STUDIES IN THE SYNTHESIS OF TETRACYCLINES

a thesis presented by

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C O N T E N T S

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Jose M. Cardoso,
Whiffen Laboratory,
Imperial College.
September 1977.

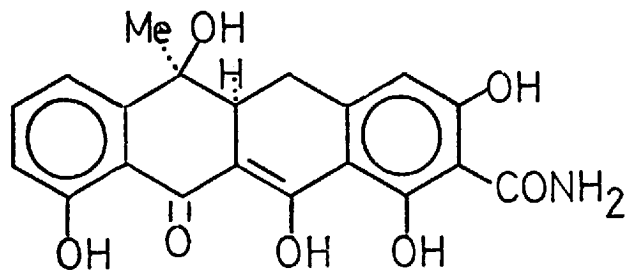
ABSTRACT

The first chapter is divided into three sections:

1.1 An introduction to the properties of the tetracycline antibiotics.

1.2 A brief summary of recent achievements in the field of of tetracycline synthesis.

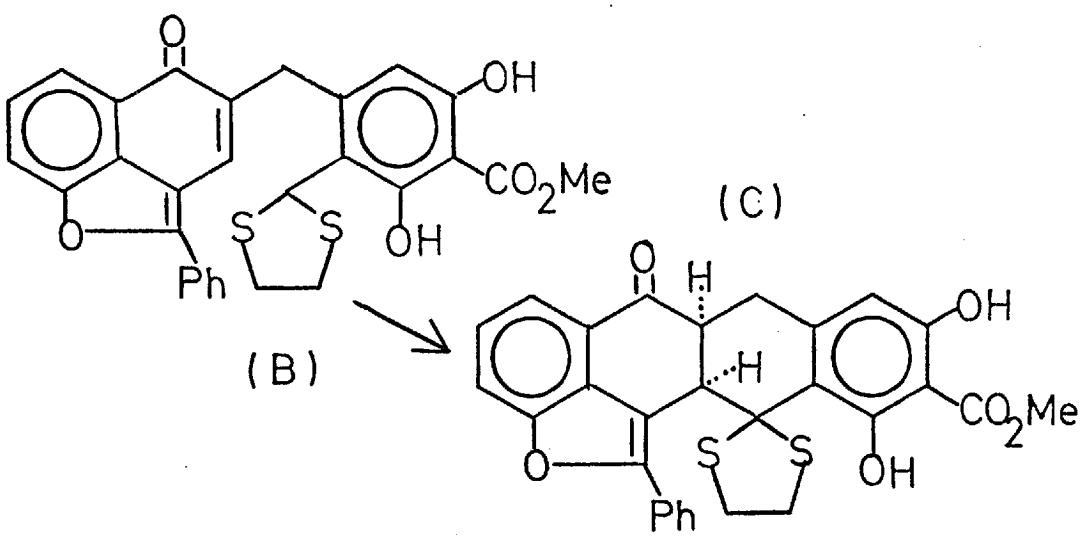
1.3 An outline of the Imperial College approach to the synthesis of tetracyclines, and a brief description of the projected route to the diphenol (A).



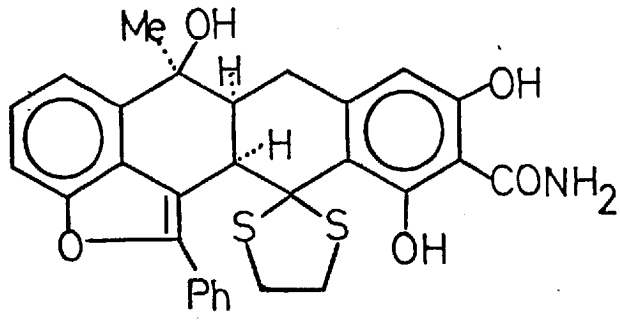
(A)

2.1 The discussion of results begins with a description of modifications of the established methods for the preparation of rings ACD tricyclic intermediates, resulting in an improvement of the overall yield.

2.2 Section 2.2 depicts the preparation of various tricyclic acetals and subsequent photocyclisation studies. The 1,3-dithiolane (B) was successfully converted in the tetracyclic ester (C), by base-catalysed photolysis.



2.3 Subsequent transformations of the ester (C) led to the synthesis of the carbinol (D). Finally, studies on the hydrolysis of the 1,3-dithiolane group are also described in this section.

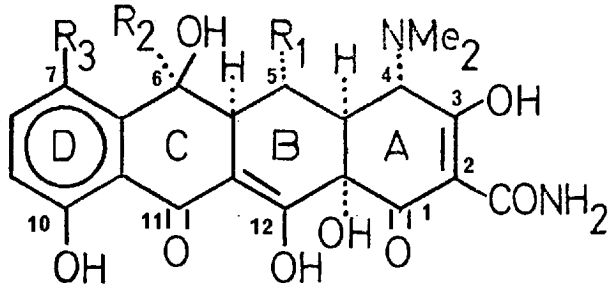


(D)

INTRODUCTION

1.1 - The tetracycline antibiotics.

The role of tetracyclines (1) in human and veterinary medicine, and animal nutrition is well known.[1] They are readily obtained by fermentation of diverse strains of streptomyces. The elucidation of their structure began with the work of Woodward[2] on terramycin. Confirmation of this structure and that of aureomycin was obtained later by X-ray and N.M.R. studies.[3]

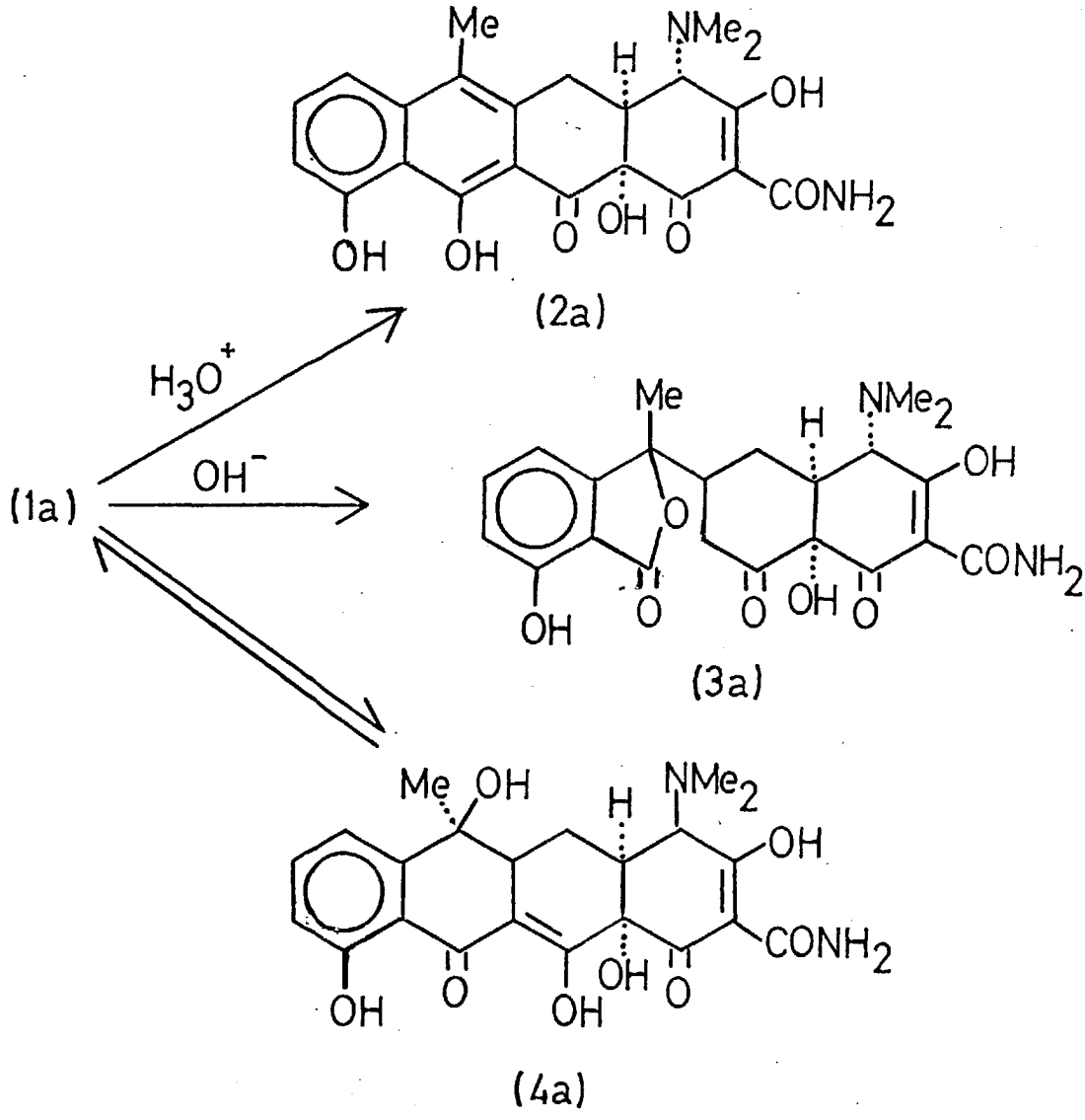


(1)

The main natural tetracycline antibiotics are: tetracycline (1a; R_1=R_3=H, R_2=Me), oxytetracycline (terramycin) (1b; R_1=OH, R_2=Me, R_3=H), chlorotetracycline (aureomycin) (1c; R_1=H, R_2=Me, R_3=Cl), 6-demethyltetracycline (1d; R_1=R_2=R_3= =H), and 6-demethylchlorotetracycline (1d; R_1=R_2=H, R_3=Cl). Being a linear four ring system their nomenclature is analogous to naphthacene, and is shown above.

These compounds have characteristic U.V. spectra with two distinct chromophoric regions.[4] The BCD chromophore absorbs at 225, 285, 320, and 360 nm, and the ring A chromophore absorbs at 262 nm. A band at 275 nm is the result of composite absorptions.

They are slightly soluble in the physiological pH region, and show amphoteric behaviour in solution.[5]



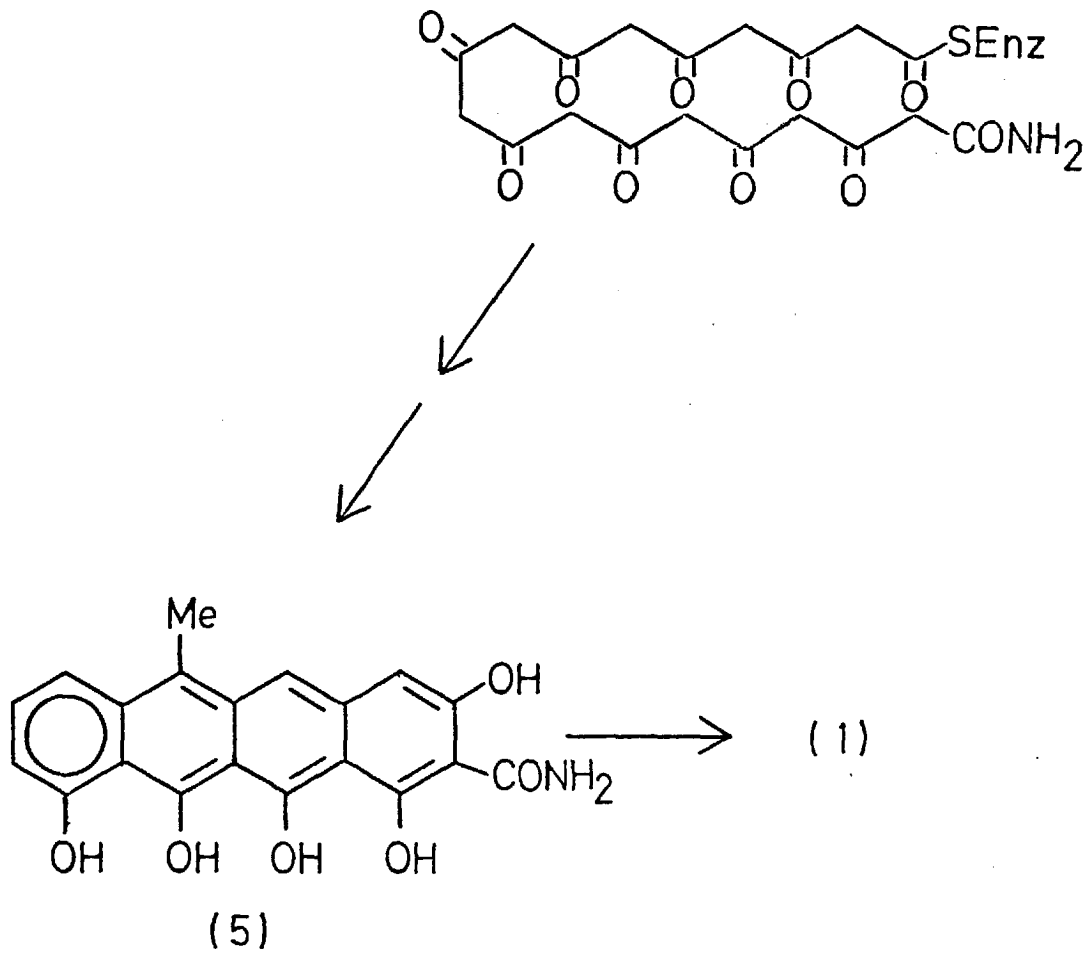
The chemistry of the tetracyclines has been extensively reviewed.[3],[6] Examples of the labile nature of these compounds are illustrated above. For instance, they are easily dehydrated by mineral or strong organic acids to form anhydrotetracyclines (2). Weak bases readily isomerise tetracyclines to isotetracyclines (3). The reversible epimerisation of 4-dimethylamino group can be accomplished at between pH 2 and 6.

The hypothesis, by Robinson and Birch, that the tetracyclines are derived from a chain of acetate units was confirmed by McCormick.[7] The 2-amide group was believed to be incorporated in the polyketide chain, before cyclisation to the tetracyclcic naphthacene (5) occured.

$H_2NCOCH_2COSCoA +$

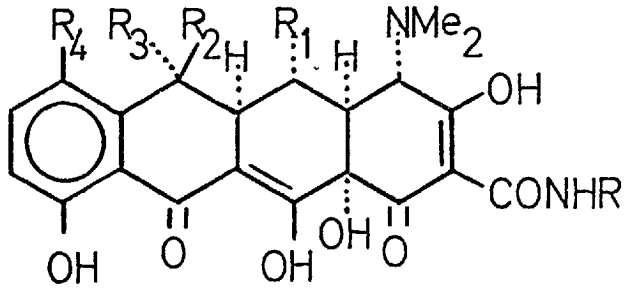
8 $HO_2CCH_2COSCoA +$

$CH_3COSCoA$



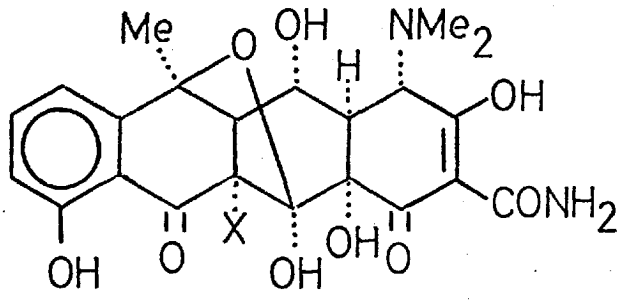
1.2 - Achievements in the field of Tetracycline Synthesis

Owing to the poor solubility and stability of natural tetracyclines at the physiological pH, considerable effort has been spent modifying these compounds. Several synthetic derivatives showed marked advantages over the natural antibiotics. For example, substitution of the 2-amido group by a Mannich type reaction, led to pyrrolidinomethyltetracycline[8] (6a; R=CH_2-pyrrolidino, R_1=R_4=H, R_2=OH, R_3=Me), which has high solubility in water. Methacycline[9](6b; R=R_4=H, R_1=OH, R_2,R_3=CH_2),



(6)

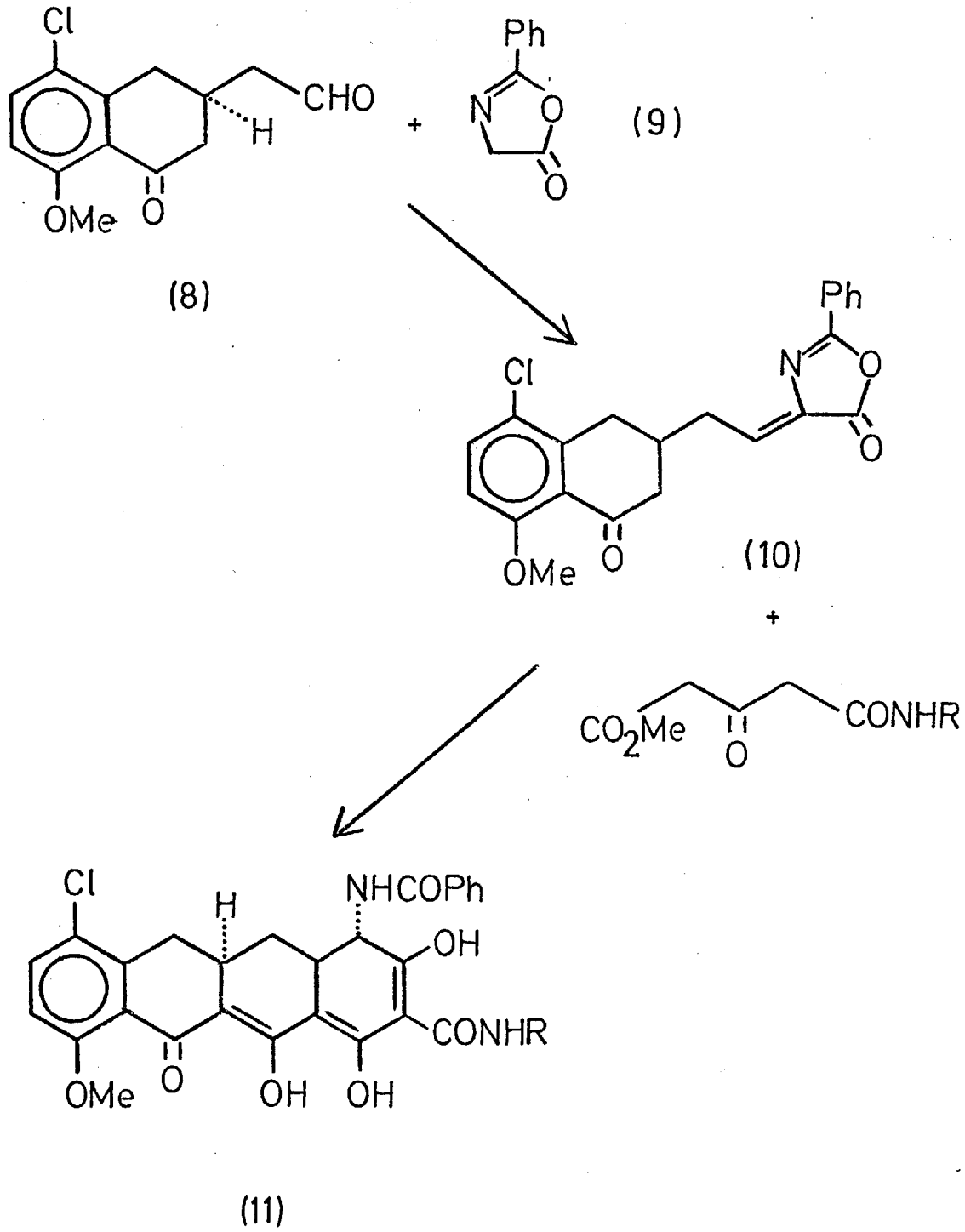
and doxycline[10](6c; R=R_2=R_4=H, R_1=OH, R_3=CH_3), both obtained from 11a-chloro-5-hydroxytetracycline (7), also show marked improvements in their stability and capacity of absorption by living organisms. The most important of the semi-synthetic tetracyclines is minocycline, (6d; R=R_1=R_2=R_3=H, R_4=NMe_2) as it is effective against certain staphyloccocal strains which are already resistant to other tetracyclines.



(7)

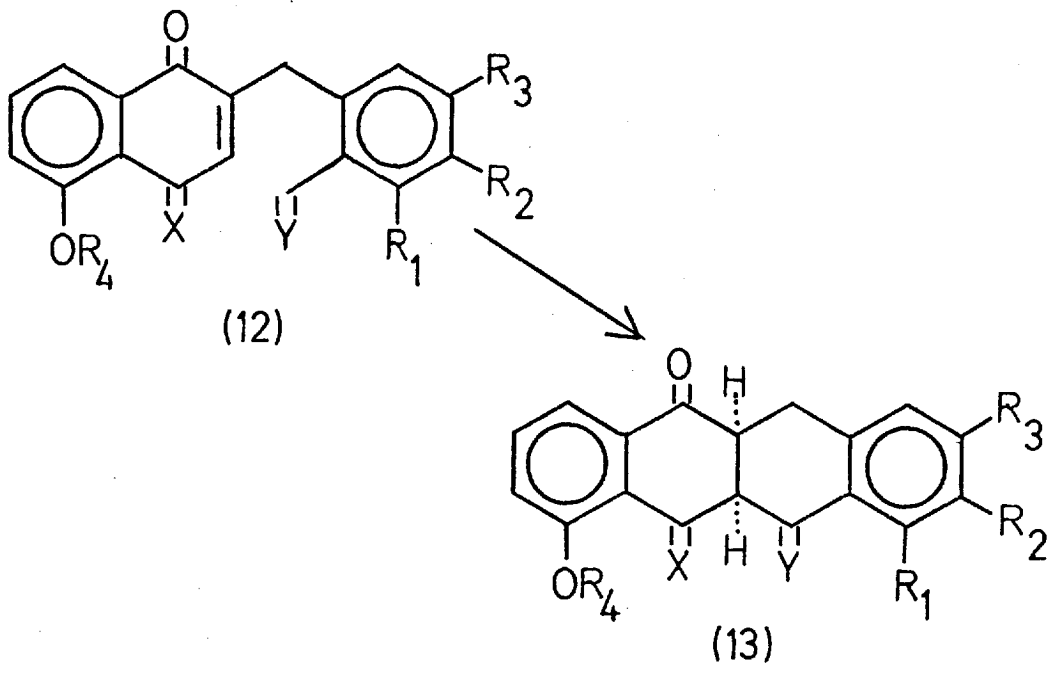
Several tetracyclic compounds were prepared by Muxfeldt[11] and others,[12] but the first total synthesis of a biologically active tetracycline, (+,-)-6-demethyl-6-deoxytetracycline (6e; $R=R_1=R_2=R_3=R_4=H$) was achieved by Woodward[13] in 1962, with an overall yield of around 10^{-3}%.

The most successful synthesis of these compounds was latter achieved by Muxfeldt.[14] The tetracyclic structure (11) could be obtained by an elegant cyclisation reaction, simultaneously forming rings A and B. By this method (+,-)-6--demethyl-6-deoxychlorotetracycline (6f; $R=R_1=R_2=R_3=H$, $R_4=Cl$) was prepared. Modifications in the CD precursor (8) led to the synthesis of terramycin[15] (1b) and latter of anhydroaureomycin,[16] which can be subsequently transformed to aureomycin (1c).[17]


Cl
CHO
H
OMe
O
(8)
+
Ph
N
O
O
(9)
Cl
Ph
N
O
O
OMe
O
(10)
+
CO2Me
O
CONHR
Cl
H
NHCOPh
OH
CONHR
OMe
O
OH
OH
(11)

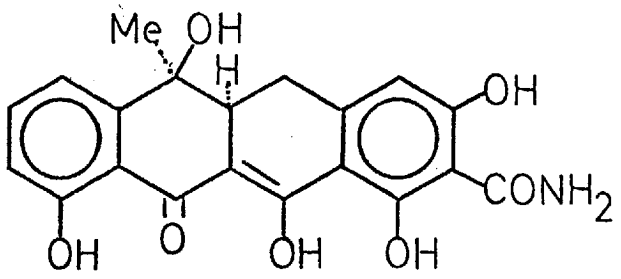
1.3 - Synopsis of the Imperial College approach to tetracycline synthesis.

The approach used at Imperial College to synthesize a tetracyclic structure employed an ACD tricyclic intermediate (12), in which rings A and D were aromatic.



The use of a carbonyl group (12; Y=CHO) or its masked equivalent would produce, by cyclisation, the tetracyclic structure (13). Further transformations on the 6-carbonyl group, 12-hydroxylation with reduction of ring A, could lead to total synthesis.

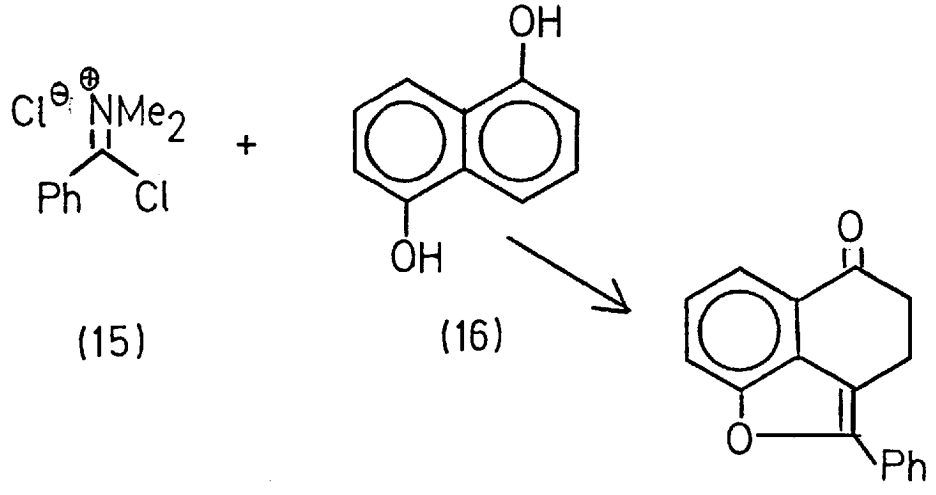
The chemistry described in this thesis compiles the attempts at the preparation of the diphenol (14).



(14)

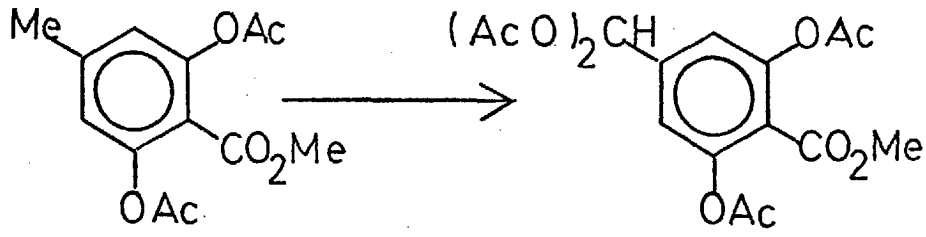
Since this compound is readily obtained by degradation of tetracycline,[18] it could act as a possible relay point, and as a substrate for 12a-hydroxylation studies.

In order to prepare the ACD tricyclic intermediate, the coupling of two structural units can be considered. The CD unit employed in all this work was the dihydronaphthofuran (17) produced by the attack of the Vilsmeir salt (15) on 1,5-dihydroxynaphthalene (16), and subsequent hydrogenation.[19]



(15) (16) (17)

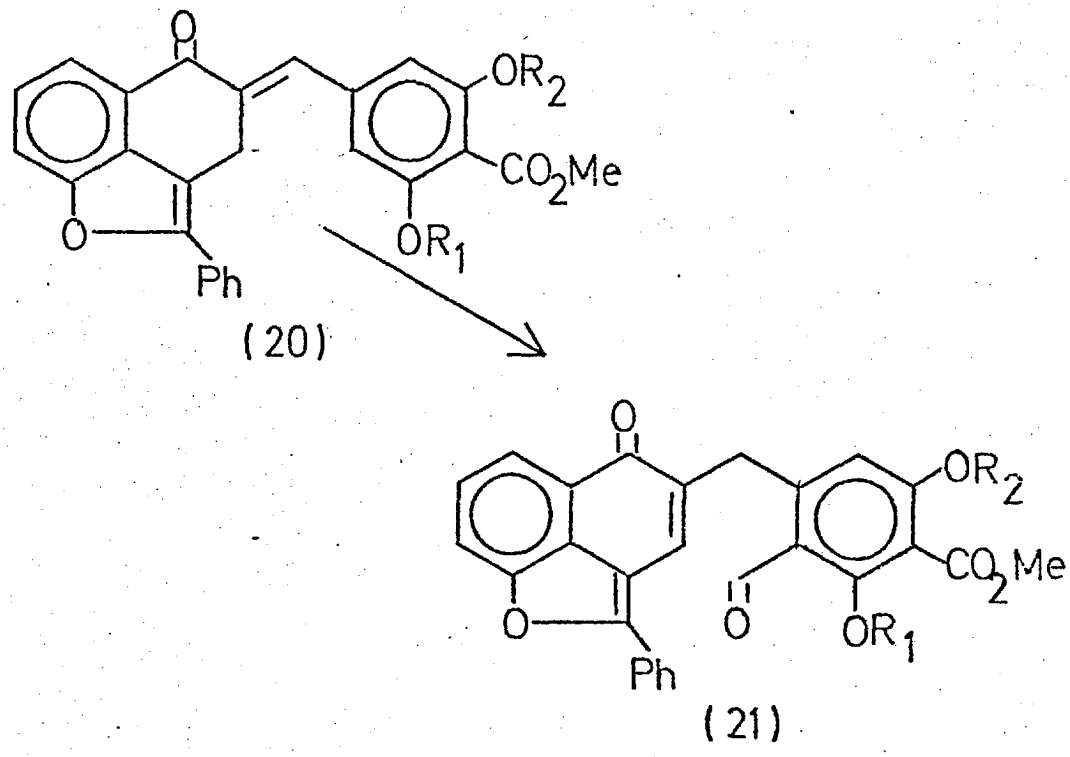
The chemistry of this compound was studied,[20] and found to be acceptable for further synthetic work.



(18) (19)

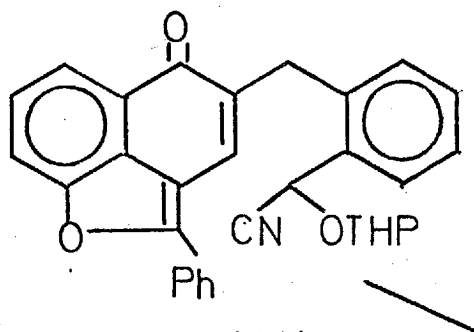
The aromatic ring A portion was provided by the formyldiacetate[21] (19), which can be obtained from methyl diacetyl-p-orsellinate (18) by oxidation with chromic oxide, under Thiele conditions.[21] A modification involving the use of Mn^{2+} ions was shown to improve the yield of this reaction.[19]

Condensation of the two units (17) and (19) by sulphuric acid / acetic acid[21] was now possible, and after acidic hydrolysis, the ACD tricyclic precursor (20) is obtained. Isomerisation of the exocyclic double bond, by the action of hot anhydrous triethylamine, followed by treatment with orthoformate / aluminium trichloride,[21] or α,α-dichloromethyl, methyl ether[22] in nitrobenzene, gave the required ACD tricyclic aldehyde (21; R_1=R_2=H).

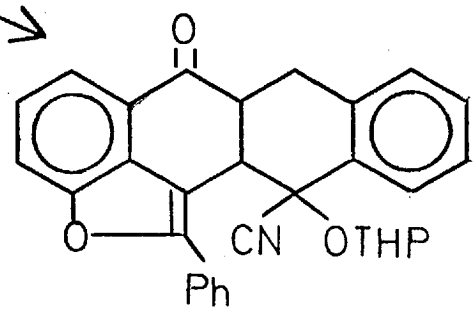


Various approaches have been used to achieve the cyclisation of the ACD unit to the tetracyclic species. It was thought that the benzylic anion of the masked aldehyde (21) could attack the enone, by a Michael type reaction, to form the required tetracyclic molecule. Reaction of a tetrahydropyranyl stabilised cyanohydrin (22), gave the derivative (23), on treatment with potassium t-butoxide.[23]

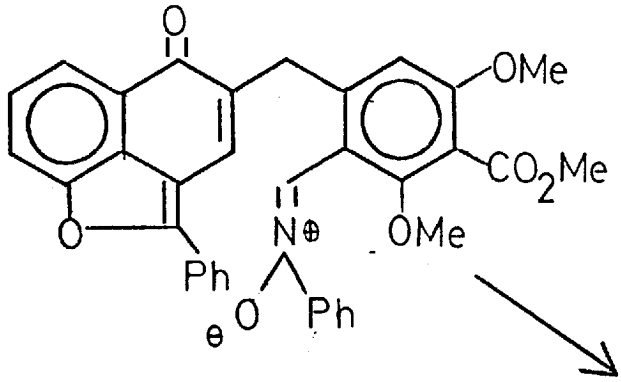
When similar conditions were used on the tetracyclic aldehyde (21; $R_1=R_2=H$)[23] poor results were obtained. No cyclisation was obtained when another protecting group, the trimethylsilyl function, was used.[19]


O
O
CN
OTHP
Ph

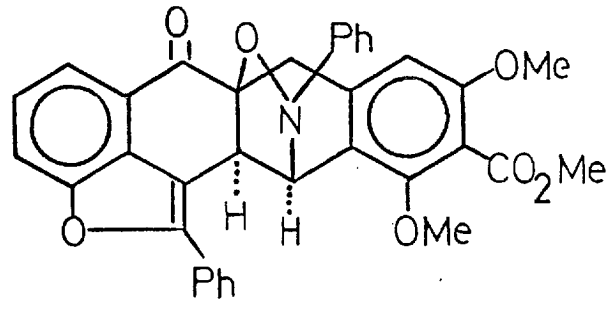
(22)


O
O
CN
OTHP
Ph

(23)

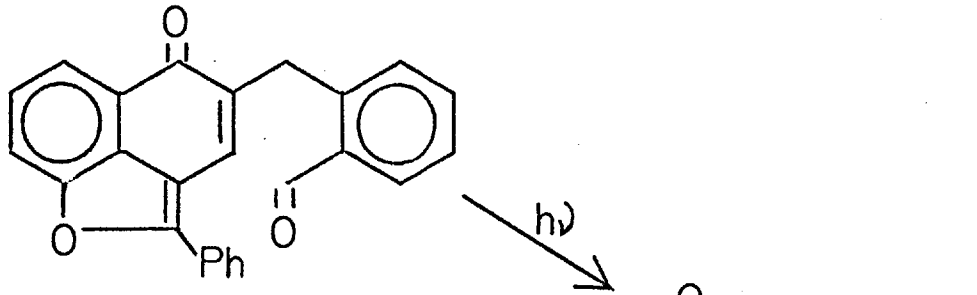

O
OMe
CO2Me
O
N⊕
OMe
Ph
e O
Ph

(24)


O
O
Ph
OMe
N
CO2Me
H
H
O
OMe
Ph

(25)

An alternative method, using the nitrone (24) in a 1,3 dipolar addition, was attempted.[24] Although the desired cyclised product (25) was obtained, it could not be converted to the required 12-keto compound.



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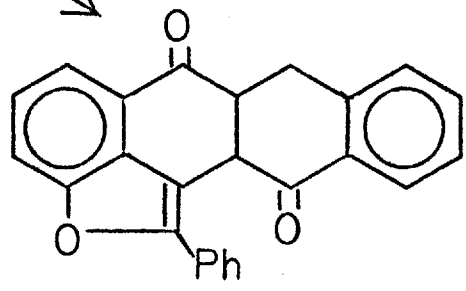
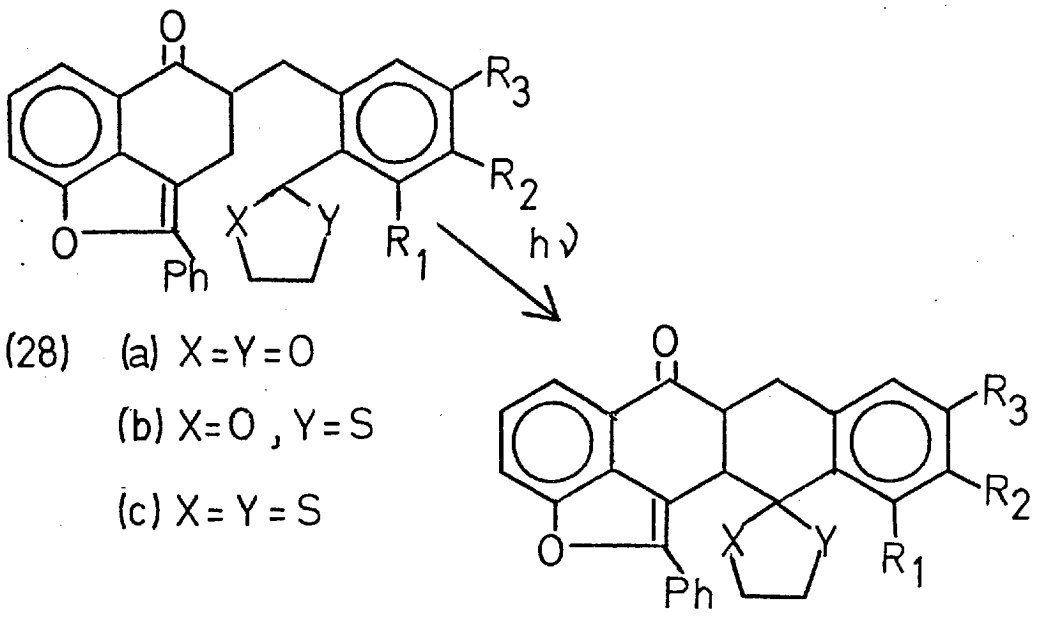


(27)

The ring closure was achieved by the use of visible light in conjunction with certain acids or bases as catalysts. For example the model aldehyde (26) could be photocyclised, albeit in low yield, to the tetracyclic diketone (27) with benzoic acid as catalyst.[25] However the yields of the cyclisation could be improved (up to 80%) by using the corresponding acetals or thioacetals (28; $R_1=R_2=R_3=H$).[25]



(28) (a) X=Y=O

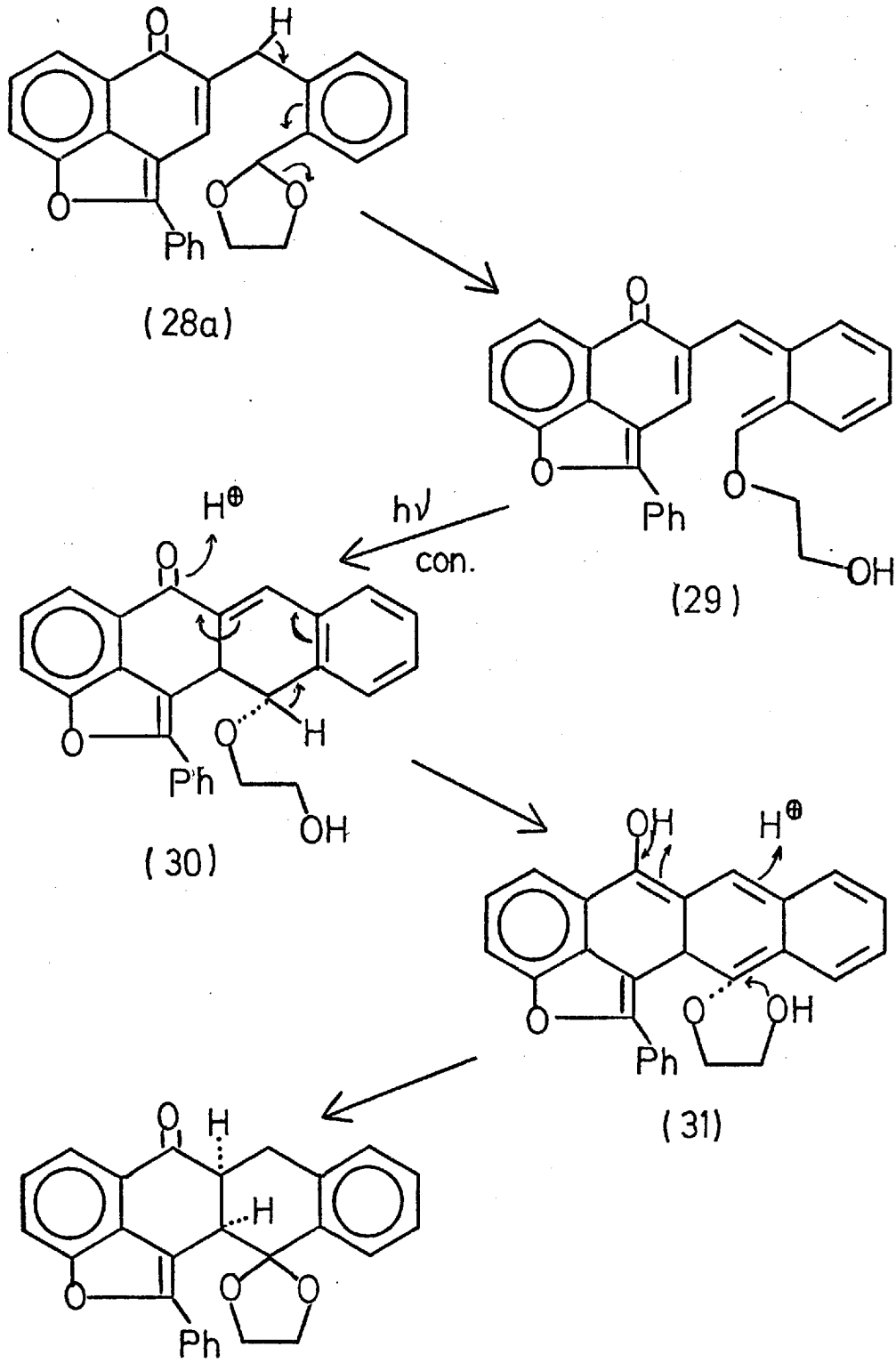
(b) X=O , Y=S

(c) X=Y=S

(29)

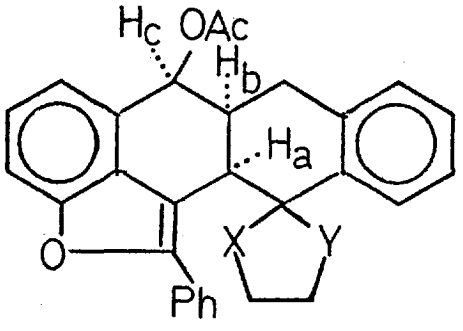
The preparation of these compounds by reacting the corresponding aldehydes with ethylene glycol in the presence of p-toluenesulphonic acid[26] or using Fieser's conditions,[27] was successful. In order to prepare compound (28a; R_1= =R_3=OH, R_2=CO_2Me) a new reagent, diethylene orthocarbonate was developed in these laboratories.[28]

The mechanism proposed for this cyclisation is outlined in scheme 1.[25] It was thought that the acetal (28a) undergoes an acid - catalysed isomerisation to the triene (29), which by a photochemical conrotatory process would give the tetracyclic structure (30). After an acid - catalysed enolisation followed by closure of the acetal and ketonisation, the tetracyclic acetal could be formed.


O
H
Ph
O
O
(28a)
O
O
Ph
O
OH
(29)
hν
con.
H⊕
O
H
O
Ph
OH
(30)
OH
H⊕
O
OH
Ph
(31)
O
H
H
O
O
Ph
(29a)

SCHEME 1

The above mechanism may account for the necessary formation of the cis - fused rings BC system. As the tetracyclines require a trans relationship between the 5a-proton and the 6-hydroxyl function, compounds (32; X=Y=O) and (32; X=Y=S) were prepared from the ketals (29) by reaction with sodium borohydride, followed by acetylation,[25] and the relative stereochemistry of protons Ha,Hb, and Hc were studied by N.M.R. coupling thecniques.



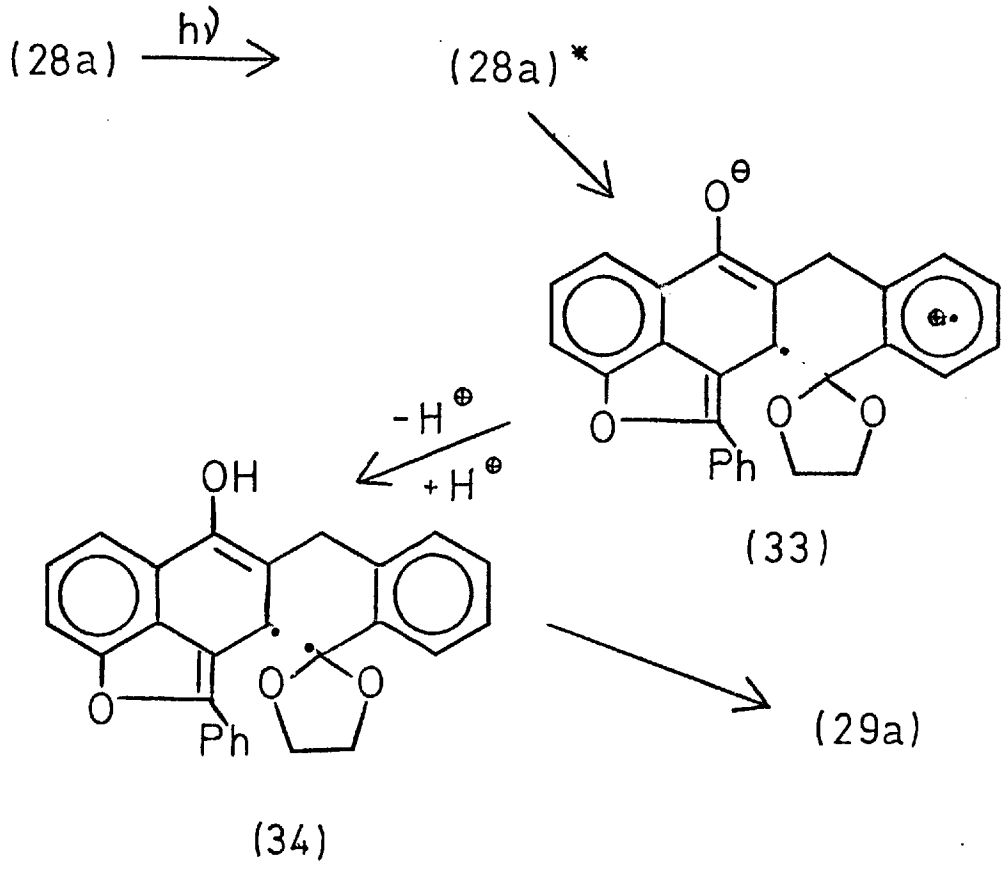
(32)

The spin-spin coupling constants of the doublets assigned to Ha and Hc were low (3.5 Hz - 4.5 Hz) therefore indicating the cis relationship. X-ray chrystallographic studies with a bromo derivative of (32) later confirmed this result.

The normal photocyclisation conditions were also applied to various ring A substituted acetals (28a; R_1=R_3=OAc, R_2=CO_2Me), (28a; R_1=R_3=CH_2OMe, R_2=CO_2Me), and (28a; R_1=R_3=OMe, R_2=CO_2Me). However, generally low yields of the tetracyclic species were obtained, and the unprotected diphenol

(28a; R_1=R_3=OH, R_2=CO_2Me) failed to react.[30] Consequently the photocyclisation was studied in the presence of non nucleophilic bases.[30] By using 1 molar equivalent of potassium t-butoxide the tetracyclic ketal (29a; R_1=R_2=R_3=H) was prepared in 85% yield. Similar conditions were successfully applied to compound (28a; R_1=R_3=OH, R_2= CO_2Me).[30]

The mechanism proposed for the acid catalysed photocyclisation could not be applied to the new conditions since it was difficult to see how the species (31) could be isomerised to the ketal (29a) in the presence of base. A new mechanism was proposed[30] involving the formation of a radical cation - radical anion (33) by electron transfer.

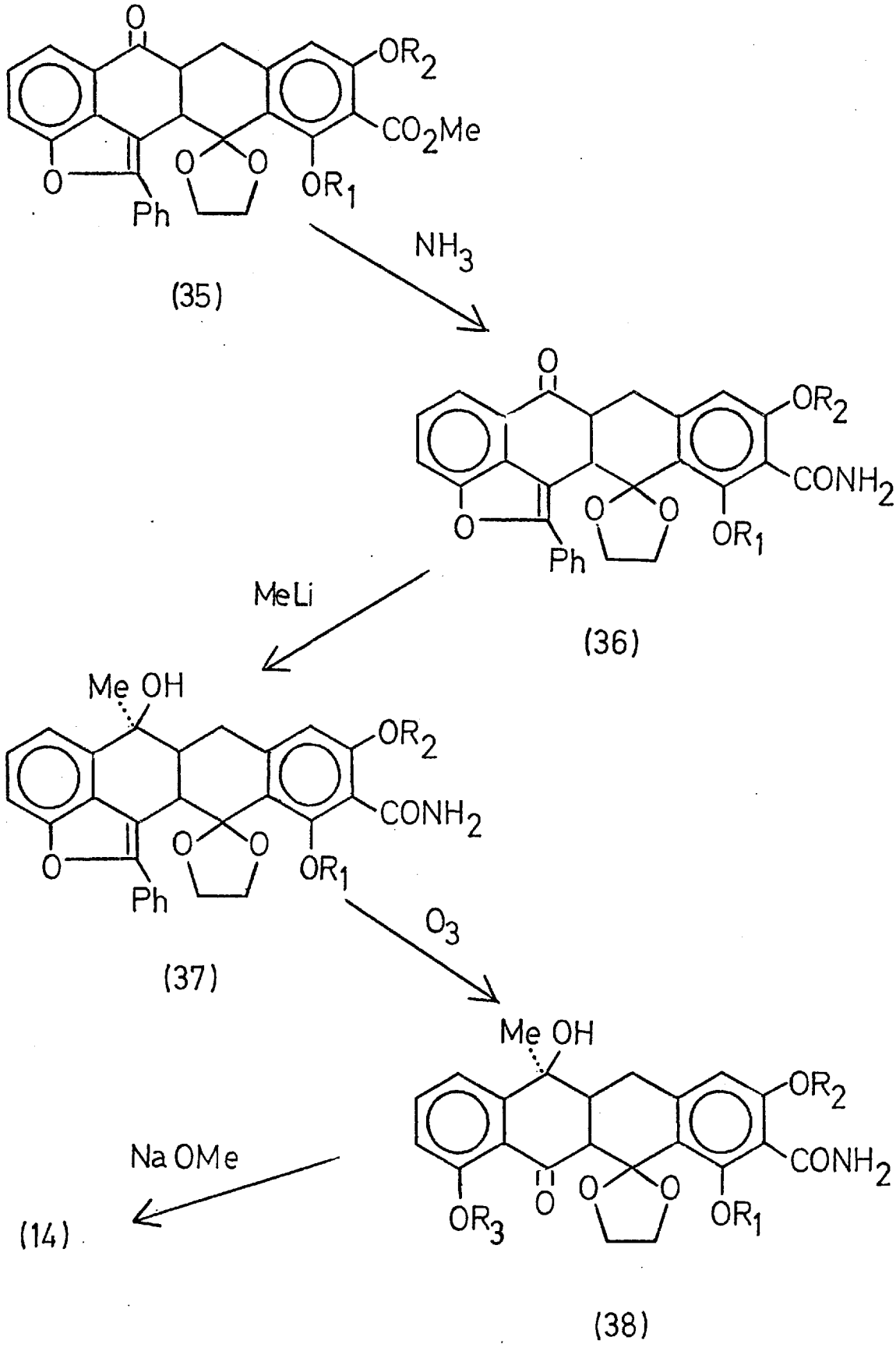


In the presence of the base, the radical-cation would be deprotonated and, the diradical (34) could be formed by further protonation. Cyclisation of this species would lead to the tetracyclic ketone (29a).

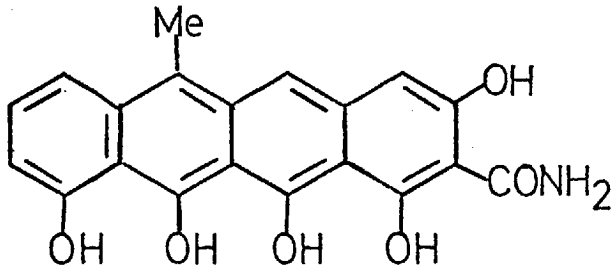
Using the acid-catalysed photocyclisation procedure, only small amounts of ring A substituted acetals could be used, giving the tetracyclic ketals in poor yields. In the base-catalysed reactions, the yields were improved, but only up to 300 mg of substrate could be used in any one reaction.

Starting with these tetracyclic ketals, the proposed synthesis of the diphenol (14) would involve the preparation of the amide (36), methylation of this compound, and ozonolysis of the resulting carbinol (37) to give a benzoic ester (38). Deprotection of the ketal function followed by hydrolysis of the ester would complete this work.

Several attempts were made to prepare compound (14). At first, the amide (36; R_1=R_2=Me) was obtained in 69% yield by basic hydrolysis of the ester (35; R_1=R_2=Me) and subsequent treatment with thionyl chloride / dimethylformamide and ammonia. Repeated additions of ethereal methyl lithium gave the tertiary alcohol (37; R_1=R_2=Me) in 54% yield. The furan ring was cleaved by ozone and compound (38; R_1=R_2=Me, R_3=H) was obtained after hydrolysis of the intermediate benzoic ester (38;R_1=R_2=Me,R_3=Bz). Attempts to cleave the methyl ether


O
OR2
CO2Me
O
O
O
OR1
Ph
NH3
(35)
O
OR2
CONH2
O
O
O
OR1
Ph
MeLi
(36)
Me OH
OR2
CONH2
O
O
O
OR1
Ph
O3
(37)
Me OH
OR2
CONH2
O
O
O
OR3
OR1
Na OMe
(14)
(38)

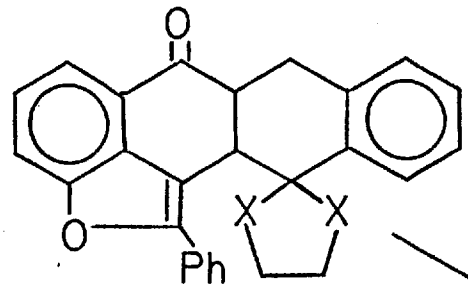
groups,with concommitant deprotection of the 12-dioxolane function, using hot hydrogen iodide in phenol, led to aromatisation and formation of 6-methylpretetramide (5).[21]



(5)

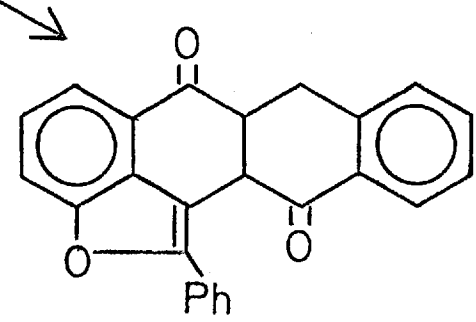
For this reason it was decided to use the unprotected phenols directly in subsequent transformations.[31] Thus the amide (36; R_1=R_2=H) was obtained in high yields by reaction of the ester (35; R_1=R_2=H) with an ammonia saturated tetrahydrofuran / water solution, but all attempts to obtain the tertiary alcohol (37; R_1=R_2=H) using methyl magnesium iodide or methyl lithium, failed.[31]

The deprotection of the 12-keto group required neutral reagents, owing to the acid and base sensitivity of the 6-alcohol function. The failure of the literature methods[32] to achieve this hydrolysis led to a study of new conditions: treatment of a series of model 1,3 dioxolanes (39; X=O) with trityl tetrafluoroborate[33] gave the diketone in 65% yield.

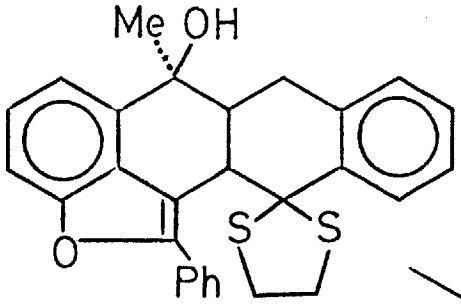


(39)

$Ph_2Se_2O_3$

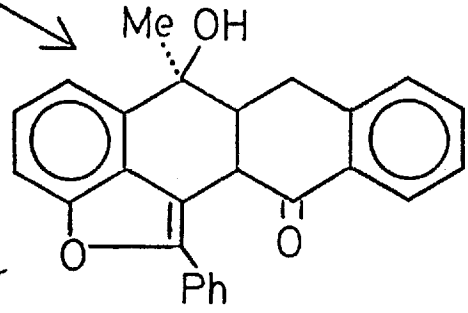


(27)



(40)

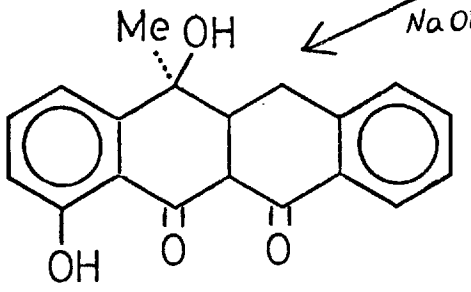
$Ph_2Se_2O_3$



(41)

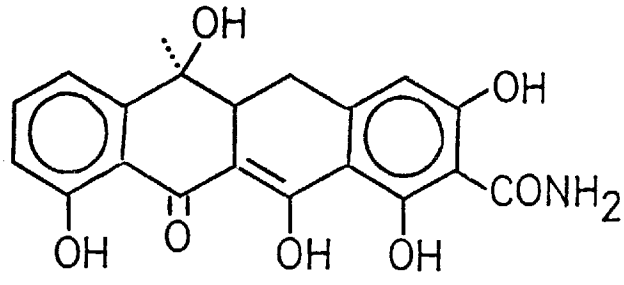
O_3

NaOMe



(42)

Another reagent, benzeneseleninic anhydride, was effective in the hydrolysis of the 1,3-dithiolane function in compounds (39; X=S) and (40).[34] Ozonolysis of the keto carbinol (41) formed by this process from the model carbinol (40), and basic hydrolysis of the 10-benzoate, gave compound (42), which acts as a suitable model for the synthesis of the desired diphenol (14).



(14)

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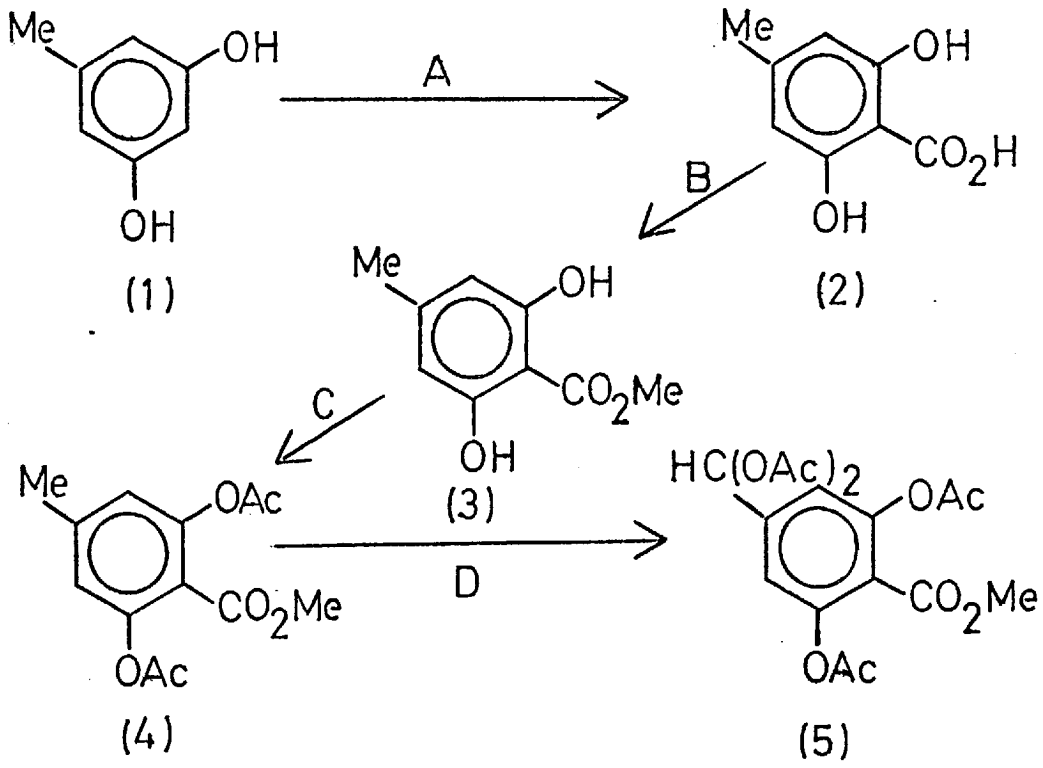
DISCUSSION AND RESULTS

2.1 - Modifications of the established methods for the preparation of the tricyclic ACD intermediates

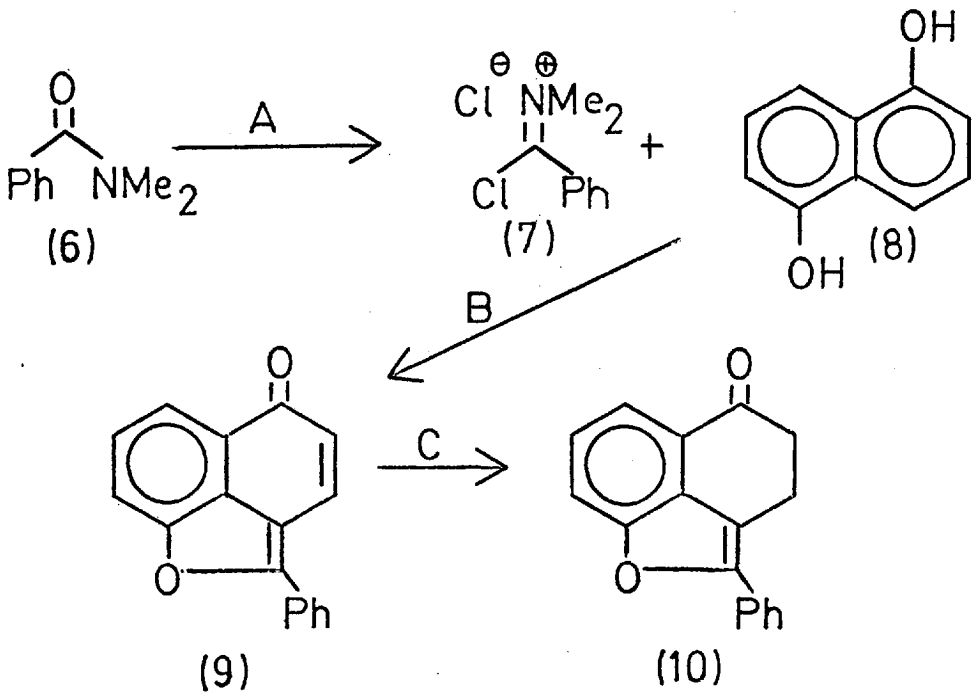
The preparation of the tricyclic aldehyde (14), summarised in schemes 1, 2 and 3, was well established at the outset of this work.[1],[2],[3]



Scheme 1

A) $KHCO_3$/ $HOCH_2CH_2OH$, 120°C. B) Me_2SO_4/$NaHCO_3$, Me_2CO, .

C) Ac_2O/NaOAc, 100°C. D) CrO_3/Ac_2O, AcOH, $MnSO_4$, -10°C.

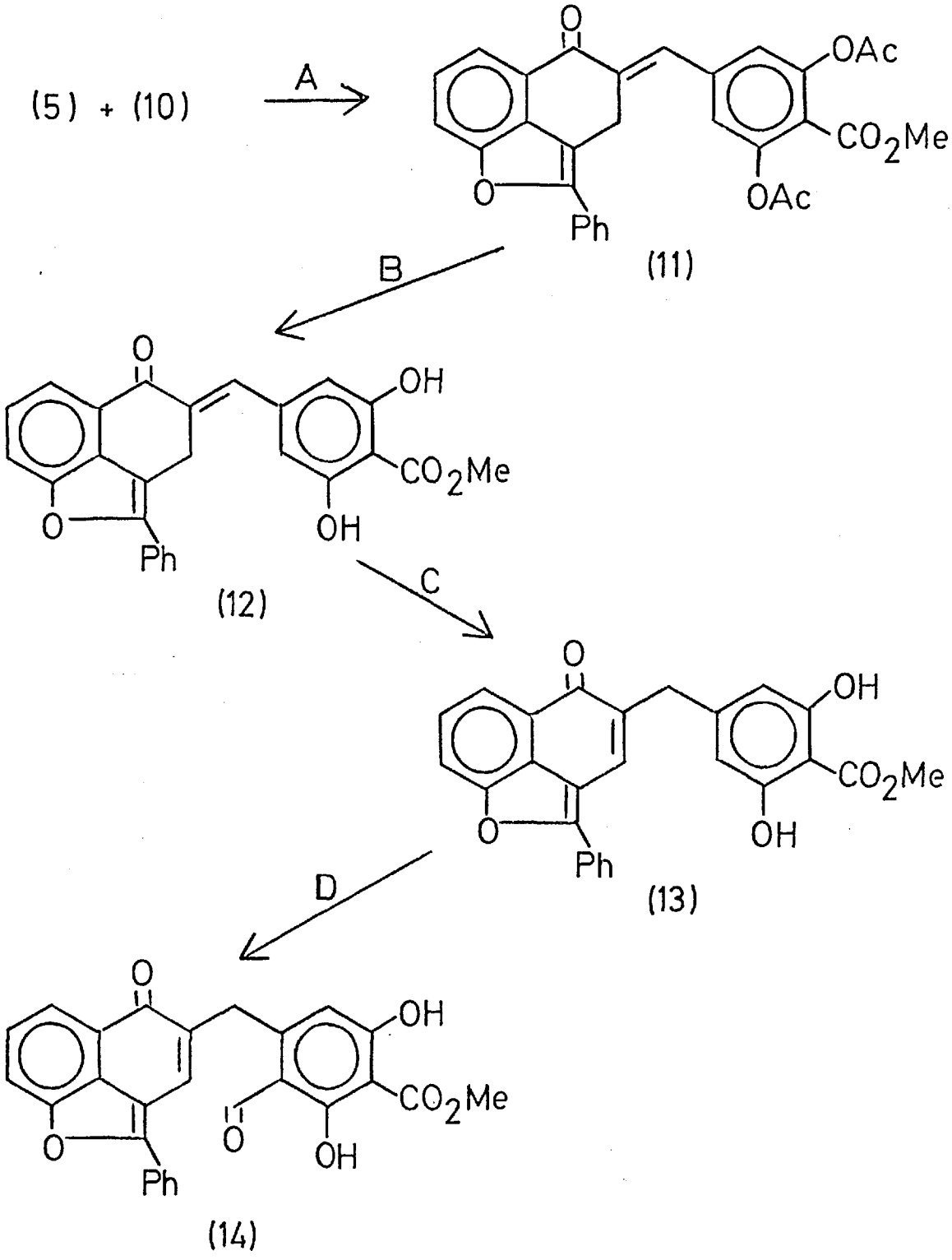


Scheme 2

A) $COCl_2$ R.T. B) Et_3N, NO_2Ph, 80°C. C) H_2/Ni, toluene, R.T.

The majority of the steps outlined in schemes 1, 2, and 3, proceed in excellent yields, with the exception of the condensation between the dihydronaphthofuran (10) and the tetraacetate (5). The use of acetic acid/sulphuric acid mixtures, as condensing agents, gave rather variable results. Consequently alternative methods to effect the transformation were studied. After some experimentation, consistent yields (≃85%) of the benzylidene diacetate (11) were obtained, when the two substrates (5) and (10) were dissolved in boron trifluoride etherate/acetic acid, as the condensing mixture.

The overall yield of the aldehyde (14) was increased to 68%, which compares favourably with the yields obtained by earlier workers: 41%,[4] and 48%.[5]

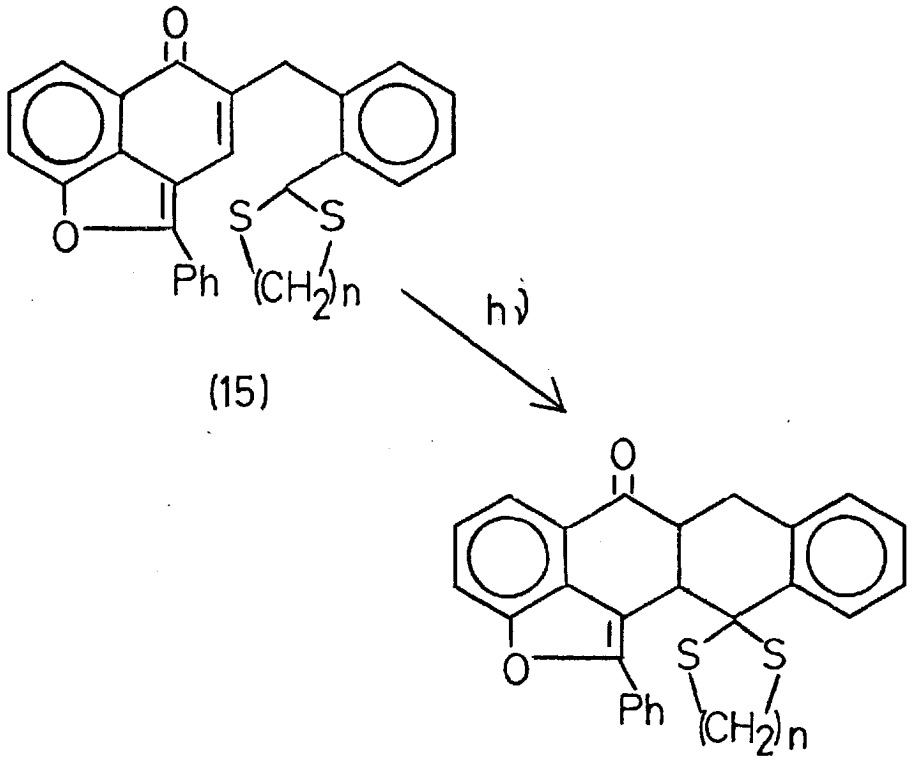


Scheme 3

A) H_2SO_4 - AcOH, R.T. B) HCl - dioxane / H_2O, . C) Et_3N, .
D) Cl_2CHOMe - $AlCl_3/PhNO_2$, R.T.

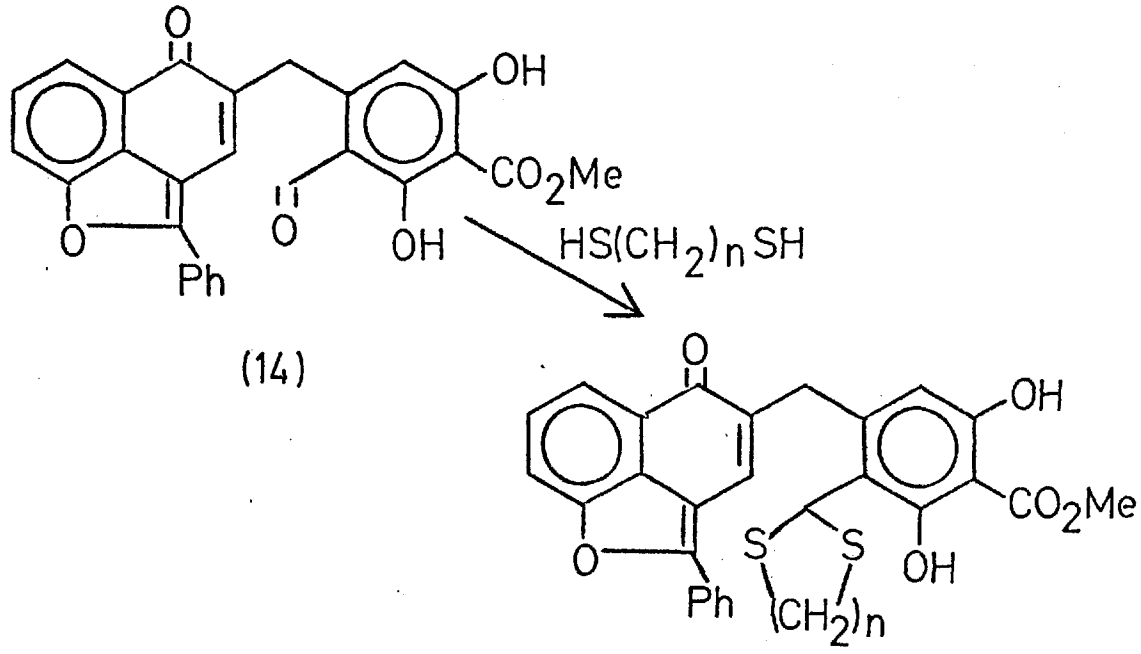
2.2 - Photocyclisation Studies.

Since all previous attempts to prepare the tetracyclic diphenol (51) failed,[2],[5],[6] alternative pathways were developed. As photolysis of the 1,3-dithiolane (15; n=2)[7] and 1,3-dithiane (15; n=3)[3] models gave good yields of the tetracyclic thioketals (16; n=2) and (16; n=3), it was decided to study the possible photocyclisation of the related thioacetals (17; n=2) and (17; n=3).



(15)

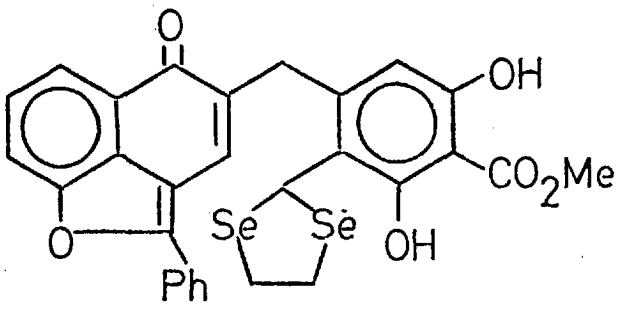
(16)



(17)

High yields of the 1,3-dithiane (17; n=3)[3] and 1,3-dithiolane (17; n=2) were obtained when the aldehyde (14) reacted respectively with propane-1,3-dithiol and ethane--1,2-dithiol, in the presence of acetic acid and boron trifluoride etherate.[8] Careful removal of the last traces of thiols by chromatography on silica gel, followed by sucessive recrystallisations, was necessary, as these compounds interfered during the photolysis experiments.

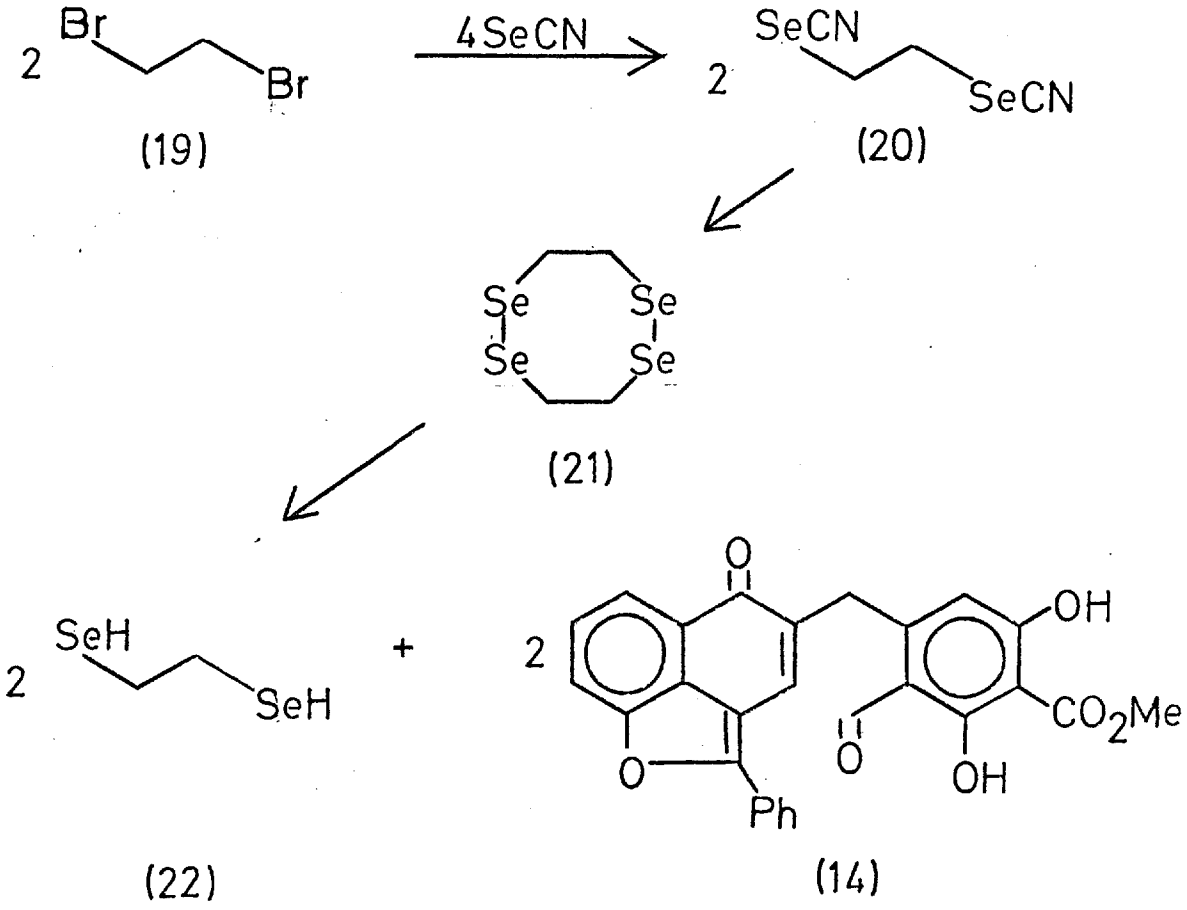
In the search for alternative acetals, the seleno-acetal (18) was thought to be a suitable candidate.



(18)

Selenoacetals are commonly prepared by reacting aldehydes with selenols, in the presence of an acid.[9],[10] These last compounds are however unstable, being very easily oxi-ised to diselenides.[11] Consequently, it was thought advantageous to react the aldehyde (14) with the diselenol (22), formed *in situ*, by reduction of 1,2,5,6-tetraselenocyclooctane (21).

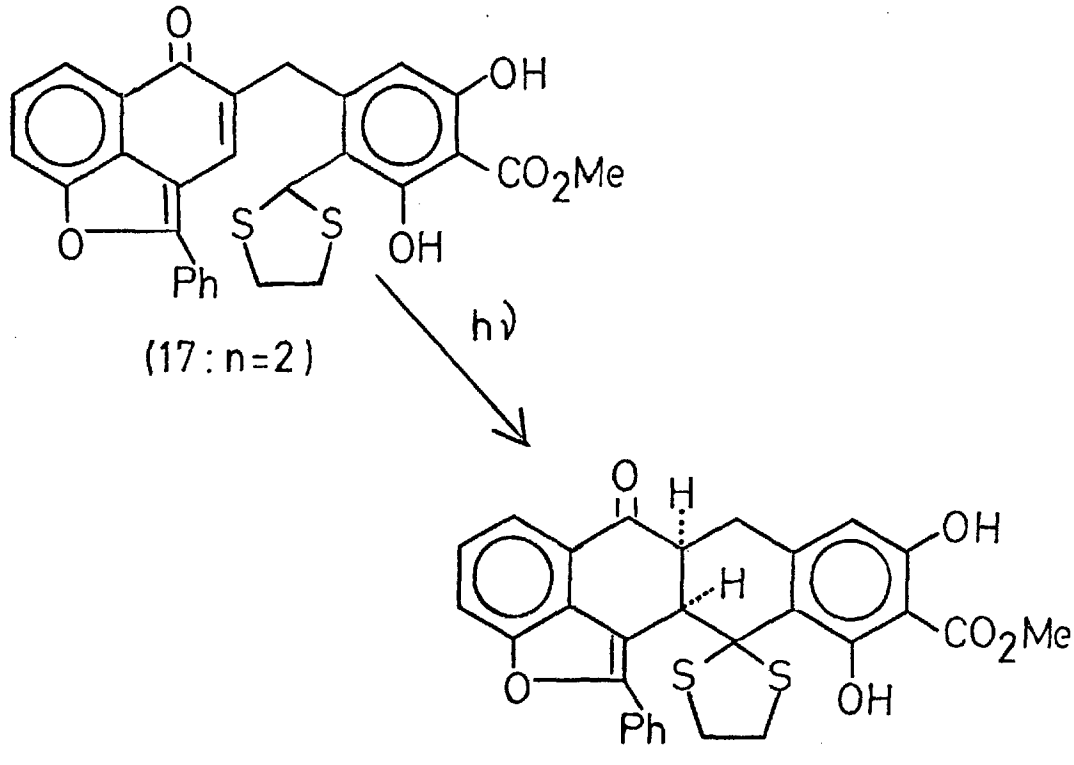
Attempts to prepare compound (21), by mixing ethane-1,2-dibromide with sodium diselenide, formed *in situ*, by reduction of selenium with sodium borohydride[12] or sodium in liquid ammonia,[13] failed. The preparation of the bisdiselenide (21) was accomplished by reacting the ethane--1,2-dibromide with potassium selenocyanate, and hydrolysing the resulting ethane-1,2-diselenocyanate (20).[14]



In order to prepare the selenoacetal (18), the compound (21) was reduced with sodium in liquid ammonia, and the solvent removed.[13] The resulting residue, and the aldehyde (14) were treated with boron trifluoride etherate in acetic acid, under an oxygen free atmosphere. An infrared spectrum of the crude mixture showed that all the starting material (14) had been used up (absence of the 1665 cm^{-1} band). The main product of the reaction could not be recrystallised, as it was unstable in solution, and for this reason no further work was carried out on this system.

Diverse results were found on the photolysis of the dithioacetals (17; n=3 , and n=2) prepared earlier.

As in previous experiments[3] all attempts to isolate and characterize the product of the photolysis of the 1,3-dithiane (17; n=3) with a 100 W tungsten lamp in deoxygenated benzene, using lithium bis-(trimethylsilyl)-amide[15] as the catalytic base, failed. Attempted acetylation of the crude product, in an inert atmosphere, was also unsuccessful.

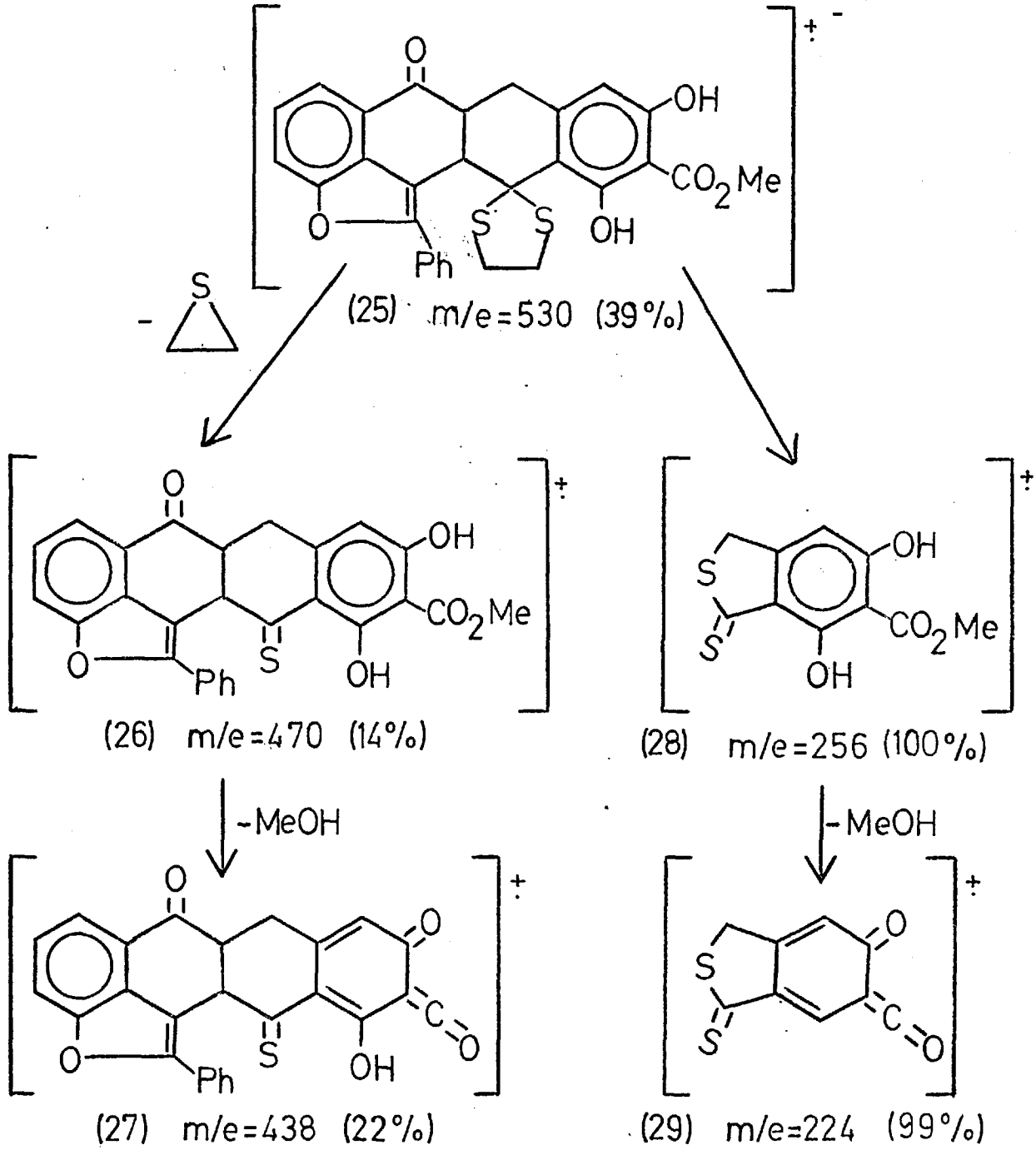


(24)

When the 1,3-dithiolane (17; n=2) was submitted to the same conditions, the corresponding tetracyclic ester (24) was isolated, as a stable and crystalline compound, whose spectral characteristics were similar to the other known ketals[2],[5],[6] and thioketals[7] of this series: ν max, 1671, and 1629 cm^{-1}; λ max, 243, 266, and 349 nm (ε=26 170, 23 664, and 17 050); δ, 1.70 - 2.00 (1H, m), 2.80 - - 3.90 (6H, m), 4.03 (3H, s), 4.73 (1H, J=5Hz), 6.44 (1H, s), 7.26 - 7.99 (8H, m), 9.33 (1H, s), and 11.10 (1H, s) ppm; m/e, 530 (M^+, 39%), 470 (14%), 438 (22%), 256 (100%), 247 (98%), and 224 (99%).

The infrared spectrum showed a band at 1671 cm^{-1} which can be assigned to the 6-keto function. Its ultraviolet spectrum has all the characteristics of similar compounds of this series. Information about the fusion of the rings B and C is provided by an ^1H Fourier, Transform N.M.R. spectrum, showing a doublet at 4.73 (J=5Hz) ppm, corresponding to a 12a-proton cis to the 6a-hydrogen atom. Finally, the mass spectra of compound (24) and its derivatives are characteristic, giving large molecular ion peaks. Possible fragmentation patterns are shown in Scheme 4. These observations are supported by related mass spectral studies of thiacyclopentane,[16] salicylic esters,[17] and previous tetracyclic examples.[18]

Preliminary experiments demonstrated that both irradiation and lithium bis-(trimethylsilyl)-amide as catalyst were important factors in order that the reaction proceeded smoothly. Thus formation of the tetracyclic ester (24) was


(25) m/e=530 (39%)
(26) m/e=470 (14%)
(28) m/e=256 (100%)
-MeOH
-MeOH
(27) m/e=438 (22%)
(29) m/e=224 (99%)

Scheme 4

not observed when the solution of 1,3-dithiolane (17; n=2), in benzene, was heated in reflux in the dark, in the presence of one molecular equivalent of lithium bis-(trimethylsilyl)--amide (LiBSA). Also, the photolysis of (17; n=2), in the absence of base, led to complex mixtures with only trace amounts of the tetracyclic ester (24) being formed (t.l.c. analysis).

Several other factors affected the course of the reaction and extensive modifications of the initial conditions were made. In the first experiments, a 10^{-3} molar solution of (17;n=2), in dried benzene, was irradiated in the presence of 1 - 1.5 molar equivalents of LiBSA, using a 100 W tungsten filament lamp. Rather variable results were obtained, and the purity of the reagents and the conditions of the reaction were investigated:

a) Purification of the Reagents

It was found, that only when the starting material had been carefully purified, did the reaction proceed. The formation of side products was probably due to the presence of trace amounts of ethane-1,2-dithiol.

The purification of the solvent was important and was achieved by passage through a silica column, followed by distillation. The reaction vessel and contents were deoxygenated by heating the solvent under reflux for three

hours while bubbling a gentle stream of dried nitrogen through the solution. The last traces of water were removed azeotropically by distillation of aproximately 10% of the benzene, just prior to starting the reaction.

The reaction was followed by t.l.c. crosschecked by U.V., for the desappearance of a 400 nm band (starting material) and the simultaneous growth of the 350 nm band (product).

b) Thermal Requirements

Optimum temperatures for the reaction were found to be at $\simeq$ 80°C. Insertion of a cold finger in the reaction mixture caused the reaction to stop. Similar observations were made by earlier workers.[18]

c) Variation of the Catalyst

It was found that the amount of base used was also a critical factor. Optimum results were obtained when, as little as .1 - .25 molar equivalents of LiBSA were used (Table 1 - Exp. 2). The use of sodium bis-(trimethylsilyl)-amide (NaBSA) gave rise to appreciable quantities of side products.

d) Variation of the Solution Concentration

Solubility problems limited the concentration of 1,3-dithiolane (17; n=2) to 6.2×10^{-4} moles/l.

e) Variation of Solvents

The use of a more polar solvent, acetonitrile, carefully dried and deoxygenated, shortened the reaction time, and increased the yield(Table 1, Exp. 5). However, a t.l.c. of the crude product showed the existence of another contaminating compound. This side product was due to a thermal reaction, since the heating of a pure sample of the tetracyclic ester (24) with LiBSA in acetonitrile, in the dark, resulted in the formation of the same compound. Unfortunately, isolation of the contaminating product was not possible, owing to difficulties in separation from the starting material (24). Consequently, the use of acetonitrile as solvent was abandoned.

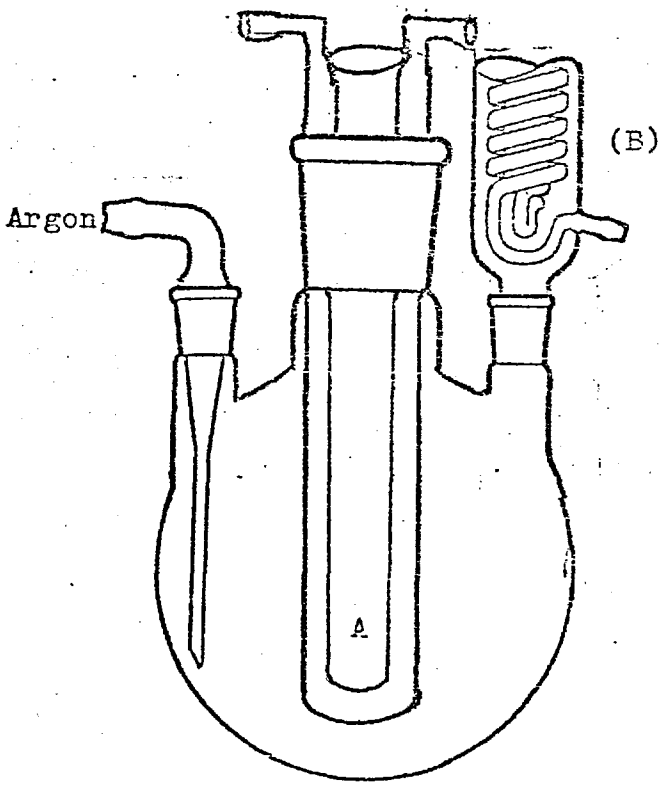
f) Light Sources

The amount of side products increased substantially with the reaction time. To minimise this effect, different light sources and reaction vessels were used.

A 100 W tungsten lamp was found to be ineffective, if used to irradiate amounts of 1,3-dithiolane superior to 100 mg, and the power of the light source was increased gradually. Three 250 W and latterly 3x750 W tungsten lamps were used for experiments with 300 mg and 500 mg of 1,3-dithiolane. They were used in a reflecting enclosure, mounted on a tripod, with the reaction vessel in the middle. Optimum conditions were very difficult to standardise, as various factors like the

size and shape of the reaction vessel, distance and relative angles between the solution and the lamps, seemed to affect the reaction course dramatically.

Clearly, other conditions were necessary, if the cyclisation was to be a synthetically useful reaction. A satisfactory solution for this problem was found when a tungsten-halogen "Atlas Al 233" lamp was used, irradiating the solution through a glass insert in the center of the reaction vessel (fig. 1). Reaction times decreased dramatically (10 - 25 min.) and the tetracyclic ester (24) could at last be prepared in consistent yields (Table 1; exp. 7,8).



A - Lamp
B - Reflux condenser

Fig. 1

Table 1 - Photolysis of 1,3-dithiolane (17; n=2)

Exp. n	S.M.(23) (mg-mM)	Base molar eq.	Solvent (ml)	Light Source	Time (min)	Comp (24) (yield)
1	25 mg .94 mM	LiBSA .25 eq	benzene 50 ml	100 W tungsten l.	60 min	0 - 45%
2	50 mg .94 mM	LiBSA .23 eq	benzene 100 ml	"	45 min	66%
3	100 mg .94 mM	LiBSA .23 eq	benzene 200 ml	3x250 W tungsten l.	80 min	42%
4	100 mg .62 mM	LiBSA .28 eq	benzene 300 ml	"	90 min	60%
5	100 mg .62 mM	LiBSA .25 eq	MeCN 300 ml	" "	45	78%
6	300 mg .62 mM	LiBSA .25 eq	benzene 900 ml	"	90 min	60%
7	300 mg .62 mM	LiBSA .25 eq	benzene 900 ml	Atlas A233 lamp	15 min	70%
8	500 mg .62 mM	LiBSA .25 eq	benzene 1.5 l	"	20 min	60 - 70%

g) Deoxygenation of the reaction atmosphere

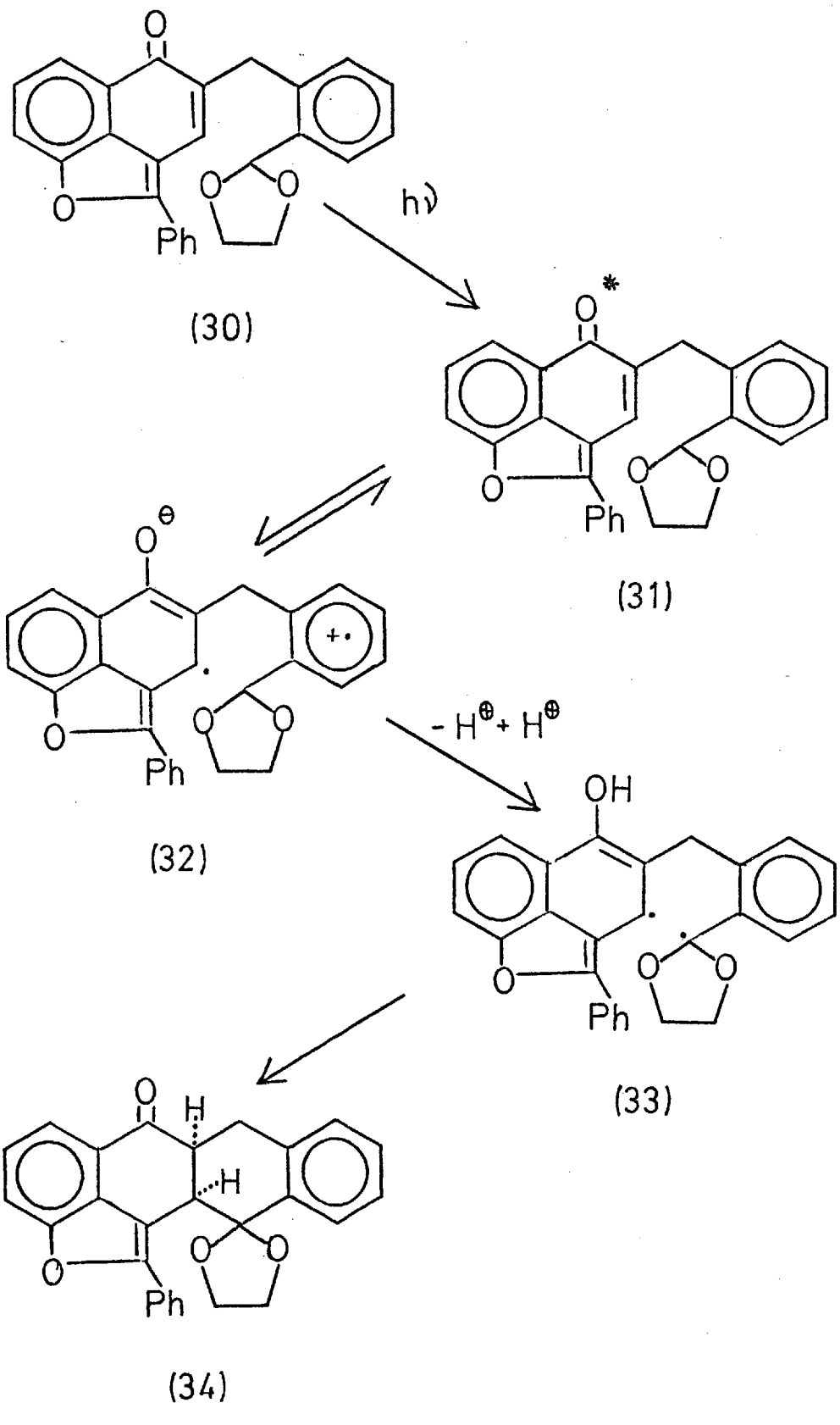
The course of the reaction was affected by trace amounts of oxygen, and consequently it was necessary to pass, dry, oxygen free, nitrogen, through the hot solvent prior to irradiation. The amount of side products decreased when the time of the above deoxygenation process was increased from 3 h to 18 h.

Even better results were obtained using argon as the inert atmosphere.

MECHANISM

The mechanism proposed by Barton[19] for the photocyclisation of 1,3-dioxolanes like (30) can be extended to the present reaction. This process involves the formation of a radical ion pair (32) from the excited enone (31). The species (32), by acid or base catalysis, collapses to the diradical (33), followed by cyclisation to the tetracyclic compound (34).

In fact, the interference of oxygen in the normal cause of the reaction and the fact that long reactions times increased the amount of side products, seems to support the existence of the diradical (33). It includes a ketyl radical, species that is well known[20], and whose characteristics are in close agreement with the above presented facts, since the



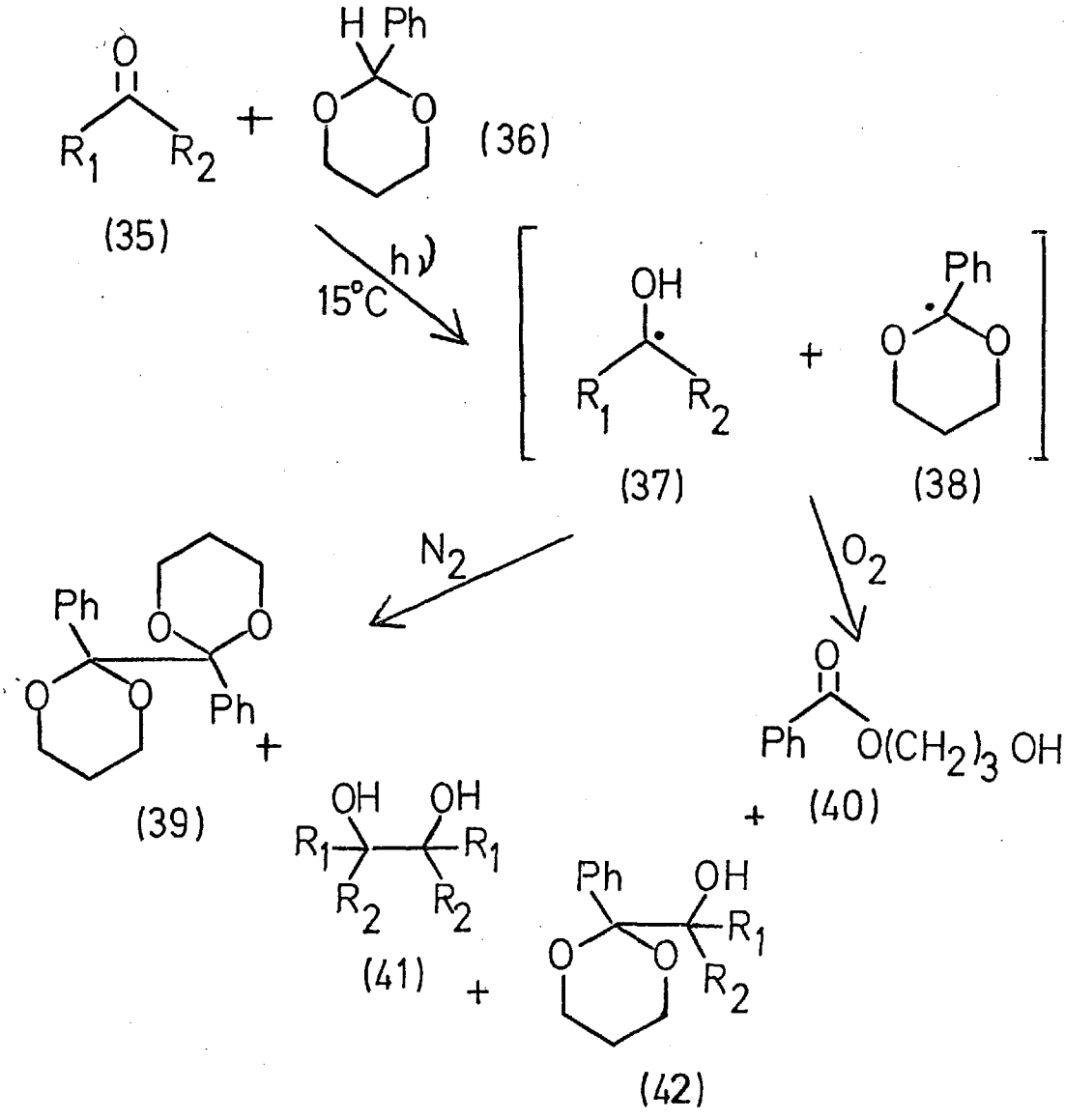
(30)

(31)

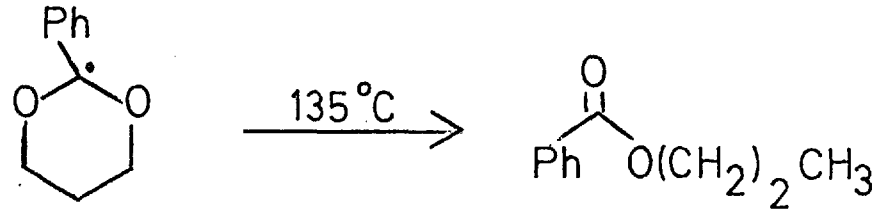
(32)

(33)

(34)

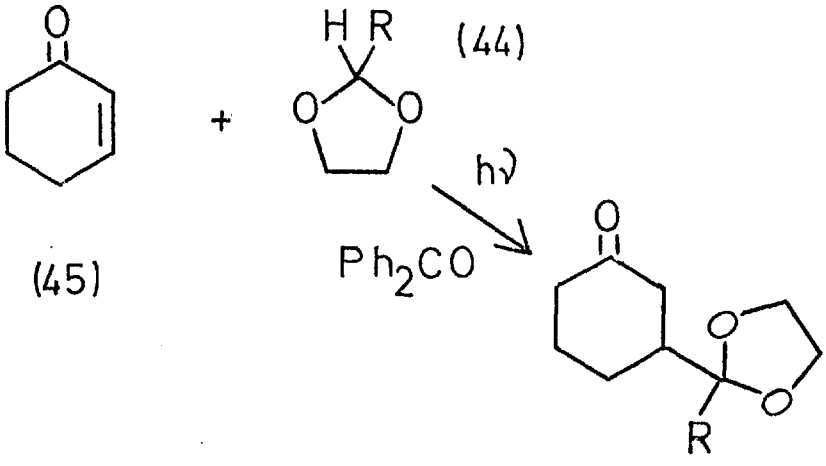


photoreduction of various ketones (35) in the presence of 2-phenyl-1,3-dioxane (36) is very sensitive to oxygen;[21] in dry nitrogen, the products of the reaction are the pinacol (41), the mixed adduct (42) and the dimer (39). This last compound is absent, when species (35) and (36) are irradiated in the presence of oxygen, and instead, the ester (40) is isolated besides compounds (41) and (42).



(38) (43)

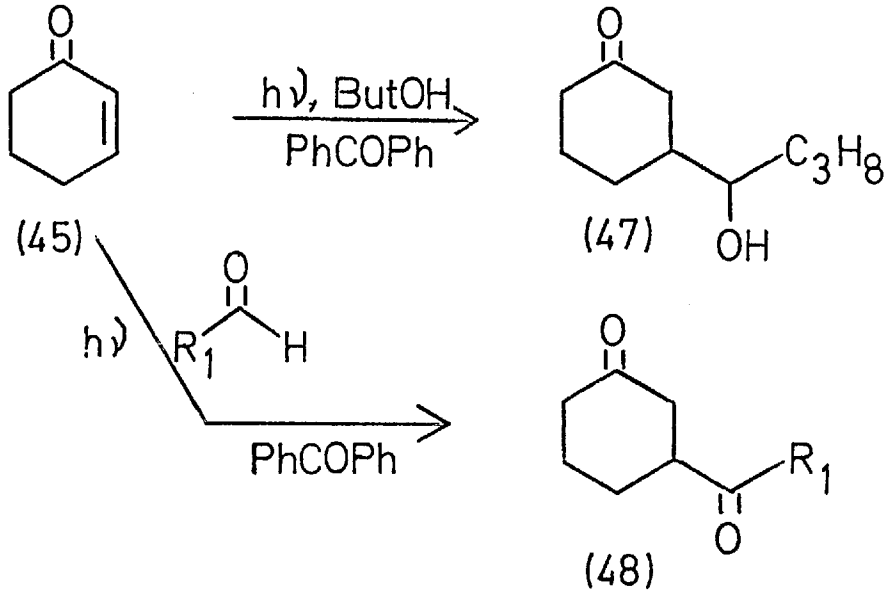
Moreover, cyclic ketyl radicals (38) are unstable in high temperatures,[22] giving rise to esters (43).



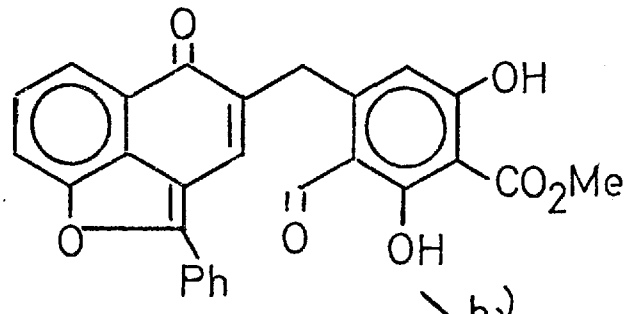
(45) (46)

Further evidence of the existence of these radicals is the related photochemical addition of 1,3--dioxolane (44) to simple enones like (45), to give 1,4-ketoketals (46) in good yields ($R=C_3H_8$- 64%, R=Me -- 58%).[23]

This reaction, which is sensitised by such species as benzophenone, was extended recently to the attack of alcohols;[24] and aldehydes[25] to enones.

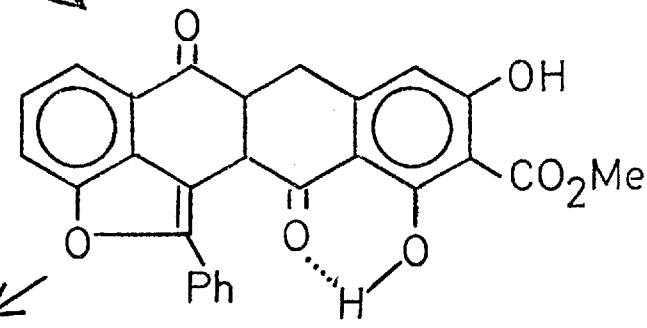


A possible alternative to the photocyclisation of the dithiolane (17; n=2). was the closure of the aldehyde (14) to give the tetracyclic 1,4-diketone (49), even if previous studies suggested this reaction proceeded only in low yields.[7] The tetracyclicic 1,4-diketone (49) would be a valuable intermediate in the present synthesis, as methylation would be expected to give compound (50), since the 11-phenolic hydroxyl group would protect the 12-keto function by hydrogen bonding.

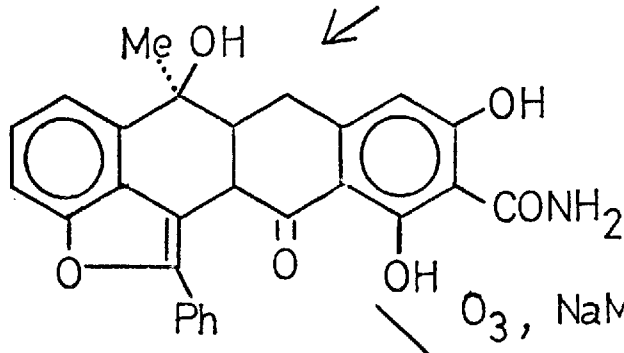


(14)

hν

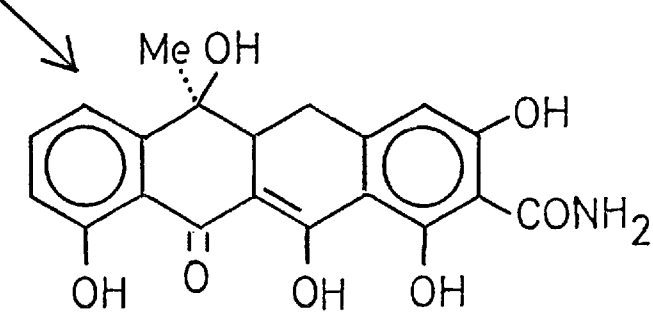


(49)



(50)

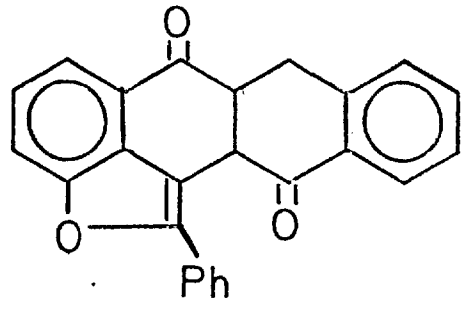
O_3, NaMeO



(51)

Preparation of the diphenol (51) would be easily accomplished, by ozonolysis of a protected derivative of (50), and subsquent hydrolysis of the resulting benzoate.

Irradiation of (14), in dried and deoxygenated benzene, resulted in the slow formation of a rather complex mixture of products. One of the compounds, present only in trace amounts, had spectral characteristics close to the expected diketone. For example, it showed a bright blue fluorescence under a far ultraviolet lamp, a U.V. spectrum (Table 2) similar to the model 6,12-diketone (52), and a mass spectrum showing a molecular ion peak (M^+ - 454) corresponding to the molecular weight of compound (49)



(52)

Table 2 - U.V. spectra of tetracyclic 1,4-diketones.

(49)	nm	253		292	337	358
	ϵ	18 405		15 800	14 360	12 980
(52)	nm	264	281	299	310	360
	ϵ	25 580	18 690	15 740	13 380	12 590

From all the different conditions tried, summarised in table 3, only the use of one molar equivalent of acetic anhydride, or a crystal of hydroquinone enhanced the formation of (49). The use of ethyl iodide as solvent, even if it did not increase the yield of the reaction, diminished remarkably its time.

However , since even under an inert atmosphere at low temperature, compound (49) decomposed in solution, giving tars, its isolation in significant amounts proved impossible.

Table 3 - Photolysis of a 2.1×10^{-2} molar solution of the aldehyde (14), using a 500W tungsten lamp, under N_2

Substrate (14)	Catalyst molar eq	Solvent	Time	Yields
10 mg	--	benzene	20 h	traces of (49)
"	ABN	"	17 h	" " "
"	I_2	"	24 h	" " "
"	$PhCO_2H$	"	24 h	" " "
"	I_2+ K t-butO	"	7 h	-- -- --
"	LiBSA (1 eq)	MeCN	17 h	- -- --
"	Ac_2O (1 eq)	"	17 h	15% of (49)
"	Ac_2O (10 eq)	"	24 h	-- -- --
"	QH_2	"	24 h	15% of (49)
"	Ac_2O	EtI	1.5 h	" " "

At the same time, the solid state photolysis of the aldehyde (14) was being studied. Finely powdered aldehyde was irradiated by a 500W tungsten lamp, under an inert atmosphere, for periods of 12 h to 24 h. In all attempts, summarised in table 4, the starting material was recovered unchanged, and hence no further studies were carried out.

Table 4 - Solid state photolysis of the aldehyde (14), using a 500W tungsten lamp, under N_2, at 15 C.

Substrate (14)	Catalyst	Time	Results
5 mg	--	24 h	No reaction
5 mg	$PhCO_2H$	24 h	" "
5 mg	Ac_2O	24 h	" "

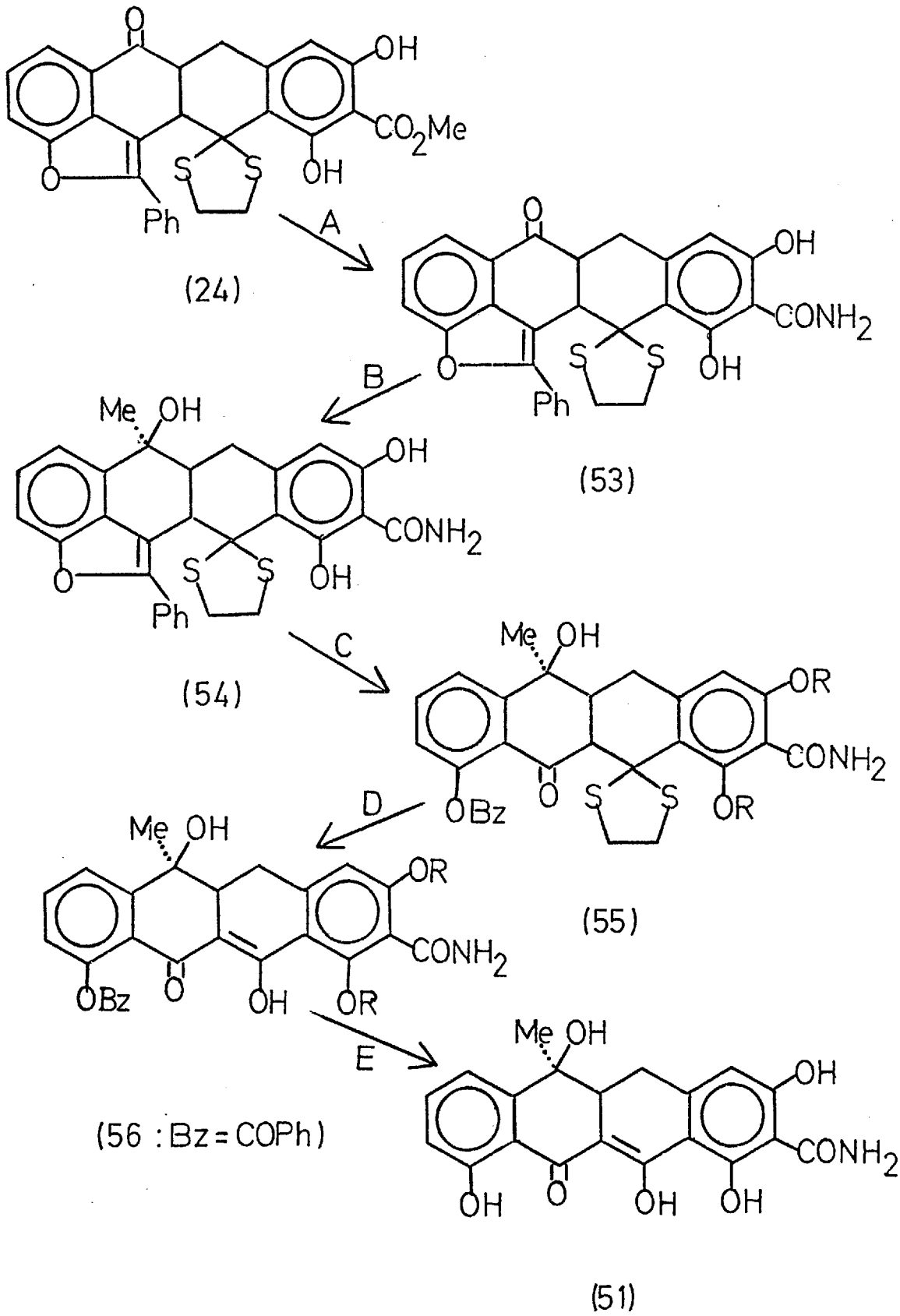
2.3 - Studies on the Preparation of Tetracyclic Carbinol Derivatives

Based on the behaviour of similar tetracyclic molecules already studied;[2],[6],[14] the proposed synthesis of the diphenol (51), starting from compound (24) would include the following steps (Scheme 5).

Initially, the treatment of the tetracyclic ester (24) with an ammonia saturated solution of tetrahydrofuran/water afforded the amide (53), characterised by I.R., U.V., N.M.R. and Mass Spectrum (ν max, 3403, 3300 - 3100, 1703, 1682, 1655, and 1618 cm^{-1} λ max, 258, 276, and 350nm (ε=12 929, 12 402, and 10 726); δ, 2.89 - 4.15 (m), 4.91 (1H, d, J=4.8 Hz), 6.54 (1H, s), 7.29 - 8.01 (8H, m), 8.70 (1H, s), and 10.10 (1H, s), m/e 515 (M^+), 455, 438, 247, 241, and 224. Confirmation of the empirical formula was obtained by micro analysis.

Recently, the same compound could be obtained in higher yields (78%) by precipitation from a diglyme/aqueous ammonia solution.

The following step was the preparation of the tetracyclic carbinol (54) by attack of a Grignard reagent or methyl lithium on the 6-keto group, and previous examples (Table 5) showed that this reaction, even if resulting in

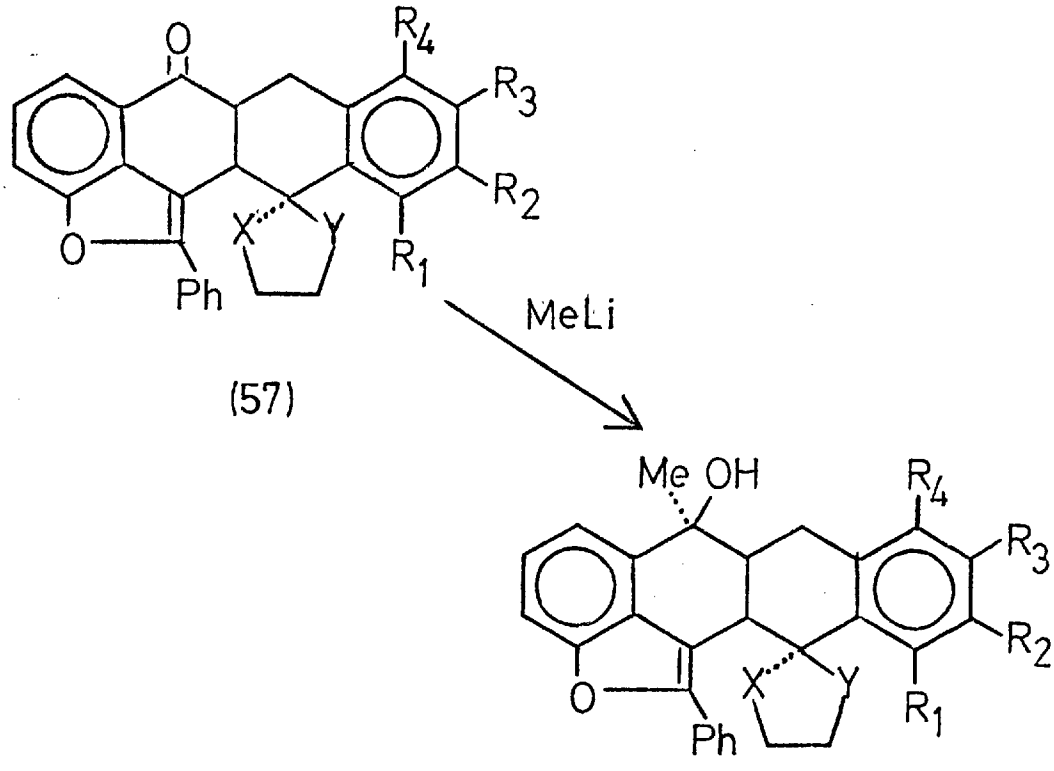


Scheme 5

A) NH_3, THF, H_2O, R.T. B) MeLi / THF, -78 C. C) O_3/MeOH, CH_2Cl_2 -78 C, Me_2S, R.T. D) $Ph_2Se_2O_3/CH_2Cl_2$, R.T. E) NaOMe/MeOH, R.T.

compounds with the correct stereochemistry,[7] was found to be experimentally difficult. Addition of these reagents under a variety of conditions to the ketones (57) gave, generally, mixtures of starting material and the desired product (58). This result was attributed to substantial enolisation of the 6-keto group, the relative composition of the mixture being dependent on the substrate used.

The process usually adopted, involved repeated reactions with ethereal solutions of methyl lithium, a process which was both lengthy and gave generally poor yields.



(57)

(58)

Table 5 - Addition of ethereal methyl lithium to various tetracyclic ketones (57)

S. M. (57)	nº of repeated additions of methyl lithium	Yield of (58)	Ref.
X=Y=O, R_1=R_2= =R_3=R_4=H	2 times	55%	(7)
X=O, Y=S, R_1= =R_2=R_3=R_4=H	2 times	53%	(7)
X=Y=O, R_1=R_3=OMe R_2=$CONH_2$, R_4=H	2 times	54%	(2)
X=Y=O, R_1=R_3=R_4= =OMe, R_2=$CONH_2$	1 time	60%	(6)
X=Y=O, R_1=R_3=OH R_2=$CONH_2$, R_4=H	3 times	--	(5)

A similar procedure was reported to be unsuccessful when applied to compound (57; X=Y=O, R_1=R_3=OH, R_2=$CONH_2$, R_4=H) with the two phenolic functions unprotected. Starting material was always present in large quantities and the carbinol proved to be very unstable as all attempts to isolate it failed.(5)

Attempts to react the tetracyclic amide (53) with methyl magnesium iodide were unsuccessful, as the starting material was always recovered unchanged. Remarkably however, when a large excess of methyl lithium (25 molar equivalents) was added to the amide (53), the carbinol (54) was cleanly formed.

The spectroscopic characteristics of this compound, (ν max, 3500, 3400 - 3250, 1702, 1654, and 1603 cm^{-1}; λ max 250, 296, 312, and 324 nm (ε = 14 390, 14 360, 14 390, and 14 140); δ, 1.58 (3H, s), 2.70 - 4.06 (m), 4.84 - 4.89 (1H, d, J=5 Hz), 6.52 (1H, s), 7.38 - 8.00 (8H, m), and 10.00 (1H, s); m/e 513 (M^+ - 18), 453, 436, 241, and 224), were very similar to previous examples of the carbinol series, and confirmation of elemental composition was obtained by micro analysis. Very important was the existence in the infrared spectrum of a sharp band near 3500 cm^{-1} attributed to the 6a-hydroxyl group, and the absence of a band at 1670 cm^{-1} corresponding to the starting 6-ketone group. The ultraviolet spectrum was similar to previously reported examples, as shown in Table 6. The sharp singlet in the N.M.R. spectrum at 1.58 ppm, with a relative integral for 3 protons, indicated the presence of the 6a-methyl group. Finally, the base peak in the mass spectrum was 18 units less than the expected molecular weight, thus indicating the lability of the hydroxyl function to dehydration.

Table 6 - U.V. Spectra of various tetracyclic carbinols

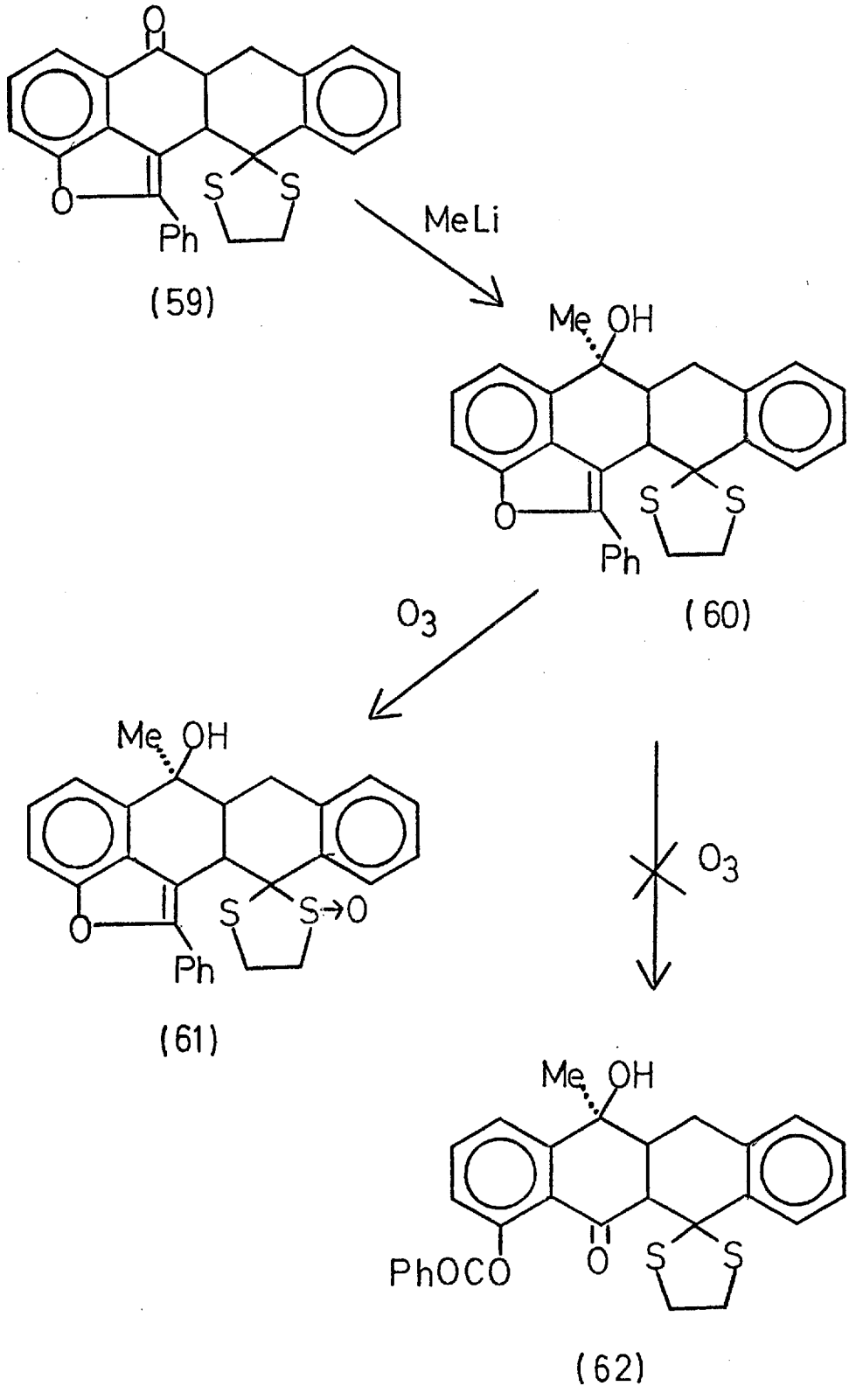
Carbinol	nm (ε)						Ref.
(58) X=Y=O, R_1=R_2= =R_3=R_4=H				296 (22 420)	308 (28 820)	322 (21 430)	(7)
(58) X=Y=O, R_1=R_3= =OMe, R_2=$CONH_2$ R_4=H	231 (29 000)	250 (15 700)	279 (18 700)	291 (24 750)	310 (30 250)	324 (22 850)	(2)
(58) X=O, Y=S, R_1= =R_2=R_3=R_4=H				294 (13 670)	310 (12 420)	326 (8 921)	(7)
(54)		250 (14 390)		296 (14 360)	312 (14 390)	324 (14 140)	

The success of this reaction was dependent upon using a vast excess of methyl lithium (25 molar equivalents). Experiments employing 5, 10, or 15 molar equivalents of the reagent led to mixtures of starting material and product. The yields varied considerably ($\simeq$ 50 - 70%) depending on the work up procedure used: the carbinol was shown to be very sensitive to chlorinated solvents and decomposed readily when chromatography on silica was attempted. Recrystallisation of the product was best performed by dissolving the residue in a small quantity of freshly distilled dichloromethane, and adding methanol until precipitation ocurred. Bench dichloromethane, and especially chloroform decomposed the compound readily.

Further studies were made possible by this useful result. However, as only small amounts of the carbinol (54) had been prepared, model compounds were used to investigate other steps in the proposed reaction sequence, prior to studying the real system.

The model tetracyclic ketone (59) used in these studies, was prepared according to an improved procedure.[26]

Only after multiple treatment with methyl lithium could this compound (59) be totally transformed into the carbinol (60). Consequently the yields of this reaction were very low and only small amounts of compound (60) were prepared.



(59)

(60)

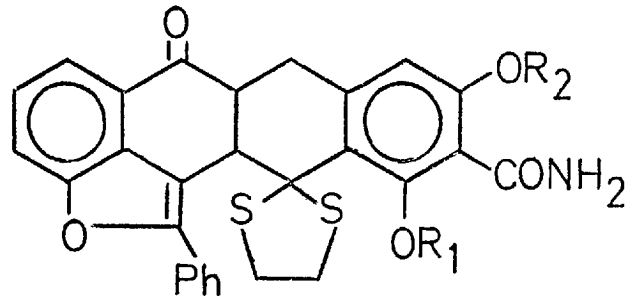
(61)

(62)

Ozonolysis of the carbinol (60) at -78 C gave a low yield (36%) of the monosulphoxide (61), which was characterised by I.R., U.V. and mass spectrometry. There was no evidence for the formation of the expected keto--benzoate (62), since by t.l.c. analysis, only very polar tars were detected as side products. The initial experiments indicated however that the 12-dithiolane function protects the furan ring from the oxidation by ozone. On this basis, it was decided to attempt to remove this function prior to ozonolysis.

Owing to certain characteristics of these compounds, mild reagents had to be used to accomplish this task.[27] Mercury salts were found to be ineffective or too reactive, in related systems,[28] and were, therefore, of no use. Preliminary small scale experiments tried on a number of these methods are summarised in table 7.

Treatment of the tetracyclic amide (53) with methyl iodide,[29] afforded in low yield, two products which had a bright fluorescence under the 366 nm U.V. lamp. Mass spectra of these compounds sugested the formation of compounds (63; R_1=H, R_2=Me) and (63; R_1=R_2=Me).

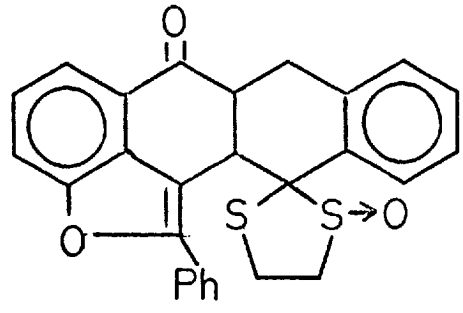


(63)

As a consequence of these results, more powerful alkylating agents, such as methylfluorosulphonate[30] and triethyloxonium tetrafluoroborate,[31] could not be used.

Chloramine-T[32] was ineffective, and treatment of (53) with N-bromosuccinimide[33] gave rise to a complex mixture of products.

Alternatively, since ethylenethioketal sulphoxides[34] and sulphones[35] are susceptible to alkaline hydrolysis, a similar approach was used on the monosulphoxide (64), however without success.

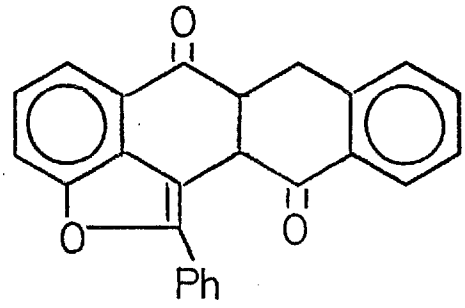


(64)

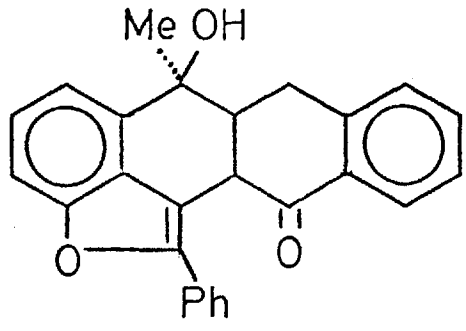
Table 7 - Attempted dethioketalisation of various tetracyclic thioketals.

Substrate	Reagents	Solvents and conditions	Time	Results
(53)	MeI	T.H.F./H_2O 60 C.	2h	(63; R_1=H, R_2=Me) (63; R_1=R_2=Me) tars
	chloramine T	T.H.F./MeOH/ /H_2O. R.T.	1 week	No reaction
	N-bromo-succinimide	MeOH/H_2O R.T.	5 min	Complex mixture of products
(64)	NaOMe	MeOH R.T. N_2	36 h	No reaction
	Kt-buto-xide	DMSO R.T. N_2	36 h	No reaction
	LiBSA	T.H.F. R.T. N_2	1 min	Complex mixtures of products

Meanwhile, efforts to promote the dethioketalisation of these and other compounds, were being made in our laboratories. A new method to solve this problem was found to be the treament of thioketals with benzeneseleninic anhydride,[36] a reagent used previously in phenolic hydroxylation studies.[37] By this method, the tetracyclic diketone (52) and keto-carbinol (65) were formed in high yields.[36]



(52)

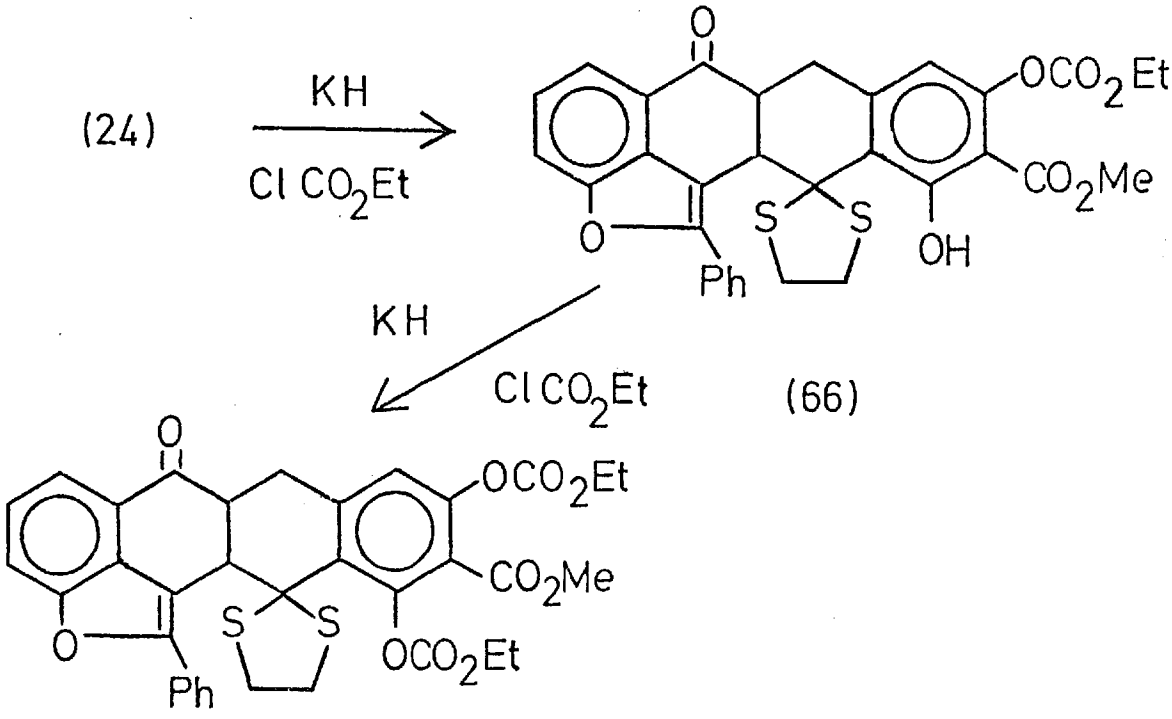


(65)

Since benzeneseleninic anhydride was known to attack phenols quite easily[37] it was necessary to find a suitable protection for these groups, prior to treatment of (54). Moreover, the protecting group had to be removed under mild basic conditions, due to the lability of the 6-hydroxyl function in these compounds. Groups such as acetates and cathylates were thought to be suitable to this purpose.

However attempts to acetylate the carbinol (54) with acetyl chloride or acetic anhydride in pyridine, and acetic anhydride in triethylamine, catalysed by 4-dimethyl-aminopyridine[38] failed to give a stable crystaline product.

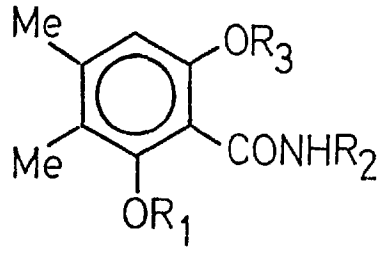
Cathylation experiments were investigated using first the tetracyclic ester (24). After some experimentation, the 9-cathylate (66) was prepared, by reacting the salt formed from the ester (24) and tetrabutylammonium hydrogen sulphate in a weak alkaline solution, and quenching with ethylchloro-formate. Spectral evidence (ν max, 1767, 1698, 1670, and 1622 cm^{-1} λ max, 246, 280, and 355 nm (ε =27 630, 24 660, and 17 980), δ, 1.40 (3H, t), 2.70 - 3.60 (m), 3.80 (3H, s), 4.32 (2H, q), 4.70 (2H, d), 6.70 (1H, s), and 7.21 - 8.10 (m), m/e, 602 (M^+), 541, 328, 296, 256, and 224) was not very helpful in assigning the position of cathylation. However, molecular models indicated that the 11-hydroxyl group was considerably hindered by adjacent 12-ethylenethioketal and 10-carboxylate functions, and thus less likely to be cathylated than the 9-OH.



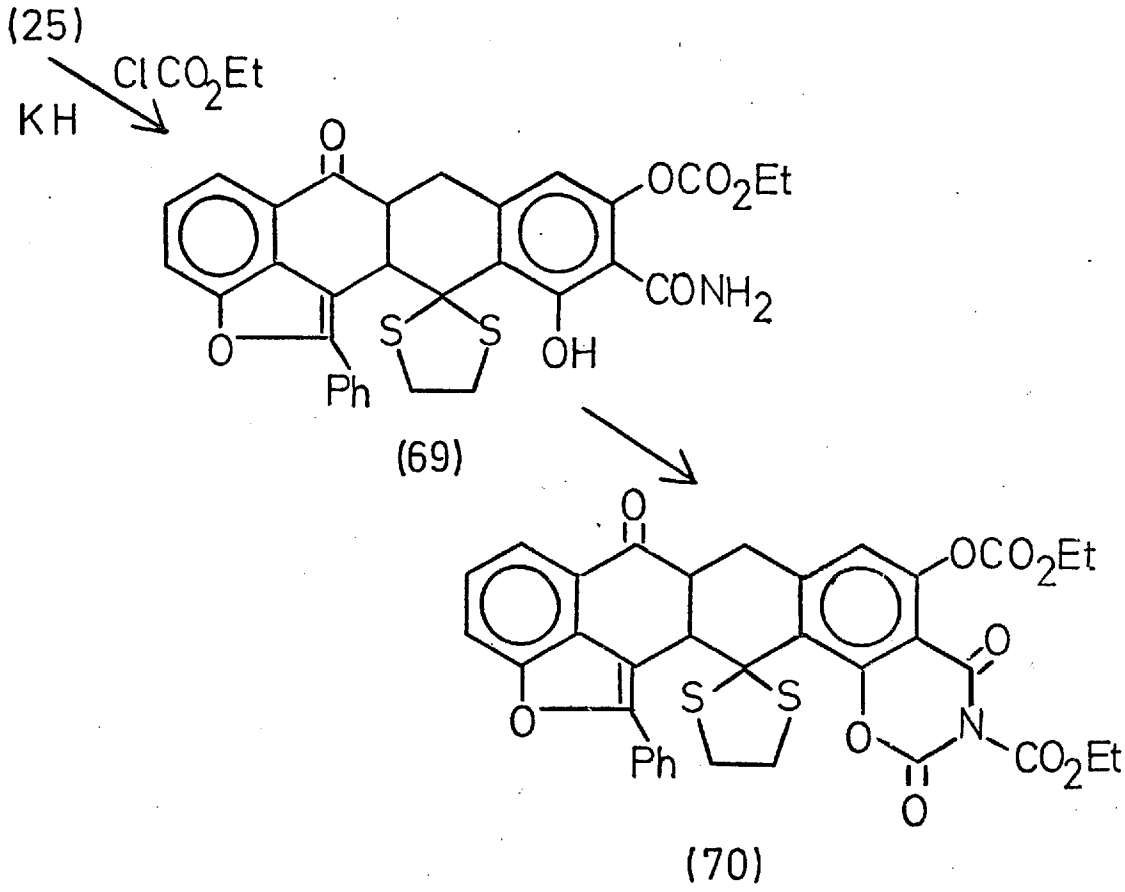
(67)

Under more forcing conditions, the monocathylate (66) was treated with potassium hydride, followed by addition of ethylchloroformate in hot tetrahydrofuran, to afford the dicathylate (67).

Similar conditions were applied to the model benzamide (68; $R_1=R_2=R_3=H$) and tetracyclic amide (25), from which compounds (68; $R_1=R_2=R_3=CO_2Et$) and (70) were respectively isolated.



(68)



(70)

Structure (70) is supported by I.R. (ν max, 1790 - 1774, 1700, and 1618 cm^{-1}), N.M.R. (δ, 1.10 - 1.60 (6H, m), 2.80 - 4.00 (7H, m), 4.00 - 4.21 (4H, m) 4.80 (1H, d), and 7.22 - 8.00 (9H, m) ppm), and mass spectral (m/e, 685 (M^+), 641, 613, and 247) data, but micro analytical data could not be obtained. Trace amounts of a contaminating side product could not be eliminated by p.l.c. or recrystallisation.

Preliminary studies on the behaviour of benzeneseleninic anhydride with these systems is described below

The model benzamide (68; $R_1=R_2=R_3=CO_2Et$) was recovered unchanged after treatment with benzeneseleninic anhydride for one week, at room temperature.

Both cathylates (67) and (70) reacted slowly with this reagent at room temperature (3 - 7 days), affording complex mixtures of compounds.

This subject is now being investigated in these laboratories.

EXPERIMENTAL

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

Melting points were measured on a Kofler block and are uncorrected. Infrared spectra were taken on a Perkin Elmer 157 spectrometer. Ultraviolet spectra were recorded on a Unicam SP 800 spectrophotometer. N.M.R. spectra were recorded on a Varian 360 A, and a Varian XL 100 Fourier Transform spectrometers. Mass spectra were recorded on a V.G. 7070 double focusing mass spectrometer.

The following observations refer to N.M.R. data:

s= singlet

d= doublet

b= broad

t= triplet

m= multiplet

All solvents and reagents were dried and purified by standard techniques. The silica gel for t.l.c. (thin layer chromatography) and for p.l.c. (preparative layer chromatography) were Merck $G.F._{254}$ and M.F.C. silica.

EXPERIMENTAL TO SECTION 2.1

p-Orsellinic acid (2)

Prepared by carboxilation of orcinol by the method of Robertson and Robinson,[39] m.p. 167 - 168 °C (lit.[39] m.p. 165 - 166 C).

Methyl, p-orsellinate (3)

Prepared by esterification of p-orsellinic acid (2) with hydrogen carbonate - dimethyl sulphate, by the method of Barton et al,[1] m.p. 97 °C (lit[1] m.p. 98° - 99°C).

Methyl, 2,6-diacetoxy-4-methylbenzoate (4)

Prepared by acetylation of methyl, p-orsellinate (4) with sodium acetate - acetic anhydride, by the method of Barton et al,[2] m.p. 70 °C (lit.[2] m.p. 70°C).

Methyl, 2,6-diacetoxy-4-diacetoxymethylbenzoate (5)

Prepared by oxidation of (4) with chromium trioxide sulphuric acid and manganous sulphate,[3] m.p. 110°C (lit[3] m.p. 112°C).

α-Chloro-benzaldehydo-N,N -dimethylimidinium chloride (7)

Prepared by reaction of phosgene and N,N -dimethyl-benzamide.[40]

2-Phenylnaphtho[1,8-bc]furan-5-one (9)

Prepared by the action of (7) on 1,5-dihydroxy-naphthalene[3], m.p. 137°- 139°C (lit.[1] m.p. 137.5°- 138.5°C).

3,4-Dihydro-2-phenylnaphtho[1,8-bc]furan-5-one (10)

Prepared by hydrogenation of naphthofuran (9) over Raney nickel, at atmospheric pressure,[1] m.p. 112°- 113°C (lit.[1] m.p. 113 - 114°C).

4-(3,5-Diacetoxy-4-methoxycarbonylbenzylidene)-3,4-dihydro--2-phenylnaphtho[1,8-bc]furan-5-one (11)

To a stirred mixture of dihydronaphthofuran (10) (2.64 g - 1.01 mM) and the tetra-acetate (5) (3.85 g - 1.01 mM) in glacial acetic acid (32.5 ml) and diethyl ether (67 ml), was added dropwise boron trifluoride etherate (32.5 ml) over 20 min., at 0°C. The dark solution was stirred for 48 h at room temperature; yellow crystals of the benzylidene diacetate separated, and were washed with diethyl ether, 4.33 g (85%), m.p 218 - 220°C (lit.[2] m.p. 220 - 221°C).

4-(3,5-Dihydroxy-4-methoxycarbonylbenzylidene)-3,4-dihydro--2-phenylnaphtho[1,8-bc]furan-5-one (12)

The benzylidene diacetate (11) (3.4 g) was suspended in dioxane (28 ml) and a solution of concentered sulphuric acid (5.6 ml) in methanol (47 ml) was added dropwise, at room temperature, with stirring. The resulting suspension was heated for 30 min. under reflux (≃80°C). The yellow crystals that separated, were isolated by filtration and washed with methanol, affording benzyledene diphenol (12) (2.8 g -(98%), m.p. 204-206°C (ethyl acetate) (lit.[2] m.p. 204 - 208°C).

4-(3,5-Dihydroxy-4-methoxycarbonylbenzyl)-2-phenylnaphtho [1,8-bc]furan-5-one (13)

Prepared by isomerisation of (12) with dry triethylamine[2], m.p. 235°C (lit.[2] m.p. 238°C).

4-(2-Formyl-3,5-dihydroxy-4-methoxycarbonylbenzyl)-2-phenyl-naphtho[1,8-bc]furan-5-one (14).

Prepared by formylation of (13) with dichloromethyl methyl ether - aluminium chloride in nitrobenzene[2]; m.p. 228 - 229°C (lit.[2] m.p. 228 - 229°C).

EXPERIMENTAL TO SECTION 2.2

12-Ethylenedithio-6aα,7,12,12aα-tetrahydro-1-phenyl--naphthaceno[1,12-bc]furan-6-one[26](16):

Anhydrous benzene (600 ml) was heated under reflux, in a nitrogen atmosphere for 3 h. The thioacetal (15) (1 g-2.27 mM) was added and traces of water were removed by distillation of 10% of the solvent. Freshly prepared lithium bis-(trimethylsilyl)-amide (94.7 mg - 0.57 mM) was indroduced and the solution was irradiated (3x750 W tungsten lamps) under reflux. After 1.5 h U.V. spectroscopy indicated complete disappearance of the starting material. The cooled solution was washed with a saturated aqueous potassium dihydrogen phosphate solution (2x100 ml) and water (1x100 ml). The organic phase was dried over sodium sulphate, and the solvent removed under reduced pressure. The residue was recrystallised from dichloromethane - methanol, giving the tetracyclic model ketone (16), 720 g (72%), m.p. 223°C (lit.[7] m.p. 221 - 228°C).

4-(2-trimethylenedithiomethyl-3,5-dihydroxy-4-methoxycarbonyl-benzyl)-2-phenylnaphtho[1,8-bc]furan-5-one[3](17; n=3)

The aldehyde (14) (1g- 2.21 mM) was suspended in glacial acetic acid (50 ml) and propane-1,3-dithiol (5 ml - 50 mM) and boron trifluoride etherate were added.

The solution was stirred at room temperature for 20 min. water was poured into the reaction, and the products extracted with chloroform. The organic layer was washed with water and dried over sodium sulphate. The solvent and excess dithiol were removed in vacuum, at 80°C, for 5 hours. The residue was recrystallised from chloroform - ethanol and gave the 1,3 dithiane (17; n=3) 1.15 g (97%), m.p. 195 - 196°C (lit.[3] m.p. 196 - 198°C).

4-(2-ethylenedithiomethyl-3,5-dihydroxy-4-methoxycarbonylbenzyl)--2-phenylnaphtho[1,8-bc]furan-5-one (17; n=2)

To the aldehyde (14) (200 mg - .45 mM) in benzene (6 ml), acetic acid (9 ml), and ethane-1,2-dithiol (1.2 ml - - .14 mM) was added boron trifluoride etherate (.5 ml). The solution was stirred at room temperature for 30 min. after which time the reaction was quenched by the addition of water. The organic layer was separated, washed with a saturated solution of sodium hydrogen carbonate till pH 7, water, and dried over sodium sulphate. Removal of solvent and excess ethane 1,2-dithiol in vacuum, at 80°C, for 5 h gave a residue which was recrystallised from ethyl acetate - ethanol to afford pale yellow crystals of 1,3-dithiolane (17; n=2), m.p. 145 - 147°C, ν max (nujol) 3 350, 1660, and 1630 cm^{-1}, λ max (CH_2Cl_2) 238, 252, 264, and 401 nm (ε=30 180, 26 230, 27 780 and 28 100)

δ ($CDCl_3$), 3.40 - 3.65 (4H, m), 4.1 (3H, s), 4.35 (2H, s), 5.40 (1H, s), and 7.30 ppm (1H, s), m/e, 530 (M^+), (Found; C, 65.06; H, 4.12; S, 12.08%. $C_{29}H_{22}O_6S_2$ requires: C, 65.64; H, 4.18; S, 12.08%.

Attempted preparation of 4-(2-ethylenediselenomethyl-3,5--dihydroxy-4-methoxycarbonylbenzyl-2-phenylnaphtho[1,8-bc]furan-5-one (18)

Pieces of sodium (28.6 mg - 1.25 mM) were added slowly to a suspension of 1,2,4,5-tetraselenocyclooctane (105 mg - .24 mM) in liquid ammonia (50 ml), under nitrogen, at -78°C, and the solution stirred for 1 h. After warming to room temperature, the residue was dissolved in dry, deoxygenated acetic acid (2 ml), and a solution of the aldehyde (14) (50 mg - .11mM) in acetic acid (3 ml), benzene (2 ml), and boron trifluoride etherate (6.5 ml) was introduced. After 2 h, water was added, and the solution extracted with dichloromethane. The organic layer dried over sodium sulphate, and the solvent removed under reduced pressure. An infrared spectrum revealed the absence of starting material (ν max, ($CHCl_3$) 3410 - 3300, 1645, and 1618 cm^{-1}). Purification by p.l.c. afforded 44.5 mg of a product. Recrystallisation attempts failed, as the compound decomposed on dissolution in dichloromethane.

Ethane-1,2-diselenocyanate[14](20)

Dried potassium selenocyanate (3.1 g - 21.5 mM) was dissolved in dry methanol in an atmosphere of nitrogen, and ethane-1,2-dibromide (.49 ml - 5.9 mM) was added to the stirred solution. Immediately crystals formed in the reaction flask. After 5 h, the solvent was removed under reduced pressure, and the residue recrystallised from ethanol giving ethane--1,2-diselenocyanate, 1.8 g (72%), m.p 137°C (lit.[14] 138°C).

1,2,4,5-tetraselenocyclooctane[14](21)

a) Ethane-1,2-diselenocyanate (122 mg - .51 mM) was added portionwise to a stirred solution of potassium hydroxide (150 mg) in methanol (1.1 ml), at 32°C, forming an yellow precipitate. After 1.5 h the precipitate was isolated, washed with water, and dried, giving 1,2,4,5-tetraselenocyclo-octane, m.p. 128°C (lit.[14] m.p. 129°C).

b) Attempted preparation of (21) using sodium in liquid amnonia[13]

Sodium (2.3 g - .1 M) was dissolved in liquid ammonia (300 ml), under a nitrogen atmosphere, with vigorous stirring, at -78°C. Selenium (7.8 g - .1M) was added, to form a brown suspension.

Ethane-1,2-dibromide (4.1 ml - .05 M) was introduced dropwise over 15 min,and the solution stirred for 3 h. After warming to room temperature (overnight), the residue was leached with hot chloroform. Removal of solvent and excess of ethane-1,2-dibromide under reduced pressure (35°C - 10 mmHg) failed to give any remaining products.

b) Attempted preparation of (21) using sodium borohydride.

To a stirred suspension of selenium (3 g - 38 mM) in absolute ethanol (150 ml), under nitrogen, at 0°C, sodium borohydride (1 g - 27 mM) was added. After initial evolution of a gas, the mixture was heated to boiling for 3 h. Ethane--1,2-dibromide (.49 ml - 6 mM) was added, the mixture heated under reflux for a further 3 h. After cooling and removal of the solvent, the residue was leached with hot dichloromethane. No product was, however, obtained.

Lithium bis-(trimethylsilyl)-amide[15] (LiBSA)

n-Butyl lithium (2.4 M; 1 ml) in pentane, was added slowly to a stirred solution of hexamethyldisilazane (370 mg - .48 ml) in tetrahydrofuran, under nitrogen atmosphere, at room temperature. Slow removal of the solvents in vacuum, gave white crystals of lithium bis(trimethylsilyl)-amide,

230 mg (61%), m.p. 69 - 70°C. (lit.[15] m.p. 71 - 72°C)

Sodium bis-(trimethylsilyl)-amide[41] (NaBSA)

A stirred solution of hexamethyldisilazane (810 mg - .55 mM) and sodamide (650 mg) in benzene (10 ml) was heated to reflux, in a nitrogen atmosphere for 5 h. The solvent was removed under reduced pressure, and the residue dissolved in hexamethyldisilazane (2 ml), filtered quicky under nitrogen, and the solvent removed. Recrystallisation from benzene afforded sodium bis-(trimethylsilyl)-amide, m.p. 164°C (lit.[41] m.p. 165 - 167°C).

Methyl, 12-ethylenedithio-6aα,7,12,12aα-tetrahydro-9,11--dihydroxy-6-oxo-1-phenyl-6H-naphthaceno[1,12-bc] furan-10--carboxylate (24)

Anhydrous benzene (300 ml- purified by passage through a silica gel column and distillation) was heated under reflux in a nitrogen atmosphere (oxygen free and dried) for 3 h. 1,3-dithiolane (17; n=2) (100 mg - .188 mM) was added, and traces of water were removed by distillation of 10% of the solvent. Freshly prepared lithium bis-(trimethylsilyl)-amide (7.8 mg - .047 mM) was introduced and the solution was irradiated (3x250 W tungsten lamps) under reflux. After 90 min U.V. spectroscopy indicated complete

disappearance of the starting material. The cooled solution was washed with saturated aqueous potassium dihydrogen phosphate solution (2x50 ml), and water (1x50 ml). The organic phase was dried over sodium sulphate and the solvent removed under reduced pressure. The resulting residue was recrystallised from chloroform - ethanol and gave the tetracyclic ester (24) 60 mg (60%), m.p. 243°C (with decomposition), ν max ($CHCl_3$), 1671, and 1629 cm^{-1} λ max ($CHCl_3$), 243, 266, and 349 nm (ε=26 170, 23 664, and 17 050), δ (^1H F.T. - 100MHz) ($CDCl_3$), 1.7 - 2.0 (1H, m), 2.80- 3.90(6H, m), 4.03 (3H, s), 4.73 (1H, d, J=5 Hz), 6.44 (1H, s), 7.26 - 7.99 (8H, m), 9.33 (1H, s), and 11.10 (1H, s), m/e, 530 (M^+, 39%), 470 (14%), 438 (22%), 256 (100%), 247 (98%), and 224 (99%), (Found: C, 65.43%; H, 4.26%, S, 12.46%. $C_{29}H_{22}O_6S_2$ requires C, 65.6%, H, 4.18%; S, 12.08%).

Experiments using different conditions are summarised in Table 1, (page 46). Initial deoxygenation time was extended to 18 h, the inert gas was changed to argon and the light source used became the tungsten - halogen "Atlas Al 233" lamp in the preparative scale reactions.

Attempted preparation of methyl, 6aα,7,12aα-trihydro-9,11--6,12-dioxo-1-phenyl-6H-naphthaceno[1,12-bc]furan-10--carboxylate (49)

a) In solution

Reactions employing different catalysts and solvents are summarised on Table 3 (pag. 55).

A typical experiment was conducted as follows:

A solution of the aldehyde (14) (50 mg - .11 mM) in dried and deoxygenated acetonitrile (500 ml) was irradiated (500 W tungsten lamp) under reflux. After 17 h, U.V. spectroscopy indicated the complete desappearance of starting material. After removal of the solvent, the residue was dissolved in chloroform, and the dark solution stirred with activated charcoal for ½ h . After removal of the charcoal, compound (49) was crystallised from chloroform - methanol, λmax 253, 292, 337, and 358 nm (shoulder) (ε=18 405, 15 800, 14 360, and 12 980), m/e 454.

b) Solid State Photolysis

All the different conditions tried in this reaction are summarised on Table 4 (pag.56).

A typical experimet was conducted as follows:

Dried and finely powdered aldehyde (14) (10 mg) was irradiated (500 W tungsten lamp) for 24 h, in an inert

atmosphere, at 15 C. The starting material was recovered unchanged, m.p. 227 - 228°C (lit.[2] m.p. 228 - 229°C).

EXPERIMENTAL TO SECTION 2.3

12-Ethylenedithio-6aα,7,12aα-tetrahydro-9,11-dihydroxy-6-oxo--1-phenyl-6H-naphthaceno[1,12-bc]furan-10-carboxamide (53)

a) The tetracyclic ester (24) (100 mg - .19 mM) was added to a tetrahydrofuran - aqueous solution (2/1; 15 ml), which had been previously saturated with ammonia gas. The solution was stirred for 24 h, at room temperature. A saturated aqueous potassium dihydrogen phosphate solution was added, and the mixture extracted exaustively with chloroform. The organic layer was washed with water, dried over sodium sulphate, and the solvent removed under reduced pressure. The residue was recrystallised from dichloromethane - light petroleum ether, and gave the tetracyclic amide (53), 71.9 mg (70%), m.p. 210°C (with decomposition), ν max (nujol), 3403, 3300 - 3100, 1703, 1682, 1655, and 1618 cm^{-1}, λ max ($CHCl_3$) 258, 276, and 350 nm (ε=12 929, 12 402, and 10 726), δ(^{1}H F.T., 100 MHz), ($CDCl_3$), 2.89 - 4.15 (m), 4.91 (1H, d, J=4.8 Hz), 6.54 (1H, s), 7.29 - 8.01 (8H, m), 8.70 (1H, s) and 10.10 (1H, s), m/e, 515 (M^+), 455 (8%), 438 (12%),

247 (92%), 241 (88%), and 224 (100%), (Found: C, 65.32; H, 4.18; N, 2.72%. $C_{28}H_{21}NO_5S_2$ requires: C, 65.22; H, 4.11; N, 2.72%)

b) To a stirred suspension of the tetracyclic ester (500 mg - .95 mM) in diglyme (7 ml), an aqueous solution of ammonia (35%; 5 ml) was added, at room temperature. After 4 to 5 h all the starting material had been consumed (t.l.c. analysis) and the resulting solution was cooled in an ice bath, and neutralised with dilute hydrochloric acid (2N), and precipitation occured. Recrystallisation from methanol afforded the tetracyclic amide (53), 375 mg (77%), m.p. 209°C.

12-Ethylenedithio-6aα,7,12,12aα-tetrahydro-6β,9,11-trihydroxy-6α-methyl-1-phenyl-6H-naphthaceno[1,12-bc]furan-10-carboxamide (54)

a) Using ethereal methyl lithium

The tetracyclic amide (50 mg - .095 mM), in anhydrous tetrahydrofuran (previously kept at reflux temperature, under a nitrogen atmosphere, for 3 h) (50 ml), cooled to -78°C, was treated with a large excess of ethereal methyl lithium (1.8 M - 1.8 ml) under nitrogen. The reaction was quenched with an aqueous saturated solution of ammonium chloride (5 ml) at -78 C, and the mixture allowed to warm to 0°C. The solution was exaustively extracted with chloroform,

The organic phase was separated, washed with water, dried over sodium sulphate, and the solvent removed under reduced pressure. Crystallisation of the residue from chloroform - methanol afforded the tetracyclic carbinol (54), 25.2 mg (48.9%), m.p. 198 - 200°C (with decomposition), ν max ($CHCl_3$), 3500, 3400 - 3250, 1702, 1654, and 1603 cm^{-1} λ max (CH_2Cl_2), 250, 296, 312, and 324 nm (ε=14 390, 14 360, 14 390, and 14 140), δ,(^{1}H F.T., 100 MHz) ($CDCl_3$), 1.58 (3H, s), 2.70 - 4.06 (m), 4.84 - 4.89 (1H, d, J=5Hz), 6.52 (1H, s), 7.38 - 8.00 (8H, m), and 10.00 (1H, s), m/e, 513 (M^+ - H_2O, 100%), 453 (75%), 436 (79%), 241 (92%), and 224 (99%), (Found: C; 65.26; H, 4.67; N, 2.47%. $C_{29}H_{25}NO_5S_2$ requires C, 65.52; H, 4.74; N, 2.63%).

b) Improved procedure

The tetracyclic amide (53) (100 mg - .189 mM) in anhydrous tetrahydrofuran (50 ml) (previously kept at reflux temperature, under a nitrogen atmosphere for 3 h), cooled to -78°C, was treated with a large excess of ethereal methyl lithium (1.8 M; 4 ml), under nitrogen. The reaction was quenched with an aqueous saturated solution of ammonium chloride (5 ml) at -78°C, and the mixture allowed to warm to 0°C. The solution was passed through a column of sodium sulphate, and the solvent removed under reduced pressure.

The residue was recrystallised from dichloromethane - methanol affording the tetracyclic carbinol (54) 74.2 mg (72%), m.p. 198 - 200 C (with decomposition).

c) Attempted methylation with methyl magnesium iodide

A solution of the tetracyclic amide (53) (25 mg - .047 mM) in anhydrous and deoxygenated tetrahydrofuran (30 ml), cooled to -78°C, was treated, for a period of ½ h, with a 100 fold excess of ethereal methyl magnesium iodide, prepared from magnesium turnings (300 mg) and methyl iodide (1.8 g), under nitrogen. The reaction mixture was allowed to warm to 0°C, and a saturated aqueous ammonium chloride solution was added. The liquid phase was decanted, passed through a sodium sulphate column, and the solvent removed under reduced pressure. The residue was recrystallised from dichloromethane - methanol, and the tetracyclic amide (53), 20 mg, m.p. 209°C, recovered unchanged.

12-Ethylenedithio-6aα,7,12 12aα-tetrahydro-6β-hydroxy--6α-methyl-1-phenyl -naphthaceno[1,12-bc]furan (60)

A stirred solution of the tetracyclic model ketone (16; n=2) (300 mg - .68 mM) in anhydrous tetrahydrofuran (30 ml) (previously kept at reflux temperature, under a nitrogen atmosphere, for 3h), cooled to -78°C, was treated with a large excess of ethereal methyl lithium (1.67 M, 3 ml) under nitrogen. The reaction was quenched with an aqueous saturated solution of ammonium chloride (5 ml), at -78°C, and the mixture allowed to warm to 0°C. The liquid phase was decanted, passed through a sodium sulphate column, and the solvent removed under reduced pressure. The mixture of tetracyclic model carbinol (60) and starting material (t.l.c. analysis) was submited to the same process three times, until all the starting material disapeared (t.l.c. analysis). Recrystallisation from dichloromethane - methanol afforded the tetracyclic model carbinol - 62 mg (20%), m.p. 217 - 218°C (lit.[7] m.p. 218 - 220°C).

12-Ethylenedithiomonosulphoxide-6aα,7,12,12aα-tetrahydro--6β-hydroxy-6α-methyl-1-phenyl-6H-naphthaceno[1,12-bc]furan (61)

A solution of the model tetracyclic carbinol (60) (40 mg - .088 mM) in dry dichloromethane (5 ml), was treated with ozone at -78°C. After 1.5 h excess ozone was removed by passage of a stream of nitrogen, and dimethyl sulfide (1 ml) was added. Partial evaporation of the solvent induced crystallisation of the sulphoxide (61) - 15 mg (36%), m.p. 146°C, ν_{max} 1040 cm^{-1} λ_{max} (EtOH), 208, and 306 nm (ϵ=30 722, and 16 314).

12-Ethylenedithiomonosulphoxide-6aα,7,12,12aα-tetrahydro--1-phenyl-naphthacene[1,12-bc]furan-6-one (64)

A stirred solution of the tetracyclic model ketone (16; n=2) (50 mg - .11mM) in dried dichloromethane, was treated with metachloroperbenzoic acid (96%; 25 mg - .15 mM) at -78°C, under nitrogen. After 5 min., water was introduced, the organic phase dried over sodium sulphate, and the solvent removed under reduced pressure. Crystallisation from dichloromethane - light petroleum ether, afforded the sulphoxide (64): 40 mg (77%), m.p. 161 C (lit.[26] m.p. 161 C).

Methyl,12-ethylenedithio-6aα,7,12,12aα-tetrahydro-9-ethylcarbonate--11-hydroxyl-6-oxo-1-phenyl-6H-naphthaceno[1,12-bc]furan-10--carboxylate (66).

To a stirred solution of the tetracyclic ester (24) (200 mg - .38 mM) and tetrabutylammonium hydrogen sulphate (300 mg - .89 mM) in chloroform (ethanol free) (5 ml), an aqueous sodium hydroxide soltion (.1 N, 14 ml) was added at room temperature, under nitrogen. After 1 h, the dark organic phase was separated from the aqueous solution which was repeatedly washed with ethanol free chloroform. The organic phase was then dried over sodium sulphate, and the solvent partially removed under reduced pressure. Ethyl chloroformate (.1 ml) was introduced, the solvent was removed under reduced pressure, and the residue chromatographed in a silica gel column (MFC / GF_{254} silica; 1/1). Elution with dichloromethane -- benzene (4:1) followed by crystallisation from ethanol, gave the tetracyclic monocathylate (66): 120 mg (53%), m.p. 199 - 200°C, νmax ($CHCl_3$), 1767, 1698, 1670, and 1622 cm^{-1} λmax ($CHCl_3$), 246, 280, and 355 nm (ε=27 630, 24 660, and 17 980), δ ($CDCl_3$), 1.40 (3H, t), 2.70 - 3.60 (m), 3.80 (3H, s), 4.32 (2H, q), 4.70 (2H, d), 6.70 (1H, s), and 7.21 - 8.10 (m), m/e, 602 (M^+), 541, 328, 296, 256, and 224, (Found: C, 63.95; H, 4.26; S, 11.17%. $C_{32}H_{26}O_6S_2$ requires: C, 63.77; H, 4.35; S, 10.64%).

Methyl, 12-ethylenedithio-6aα,7,12,12aα-tetrahydro-9,11-diethyl-carbonate-6-oxo-1-phenyl-6H-naphthaceno[1,12-bc]furan-10--carboxylate (67)

To a stirred solution of tetracyclic monocathylate (66) (36 mg - .06 mM) in freshly dried tetrahydrofuran, an excess of potassium hydride was added, under nitrogen, at room temperature. After ½ h, ethylchloroformate (.1 ml) was introduced, and the system heated under reflux, for ½ h. The solvent was removed under reduced pressure, and the residue was chromatographed in a silica column (MFC / GF_{254} silica; 1/1). Elution with dichloromethane-ethyl acetate (100:5) and crystallisation from ethyl acetate - methanol and benzene - methanol afforded the tetracyclic dicathylate (67): 22 mg (55%), ν max ($CHCl_3$), 1768, 1731, 1698 (sh), 1672 (sh), 1660, and 1615 cm^{-1}, λ max (CH_2Cl_2), 242, 278, and 355 nm (ε=29 160, 25 430, and 17 860), δ (^1H F.T., 100 MHz) ($CDCl_3$), 1.20 (3H, t), 1.38 (3H, t), 1.74 (3d), 2.74 - 3.74 (m), 3.78 (3H, s), 4.14 (2H, q), 4.52 (2H, q), 4.70 (d, J=5Hz), 7.06 (1H, s), and 7.26 - 8.0 (m) ppm, m/e 674 (M^+, 25%), 613 (15%), 541 (23%), 436 (54%), and 224 (100%), (Found: C, 62.01, H, 4.42%; $C_{35}H_{30}O_{10}S_2$ requires C, 62.30; H, 4.48%).

N-Ethoxycarbonyl, 2,6-ethoxycarbonate-3,4-dimethylbenzamide (68)

To a stirred solution of 2,6-dihydroxy-3,4-dimethylbenzamide (68; $R_1=R_2=R_3=H$) (90 mg - .5 mM) in dried tetrahydrofuran (5 ml), was treated with an excess of potassium hydride. After ½ h an excess of ethylchloroformate (.5 ml) was added. The solvent was removed under reduced pressure, the residue washed with dilute aqueous hydrochloric acid (1N) and extracted with ethylacetate. The resulting oil was purified by p.l.c., followed by crystallisation from diethyl ether, affording the tricathylate (68; $R_1=R_2=R_3=CO_2Et$): 170 mg (87%), m.p. 110°C, νmax, 1770, 1730, and 1700 cm^{-1} λ max (CH_2Cl_2) 258, and 295 nm (ε= 42 290, 28 250), δ($CDCl_3$) 1.40 (9H, t), 2.15 (3H, s), 2.25 (3H, s), 4.3 (6H, q) and 7.00 (1H, s) ppm, m/e 397 (M^+), 353, and 325, (Found: C, 54.56; H, 5.94; N, 3.45%. $C_{18}H_{23}NO_9$ requires C, 54.40; H, 5.38; N, 3.52%).

Cathylation of the tetracyclic amide (53)

To a stirred solution of the tetracyclic amide (53) (150 mg - .29 mM) and tetrabutylammonium hydrogen sulphate (200 mg - .59mM) in chloroform (ethanol free), an aqueous sodium hydroxyde solution (.1N - 15 ml) was added, at room temperature, under nitrogen. After 1 h, the dark organic phase was separated from the aqueous solution which was repeatedly washed with chloroform (ethanol free). The organic phase

was then dried over sodium sulphate, and the solvent partially removed under reduced pressure. Ethyl chloroformate (.005 ml) was introduced. After 10 min. at room temperature, the solvent was removed. A part of the residue was purified by column chromatography and crystallised from methanol, giving the monocathylate (69): ν max ($CHCl_3$) 3500, 3380, 1777, 1695, 1653, and 1605 cm^{-1}; δ (^1H F.T., 100 MHz) ($CDCl_3$) 1.40 (3H, t), 1.86 (1H, 3d), 2.90 (2H, m), 3.16 (1H, d), 3.48 (2H, m), 3.84 (1H,d), 4.32 (2H, q), 4.66 (1H, d, J=5 Hz), 5.6 - 5.8 (br, m), 6.62 (1H, s), and 7.34 - 8.0 (m).

Another part (64.8 mg - .11 mM) of the residue was dissolved in freshly dried tetrahydrofuran (5 ml), and an excess of potassium hydride added, under nitrogen, at room temperature. After ½ h, ethylchloroformate (.1 ml) was introduced and the system heated to reflux for 1 h. The solvent was removed, and the residue chromatographed on a silica column (MFC/GF_{254} silica, 1:1). Elution with dichloromethane - ethylacetate (100;5) and crystallisation from ethyl acetate - methanol afforded compound (70): 40.8 mg (47.3%), ν max ($CHCl_3$), 1790 - 1774, 1700, and 1618 cm^{-1}; δ ($CDCl_3$), 1.10 - 1.60 (6H, m), 2.80 - 4.00 (7H, m), 4.10 - 4.21 (4H, m), 4.80 (1H, d), 7.22 - 8.00 (9H, m), m/e 685, 641, 613, and 247.

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