

STUDIES RELATED TO THE SYNTHESIS
OF TETRACYCLINE

a thesis presented by

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in partial fulfilment of the requirements
for the award of
the degree of

DOCTOR OF PHILOSOPHY

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September 1975

To my family.

He who knows, and knows that he knows,
is a wise man; seek him.

He who knows not, and knows that he knows not,
is a child; teach him.

He who knows not, and knows not that he knows not,
is a fool; shun him.

(Arabian).

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Clive Dawes,
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Imperial College.

September 1975.

ABSTRACT

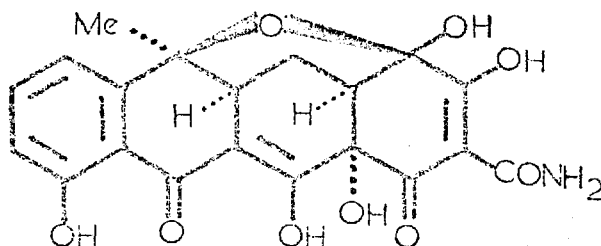
The first chapter is divided into two sections:

1st. Section

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

2nd. Section

An outline of some major achievements in these laboratories towards the synthesis of tetracycline; also a brief description of the projected route to the cyclooxide (A).



A.

PART I

Modification of established methods for the preparation of ring A and CD bicyclic precursors for the synthesis of tetracycline.

PART II

Investigation of potential acetalisation reagents and the establishment of diethylene orthocarbonate* (B) as an active

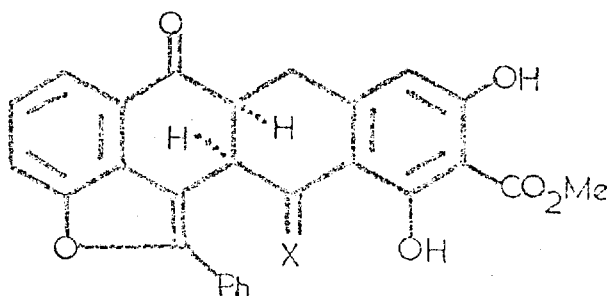
transacetalisation reagent.



B.

PART III

The cyclisation of tricyclic ACD compounds to form tetracyclic intermediates of the type (C). Where X is a substituent that is readily convertible into a carbonyl group.



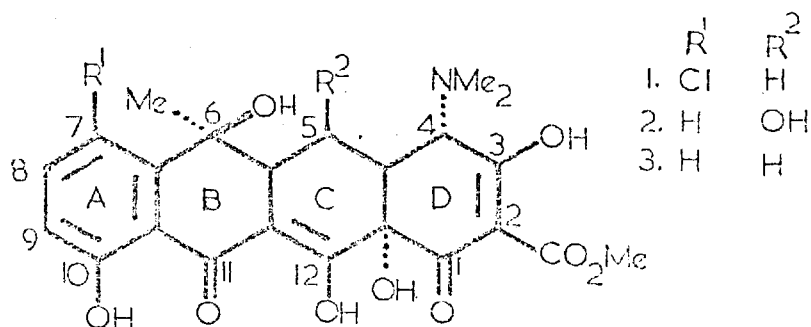
C.

* A new acetalisation reagent: Ethylene orthocarbonate. D.H.R. Barton, C.C. Dawes, P.D. Magnus, J.Chem. Soc. (C), 1975, 432-433.

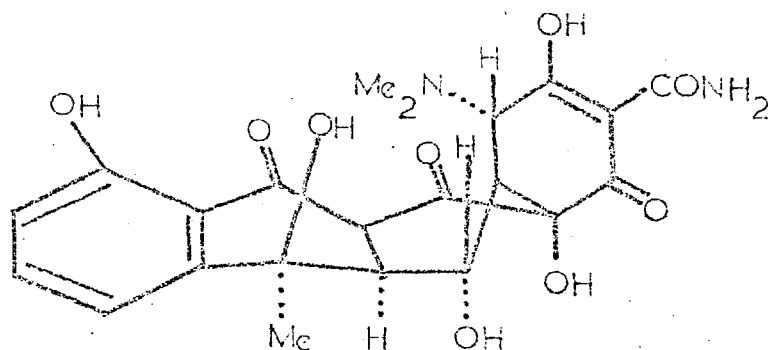
INTRODUCTION

The tetracyclines are a series of closely related compounds produced in nature by various strains of streptomyces. These compounds act as antibiotics by inhibiting the growth of bacterial protein.

Aureomycin (1) was the first member of the series to be isolated, and was obtained from a culture of streptomyces aureofaciens.¹ Terramycin (2) was isolated two years later from streptomyces rimosus.² Utilisation of spectral methods determined the structure of terramycin³ and that of aureomycin⁴ followed. The parent tetracycline (3) was isolated from streptomyces alboniger and was shown to be identical with the hydrogenolysis product of aureomycin.^{5,6,7}



The tetracycline and aureomycin molecules possess five asymmetric centres: C-4, -4a, -5a, -6 and -12a, whilst terramycin with its C-5 hydroxyl function possesses six asymmetric centres. X-ray analysis has confirmed the assigned structures of terramycin⁸ and aureomycin.^{9,10} The relative configuration of the C-5 hydroxyl in terramycin (4) was deduced from n.m.r. data.¹¹

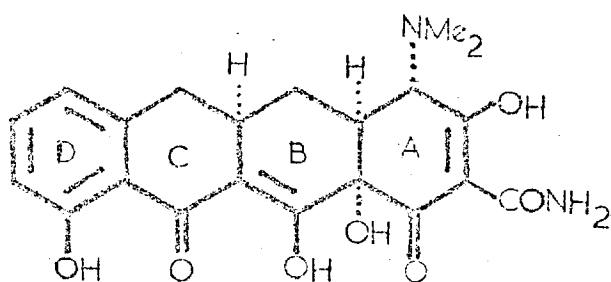


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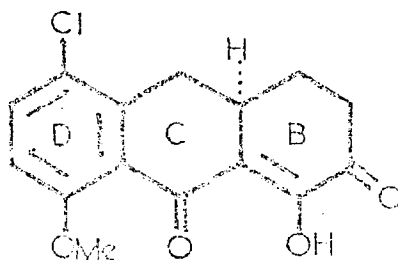
The structure-activity relationship which prevails in the tetracyclines has been moderately well defined. Defunctionalisation at positions 5, 6 and 7 may be carried out without appreciable loss of antimicrobial properties. Epimerisation at C-5a and C-4 or dehydration at C-5a-C-11a results in loss of activity. The natural α -configuration at C-4 is essential; equilibration involving C-4 leads to relatively inactive 4-epi-tetracyclines.^{12,13} It has been postulated that the principal active centre is the C-11, C-12 diketone system of rings B and C.^{14,15,16}

Recent achievements in the field of tetracycline synthesis

The first synthesis of a tetracyclic molecule exhibiting anti-microbial properties was carried out by Woodward in 1962.¹⁷ The compound obtained was dl-6-demethyl-6-deoxytetracycline (1). The precursor in the form of a DCB unit, was the diketone (2).

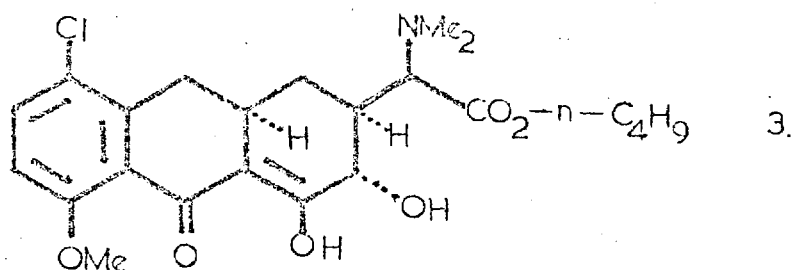


1.

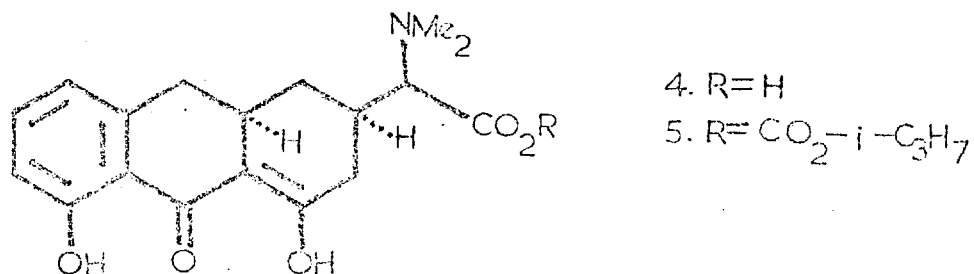


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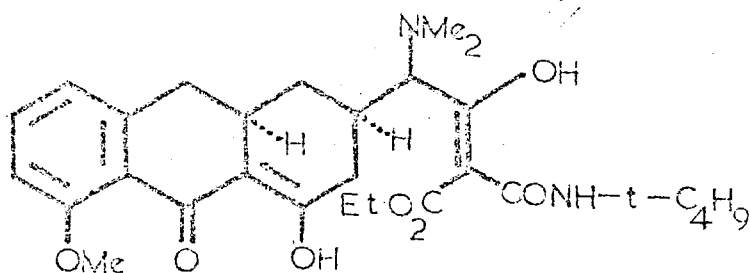
Conjugate addition of dimethylamine to the glyoxidene derivative of (2), followed by reduction by sodium borohydride gave (3). Lactone formation, followed by two reductive processes gave (4).



Treatment of the acid (4) with isopropyl chloroformate gave the mixed anhydride of (5). Subsequent treatment with the ethoxy-



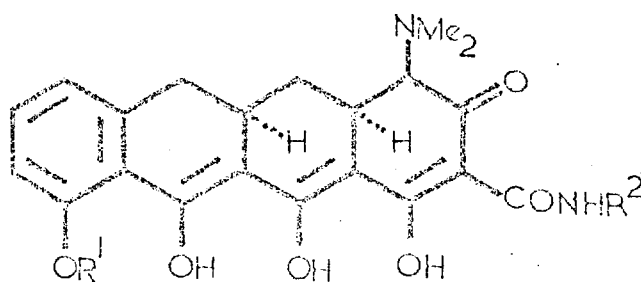
magnesium derivative of ethyl-N-t-butylmalonate gave the amide (6). The action of sodium hydride in dimethylformamide produced (7). Treatment of (7) with hydrobromic acid produced the tetracyclic compound (8). 12a - Hydroxylation was achieved by careful treatment of the 12a-deoxytetracyclic hydrochloride, with



6.

cerous ion-oxygen affording 6-demethyl-deoxytetracycline (1).

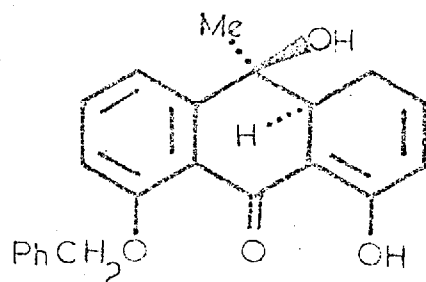
The 12a-hydroxylation proceeded in only 6.5% yield.



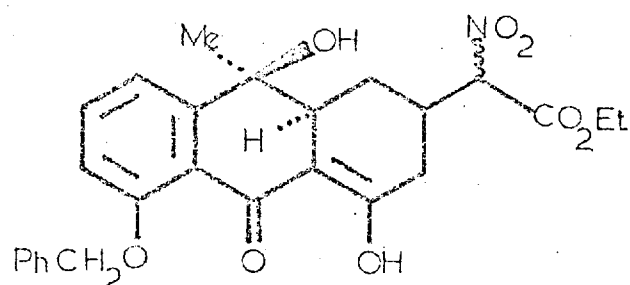
7. $R^1 = \text{Me}, R^2 = t\text{-C}_4\text{H}_9$.

8. $R^1 = \text{H}, R^2 = \text{H}$.

The first total synthesis of tetracycline was achieved by Shemyakin and co-workers in 1967.¹⁸ A six stage sequential conversion from juglone gave the dienediolone (9). Treatment of (9) with the triethyl ammonium salt of ethyl nitroacetate gave the nitroester (10) as an epimeric mixture. Further transformations via the amide (11), culminating in the tetracyclic 6-deoxy-compound

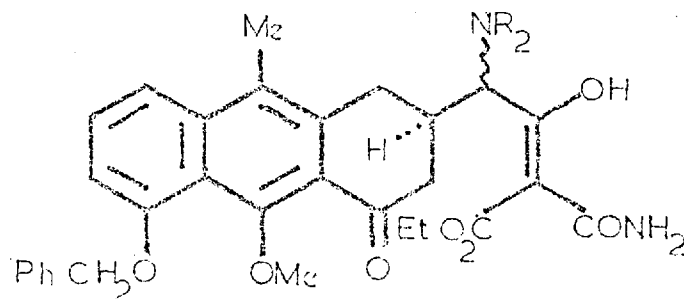
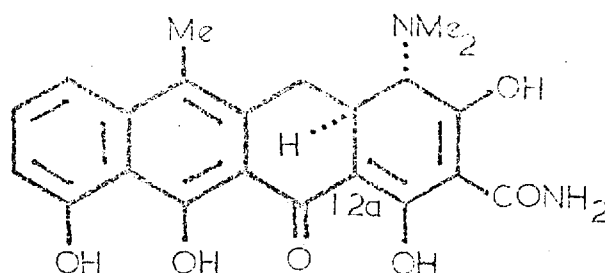


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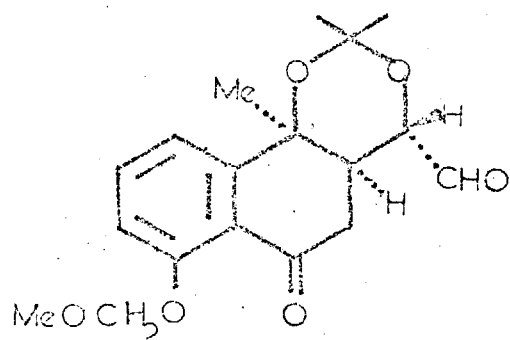
(12) as a racemic mixture, constitute the total synthesis since the (-) component of the racemic mixture has been converted to tetracycline by 12 a-hydroxylation,¹⁹ followed by photooxidation²⁰ and reduction.²¹

11. R₂ = phthal.

12.

The work of Muxfeldt²² (1968) has led to a spectacular synthesis of dl-tetracycline. Combination of the three units 13-15 by stepwise carbanionic condensations gave the tetracyclic compound (16). The methoxy-methyl group was removed at the 10-position,

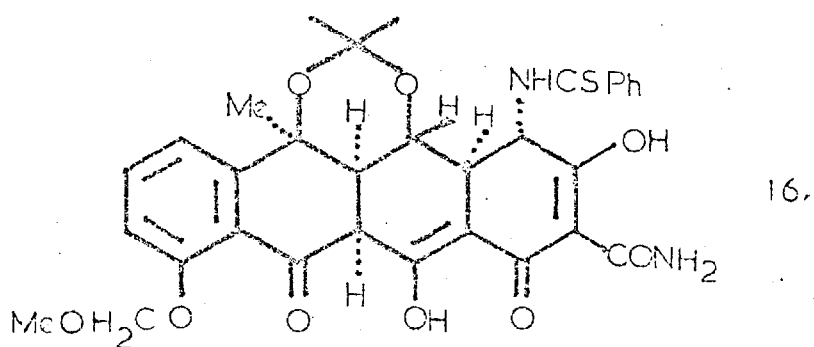
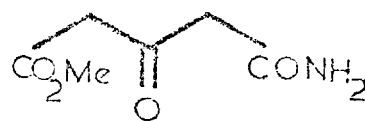
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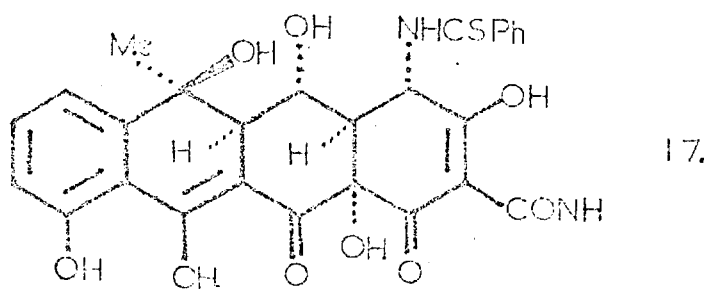
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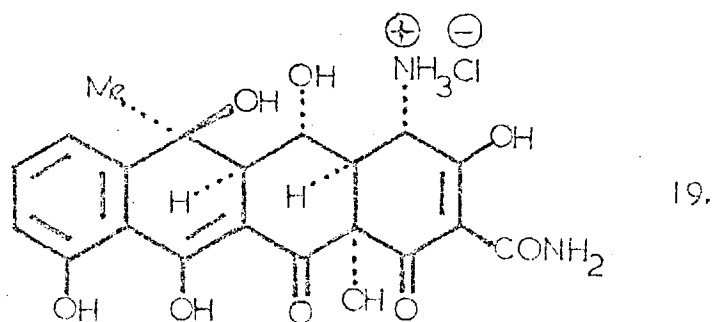
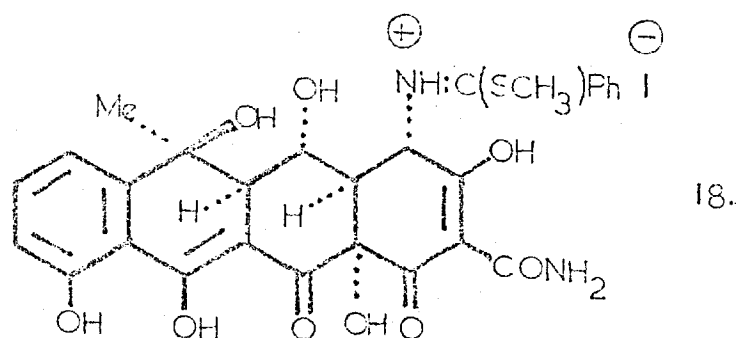
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and 12a-hydroxylation was carried out in basic media with molecular



oxygen. Deacetalisation by mild acid treatment gave (17).
Methylation with methyl iodide afforded (18), which on acid

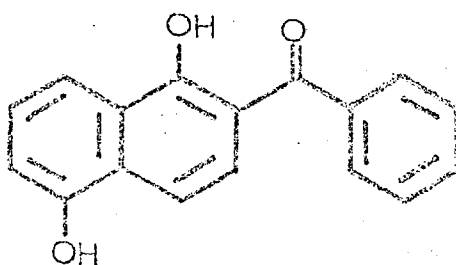


hydrolysis gave the crystalline hydrochloride (19). Alkylation to give terramycin was achieved by treatment with dimethyl sulphate.

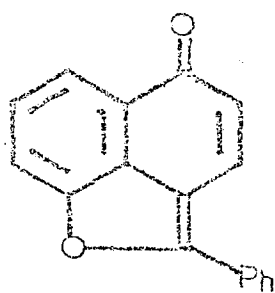
Synopsis of previous work

The pathway employed at Imperial College for the synthesis of tetracycline involves the construction of an ACD unit formed by condensation of a suitably functionalised aromatic ring A and a protected DC moiety. Subsequent formation of ring B may then be afforded by cyclisation. A large amount of the work carried out in these laboratories has been published.²³⁻³²

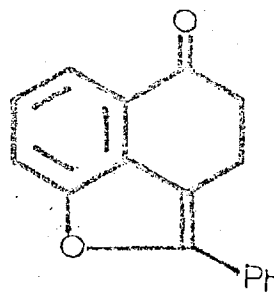
Preliminary experiments designed to produce the phenolic ketone (1) by condensation of 1,5-dihydroxynaphthalene with benzoic acid in the presence of zinc chloride as catalyst, in fact gave rise to an unexpected major product the



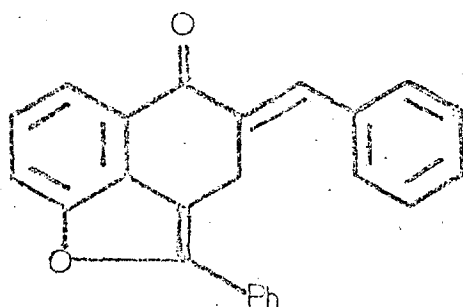
perinaphthofuran²⁴ (2). The value of this compound as a potential CD component soon became apparent when several experiments were carried out to determine its suitability. Hydrogenation over Raney nickel gave the dihydro-compound (3). Treatment with benzaldehyde in concentrated sulphuric acid and glacial acetic acid yielded the enone (4) and subsequent reduction over Raney nickel led to the dihydro-ketone (5). Treatment with MeMgI led



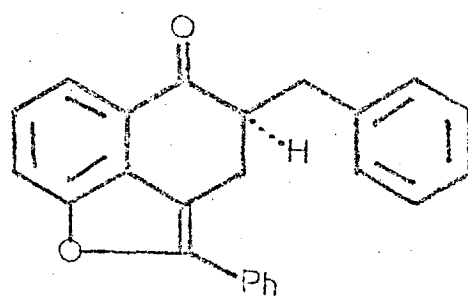
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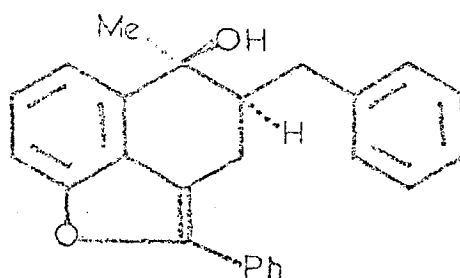


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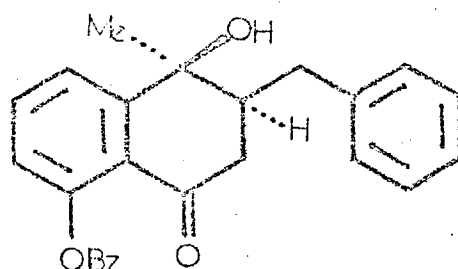
5.

to the carbinol (6), and ozonolysis led to the keto-benzoate (7).



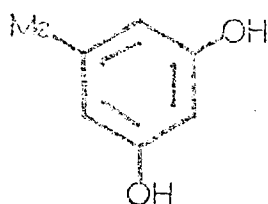
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In principle the problems of functionality and stereochemistry in rings C and D had thus been solved.

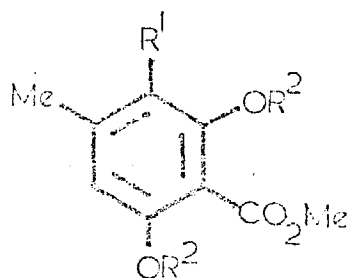


7.

Various suitably substituted ring A precursors have been synthesised. Commercially available orcinol (8) has provided a suitable starting material for these precursors. Carboxylation,³³

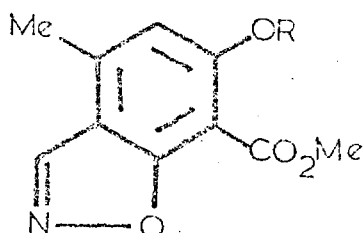


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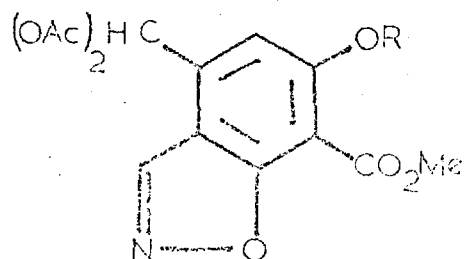
9.

followed by methylation of the carboxyl group,^{24,34} provided the known ester (9; $R^1=R^2$). The classical Gatterman reaction gave excellent yields of the formyl derivative (9; $R^1=CHO$, $R^2=H$).²⁴ When the corresponding oxime (9; $R^1=CH:N.OH$, $R^2=H$) was treated with acetic anhydride at 95° followed by pyrolysis in refluxing toluene the isoxazole (10; $R=H$) was formed.



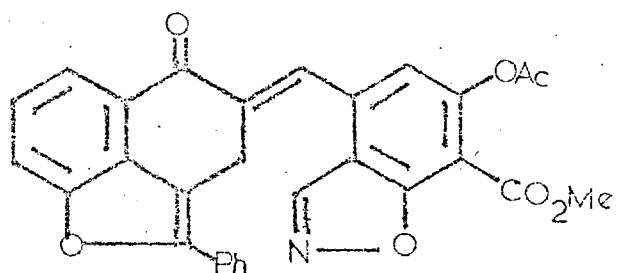
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Oxidation of the corresponding acetate (10; R=Ac) by the Thiele method, gave the formyldiacetate (11; R=Ac) but only in poor

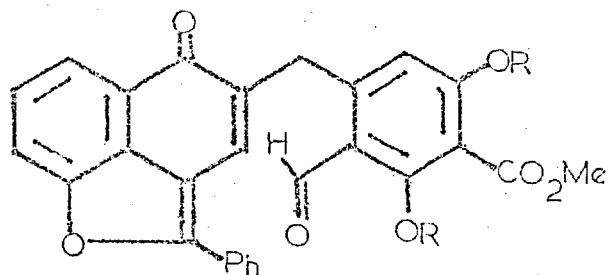


11.

yield (30%). Subsequent condensation of the isoxazole with the pernaphthofuran (3) yielded the tricyclic compound (12). However, in order to obtain the required endocyclic compound (13; R=Me) a cumbersome reduction-dehydrogenation sequence had to be employed, since catalytic reduction required for



12.



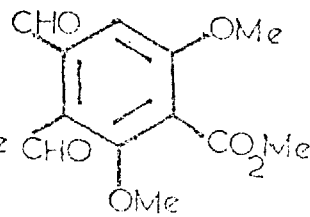
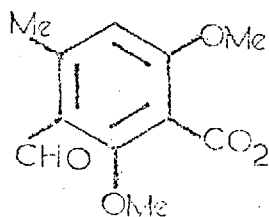
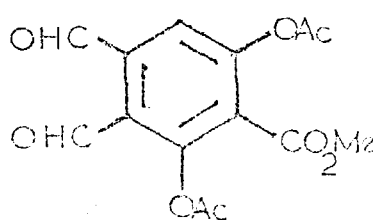
13.

isoxazole ring opening was found to reduce the C-5-C-5a double bond in the tricyclic compound (12). Further, the convenient

14.

15.

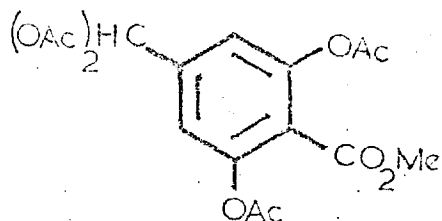
16.



method of rearranging the exocyclic C-5 - C-5a double bond by refluxing in triethylamine could not be employed because of the extreme sensitivity of the isoxazole to such conditions.

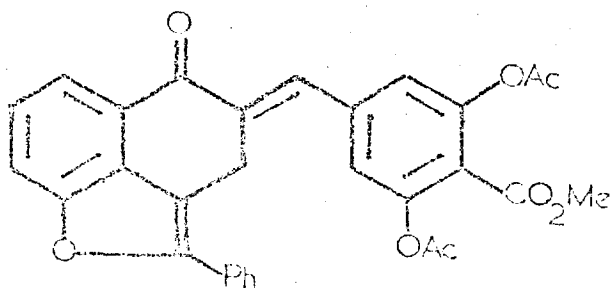
All attempts to prepare the substituted phthalaldehyde Ring A precursor ²⁵(14) were unsuccessful. Attempted oxidation of the methyl group in the aldehyde (15) to form the phthalaldehyde

(16)²⁵ led to attack on the formyl function. The formyldiacetate
 (17)²⁹ was synthesised by the oxidative acetylation (Thiele)



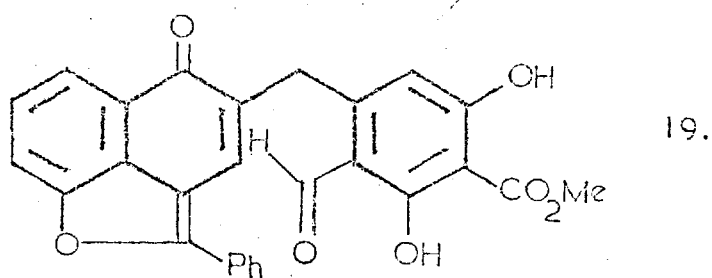
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of (9; R¹=H, R²=Ac) in the presence of acetic acid, acetic anhydride, sulphuric acid and chromium trioxide. This compound

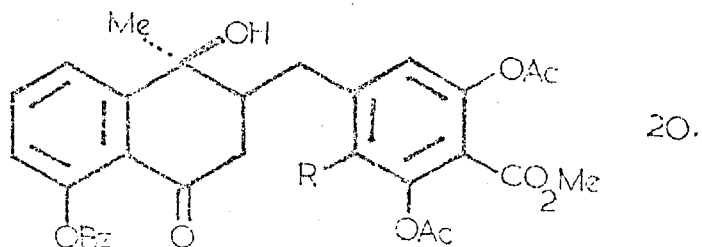


18.

was condensed with the dihydroperinaphthofuran (3) under acidic conditions to form the benzilidene compound (18) in good yield. De-acetylation under acid conditions followed by rearrangement of the exocyclic double bond by refluxing in triethylamine and finally formylation by the action of dichloromethyl-methyl

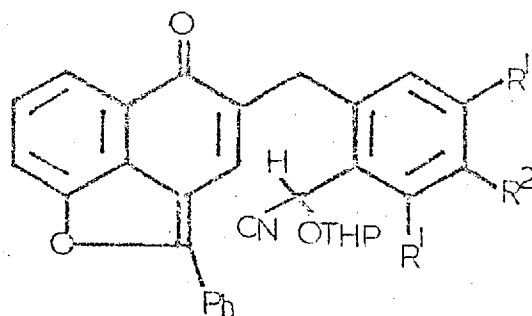


ether in the presence of aluminium trichloride led to the aldehyde (19).



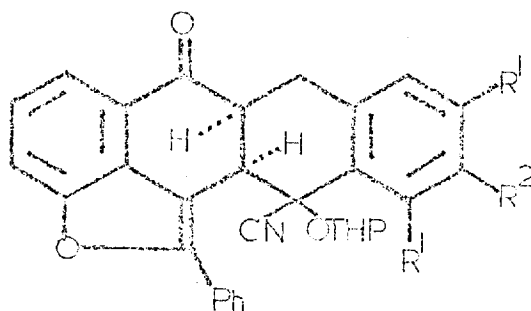
Various approaches have been employed to attempt the cyclisation of suitably substituted AGD compounds to generate a tetracyclic skeleton. The keto nitrile (20; $R=CN$) and the corresponding ester (20; $R=CO_2Me$), were subjected to various basic media in order to induce ring closure by a Dieckmann type reaction.²⁴ All attempts were unsuccessful.

Attempts were also made to induce ring closure by a Michael type cyclisation via the cyanohydrin tetrahydro-pyranyl ether (21).²⁵ The model ring A unsubstituted compound (21; $R^1=R^2=H$) was found to cyclise



21.

readily in the presence of sodium tertiary butoxide to form the tetracyclic compound (22; $R^1=R^2=H$). The reaction could not, however, be extended to the ring A substituted compound-

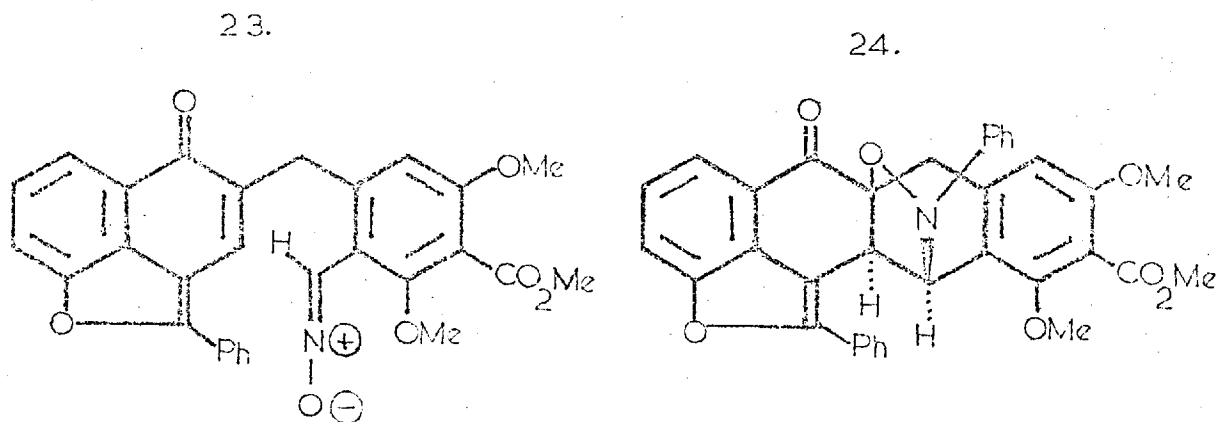


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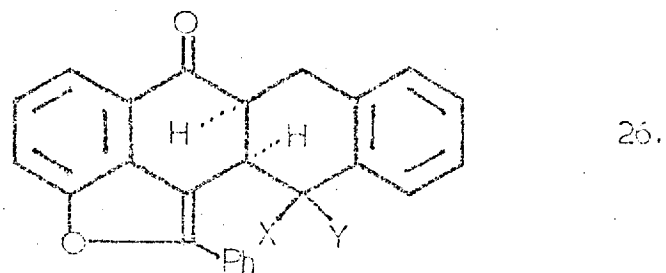
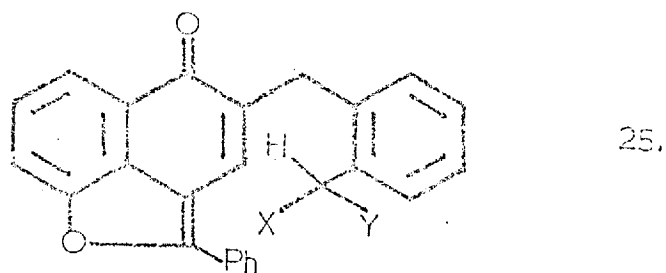
(21; $R^1=OH$, $R^2=CO_2Me$).

Closure by an alternative method, namely 1:3 dipolar addition²⁶, was attempted using the nitron (23), which was prepared by the action of phenyl hydroxylamine on the aldehyde (13; $R=Me$). Although the desired cyclised product (24) was

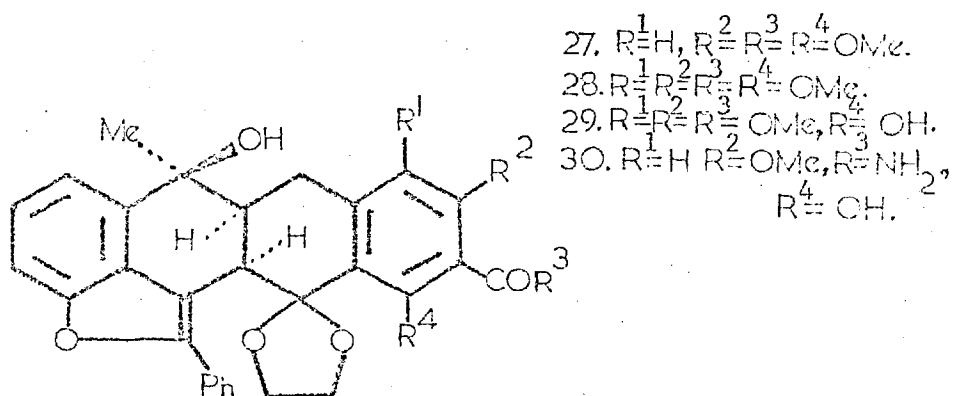
obtained, it could not be converted to the required 12-keto compound.



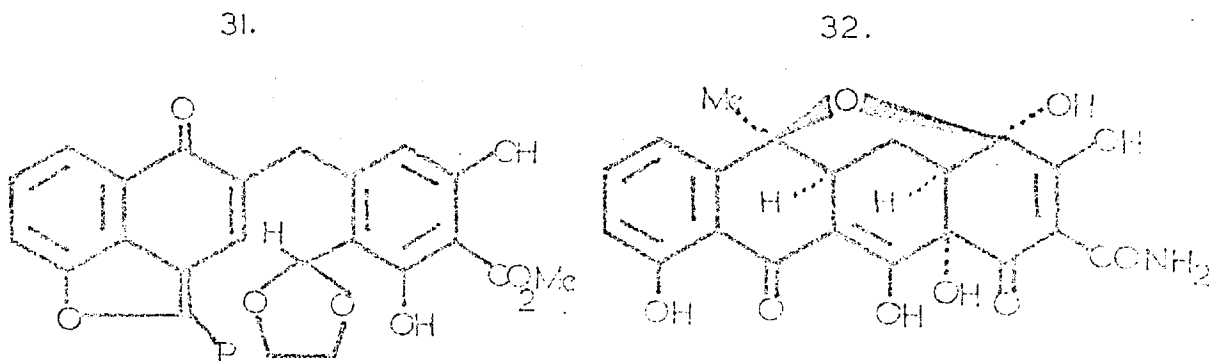
A photochemical²⁷ method of ring closure was then developed facilitating the transformation of the acetals (25; XY = $-\text{OCH}_2\text{CH}_2\text{O}-$, XY = $-\text{OCH}_2\text{CH}_2\text{S}-$, XY = $-\text{SCH}_2\text{CH}_2\text{S}-$) to the corresponding tetracyclic acetals (26; XY = $-\text{OCH}_2\text{CH}_2\text{O}-$, XY = $-\text{OCH}_2-\text{CH}_2\text{S}-$, XY = $-\text{SCH}_2\text{CH}_2\text{S}-$). The principle was found to be readily



applicable to ring A substituted ACD tricyclic compounds giving rise to the corresponding acetals (27),²⁹ (28),³⁰ (29)³² and (30).³⁵ It is now hoped that the acetal (31) may be transformed

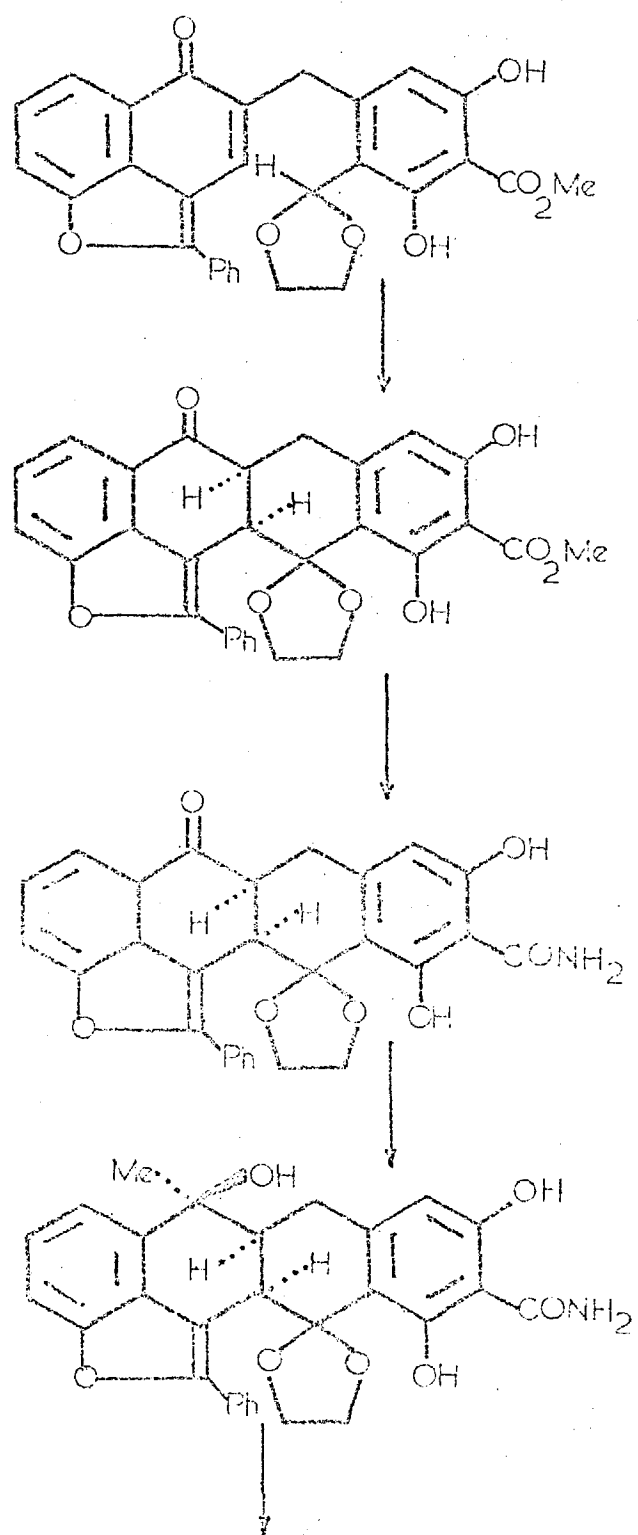


(according to scheme 1) into the cyclooxide (32). Since it is

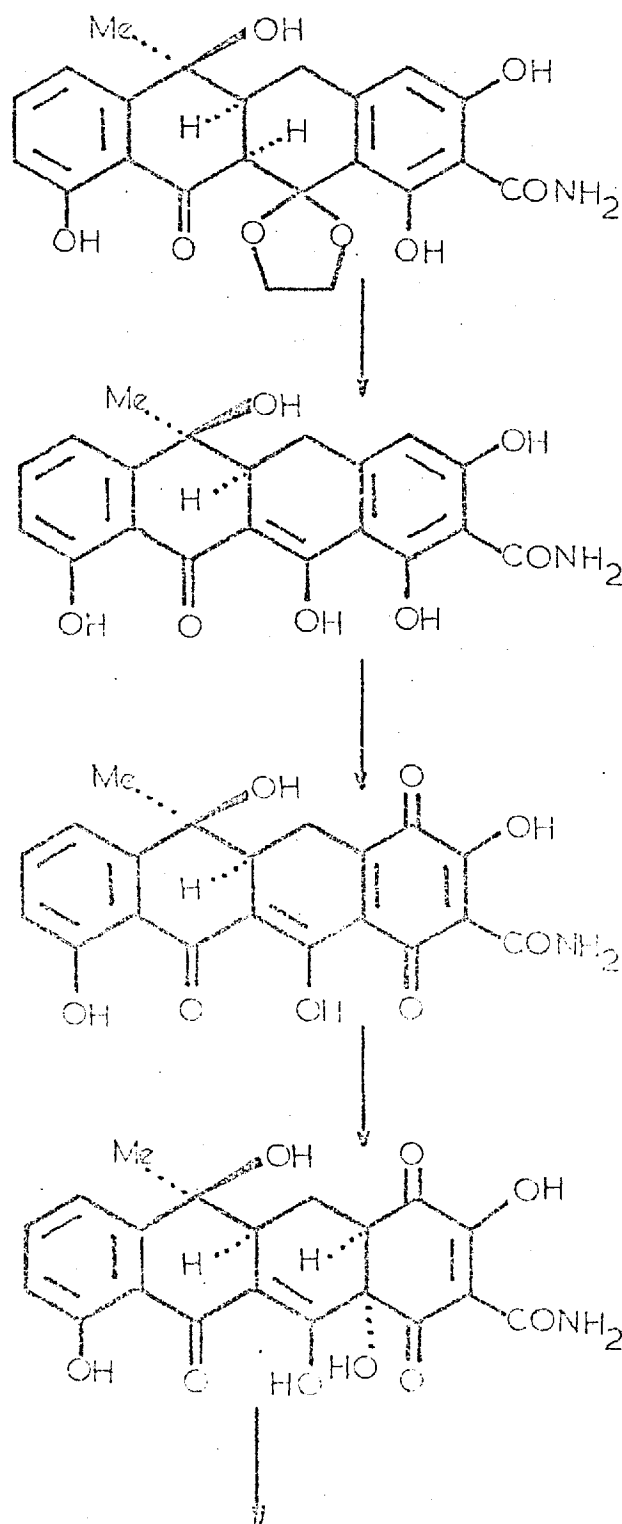


established that (32) may be converted into tetracycline^{36,37,38} by reductive amination, followed by epimerisation at C-4, the synthesis of (32) constitutes the synthesis of tetracycline.

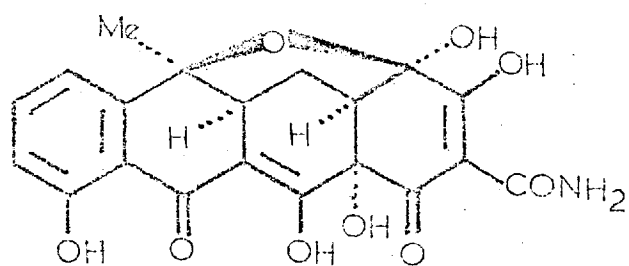
SCHEME 1



SCHEME I CONT'D



SCHEME 1 CONT'D



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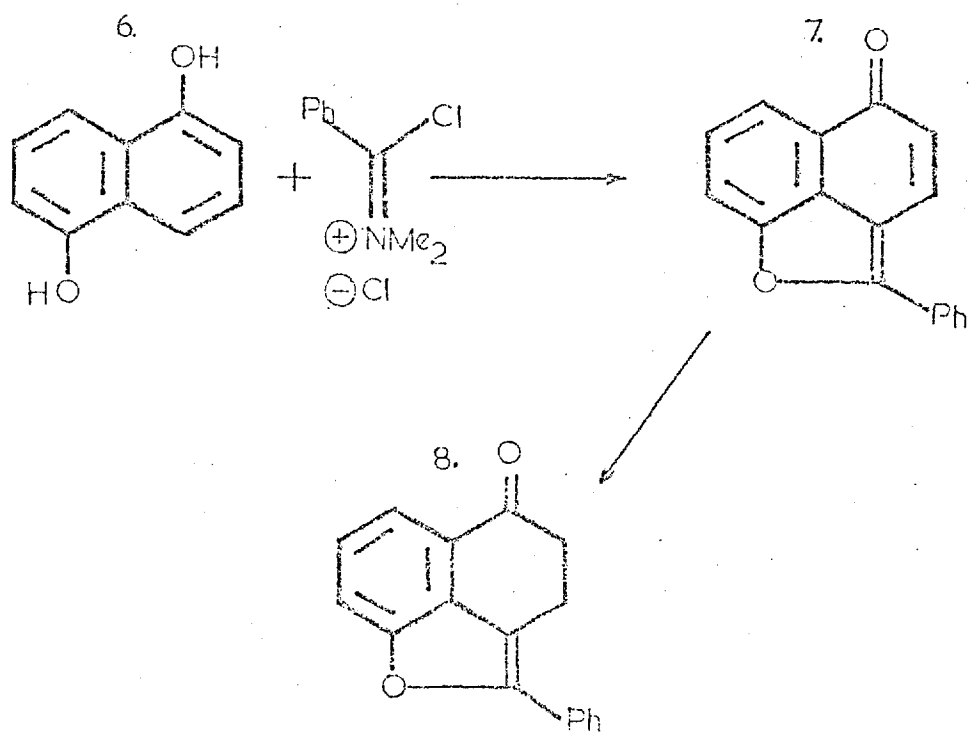
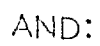
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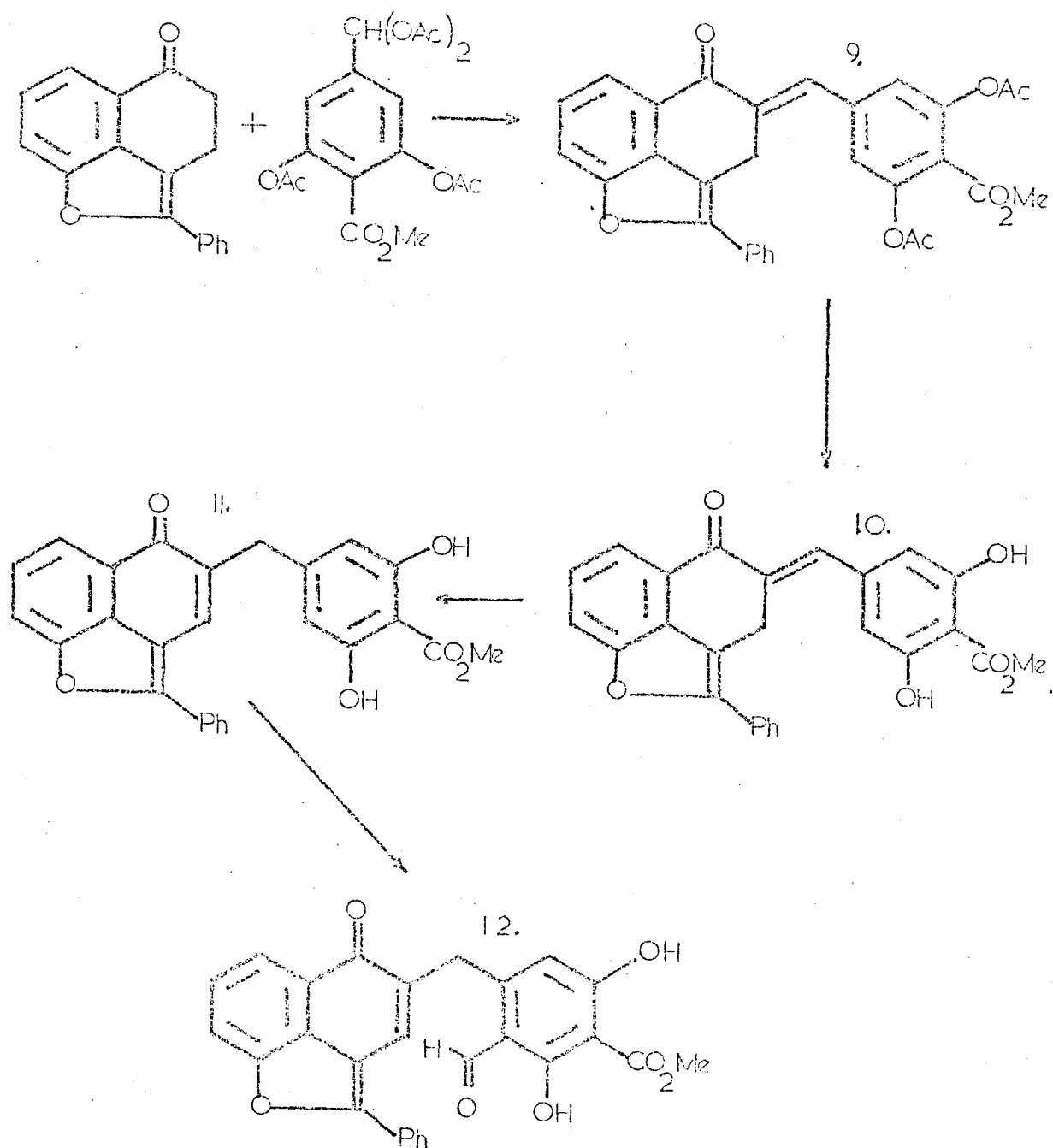
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DISCUSSION (PART I)MODIFICATION OF ESTABLISHED METHODS FOR THE PREPARATION OF RING A
AND CD BICYCLIC PRECURSORS FOR THE SYNTHESIS OF TETRACYCLINE

The aldehyde (12) is an important intermediate in the synthetic route to tetracycline employed at Imperial College. The established route to (12) is summarised in schemes 1 and 2. Most of the stages outlined in the schemes proceed in excellent yield but the conversion of (4) to (5) and of (6) to (7) proceed in unacceptably low yields. The formation of the formyldiacetate (5) involved the oxidative acetylation of (4) by the action of chromium trioxide and sulphuric acid in the presence of acetic anhydride and acetic acid.⁵ The product could be obtained only in yields of up to 40%. The effect of addition of manganous ion (manganous sulphate) was studied. It was found that addition of manganous ion led to a marked increase in the yield and variation of manganous ion, chromium trioxide and sulphuric acid led to yields of up to 57%. Addition of dichloromethane to homogenise the reaction mixture, and exhaustive extraction of the mother liquors after work up increased the yield still further to 75%.

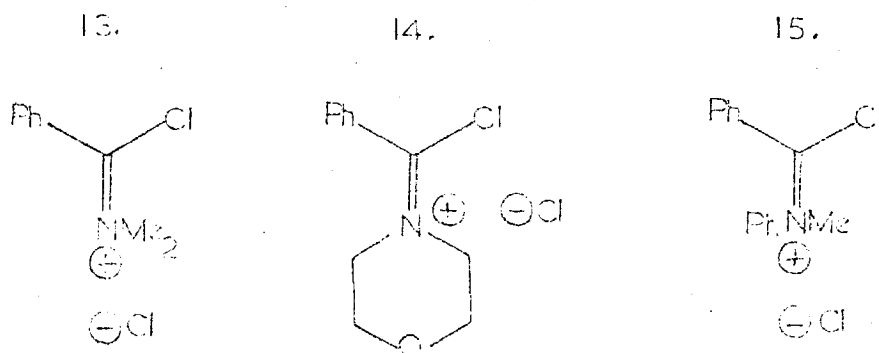
The established synthesis of the perinaphthofuran (7) proceeds via a Friedel-Crafts reaction on the naphthol (6) in the presence of benzoic acid and zinc chloride. The procedure² is complicated and involves the ungainly handling of the reaction mixture during work up and a protracted extraction with large amounts of benzene. The yield from this reaction is seldom more than 25%. It was decided that a new approach to the reaction was required. The Vilsmeier-type reaction between the imidinium chloride (13) and the naphthol (6) was investigated. The imidinium chloride (13) was readily obtainable by the action of phosgene on N-dimethyl benzamide.⁷ Some difficulty was encountered in the choice of suitable solvent. Aromatic solvents





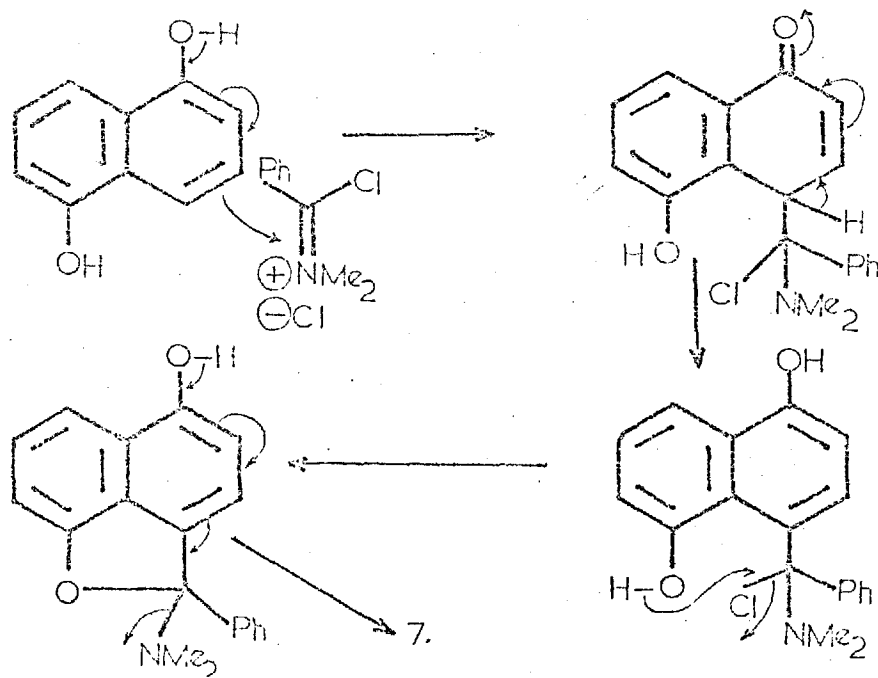
SCHEME 2.

such as benzene, toluene and chlorobenzene were found to be unsuitable since the reactants would not fully dissolve to form a homogeneous mixture, often resulting in an unmanagable gum in the reaction flask. It was, however, obvious by t.l.c. analysis that the desired product was being formed cleanly if not efficiently. The use of nitro-benzene was found to overcome all solubility problems and in the presence of a one-fold excess of the imidinium chloride (13) and a four-fold excess of triethylamine the naphthol (6) was transformed into the perinaphthofuran (7) in 75% yield. Water miscible solvents such as dimethylformamide and diglyme were tried in order that the product might be precipitated out of solution by the addition of water. Only in diglyme was the perinaphthofuran formed cleanly (observed by t.l.c.), but addition of water led to the formation of an emulsion from which the perinaphthofuran could not readily be separated.

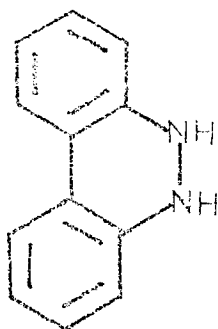


The action of phosgene on N-benzoyl morpholine and N-methyl benzanilide led to the formation of two highly unstable compounds thought to be the imidinium chlorides (14) and (15) respectively. Both (14) and (15) were reacted with the naphthol (6) immediately upon their isolation. Treatment of the naphthol with (14) yielded the perinaphthofuran in some quantity (by t.l.c.

SCHEME 3.



analysis), but in the company of various decomposition products. Reaction of the naphthol (6) with the imidinium chloride (15) did not lead to the formation of the perinaphthofuran; evidently the N-dimethyl imidinium chloride (13) afforded the most efficient means of obtaining the desired perinaphthofuran (scheme 3).



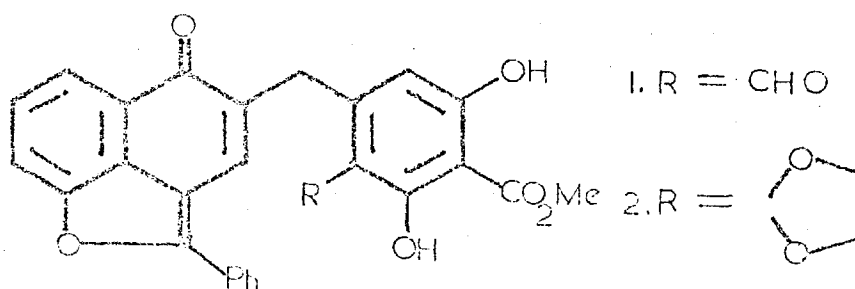
16.

Hydrogenation of the dehydro-perinaphthofuran (7) by the established² method in the presence of Raney nickel led to the dihydroperinaphthofuran (8) in reasonably good yield (70%).

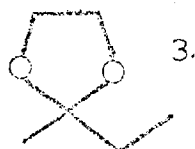
It was decided to attempt transhydrogenation by the action of dihydrobenzocinoline⁸ (16). The dihydro compound (16) was readily generated by the reduction of benzocinoline by zinc dust and hydrochloric acid.⁹ Treatment of (7) with dihydrobenzocinoline in benzene gave rise to extensive decomposition which was not accompanied by any formation of the desired dihydroperinaphtho-furan (by t.l.c. analysis).

DISCUSSION (PART II)INVESTIGATION OF POTENTIAL ACETALISATION REAGENTS

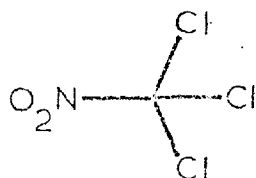
Attempts to convert the aldehyde (1) to the corresponding acetal (2) by known procedures have failed.



All efforts to effect direct acetalisation by ethylene glycol in the presence of toluene-*p*-sulphonic acid or exchange acetalisation by butan-2-one ethylene acetal (3) were unsuccessful. The spiro-acetal (4) appeared a promising reagent for the transacetalisation.



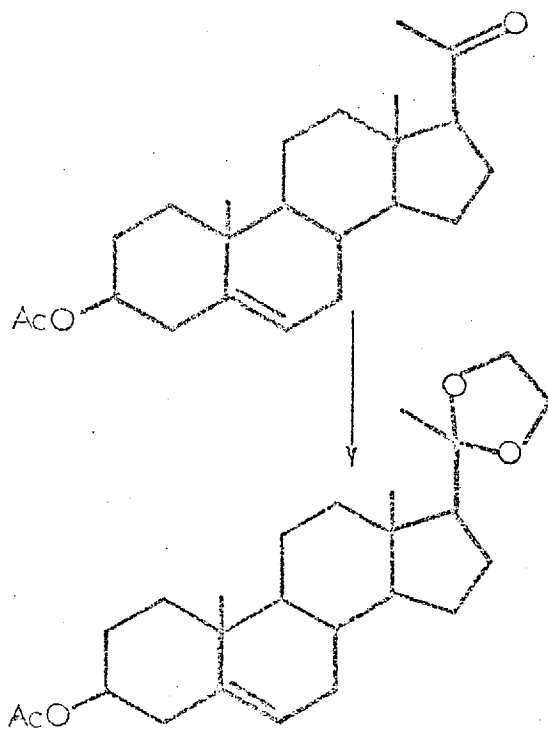
Other workers have recently described the use of thallium glycolates² and tin glycolates³ to prepare diethylene orthocarbonate (4). The reagent (4) has been prepared in these laboratories by the treatment of tetramethyl-orthocarbonate with ethylene glycol in the presence of toluene-*p*-sulphonic acid. More conveniently sodium glycolate reacted with chloropicrin (5), to give (4) in 40% yield. Attempts to prepare (4) by the action of sodium glycolate on carbon



5.

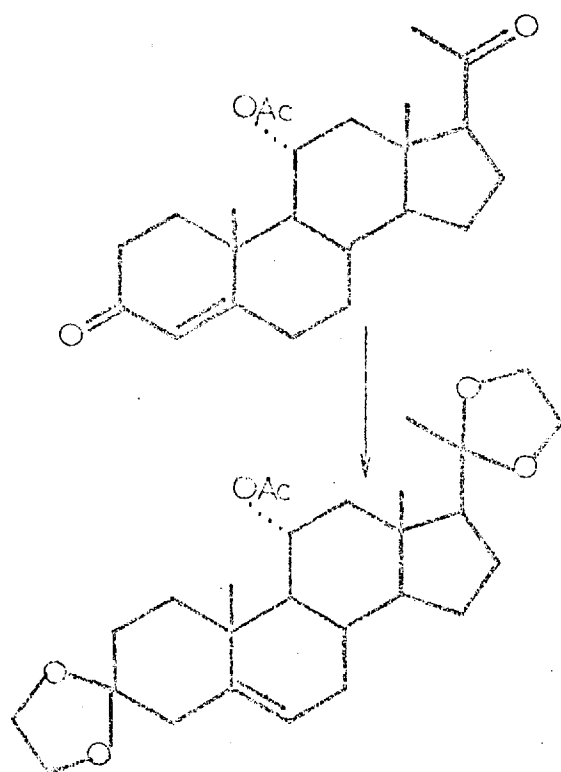
tetrachloride were unsuccessful. The reagent was found to be effective for the desired transacetalisation resulting in the transformation of (1) to (2) in the presence of toluene-*p*-sulphonic acid or slightly wet borontrifluoride-etherate. The transacetalisation was carried out at room temperature and was complete in four hours with yields of up to 95%.

In order to assess the generality of the reagent, it was decided to try the procedure with various aldehydes and ketones (6) - (12).



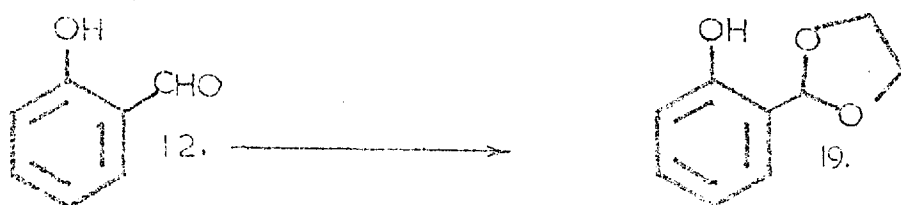
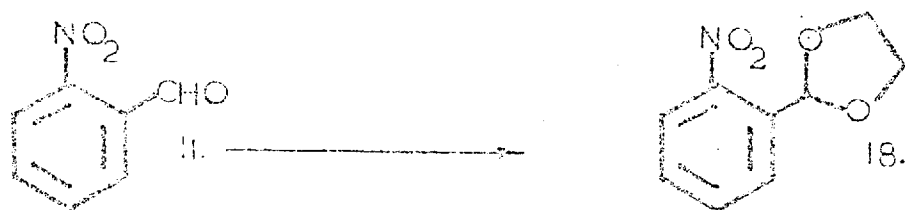
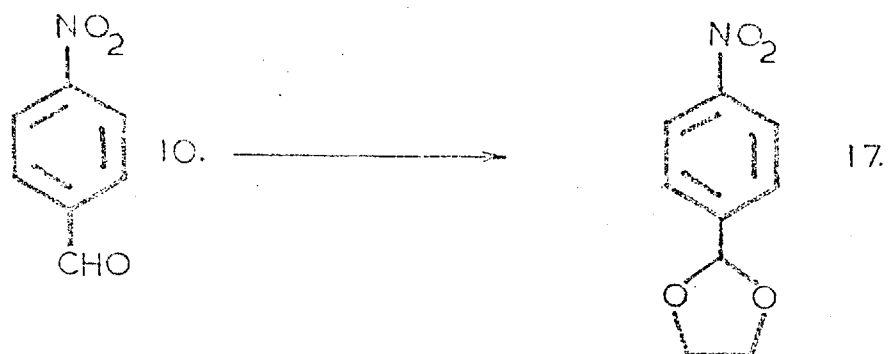
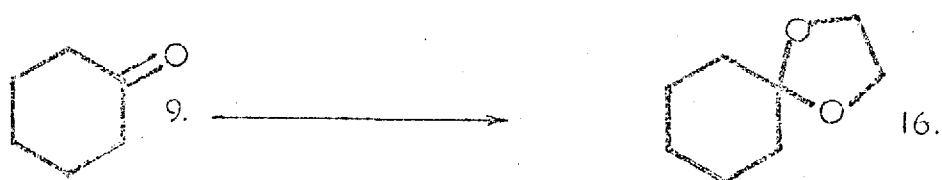
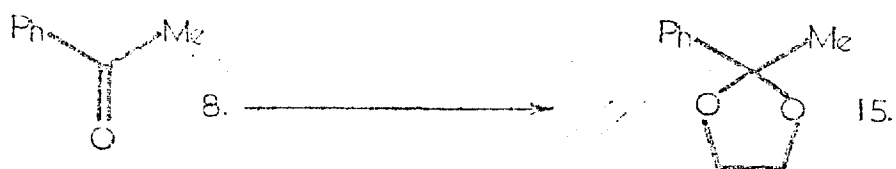
6.

13.



7.

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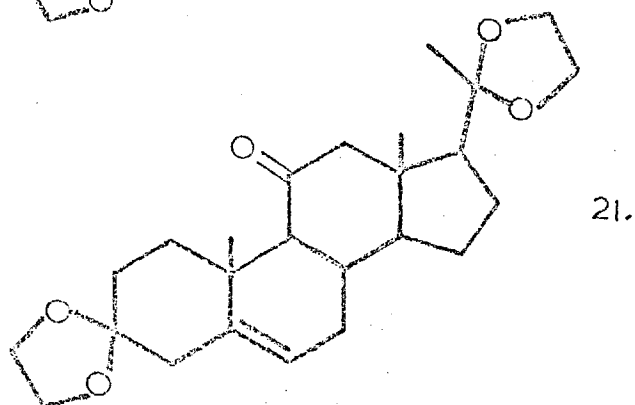
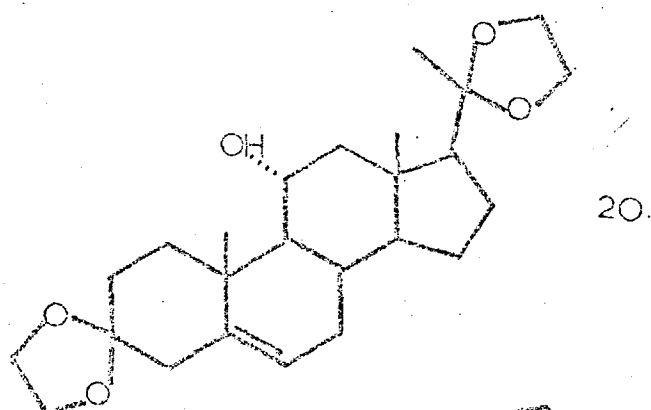


Treatment with diethylene orthocarbonate in the presence of toluene-*p*-sulphonic acid afforded the corresponding acetals (13) - (19) in good yields (see table 1)

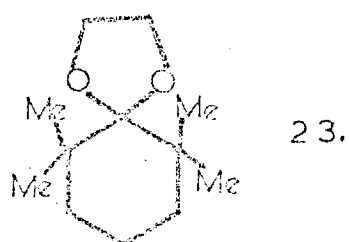
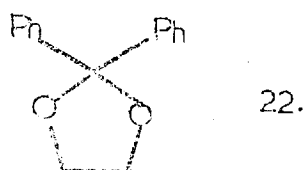
TABLE I

Substrate	Temp.	reaction time/h	Product	Yield %
(1)	R.T.	4	(2)	80
(6)	R.T.	4	(13) ¹¹	82
(7)	R.T.	8	(14) ⁷	78
(8)	R.T.	2-3	(15)	74
(9)	R.T.	0-5	(16) ¹³	71
(10)	R.T.	1	(17) ¹²	79
(11)	R.T.	1	(18) ¹⁴	78
(12)	R.T.	3	(19) ¹⁵	73

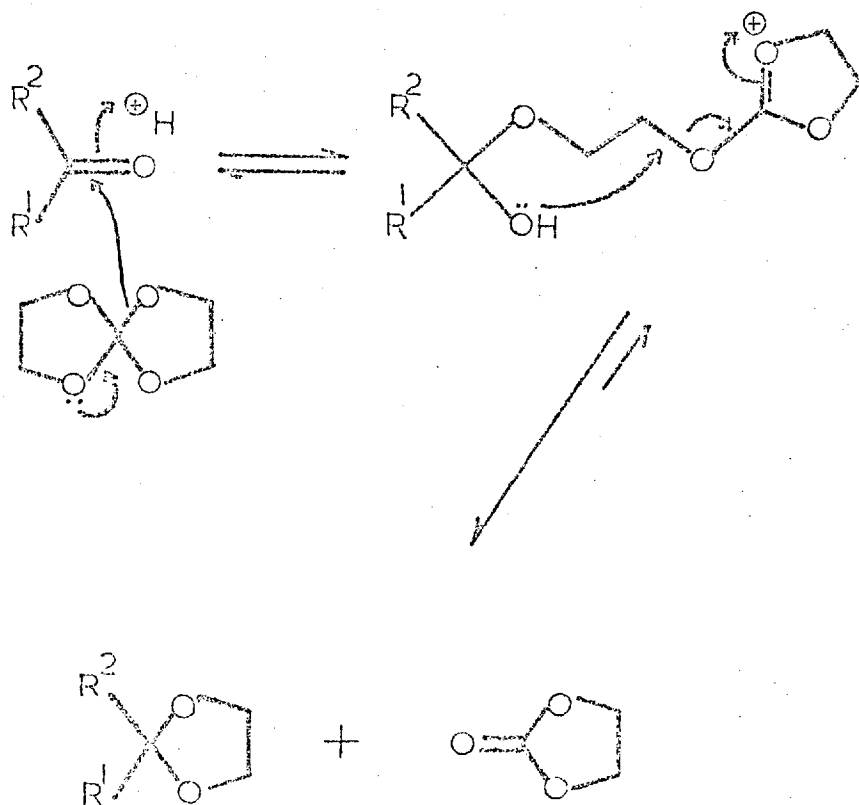
The known acetals (13),¹¹(14),⁷(16),¹³(17),¹²(18)¹⁴ were also prepared by the established procedure with ethylene glycol in the presence of toluene-*p*-sulphonic acid. The products were identical to those obtained using diethylene orthocarbonate. The structure of the bis acetal (14) of 11 α -acetoxyprogesterone (7) was established by saponification of (14), (MeONa-MeOH), to form the 11 α -hydroxy compound (20).⁸ Subsequent oxidation by chromium trioxide/pyridine in dichloromethane led to the known 11-keto compound (21),⁹ thereby demonstrating the position of the Δ^5 double bond.



Extensive efforts to prepare the acetals (22) and (23) by the action of diethylene orthocarbonate on benzophenone and 2, 2; 6, 6 - tetramethylcyclohexanone, respectively, were unsuccessful. This is probably due in part to the difficulty

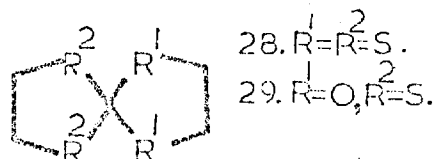
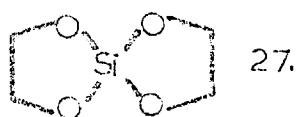
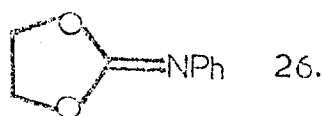
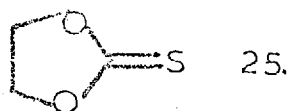
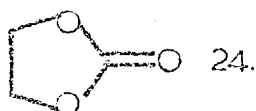


encountered by the bulky reagent molecule in overcoming the hindered approach to the active carbonyl site (scheme 1)



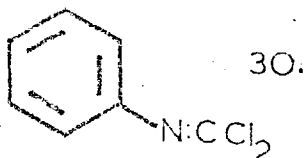
(SCHEME 1)

The success of diethylene orthocarbonate as a transacetalisation reagent, led to the consideration of other compounds that might behave in a similar manner. We decided to prepare the acetals (24) - (29) and determine their transacetalisation properties. Ethylene carbonate (24) was readily prepared by the action of phosgene on ethylene glycol.¹⁶ Attempts were made to convert the two steroid ketones (6) and (7) to the



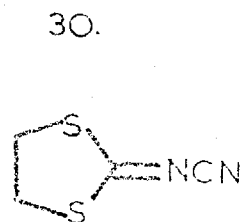
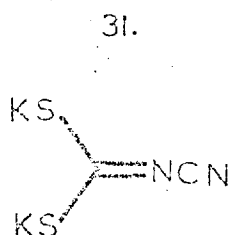
corresponding acetals (13) and (14) by the action of ethylene carbonate (24). Variation of temperature, solvent, acid catalyst and amount of reagent failed to afford the desired acetals (13) and (14) in any quantity. In view of the lack of success met with this compound, plans to prepare and investigate the sulphur analogue (25) of ethylene carbonate, were abandoned. N-phenyliminocarbonate (26) was prepared by a two step process.¹⁷ First the action of chlorine gas on phenyl-

isothiocyanate formed N-dichloromethylenedianiline (30). This was

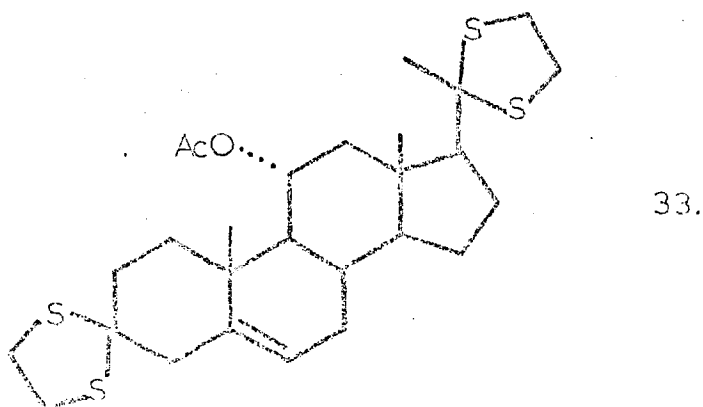


followed by treatment with sodium glycolate to give the iminocarbonate (26). All attempts to convert the ketones (6) and (7) to the corresponding acetals (13) and (14) by the action of the imino-carbonate (26) were unsuccessful.

Efforts were made to prepare the orthosilicate (27) by the action ethylene glycol on silicon tetrachloride,¹⁸ and also on silicon tetra acetate. In each case the product obtained was a white amorphous solid which did not melt below 360° and was found to be insoluble in any solvent. It was assumed that a polymeric product had been obtained and further work on the preparation of this compound was abandoned. The tetrathioorthocarbonate (28), was prepared in 3 steps.¹⁹ The action of ethanolic KOH on a mixture of cyanamide and carbon disulphide gave potassium cyanodithioimidocarbonate (31).



Treatment of (31) with 1,2-dibromoethane gave 2-cyanoimino-1,3-dithiolane. Finally, careful addition of ethane-1,2-dithiol in the presence of hydrochloric acid afforded the tetrathioorthocarbonate (28). The tetrathioorthocarbonate (28) was reacted with 11 α -acetoxyprogesterone (7) in the presence of toluene-p-sulphonic acid at room temperature with no diminution of starting material (by t.l.c. analysis) after 24 hours. However, after refluxing in chloroform for 72 hours, t.l.c. indicated the total disappearance of starting material and the clean formation of a new product found to be the bisthioacetal (33) in 82% yield. The infra-red spectrum showed the disappearance of the two ketone carbonyl bands at 1710 and 1675 cm^{-1} . The mass spectrum showed the molecular ion at m/e 524.



The steroid ketone (6) was subjected to treatment with the tetrathioorthocarbonate (28) in the presence of toluene-p-sulphonic acid at room temperature. T.l.c. showed no change in the starting material and the infra-red spectrum of the reaction mixture showed no diminution of the ketone carbonyl band at 1712 cm^{-1} . Variation of temperature, acid catalyst, amount of acid catalyst and amount of reagent did not lead to the clean

formation of a tractable major product. The obvious limitations of the tetrathioorthocarbonate (28) as a transacetalisation reagent led to the abandonment of any further work on it.

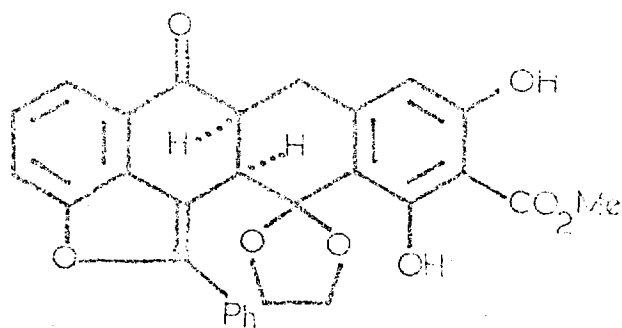
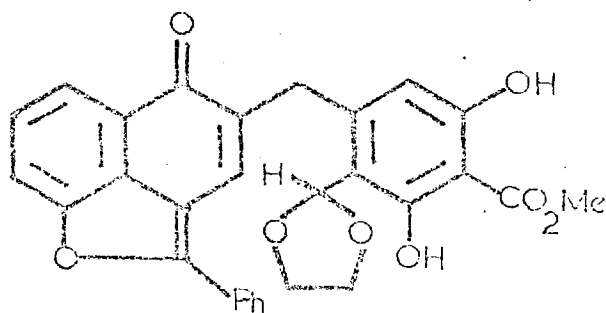
Finally it was decided to attempt to prepare the dithioorthocarbonate (29). Two attempts were made to prepare (29);

(i) Action of ethylene glycol on (32)

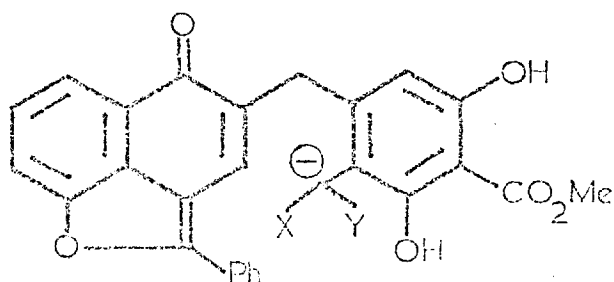
(ii) Reaction of carbon disulphide and ethylene glycol in ethanolic KOH in an attempt to form the di-potassium salt (33) and subsequent treatment with 1,2-dibromoethane. Neither method yielded to the desired dithioacetal (29). No further attempts were made to prepare (29).

DISCUSSION (PART III)CYCLISATION OF TRICYCLIC ACID INTERMEDIATES

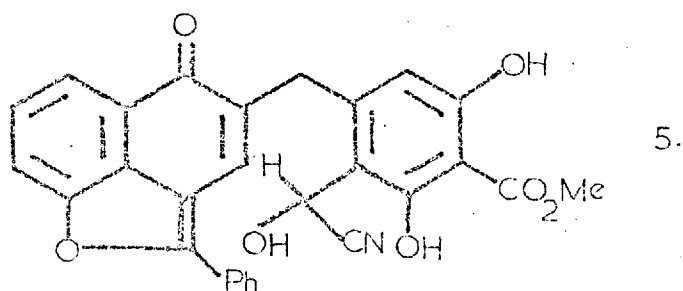
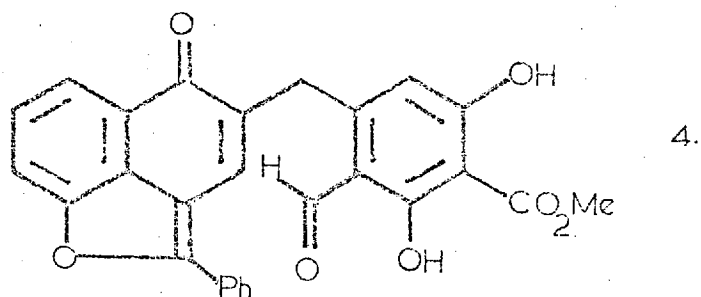
The preparation of the acetal (I) as described in PART II, and its subsequent photocyclisation by other workers in these laboratories,¹ has led to the tetracyclic acetal (2). The yield



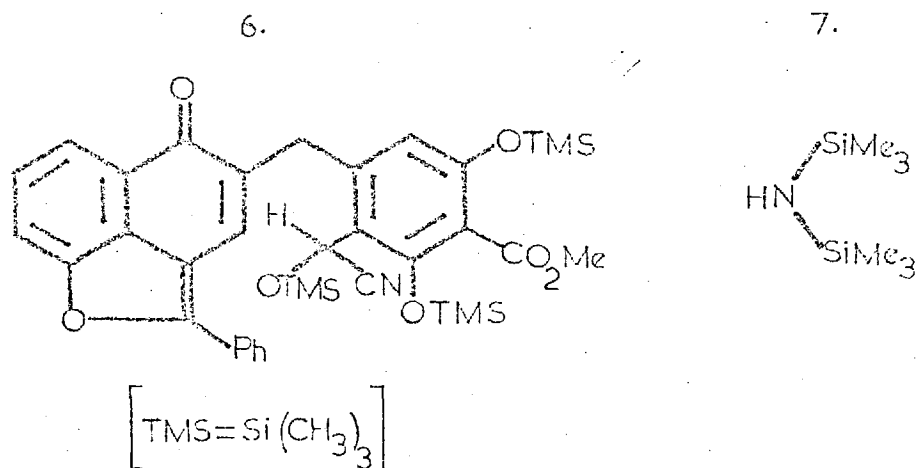
of the tetracyclic acetal by this procedure is not unacceptable, up to 68%, but the concentration of the acetal (I) in the reaction solution is necessarily very low in order to obtain a cleanly formed product. It has been found that a concentration of not more than 2m moles L.⁻¹ of solvent is necessary for the reaction to proceed to give acceptable yields. This is considered too low to constitute a viable stage in the synthetic route. In view of this it was decided to again attempt an intramolecular Michael-type cyclo-addition of a benzylic anion to the enone system.² An attempt to generate a species of the type (3) was made, where substituents X and Y must be capable of anion stabilisation and yet be readily convertible into a carbonyl group.



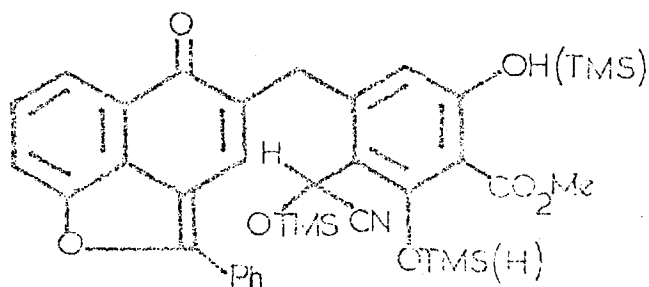
Initially the aldehyde (4) was treated with aqueous NaCN and sulphuric acid in tetrahydrofuran. The reaction failed to yield the desired cyanohydrin (5) as a stable, isolable product. In an effort to stabilise the cyanohydrin (5), 1,3-dihydropyran was added to the neutralised reaction mixture in the hope that the cyanohydrin might be isolated as the tetrahydropyranyl ether. This also failed to yield a stable intermediate. At the same time



work was being carried out in an attempt to prepare the tri-
 trimethylsilyl cyanohydrin (6) by the action of trimethylsilyl
 cyanide on (4). It has been established that the action of
 trimethylsilyl cyanide on aldehydes and ketones gives rise to the
 high yield formation of trimethylsilyl cyanohydrins.³ The reagent
 may be prepared by the action of liquid hydrogen cyanide on
 hexamethyldisilazane (7).⁴ Or more conveniently by the action
 of silver cyanide on trimethyl silyl chloride.⁵

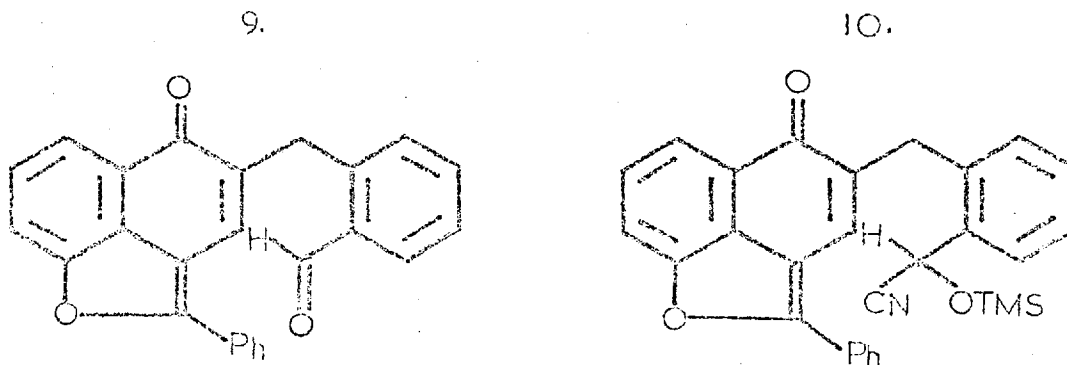


When the aldehyde (4) was stirred with an excess of trimethylsilyl cyanide at room temperature, in the absence of solvent and Lewis acid catalyst, the tris-trimethyl cyanohydrin (6) was, in fact, obtained in excellent yield. Although (6) could not be obtained as a crystalline compound, it has been fully characterised as a yellow foam; ν_{max} . 2900, 1730, 1640 cm.⁻¹, λ_{max} . 405, 325, 268 nm, (ϵ 28,478, 9,380 and 25,128), τ 9.83 (9H, s), 9.85 (9H, s), 9.66 (9H, s), 6.12 (3H, s), 5.67 (2H, s), 4.00 (1H, s), 3.52 (1H, s), 1.68 - 2.74 (9H, cpx m). All attempts to crystallise (6) led to the formation of the bis-trimethylsilyl cyanohydrin (8) as a yellow crystalline solid m.p. 172 - 175°C.

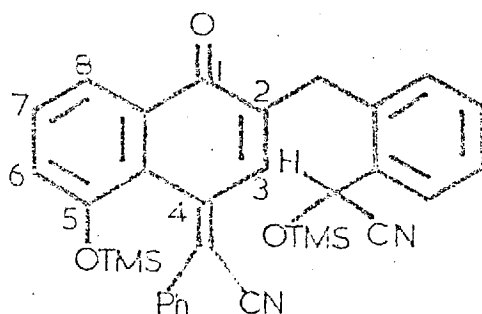


The exact position of desilylation is uncertain, but the N.M.R. spectrum shows the cyanohydrin proton present at τ 4.06, thereby confirming that the silyl cyanohydrin had not suffered desilylation. It seems most likely that desilylation occurs from the most accessible ring A silyl ether function.

In order to avoid unnecessary use of ring A substituted ACD tricyclic material, it was planned to prepare the silyl cyanohydrin (10) of the model aldehyde (9),² to carry out preliminary experiments. When the aldehyde (9) was treated with

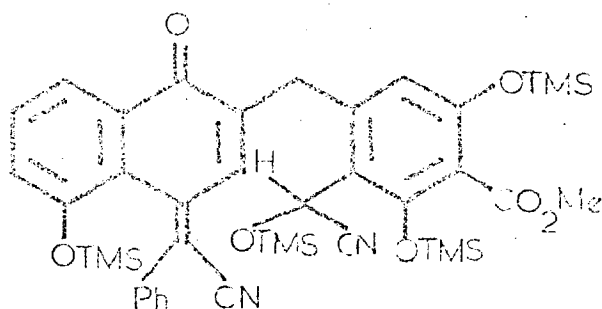


trimethylsilyl cyanide (one equivalent) in the absence of catalyst only very small amounts of a new product could be detected by t.l.c. The addition of a large excess of the reagent did not appear to appreciably diminish the amount of starting material present (the reaction was followed by t.l.c. and n.m.r.). When a crystal of zinc iodide was added, t.l.c. showed the rapid disappearance of starting material and the emergence of a new, blue fluorescent product. When the reaction appeared by t.l.c. to be complete, the excess of reagent was removed by vacuum pump to leave a colourless foam. The compound was found to be the bis-trimethylsilyl compound (11). The n.m.r. spectrum showed that



11.

the silyl methyl protons at the C-5 position formed two singlets [9.91. This indicates that (11) was formed as a mixture of geometrical isomers at C-4. The aldehyde (4) was found to react in the same way when treated with an excess of trimethylsilyl cyanide in the presence of a crystal of zinc iodide. The tetra-



12.

trimethylsilyl cyanohydrin (12) was formed.

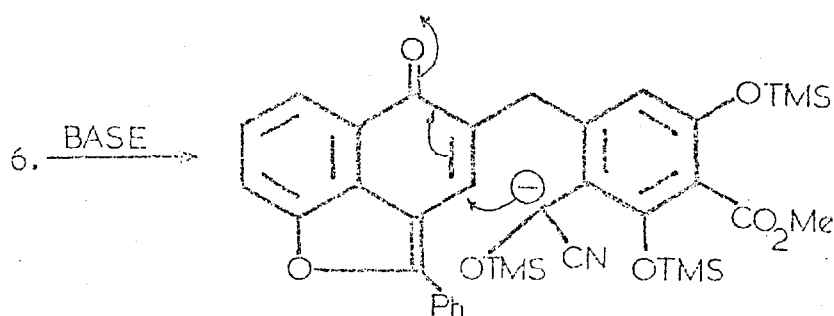
Some experiments were carried out on the tris-trimethylsilyl cyanohydrin (6) in an attempt to cyclise ring B by an intramolecular Michael-type addition. Ring closure

did not occur despite the variation of a wide range of reaction conditions;

Variation of base

A number of different bases were investigated in order to effect cyclisation;

1. Potassium-*t*-butoxide.
2. Sodium hydride.
3. Sodium bis trimethylsilyl amide.⁶
4. Lithium bis trimethylsilyl amide.⁶
5. Lithium salt of 2,2; 6,6-tetramethyl piperidine.



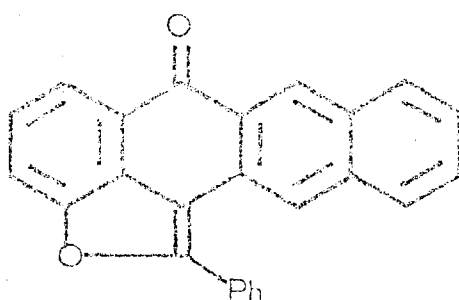
The amount of base was varied from 1 equivalent of base per equivalent of substrate, to 5 equivalents of base per equivalent of substrate.

Variation of temperature

The reaction temperature was varied from -78°C to 60°C.

In no instance was the formation of the desired cyclised product observed.

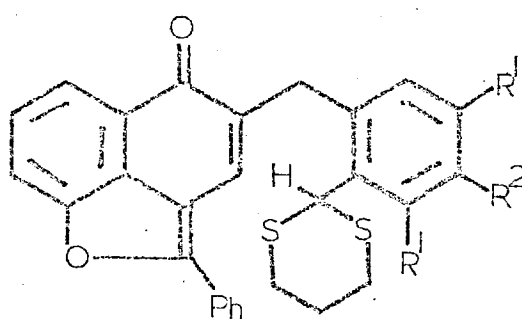
Attention was now shifted to the possibility of ring closure by an intramolecular benzoin-type condensation of the aldehydes (4) and (9). The aldehydes were subjected to treatment with sodium cyanide in aqueous ethanol. Variation of temperature and variation of sodium cyanide concentration did not lead to the formation of cyclised products. It was felt that the alkaline reaction conditions might not be conducive to the required cyclisation. It was decided to buffer the reaction, by the addition of potassium dihydrogen phosphate, over the range pH6 - 10. These attempts still failed to lead to the formation of cyclised products. Some further experiments were carried out in hexamethylphosphoramide instead of aqueous ethanol. In the case of the ring A substituted aldehyde (4) no trace of the desired cyclised product was observed (by t.l.c.). In the case of the model (9) one major product was observed (t.l.c.) and on isolation it was found to be the naphthacene (13). Failure of the benzoin-type reaction to produce the desired



13.

cyclisation led to reconsideration of a Michael-type reaction but this time the benzylic anion stabilising function was a thioacetal.

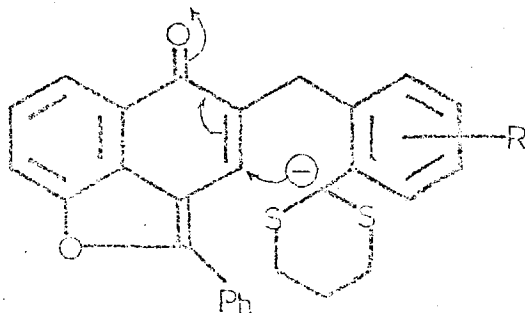
The aldehydes (4) and (9) were treated with propane-1,3-dithiol to form the thioacetals (14) and (15) respectively.



14. $R^1=OH, R^2=CO_2Me$

15. $R^1=R^2=H$

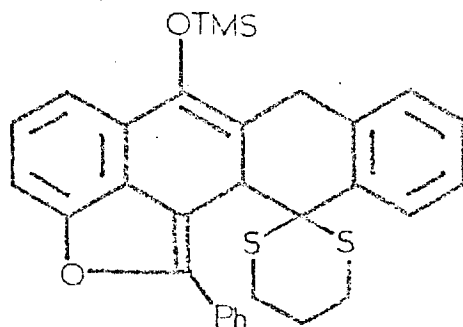
It was hoped that in the presence of base, the intermediate formation of the stabilised anion might lead to the closure of



ring B. Treatment of the model thioacetal (15) with 1 equivalent of potassium tertiary butoxide was not effective. When the amount of base was increased decomposition of starting material occurred without formation of the cyclised product. When 1 equivalent of lithium diisopropylamide was added to (15) in T.H.F. at $-78^{\circ}C$ and

the temperature allowed to rise to room temperature, the clean formation of a new, product was observed by t.l.c. The material was seen as a bright blue fluorescent spot on t.l.c. exhibiting the correct ultra violet characteristics of the desired cyclised product. The reaction appeared to reach equilibrium after a short while, since no more than about 10% (by t.l.c.) of the starting material had been converted, leaving the remaining starting material intact. Attempts to isolate the product by p.l.c. were unsuccessful since decomposition occurred. Increases in the amount of base did not appear to increase the amount of product formed and at temperatures higher than -78°C decomposition occurred. As it seemed an equilibrium existed between formation of product and reversion to starting material, it was decided to carry out some experiments that might alter the balance of the equilibrium to yield the desired product. It was considered that the addition of cuprous iodide to the reaction might form the cuprate of the benzylic anion, thereby facilitating intramolecular addition to the enone system. In fact treatment of (15) with 1 equivalent of lithium diisopropylamide in the presence of 1 equivalent of cuprous iodide again led to the formation of the new product. The addition of cuprous iodide appeared, by t.l.c., to have had a marked beneficial effect on the reaction with perhaps as much as 20% product formation. The complete exhaustion of starting material was not accomplished and the product was not present in sufficient quantity to facilitate isolation by selective crystallisation. Another attempt was made to alter favourably the balance of the equilibrium. This time the thioacetal (15) was treated with 1 equivalent of lithium diisopropylamide in the presence of trimethylsilyl chloride in the hope that the enol form of the cyclised product might be trapped in the form of the trimethylsilyl ether (16). The addition of trimethylsilyl chloride to the reaction had no apparent effect, and the blue fluorescent product observed by

t.l.c. was still only formed in small quantity.



16.

When the ring A substituted thioacetal (14) was subjected to treatment with potassium tertiary butoxide or lithium diisopropylamide under similar conditions as those outlined for the model (15), no formation of cyclised acetal was observed.

At this juncture it was decided to attempt ring B closure by photochemical means. The source of radiation was a 750 Watt Tungsten lamp set in a reflecting enclosure. Three preliminary experiments were carried out on the model thioacetal (15) in refluxing benzene under the illumination of the tungsten lamp:

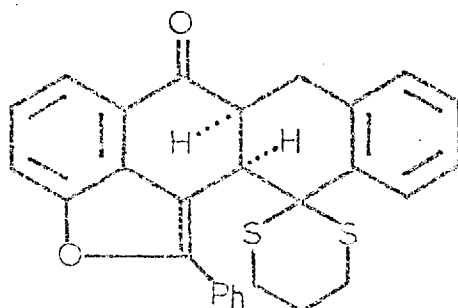
- (i) In the absence of catalyst.
- (ii) In the presence of benzoic acid.
- (iii) In the presence of potassium-t-butoxide.

In the absence of catalyst, a small amount of the blue fluorescent compound was formed which was identical by t.l.c. to the compound obtained by the action of lithium diisopropylamide

on (15) as described. No more than a trace of the compound was formed after about 8 hours.

In the presence of 1 equivalent of benzoic acid, after 12 hours the starting material appeared to be virtually intact, with just a small amount of the blue fluorescent product accompanied by several decomposition products.

In the presence of 1 equivalent of potassium tertiary butoxide, the reaction proceeded cleanly leading to the formation of the desired cyclised product (17) in 85% yield. The time taken for complete exhaustion of starting material was less than 40 minutes.

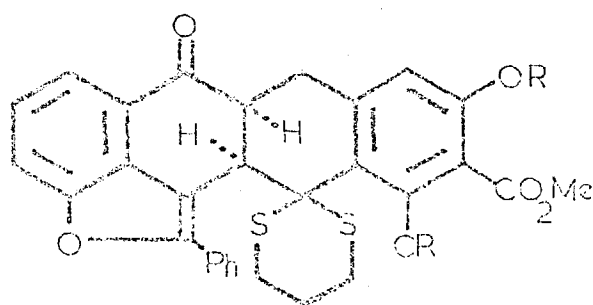


17.

The ring A substituted thiacetal (14) was then subjected to the same preliminary conditions. In benzene, in the absence of catalyst, after irradiation for less than one hour by the tungsten lamp, a small amount of a new blue fluorescent product was observed by t.l.c. The formation of the new product was accompanied by traces of decomposition products.

In the presence of 1 equivalent of benzoic acid only a very small amount of the new product was formed after 2 hours, with concomitant decomposition.

In the presence of 1 equivalent of potassium tertiary butoxide, the new product was formed in substantial quantity (approximately 40-50% by t.l.c.), but was not formed cleanly, and after 2 hours product formation was accompanied by considerable decomposition. Change of solvent to acetonitrile did not afford a cleaner reaction. Various other bases were used. Lithium diisopropylamide was ineffective. When the thioacetal (14) was irradiated in the presence of sodium bis-trimethylsilyl amide, the reaction proceeded cleanly to completion in less than 2 hours. In the presence of lithium bis-trimethylsilyl amide, the reaction was complete in 40 minutes, when t.l.c. analysis showed the complete disappearance of starting material and the formation of a new blue fluorescent product, thought to be (18). When the reaction solution was heated under reflux in the



18. R=H

19. R=Ac

absence of light, formation of the new product was not observed. The product was found to be very sensitive to atmospheric oxidation and great difficulty has been encountered in fully characterising the material. Work is now being carried out in these laboratories, in an attempt to isolate the product probably in the form of acetate (19).

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. Infra red were taken on Unicam SP 200 or Perkin Elmer P.E. 157 spectrometers. Ultra violet spectra were recorded on the Unicam SP 800. N.m.r. spectra were measured in deuteriochloroform with T.M.S. as internal standard on the Varian T 60 spectrometer.

The following abbreviations refer to the n.m.r. data:-

s = singlet
d = doublet
b = broad
t = triplet
m = multiplet
cpx = complex

All solvents and reagents were dried and purified by the standard techniques. The silica gel for t.l.c. (thin layer chromatography) and for p.l.c. (preparative layer chromatography) was Merck

G.F. 254

EXPERIMENTAL TO PART IP-Orsellinic acid (2).

Prepared by the carboxylation of orcinol by the method of Robertson and Robinson, ¹ m.p. 164-165° (lit. m.p. 163-166°).¹

Methyl p-orsellinate (3).

Prepared by the esterification of the acid (2) with sodium hydrogen carbonate-dimethyl sulphate by the method of Barton et al,² m.p. 98-99° (lit. m.p. 98-99°).^{2,3}

3,5-Diacetyl-4-methoxycarbonyltoluene (4).

Prepared by the acetylation of the ester (3) with sodium acetate-acetic anhydride by the method of Saraiya and Shah,⁴ m.p. 70° (lit. m.p. 70°).⁴

2,6-Diacetoxy-4-diacetoxymethylbenzoate (5).

(The established method of Magnus⁵ was modified by the addition of manganous sulphate and the variation of the proportions of chromium trioxide and sulphuric acid. Also the reaction mixture was homogenised by the addition of dichloromethane; and an exhaustive solvent extraction was incorporated into the work-up).

3,5-Diacetyl-4-methoxycarbonyltoluene (4; 1.0g) was added to a mixture of acetic anhydride (13.5ml), acetic acid (13.5 ml) and dichloromethane (10 ml). The solution was stirred vigorously at -5° while concentrated sulphuric acid (1.8 cm³) was added over a period of one hour. Finely-ground anhydrous manganous sulphate (4.1g) was added immediately.

Chromium trioxide (1.8 g) was added over a period of one hour while the temperature was maintained at -5° . The reaction was stirred at -5° for about 4 hours until all the starting material had been consumed (t.l.c. analysis). The mixture was poured over an ice-water mixture (100 ml) and stirred for 2 hours. The organic layer was separated and the aqueous layer extracted with dichloromethane, (3 X 30 ml). The collected extracts were dried over sodium sulphate and evaporated to small bulk. The resulting oil was evaporated further (oil pump; 1 mm Hg; 80° , 2 hours) to yield, after recrystallisation from benzene-petroleum ($60-80^{\circ}$), the formyldiacetate (5; 1.08g, 75%), m.p. $110-111^{\circ}$ (lit. m.p. 112°),⁵ $\nu_{\max}$. 1780 and 1730 cm^{-1} .

N-Dimethylbenzamide.

Benzoyl chloride (35g) was dissolved in dichloromethane (100 ml). An aqueous solution of dimethylamine (25%^{v/v}; 90 ml) was added slowly at 0° and the mixture shaken vigorously for 10 minutes. The dichloromethane layer was separated and washed with water. The washed solution was dried and the solvent removed to yield colourless rosettes of the benzamide, m.p. 41° (lit. m.p. 41°).⁶

α -Chloro-benzaldehyde-N,N-dimethylimidinium chloride (13).

Prepared by the action of phosgene on N-dimethylbenzamide.⁷

2-Phenylnaphtho (1,8-bc) furan-5-one (7).

(i) Prepared by the action of benzoic acid on 1,5-dihydroxynaphthalene in the presence of zinc chloride by the method of Barton² et al, m.p. $137-137.5^{\circ}$ (lit. m.p. $137-137.5^{\circ}$),² $\nu_{\max}$ 1645 cm^{-1} .

(ii) 1,5-Dihydroxynaphthalene (1.00 g) was added to freshly distilled nitrobenzene (30 ml) and heated with stirring to 80°. Triethylamine (3.20 ml) was added followed by the addition of the imidinium chloride (13; 2.55g) under a stream of dry, oxygen free nitrogen. The mixture was stirred under nitrogen at 80° for 40 minutes until t.l.c. analysis indicated that all the starting material had been consumed. The reaction mixture was poured into water (100 ml) and shaken vigorously. The solution was extracted with benzene (3 X 30 ml) and the collected extracts were dried over sodium sulphate. The solvent was removed and the residue chromatographed on silica gel (elution with ethyl acetate-petroleum 60-80°) to afford the perinaphthofuran (7; 1.17g, 76%), m.p. 137-137.5°, $\nu_{\max}$ 1645 cm.⁻¹

3,4-Dihydro-2-phenylnaphtho (1,8-bc) furan-5-one (8).

The naphthofuran (7; 5g) in freshly distilled toluene (250 ml) was hydrogenated over alcohol-free Raney nickel at room temperature and atmospheric pressure. After 2 hours (uptake of H₂ 460 ml), the solvent was removed and the residue recrystallised from methanol as pale yellow crystals of the dihydronaphthofuran (8; 3.5g, 70%), m.p. 113-114° (lit. m.p. 113-114°²), $\nu_{\max}$. 1686 cm.⁻¹

NN¹-Dihydrobenzo (C) cinnoline (16).

Prepared by the action of zinc dust and hydrochloric acid by the method of Kuhne and Ehrlenmeyer.⁹

Attempted transhydrogenation of the naphthofuran (7) in the presence of NN¹-dihydrobenzo (C) cinnoline.

The naphthofuran (7; 20mg) in benzene (2 ml) was treated with NN¹-dihydrobenzo (C) cinnoline (18g). The mixture was

stirred under nitrogen at room temperature. T.l.c. analysis indicated the formation of several products, none of which was the desired dihydronaphthofuran (8).

4-(3,5,-Dihydroxy-2-formyl-4-methoxycarbonyl benzyl)-2-phenylnaphtho-[1,8-bc] furan-5-one (12).

Prepared⁵ by the condensation of the formyldiacetate (5) and the furanone (8) to form the benzilidene diacetate (9); subsequent transformation to the aldehyde (12) was effected by the procedure of Barton et al, m.p. 228-229° (lit. m.p. 228-229°),⁵ ν_{max} . 3370, 1665, 1638, 1617 cm^{-1}

EXPERIMENTAL TO PART II

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

(i) By the action of ethylene glycol and toluene-p-sulphonic acid.

The aldehyde (1; 150mg) in benzene (30 ml) was treated with ethylene glycol (4 ml) and toluene-p-sulphonic acid (10 mg). The mixture was refluxed for 6 hours through a soxhlet apparatus filled with calcium hydride. A portion of the reaction mixture (6 ml) was withdrawn and washed with saturated aqueous sodium bicarbonate solution. The organic solution was washed with water and dried over sodium sulphate. The solvent was removed and the remaining solid dissolved in deuteriochloroform containing T.M.S. as an internal standard. An n.m.r. spectrum was recorded showing the isolated solid to be essentially unchanged starting material. Further heating of the reaction mixture under reflux for 16 hours did not form the desired acetal (2).

(ii) By the action of butan-2-one ethylene acetal (3).

The aldehyde (1; 100mg) in butan-2-one ethylene acetal (5 ml) was treated with (a) toluene-p-sulphonic acid (3mg), and (b) $\text{BF}_3 \cdot \text{OEt}_2$ (2mg). Experiments were carried out at various temperatures; -10° , 0° , R.T., 60° . In no instance was the desired product formed.

Tetramethyl orthocarbonate.

Prepared by the action of sodium methoxide on chloropicrin, by the method of Hartel, b.p. $112-114^\circ$ (lit. b.p. 114°), n_D^{20} 1.3862 (lit. n_D^{20} 1.3864).

Diethylene orthocarbonate (4).

(i) Tetramethyl orthocarbonate and ethylene glycol.

To a solution of tetramethyl orthocarbonate (1.5g) and ethylene glycol (1.4g) in benzene (40 ml), was added toluene-p-sulphonic acid (one crystal). The mixture was refluxed through a Soxhlet apparatus containing a thimble of calcium hydride, for 24 hours. The solution was evaporated to small bulk and then shaken with hot petroleum (60-80°) (3 X 40 ml). The petroleum was decanted each time from the remaining small amounts of insoluble residue and the collected extracts evaporated to yield the orthocarbonate (4; 0.125g, 8.6%), m.p. 141-142° (lit. m.p. 143°)³, $V_{\max}$. (C Cl₄) 1356, 1245, 1200, 1060, 1019, 945 cm.⁻¹

(ii) Via chloropicrin and sodium glycolate.

Finely-cut sodium (4.6g) was slowly dissolved in freshly distilled ethylene glycol (50 ml) under a stream of nitrogen. The solution was allowed to cool to 90-100° and chloropicrin (7g) was added cautiously with stirring, under nitrogen. The mixture was allowed to cool to room temperature and stirred overnight. It was then continuously extracted with petroleum (60-80°) for 12 hours. The petroleum was evaporated to small bulk, whereupon the orthocarbonate (4) was deposited as colourless crystals (2.3g, 41%). The product was purified further by sublimation (0.5mm Hg, 60-70°), m.p. 141-142°, $V_{\max}$. 1356, 1245, 1200, 1060, 1019, 945 cm.⁻¹

(iii) Attempted preparation by the action of sodium glycolate on carbon tetrachloride.

All attempts to prepare the orthocarbonate (4) by this method lead to vigorous decomposition.

4-(2-Ethylenedioxyethyl-3,5-dihydroxy-4-methoxycarbonylbenzyl)-2-phenylnaphtho [1,8-bc] furan-5-one (2),
by the action of diethylene orthocarbonate (4).

A suspension of the aldehyde (1; 200mg) in ethanol-free chloroform (10 ml) was stirred with an excess of diethylene orthocarbonate (400 mg, 7.5 equivalents) in the presence of toluene-*p*-sulphonic acid (2mg) at room temperature for 4 hours. Triethylamine was added to the solution and stirred for a further 15 minutes. The solution was washed with saturated aqueous sodium bicarbonate solution and the aqueous washings extracted with a further portion of chloroform. The combined organic layers were dried and evaporated to give a yellow solid (205mg). Crystallisation from chloroform-benzene gave the acetal (2) as yellow microcrystals (185mg, 84%), m.p. 220-224°, ν_{max} . 3380, 1662, 1641 cm^{-1} , λ_{max} 222, 264, 327, 404 nm. (ϵ 24600, 8100, 23800 and 28800), τ 5.85 (4H, m), 5.83 (3H, s), 5.70 (2H, s), 3.55 (1H, s), 3.45 (1H, s), 1.8-2.5 (8H, cpx m), 0.37 and 0.42 (each 1H, s, D_2O exchangeable). (Found: C, 69.8; H, 4.6%; m/e 498. $\text{C}_{29}\text{H}_{22}\text{O}_8$ requires C, 69.9; H, 4.45%; M^+ 498).

Preparation of (2) was done in conjunction with Drs. M. Bolton and J.H. Bateson.⁵

11 α -Acetoxy-3,20-dioxopregn-4-ene (7).

To a solution of 11 α -hydroxyprogesterone (3g) in dichloromethane (50 ml) were added pyridine (4g) and acetyl chloride (4g), while the mixture was maintained at 0°. The mixture was stirred for 1 hour, washed with water and dried over sodium sulphate. The solvent and excess of reagent were removed, (oil pump; 1 mm Hg; 80°, 3 hours) to yield the crude acetoxy derivative (7). Crystallisation from ethanol-chloroform gave the

pure compound (3.2g, 86%), m.p. 172-174° (lit. m.p. 175-177°),⁶
 ν_{max} . 1740, 1718, 1685 cm^{-1}

11 α -Acetoxy-3,20-bisethylenedioxy pregn-5-ene (14).

11 α -Acetoxypregesterone (7; 1.0g) in ethanol-free chloroform (5 ml) was treated with diethylene orthocarbonate (2.8g, 8 equivalents) and toluene-*p*-sulphonic acid (100mg). The solution was stirred at room temperature for 8 hours. The solution was washed with saturated aqueous sodium bicarbonate solution and then with water. The organic layer was separated, dried and evaporated to small bulk and then eluted through a bed of grade 3 alumina by petroleum ether (60-80°) - ethyl acetate (4:1). The collected solution was evaporated to yield the bis acetal (14) as a colourless solid. Recrystallisation from ethyl acetate and petroleum (60-80°) yielded the pure product (960mg; 78%) m.p. 185-190° (lit. m.p. 186-190°),⁷ ν_{max} . 1738 cm^{-1} , $[\alpha]_{\text{D}}^{20}$ = 44° (lit.⁷ 40°). The product was found to be identical with the product obtained by the action of ethylene glycol⁷ on (7), m.p. 185-189°, mixed m.p. 185-190°, ν_{max} . 1738 cm^{-1} , $[\alpha]_{\text{D}}^{20}$ = 43°.

11 α -Hydroxy-3,20-bisethylenedioxy pregn-5-ene (20).

The bis acetal (14; 1g) in tetrahydrofuran (25 ml) was treated with 5 cm^3 of a 1N solution of sodium hydroxide in methanol-water (9:1) and the mixture stirred at room temperature for 24 hours. Dichloromethane (150 ml) and water (50 ml) were added. 1N Hydrochloric acid was added until the reaction mixture was at pH 7. The organic layer was separated, dried over sodium sulphate and evaporated to small bulk. The resulting oil was purified by p.l.c. to yield the 11 α -hydroxy bis acetal (20; 1.2g, 66%), m.p. 212-215°, (lit. m.p. 214-217°).⁸

11-Oxo-3,20-bisethylenedioxy pregn-5-ene (21).

The 11 α -hydroxy bis acetal (20; 0.5g) was added to a mixture of pyridine (5 ml) at room temperature and stirred for 15 hours. The solution was shaken with water (50 ml) and the mixture extracted with benzene-diethyl ether (1:1) (3 X 30 ml). The collected extracts were dried over sodium sulphate and the solvent was removed to yield a pale yellow oil. The oil was purified by p.l.c. to give the 11-oxo compound (21; 250 mg, 50%), m.p. 172-178° (lit. m.p. 175-179°),⁹ $V_{\max}$. 1695 cm⁻¹ $[\alpha]_D^{20}$ + 25° (lit.⁹ + 25°).

3 β -Acetoxy-20-oxopregn-5-ene (6).

To a solution of pregnenolone (1.5g) in dichloromethane (25 ml) were added pyridine (2g) and acetyl chloride (2g) while the mixture was maintained at 0°. The reaction was then stirred at room temperature for 90 minutes. The solution was washed with water and dried over sodium sulphate. The solvent was removed to afford the crude acetate (6); recrystallisation from ethanol-chloroform gave the pure compound (1.5g, 89%) m.p. 146-147° (lit. m.p. 146-147°),¹⁰ $V_{\max}$. 1740, 1710 cm⁻¹.

3 β -acetoxy-20-ethylenedioxy pregn-5-ene (13).

The acetate (6; 1.0g) in ethanol-free chloroform (5 ml) was treated with diethylene orthocarbonate (1.5g, 4 equivalents) and toluene-p-sulphonic acid (100 mg) and the solution was stirred at room temperature for 4 hours. The solution was washed with saturated aqueous sodium bicarbonate solution and then with water. The solvent was removed and the residue was eluted through a bed of grade 3 alumina by petroleum (60-80°) - ethyl acetate (4:1). The solution was evaporated to yield the acetal (13) as a colourless

solid. Recrystallisation from ethyl acetate - petroleum (60-80°) gave the pure acetal (13; 0.92g, 82%), m.p. 158-161° (lit. m.p. 159-160°),¹¹ $V_{\max}$. 1735 cm^{-1} , $[\alpha]_D^{20}$ -43° $\pm$ 2° (lit. -40°). The product was found to be identical with the product obtained by the action of ethylene glycol¹¹ on (6), m.p. 159°, mixed m.p. 157-160°, $V_{\max}$. 1735 cm^{-1} , $[\alpha]_D^{20}$ -46°.

Acetophenone-ethylene acetal (15).

Acetophenone (200mg) in ethanol-free chloroform (1 ml) was treated with diethylene orthocarbonate (880mg, 4 equivalents) and toluene-*p*-sulphonic acid (100mg) and the solution was stirred at room temperature for 2 hours. The solution was washed with saturated aqueous sodium bicarbonate solution and then with water. The solvent was removed and the residual solid purified by p.l.c. [elution with ethyl acetate-petroleum (60-80°) (1:3)] to afford the acetal (15; 0.20g, 74%). Further purification could be afforded by sublimation (0.5mm Hg, 70-80°) to form spectacular colourless prisms, m.p. 57-59°C, (the infra-red spectrum shows the disappearance of the carbonyl band at 1685 cm^{-1}), τ 8.35 (3H, s), 6.85 (4H, m), 2.4-2.8 (5H cpx m). (Found: C, 73.23; H, 7.51%; m/e 149. $\text{C}_{10}\text{H}_{12}\text{O}_2$ requires C, 73.15; H, 7.37%; M_r 154).

The product was found to be identical to that obtained by the action of ethylene glycol on acetophenone: Acetophenone (1g) was dissolved in benzene (100 ml). Ethylene glycol (10g) and toluene-*p*-sulphonic acid (30mg) were added and the mixture refluxed through a Soxhlet apparatus containing calcium hydride. After 36 hours t.l.c. indicated the total consumption of starting material. The solution was washed with saturated aqueous sodium bicarbonate and then with water. After removal of solvent the residual solid was purified by p.l.c. subsequent sublimation gave the pure product identical (i.r. spectrum) to the one

described above, m.p. 57-59°, mixed m.p. 57-59°.

p-Nitro benzaldehyde-ethylene acetal (17).

p-Nitro benzaldehyde (200mg) in ethanol-free chloroform (1 ml) was treated with diethylene orthocarbonate (700mg, 4 equivalents) and toluene-p-sulphonic acid (20mg). The solution was stirred at room temperature for 1 hour until the infra-red spectrum showed the disappearance of the carbonyl band at 1710 cm⁻¹. The solution was washed with saturated aqueous sodium bicarbonate solution and then with water. The solution was dried over sodium sulphate and evaporated to yield a colourless solid. Excess of reagent and reagent by-products were removed by sublimation (10⁻⁴ mm Hg, 80°). Crystallisation from ethanol afforded the pure compound (17; 203mg, 79%), m.p. 90.5°. The product was found to be identical (i.r. spectrum) with the product obtained by the action of ethylene glycol on p-nitro benzaldehyde,¹² m.p. 90.5° (lit. m.p. 90.5°),¹² mixed m.p. 90.5°.

Cyclohexanone-ethylene acetal (16).

Cyclohexanone (200 mg) in ethanol-free chloroform (1 ml) was treated with diethylene orthocarbonate (1.01g, 4 equivalents) and toluene-p-sulphonic acid (20 mg). The solution was stirred at room temperature for 30 minutes and was then washed with saturated aqueous sodium bicarbonate solution. The solution was washed with water and dried over sodium sulphate. Solvent removal afforded an oil which was purified by p.l.c. [elution with ethyl acetate-petroleum (60-80°) (1:3)] and finally isolated as an oil (16; 200 mg, 71%), n_D^{20} 1.4562. The product was found to be identical (i.r. spectrum) to that obtained by the action of ethylene glycol on cyclohexanone, n_D^{20} 1.4562 (lit.¹³ 1.4562).

O-Nitrobenzaldehyde-ethylene acetal (18).

o-Nitrobenzaldehyde (200mg) in ethanol-free chloroform (1 ml) was treated with diethylene orthocarbonate (700mg, 4 equivalents) and toluene-*p*-sulphonic acid (20mg). The solution was stirred at room temperature for 1 hour after which time the infra red spectrum showed the disappearance of the carbonyl band at 1695 cm^{-1} . The solution was washed with saturated aqueous sodium bicarbonate solution and then with water. The solution was dried over sodium sulphate and evaporated to small bulk. The resulting oil was purified by p.l.c. [elution with ethylacetate-petroleum (60-80°) (1:3)] to yield (18) as a colourless oil (200mg, 78%), n_D^{20} 1.5487. The product was found to be identical (i.r. spectrum) to that obtained by the action of ethylene glycol on *o*-nitrobenzaldehyde, $^{14}n_D^{20}$ 1.5487 (lit.¹⁴ 1.5487).

Salicylaldehyde-ethylene acetal (19).

Salicylaldehyde (200mg) in ethanol-free chloroform (1 ml) was treated with diethylene orthocarbonate (866mg, 4 equivalents) and toluene-*p*-sulphonic acid and the solution was stirred at room temperature for 3 hours until t.l.c. analysis indicated total consumption of starting material. The solution was washed with an aqueous solution of sodium bicarbonate (0.5% w/v, 10 ml) and then with water. The organic layer was separated and dried over sodium sulphate. The solvent was removed by evaporation, excess reagent and reagent by-products were removed by sublimation (10^{-4} mm Hg, 80° for 24 hours) to give the acetal (19; 197mg, 73%), m.p. 69-70°C (lit. m.p. 69-70°).⁵ The infra-red spectrum shows the disappearance of the carbonyl band at 1670 cm^{-1} .

Attempted acetalisation of benzophenone (22).

Benzophenone (200mg) in ethanol-free chloroform (1 ml) was treated with diethylene orthocarbonate (580 mg, 4 equivalents) and toluene-*p*-sulphonic acid (20mg). There was no reaction (t.l.c. and i.r.) after 24 hours at room temperature. Extensive variation of the reaction conditions did not lead to the formation of the desired acetal (22).

Attempted acetalisation-2, 2; 6, 6-tetramethyl cyclohexanone (23).

2, 2; 6, 6-Tetramethyl cyclohexanone (200 mg) in ethanol-free chloroform (1 ml) was treated with diethylene orthocarbonate (685mg, 4 equivalents) and toluene-*p*-sulphonic acid (20mg). There was no reaction (t.l.c. and i.r.) after 24 hours at room temperature. Extensive variation of the reaction conditions did not lead to the formation of the acetal (23).

Ethylene carbonate (24).

Prepared by the action of phosgene on ethylene glycol by the method of Allpress and Maw,¹⁶ m.p. 38.5-39° (lit. m.p. 38.5-39°).¹⁶

N-Phenyliminocarbonate (26).

Prepared by the method of Gulbins and Hamann,¹⁷ m.p. 69-71° (lit. m.p. 69-71°), $\nu_{\max}$ 1712 cm⁻¹, τ 4.47 (4H, s), 2.5-3.1 (5H, cpx m).

Tetrathiodiethylene orthocarbonate (28).

Prepared by the method of Amico and Campbell,¹⁹ m.p. 141-143° (lit. m.p. 142-143°), γ_{max} . (CHCl_3) 3000, 2910, 1435, 1283, 980, 963, 868 cm^{-1} .

11 α -Acetoxy-3,20-bisethylenedithiopregn-5-ene (33).

11 α -Acetoxypregesterone (7; 200mg) in ethanol-free chloroform (1 ml) was treated with tetrathiodiethylene orthocarbonate (900mg, 4 equivalents) and toluene-p-sulphonic acid (100mg) and the solution was refluxed for 3 days. The solution was washed with saturated aqueous sodium bicarbonate solution and then with water. The solution was dried over sodium sulphate and evaporated to small bulk and the resulting solid purified by p.l.c. [elution with ethylacetate-petroleum (60-80°) 1:3] to give the bithioacetal (33; 231mg, 82%), m.p. 225-228°, γ_{max} . 1715 cm^{-1} , $[\alpha]_{\text{D}}^{20}$ (CHCl_3 ; 8.75mg. ml^{-1}) +34.5° (Found: C, 61.63; H, 7.61; S, 24.64%; m/e 524. $\text{C}_{27}\text{H}_{40}\text{O}_2\text{S}_4$ requires C, 61.72; H, 7.68; S, 24.44%; M^+ 524).

EXPERIMENTAL TO PART III

Attempted preparation of 4-{2-[Cyano (hydroxy) methyl] - 3,5 dihydroxy-4-methoxycarbonylbenzyl}-2-phenylnaphtho [1,8-bc] furan-5-one (5).

The aldehyde (4; 50mg) in dried tetrahydrofuran (10 ml) was treated with a solution of sodium cyanide (0.3g) in water (10 ml) and the solution was maintained at 0°. The reaction was maintained at neutrality by the dropwise addition of 0.5N sulphuric acid. After stirring at 0° for 1 hr., t.l.c. analysis indicated the formation of a new product. All attempts to work up the new product led to reversion to starting material.

Trimethylsilyl cyanide.

(i) Prepared by the action of hydrogen cyanide on hexamethyldisilazane by the method of T.A. Bither, W.H. Knoth, R.V. Lindsey, Jr., and W.H. Sharkey.⁴

(ii) Prepared by the action of silver cyanide on trimethyl silyl cyanide by the method of E.C. Evers, W.O. Freitag, J.N. Kieth, W.A. Kriner, A.G. Mac Diarmid and S. Sujishi, b.p. 116-117° (lit. b.p. 116-117°), n_D^{25} 1.3893, (n_D^{26} 1.3892), V_{max} . 2980, 2180 cm^{-1} , T 9.60 (s).

4-{2-[Cyano (trimethylsilyloxy) methyl] - 3,5-bistrimethylsilyloxy-4-methoxycarbonylbenzyl}-2-phenylnaphtho [1,8-bc] furan-5-one (6).

The aldehyde (4; 50mg) was added to trimethylsilyl cyanide (55mg, 5 equivalents) and stirred for 48 hours. The excess reagent was removed *in vacuo* to yield (6; 74mg, 98%) as a yellow foam, V_{max} . 1730, 1635 cm^{-1} , T 9.38 (9H, s), 9.85 (9H, s), 9.66 (9H, s), 6.12 (3H, s), 5.67 (2H, s), 4.00 (1H, s), 3.52 (1H, s), 1.68-2.74 (9H, cp X m), λ_{max} . (CHCl₃) 267, 325, 405 nm. (ϵ 25, 100, 9380 and 28,500) (Found: C, 63.56; H, 6.21; N, 2.15% C₃₇H₄₃N₇Si₃ requires C, 63.67, H, 6.21; N, 2.01%). All attempts to crystallise

the foam caused desilylation, affording 4-(2-[cyano (trimethylsilyloxy) methyl]-3-hydroxy,5-trimethylsilyloxy-4-methoxycarbonylbenzyl)-2-phenylnaphtho [1,8-bc] furan-5-one (8), m.p. 172-175° (from chloroform-petroleum (60-80°)), ν_{max} . 3380, 1730, 1635 cm^{-1} , τ 10.00 (9H, s), 9.70 (9H, s), 4.06 (1H, bs), 3.63 (1H, s), 1.82-2.6 (9H, cpx m), 1.82-2.60 (9H, cpx m), λ_{max} . (CHCl_3) 267, 327, 406 nm. (ϵ 27,770, 11,750 and 26,700) (Found: C, 65.07; H, 5.47; N, 2.03%. $\text{C}_{34}\text{H}_{35}\text{NO}_7\text{Si}_2$ requires C, 65.25, H, 5.64; N, 2.24%).

Attempted preparation of 4-(2-[cyano (trimethylsilyloxy) methyl]benzyl)-2-phenylnaphtho [1,8-bc] furan-5-one (10).

The aldehyde (9; 50mg) in ethanol-free chloroform (0.1 ml) was treated with trimethylsilyl cyanide (68mg, 5 equivalents) and the solution stirred at room temperature for 24 hours. The solvent and excess reagent were removed in vacuo to leave a yellow solid. T.l.c. and n.m.r. showed only partial consumption of starting material and the formation of a new product. The new product was not isolable by p.l.c. since reversion to starting material occurred. Increasing the reaction time to 72 hours did not increase the amount of product formed. Addition of a crystal of zinc iodide led to the rapid consumption of starting material, with the formation of another compound that was blue and fluorescent by t.l.c. analysis. Evaporation of the solvent and excess reagent yielded a colourless foam; all attempts to crystallise the foam led to decomposition. Investigation of the foam showed it to be 2-(2-[cyano(trimethylsilyloxy) methyl]benzyl)-4-deoxy-4(cyano-benzilidene)-5-trimethylsilyloxynaphthoquinone (11). (70 mg., 91%), ν_{max} . 1640, 1605 cm^{-1} , τ 9.92 (9H, d), 9.58 (9H, s), 5.68 (2H, s), 4.41 (1H, s), 2.20-3.24 (13H, cpx m). λ_{max} . 340, 323 and 308 nm. (Found: M/e 562. $\text{C}_{33}\text{H}_{34}\text{N}_2\text{O}_3\text{Si}_2$ requires M+ 562). Similarly the ring A substituted aldehyde (4; 50mg) was stirred with trimethylsilyl cyanide (55mg, 5 equivalents) and zinc iodide (one crystal) at room temperature for 1 hour. Removal of solvent and excess

reagent gave a colourless foam which was found to be 2-(2-(Cyano (Trimethylsilyloxy) methyl)-3,5-bis trimethylsilyloxy-4-methoxy-carbonylbenzyl)-4-deoxy-4-(cyanobenzilidene)-5-trimethylsilyloxy-naphthoquinone (12). (81.6 mg, 93%), ν_{max} . 1735, 1660, 1617, 1605 cm^{-1} , τ 9.60-10.00 (36H, cpx m), 6.10 (3H, d), 5.50 (2H, s), 3.98 (1H, s), 3.60-3.83 (1H, m), 2.20-3.31 (9H, cpx m). λ_{max} . (CHCl_3) 340, 323 and 307 nm. (Found: m/e 979. $\text{C}_{41}\text{H}_{52}\text{N}_2\text{O}_7\text{Si}_4$ requires M+ 979).

Attempted base catalysed cyclisation of the tris trimethylsilyl cyanohydrin (6).

A number of experiments were performed on the tris trimethylsilyl cyanohydrin (6) in the presence of various bases dissolved in suitable solvents such as benzene, toluene and tetrahydrofuran. The bases used were:

- (i) Potassium tertiary butoxide.
- (ii) Sodium hydride.
- (iii) Sodium bistrimethylsilyl amide.⁶
- (iv) Lithium bistrimethylsilyl amide.⁶
- (v) Lithium salt of 2,2; 6,6-tetramethyl piperidine.

Extensive variation of the reaction conditions failed to lead to the formation of the desired cyclised product.

Attempted intramolecular benzoin-type cyclisation of the aldehyde (4) in the presence of cyanide ion.

A solution of the aldehyde (4; 23mg) and sodium cyanide (3 mg) in ethanol (0.5ml) was cooled to -10° for 1 hour. No diminution of starting material was observed by t.l.c. Extensive variation of the reaction conditions

including the introduction of potassium dihydrogen phosphate as a buffer over the range pH 6.0-10.0, did not lead to the formation of a cyclised product.

Attempted intramolecular benzoin-type cyclisation of the model aldehyde (9)

The aldehyde (9; 36mg) in hexamethyl phosphoramide (1 ml) was stirred at room temperature under nitrogen. Sodium cyanide (2.5 mg, 1.1 equivalents) was added. The mixture was stirred for a further 2 hours at room temperature. T.l.c. analysis indicated the formation of a new product accompanied by some decomposition. The product, which was isolated by p.l.c. was found to be the naphthacenofuranone (13; 19 mg, 55%) m.p. 245° (lit. m.p. 245°), $\nu_{\max}$. 1640cm^{-1} .

4-(2-(Propane-1,3-dithio) methylbenzyl)-2-phenylnaphtho [1,8-bc] -furan-5-one (15).

(i) Hydrogen chloride as catalyst.

The aldehyde (9; 50mg) and propane-1,3-dithiol (15mg) were added to mixture of methanol-toluene (1:1; 1 ml). A slow stream of hydrogen chloride gas was passed through the solution at $5-10^{\circ}$ for 2 hours. The solvent and excess reagent were removed in vacuo (1 mm Hg, 80° , 2 hours). Crystallisation of the residual solid from chloroform-petroleum ($60-80^{\circ}$) gave the dithioacetal as yellow clusters (15; 59mg, 95%), m.p. $196-198^{\circ}$, $\nu_{\max}$. 1635cm^{-1} (shows disappearance of carbonyl band at 1688cm^{-1}), $\lambda_{\max}$. (ethanol) 265 and 400 nm. (ϵ 24,190 and 28,800), τ 7.96 (2H, bs), 7.20 (4H, bs), 5.86 (2H, s), 4.62 (1H, s), 1.86-2.92 (13H, cpx m).

(Found: C, 73.94; H, 4.75; S, 13.78%; m/e 454. $C_{28}H_{22}O_2S_2$ requires C, 74.00, H, 4.88; S, 14.08%; M^+ 454).

(ii) Acetic acid and boron trifluoride-etherate
as catalyst.

To a suspension of the aldehyde (9; 400mg) in glacial acetic acid (24 ml) was added boron trifluoride-etherate (40 ml). Propane-1,3-dithiol (1 ml) and the mixture stirred at room temperature for 30 minutes. The reaction mixture was poured into water (150 ml) and extracted with chloroform (150 ml). The organic layer was washed with water (3 X 150 ml), separated and dried over sodium sulphate. The solvent was removed to yield an orange oil. The remaining solvent and reagent were removed (oil pump; 1 mm Hg; 80° ; 3 hours). The resulting yellow solid was crystallised from benzene-petroleum ($60-80^\circ$) to give the dithioacetal (15; 454g, 91%), m.p. $196-198^\circ$, ν_{max} 1635 cm^{-1} .

12-(Propane-1,3-dithio)-6 α ,7,12,12 α -tetrahydro-1-phenylnaphthaceno
[-1,12-bd] furan-6-one (17).

Anhydrous benzene (50 ml) was placed in to a 250 ml, three necked, round bottom flask, and a stream of dried, oxygen free nitrogen was passed through the solution at reflux temperature for 30 minutes. The flask was positioned in a reflecting enclosure so that its bottom was 5-6 cm from the surface of a 750 Watt tungsten lamp. The dithioacetal (15; 50mg) and freshly-prepared potassium tertiary butoxide (6.7mg, 1 equiv.) was added. The solution was irradiated under reflux while the stream of nitrogen was passing through. After 30 minutes, t.l.c. and u.v. analysis indicated complete consumption of starting material, with the clean formation of a new product. The cooled benzene solution was washed with an aqueous solution of potassium dihydrogen

phosphate, and then with water. The organic phase was separated and dried over sodium sulphate. The solvent was removed to give a colourless solid. Crystallisation from benzene-petroleum (60-80°) gave the tetracyclic dithioacetal (17; 42.5mg, 85%) m.p. 228-231°, ν_{max} . 1692 cm^{-1} , λ_{max} . (ethanol) 278 and 354 nm. (ϵ 22,370 and 12,500), τ 5.60-8.79 (9H, cpx m), 5.18 (1H, d, J 5Hz), 1.82-3.05 (12H cpx m). (Found: C, 74.00; H, 5.04; S, 13.80%; m/e 454. $\text{C}_{28}\text{H}_{22}\text{O}_2\text{S}_2$ requires C, 74.00; H, 4.88; S, 14.08%; $M+454$).

4-(2-[(propane-1,3-dithio)methyl]-3,5-dihydroxy-4-methoxycarbonyl-benzyl)-2-phenylnaphtho [1,8 bc]furan-5-one (14).

The aldehyde (4; 200mg), was suspended in glacial acetic acid (24 ml). Boron trifluoride-etherate (4 ml) and propane-1,3-dithiol (1 ml) were added. The solution was stirred at room temperature for 30 minutes. The reaction mixture was poured into water (150 ml) and extracted with chloroform (1 aliquot, 150 ml). The chloroform solution was washed with water (3 X 150 ml) and dried over sodium sulphate. The solvent and excess of reagent were removed in vacuo (1 mm Hg, 80°, 3 hours). The residue was recrystallised from benzene-petroleum (60-80°) to give the thioacetal (14; 234mg, 98%), m.p. 196-198°, ν_{max} . 3370, 1675, 1638 cm^{-1} , λ_{max} . (ethanol) 265, 400 nm (ϵ 27,300 and 15,360), τ 8.00 (2H, m), 7.18 (4H, bs), 5.98 (3H, s), 5.32 (2H, m), 3.33-3.87 (2H, cpx m), 1.77-2.77 (cpx m). (Found: C, 66.28; H, 4.74; S, 11.39%; m/e 544. $\text{C}_{30}\text{H}_{24}\text{O}_6\text{S}_2$ requires C, 66.17; H, 4.44; S, 11.76%; $M+544$).

12-(Propane-1,3-dithio)-6a,7,12,12a-tetrahydro-9,11-dihydroxy-6-oxo-1-phenyl-6H-naphthaceno [1,12 bc]furan-10-carboxylate (18)

Anhydrous benzene (50 ml), contained in a 250 ml round-bottomed flask, was de-oxygenated by the passage of a

stream of dry, oxygen-free nitrogen at reflux temperature for 30 minutes. The thioacetal (14; 27mg) and lithium bistrimethylsilyl amide (8.3mg; 1 equivalent) were added and the solution was irradiated under reflux as previously described in an atmosphere of nitrogen. After 40 minutes, t.l.c. and the ultra-violet spectrum showed the complete consumption of starting material and the formation of a blue fluorescent product. The cooled solution was washed with saturated aqueous potassium dihydrogen phosphate solution and then with water. The organic layer was separated and dried over sodium sulphate. The solvent was removed to afford a colourless semi-crystalline solid (22mg), m.p. 220-223,^o ν_{max} . 3400, 1680 and 1638 cm^{-1} , λ_{max} . (CHCl_3) 265 and 345 nm (ϵ 24,840 and 12,900). All attempts to recrystallise the product for further characterisation led to decomposition.

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