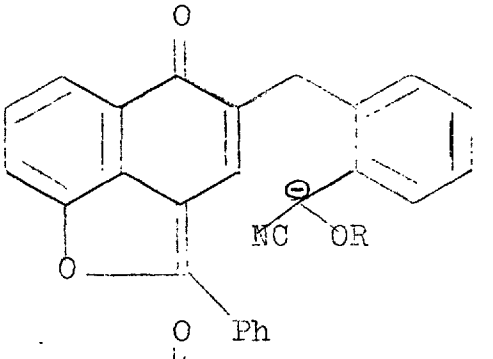
This mechanism is not entirely satisfactory since it does not explain the formation of the ester (38) which is isolated in low yield when the reaction is carried out in the presence of benzoyl peroxide or benzoic acid. This may be due to a radical side reaction. There is the possibility of the reaction being able to go via a radical path since this would explain the results obtained from using dioxan as the solvent. However, no more mechanistic work was carried out since our main interest was to use the reaction in the synthetic scheme to produce tetracycline.



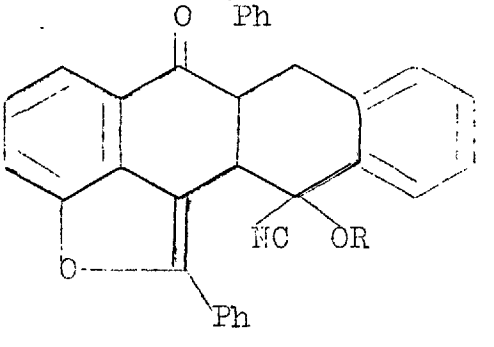
(38)

3. The stereochemistry of the tetracyclic ketal.

The first linear tetracyclic compound prepared in these laboratories was from the intramolecular Michael addition of the benzylic cation (39) to give the cyclised material (40)[16]. Meerwein-Pondorff reduction of the cyanohydrin (41) gave the 6-alcohol, which was acetylated to furnish the 6-acetate (42). The n.m.r. spectrum showed a coupling constant of 3c.p.s. for the 5a,6a proton and one of 6 c.p.s. for the 5a,11a protons. This was used to assign a cis configuration[17] to the molecule as shown in the formula. The acetate methyl signal was at 8.86τ, as compared with a normal benzylic acetate at ca. 7.9τ. This was claimed to be due to a strong shielding effect of the aromatic ring A which can only come about if the ring junction is cis.

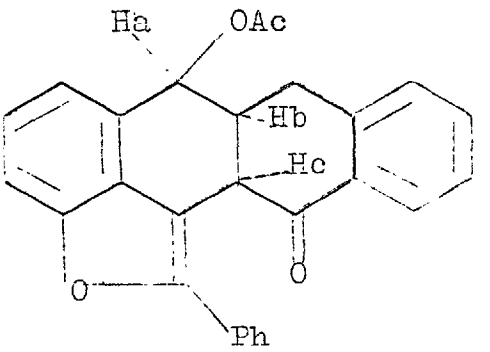


(39) R= 



(40) R= 

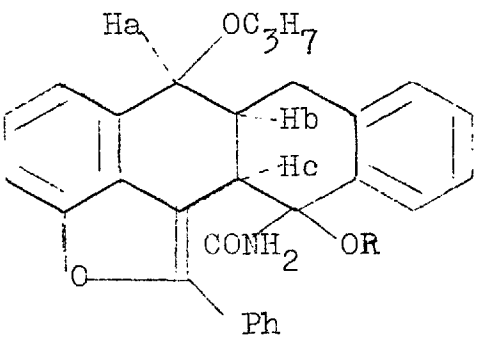
(41) R=H



(42) J_{ab}=3cps

J_{bc}=5.5cps.

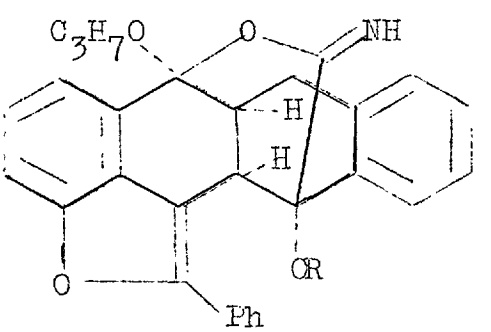
Meerwein-Pondorff reduction of the tetrahydropyranyl ether (40) gave the amide (43). This was explained by the formation of an imino lactone (44) from attack of iso-propoxide ion on the 6-ketone. This mechanism requires that the ring junction be cis and also that the cyano function bears a trans relationship with the adjacent proton.



(43) R= 

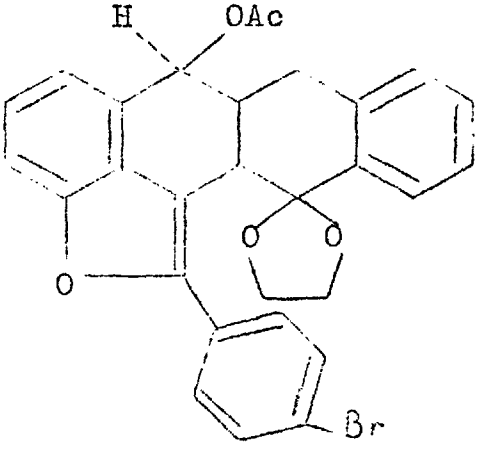
J_{ab}=3cps

J_{bc}=6cps.



(44) R= 

The coupling constants for the 5a,11a proton in these compounds has been used as a diagnostic test for a cis fused ring system[17]. In the photocyclisation products the observed coupling constants are in the range 4.5-6cps and for this reason a cis configuration has been assigned to the 5a,11a protons. The coupling constants whilst consistent, are not conclusive, and since the relative stereochemistry at 5a,6 is of vital importance to biological activity it was essential to settle this arguable point by the use of X-ray crystallography. The bromo-acetate (45) was chosen as a suitable heavy atom derivative for the X-ray study.



(45)

The route used to synthesise this compound is shown in Fig. B..

The preparation of the bromo-perinaphthofuran (46) was first attempted by a Friedel-Craft reaction between 1,5 dihydroxy naphthalene and p-bromobenzoyl chloride in nitrobenzene. The product was, however,

obtained in only 1.6% yield. The spectral and analytical data confirmed the structure. The condensation in polyphosphoric acid[18] was then tried under various conditions and the optimum yield obtained was 22%, as shown in Table 5.

TABLE 5

Reaction Time (hrs)	Temp. (°C)	Yield (%)
1/2	80	5
8	80	17
5	120	19.5
18	110	22

The hydrogenation to the bromo-dihydropernaphthofuran (47) was carried out in tetrahydrofuran over W-4 Raney nickel catalyst in 68% yield. The dihydro compound was then condensed, under basic conditions, with o-phthalaldehyde to give the tricyclic aldehyde (48). This was not characterised but converted immediately to the ethylene acetal (49) by refluxing in benzene with ethylene glycol and p-toluenesulphonic acid, the water being removed with a calcium hydride filled Soxhlet extractor. The acetal was then photolysed in the usual way, in the presence of two equivalents of

benzoic acid to give the tetracyclic ketal (50) in 74% yield. Reduction with sodium borohydride followed by acetylation with acetic anhydride/pyridine gave the bromo-acetate (45) in an overall yield of 7.5% from p-bromobenzoyl chloride. The bromo-acetate was then recrystallised from acetonitrile, producing satisfactory crystals for the X-ray crystallography.

The X-ray studies were carried out by Professor D. Rogers and Mr. D.L. Sales, of this department. The crystals were triclinic with a $P\bar{1}$ space group. The density of the crystals was measured by the flotation method which gave a result of 1.49gm cm^{-3}. The calculated density was 1.5gm cm^{-3} and using this it was found that there were two molecules per unit cell. The dimensions of the unit cell were a=7.83Å, b=10.96Å and c=17.04Å with the cell angles $\alpha=94^{\circ}2'$, $\beta=94^{\circ}43'$ and $\gamma=125^{\circ}11'$. The bond lengths and angles measured are shown in Fig. C and the structural features produced by a computer print out of the crystallographic data are shown in Fig. D.

This confirms the cis stereochemistry of the protons at C 5a,6 and 11a in the bromo-acetate. If a model is made up using the X-ray data it can be seen that the

Fig. B

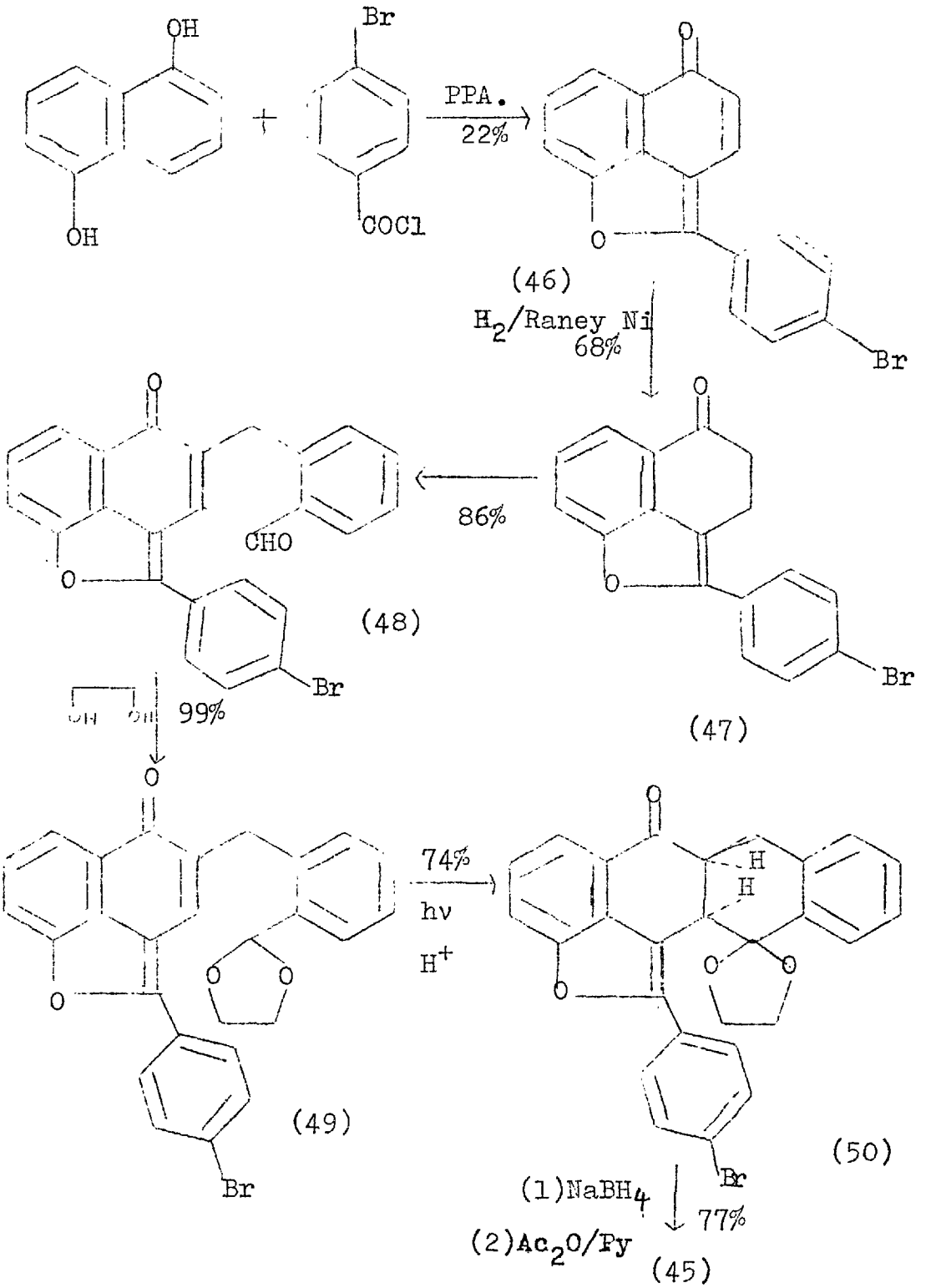

OH
OH
Br
COCl
PPA.
22%
O
O
Br
(46)
H_2/Raney Ni
68%
86%
CHO
(48)
(47)
99%
74%
hν
H^+
(49)
(50)
(1)$NaBH_4$
(2)Ac_2O/Py
77%
(45)

FIG. C

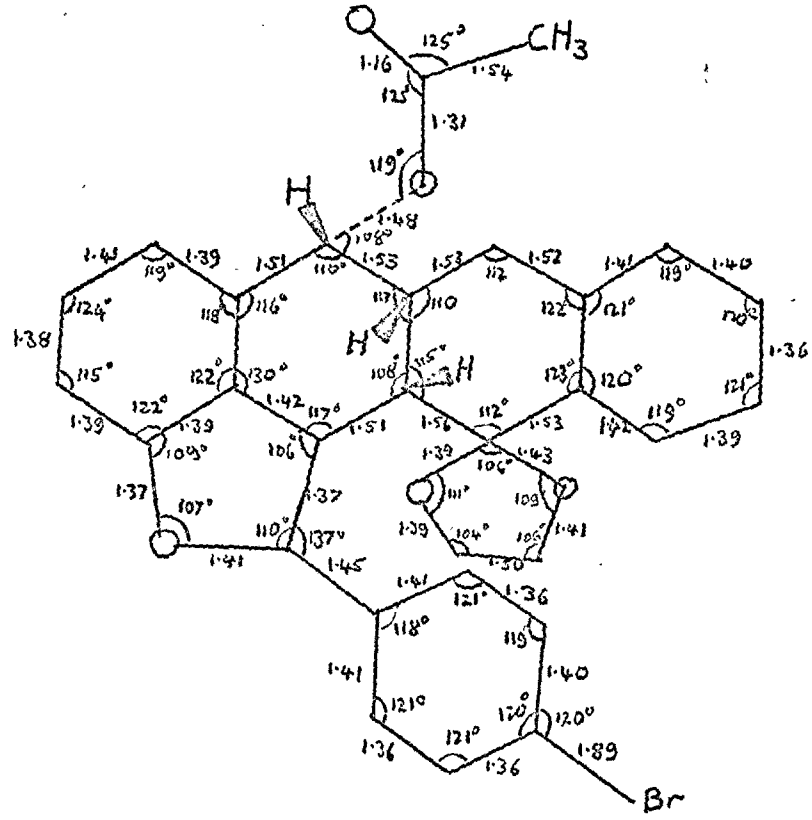
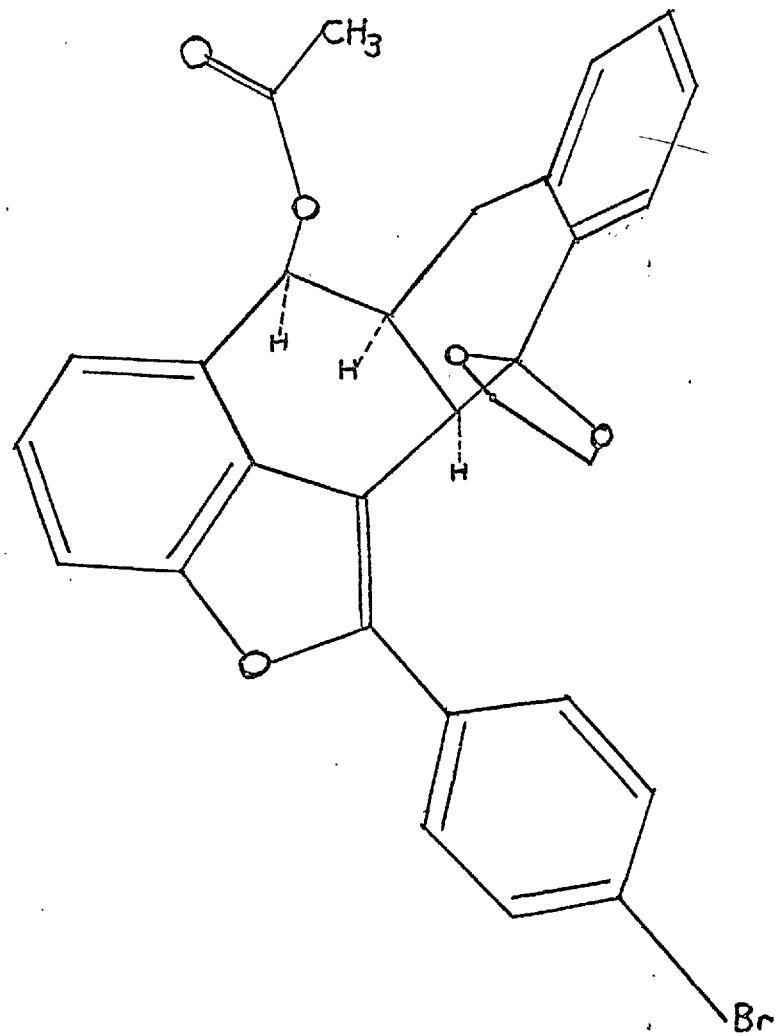
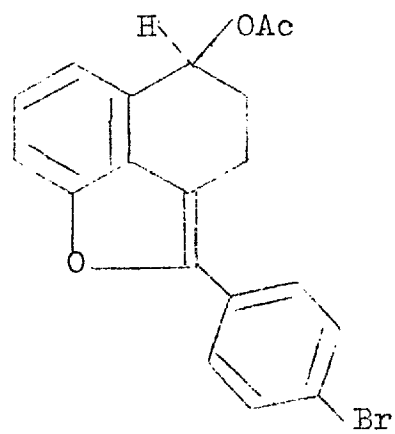


FIG.D



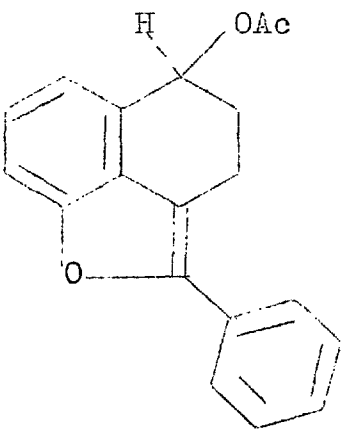
acetate methyl group is held in the shielding region of the ring A hence explaining its abnormally high position in the n.m.r. spectrum. The dished shape of the molecule explains the stereoselectivity of the hydride reduction of a 6 ketone function since attack on the β face by a hydride ion is severely hindered.

To show that the tetracyclic acetate (3) had the same stereochemistry as the bromo-acetate (45) it was necessary to remove the bromine atom from (45) and show that the product was identical to (3). The CD bromo-acetate (51) was prepared as a model compound on which various debromination procedures could be attempted.



(51)

It was hoped to remove the bromine atom by trans-metallation with a suitable organolithium compound and then quenching with water to give the acetate (52).



(52)

Treatment of the bromo-acetate (51) with methyl lithium in ether quenching with water failed to remove the bromine atom. Butyl lithium is reported[19] as a better reagent for transmetallations and when this was used the debromo-acetate (52) was obtained. However, when the reaction was repeated on the bromo-acetate (45) a complex mixture of compounds was obtained. Due to the small amount of the bromo-acetate (45) available these debromination experiments were then abandoned.

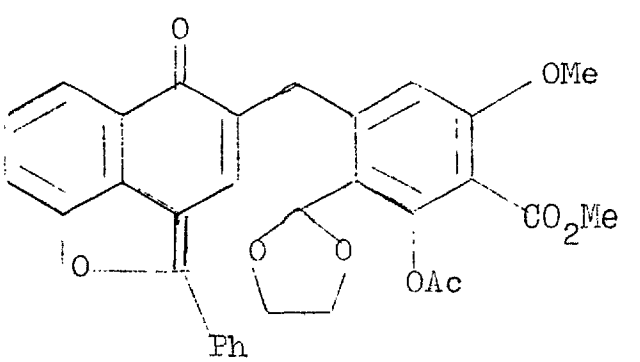
The analytical data on the bromo-compounds prepared showed that one hydrogen had been replaced by bromine and the spectral properties were almost identical to those of the corresponding debromo-compound. This, it

was felt, was sufficient evidence for assuming that the stereochemistry of the debromo series of compounds was identical to that of the brominated series. Hence the X-ray studies have shown that the products from the photocyclisation have the correct relative stereochemistry at C 6, 5a, the two centres that are not epimerisable apart from C 12a, for further elaboration to tetracycline.

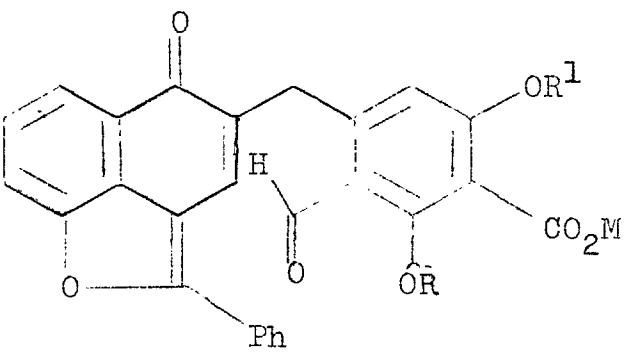
4. Studies on the 1,3-dimethoxy-2-carbomethoxy substituted ring A series of compounds.

Previous workers[20] have shown that the use of acetate protecting groups in the substituted ring A series of compounds was not possible owing to their lability during the photocyclisation reaction. It was thought advisable to re-investigate this aspect of the work in the light of the results obtained from examining the photocyclisation reaction.

The first aim was to synthesise the mono-acetate (53) and to photolyse this in the presence of acetic acid and acetic anhydride. The diphenol (54) was prepared by the method described by Hase[20] using αα-dichloromethyl methyl ether as the formylating reagent. Methylation with one equivalent of dimethylsulphate/potassium carbonate in acetone gave a mixture of the starting diphenol (54) and the dimethyl ether (55), with none of the required mono ether (56).



(53)



(54) R=R^1=H
(55) R=R^1=Me
(56) R=H R^1=Me
(57) R=Ac R^1=Me
(58) R=Ac R^1=Ac

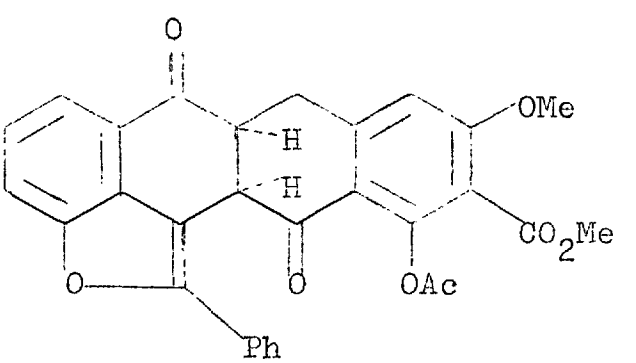
Consequently the dimethyl ether was treated with boron trichloride[21] in dichloromethane at -76° to give the mono-demethylated compound (56). The direction of the demethylation was assigned on the basis of previous work on analogous model compounds. The n.m.r. spectrum of the demethylated compound showed the two methyl groups as sharp singlets at 6.12τ and 6.03τ with the formyl and hydroxyl protons at -0.18τ and -2.60τ respectively. The analytical data confirmed the empirical formula as $C_{28}H_{20}O_7$.

Acetylation of (56) with acetic anhydride in pyridine, at 90° for 6 minutes, gave (57). The i.r. spectrum, ν_{max} 1770, 1738, 1680, 1638 cm^{-1}, showed that the formyl group was not acetylated. This acetate (57)

appeared to be rather unstable and readily decomposed to the phenol (56), and was not completely characterised.

The next stage was to prepare the acetal (53) from the aldehyde (57). This was first attempted by an exchange reaction using ethyl methyl ketal and boron trifluoride etherate in benzene. Extensive degradation occurred and no acetal was isolated. This is probably due to the effect of the methyl ether grouping since the diacetate (58) readily forms an acetal under these conditions. When the aldehyde (57) was refluxed with ethylene glycol and p-toluenesulphonic acid in benzene, with the condensate passing through a calcium hydride packed Soxhlet thimble, the phenol (56) was slowly formed.

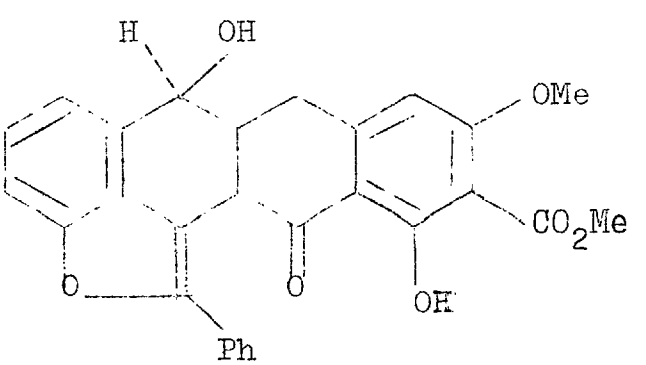
Since the acetal (53) was not readily available it was decided to photolyse the aldehyde (57) in the hope of obtaining the diketone (59).



(59)

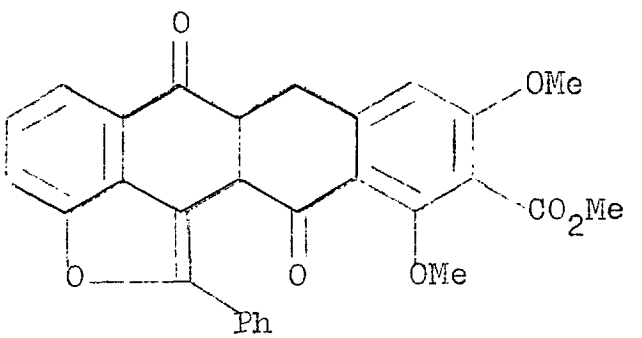
Acetic acid was used as the necessary proton source and, to reacetylate any phenolic material formed, acetic anhydride was added. Photolysis of this mixture in benzene, with a tungsten lamp, gave a complex mixture of at least ten compounds. Reacetylation of the mixture with acetic anhydride/pyridine failed to decrease the number of compounds formed.

It was apparent that acetate protecting groups were unsuitable for the photolysis reaction and it was decided to return to the use of methyl ethers as the protecting group. The immediate aim was to prepare a tetracyclic compound with a free phenolic group at the 1 position and a carbonyl function at the 12 position. Since it was known that the 6,12 diketone system was very susceptible to autoxidation it was also decided to reduce the 6-ketone. Therefore, it was hoped to prepare the keto-phenol (60), which could be used for studies on the oxidation of ring A.



(60)

The dimethoxy-aldehyde (55) was photolysed in the usual way in the presence of benzoic acid and the diketone (61) rapidly formed. This was isolated by preparative thin layer chromatography in 15% yield. A large number of highly coloured compounds were also formed during the reaction, probably from the autoxidation of the diketone.



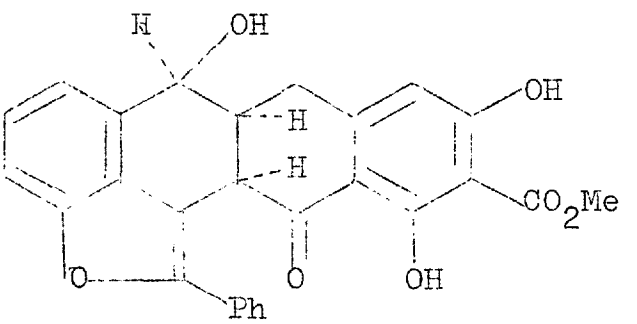
(61)

The structure of the diketone was assigned on the basis of the i.r. spectrum, ν_{max} 1725, 1690 cm^{-1}, and u.v. spectrum, λ_{max} 277, 294, 360 n.m. (ε 23000, 22000, 18100). The analytical data confirmed the empirical formula as $C_{29}H_{22}O_7$.

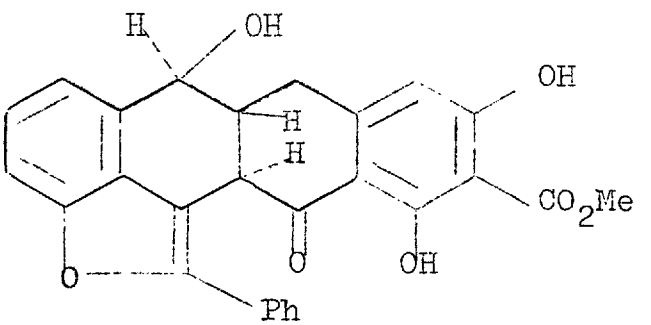
The diketone (61) was then treated with an excess of boron trichloride in dichloromethane at -76^{o}. The product formed was not isolated but reduced immediately with sodium borohydride in tetrahydrofuran/methanol. This gave a mixture of compounds and the major product was isolated in 38% yield. The mass spectrum showed a

molecular ion at m/e 456 and the structure of the product was tentatively assigned as the didemethylated compound (62). Very little of this compound could be isolated and so a n.m.r. spectrum could not be obtained. Hence the alternative structures (63), (64) and (65) cannot be ruled out, although they are less likely.

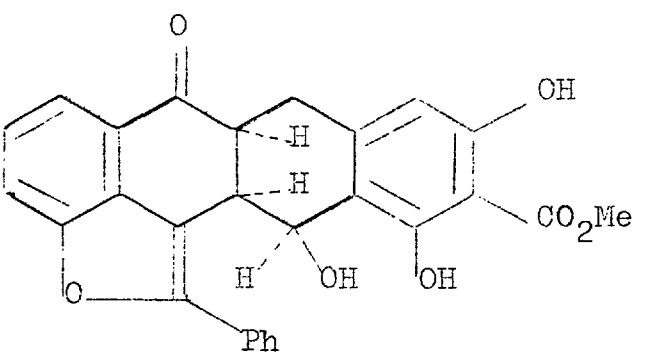
When the diketone was treated with less boron trichloride a mixture of mono- (35%) and di- (25%) demethylated products was formed. These were separated by thin layer chromatography and the mono-demethylated compound (66) reduced with sodium borohydride. A mixture of compounds was formed and from this one major product was isolated in 32% yield (based on the assigned structure). The mass spectrum showed a molecular ion at m/e 470, consistent with the required compound (67). The base peak, however, was at m/e 454. This was not derived from the peak at m/e 470 since no metastable ion could be observed in the spectrum for this fragmentation. The 454 peak is probably due to the reduction of both carbonyl functions in (66) with subsequent dehydration of one of them, either during the work up or in the heated inlet of the mass spectrometer to give, probably, the alcohol (68).


H
OH
H
H
OH
CO2Me
O
O
OH
Ph

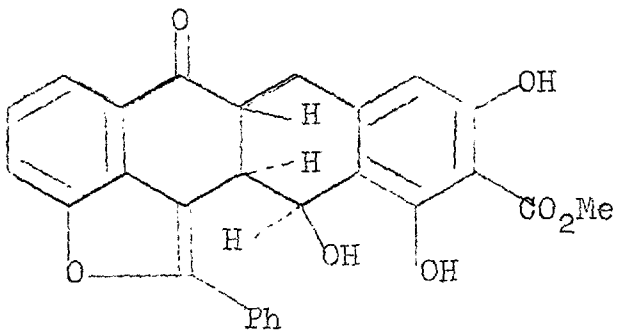
(62)


H
OH
H
H
OH
CO2Me
O
O
OH
Ph

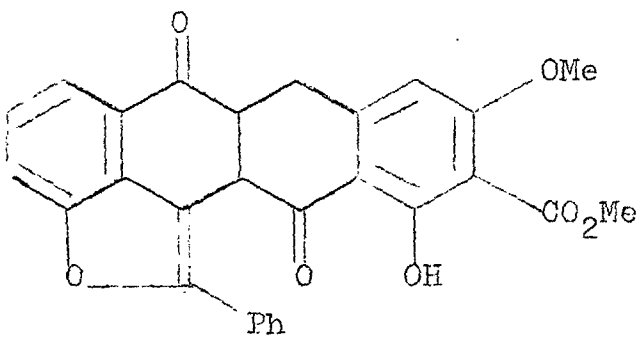
(63)


O
OH
H
H
CO2Me
H
OH
OH
O
Ph

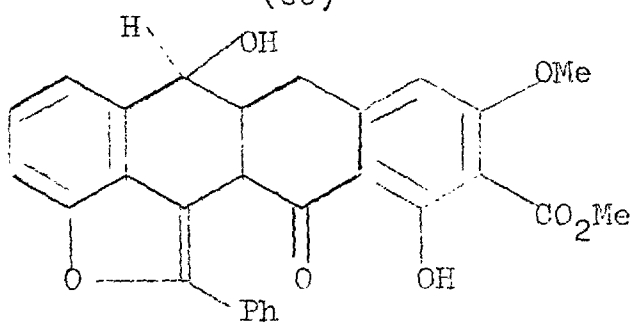
(64)


O
OH
H
H
H
OH
OH
CO2Me
O
Ph

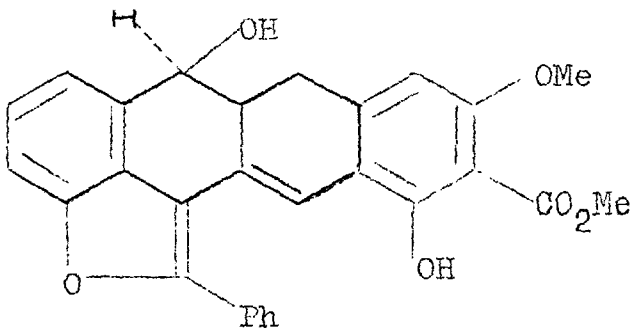
(65)


O
OMe
CO2Me
O
O
OH
Ph

(66)


H
OH
OMe
CO2Me
O
O
OH
Ph

(67)

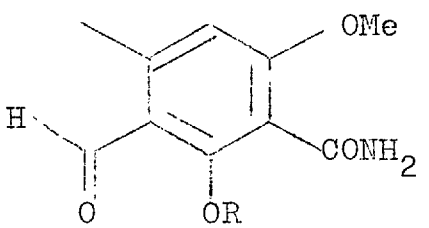

H
OH
OMe
CO2Me
O
OH
Ph

(68)

The lack of selectivity of attack of boron trichloride and of sodium borohydride on the ester diketone led us to abandon this route and to move on to the use of a carboxamido substituted ring A.

5. Studies on the 1,3-dimethoxy-2-carboxamido substituted ring A series of compounds.

The reasons for moving into the carboxamido series of compounds were twofold. Firstly, in the eventual synthesis of tetracycline a carboxamido group would have to be present and it was thought that this should be introduced as early as possible due to the vigorous conditions needed for the hydrolysis of the ester function. Secondly, it was known[12] that the carboxamido group makes boron trichloride more selective in its demethylation reactions. Hence the model amide (69) was demethylated to the phenol (70) in high yield.

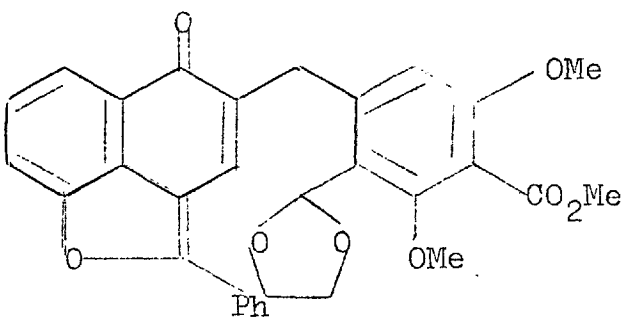


(69) R=Me

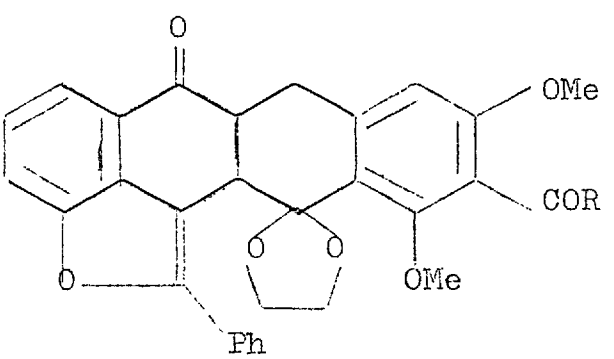
(70) R=H

The amide (71) was prepared using the method developed by Magnus[12]. This involved the photocyclisation of the acetal (72) to the ketal (73), hydrolysis of the ester function, formation of the acid chloride and amination. The photocyclisation was carried out in the

presence of benzoic acid and yields of 40-45% were consistently obtained. This is an improvement on the yield (25-35%) obtained earlier[20]. The hydrolysis involved the use of large amounts of potassium hydroxide and a fairly long reaction time which led to the formation of a number of by-products. Lithium iodide has been used[22] for the hydrolysis of sterically hindered esters, but when it was tried on the ester (73) no reaction could be observed at 80° or 150° in dimethyformamide.



(72)



(71) R=NH_2

(73) R=OMe

It was hoped that treatment of the amide (71) with boron trichloride would remove the ketal group and then demethylate the methyl ether peri to the

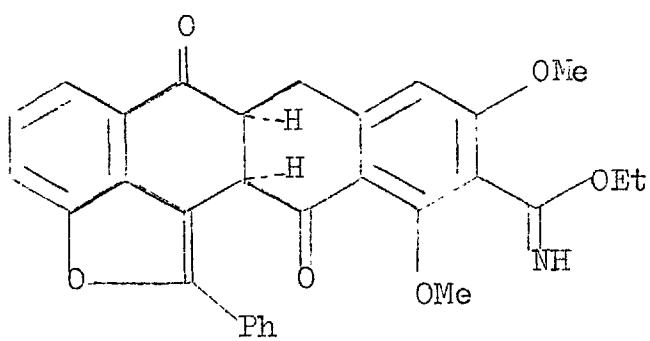
resulting carbonyl function. When this was tried, however, a complex mixture of compounds was formed and no major product could be isolated.

Magnus[12] has successfully used hydrogen bromide in glacial acetic acid as a selective demethylating reagent. When the amide (71) was reacted with this reagent two new orange compounds were rapidly formed. These were isolated, in low yield, and the u.v. spectrum suggested that they were naphthalenes and the compounds were not investigated further.

In an attempt to hydrolyse the ketal function, the amide (71) was reacted with hydrogen chloride in both glacial acetic acid and formic acid in tetrahydrofuran at room temperature and at reflux. None of these conditions led to the hydrolysis of the ketal function.

It was, therefore, decided to return to the idea of using a Lewis acid to hydrolyse the ketal function. The first one suggested was triethyloxonium fluoroborate and a search of the literature revealed that it had been reported[23] that this salt indeed cleaves simple ketals.

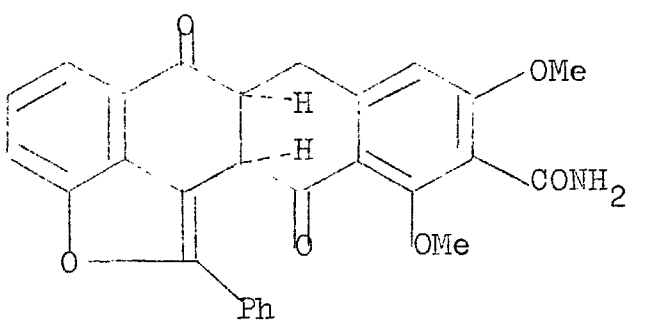
When the amide (71) was reacted with a nine fold excess of triethyloxonium fluoroborate in dichloromethane a slow reaction ensued. After 24 hours at room temperature two products were isolated, both of which had the characteristic diketone fluorescence on a t.l.c. plate. The major compound (46%) was less polar than the starting amide and had ν_{max} 3350, 1690, 1680, 1650 cm^{-1}. The n.m.r. spectrum showed that the two methoxyl groups were still present and that an ethyl group was also present. Since amides are known[24] to form imino ethers on treatment with triethyloxonium fluoroborate the structure assigned to this product was the diketone imino ether (74). The mass spectrum showed the molecular ion at m/e 495, consistent with this structure.



(74)

The minor compound (31%) was more polar than the starting material and had ν_{max} 3450, 3220, 1680 1660 cm^{-1}. The n.m.r. spectrum was identical to that of

the major compound except that it lacked the signals due to the ethyl grouping and the mass spectrum showed the molecular ion at m/e 467. The cracking pattern showed the facile loss of two hydrogen atoms to give the aromatic ring B compound and then loss of ammonia and methanol. From this collection of evidence the compound was assigned the structure (75). A satisfactory elemental analysis could not be obtained for this compound, probably due to solvation and its easy oxidation to an aromatic ring B compound.

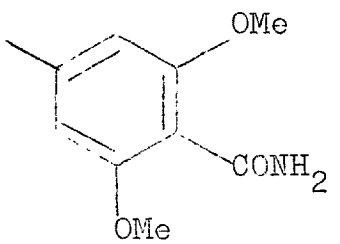


(75)

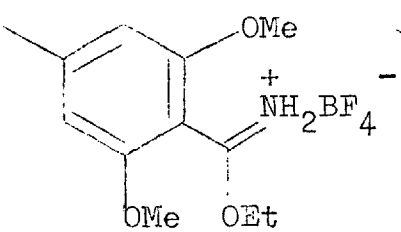
The use of less triethyloxonium fluoroborate or of nitro methane as the solvent failed to stop the alkylation of the amide function.

It was thought possible that the triethyloxonium fluoroborate was alkylating the amide function on the nitrogen atom rather than on oxygen. To investigate

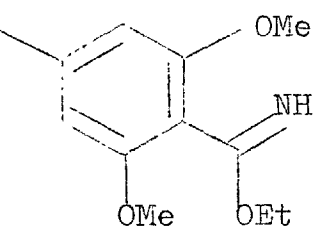
this the model amide (76) was reacted with triethyloxonium fluoroborate under the normal conditions to give amor. polar compound whose spectral and analytical data showed it to be the salt (77). When the reaction was worked up with base the free imine (78) was obtained as an oil. The possibility of alkylation on nitrogen was eliminated by synthesising the amide (79) from the acid (80). This was different from the product obtained from the triethyloxonium fluoroborate reaction.



(76)



(77)



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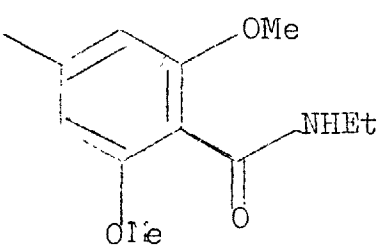

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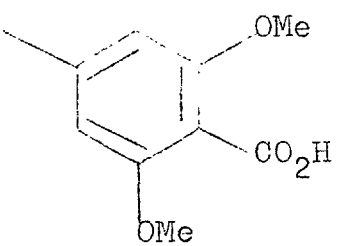
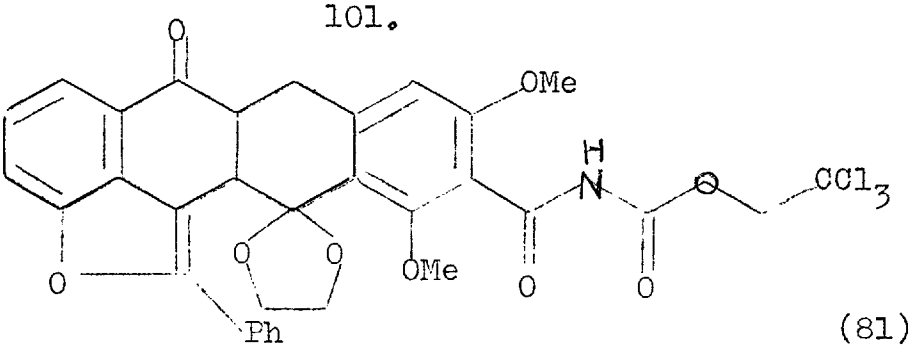


(80)

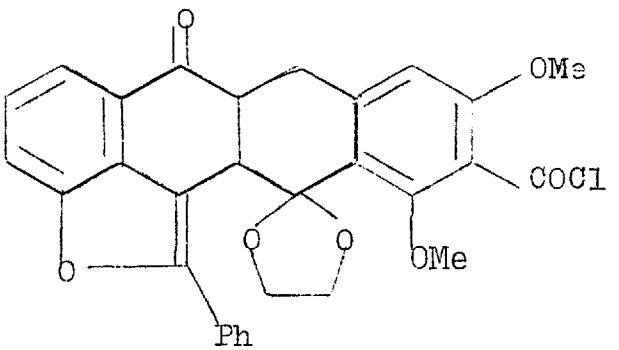
To overcome the difficulty of alkylation of the amide function three alternatives were available. The first of these was to return to the ester series, the second to protect the amide function and the third to find a sufficiently sterically hindered Lewis acid that would not react with the amide function.

The first course, to return to the ester series, was tested by reacting the ester (73) with triethyloxonium fluoroborate to give the previously prepared diketone (61). The yield, however, was only 16%, which made this route unattractive.

The second alternative, to protect the amide function, was then considered. To be of any synthetic use the protecting group had to be large enough to prevent attack by triethyloxonium fluoroborate on the amide function and easily removable under mild conditions. To meet these criteria the trichloroethoxy carbonyl protecting group[25] was chosen. It was hoped to prepare the protected amide (81) by reaction of the acid chloride (82) with the urethane (83) or its sodium salt.



(81)



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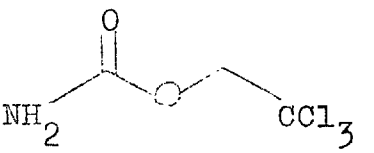
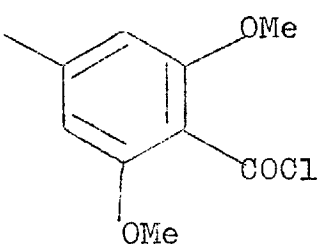
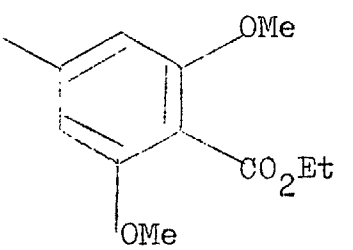


(83)

As a model experiment the sodium salt of ethyl urethane was reacted with the ring A acid chloride (84). The only product isolated, apart from the free acid, was ethyl orsellinate (85). This was presumably formed by the decomposition of the sodium salt of the urethane to give ethoxide ions which subsequently attacked the acid chloride.

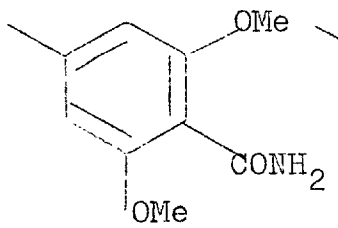


(84)

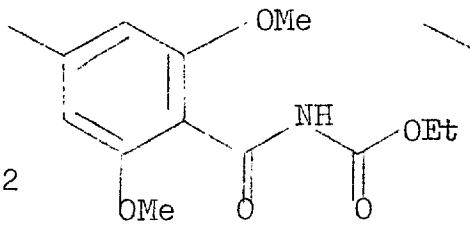


(85)

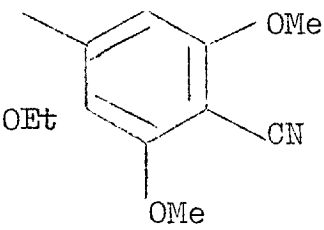
The alternative method of preparing the protected amide by reaction of the amide with βββ trichloroethoxycarbonyl chloride was then examined. The model amide (86) was reacted with ethyl chloroformate in pyridine in the hope of obtaining the protected amide (87). However, the compound isolated was the nitrile (88).



(86)



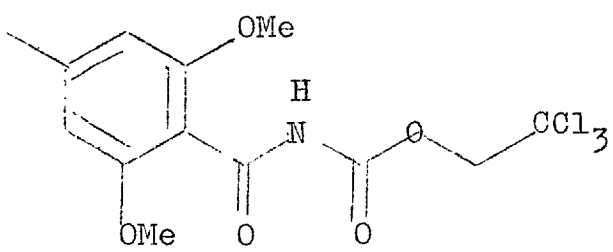
(87)



(88)

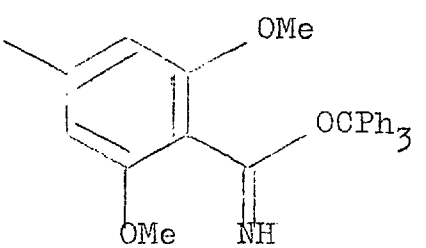
The reaction of the sodium salt of (86) with ethyl chloroformate in refluxing benzene yielded the nitrile (15%) and the required compound (87) (44%).

Repetition of this reaction, using βββ-trichloroethoxycarbonyl chloride led to the formation of the protected amide (89) in 34% yield, along with 53% of the nitrile (88).

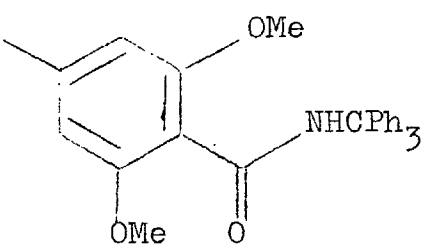


(89)

The low yields of the desired products obtained from these reactions precluded their use in the main series and we then moved on to the third alternative, namely the use of a sterically hindered Lewis acid. Triphenyl carbonium (trityl) fluoroborate was readily prepared by the method of Dauben et.al.[26] and was chosen as a suitable reagent. Before this was used in the main series its reactivity towards the amide function was tested by reacting it with the model amide (86) in dichloromethane. This led to the formation of a new compound whose spectroscopic and analytical data suggested that the structure was either (90) or (91).

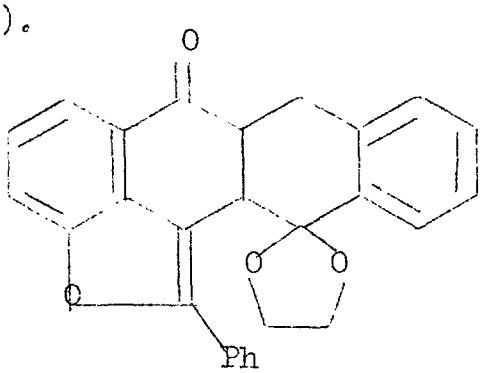


(90)

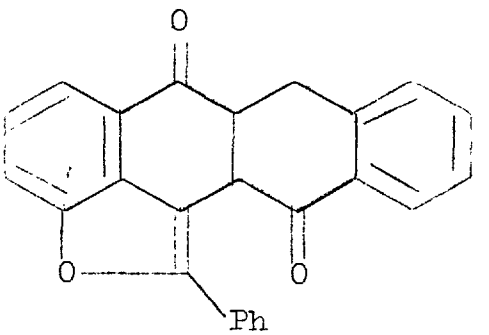


(91)

The model tetracyclic ketal (2) was then reacted with trityl fluoroborate to give a 65% yield of the diketone (12).



(2)



(12)

The dimethoxy amide (71) was then reacted under the same conditions and slowly gave the diketone (75) in 16% yield. This was less than that obtained from the use of triethyloxonium fluoroborate.

The use of a trialkoxycarbonium salt should overcome the difficulty of the alkylation of the amide function since the product formed would be unstable. Triethoxycarbonium fluoroborate (92) was prepared[27] from diethyl carbonate and triethyloxonium fluoroborate. The reaction of a three fold excess of this reagent with the amide (71), in dichloromethane at room temperature, was very slow and several products were formed, among them the required diketone (75). The use of a large excess of the reagent in refluxing dichloromethane gave a 65% yield of the required diketone (75).

$(EtO)_3C^+BF_4^-$

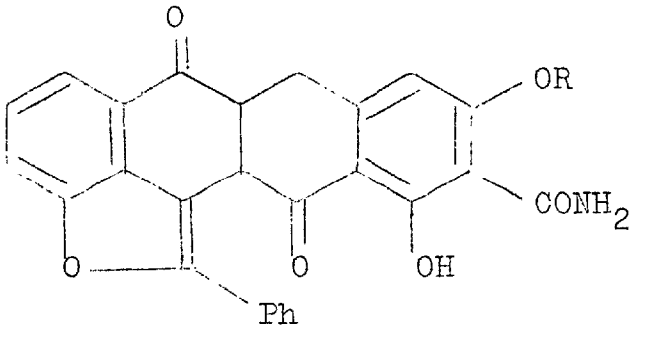
(92)

This yield, however, proved to be unreproducible and in further experiments the yields were much lower due to the formation of large quantities of oxidation products. To overcome this various additives were tried. Acetone and cyclohexa-1,4-dione were ineffective but the Diels-Alder adduct of benzoquinone and butadiene helped reduce the formation of these oxidation products.

Trimethoxycarbonium fluoroborate[28] was tried but gave no observably different results to triethoxycarbonium fluoroborate. The next stage was the demethylation of the diketone to the phenol (93). This was accomplished by treating the diketone, in dichloromethane at -76°, with boron trichloride. The phenol (93), however, was even more sensitive to oxidation than the diketone and the maximum yield obtained was only 22%. It proved impossible to purify the phenol and the only evidence for its structure was the i.r. spectrum, ν_{max} 3480, 3230, 1685, 1605 cm^{-1}, which showed that the amide frequency had dropped from 1660cm^{-1} to 1605cm^{-1} due to hydrogen bonding with the ortho-phenolic hydroxyl.

If the reaction was continued until all of the starting material had been destroyed considerable amounts of di-demethylation occurred to give the phenol (94).

This product was identified by its mass spectrum with the molecular ion at m/e 439.



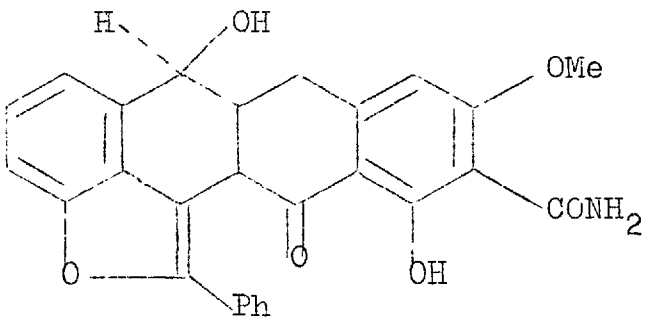
(93) R=Me

(94) R=H

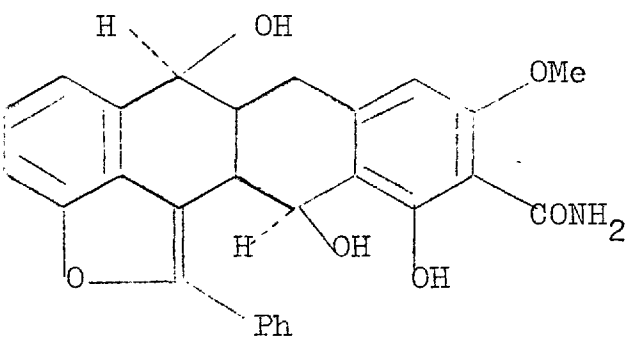
The selective reduction of the 6-keto function in the mono-demethylated compound (93) was attempted with lithium tri-tert-butoxy aluminium hydride, but this led to a mixture of compounds including recovered starting material.

Sodium borohydride reduction slowly gave a new compound along with many coloured oxidation products. This compound was isolated, in poor yield, by thin layer chromatography and had ν_{max} 3500, 3400, 1610 cm^{-1}. The mass spectrum showed a molecular ion at m/e 439 with peaks at m/e 422 and m/e 404. Hence the product readily loses ammonia and then water in the mass spectrometer. The expected product (95) should show a molecular ion at m/e 455. The difference of 16 mass units suggested that both carbonyl functions of (93) had been reduced and that one of the secondary hydroxyls was lost in a

dehydration either in the work up or in the heated inlet of the mass spectrometer. The tentative structure assigned to this reduction product is (96).



(95)



(96)

At this stage a halt was called to the work in this series of compounds. Obviously the penalty of working with a 6,12 diketone system was too great, and the instability of the products obtained was such as to preclude this route from being used in the total synthetic scheme.

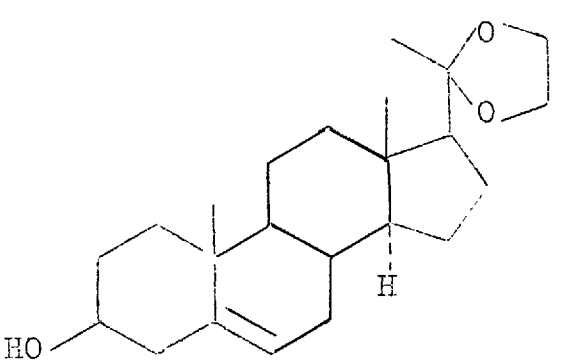
The alternative is to carry the ketal protecting group through the synthesis until the furan double bond has been cleaved. It could then be removed fairly easily by acid hydrolysis. This means that the methyl ether group at position C-1 would have to be removed under conditions which did not deketalise the carbonyl function at position C-12.

Another alternative is to have the C-1 position as a free phenol from as early on in the synthesis as possible, although this might create problems in forming an acetal of the ortho formyl group.

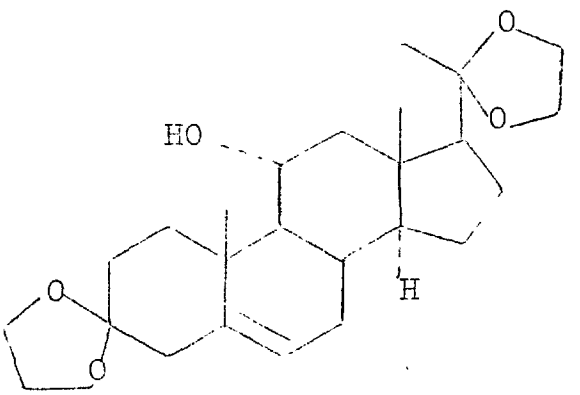
6. Deketalisation and related reactions using oxonium and carbonium salts.

Since oxonium and carbonium salts had proved useful in deketalising the tetracyclic compounds we investigated the possibility of extending their use to steroidal ketals and related compounds.

Pregnenolone ethylene ketal[29] (97) and 11α-hydroxy progesterone ethylene ketal[30] (98) were prepared and reacted with triethoxycarbonium fluoroborate in dichloromethane. The pregnenolone ketal reacted completely in 8 minutes to give pregnenolone in about 80% yield. The 11α-hydroxy progesterone ketal reacted in 20 minutes and a 70% yield of 11α-hydroxy progesterone was obtained.

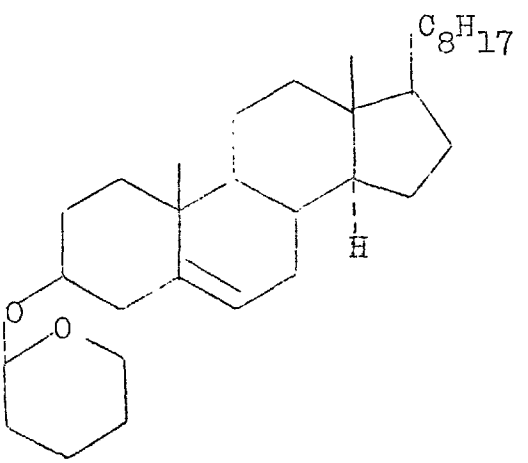


(97)



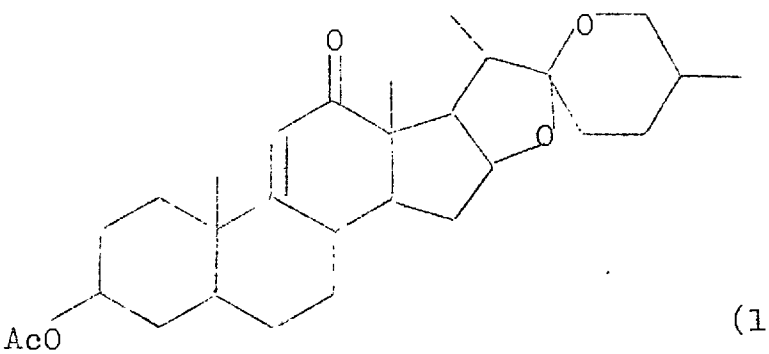
(98)

The use of these reagents to remove tetrahydropyranyl ethers was investigated using cholesterol tetrahydropyranyl ether[31] (99). The protecting group was successfully removed with triethyloxonium fluoroborate in 64% yield.



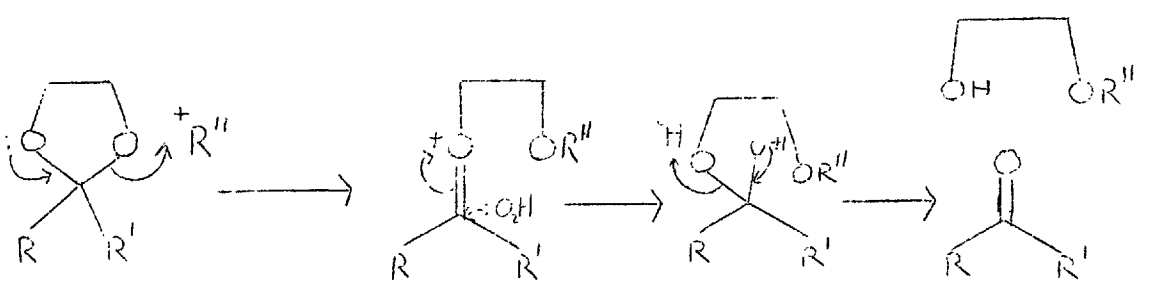
(99)

The sapogenins contain a ketal linkage which should be cleaved by oxonium or carbonium salts. Δ-9 hecogenin acetate (100) was mixed with triethyloxonium fluoroborate in dichloromethane but no reaction was observed, even after a prolonged period and with the use of a large excess of the salt. The use of an equivalent amount of trityl fluoroborate gave no reaction while larger amounts led to the slow formation of many products.



(100)

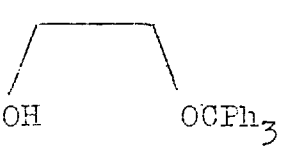
The mechanism of the hydrolysis of ketals is thought to involve the ionic intermediate (101)[32], which is quenched by water to give ethylene glycol when R^{11}=H, and the ketone.



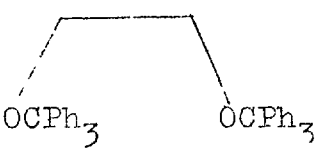
(101)

When an oxonium or carbonium ion is used as the cation it should be possible to isolate the resulting mono-ether of ethylene glycol.

To study this proposed mechanism cyclohexanone ethylene ketal[33] was prepared as a model ketal. This was reacted with trityl fluoroborate in dichloromethane and after 3 hours the reaction was quenched with water. A 46% yield of cyclohexanone was obtained but neither of the trityl ethers (102) and (103) was formed. Authentic samples of these were prepared by reacting ethylene glycol with trityl chloride in pyridine. Treatment of these ethers under the reaction and work up conditions showed that they were not stable.



(102)



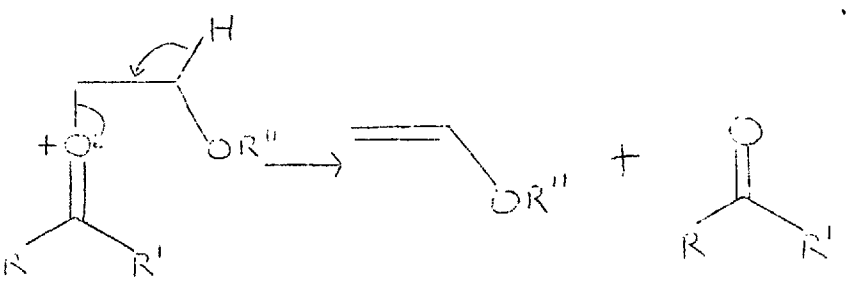
(103)

The reaction of cyclohexanone ethylene ketal with triethyloxonium fluoroborate was then carried out. G.l.c. examination of the products showed the presence of

cyclohexanone (38%), cyclohexanone ethylene ketal (62%) and a small amount of the monoethyl ether of ethylene glycol. The aqueous phase from the work up contained larger amounts of this ether.

If the ionic intermediate (101) is involved in the mechanism it should be possible to trap it by means of a hydride reduction. When this was tried, using lithium aluminium hydride as the hydride source and triethyl-oxonium fluoroborate as the cation, a complex mixture of compounds was obtained, amongst them cyclohexanol. This is due to the formation of cyclohexanone during the reaction with the triethyl oxonium fluoroborate. To check whether this was happening the reaction mixture was monitored by i.r. spectroscopy without any work up. This showed that cyclohexanone was being formed from the start of the reaction.

It was thought that this was due to the intermediate (101) breaking down to a vinyl ether as follows:-

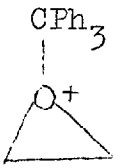


If this is correct it should be possible to hydrolyse the vinyl ether to acetaldehyde and to trap this as its 2,4-DNP. When this was tried the only 2.4-dinitrophenylhydrazone formed was that of cyclohexanone.

In order to follow the reaction more closely it was decided to carry it out in a n.m.r. tube. Trityl fluoroborate was used as the cation and deuterochloroform as the solvent. The salt appeared to be only sparingly soluble and the spectrum was run on the resulting suspension. After mixing the reactants the n.m.r. spectrum showed the presence of cyclohexanone (10%) in the mixture, and the amount of this gradually increased with time. After two days traces of triphenyl methane were observable but no signals could be observed for any protons on a carbon atom α to the oxygen atoms of the ethylene ketal portion except those of cyclohexanone ethylene ketal itself. There was also no sign of any vinylic protons.

To explain this result the intermediate in the reaction must be symmetrical and the τ value of the hydrogen atoms coincide with those of the ketal protons

of cyclohexanone ethylene ketal. One possibility is ethylene oxide or its oxonium salt with trityl fluoroborate (104).



(104)

The n.m.r. spectrum of ethylene oxide consists of a singlet at 7.32τ and that of a mixture of ethylene oxide and trityl fluoroborate at 6.30τ. Neither of these coincide with the signal at 6.15τ of cyclohexanone ethylene ketal.

It is possible that traces of water in the system were producing acid which was the true reagent for the deketalisation. To eliminate this possibility a ketal that was more resistant to acid hydrolysis was required. 2,2,6-trimethylcyclohexanone ethylene ketal was prepared to meet this requirement. This was reacted with trityl fluoroborate as usual but the work up was carried out with ammonia gas in an attempt to eliminate aqueous conditions at any stage. In this case both of the trityl ethers (102) and (103) were detected in the

solution after quenching with ammonia. When the reaction was carried out in an n.m.r. tube the ketone was again formed slowly but neither of the ethers (102) and (103) were observable in the spectrum. On work-up, however, both of these ethers were visible in the n.m.r. spectrum. The formation of these ethers implies that water must have been present at some stage in order to furnish the extra oxygen atoms required. The reaction was repeated using freshly prepared materials and carefully dried dichloromethane, and in this case very little of the ketone was formed. When the reaction was carried out in the presence of a trace of water the ketone (48%) was again formed. Use of triethyloxonium fluoroborate gave the same results.

It seems, therefore, that water is a necessary component of the mixture for the deketalisation. Whether this reacts with the oxonium or carbonium salt present to form an acid which acts as the true reagent is doubtful since this should produce ethylene glycol, which is not observed in the n.m.r. spectrum. The fact that the trityl ethers are only visible in the n.m.r. spectrum after work up may imply that the fragment from the ethylene ketal portion is complexed as a salt which is not soluble in the deuterochloroform and hence not observed in the

n.m.r. spectrum. This possibility could be investigated using other deuterated solvents in which the trityl fluoroborate is more soluble. This work is being followed up by other workers.

Experimental

Unless otherwise specified in the text the following conditions apply to the experiments described in this section.

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

Infra red spectra were measured as a nujol mull, thin film or chloroform solution on a Unicam S.P. 200 spectrometer. Ultra violet spectra were measured in absolute ethanol on a Unicam S.P. 800 spectrometer. N.m.r. spectra were taken in deuterochloroform solution with tetra-methyl silane as internal standard using a Varian A-60 or HA-100 spectrometer.

Mass spectra were taken with an A.E.I. MS9 high resolution mass spectrometer.

Alumina for column chromatography was Brockmann activity 3 and the silica gel for t.l.c. was Merck $^{GF}254$.

Sodium sulphate was used to dry all organic solutions and these were evaporated *in vacuo*.

The following abbreviations have been used in describing the n.m.r. spectra:-

s = singlet	t = triplet
bs = broad singlet	q = quartet
d = doublet	m = multiplet.

Cis-6a,12a-12-ethylenedioxy-6a,7,12,12a-tetrahydro-1-phenylnaphthaceno (1,12-bc) furan-6-one. (2)

This was prepared by the method described by Clive[9].

Cis-6a,12a-12 ethylenedioxy-6a,7,12,12a-tetrahydro-1-phenyl-naphthaceno (1,12,-bc) furan-6α-methyl-6β-ol.(1)

The ketal (2) (116mg) was dissolved in dry benzene (10ml) and ether (10ml). To the solution at room temperature, methyl lithium (0.34N, 2ml) was added under nitrogen. The dark solution was stirred for 1/2 hour at room temperature and then an aqueous solution of ammonium chloride (0.5gm in 5ml of water) was added. After stirring for 5 minutes the two phase solution was extracted with chloroform, dried and evaporated. The residue was chromatographed on several silica gel plates to give the required alcohol (64mg), m.p. 238° ν_{max} 3450 cm^{-1} identical to a sample prepared by Clive [9].

Reaction of methyl lithium with ketal (2) in the presence of acetyl acetone.

The ketal (2) (91mg) was dissolved in dry benzene (10ml) and dry ether (10ml). Methyl lithium solution (1ml, 0.3N) was added to the stirred solution at room temperature under nitrogen. This was followed by one drop of acetyl acetone. After 1/2 hour t.l.c. showed no change in the amount of alcohol formed so a further portion of methyl lithium solution (1ml) was added followed by 2 drops of acetyl acetone. After stirring for 1/2 hour aqueous ammonium chloride solution (0.5gm in 5ml) was added and the two phase system stirred for 5 minutes. The mixture was then extracted with chloroform, the extracts dried and evaporated. Purification by thin layer chromatography gave the alcohol (1) in 57% yield.

Reaction of methyl lithium with ketal (2) in the presence of cyclopentadiene.

The ketal (2) (91mg) was dissolved in dry benzene (10ml) and dry ether at room temperature. Methyl lithium solution (1ml, 0.3N) was added under nitrogen and the solution stirred for 10 minutes. Cyclopentadiene (2 drops)

was then added and the solution stirred for a further 30 minutes. Aqueous ammonium chloride solution (0.5gm in 5ml) was added and the mixture stirred for 10 minutes. The mixture was extracted with chloroform, dried and evaporated. The residue on chromatography on silica plates gave 55% of the alcohol (1).

Reaction of potassium tert-butoxide on the ketal (2).

The ketal (2) (10mg) was dissolved in dry benzene (2ml) and tert-butanol (10ml) added. The solution was degassed and then potassium tert-butoxide (6mg) was added and the solution stirred at room temperature until a steady state had been reached (t.l.c. control). The solution was acidified with glacial acetic acid, diluted with water, extracted with chloroform, dried and evaporated. The residue had ν_{max}^{chf} 3450, 1750, 1710, 1660, 1630 cm^{-1}. λ_{max}^{EtOH} 292,305, 320, 342, 425 n.m.

Ozonolysis of cis-6a,12a-12 ethylenedioxy-6a,7,12,12a-tetrahydro-1-phenyl-naphthaceno (1,12-bc) furan-6α-methyl-6β-ol (1).

The tertiary alcohol (1) (15mg) was dissolved in methanol (11ml) and chloroform (12ml). The solution was

cooled to -20° and ozone bubbled through until t.l.c. indicated that all the starting material had been destroyed. Nitrogen was then bubbled through the solution to remove excess of ozone, and a solution of triphenyl phosphine (30mg) in chloroform was added dropwise to the solution. After 1 hour the solution was evaporated to give a yellow oil. On purification on silica plates an amorphous orange solid was obtained, ν_{max}^{chf} 3230, 1730, 1620, 1595 cm^{-1}; λ_{max}^{EtOH} 278, 307, 316, 417 n.m.; after treatment with NaOH λ_{max}^{EtOH} 278, 336, 445 n.m. Mass spectrum showed molecular ion at m/e 410.

2-phenyl-3,4-dihydro-naphtho (1,8-bc) furan-5-α-methyl-5-β-ol (4).

Magnesium turnings (0.4gm) were placed in a flask under dry ether (10ml). Methyl iodide (1ml) in ether (5ml) was then slowly added under a stream of nitrogen. When all the magnesium had reacted a slurry of dihydro-perinaphthofuran (1gm) in ether (10ml) was added and the solution stirred at room temperature. After 2 hours aqueous ammonium chloride solution was added and the mixture stirred for 5 minutes. The solution was extracted with dichloromethane, washed with sodium bicarbonate solution, dried and evaporated. The residue

was chromatographed on alumina eluting with benzene to give the methyl alcohol (4) as a yellow oil. This, on scratching under petroleum ether gave white needles m.p. 90°-91°, ν_{max}^{nujol} 3360 cm^{-1}, λ_{max} 230, 245, 294, 305, 320 n.m. (ε 12600, 8350, 24180, 30800, 25000). The n.m.r. spectrum had signals at 8.32τ (1H,s), 8.04τ (1H,bs, exchangeable with D_2O), 7.93τ (2H,m), 6.90τ (2H,m), 2.05-2.80τ (8H,m). (Found C 81.72%, H 6.29%; $C_{19}H_{16}O_2$ requires C 81.79% H 6.10%).

4-α-methyl-4-β-hydroxy-8-benzoyloxy-tetralone (5).

The alcohol (4) (525mg) was dissolved in chloroform (75ml, distilled from P_2O_5) and methanol (75ml, distilled from sodium). Ozone was bubbled through the solution at -30° until the u.v. spectrum showed 95% reaction. Nitrogen was then passed through the solution for 1 hour to remove any excess of ozone. Triphenyl phosphine (1.25gm) in chloroform was then added dropwise to the stirred solution. After 2 hours stirring the solution was evaporated and the residue chromatographed on an alumina column eluting with benzene/chloroform (70:30). This gave 619mg. of a pale yellow solid which contained considerable quantities of triphenyl phosphine oxide. Attempts were made to purify the product by recrystallisation

from ether and by multiple elution on thin plates. Neither of these were successful.

The alcohol (4) (209mg) was dissolved in dry chloroform (50ml) and dry methanol (50ml). Ozone was bubbled through the solution at -40° until u.v. indicated that the reaction was 95% complete. Excess of ozone was removed by passing nitrogen through the solution for 1 hour and then dimethyl sulphide (1.5ml) was added and the solution left overnight. The solution was then evaporated and chromatographed on a silica gel column to give 167mg. (70%) of the keto benzoate (5) m.p. 134-135°, ν_{max} 3500, 1718, 1692, 1605 cm^{-1}, λ_{max}^{EtOH} 234, 286, 294 (21,420, 2,570, 2,460). The n.m.r. spectrum showed signals at 8.42τ (3H,s), 7.78τ (2H,m), 6.4τ (2H,m), 5.25τ (1H bs, exchangeable with D_2O), 1.7-3.0τ (8H,m). (Found C 73.19%, H 5.43%; $C_{18}H_{16}O_4$ requires C 72.96% H 5.44%).

4-α-methyl-4-β-hydroxy-8-hydroxy tetralone (6).

The keto-benzoate (5) (140mg) was dissolved in dry methanol (20ml) and sodium methoxide solution (1.5 equivalents) added under nitrogen. After 9 hours the reaction was poured into water, chloroform added and the

solution acidified with solid carbon dioxide. The chloroform layer was separated, dried and evaporated to give an oily residue. This was chromatographed on silica plates to give an 85% yield of the phenol (6). This failed to crystallise but showed ν_{max} 3580,3430, 1645 cm^{-1}; the n.m.r. spectrum had signals at 8.40τ (3H,s), 7.76τ (3H m, 1 exchangeable with D_2O), 7.24τ (2H,m), -2.50τ (1H,s exchangeable with D_2O). The mass spectrum showed the molecular ion at m/e 192 with other peaks at m/e 177 (M^+-CH_3), 174 (M^+-H_2O) and 164 (M^+-CO).

Cis-5a,11a,-6β-hydroxy-6α-methyl-10-benzoyloxy-11-oxo-12-ethylenedioxy-5,5a,6,11,11a,12-hexahydro-naphthacene (7a,R=-COPh).

The tertiary alcohol (1) (238mg), in chloroform-methanol (100ml) containing 3 drops of pyridine, was ozonised at -70° until 95% complete (u.v. control). Excess of ozone was then removed by bubbling nitrogen through the solution for 1 hour. Redistilled dimethyl sulphide (1ml) was added and the solution stirred overnight at room temperature. Evaporation, and purification by thick layer chromatography gave the keto-benzoate m.p. 194-196°; ν_{max}^{nujol} 3440, 1735, 1675, 1605 cm^{-1}; λ_{max}^{EtOH} 234, 286 n.m. (ε 24,220, 4,270). The n.m.r. spectrum

had signals at 8.30τ (3H,s), 8.20τ (1H,bs, exchangeable by D_2O), 7.1τ (2H,m), 6.0-6.4τ (6H,m), 6.07τ (1H,d J=4cps) amd 1.8-3.0τ (12H,m). (Found:- C 73.67% H 5.30%, $C_{28}H_{24}O_6$ requires C 73.71% H 5.56%).

Cis-5a,11a-6β,10-dihydroxy-6α-methyl-11-oxo-12 ethylenedioxy-5,5a,6,11,11a,12-hexahydronaphthacene (7b, R=H).

The keto-benzoate (7a) (32mg) in dry methanol (8ml) under nitrogen, was treated with sodium methoxide solution (2.5 equivalents). The pale yellow solution was stirred at room temperature for 4 hours, then chloroform and water were added and the solution acidified with solid carbon dioxide. The chloroform layer was separated, dried and evaporated at room temperature. Preparative thin layer chromatography gave the keto-phenol (70%), m.p. 176-179°; ν_{max}^{chf} 3420, 1645 cm^{-1}; λ_{max}^{EtOH} 213, 263, 336 n.m. (ε 29,050, 9,980, 3,080). The n.m.r. spectrum showed signals at 8.28τ (3H,s), 7.75τ (1H,bs exchangeable by D_2O), 6.62-7.40τ (3H,m), 5.80-6.20τ (4H,m), 5.65τ (1H,d J=5.5cps), 2.40-3.40τ (7H,m), -2.02τ (1H,s exchangeable with D_2O). (Found C 71.58%, H 5.77% $C_{21}H_{20}O_5$ requires C 71.39%, H 5.82%).

Attempted hydrolysis of keto-phenol (7b).

The keto-phenol (7b) (23mg) was dissolved in dichloro-methane (10mls) and an aqueous solution of oxalic acid (2 equivalents) added. The mixture was stirred at room temperature for 18 hours when t.l.c. indicated that there was no reaction. On working up starting material was recovered.

6α-methyl-6β,10-dihydroxy-11,12-dioxo-5,5a,6,11,11a,12 hexahydro-naphthacene (8).

The keto-phenol (7b) (32mg) was dissolved in acetone (20ml) and 6N hydrochloric acid (4 drops) added whilst stirring under dry nitrogen at room temperature. After 1/2 hour t.l.c. indicated that no starting material remained and the reaction was worked up by pouring into water, extraction with dichloromethane, drying and evaporation. The residue was purified by thin layer chromatography to give (8,8mg), m.p. 174-178°; ν_{max}^{nujol} 3510, 1620, 1603 cm^{-1}, λ_{max}^{EtOH} 220, 242, 247, 260, 311, 392, 409 n.m. (ε 13,800; 7,800; 7,840; 6,210; 3.684; 24,760; 21,520); in the presence of base λ_{max}^{EtOH} 220, 245, 263, 399, 416 n.m. (ε 19,600; 12,000; 18,400; 21,600; 19,400). The n.m.r spectrum had signals at 8.33τ (1H,bs

exchangeable by D_2O), 8.25τ (3H,s), 6.50-7.10τ (3H,m), 2.00-3.16τ (7H,m), -2.24τ (1H,s exchangeable by D_2O), -5.64τ (1H,s exchangeable by D_2O).

6β-acetoxy-10-benzoyloxy-11,12-dioxo-5,5a,6,11,11a,12 hexahydronapthacene (11a).

The keto-acetate (10, 316mg) was dissolved in chloroform-methanol (100ml) and ozonised at -80° with u.v. control. Dimethyl sulphide (1ml) was added to the ozonide, and the solution stirred overnight. After evaporation and chromatography the benzoate (11a) was obtained (32mg), m.p. 218-226°, ν_{max}^{nujol} 1738, 1720, 1600 cm^{-1}, λ_{max}^{EtOH} 223, 238, 262, 310, 383, 400 n.m. (ε 21,000; 21,000; 21,000; 4,810; 18,400; 14,400). The n.m.r. spectrum exhibited signals at 8.05τ (3H,s), 6.20-7.80τ (3H,m), 3.99τ (1H,d J=4cps), 1.70-3.20τ (12H,m). (Found C 73.63% H 4.58%; $C_{27}H_{20}O_6$ requires C 73.79%, H 4.80%).

Deketalisation of (2).

The ketal (2, 121mg) was dissolved in aqueous dioxan (10ml) and a few drops of 6N-hydrochloric acid added. The solution was refluxed under dry nitrogen

for 10 hours. The mixture was then worked up by extracting the solution with dichloromethane, drying and evaporation. The oily residue was purified by thin layer chromatography to give the diketone (12) in 10% yield.

Deketalisation of (2) with boron trichloride.

The ketal (14mg) was dissolved in dry dichloromethane (10ml) and cooled to -76°. Boron trichloride (3 drops) was added and the solution stirred at -76°. After 1 hour t.l.c. showed a 50:50 mixture of starting ketal and diketone. This was unchanged on adding more boron trichloride, raising the temperature or on adding some benzaldehyde (70mg).

Deketalisation of (13) and (14).

A mixture of the hemithioketals (113mg) was mixed with mercuric chloride (222mg, 3 equiv.) and potassium acetate (178mg. 3 equiv.) in glacial acetic acid. A few drops of water were added and the resulting suspension stirred at room temperature for 24 hours, during which time the mixture became homogeneous, and then a fine precipitate separated. The total reaction

mixture was poured into aqueous sodium bicarbonate, extracted with dichloromethane, dried and evaporated. The residue was crystallised from benzene-petrol to give the diketone (12) in 70% yield.

Reaction of diketone (12) with methyl lithium.

The diketone (34mg), in dry benzene (10ml) and dry ether (20ml) at -15° under nitrogen, was treated with ethereal methyl lithium (1 equiv.) and stirred for 1/2 hour. Work up with aqueous ammonium chloride and extraction with dichloromethane gave, after evaporation, a gummy residue. Thin layer chromatography gave the pure product (28mg) ν_{max} 3430, 1690, 1680, 1605 cm^{-1}. The n.m.r. spectrum showed two methyl groups at 8.55τ and 8.27τ.

Reaction of (13) and (14) with methyl lithium.

A mixture of the hemithioketals (13) and (14) (103mg) was dissolved in dry benzene (10ml) and dry ether (10ml). The solution was stirred under nitrogen at 0° and methyl lithium solution (3ml,1N) added. After stirring at room temperature for 1 hour the reaction mixture was worked up in the usual way and after thin

layer chromatography the mixture of alcohols (15) and (16) (40mg) was obtained.

Cis-6a,12a-6α-methyl-6β-hydroxy-6a,7,12,12a-tetrahydro-1-phenyl-naphthaceno (1,12-bc) furan-12-one (17)

The mixture of hemithioketals (15) and (16) (36mg) was dissolved in absolute ethanol (30ml) and D.M.F. (3ml). The solution was stirred at room temperature as mercuric chloride (52mg) in ethanol was added followed by aqueous sodium hydroxide (12 equiv.). The solution was stirred for 26 hours, then poured into dichloromethane, water added and the solution neutralised with solid carbon dioxide. The organic phase was separated, dried and evaporated. The residue was chromatographed on silica plates to give the keto-alcohol (17) (24mg) m.p. 180-183°, ν_{max} 3400, 1675 cm^{-1}, λ_{max}^{chf} 296, 307, 322 n.m. (ε 23,000, 23,000, 13,500).

The n.m.r. spectrum had signals at 8.25τ (3H,s), 7.16τ (1H,q), 6.65τ (2H,m), 5.58τ (1H,d J=5cps) and 2.08-3.05τ (12H,m). (Found C 82.30% H 5.57%; $C_{26}H_{20}O_3$ requires C 82.08% H 5.30%).

Reaction of ketones (13) and (14) separately with methyl lithium.

The mixutre of diastereoisomers was separated by preparative thin layer chromatography to give 40.5% of (13) and 59.5% of (14). The α-thio compound (13) (129mg) was dissolved in dry benzene (20ml) and dry ether (10ml) added. The solution was stirred under nitrogen at room temperature and methyl lithium (12 equiv.) was added. The solution was stirred for 30 minutes and then quenched with aqueous ammonium chloride (1gm in 5ml of water). The mixture was stirred for 10 minutes and then extracted with dichloromethane, dried and evaporated. The residue was chromatographed on a large thick (1m.m) silica plate to give cis-6a,12a-12(ethylene-α-oxy-βthio)-6a,7,12,12a-tetrahydro-1-phenyl-naphthaceno (1,12-bc) furan -6α-methyl-6β-ol (15) (69mg). It has m.p. 209-212°; ν_{max} 3450 cm^{-1}; λ_{max} 264, 286, 307, 323 n.m. (ε 12,500, 11,500, 8,260, 4,500). The n.m.r. spectrum showed signals at 8.32τ (3H,s) 6.92-7.60τ (3H,m), 6.60-6.92τ (3H,m), 5.98-6.36τ (2H,m), 5.74τ (1H,d J=4.5cps) and 2.0τ-3.00τ (12H,m). (Found C 76.49% H.5.67% S 7.42%; $C_{28}H_{24}O_3S$ requires C 76.35% H.5.49% S 7.28%).

The other epimer (14) was reacted as above to give cis-6a,12a-12(ethylene-β-thio-αoxy)-6a,7,12,12a-tetrahydro-1-phenyl-naphthaceno (1,12-bc) furan-6α-methyl-6β-ol (16), in 30% yield. It had m.p. 177-187°; ν_{max} 3450 cm^{-1}, λ_{max} 294, 310, 326 (ε 13,670, 12,420, 8,921). The n.m.r. showed signals at 8.28τ (3H,s), 7.46-7.88τ (2H,m), 7.14-7.40τ (2H,m), 6.60-6.80τ (2H,m), 5.84-6.40τ (2H,m), 5.61τ (1H,d J=5cps) and 2.06-2.96τ (12H,m). (Found C 76.36% H 5.72% S 7.20%; $C_{28}H_{24}O_3S$ requires C 76.35% H 5.49% S 7.28%).

Cis-6a,12a-12-(ethylene-β-oxy-αthio)-6a,7,12,12a-tetrahydro-1-phenyl-naphthaceno (1,12-bc) furan-6α-H-6β-ol (21a).

The α-thio ketal (13) (396mg) was dissolved in dry T.H.F. (50ml) and diluted with dry methanol (15ml). Sodium borohydride (400mg) was added and the solution stirred under nitrogen for 3 hours when t.l.c. showed that no starting material was left. The solution was poured into water and extracted with dichloromethane. The extracts were dried and evaporated to give a crystalline residue which on recrystallisation from acetonitrile gave a 95% yield of the alcohol (21a).

It had m.p. 230-233°; ν_{max} 3470 cm^{-1}; λ_{max} 299, 310, 322 n.m. (ε16,200, 17,400, 11,000). The n.m.r. spectrum had signals at 7.00-7.50τ (3H,m), 6.60τ (2H,m), 6.08-6.42τ (2H,m), 5.67τ (1H,d J=4.5cps), 5.25τ (1H,d J=4cps) and 2.00-2.85τ (12H,m). (Found C 76.29% H 5.15% S 7.49%; $C_{27}H_{22}O_3S$ requires C 76.04%H 5.20%S 7.52%).

Cis-6a,12a-12(ethylene-β-thio-α-oxy)-6a,7,12,12a-tetrahydro-1-phenyl-naphthaceno (1,12-bc) furan -6α-H-6β-ol (22a).

The β thioketal (14) (550mg) was reduced with sodium borohydride as described for the α-thio epimer and the alcohol isolated in 95% yield. It had m.p. 178-180°, ν_{max} 3520 cm^{-1}, λ_{max} 300, 312, 326 n.m. (ε 17,400, 21,500, 15,900). The n.m.r. spectrum had signals at 7.96τ (1H s, exchangeable by D_2O), 7.00-7.83τ (3H,m), 6.50-6,72τ (2H,m), 5.80-6.42τ(2H,m), 5.53τ (1H, d J=5.5cps), 5.04τ (1H,d J=4cps) and 1.80-2.92τ (12H,m). (Found C 75.97%, H 5.07%, S 7.49%; $C_{27}H_{22}O_3S$ requires C 76.04%, H 5.20% S 7.52%).

Cis-6a,12a-12(ethylene-α-thio-β-oxy)-6a,7,12,12a-tetrahydro-1-phenyl-naphthaceno (1,12-bc) furan-6α-H-6β-acetate (21b).

The α-thio alcohol (21a) (200mg) was dissolved in dry pyridine (3ml) and acetic anhydride (4ml) added. The solution was stirred at room temperature and the reaction monitored by t.l.c. After 1 hour 50% of the starting material had been converted to the acetate and the reaction was complete after 3 hours. The solution was evaporated to dryness under high vacuum, and the residue recrystallised from benzene petrol to give the acetate (21b) (203mg), m.p. 178-180°; ν_{max}^{nujol} 1738, 1235 cm^{-1}; λ_{max}^{chf} 262, 279, 288, 310, 325 n.m. (ε 17,050, 10,880, 10,720, 8,200, 4,700). The n.m.r. spectrum exhibited signals at 8.00τ (3H,s), 6.67-7.35τ (5H,m), 5.95-6.50τ (2H,m), 5.90τ (1Hd J=5.5cps), 3.52τ (1H,d J=4cps) and 2.58-3.18τ (12H,m). (Found C 74.08% H 5.23% S 7.09%; $C_{29}H_{24}O_4S$ requires C 74.35% H 5.16% S 6.84%.

Cis-6a,12a-12(ethylene-β-thio-α-oxy)-6a,7,12,12a-tetrahydro-1-phenyl-naphthaceno (1,12-bc) furan-6α-H-6β-acetate (22b).

The reaction was carried out as above with the

same quantities. After3 hours the reaction was 50% complete and after 8 hours the reaction was worked up as before. The product was recrystallised from benzene-petrol to give the acetate (22b) (215mg), m.p. 196-198°; ν_{max}^{nujol} 1725, 1240 cm^{-1}; λ_{max}^{chf} 299, 312, 327 n.m. (ε 20,850, 28,850, 22,800). The n.m.r. spectrum had signals at 8.72τ (3H,s), 5.67-7.80τ (7H,m), 5.52τ (1H,d J=5cps), 3.70τ (1H,d J=3.5cps). (Found C 74.44% H 5.10% S 6.93%; $C_{29}H_{24}O_4S$ requires C 74.35% H 5.16% S 6.84%).

Attempted thermal cyclisations of 4-(6[1]formyl-ethylenedioxy-benzyl)-2-phenylnaphtho (1,8-bc) furan-5-one (23).

The acetal (23) (44mg) and azobisbutyronitrile (18mg) were dissolved in dry benzene (30ml) and refluxed, under nitrogen, in the dark. After 24 hours t.l.c. showed only unchanged starting material.

The reaction was repeated using benzoyl peroxide as the initiator and after 18 hours of refluxing, t.l.c. again showed only unreacted acetal.

A few crystals of the acetal were heated in a sealed capillary tube at 210° for 1 hour. After cooling to room temperature t.l.c. indicated that the acetal was recovered unchanged. On heating at 305° for 3 hours some decomposition occurred but the acetal was largely unreacted (t.l.c. control).

Reduction of photolysis product direct from reaction.

The ACD acetal (23) (305mg) was photolysed in the usual manner[9] using a tungsten lamp and benzoyl peroxide as the initiator. After 86 hours of irradiation the

solution was evaporated to dryness and the residue dissolved in dry tetrahydrofuran (20ml). This solution was diluted with anhydrous methanol (20ml) and sodium borohydride (184mg) added. The solution was stirred under nitrogen for 4 hours when some of the 6-ketone still remained. A further portion of sodium borohydride (50mg) was added and the solution stirred overnight. The reaction was worked up in the usual way[9] and the required 6-alcohol isolated, by preparative thin layer chromatography, in 63% yield. The product had identical t.l.c. and spectroscopic properties to a sample of the 6-alcohol produced from the cis ketone (2).

Photolysis of the acetal (23) in different solvents.

The general method of photolysis was as follows. The acetal (ca. 100mg) was dissolved in the solvent to be used (80ml) in a 100ml R.B., three necked flask fitted with a reflux condenser, carrying a calcium chloride drying tube, and a nitrogen inlet. The flask was clamped directly above a tungsten lamp (750 watts) and screened by sheets of aluminium foil. The lamp was cooled by a small electric fan. The initiator was then added and the solution irradiated.

The reaction was monitored by t.l.c. and when all of the starting material had been destroyed the irradiation was stopped and the solution evaporated to dryness. The residue was dissolved in benzene, the solution applied to an alumina column (20x3 cm) and the column eluted with benzene. The development of the column was followed by examination in ultra violet light; the product appearing as a bright blue fluorescent band.

The results obtained with the various solvents used are shown in Table 1; page 60.

Photolysis of acetal (23) in benzene which had previously been treated with benzoyl peroxide.

Benzene (200ml) was refluxed with benzoyl peroxide (93mg) for 80 hours and then distilled out of the solution. The distilled benzene was then used in a photolysis of the acetal in the absence of benzoyl peroxide. The yield of cyclised material (2) was 11%.

The photolysis was repeated using untreated benzene and a yield of 12% of the cyclised material was obtained.

Photolysis of acetal (23) in the presence of destroyed benzoyl peroxide.

Benzoyl peroxide was destroyed by refluxing in benzene until a negative test for peroxides was obtained. The bulk of the benzene was distilled off and aliquots of the residual solution used in the photolyses. The photolyses were carried out in the usual way and the results obtained with varying amounts of destroyed benzoyl peroxide are shown in Table 2 page 61.

Photolysis of acetal (23) in the presence of biphenyl.

The acetal (104mg) was photolysed in the usual way in the presence of biphenyl (6mg). After 68 hours t.l.c. indicated that approximately 10% of the cyclised material had been formed.

Photolysis of acetal (23) in the presence of phenyl benzoate.

The acetal (102mg) was photolysed as usual in the presence of phenyl benzoate (7mg) in benzene. The reaction was worked up after 43 hours to give a yield of 23% of the cyclised material.

Separation of residue from the thermal decomposition of benzoyl peroxide.

Benzoyl peroxide (860mg) was refluxed in benzene (800ml) for 86 hours. The bulk of the benzene was then distilled off and the remainder removed on a rotary evaporator. The residue was chromatographed on an alumina column eluting with 10% benzene/petrol. The first fraction collected (238mg) was a mixture of biphenyl and dihydrobiphenyl while the second fraction (539mg) was a mixture of tetrahydroquaterphenyls. The column was then washed with ether to give a further 196mg of residue.

Photolysis of acetal (23) in the presence of tetrahydroquaterphenyl fraction.

The acetal (102mg) was photolysed in the presence of the tetrahydroquaterphenyl fraction (13mg) for 96 hours. On work up a yield of 20% of cyclised material was obtained.

The above experiment was repeated using a larger amount of additive (180mg) and a yield of 44% was obtained.

Photolysis of acetal (23) in the presence of ether washings from the chromatography.

The acetal (100mg) was photolysed in the presence of the ether washings from the chromatography to give a yield of 44% of cyclised material in 75 hours.

Distillation of residue from thermal decomposition of benzoyl peroxide and photolyses of the acetal (23) using the resulting fractions .

The residue from the thermal destruction of benzoyl peroxide (1gm) was distilled on the high vacuum line at 2×10^{-4} mm.Hg and at 100°. This gave a mixture (303mg) of benzoic acid and biphenyl, which collected in an acetone/CO_2 trap. A second fraction (69mg) was collected in the neck of the flask and was shown to be a mixture of benzoic acid, 1,4 dihydrobiphenyl, biphenyl and some unidentified material. The residue (640mg) had ν_{max}^{film} 1720, 1710 cm^{-1}.

The acetal (103mg) was photolysed in the presence of the first fraction (53mg) and gave a yield of 57% in 18 1/2 hours.

The acetal (105mg) was photolysed in the presence of the second fraction (45mg) and gave a yield of 57%.

The acetal (100mg) was photolysed in the presence of the residue (64mg) and gave a yield of 28% in 90 hours.

The first fraction (235mg) was dissolved in benzene and washed with saturated aqueous sodium bicarbonate solution and then water. The benzene layer was separated, dried and evaporated to give a non-crystalline residue (180mg). The sodium bicarbonate extracts were acidified, extracted with dichloromethane, dried and evaporated to give a crystalline product (29mg) whose i.r. spectrum was identical to that of benzoic acid.

The acetal (102mg) was photolysed in the presence of the non-acidic fraction (45mg) to give a yield of 18% in 90 hours.

The acetal (105mg) was photolysed in the presence of the acidic fraction (28mg) and gave a yield of 78% in 55 hours.

Photolysis of acetal (23) in the presence of benzoic acid.

The acetal (101mg) was photolysed in the presence of benzoic acid (26mg) and gave a yield of 78%.

The reaction was repeated using varying quantities of benzoic acid (5mg, 72mg) to give yields of 55 and 77%.

Photolysis of acetal (23) in the presence of different acids.

The acetal (23) was photolysed in the presence of acetic, p-nitrobenzoic and p-methoxybenzoic acids. The results are shown in Table 4 page 64.

Photolysis of 2-phenylnaphtho (1,8-bc) furan-5-one (26) in the presence of benzoic acid.

2-phenylnaphtho (1,8-bc) furan-5-one (26) (107mg) was photolysed in the usual manner, in benzene (90ml), in the presence of benzoic acid (59mg). After 72 hours t.l.c. showed that the starting material was unchanged.

Preparation of N,N,N^1,N^1 tetramethyl o-phthalamide.

Phthaloyl chloride (2.6gm) in ether was slowly added to a stirred solution of dimethylamine (10ml) in ether at -20°. The solution was stirred for 1 hour at -20° and then the dimethylamine hydrochloride was filtered off. The ethereal solution was evaporated and the crude product chromatographed on alumina, eluting the column with ether. This gave the required diamide m.p. 116-119° (Lit. 120-121°), ν_{max}^{nujol} 1630, 1620 cm^{-1}.

Reduction of N,N,N^1,N^1, tetramethyl o-phthalamide with lithium aluminium deuteride.

N,N,N^1,N^1, tetramethylphthalamide (4gm) was dissolved in dry T.H.F. (80ml) and dry ether (80ml) added. Lithium aluminium deuteride (997mg) was slowly added, with constant stirring, at room temperature. The suspension was stirred overnight at room temperature and then quenched with ice. The complex was hydrolysed with dilute sulphuric acid and the product extracted with chloroform. The extracts were dried and evaporated to give crude (1,1^1-^{2}H)phthalaladehyde (1.26gm). A small sample was recrystallised from petrol and had

m.p. 52-54°, (non deuterated phthalaldehyde has m.p. 56°).

4-(6^{1}-(1^{11}-^{2}H) formyl-(1^{1}-^{2}H)-benzyl)-2-phenylnaphtho (1,8-bc) furan-5-one (27).

The crude deuterated phthalaldehyde (1gm) was dissolved in absolute ethanol (40ml) and the solution added to dihydroperinaphthofuran (1.9gm). Triethylamine (4ml) was added and the solution was then refluxed under nitrogen overnight. The solution was cooled and di-isopropyl ether added. After cooling in the cold room for several hours the crystals, which had separated out, were filtered off. These were recrystallised from dichloromethane/di-isopropyl ether to give the deuterated ACD aldehyde (27) (1.287gm) ν_{max}^{nujol} 2150,2100, 1680, 1635 cm^{-1}. The n.m.r. spectrum had signals at 5.63τ (1H,bs), 1.90-2.83τ (13H,m).

4-(6^{1}-(1^{11}-^{2}H) formyl-ethylenedioxy-(1^{1}-^{2}H)-benzyl)-2-phenyl-naphtho (1,8-bc) furan-5-one (28)

The deuterated ACD aldehyde (27) (1.28gm) was suspended in dry benzene (200ml), ethylene glycol (10ml) and tosyl acid (15mg) were added and the solution refluxed overnight through a calcium hydride filled Soxhlet extractor. The cooled solution was then poured

into saturated aqueous sodium bicarbonate solution, the benzene layer separated, washed with water, dried and evaporated. The product was recrystallised from benzene/petrol to give yellow plates of the acetal (28) (1.36gm), ν_{max}^{nujol} 2150, 1635 cm^{-1}. The n.m.r. spectrum showed signals at 5.95τ (5H,m), 1.88-2.80τ (13H,m). The mass spectrum showed the molecular ion at m/e 410 with the base peak at m/e 163.

Photocyclisation of deuterated acetal (28).

The deuterated acetal (28) (107mg) was photolysed in the usual manner in the presence of benzoic acid (59mg). After an irradiation period of 45 hours the cyclised material (29) was isolated in 74% yield, ν_{max}^{nujol} 1698 cm^{-1}. The mass spectrum showed the molecular ion at m/e 409 and the base peak at m/e 163.

Photocyclisation of ACD tricyclic aldehyde (31).

The ACD aldehyde (31) (121mg) was photolysed in the usual manner in the presence of benzoic acid (46mg). The reaction was complete after 20 hours and the diketone (32) isolated in 30% yield. The n.m.r. spectrum showed

signals at 6.71τ (1H, double doublet J=16cps and 5cps), 6.03τ (1H, double doublet J=16cps and 2.5cps), 6.25τ (1H,m), 5.19τ (1H,d J=6.5cps) and 1.88-3.20τ (12H,m).

Photocyclisation of deuterated ACD tricyclic aldehyde (27).

The deuterated aldehyde (27) (108mg) was photolysed as usual in the presence of benzoic acid (39mg). After 16 hours the reaction was worked up to give a 36% yield of the deuterated diketone (30). The n.m.r. spectrum showed signals at 6.74τ (1H,m), 6.25τ (1H,m), 6.08τ (1H,m), 5.22τ (1H,d J=6cps) and 1.88-3.20τ (12H,m).

Attempted basic exchange on deuterated acetal (28).

The deuterated acetal (28) (66mg) was suspended in dry tert-butanol (40ml) and potassium tert-butoxide (18mg) added. Dry benzene was then added and the solution stirred under nitrogen overnight. The solution was then poured into water, acidified with acetic acid, extracted with dichloromethane, dried and evaporated. The n.m.r. spectrum of the product showed that no exchange of the deuterium atoms had occurred.

The deutero acetal (54mg) was dissolved in dry T.H.F. (5ml) and the solution added to liquid ammonia (5ml). Sodamide (6mg) was added and the solution stirred, under reflux, for 1 1/2 hours. Ammonium chloride was then added, the ammonia allowed to evaporate and the product extracted with dichloromethane. T.l.c. indicated that the reaction had given several products and was abandoned.

Preparation of deuterated benzoic acid.

Benzoyl chloride (2.04gm) and deuterium oxide (1.8ml) were sealed in a small Carius tube and then heated at 100° for 2 hours. The contents of the tube were then washed out with chloroform and evaporated to dryness. The crude acid was sublimed at atmospheric pressure, to give white needles of the pure acid (1.5gm).

Photolysis of acetal (23) in the presence of deuterated benzoic acid.

The acetal (23) (104mg) was photolysed in the usual manner in the presence of deutero benzoic acid (63mg). The product obtained (81mg) contained no

deuterium (n.m.r. control).

The acetal (23) (104mg) was photolysed in the usual manner in the presence of deuterated benzoic acid (65mg). After 2 1/4 hours the reaction was worked up and the starting material recovered. The n.m.r. of this showed that no deuterium had been incorporated.

Photolysis of acetal (23) in the presence of dimethyl acetylene dicarboxylate.

The acetal (23) (107mg) was photolysed as usual in the presence of benzoic acid (60mg) and dimethyl acetylene dicarboxylate (2.998gm). After an overnight reaction period t.l.c. showed that only the normal cyclised material (2) was formed.

3. 2-(p-bromophenyl) naphtho (1,8-bc) furan-5-one (46).

p-Bromobenzoyl chloride (1.3gm) was dissolved in carbon disulphide (10ml) and aluminium trichloride (3gm) slowly added. Nitrobenzene (20ml) was then added and the solution stirred at room temperature while 1,5 dihydroxy-naphthalene (900mg) was added. After stirring for 2 hours at room temperature the mixture was warmed to 50° and stirred for a further 2 hours. The mixture was then poured into a two phase system of water and chloroform and dilute hydrochloric acid added until the complex was hydrolysed. The organic layer was separated, washed with 4N sodium hydroxide solution, dried and evaporated. The residue was chromatographed on an alumina column in benzene eluting first with petrol to remove the nitrobenzene and then with chloroform to remove the product. This was rechromatographed on an alumina column eluting with benzene to give the bromo-perinaphthofuran (46) (30mg., 1.6%), m.p. 242-243°, ν_{max}^{nujol} 1645 cm^{-1}. The n.m.r. spectrum showed signals at 3.30τ (1H,d J=10cps), 2.10τ (1H,d J=10cps). (Found C 62.58%, H 2.78%, Br 24.35%; $C_{17}H_9O_2Br$ requires C 62.8%, H 2.77%, Br 24.6%).

Preparation of the bromoperinaphthofuran (46) in polyphosphoric acid.

p-Bromobenzoyl chloride (684mg) was dissolved in polyphosphoric acid (15ml) at 90° and 1,5 dihydroxynaphthalene (468mg) added. The mixture was then stirred at 90° for 1/2 hour, cooled and water and chloroform added. Dilute hydrochloric acid was then added and the solution stirred until all of the polyphosphoric acid had hydrolysed. The organic phase was separated, washed with 4N sodium hydroxide followed by water, dried and evaporated. The residue was chromatographed on an alumina column, eluting with benzene, to give the required bromoperinaphthofuran (46) (155mg).

The reaction conditions were varied as shown in Table 5 and the yield of the bromoperinaphthofuran increased to an optimum of 22%.

3,4-dihydro-2-(p-bromophenyl)-naphtho (1,8-bc) furan-5-one (47).

The bromoperinaphthofuran (46) (304mg) was dissolved in T.H.F. (80ml) and Raney nickel (W4, 1 spoonful) added.

The suspension was hydrogenated at atmospheric pressure until the requisite amount of hydrogen (23ml) had been taken up. The catalyst was filtered off on a Celite pad and the filtrate evaporated. The residue was chromatographed on an alumina column eluting with benzene, the product was collected and recrystallised from methanol to give pale yellow needles of the required bromodihydroperinaphtho furan (47) (200mg) m.p. 179-181°, ν_{max}^{nujol} 1675 cm^{-1}, λ_{max}^{EtOH} 221, 228, 236, 278, 292, 308, 350 n.m. (ε 12100, 11750, 10100, 24600, 18700, 14700, 18350). The n.m.r. spectrum showed signals at 7.00τ (2H,m), 6.62τ (2H,m), and 2.19-2.85τ (7H,m). (Found C 62.45%, H 3.50%, Br 24.40%; $C_{17}H_{11}O_2Br$ requires C 62.4% H 3.36% Br 24.45%).

4-(6^1-formyl-benzyl)-2-(p-bromophenyl)-naphtho (1,8-bc) furan-5-one (48).

The bromo-dihydroperinaphthofuran (47) (555mg) and o-phthalaldehyde (494mg) were mixed together and absolute ethanol (80ml) added, followed by triethylamine (3ml). The solution was refluxed under nitrogen overnight and then cooled to 0°. The resulting cyrstals (614mg) were filtered off and dried. The filtrate was evaporated and chromatographed on an alumina column, eluting with

benzene/dichloromethane (50:50), to give a further amount (41mg) of the ACD compound. The total yield of the bromo-ACD aldehyde (48) was 86%. The i.r. spectrum had ν_{max}^{nujol} 1675, 1640 cm^{-1}.

4-(6^{1}-(ethylenedioxy formyl - benzyl)-2-(p-bromophenyl)-naphtho (1,8-bc) furan-5-one (49).

The bromoaldehyde (48) (550mg) was dissolved in dry benzene (200ml) and ethylene glycol (9ml) and p-toluene-sulphonic acid (20mg) were added. The solution was refluxed, with the benzene passing through a calcium hydride packed Soxhlet thimble, overnight. The cooled solution was then poured into a saturated aqueous solution of sodium bicarbonate. The benzene layer was separated, washed three times with water, dried and evaporated. Crystallisation from benzene gave the acetal (49) in 95% yield, m.p. 178-180°, ν_{max}^{nujol} 1640 cm^{-1}, $\lambda_{max}^{CHCl_3}$ 253, 275, 408 n.m. (ε 10400, 16700, 32300). The n.m.r. spectrum exhibited signals at 5.92τ (6H,m), 3.98τ (1H,s), and 1.85-2.85τ (11H,m). (Found C 66.60%, H 4.03%, Br 16.21%; $C_{27}H_{19}O_4Br$ requires C 66.53%, H 3.90%, Br 16.43%).

cis-6a,12a-(12-ethylenedioxy)-6a,7,12,12a-tetrahydro-1-(p-bromophenyl) naphthaceno (1,12-bc) furan-6-one (50).

The bromoacetal (49) (503mg) was photolysed in benzene (350ml) in the presence of benzoic acid (174mg) in the usual manner. After 18 hours the solution was evaporated and the residue chromatographed on an alumina column eluting with benzene, to give the required bromo tetracyclic ketal (50) (371mg), m.p. 229-231° (acetonitrile), ν_{max}^{nujol} 1690cm^{-1}. The n.m.r. spectrum showed signals at 5.42-7.28τ (8H,m) and 1.75-3.00τ (11H,m). (Found C 66.44%, H 4.11%, Br 16.44%; $C_{27}H_{19}O_4Br$ requires C 66.53%, H 3.90%, Br 16.43%).

cis-6a,12a-(12-ethylenedioxy)-6a,7,12,12a-tetrahydro-1-(p-bromophenyl) naphthaceno (1,12-bc)-furan-6α-H-6β-acetate (45).

The bromo-tetracyclic ketal (50) (201mg) was dissolved in dry T.H.F. (15ml) and dry methanol (20ml) added. Sodium borohydride (200mg) was then slowly added and the solution stirred under nitrogen for 1.5 hours. The reaction mixture was poured into water and extracted

with dichloromethane. The extracts were dried and evaporated. The residue was chromatographed on a 20x60 cm silica plate to give the 6β alcohol (183mg) and recovered starting material (8mg).

The alcohol was dissolved in dry pyridine (4ml) and acetic anhydride (4ml) added. The solution was heated on a steam bath overnight and then evaporated. The residue was purified on a 20x60 cm silica plate to give the required acetate (45) (170mg), m.p. 221-223°, ν_{max}^{nujol} 1720, 1250 cm^{-1}, $\lambda_{max}^{CHCl_3}$ 306, 316, 331 n.m. (ε 26300, 37000, 28600). The n.m.r. spectrum showed signals at 8.75τ (3H,s), 5.91-7.40τ (7H,m), 5.78τ (1H,d J=4.5cps), 3.63τ (1H,d J=4cps), 1.82-3.00τ (11H,m). (Found C 65.43%, H 4.38%, O 15.04%; $C_{29}H_{35}O_5Br$ requires C 65.54%, H 4.33%, O 15.07%).

The crystals for the x-ray study were grown from an acetonitrile solution of the acetate.

2-(p-bromophenyl) naphtho (1,8-bc) furan-5β-acetate (51).

The bromo-dihydroperinaphthofuran (47) (335mg) was dissolved in dry T.H.F. (30ml) and the solution diluted with anhydrous methanol (50ml). Sodium boro-hydride (200mg) was then added and the solution stirred

for 3 hours. The reaction mixture was worked up as before and the product dissolved in dry pyridine (3ml), and acetic anhydride (3ml) added. After an overnight reaction period the solvents were evaporated to give the required acetate (51) (312mg) ν_{max} 1720, 1240 cm^{-1}. The n.m.r. spectrum showed signals at 7.92τ (3H,s), 7.74τ (2H,m), 6,87τ (2H,m), 3.81τ (1H,t J=4cps) and 2.20-2.92τ (7H,m).

Attempted debromination of (51) with methyl lithium.

The bromoacetate (51) (32mg) was dissolved in dry T.H.F. (5ml) and methyl lithium solution (0.5ml, 0.8M) added at 0°. After stirring at room temperature, under nitrogen, for 1 hour the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (5ml) and extracted with dichloromethane. The extracts were dried and evaporated and the crude product reacetylated overnight in the usual manner. After work up the acetate was purified by thin layer chromatography. The i.r. spectrum indicated that little of the debromoacetate (52) had been formed.

Debromination of (51) with butyl lithium.

The bromoacetate (51) (19mg) was dissolved in dry ether (10ml) and an excess of butyl lithium solution added. The solution was stirred at room temperature, under nitrogen, for 1/2 hour, when a white precipitate was formed. Water (2ml) was then added and the ether layer separated, dried and evaporated. The residue was reacetylated in the usual manner and the acetate purified by thin layer chromatography. Two recrystallisations from 60-80 petrol gave the debromoacetate (52) (10mg), m.p. 88.5-90°. The authentic acetate (52) had m.p. 89-91°.

Attempted debromination of (45) with butyl lithium.

The tetracyclic bromoacetate (45) (19mg) was dissolved in dry T.H.F. (1ml) and dry ether (10ml) added. The solution was stirred under nitrogen and excess butyl lithium added. The solution immediately darkened in colour and after 25 minutes water (2ml) was added. The solution was extracted with dichloromethane and the extracts were dried and evaporated. The residue was reacetylated as usual and t.l.c. indicated that a complex mixture of products had been formed.

4. 4-(3^1,5^1-dihydroxy-2^1-formyl-4^1-carbomethoxy-benzyl)-2-phenyl-naphtho (1,8-bc) furan-5-one (54).

This was prepared using the scaled up directions of Hase[20].

Methylation of (54).

The aldehyde (54) (300mg) was suspended in dry acetone (30ml) and potassium carbonate (100mg) added followed by dimethyl sulphate (0.07ml). The mixture was stirred and refluxed under nitrogen. After 1 hour t.l.c indicated that the dimethyl ether (55) was being formed with none of the monomethyl ether (56). Further portions of potassium carbonate (200mg) and dimethyl sulphate (0.5ml) were added and the mixture refluxed for a further 1 hour. The suspension was then poured into water, extracted with dichloromethane, dried and evaporated. The residue was chromatographed on an alumina column eluting with chloroform to give the dimethyl ether (55) (296mg).

4-(3^1-hydroxy-5^1-methoxy-2^1-formyl-4^1-carbomethoxy-benzyl)-2-phenylnaphtho (1,8-bc) furan-5-one (56).

The dimethoxy aldehyde (55) (296mg) was dissolved in dry dichloromethane (30ml) and cooled to -76°. Boron trichloride (0.3ml) was added and the solution stirred for 1 hour. Water (5ml) was added and the mixture extracted with dichloromethane. The extracts were dried and evaporated to give the crude product, which was chromatographed on a silica gel column eluting with dichloromethane/chloroform (50:50). The material from the column was recrystallised from dichloromethane/di-isopropyl ether to give the crystalline product (168mg) and a non crystalline fraction (81mg). The hydroxy aldehyde (56) had m.p. 245-246°, ν_{max}^{nujol} 1715, 1630 cm^{-1}, $\lambda_{max}^{CHCl_3}$ 250, 270, 281, 332, 400 n.m. (ε 19650, 21200, 22500, 11100, 28700). The n.m.r. spectrum showed signals at 6.12τ (3H,s), 6.03τ (3H,s), 5.72τ (2H,bs), 3.48τ (1H,s), 1.90-2.66τ (9H,m), -0.8τ (1H,s), -2.60τ (1H,s). (Found C 71.62%, H 4.35%; $C_{28}H_{20}O_7$ requires C 71.79%, H 4.30%).

4-(3^1-acetoxy-5^1-methoxy-2^1-formyl-4^1-carbomethoxy-benzyl)-2-phenylnaphtho (1,8-bc) furan-5-one (57).

The hydroxy aldehyde (56) (27mg) was dissolved in dry pyridine (1ml) and acetic anhydride (1ml) added. The mixture was warmed on the steam bath for 6 minutes and then poured into dichloromethane/water. The organic phase was washed with water (3x), dried and evaporated to give the acetoxy aldehyde (57) (88%), ν_{max}^{nujol} 1770, 1738, 1680, 1638 cm^{-1}.

Attempted preparation of the ethylene ketal of the aldehyde (57).

a) Exchange reaction.

The acetoxy aldehyde (30mg) was dissolved in dry benzene (15ml) and butan-2-one ethylene ketal (1ml) added followed by boron trifluoride etherate (1 drop). After stirring for 5 minutes the reaction mixture was poured into water and extracted with chloroform. The extracts were dried and evaporated down. T.l.c. on the residue showed a lot of decomposition products near rhe origin and some unchanged starting material.

b) Ethylene glycol/p-toluenesulphonic acid.

The acetoxy aldehyde (159mg) was dissolved in dry benzene (80ml), ethylene glycol (4ml) and p-toluene-sulphonic acid (a few crystals) added, and the solution refluxed with the benzene passing through a calcium hydride packed Soxhlet thimble. After 48 hours the cooled solution was poured into a saturated aqueous solution of sodium bicarbonate. The benzene layer was separated, washed with water, dried and evaporated. T.l.c. indicated that the product was the aldehyde (56) and reacetylation gave the starting acetoxy aldehyde (57).

Photolysis of the acetoxy-aldehyde (57).

The acetoxy-aldehyde (57) (74mg) was dissolved in dry benzene (80ml), acetic acid (0.2ml) and acetic anhydride (0.15ml) added, and the solution photolysed as usual. After 2.5 hours t.l.c. indicated that all of the starting material had been destroyed and that a complex mixture of products had been formed. Reacetylation gave no improvement in the number of products formed.

Methyl-cis-6a,12a-9,11-dimethoxy-6,12-dioxo-1-phenyl-6a,7,12,12a-tetrahydronaphthaceno (1,12-bc)-furan-10-carboxylate (61).

The dimethoxy aldehyde (55) (248mg) was mixed with benzoic acid (105mg) and dissolved in dry benzene (200ml). The solution was photolysed as usual with the nitrogen passing through an activated catalyst before entering the photolysis flask. After 8 hours the solution was evaporated and the residue chromatographed on a 20x60 cm silica plate eluting with chloroform. The crude product (71mg) was isolated and then triturated with ether to remove the coloured impurities. This gave the required diketone (61) (38mg.,15%), m.p. 240-245°, ν_{max}^{nujol} 1725, 1690, 1680 cm^{-1}, $\lambda_{max}^{CHCl_3}$ 277, 294, 360 n.m. (ε 23000, 22000, 18100). (Found C 72.15%, H 4.53%; $C_{29}H_{22}O_7$ requires C 72.19%, H 4.60%).

Demethylation and reduction of diketone (61).

The dimethoxy diketone (61) (8mg) was dissolved in dry dichloromethane (15ml) at -76° and boron trichloride (3 drops) added. After 10 minutes water (5ml) was added

followed by dichloromethane. The dichloromethane layer was separated, dried and evaporated. The residue was dissolved in T.H.F./methanol (10ml) and sodium borohydride (22mg) added. The solution was stirred at room temperature for 15 minutes and then poured into water. Extraction with dichloromethane, drying and evaporation gave a mixture of products. The mixture was chromatographed on a 20x20cm t.l.c. plate to give the major product (2.9mg., 38%). The i.r. spectrum showed ν_{max}^{nujol} 1720 weak, 1655, 1620 cm^{-1}. The mass spectrum showed the molecular ion at m/e 456 with peaks at m/e 438 (M^+-H_2O) and m/e 424 (M^+-CH_3OH).

Demethylation of the diketone (61).

The dimethoxy diketone (61) (38mg) was dissolved in dry dichloromethane (30ml) at -76°, under nitrogen and boron trichloride (4 drops) added. After 1 hour the reaction was quenched with water, extracted with dichloromethane and the extracts dried and evaporated. The residue was chromatographed on 4 20x20 cm t.l.c. plates to give the di-demethylated product (9mg., 25%), ν_{max} 1680, 1655, 1620 cm^{-1} and the mono-demethylated product (66) (13mg., 35%) ν_{max} 1735, 1690, 1625 cm^{-1}.

Reduction of mono-demethylated diketone (66)

The mono-demethylated compound (66) (12mg) was dissolved in T.H.F./methanol (25ml. 50:50) and sodium borohydride (20mg) added. The solution was stirred, under nitrogen, at room temperature for 20 minutes and then worked up as described previously. The residue was chromatographed on a 20x20 cm t.l.c. plate and gave a major product (4mg., 32%) ν_{max} 3400, 1660, 1618 cm^{-1}. The mass spectrum showed the molecular ion at m/e 470 with peaks at m/e 454 (100%), m/e 436 (454-H_2O), m/e 422 (454-CH_3OH), m/e 404 (422-H_2O).

5. Methyl-cis-6a,12a-9,11-dimethoxy-12-ethylenedioxy-6-oxo-1-phenyl-6a,7,12,12a-tetrahydronaphthaceno (1,12-bc)-furan-10-carboxylate (73).

This was prepared using the directionsgiven by Hase[20], but with benzoic acid as the additive. The yields obtained were in the range 40-45%.

Attempted hydrolysis of the tetracyclic ester (73) with lithium iodide.

The tetracyclic ester (73) (26mg) was mixed with lithium iodide (138mg) and dry dimethylformamide (10ml) added. The solution was stirred, under nitrogen, at 85° for 24 hours, when t.l.c indicated that no reaction had occurred. The temperature was raised to 150° but again no reaction was observed.

cis-6a,12a-9,11-dimethoxy-12-ethylenedioxy-6-oxo-1 phenyl-6a,7,12,12a-tetrahydronaphthaceno (1,12-bc)-furan-10-carboxamide (71).

The tetracyclic ester (73) (677mg) was suspended in ethanol (95ml) and water (107ml) with nitrogen bubbling

under the surface. Potassium hydroxide (34gm) was added in small portions and the suspension refluxed until all of the ester had gone into solution (4-8 hours). The solution was then cooled to 0° and dichloromethane added followed by dilute hydrochloric acid until the solution was just acid. The organic phase was separated, washed with water (3x), dried and evaporated. The crude acid was dried overnight in a vacuum drying pistol, and then dissolved in dry benzene (50ml). Dimethylformamide (480mg) and thionyl chloride (380mg) were added and the solution stirred, under nitrogen, for 2.5 hours. The reaction mixture was quenched with '880' ammonia (28ml) and the mixture stirred for 10 minutes. The product was extracted with dichloromethane and the extracts dried and evaporated. Chromatography on 2 60x20cm silica plates yielded the pure amide (71) in 67% yield.

Reaction of amide (71) with boron trichloride.

The amide (71) (11mg) was dissolved in dry dichloromethane (5ml) at -76° and boron trichloride (2 drops) added. The solution was stirred, under nitrogen, for

7 minutes and then quenched with water. The mixture was extracted with dichloromethane and the extracts dried and evaporated. T.l.c. examination of the residue showed the presence of several compounds none of which was isolated.

Attempted acid hydrolysis of ketal amide (71).

a). Hydrogen bromide in acetic acid.

The amide (71) (14mg) was dissolved in glacial acetic acid (10ml) and hydrogen bromide in acetic acid (3 drops, 48%) added to the stirred solution under nitrogen. After 10 minutes the reaction was quenched with water, extracted with chloroform, the extracts dried and evaporated. T.l.c. indicated that the residue was composed of two orange components. The total reaction mixture had ν_{max} 3420, 3380, 3350, 3250, 1740, 1660, 1650 cm^{-1}.

b). Hydrogen chloride in acetic acid.

The amide (71) (7mg) was dissolved in glacial acetic acid (10ml) and a saturated solution ofhydrogen chloride in acetic acid (2 drops) was added. After 24 hours the

reaction was worked up as before and t.l.c. showed only unchanged starting material.

c). Formic acid in THF.

The amide (71) (5mg) was dissolved in dry THF (5ml) and formic acid (3 drops) added. After 24 hours t.l.c. indicated that no reaction had occurred. The solution was then refluxed for a further 24 hours but again no reaction was observed.

Reaction of amide (71) with triethyloxonium fluoroborate.

The amide (71) (108mg) was dissolved in dry dichloromethane (40ml) and triethyloxonium fluoroborate (340mg. 9 equivalents) added to the stirred solution under nitrogen. After 19 hours the reaction was quenched with aqueous ammonium chloride, extracted with dichloromethane and the extracts dried and evaporated. The residue was chromatographed on a 60x20cm silica plate to give the imino ether diketone (74) (45mg., 46%), m.p. 214-216°. ν_{max}^{nujol} 3350, 1690, 1630, 1650 cm^{-1}. $\lambda_{max}^{CHCl_3}$ 361 n.m. (ε 15,400). The n.m.r. spectrum, in D_6DMSO, showed

signals at 8.81 τ (3H,t), 6.60 τ (3H,s), 6.15 τ (3H,s), 5.90 τ (2H,q), 4.83 τ (1H,d J=6.6cps) and 1.90-3.14 τ (9H,m). The mass spectrum showed the molecular ion at m/e 495.

A second fraction from the plate gave the diketone (75) (31mg., 31%) m.p. 239-243°, ν_{max}^{nujol} 3450, 3220, 1680, 1660 cm^{-1}, $\lambda_{max}^{CHCl_3}$ 360 n.m. (ε 16,100). The n.m.r. spectrum consisted of signals at 6.58 τ (3H,s), 6.15 τ (3H,s), 4.84 τ (1H,d J=6.5cps) and 1.9-3.14 τ (9H,m). The mass spectrum showed the molecular ion at m/e 467 with peaks at m/e 465 (M^+-2H), m/e 448 (465-NH_3), m/e 433 (465-CH_3OH).

Reaction of the model amide (76) with triethyloxonium fluoroborate.

The model amide (76) (163mg) was dissolved in dry dichloromethane (25ml) and triethyloxonium fluoroborate (644mg) added to the stirred solution, under nitrogen. After 24 hours the reaction was quenched with water, the dichloromethane layer separated, dried and evaporated. The residue was crystallised from benzene to give the

imino ether salt (77) (123mg) m.p. 143-145°. ν_{max}^{nujol} 3380, 3220, 1685 cm^{-1}. The n.m.r. spectrum had signals at 8.52 τ (3H,t), 7.63 τ (3H,s), 6.16 τ (6H,s), 5.48 τ (2H,q), 3.58 τ (2H,s), 0.70 τ (2H, broad). (Found C 46.48%, H 6.07%, N 4.22%; $C_{12}H_{18}O_3NBF_4$ requires C 46.35%, H 5.79%, N 4.50%).

The reaction was repeated under the same conditions and worked up in the presence of aqueous sodium bicarbonate. This yielded the imino ether (78) ν_{max} 3350, 1645 cm^{-1}. The n.m.r. spectrum exhibited signals at 8.65 τ (3H,t), 7.70 τ (3H,s), 6.26 τ (6H,s), 5.70 τ (2H,q), 3.68 τ (2H,s), 3.55 τ (1H,bs).

N-ethyl-2,6-dimethoxy-4-methyl-benzamide (79).

2,6-dimethoxy-4-methyl-benzoic acid (80) (121mg) was suspended in dry benzene (5ml), dimethylformamide (0.1ml) and thionyl chloride (0.15ml) added and the solution refluxed for 2 hours. After cooling to room temperature ethylamine (2ml) was added and the solution stirred for 10 minutes. The solution was then poured into water, the benzene layer separated, dried and evaporated. The residue was recrystallised from benzene/

petrol to yield the amide (79) (108mg., 79%) m.p. 160-162°. ν_{max}^{nujol} 3360, 3090, 1660 cm^{-1}, the n.m.r. spectrum showed signals at 8.80 τ (3H,t), 7.68 τ (3H,s), 6.55 τ (2H,q), 6.23 τ (6H,s), 4.35 τ (1H, broad), 3.66 τ (2H,s). (Found C 64.80%, H 7.62%, N 6.46%; $C_{12}H_{17}O_3N$ requires C 64.55%, H 7.67%, N 6.27%).

Deketalisation of methyl- cis 6a,12a-9,11-dimethoxy-12-ethylenedioxy-6-oxo-1-phenyl-6a,7,12,12a-tetrahydro-naphthaceno (1,12-bc)-furan-10-carboxylate (73) with triethyloxonium fluoroborate.

The ketal ester (73) (34mg) was dissolved in dry dichloromethane (25ml) and triethyloxonium fluoroborate (103mg) added. The solution was stirrred, under nitrogen, for 24 hours and then poured into aqueous ammonium chloride. The dichloromethane layer was separated, washed with water, dried and evaporated. The diketone (61) was isolated by thin layer chromatography in 16% yield.

Reaction of the sodium salt of ethyl urethane with 2,6-dimethoxy-4-methyl benzoyl chloride (84).

Sodium hydride (62mg of a 50% dispersion) was washed with dry benzene and then suspended in dry dioxan (10ml). Ethyl urethane (111mg) was added and the mixture refluxed under nitrogen for 5 1/2 hours. The acid chloride (84) (386mg) was dissolved in dry benzene (5ml) and added to the urethane salt. The reaction mixture was left at room temperature overnight and then quenched with water. The mixture was extracted with chloroform and the extracts washed with sodium bicarbonate solution. The organic phase was dried, evaporated and chromatographed on a 60x20cm silica plate. Ethyl orsellinate (40mg) was isolated, ν_{max} 1725 cm^{-1}. The base extracts were acidified, extracted, dried and evaporated to give the acid (80) (123mg).

2,6-dimethoxy-4-methyl-benzonitrile (88).

The model amide (86) (92mg) was dissolved in pyridine (1ml) and ethyl chloroformate (1ml) added. A white precipitate separated out and was dissolved by adding a

further portion (2ml) of pyridine. The reaction mixture was left overnight and then quenched with water. The mixture was extracted with chloroform, the extracts washed with dilute hydrochloric acid (3x20ml) and with water(2x20ml). After drying and evaporation the residue was chromatographed on a large silica plate to give the nitrile (88) (49mg), m.p. 139-140°, ν_{max}^{nujol} 2260 cm^{-1}. The n.m.r. spectrum consisted of signals at 7.60τ (3H,s), 6.10 τ (6H,s) and 3.63 τ (2H,s). (Found C 67.52%, H 6.35%, N 7.81%; $C_{10}H_{11}O_2N$ requires C 67.78%, H 6.26%, N 7.90%).

N-ethoxycarbonyl-2,6-dimethoxy-4-methyl-benzamide (87).

The model amide (96) (87mg) was dissolved in dry benzene (10ml) and sodium hydride (23mg of a 50% dispersion, washed free of oil with benzene) added. The mixture was refluxed, under nitrogen, for 1 hour and then ethyl chloroformate (0.5ml) added. After 1.5 hours the solution was cooled and poured into water. The benzene layer was separated, dried and evaporated. The residue was purified by thin layer chromatography to give the nitrile (88) (12mg, 15%) and the protected amide (87) (52mg, 44%). m.p. 181-183°, ν_{max}^{nujol} 1760, 1680 cm^{-1}. The n.m.r.

spectrum showed signals at 8.90 τ (3H,t), 7.70 τ (3H,s), 6.28 τ (6H,s), 5.88 τ (2H,q) and 3.69 τ (2H,s). (Found C 58.48%, H 6.64%, N 5.07%; $C_{13}H_{17}NO_5$ requires C 58.42%, H 6.41%, N 5.24%).

N-βββtrichloroethoxycarbonyl-2,6-dimethoxy-4-methyl-benzamide (89).

The model amide (86) (140mg) was dissolved in dry benzene (20ml) and sodium hydride (34mg of a 50% dispersion, washed with benzene) added. The mixture was refluxed under nitrogen for 1 hour and then βββtrichloroethoxy-carbonyl chloride (1ml) added. After 15 minutes the reaction mixture was poured into water and the benzene layer separated. This was washed with water (2x10ml), sodium bicarbonate (2x10ml) and again with water (10ml). After drying and evaporation a non-crystalline residue was obtained. This was chromatographed on a 60x20cm silica plate to give the nitrile (88) (69mg) and the amide (89) (85mg 34%). Crystallisation from benzene/petrol gave an analytical sample m.p. 101-103°, ν_{max}^{nujol} 3250, 1730, 1685 cm^{-1}. The n.m.r. spectrum consisted of signals at 7.65τ (3H,s), 6.20τ (6H,s), 5.25 τ (2H,s), 3.60 τ (2H,s) and 1.80 τ (1H,bs). (Found C 42.09%,

H 3.82%, N 3.74%, Cl 28.74%; $C_{13}H_{14}NCl_3O_5$ requires C 42.10%, H 3.78%, N 3.78%, Cl 28.74%).

Reaction of trityl fluoroborate with 2,6-dimethoxy-4-methyl benzamide (86).

The model amide (52mg) was dissolved in dry dichloromethane (10ml) and trityl fluoroborate[26] (91mg) added. After stirring for 24 hours the reaction mixture was poured into sodium bicarbonate solution, washed with water and the organic phase dried and evaporated. Purification by thin layer chromatography gave the product (41mg) which, on crystallisation from benzene/petrol had m.p. 116-120° then resolidifies and remelts at 197°. ν_{max}^{nujol} 3470, 1690, 1610 cm^{-1}. The n.m.r. spectrum had signals at 7.68 τ (3H,s), 6.20 τ (6H,s), 3.64 τ (2H,s), 2.70 τ (15H,m) and 3.17 τ (1H,s). (Found C 79.70%, H 6.27%, N 3.34%; $C_{29}H_{27}O_3N$ requires C 79.61%, H 6.22%, N 3.20%).

Deketalisation of the model ketal (2) with trityl fluoroborate.

The ketal (2) (97mg) was dissolved in dry dichloro-

methane (20ml) and trityl fluoroborate (85mg) added. The solution was stirred under nitrogen for 5 hours, when t.l.c. showed little or no reaction. A further portion (85mg) of trityl fluoroborate was added and the solution stirred for 84 hours when it was poured into sodium bicarbonate solution. The organic phase was washed with water, dried and evaporated. The crystalline residue was triturated with ether to give the required diketone (12) (56mg 65%).

Reaction of dimethoxy ketal (71) with trityl fluoroborate.

The main series ketal (71) (46mg) was dissolved in dry dichloromethane (20ml) and nitrogen bubbled through the solution for 1/2 hour. Trityl fluoroborate (65mg) was added and the solution stirred under nitrogen for 21 hours. The reaction mixture was then poured into water, the organic phase separated, washed, dried and evaporated. Chromatography on a silica plate gave the diketone (75) (7mg, 16%).

Deketalisation of main series ketal (71) with triethoxy-carbonium fluoroborate.

The main series ketal (71) (106mg) was dissolved in

dry dichloromethane (60ml) and triethoxycarbonium fluoroborate[27] (660mg) added. The solution was refluxed, under nitrogen, for 3 hours and then poured into sodium bicarbonate solution. The organic phase was separated, washed with water, dried and evaporated. On trituration with ether the diketone (75) (52mg) was obtained. The ether washings, on chromatography, gave a further quantity (11mg) of the diketone.

Deketalisation of (71) in presence of various additives.

The deketalisations were carried out with triethoxy-carbonium fluoroborate as described above in the presence of acetone, cyclo hexa-1,4 dione and 1,4-diketo-1,4,4a, 5,8,8a hexahydronaphthalene. From t.l.c. examination of the reactions it was found that the first two additives gave no improvement whereas the third one led to a slight improvement.

Demethylation of main series diketone (75).

The total product from the deketalisation of the main series ketal (71) (127mg) was dissolved in dry

dichloromethane (30ml) at -76°. 1,4 diketo hexahydronaphthalene (147mg) was added and the solution stirred under nitrogen while boron trichloride solution (10ml of a 10% solution in dichloromethane) was added. After 2.5 hours the reaction mixture was poured into dilute sodium bicarbonate solution. The organic phase was separated, washed with water and dried. The residue was chromatographed on silica plates to give the monodemethylated material (93) (16mg) and recovered diketone (19mg). The demethylated material (93) had ν_{max}^{nujol} 3480, 3230, 1685, 1605 cm^{-1}.

When the reaction was carried to completion the didemethylated compound (94) was isolated ν_{max}^{nujol} 3450, 3380, 1680, 1655, 1605 cm^{-1}. The mass spectrum showed a molecular ion at m/e 439 with other peaks at 422 (M^+-NH_3) and 247.

Reaction of (93) with lithium tri tert-butoxy aluminium hydride.

The monodemethylated compound (93) was dissolved in dry T.H.F. (2ml) and stirred at 0°, under nitrogen, while lithium tri tert-butoxy aluminium hydride

(1.2 equivalents) was added. T.l.c. indicated that no reaction had occurred and the solution was warmed up to room temperature and a further amount (2 equivalents) of the reducing agent added. After 5 hours the solution was poured into water and extracted with dichloromethane. The extracts were dried and evaporated to give a gummy residue. T.l.c. showed that this was composed of several compounds, among them the starting material.

Reduction of (93) with sodium borohydride.

The monodemethylated compound (93) (70mg) was dissolved in dry T.H.F. (20ml) and anhydrous methanol (10ml) added. This solution was stirred under nitrogen at room temperature while a solution (10ml) of sodium borohydride (containing sodium borohydride (100mg) in methanol (25ml)) was added. After 4 hours the reaction was worked up as described above. Purification on 5 silica plates gave the alcohol (96) (10mg). ν_{max}^{nujol} 3500, 3400, 1610 cm^{-1}. The mass spectrum showed the molecular ion at m/e 439 with peaks at m/e 422 (M^+-NH_3), m/e 404 ($M^+-NH_3-H_2O$).

6. Deketalisation of pregnenolone ethylene ketal (97).

Pregnenolone ethylene ketal[29] (97) (107mg.) was dissolved in dry dichloromethane (25ml.) and triethoxy-carbonium fluoroborate (89mg) added. The solution was stirred at room temperature for 8 minutes and then poured into aqueous sodium bicarbonate. The organic phase was separated, washed with water, dried and evaporated. T.lc. showed that the residue was composed mainly (80%) of pregnenolone.

Deketalisation of 11α-hydroxy progesterone ethylene ketal (98).

11α-hydroxy progesterone ethylene ketal[30] (98) (94mg) was dissolved in dry dichloromethane (20ml) and triethoxycarbonium fluoroborate (359mg) added. The solution was stirred for 20 minutes and then poured into aqueous sodium bicarbonate. The dichloromethane layer was separated, washed, dried and evaporated. The residue was chromatographed on a 20x20cm thick plate to give 11α-hydroxy progesterone (52mg., 70%). On crystallisation from ether/hexane crystals m.p. 165-167 (Lit.[34] 166-167) were obtained.

Reaction of the tetrahydropyranyl ether of cholesterol (99) with triethyloxonium fluoroborate.

The tetrahydropyranyl ether of cholesterol[31] (99) (129mg.) was dissolved in dry dichloromethane (10ml) and triethyloxonium fluoroborate (60mg) in dichloromethane (10ml) added. After 1/2 hour the solution was worked up as before. The residue was chromatographed on an alumina column eluting with benzene and then with ether/benzene (1:1) to give cholesterol (67mg., 64%). On recrystallisation from ethanol the m.p. was 148-149° (Lit.[35] 149-150°).

Reaction of Δ-9 hecogenin acetate (100) with triethyloxonium fluoroborate.

Δ-9 hecogenin acetate (100) (51mg) was dissolved in dry dichloromethane (10ml) and triethyloxonium fluoroborate (184mg) added. After stirring for 5 days t.l.c. showed only unchanged starting material.

Reaction of Δ-9 hecogenin acetate (100) with trityl fluoroborate.

Δ-9 hecogenin acetate (100) (54mg) was dissolved in dry dichloromethane (5ml) and trityl fluoroborate (46mg) added. After stirring for 2 days t.l.c. showed no reaction and so a further amount (107mg) of trityl fluoroborate was added. After a further 2 days t.l.c. indicated that a complex mixture of products was being produced.

Preparation of mono-trityl ethylene glycol (102) and di-trityl ethylene glycol (103).

Ethylene glycol (116mg) and trityl chloride (580mg) were dissolved in dry pyridine (3ml) and stirred overnight. The reaction mixture was then poured into water and extracted with ether. The extracts were dried, evaporated and chromatographed on an alumina column to give the mono-trityl ether (102) (327mg) and the ditrityl ether (103) (132mg).

Reaction of cyclohexanone ethylene ketal with trityl fluoroborate.

Cyclohexanone ethylene ketal[33] (149mg) was dissolved in dry dichloromethane (5ml) and trityl fluoroborate (361mg) added. After 3 hours the reaction mixture was poured into aqueous sodium bicarbonate. The organic phase was separated, washed, dried and evaporated. T.l.c. showed that the ethers (102) and (103) were not present. A quantitative i.r. spectrum showed that the yield of cyclohexanone was 46%.

Stability of trityl ethers (102) and (103).

The mono-trityl ether (102) (13mg) was dissolved in dry dichloromethane (2ml) and trityl fluoroborate (26mg) added. After stirring overnight the reaction mixture was worked up as above and t.l.c. showed that none of the mono trityl ether remained. The major product was trityl alcohol.

The reaction was repeated with the ditrityl ether (103) with same result.

Reaction of cyclohexanone ethylene ketal with triethyl-oxonium fluoroborate.

Triethyloxonium fluoroborate (1.588gm) was dissolved in dry dichloromethane (10ml) and cyclohexanone ethylene ketal (372mg) added. After 2 hours the reaction was worked up as above. The aqueous phase was continually extracted with ether overnight. G.l.c. examination of the organic phase using a carbowax column showed cyclohexanone (38%), cyclohexanone ethylene ketal (62%) and a trace of mono-ethyl ethylene glycol. The ether extracts showed only the monoethyl ethylene glycol.

Reaction of cyclohexanone ethylene ketal with triethyl-oxonium fluoroborate and then reduction with lithium aluminium hydride.

Cyclohexanone ethylene ketal (381mg) and triethyl-oxonium fluoroborate (1.47gm) were stirred together in dry dichloromethane (20ml) for 24 hours. Lithium aluminium hydride (325mg) was then added, followed by dry ether (10ml). After 1/2 hour the reaction was

quenched with aqueous ammonium chloride and worked up in the usual manner. T.l.c. indicated that a complex mixture of compounds had been formed. The n.m.r. and i.r. spectra showed the presence of cyclohexanol.

Reaction of cyclohexanone ethylene ketal with triethyloxonium fluoroborate and work-up with Brady's reagent.

Cyclohexanone ethylene ketal (443mg) and triethyloxonium fluoroborate (1.18gm) were stirred together in dry dichloromethane (10ml) for 4 hours. Methanol and dilute sulphuric acid were then added and the solution stirred for a further 10 minutes. Brady's reagent was then added and the dinitrophenylhydrazone formed filtered off. T.l.c showed this to be cyclohexanone dinitrophenylhydrazone, and t.l.c. examination of the filtrate showed that no acetaldehyde dinitrophenylhydrazone had been formed.

Reaction of cyclohexanone ethylene ketal with trityl fluoroborate in a n.m.r. tube.

Trityl fluoroborate (73mg) and cyclohexanone ethylene ketal (38mg) were mixed together in a n.m.r. tube with deutero chloroform. The n.m.r. spectrum was run at

intervals and after 5 days the spectrum consisted of signals due to cyclohexanone, cyclohexanone ethylene ketal and triphenyl methane.

Reaction of 2,2,6 trimethylcyclohexanone ethylene ketal with trityl fluoroborate.

Trimethyl cyclohexanone ethylene ketal (119mg) was dissolved in dry dichloromethane (20ml) and trityl fluoroborate (429mg) added. After 41/2 hours dry ammonia gas was bubbled through the solution until it was colourless. After filtration the solution was evaporated. T.l.c. showed the presence of both of the trityl ethers (102) and (103).

Reaction of 2,2,6 trimethyl cyclohexanone ethylene ketal with trityl fluoroborate in a n.m.r. tube.

Trityl fluoroborate (67mg) and trimethyl cyclohexanone ethylene ketal (39mg) were mixed together with deutero chloroform in a n.m.r. tube. The n.m.r. spectrum was run at intervals and after 3 days it showed that

46% of trimethyl cyclohexanone had been formed but no signals due to the trityl ethers (102) and (103) could be observed. The reaction was then worked up with ammonia gas as before and the n.m.r. spectrum of the residue run again. This showed the presence of the trityl ethers (102) and (103) as well as trimethyl cyclohexanone and trimethylcyclohexanone ethylene ketal.

Reaction of 2,2,6 trimethyl cyclohexanone ethylene ketal with triethyloxonium fluoroborate a) under anhydrous conditions and b) in the presence of water.

a) The ketal (685mg) and triethyl oxonium fluoroborate (1.37gm) were mixed in dry dichloromethane (10ml). After 4 1/2 hours the reaction was worked up in the usual way with aqueous sodium bicarbonate. The n.m.r. spectrum showed that less than 10% of the ketone was formed.

b) The reaction was repeated as above in the presence of water (1 drop). The n.m.r. showed the formation of the ketone (45%).

The above reactions were repeated with trityl fluoroborate as the cation, working up with ammonia, and again less than 10% of the ketone was formed under the anhydrous conditions. In the presence of water (1 drop) ketone (48%) was formed.

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