

THE SYNTHESIS OF LINEAR AROMATIC SYSTEMS

a thesis presented by

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

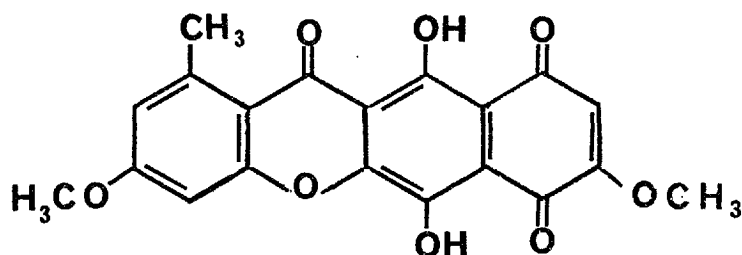
DOCTOR OF PHILOSOPHY

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October 1973

ABSTRACT

The first section of this thesis briefly describes the chemistry of bikaverin (1) and related compounds. A short account of the published chemistry of bikaverin is included. This is followed by a summary of the progress made in these laboratories towards the synthesis of linear aromatic systems with the attention focused mainly on the work relevant to the author's contribution.



(1)

The second section contains a discussion of the author's work directed towards the synthesis of linear aromatic systems.

The discussion is divided into two parts:

PART I describes the synthesis of a bikaverin precursor series, and the tetrahydrobenzoxanthone with an unsubstituted ring A.

PART II describes the synthesis of various chroman-4-one, chromone intermediates, some ACD systems and contains a subsection dealing with the dichlorodicyanoquinone oxidation step used in the synthesis.

ACKNOWLEDGEMENTS

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Kurt A. Freund,
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October 1973

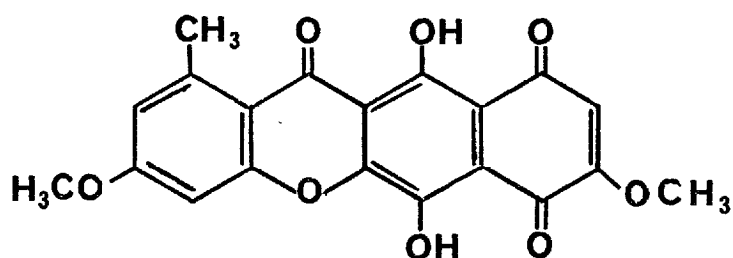
To my parents.

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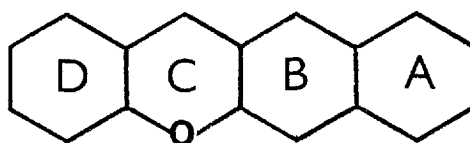
INTRODUCTION

Bikaverin (1), a wine red pigment with specific antiprotozoal activity has been isolated from cultures of Gibberella Fujikuri,^{1,2,3} Fusarium oxysporum and later from cultures of Fusarium f. sp. Lycopersici.⁴ It belongs to a series of linear aromatic compounds known as hydroxy-quinonoid benzoxanthenes.



(1)

The nomenclature used throughout this thesis, in referring to the tetracyclic derivatives will correspond to the following numbering scheme:-



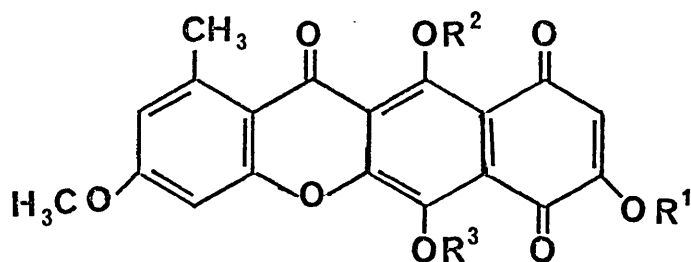
The structure determination of the red pigment by Cornforth⁵ and co-workers from a culture medium of Fusarium oxysporum and simultaneously by Kjaer and J. D. Bu'Lock¹ on the pigment bikaverin from Gibberella Fujikuroi (Fusarium moniliforme) carried out using spectrophotometric, nuclear magnetic resonance, mass spectral data and chemical reactions. The structure was confirmed by X-ray studies carried out by de Boer.⁶

It appears likely that the pigment Lycopersin isolated and examined chemically ^{2,7,8,9,10} may also be identical with bikaverin although the ascribed formula $C_{20} H_{15} O_5$ is different. Many of the properties correspond and both pigments can be obtained from Fusarium oxysporum f. sp. lycopersici. Another two pigments ^{3,11} described in the literature might possibly be bikaverin.

The linear ring system (1) is not novel, ^{12,13} but it has not been previously encountered in natural products. Its biosynthesis and chemo-taxonomic implications are presently being investigated.¹ This compound is a clear example of a polyketide, but with a unique cyclisation pattern and an unusually long C_{20} polyketide chain.

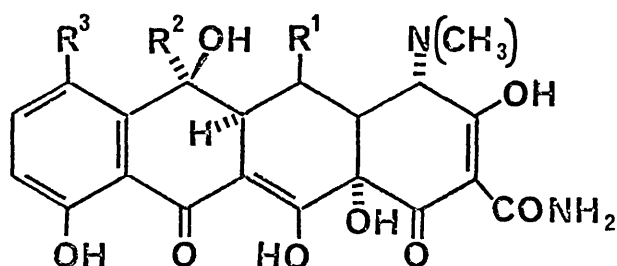
THE CHEMISTRY OF LINEAR AROMATIC COMPOUNDS

Due to the novelty of these types of structures as naturally occurring compounds no total synthesis of bikaverin ¹⁻¹⁰ ($R^1=CH_3$; $R^2=R^3=H$) or the related norbikaverin ($R^1=R^2=R^3=H$) (2) has been



(2)

described in the literature, although many compounds with similar tetracyclic structures exist.^{14,15,16} Among these are the tetracyclines (3),



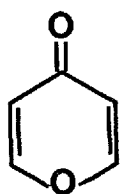
(3)

which has been excellently reviewed both in the literature ^{17,18} and previous theses from this laboratory.^{19,20}

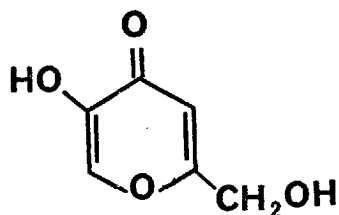
The study of flavones, isoflavones, coumarins and rotenoids, which are not biogenetically related to bikaverin, but include the

CD rings is extensive and has been reviewed by Geissman ²¹ and others.²²

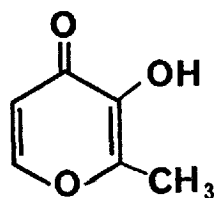
Numerous natural products contain the pyran ring (4). Kojic acid ²³ (5), formed in the fermentation of starch by Aspergillus oryzae, maltol ²⁷ (6) isolated from larch bark and chelidonic acid (7) from Chelidonium majus, are γ -pyrones.



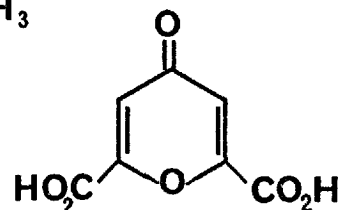
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(5)

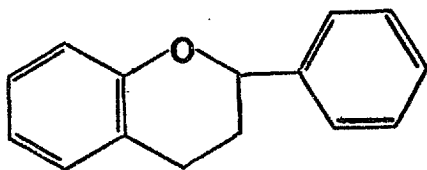


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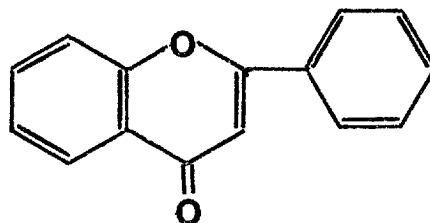


(7)

Benzopyrans frequently are found in plants. Benzo [b] dihydropyran is called chroman and 2-phenylchroman is called flavan (8), and the flavones are benzo- γ -pyrones (9)



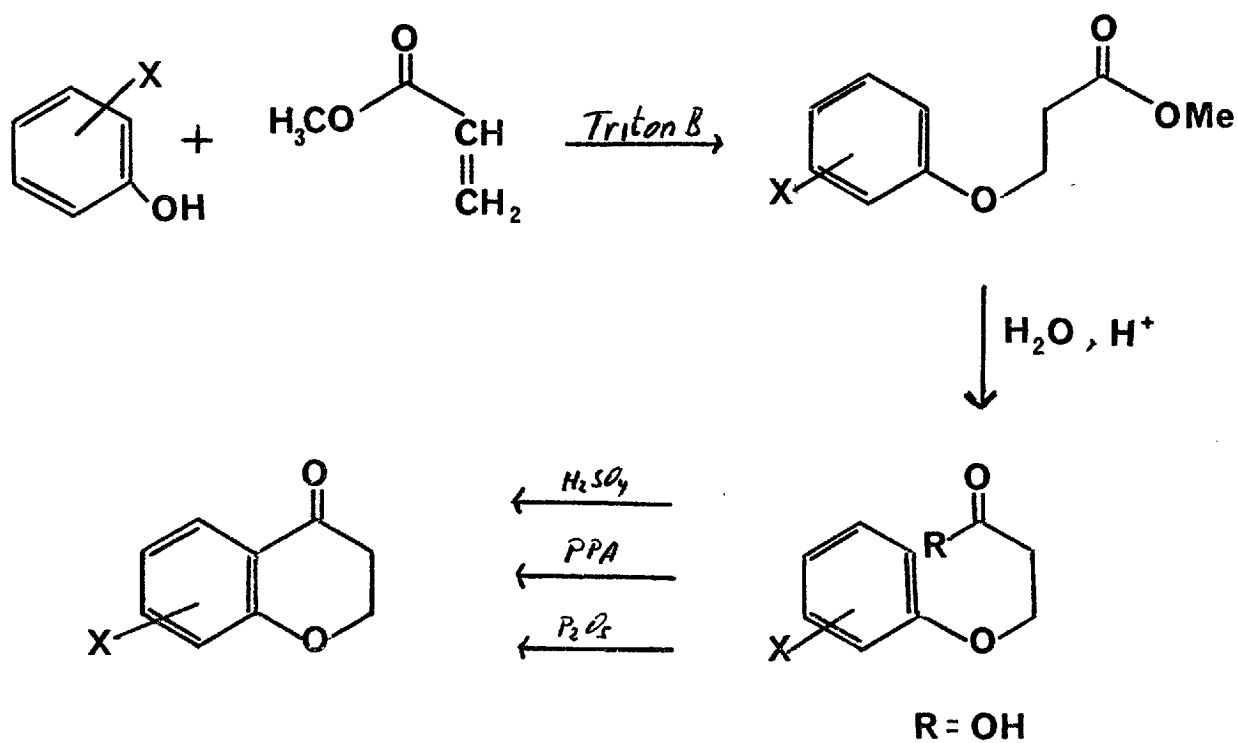
(8)



(9)

Various methods of synthesising chromanones are to be found in the literature.²⁶⁻³²

Scheme I

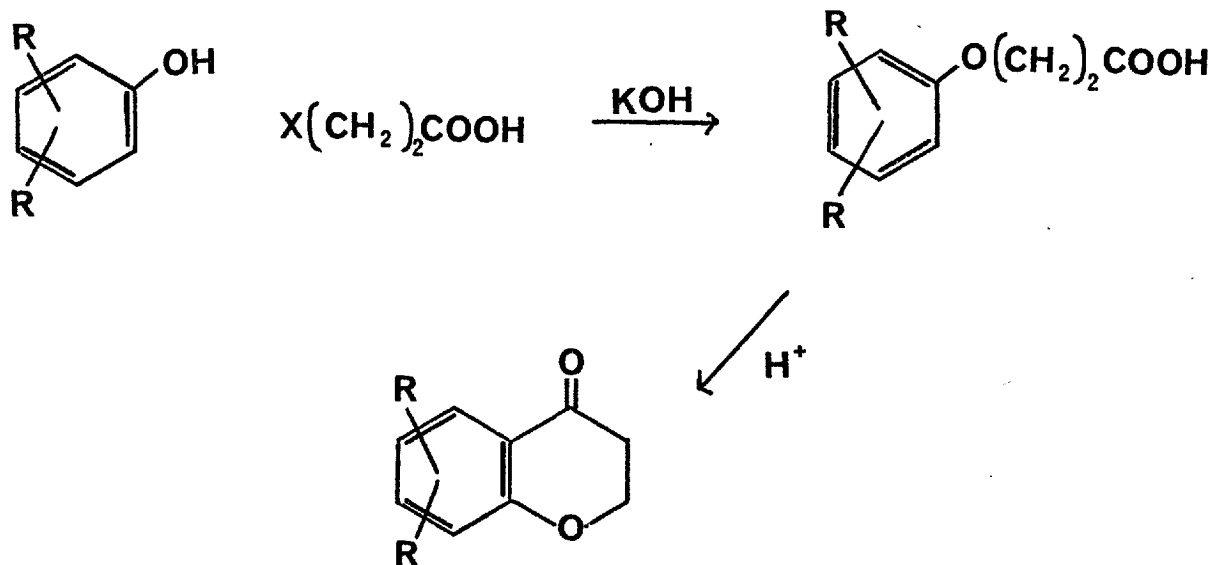


(10)

Scheme (I) ³¹ gives the chromanone (10) in yields between 25% and 45%.

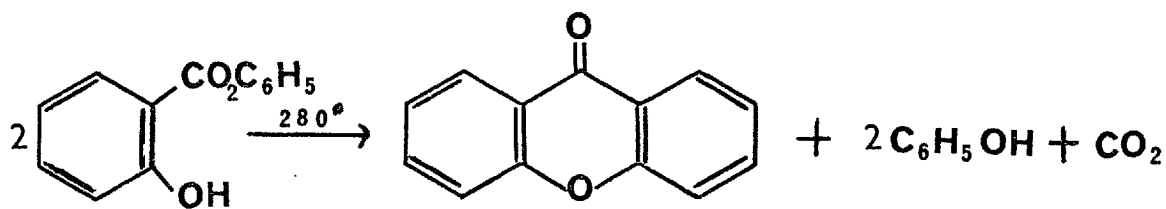
Wiley ³³ reported a different method for the synthesis of chromanones:

(over leaf)



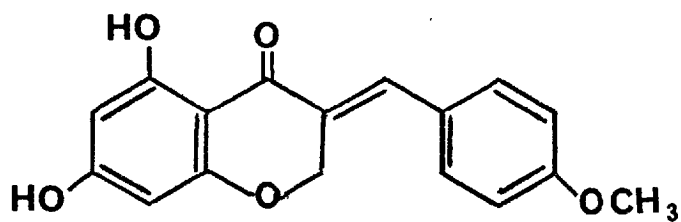
These were prepared with the objective of studying therapeutical activity of such compounds by lower organisms. Ramage ^{34,35} prepared the chromanones by cyanoethylation of the monomethyl ether, followed by hydrolysis of the resulting nitrile and subsequent cyclisation of the β -phenoxy propionic acid.

Xanthone (11) is prepared by thermal decomposition of phenyl salicylate.

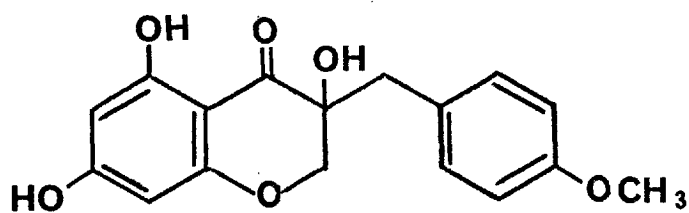


(11)

Eucomin (12) and (+) Eucumol (13), two natural occurring oxygen heterocyclics ACD rings have been isolated by Bohler and Tamm.³⁶

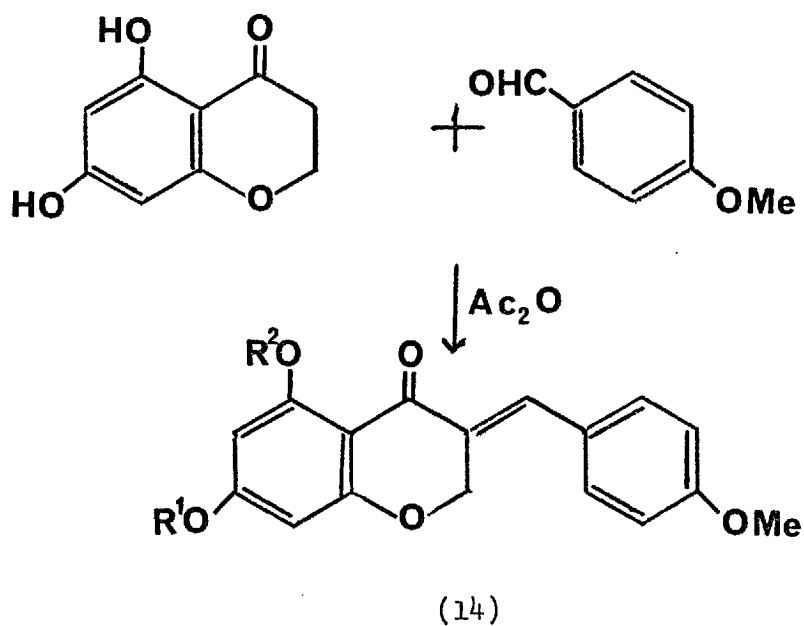


(12)

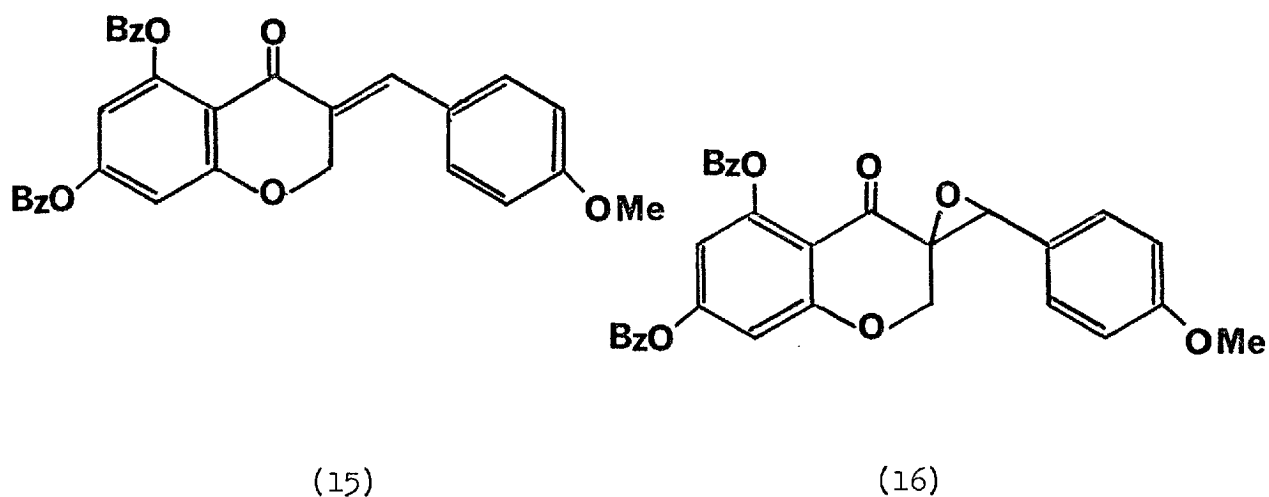


(13)

In the reported synthesis of these compounds (12,13) by Farkas ³⁷ the chroman-4-ones are condensed with aromatic aldehydes in acetic anhydride to give the eucomin diacetate (14; $R^1=R^2=Ac$).

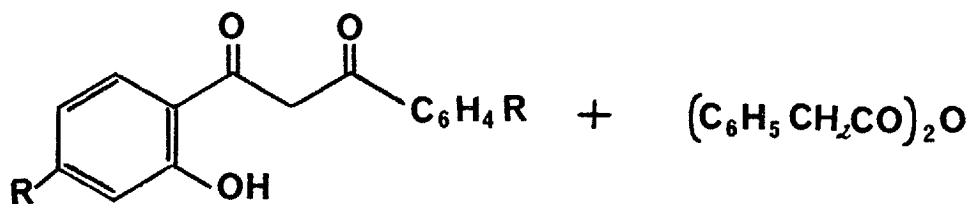


Saponification of (14; $R^1=R^2=Ac$) gave a compound identical to (12). Benzylation of eucomin gave dibenzyl eucomin (15) and treatment of (15) with alkaline hydrogen peroxide gave the epoxide (16).

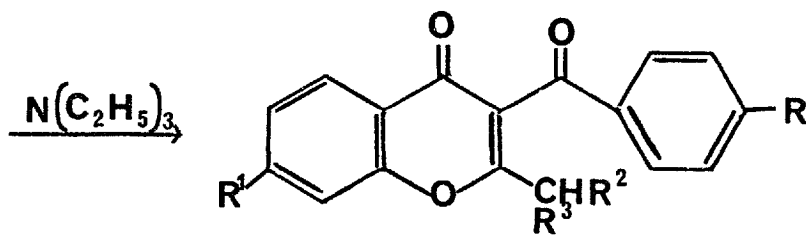


This is smoothly converted by hydrogenation to ($\pm$)-3-(4¹-methoxybenzyl)-3,5,7 trihydroxy chroman-4-one (13).

Ullman and co-workers^{14,15} have prepared 3-aryl-2-methyl chromanones (17) (Table I) based on analogy with the synthesis of other 3-acyl-chromones by Ollis.²⁵ This method involves condensing an arylacetic anhydride and a suitably substituted o-hydroxydibenzoyl-methane (18) in the presence of a slight excess of triethylamine.



(18)

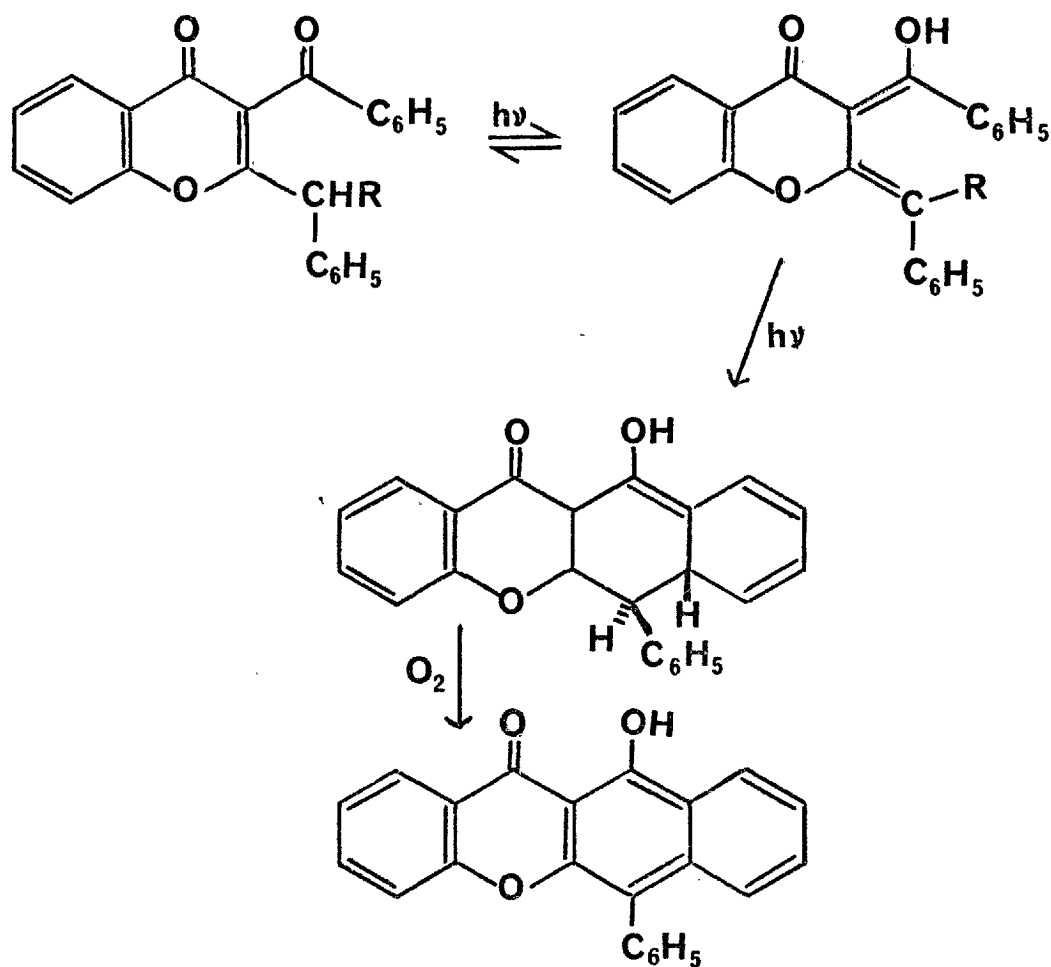


(17)

TABLE I

Compound (17)	R	R ¹	R ²	R ³
a)	H	H	C ₆ H ₅	H
b)	H	H	pC ₆ H ₄ OCH ₃	H
c)	H	CN	C ₆ H ₅	H
d)	H	NO ₂	C ₆ H ₅	H

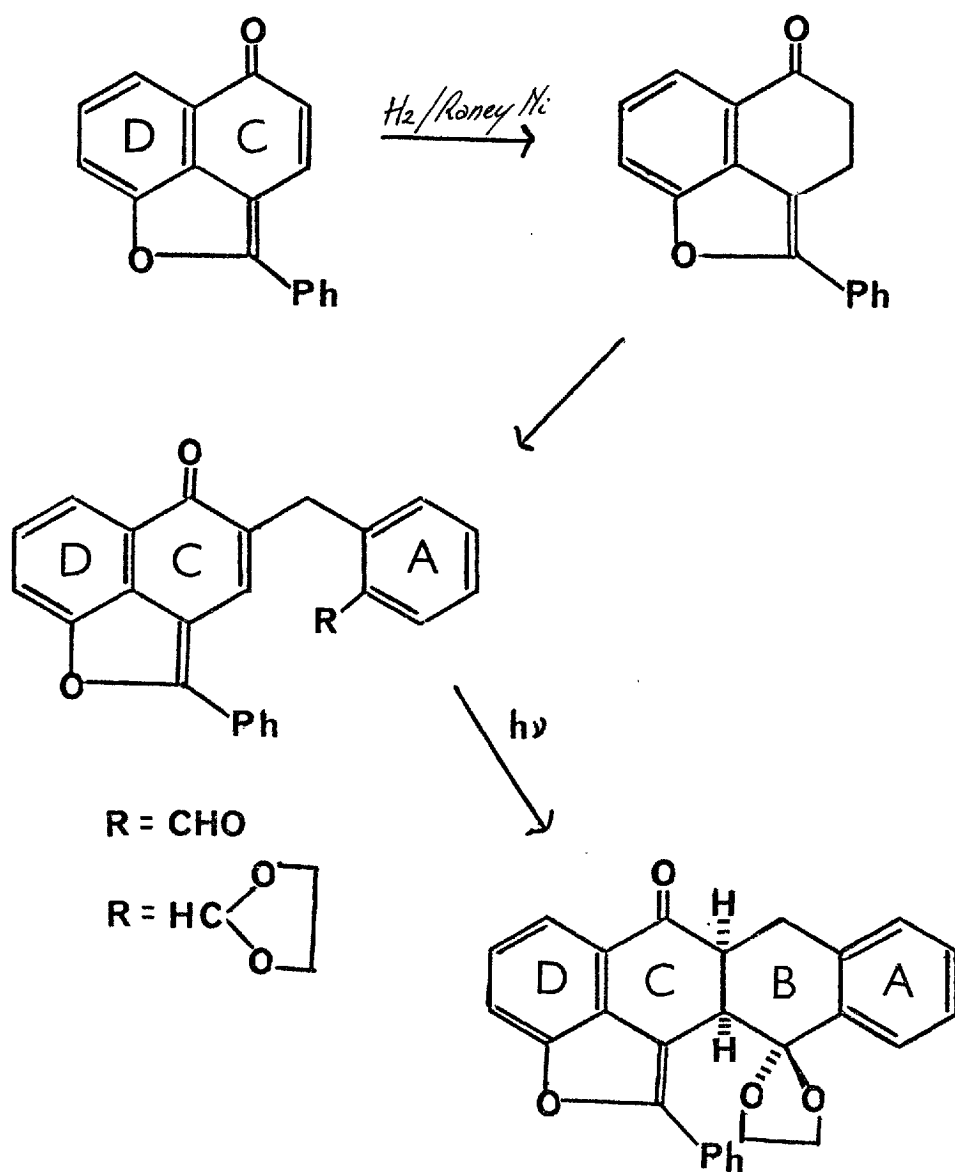
These compounds all displayed infrared absorption near 1670cm^{-1} corresponding to the benzoyl carbonyl and near 1625cm^{-1} corresponding to the chromone carbonyl grouping. Photolysis of (19) gave a benzo[bl-xanthen-12-one (20).



SUMMARY OF PREVIOUS WORK

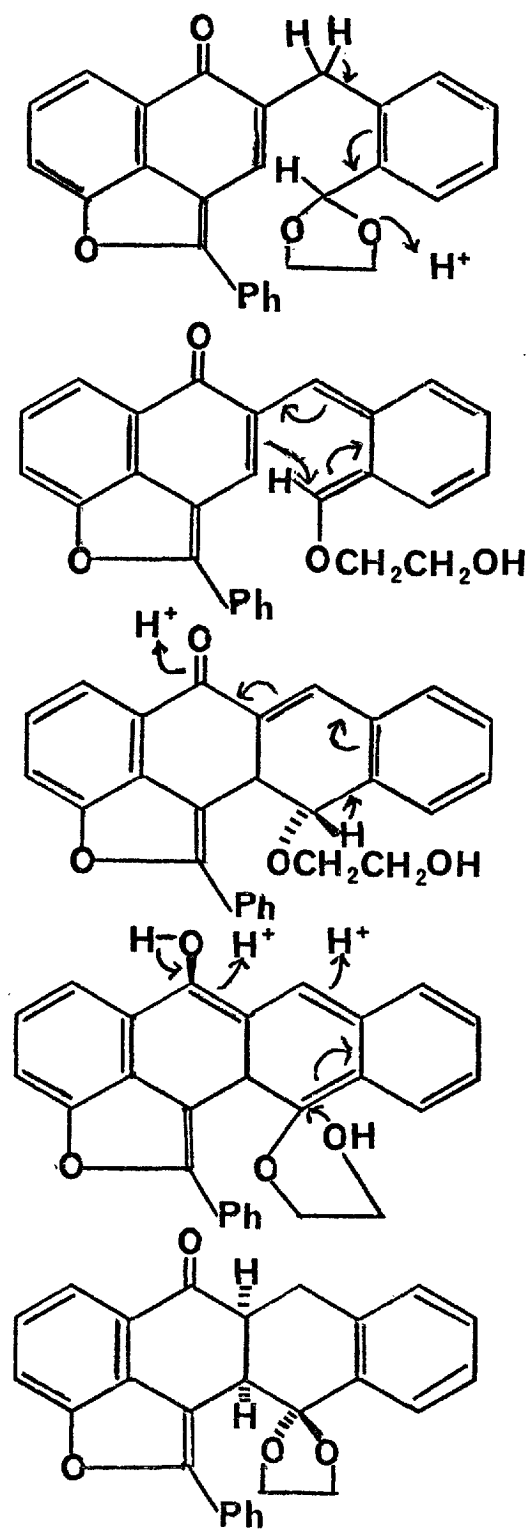
An account of the progress made towards the synthesis of heterocyclic systems in these laboratories up to 1973 is presented. The project originated with the purpose of synthesising tetracycline.^{17,18}

Various compounds were made in order to study the mechanism of the photochemical cyclization of ring B.



The synthetic approach that has been developed by Barton and co-workers ^{18,19} involves joining a ring A residue to a ring CD moiety. The synthesis is completed by cyclising the ACD compound to the ABCD skeleton by a photochemical reaction. A postulated mechanism is outlined in Scheme II. (see over leaf)

Scheme II



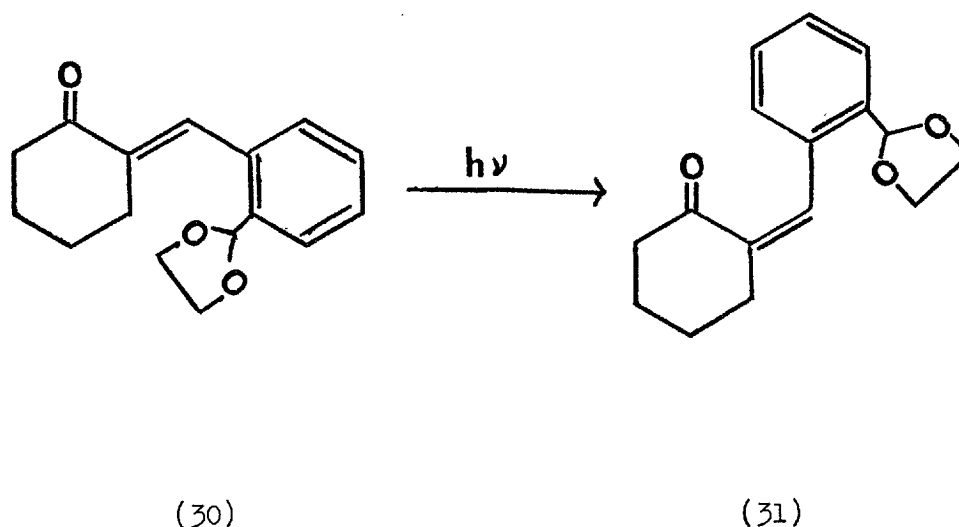
This mechanism is currently under investigation by other workers in these laboratories.

The naphthofuran (21) was catalytically hydrogenated to its dihydro-derivative (22). Condensation of (22) with o-phthaldehyde in the presence of triethylamine gave (23) which was converted to the acetal (24) by reaction with ethylene glycol in the presence of catalytic amounts of p-toluene sulphonic acid.

The acetal (24) constituted the ACD nucleus which on photolysis in the presence of acid gave the tetracyclic ketal (25).

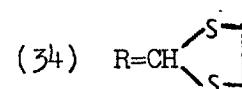
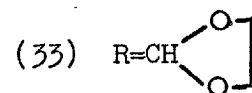
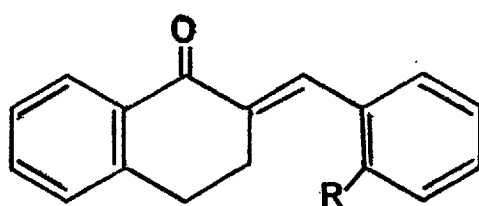
The Photocyclisation reaction ¹⁸ is thought to involve a conrotatory ³⁸ cyclisation of a intermediate triene (26) to give (27). The intermediate (27) then undergoes a thermal 1,5 sigmatropic hydrogen shift to give (28) which is isomerized to (29).

Experiments ¹³ using a ketone with an exocyclic double bond such as (30) have failed to give the cyclised product on irradiation in presence of 1 eq. of benzoic acid. Instead simple double bond isomerisation occurred affording the cis compound (31).



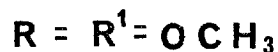
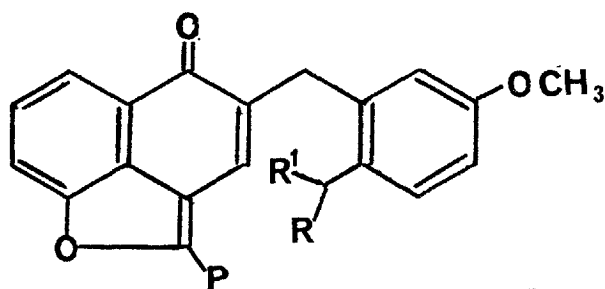
This type of isomerisation has been observed earlier for benzal-acetone ³⁹ and naphthofuran derivatives.¹⁹

No cyclised products were observed in the cases of the α -tetralones ¹² (33) and (34).



This suggests that the α,β unsaturation of the keto-group must be endocyclic for photocyclisation to occur.

The necessity of a cyclic acetal has been demonstrated.⁴⁰ When the open acetal (35) was photolysed under the usual conditions a large number of products were observed, none corresponding to the desired linear tetracyclic structure.



(35)

The effect of solvents on the yield and rate of reaction for the photolysis of the tetracycline series has been studied.²⁰ Acetonitrile and ethyl acetate are the best solvents for the cyclisation to the ABCD compounds. An abbreviated example of these results is

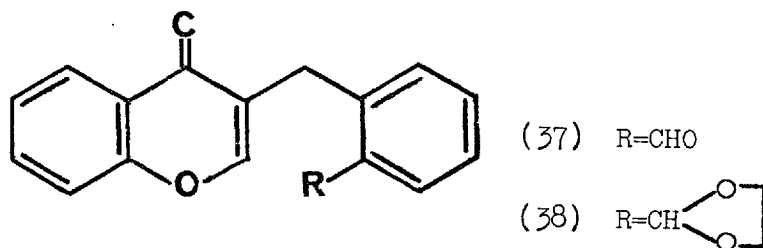
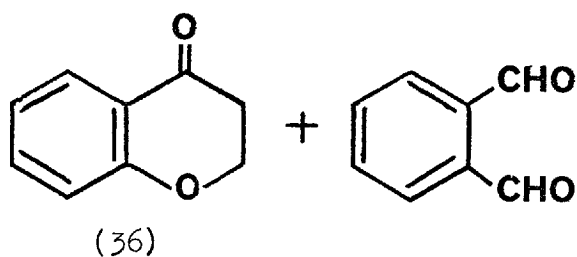
given in the following table:

TABLE II ²⁰

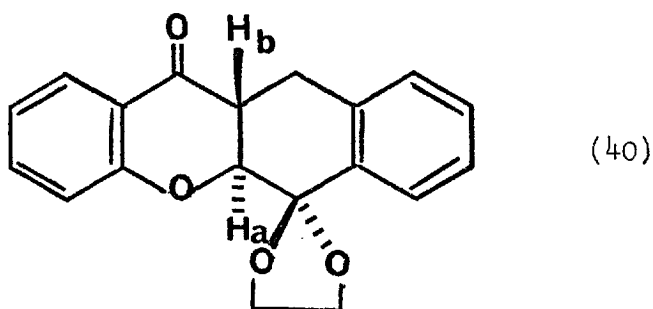
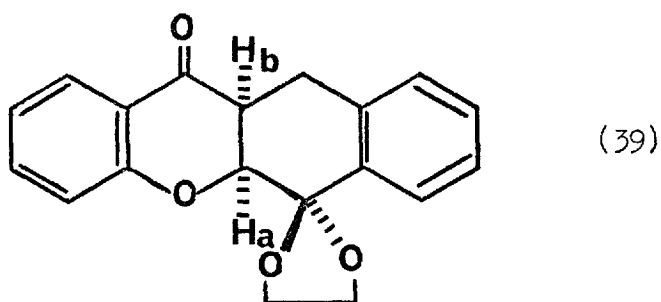
All experiments: acetal (50mg), solvent (40ml), benzoic acid (1.2 eq.)
and triethylamine (5 eq.)

Solvent	Time (h)	Yield % ^(+5%) _(-5%)
Acetonitrile	12	80
Ethylacetate	12	78
DMF	6	70
Glyme	6	70
Benzene	4.5	60
Cyclohexane	10	60
Nitromethane	16	55
Ethanol	8	30

Chromanone ¹² (36) readily available from the hydrolysis of β -phenoxypropionitrile followed by polyphosphoric acid cyclisation of the resulting β -phenoxypropionic acid was condensed with o-phthaldehyde in ethanol with triethylamine as base at 140°- 170°C.

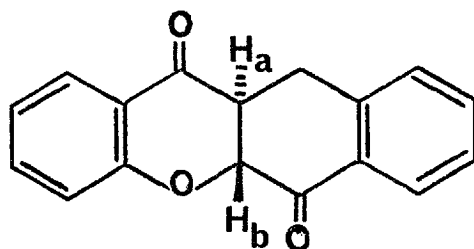


The resulting aldehyde (37) was converted into its acetal (38) by standard methods. Photolysis of a benzene solution of the acetal (38) containing o-chlorobenzoic acid, using a medium pressure mercury arc lamp proceeded rapidly to give 6,6 ethylenedioxy, 5a,6,11, 11a-tetrahydrobenzo[blxanth-12-ones (39) and (40).

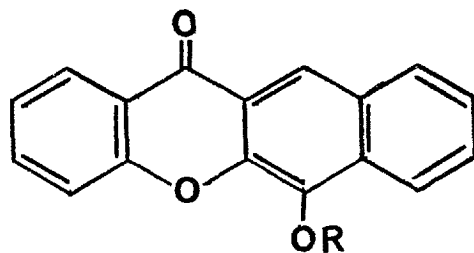


The first formed product was the cis isomer (39) which slowly epimerised to the trans isomer on work-up (Al₂O₃ chromatography). The ketal (40) was converted to the diketone (41) by treatment with trityl fluoroborate ^{18,41} in dichloromethane followed by aqueous sodium bicarbonate.

Direct acid hydrolysis of (40) gave a complex mixture containing very little of the diketone (41).



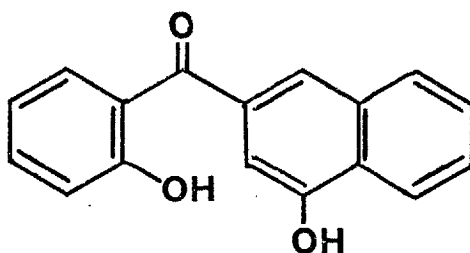
(41)



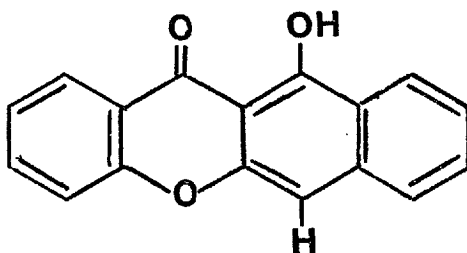
(42) R=H

(43) R=COCH₃

When the diketone (41) was treated with sodium hydroxide in aqueous methanol, 6-hydroxybenzo[blxanth-12-one (42) was formed presumably through autoxidation of the enolate anion. No product was isolated that corresponded to the naphthalene (44) which would be formed by retroaldol cleavage⁴² of (41).



(44)

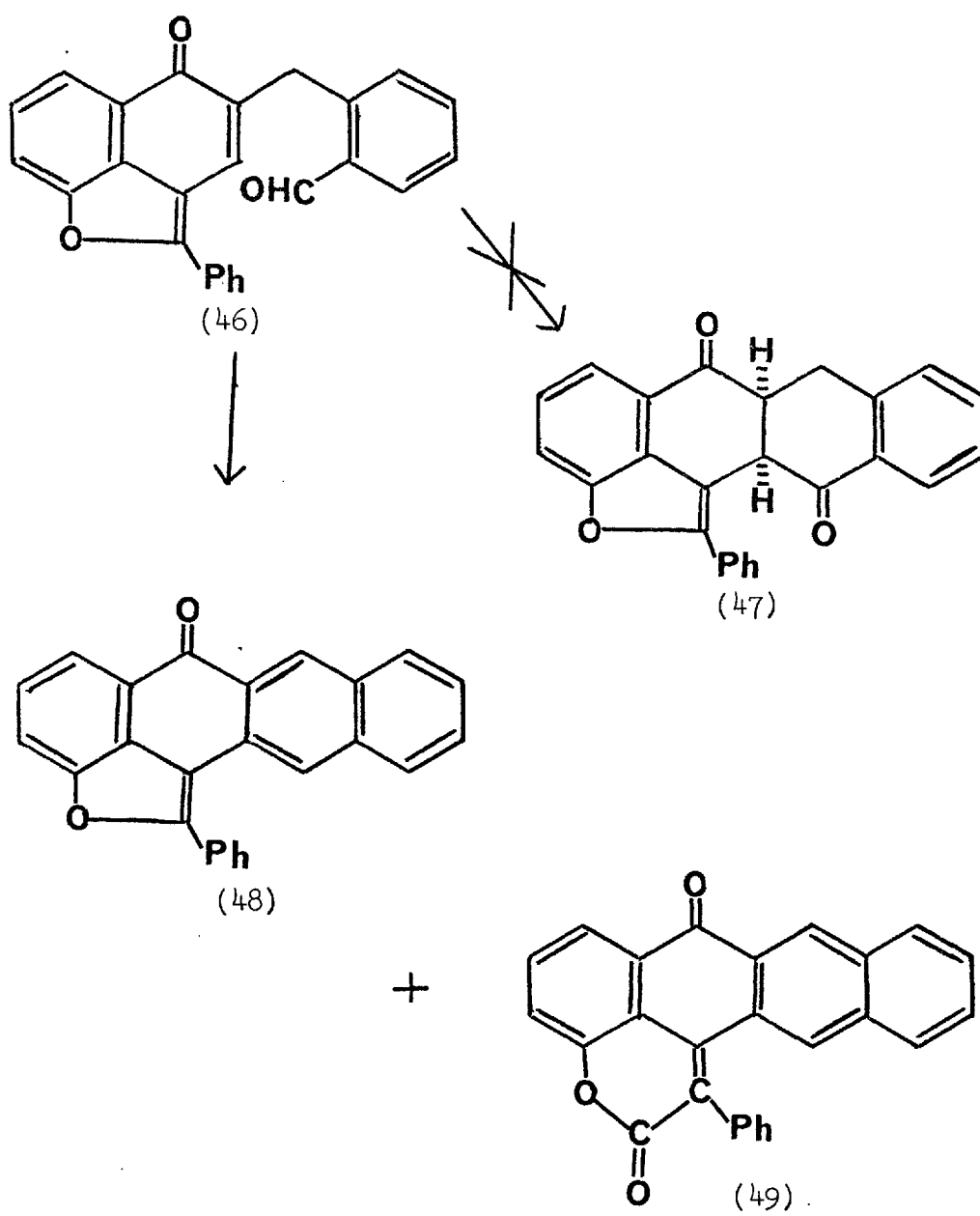


(45)

The ultraviolet spectrum of the benzoxanthone (42), closely resembled that of its 11-hydroxy isomer (45). Treatment of (41) with acetic anhydride in pyridine gave the acetoxy xanthone (43). Presumably via autoxidation in the presence of air.

Various alternative methods of preparing tetracyclic compounds have been studied.^{18,19} It was predicted that treatment of the aldehyde (46) with sodium cyanide in refluxing ethanol would give the diketone derivative (47). In fact, however, two compounds were isolated:

(over leaf)



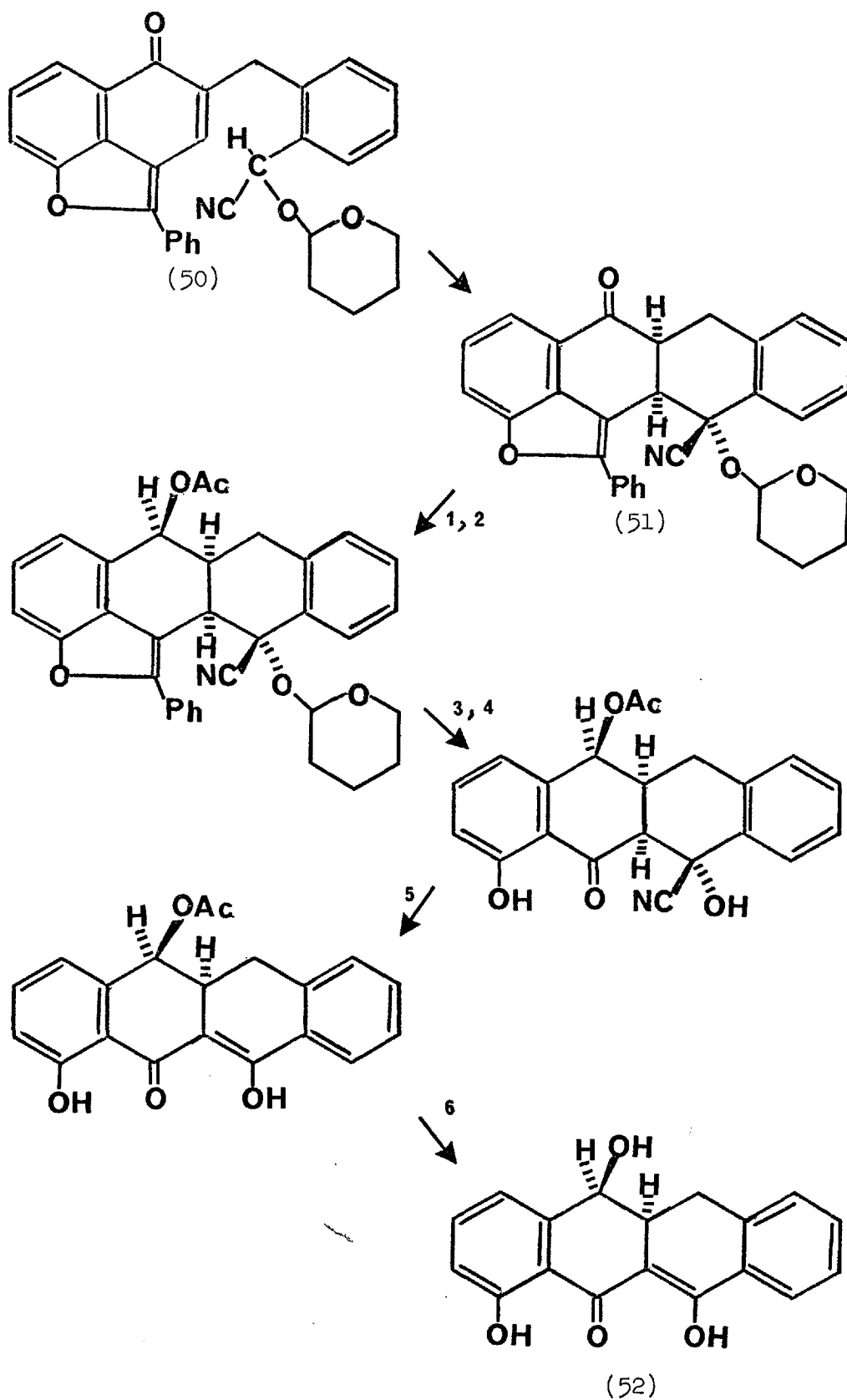
The first was the aromatic ketone (48) and the second, the ketolactone (49) formed by conjugate addition of the furan.¹⁹

A more successful cyclisation procedure was to the potassium t-butoxide promoted reaction of the cyanohydrin pyranylether (50) in refluxing ether,^{19,43} Scheme III.

The cyclised cyanohydrinpyranylether (51) was converted into the simple tetracycline model (52).

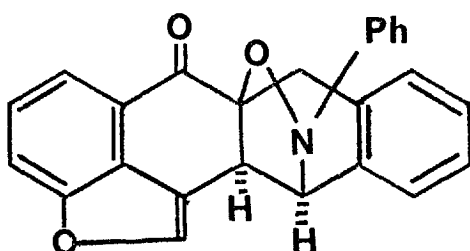
(Scheme III over leaf)

Scheme III



Reagents: 1. $\text{Li}(\text{t-BuO})_3\text{AlH}$ 2. $\text{Ac}_2\text{O}/\text{pyridine}$ 3. H^+ 4. O_3
 5. Al_2O_3 6. Mild base

In a more elegant cyclisation procedure Martin ⁴⁴ demonstrated that the nitron derivative of the aldehyde (46) reacted intramolecularly with the endocyclic double bond of ring C. The 1,3 dipolan addition product, the isoxazolidine (53) subsequently referred to as ''isolidine'' was investigated by Martin ⁴⁴ and Aufderhaar.⁴³



(53)

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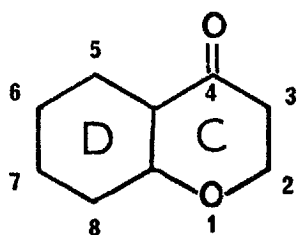
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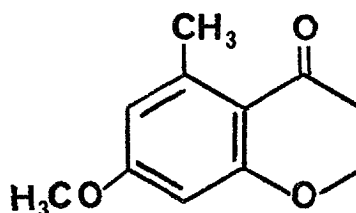
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PART I

The first synthetic goal was the preparation of the CD unit. The unsubstituted chromanone (1) was used as a model compound, and 7methoxy-5methyl chroman-4-one (2) was prepared as the precursor of the CD rings of bikaverin.



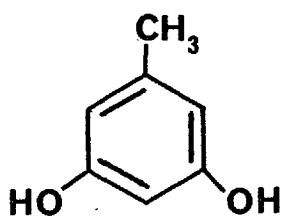
(1)



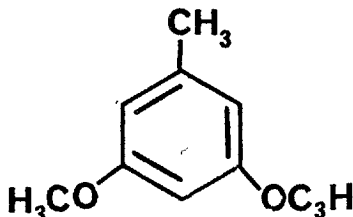
(2)

The Chromanone (1) was readily available from the hydrolysis ¹ of β -phenoxypropionitrile ² followed by polyphosphoric acid cyclisation.³

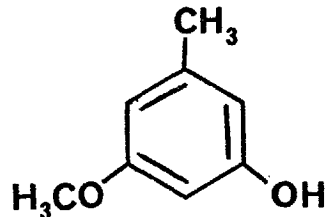
Orcinol (3) was the starting material chosen for the synthesis of 7methoxy-5methyl chroman-4-one, the CD rings of the main series. This compound was obtained by two routes.



(3)



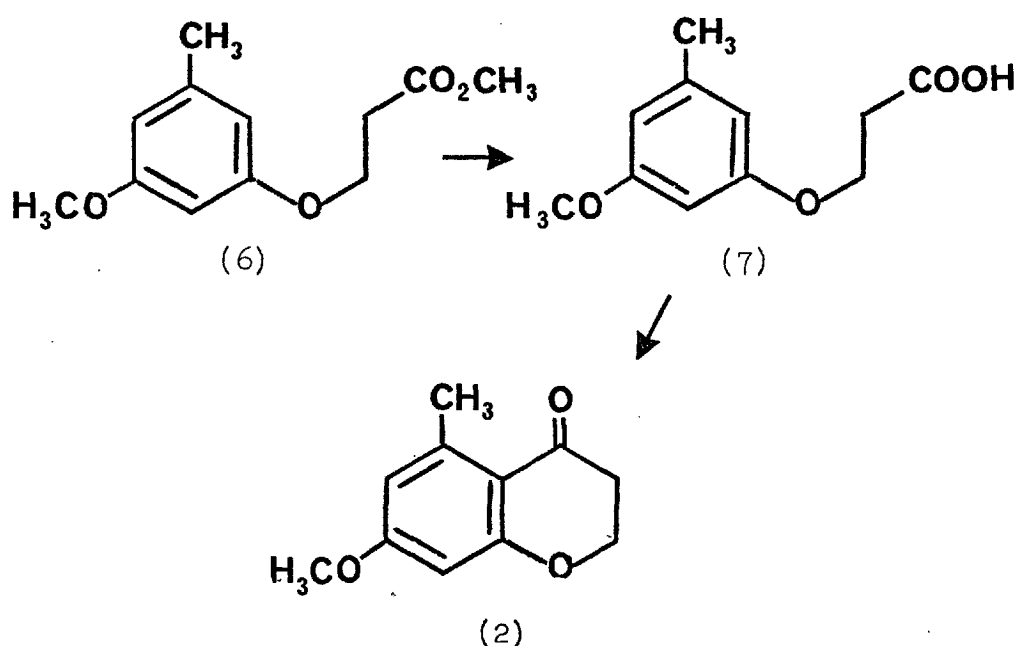
(4)



(5)

3,5 Dimethoxy toluene was prepared by methylation of orcinol with dimethyl sulphate ⁴ in good yield. Demethylation of the aryl methyl ether with thioethoxide ion to give the monomethyl ether ^{4,5} (5) was carried out with ethanethiol /NaH in the presence of a dipolar aprotic solvent, DMF.

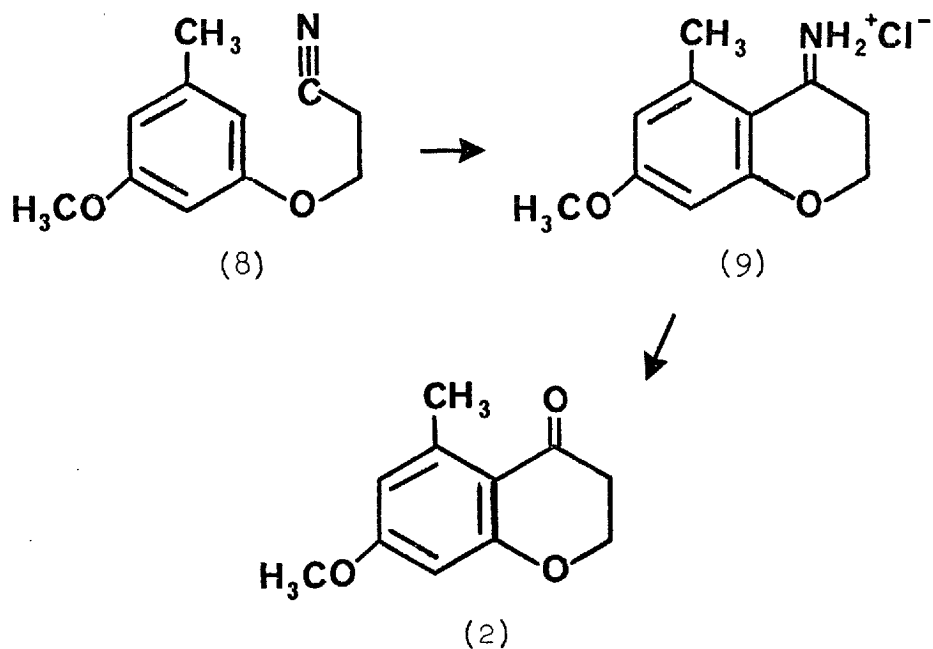
Compound (5) was reacted with methylacrylate to give the phenoxymethyl propionate (6) in 55% yield.



Saponification of (6) gave the aryloxypropionic acid ^{2,6} (7) m.p. 81°C , ν_{max} 1708, 1605, 1164cm^{-1} in 89% yield. Polyphosphoric acid cyclisation of (7) gave the chroman-4-one (2), m.p. 68°C ν_{max} 1665, 1618cm^{-1} in 72% yield.

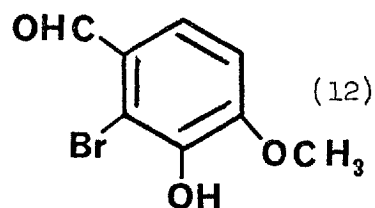
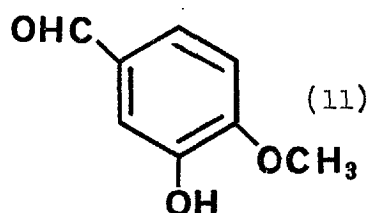
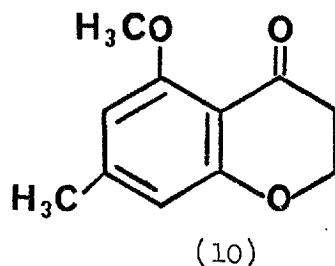
In view of the low overall yield 30%-35%, of this scheme an alternative method was examined. The aryloxypropionitrile (8) was made from a Michael addition of hydroxymethoxy toluene (5) to acrylonitrile in the presence of a catalytic amount of Triton B (aqueous

solution). The nitrile (8) was prepared in 92% yield as colourless crystals m.p. $73-4^{\circ}\text{C}$ ν_{max} 2260cm^{-1} .



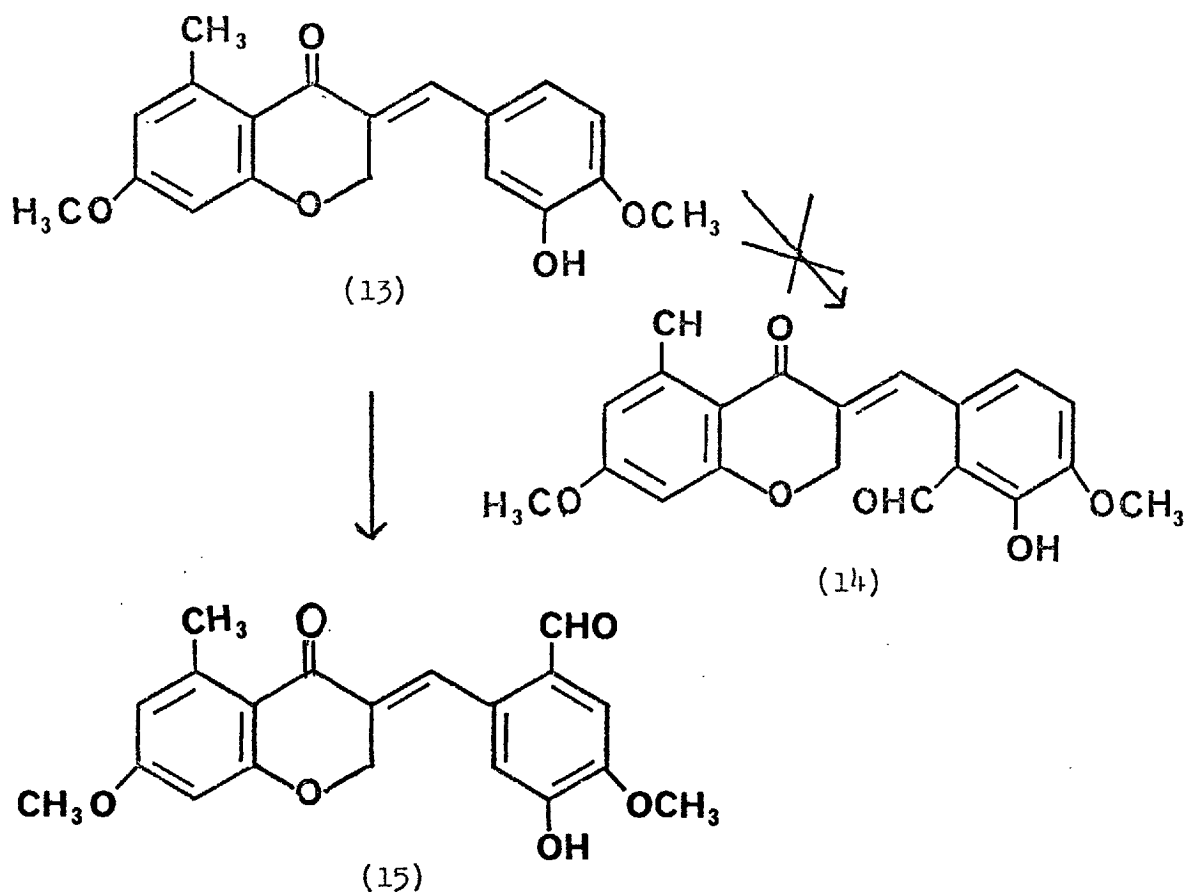
Compound (8) was then cyclised by an intramolecular Houben-Hoesch ⁷ condensation ^{8,9} via the ketimine hydrochloride ¹⁰ (9) to the corresponding ketone, giving the chromanone (2), m.p. 68°C , with identical u.v., i.r., n.m.r. and mass spectra in improved overall yield 82.7%.

A by-product of this cyclisation was 5-methoxy-7-methyl chroman-4-one (10) m.p. $65-6^{\circ}\text{C}$, ν_{max} $1665, 1620\text{cm}^{-1}$ in 2-5% yields. The yield of (10) increases when the temperature of the reaction is raised.

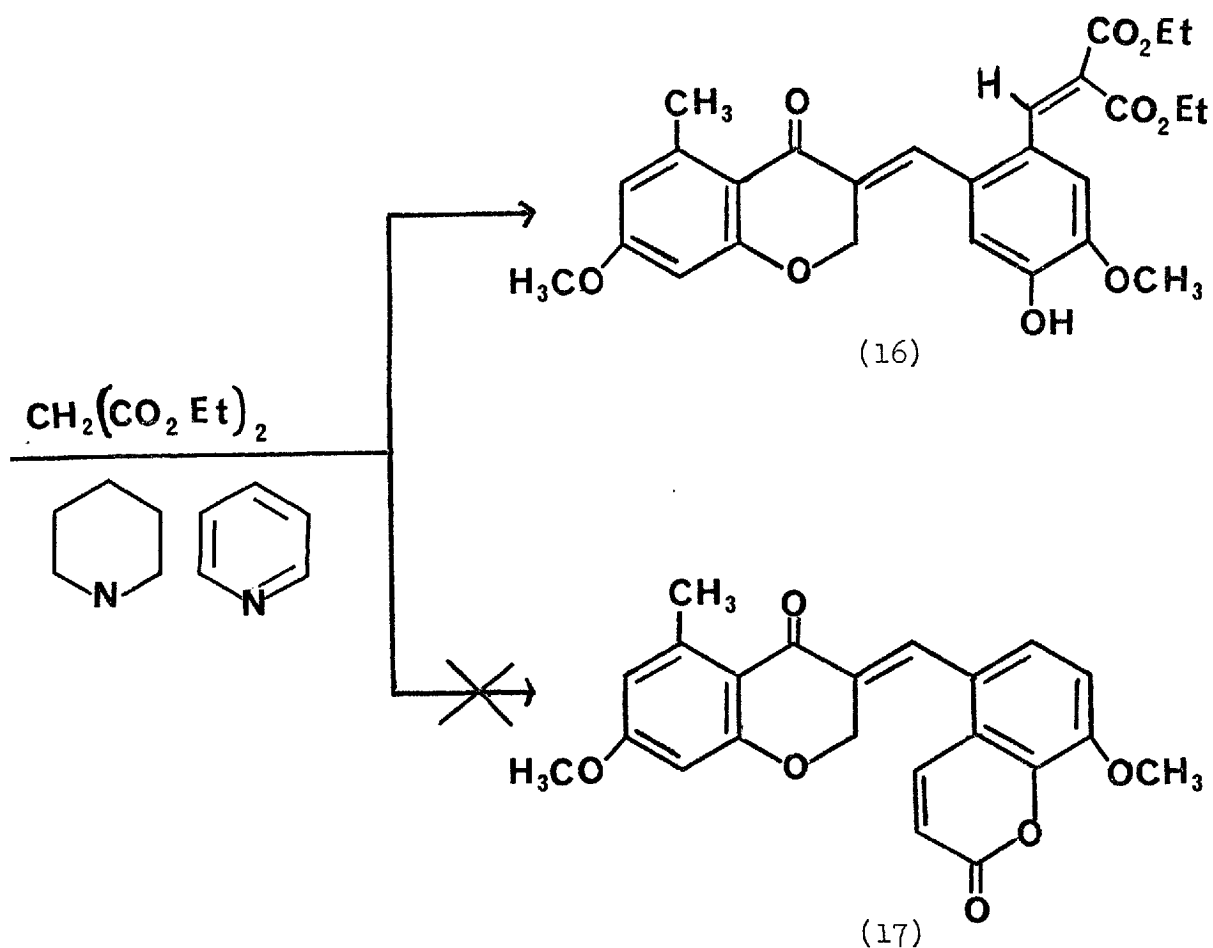


Isovanillin (11) was chosen as the starting material for ring A. It was reacted with bromine to determine the aromatic position ¹¹ most favourable to a electrophilic attack. N.m.r. data showed the compound was (12).¹²

The chromanone (2) was condensed with isovanillin in a 1:1 mixture of ethanol and triethylamine as a base.¹³ The solution was allowed to reflux for 12h. and then heated to 150-170°C distilling off the triethylamine-ethanol-water mixture to obtain the benzyldine chromenone (13) m.p. 180°C, ν_{max} . 3560, 1624, 1278 cm^{-1} , λ_{max} .351, 246n.m.

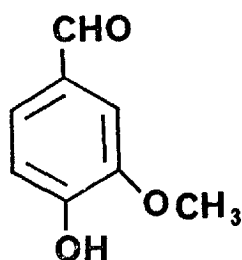


The chromanone (13) was reacted with α, α dichloromethylether ¹⁴ in presence of aluminum trichloride. After 1.5h. yellow needles of the aldehyde (15) m.p. 96-8°C, $\nu_{\max}$ 3680, 1685, 1665 cm^{-1} were obtained, instead of the desired compound (14). This structure (15) was determined by n.m.r. evidence, as there was no splitting arising from the protons in the 5 and 6 positions of ring A, but it showed instead two singlet peaks corresponding to the 3 and 5 positions at 2.3 τ and 2.8 τ . Additional verification of this structure was carried out by reacting compound (15) with diethylmalonate using piperidine as a catalyst to give the malonate derivative (16) instead of the pyran ring compound (17) expected from the aldehyde (14).

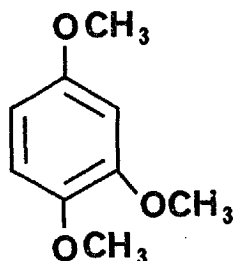


Formylation in presence of Ti Cl_4 ¹⁵ has been reported to give an aldehyde ortho to the hydroxyl group of the phenol, but when tried on compound (13) it gave again exclusively the aldehyde (15) in low yield, 45%.

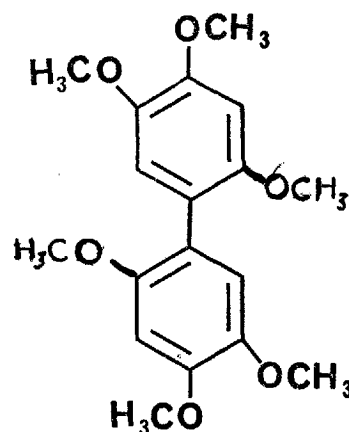
A modified ring A was required to overcome the formylation problem. 1,2,4-Trimethoxy benzene (19) was prepared through Dakin oxidation and subsequent methylation of vanillin ¹⁶ (18). The only by-product of this reaction is the biphenyl ¹⁷ (20).



(18)

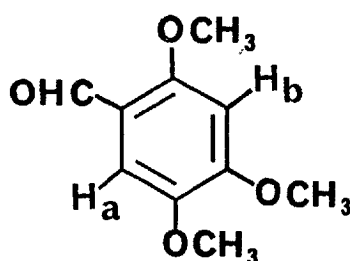


(19)



(20)

Electrophilic substitution of trimethoxybenzene (19) occurs readily, and exclusively at the 5 position. Formylation of compound (19) using Vilsmeier reaction ¹⁸ at 75°C gave 94% yield of the aldehyde (21). ν_{max} 2635, 1660 cm^{-1} . This compound is a naturally occurring product known as asaronaldehyde ¹⁹

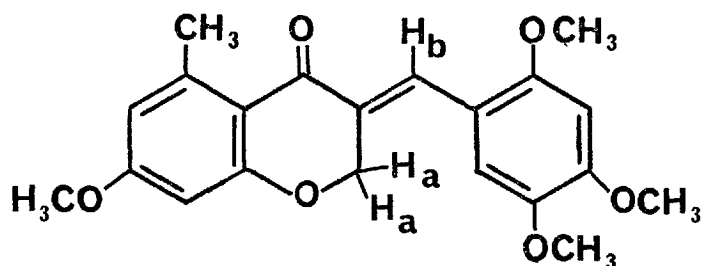


(21)

H_a occurs at 2.73 τ and H_b at 3.53 τ in its n.m.r. scan.

The most direct route to an ACD endocyclic compound is to condense the aldehyde (21) under basic conditions. 3,4,6 Trimethoxybenzaldehyde and the chromanone (2) were dissolved in an ethanol-

triethylamine 1:1 mixture under the conditions previously described ¹³ to give the formylbenzylidine chromanone (22); λ_{max} 381 nm., a characteristic ultraviolet absorption for an exocyclic double bond, contrasting with the λ_{max} 305 nm. reported ¹³ for endocyclic systems.

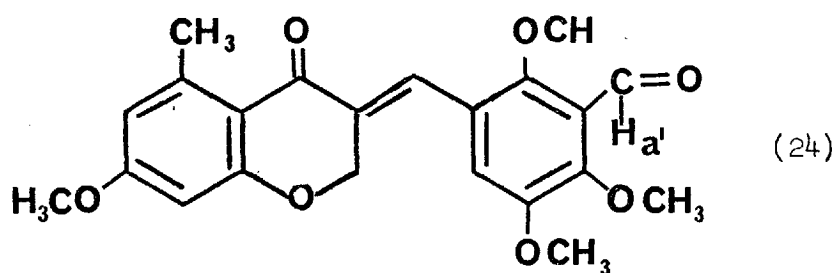
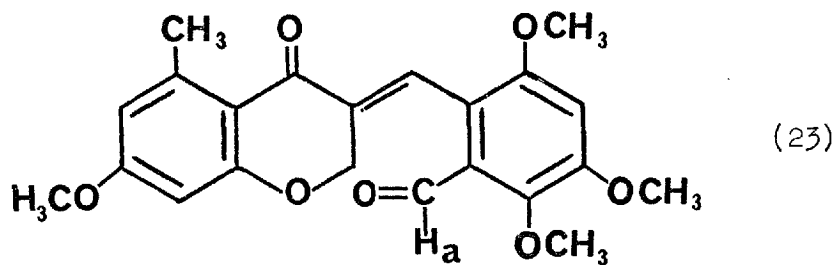


(22)

The mechanism of the condensation proceeds as expected to form the exocyclic double bond but does not rearrange in presence of base to the endocyclic isomer. Presumably the substitution on ring A increases the electronic delocalisation in the system to form the most thermodynamically stable compound. Further studies on rearrangement are discussed in part II.

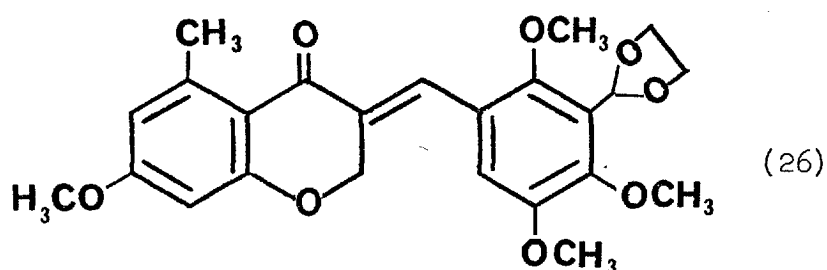
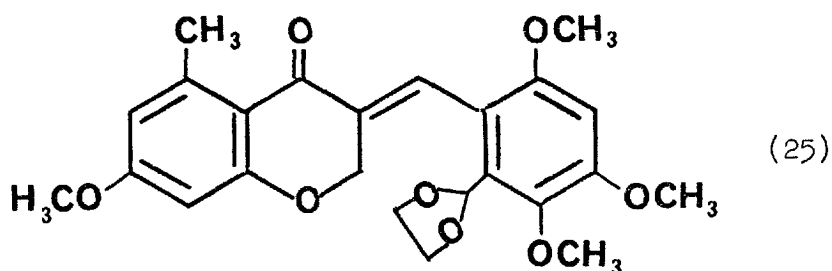
Compound (22) has an m.p. 130-2°C, ν_{max} 1675 cm⁻¹ and the n.m.r. scan shows that the H_a protons appear as a sharp doublet at 4.93 τ (J_{ab} = 3 cps.) and H_b was located as a singlet at 3.70 τ .

The formylation of compound (22) with α, α dichloromethyl-methyl ether ¹⁴ gave after 2h. the formyl (formyl benzylidine) chromanone (23) in 82% yield and its isomer (24) in 8% yield. (Arbitrarily assigned positional isomers).



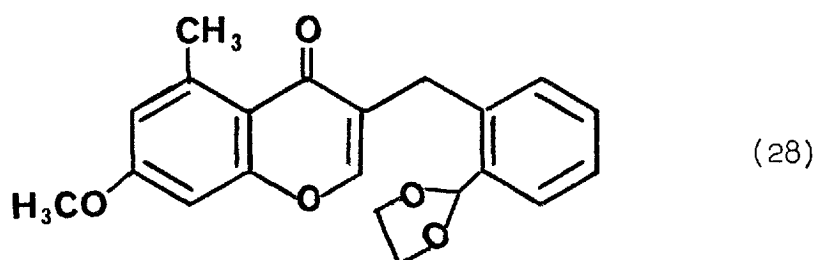
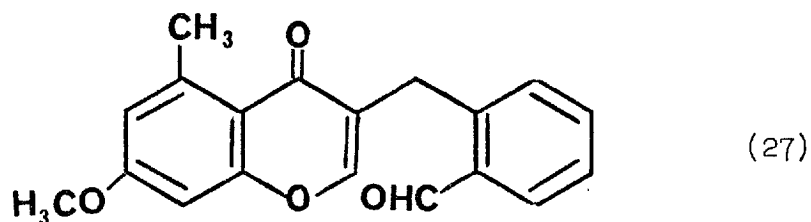
Compounds (23) and (24) show $\nu_{\max}$ at 1700 and 1675 cm^{-1} H_a appears at -0.33τ and $H_{a'}$ gives a signal at -0.29τ .

Rearrangement of the aldehydes into their endocyclic isomers was studied and is described in part II. Now we were ready to prepare acetal derivatives from (23) and (24) to examine their conversion into linear tetracyclic compounds.²⁰ Treatment of (23) with ethylene glycol in benzene, containing a trace of *p*-toluene sulphonic acid monohydrate, with provision for the removal of water gave the yellow crystals of the acetal (25) in 91% yield $\nu_{\max}$ 1670, 1603, 1165 cm^{-1} . The methine proton appeared at 3.6 τ and the dioxanyl ring protons at 6.1 τ in the n.m.r. spectra.



The same method was carried out on the aldehyde (24) to give compound (26) m.p. 170° $\nu_{\max}$ 1670, 1603 cm^{-1} . The ultraviolet shows that both compounds are chromanones (25) $\lambda_{\max}$ 375 n.m. and (26) $\lambda_{\max}$ 376 n.m. Irradiation of both compounds (25) and (26) in refluxing acetonitrile ²¹ containing a trace of o-chlorobenzoic acid using a medium pressure mercury arc lamp did not give the linear tetracyclic compound.

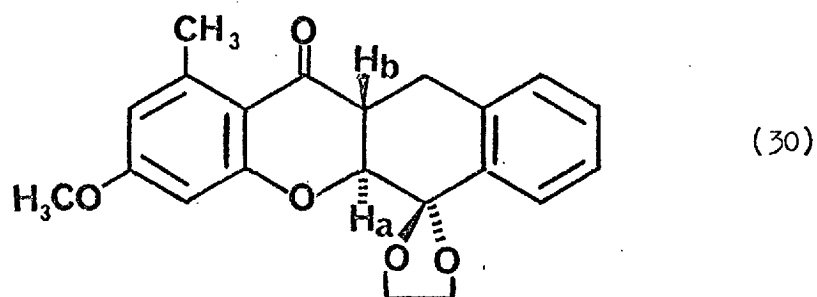
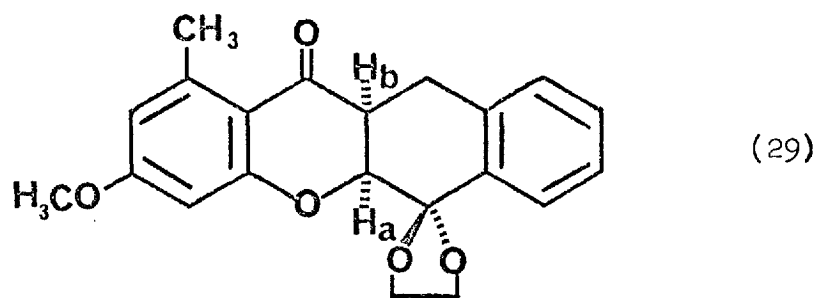
A model series was studied reacting the substituted chromanone (2) condensed with o-phthalaldehyde in ethanol/ triethylamine mixture using the conditions previously described.¹³ This reaction did not go readily but after 8h. at 140° it gave a crystalline compound m.p. 159-61°C, $\nu_{\max}$ 1706, 1655 cm^{-1} and $\lambda_{\max}$ 281 and 238, indicating the formation of the endocyclic compound (27).



The aldehyde proton was a singlet at -0.3τ , the vinyl proton was recognisable at 3.37τ and the benzyl protons appeared at 5.86τ . The spectral characters of (27) resembled those of chromone^{22,23} in the relevant aspects.

The aldehyde (27) was converted by standard methods to its crystalline acetal (28), m.p. $116-18^{\circ}\text{C}$ λ_{max} 271, 283, 299n.m. The methine proton appeared at 4.04τ and the dioxanyl ring protons showed a multiplet at 6.04τ in the n.m.r. scan.

Irradiation of a solution of (28) in refluxing benzene¹³ containing o-chlorobenzoic acid gave a clean reaction. The structure of the resulting tetrahydroxanthone (29) was immediately evident from the spectral properties. λ_{max} 282, 248, 241. The n.m.r. spectrum although complex was unravelled with the aid of spin decoupling.

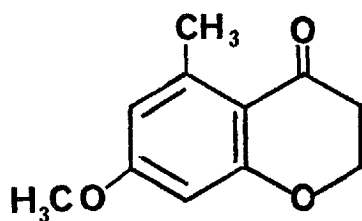


The proton Ha is a doublet coupled to H_b ($J_{ab}=8$ cps.); H_b is coupled to both benzylic protons with coupling constants of 6cps. and 12.5cps. The benzylic protons are coupled to one another by 14.5 cps. The cis isomer (29) was readily epimerized to the trans isomer¹³ upon passage through a G3 alumina column, eluted with benzene. Both isomers have similar infra red, ultraviolet and mass spectra.

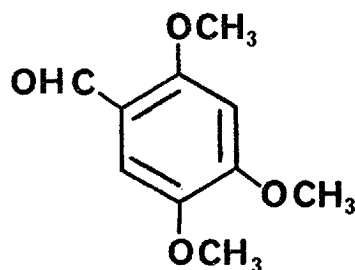
PART II a

Studies on the formation of the endocyclic double bond

The first attempts were directed at condensing rings CD (2) with ring A (21) to forming the endocyclic double bond (31).



(2)



(21)

Table I summarises the experiments carried out. From the preceeding work in the tetracycline series ¹⁸ and in the benzo-xanthenes series ¹³ it was shown that based catalysed condensation ²⁴ rearrange the exocyclic (31) double bond into the corresponding endocyclic isomer (31a), Scheme IV.

Scheme IV

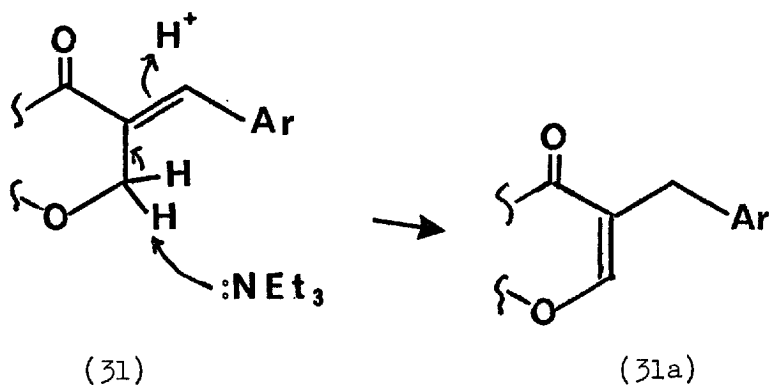
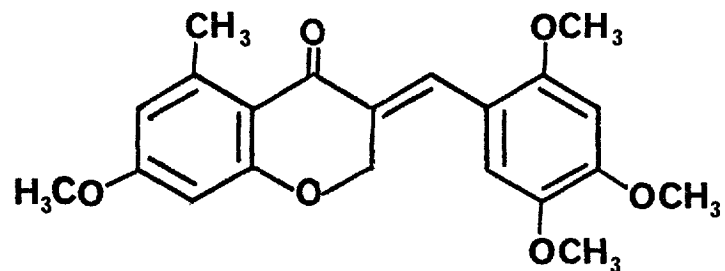
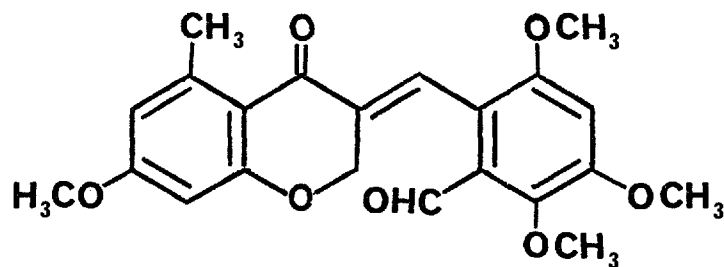


TABLE III

Rearrangement of exo- into endo- ACD ring



(22)

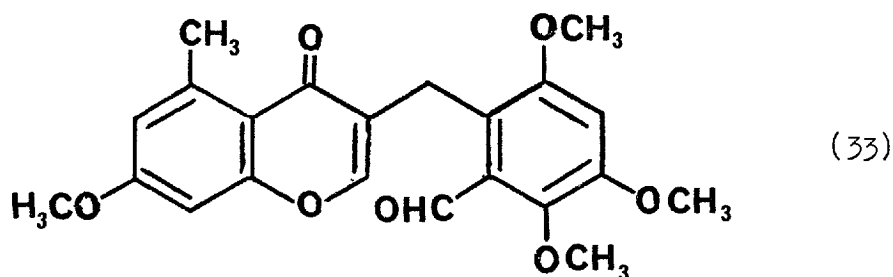
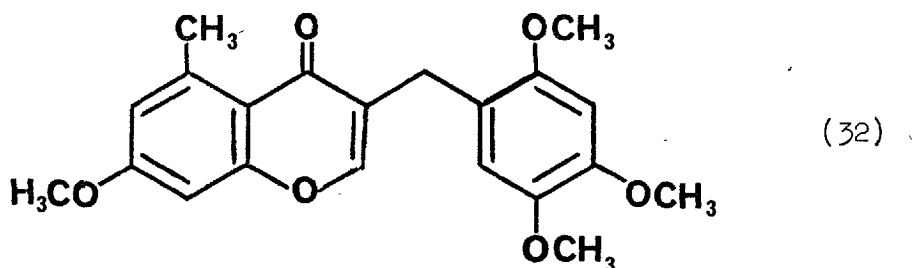


(23)

Base-solvent	(22)	(23)
NEt ₃ , EtOH	s.m.	s.m.
Pyridine-C ₆ H ₄	s.m.	s.m.
Piperidine-C ₆ H ₆	s.m.	s.m.
t-ButOH-t-ButOH	6% endo isomer 4 days, (by n.m.r.)	
DBU-C ₆ H ₆	s.m.	s.m.
DEBCO-C ₆ H ₆	s.m.	s.m.
DBU-DEBCO-C ₆ H ₆	s.m.	s.m.
Piperidine-pyridine	s.m.	s.m.

Note:- s.m.=indicates recovery of only starting material; DBU 1,5 Diazabicyclc(5.4.0) undec-5-ene

The same series of bases was used for both compounds (22) and (23). Only potassium t-butoxide in t-butanol gave 4% of the endocyclic isomer (32) when reacted with compound (22). The formation of its isomer (32) was detected by n.m.r. scan, where the vinyl proton was recognisable at 2.2 τ and the benzyl protons appeared at 5.85 τ . No further studies were carried out on the compound (32) in view of the poor yield.

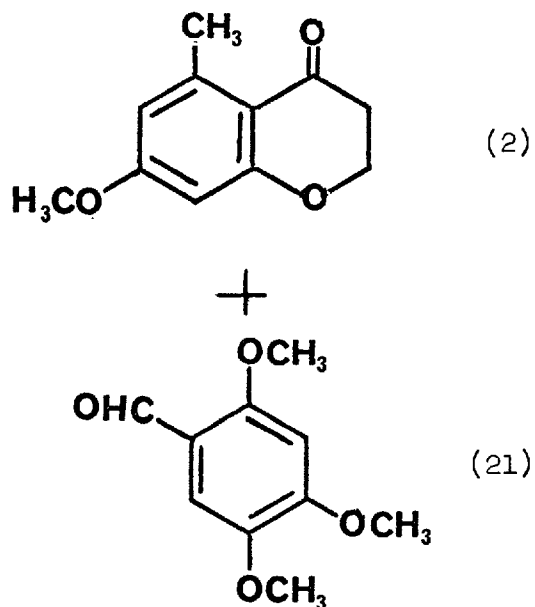


In the case of the aldehyde (23), the starting material used for the preparation of the endocyclic isomer, it was recovered in all cases except again in the treatment with potassium t-butoxide/t-butanol where a breakup of the chromanone occurred, and also deformylation occurred.

The next attempt to prepare the endocyclic compound (32) was a study of the condensation of the chromanone (2) with the aldehyde (21) in a series of reactions shown in table IV.

TABLE IV

Attempted Condensation of the Endocyclic Isomer (32)



BASE-SOLVENT	PRODUCT	YIELD
NEt ₃ -Ethanol	F	78%
Pyridine-benzene	F	⌘
Piperidine-benzene	F	88-92%
K-t-butoxide-t-butanol	F	⌘ 20%
NEt ₃ -benzene	F	⌘ 25%
DBU-benzene	F	⌘
K-t-butoxide-benzene	F	15% + deformylation of (21)
DEBCO-benzene	F	⌘
DEBCO-DBU-benzene	F	⌘
Sodium-methanol	F	⌘ 35%

Note:- F indicates the formation of exocyclic isomer : ⌘ reaction did not go to completion.
E indicates the formation of endocyclic isomer : DBU 1,5 diazabicyclo(5.4.0.)undec-5-ene

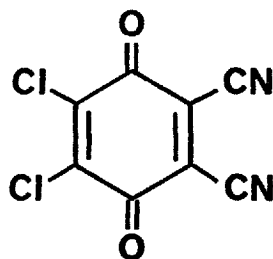
Most of these reactions gave the chromanone (22) in poor yields. Where no yields are indicated the reaction did not go to completion even after several days of reaction and no condensed product was isolated.

The condensation reaction using potassium t-butoxide/t-butanol gave a by-product 1,2,4-trimethoxybenzene (19).

The benzene-piperidine mixture gave the chromanone (22) in excellent yields (90%). The chromanone (2) and the aldehyde (21) were dissolved in benzene-piperidine (3%) solution, allowed to reflux 24h., after which the temperature was raised to 130-140°C for 2h.; if at this stage the reaction had not reached completion, more benzene-piperidine solution was added. The resulting product has identical spectral characteristics, m.p. 131-2°C, and no depression on the mixed melting point, with compound (22). This has since become the standard method of preparing the chromanones.

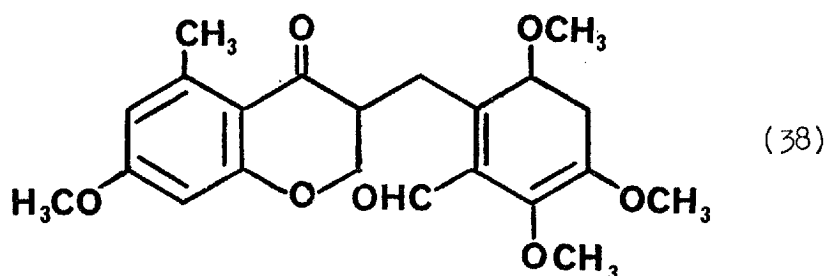
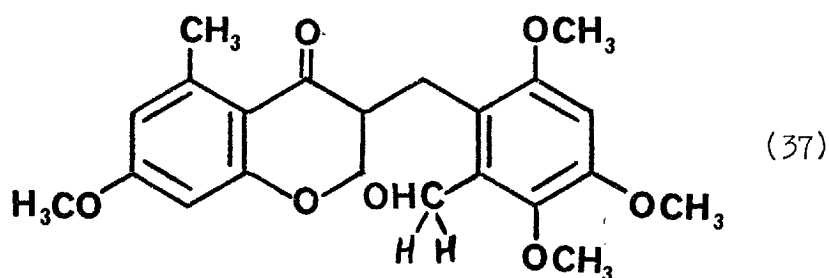
In view of the difficulty in rearranging the exocyclic double bond to prepare the endocyclic compound, the chromanone (22) was reduced, using palladium on carbon as a catalyst, to compound (34), m.p. 95°C, λ_{max} 245, 274m μ .

This compound was expected to give the chromone ^{25,26} when oxidised with DDQ (dichloro-dicyanobenzoquinone)(36).



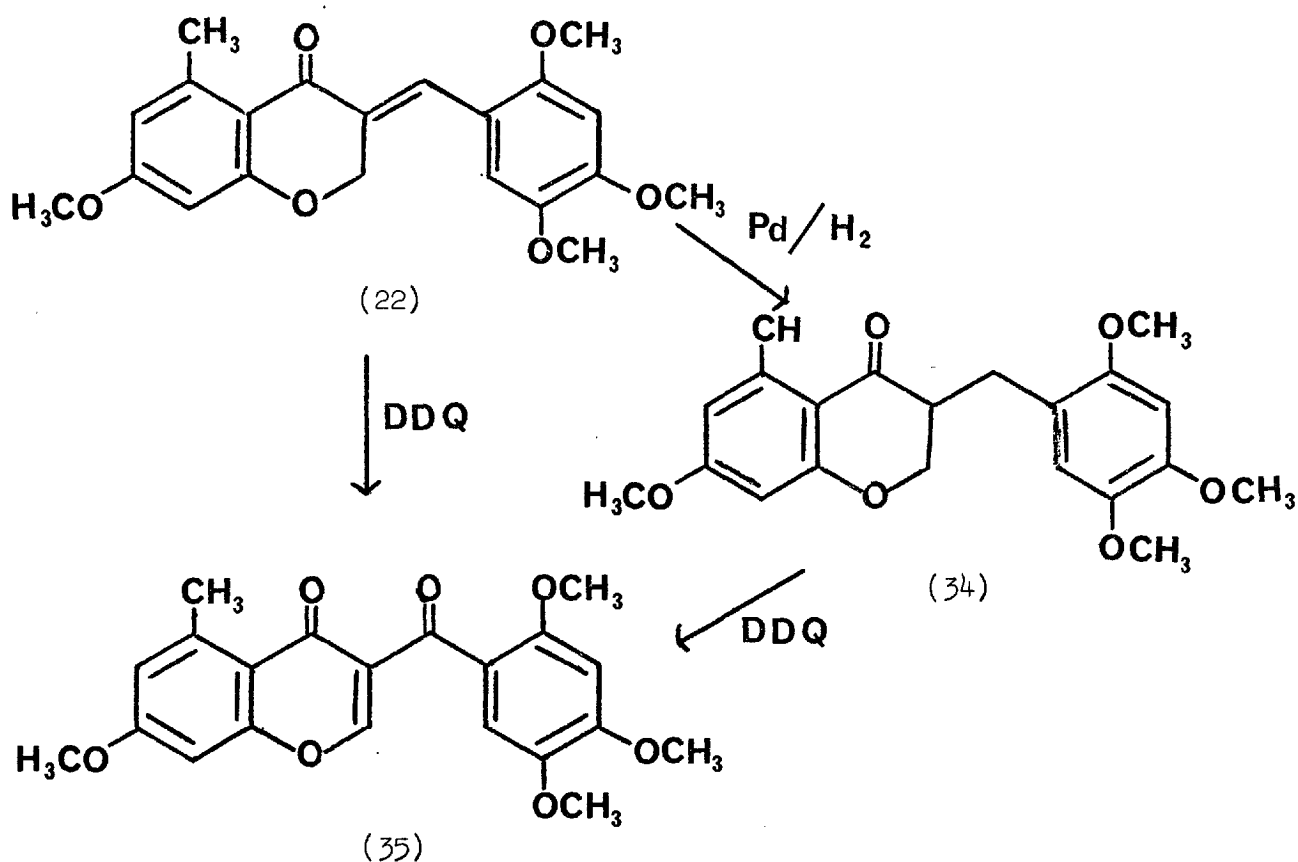
(36)

Reduction of the aldehyde (23) by hydrogenation over palladium on carbon as catalyst gave us compound (37), ν_{max} 3600cm^{-1} and disappearance of the aldehyde proton at τ -0.37. λ_{max} 229, 279m μ . No further studies were done on compound (37) which was obtained instead of product (38).



Treatment of (34) with DDQ in refluxing benzene gave a colourless crystalline product (35) that showed mass spectrum peak 384 was obtained. The mass spectrum of (34) being 382. Its infra red showed the appearance of a second carbonyl band,^{27,28} corresponding to the benzoyl carbonyl near 1675cm^{-1} . The u.v.²⁹ showed a λ_{max} 250, 345 n.m., and the n.m.r. spectrum was consistent with the proposed structure (22).

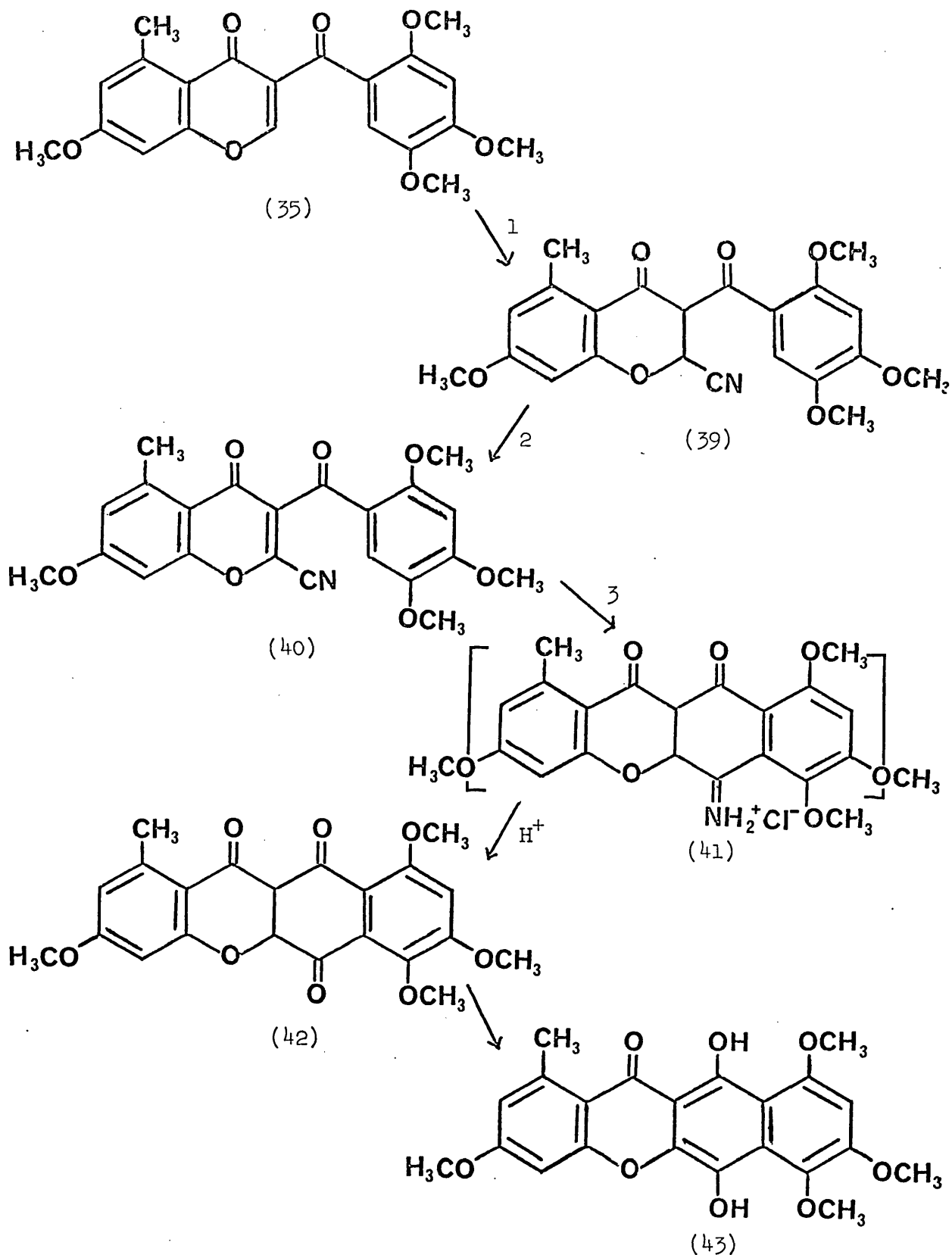
Scheme V



When the chromanone (22) was reacted with DDQ it gave the benzoyl chromone (35) with identical spectral characteristics and melting point to the compound prepared from (34), Scheme V.

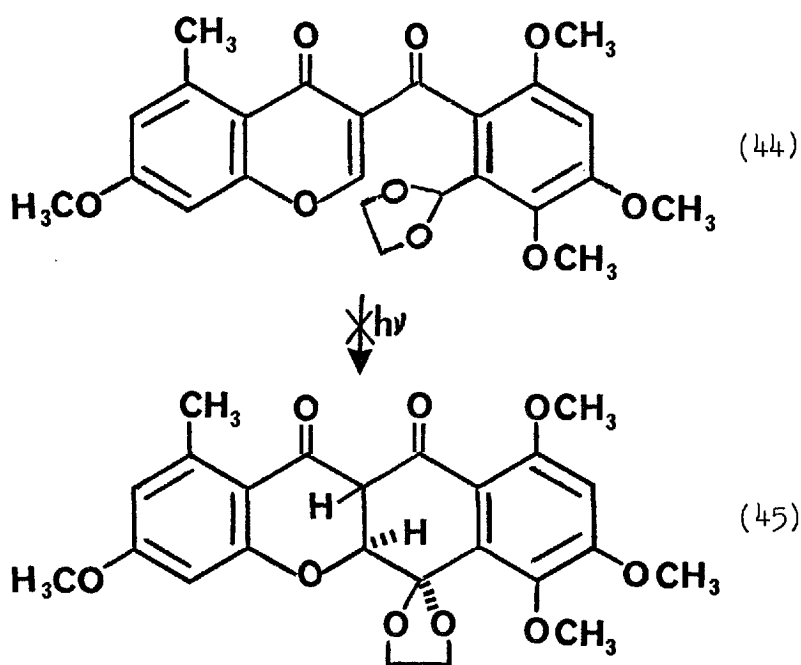
At this stage it was thought possible to cyclise the B ring with a intramolecular Houben-Hoesh reaction ^{7,8,9} (Scheme VI) but attempts to prepare the cyano derivative were completely unsuccessful.

Scheme VI



Reagents: 1. NaCN aq./THF 2. DDQ 3. HCl , $\text{ZnCl}_2/\text{Et}_2\text{O}$

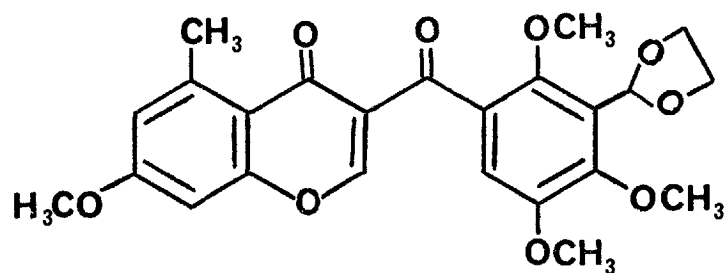
As a method had been established to prepare the benzoyl chromone (35), it was proposed to prepare the benzoyl chromone (44) from the acetal (25). This was done by the addition of two equivalents of DDQ to compound (25) in toluene at 70°C for 12h. A crystalline compound (44) m.p. 259-270°C was obtained. It showed the same spectral characteristics as the previously prepared benzoyl chromone (35). ^{There is an} appearance of the benzoyl carbonyl band at ν_{max} 1665 cm⁻¹ in the i.r. spectra; the ultraviolet showed a λ_{max} 208, 250, 345 nm and the disappearance of the benzylic proton at 4.93 τ .



Attempts to cyclise the benzoyl chromone (44)^{13,21} to the benzo-xanthone derivative (45) were unsuccessful.

The benzoyl chromone (46) of the acetal (26) also was prepared. On irradiation^{13,21} with ultraviolet light no reaction took place,

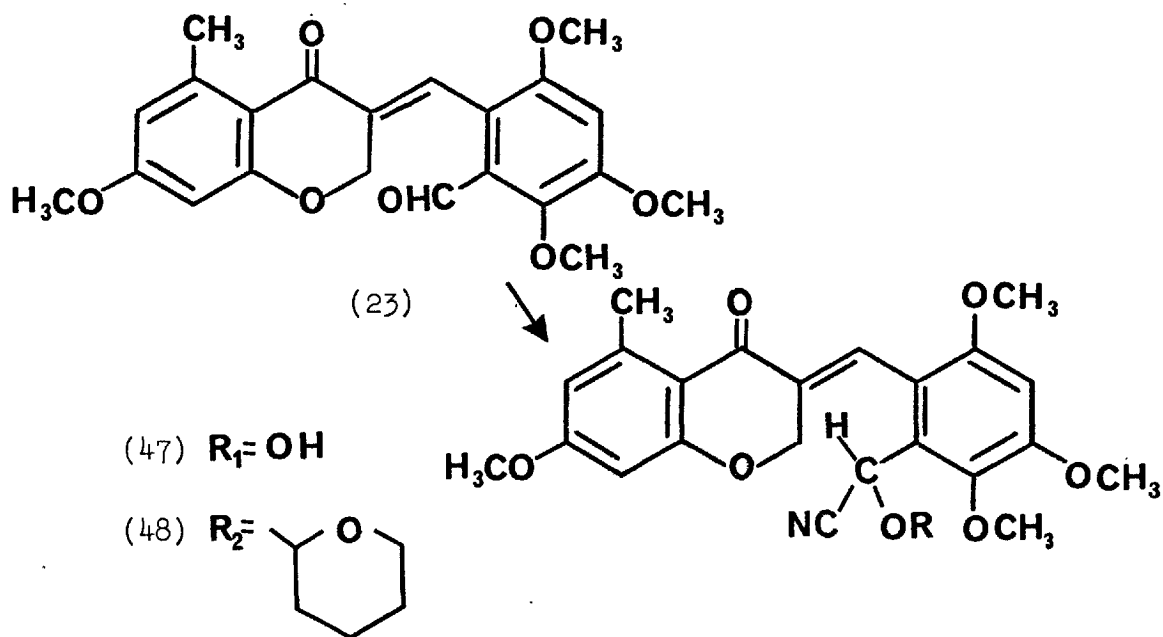
as only starting material was recovered.



(46)

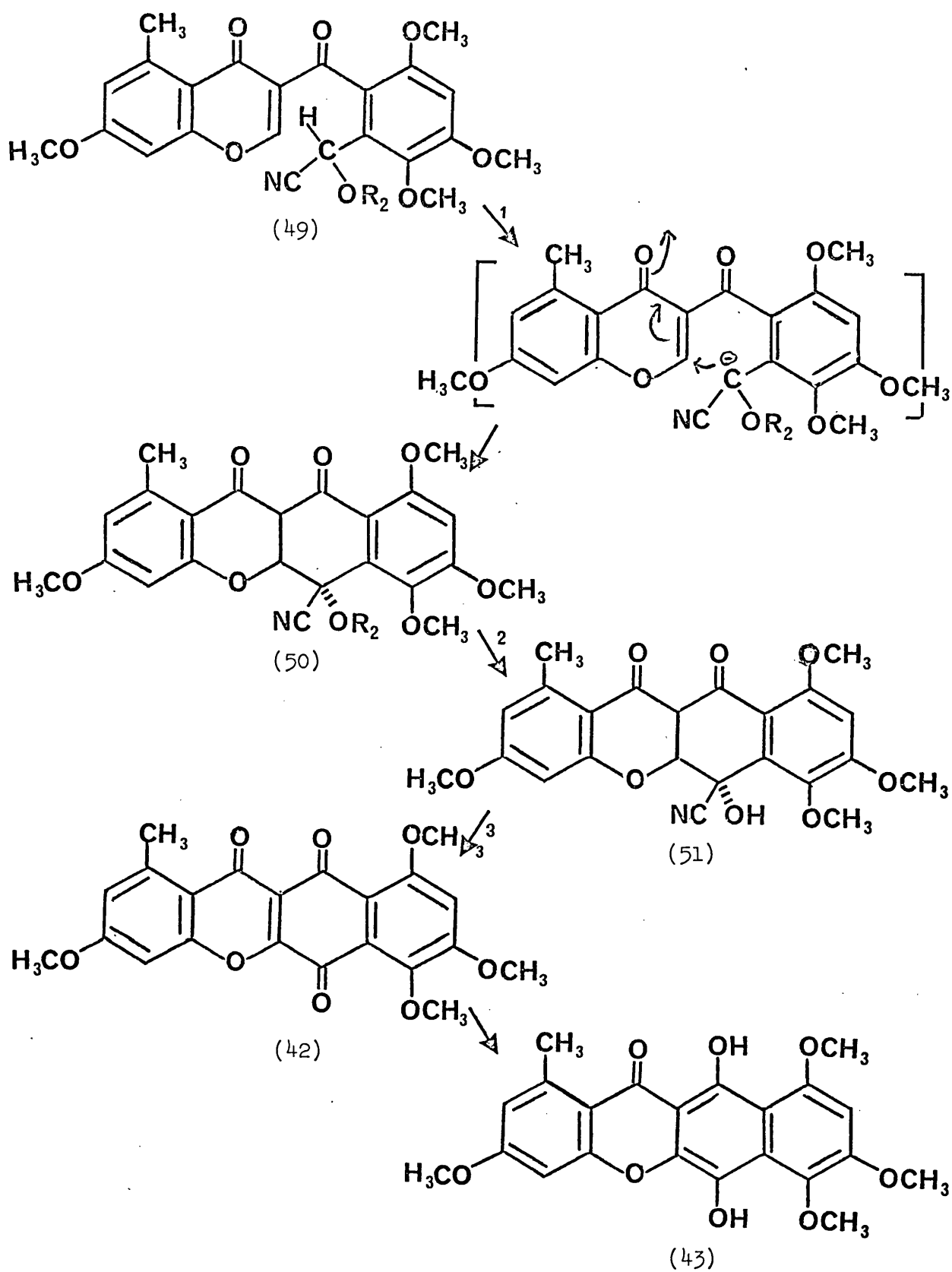
A route to prepare the tetracyclic compound using the cyanohydrin ²⁹ derivative of the aldehyde (23) was attempted. Scheme VII.

Scheme VII



(see over leaf)

Scheme VII

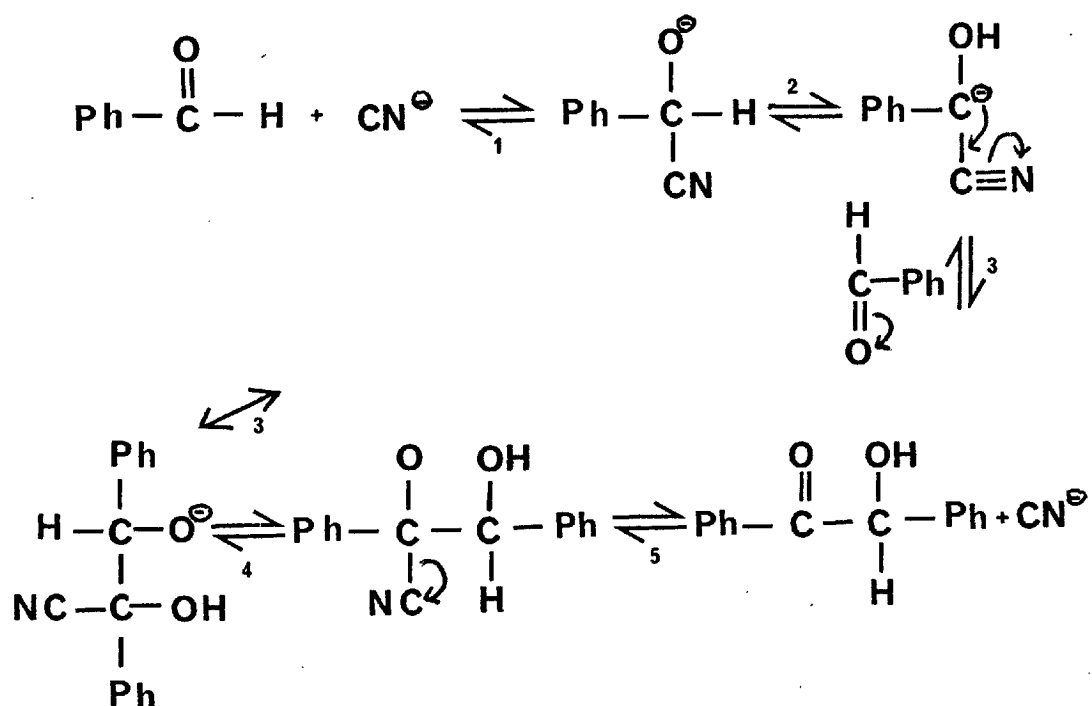


Reagents: 1. Na *t*-BuO/ Et₂O 2. H⁺ 3. Al₂O₃

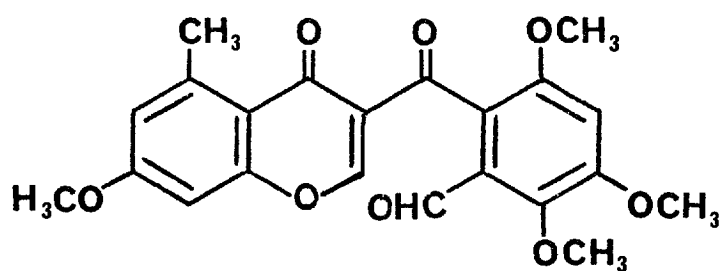
The aldehyde (23) was treated with sodium cyanide and sulphuric acid at 0°C to obtain the cyanohydrin ²⁹ (47) which shows the disappearance of the aldehyde proton at δ 9.7 and in the i.r. the aldehyde carbonyl at ν max 1690cm⁻¹ disappears while a band at ν max 3350cm⁻¹ corresponding to the hydroxyl group appears. This compound (47) was treated with 2,3-dihydropyran to obtain the cyanohydrin pyranyl ether (48) which was subsequently treated with DDQ to prepare the benzoyl chromone (49). Attempted cyclisation of this compound using one equivalent of potassium t-butoxide in refluxing ether to yield the cyclised pyranyl ether (50) was unsuccessful.

Scheme VIII

Benzoin Condensation ^{30,32}



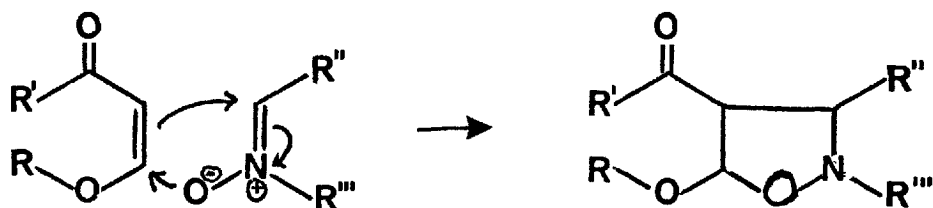
Thus it was hoped, by analogy with the tetracycline work, that the aldehyde (52), prepared by DDQ oxidation from compound (23), when treated with sodium cyanide in THF (under 5°C) and neutralized with 0.5 N hydrochloric acid would give the cyclised product (51) according to Scheme VIII,^{30,32} but in the event no cyclisation took place.



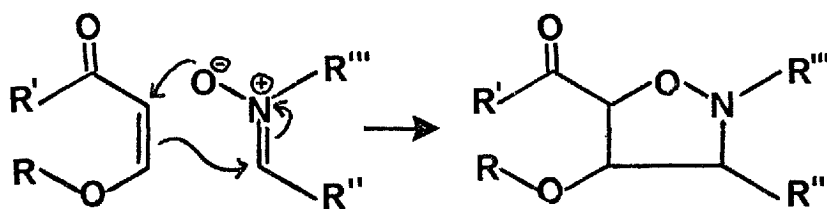
(52)

The possibility of preparing a cyclized B ring by using phenylhydroxylamine^{24,33} to prepare the isoxazolidine (53) via a 1,3 dipolar addition of a nitron^{34,35} to the double bond of the α,β unsaturated ketone. Schemes IX, X, XI were examined.

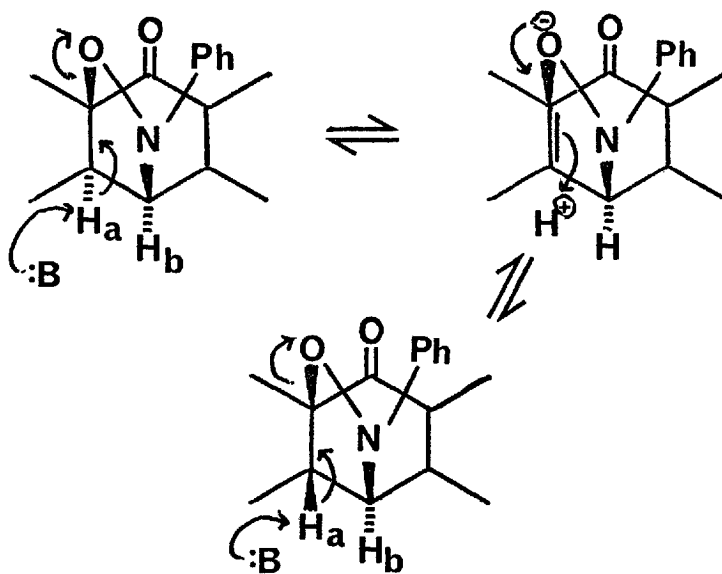
Scheme IX



Scheme X



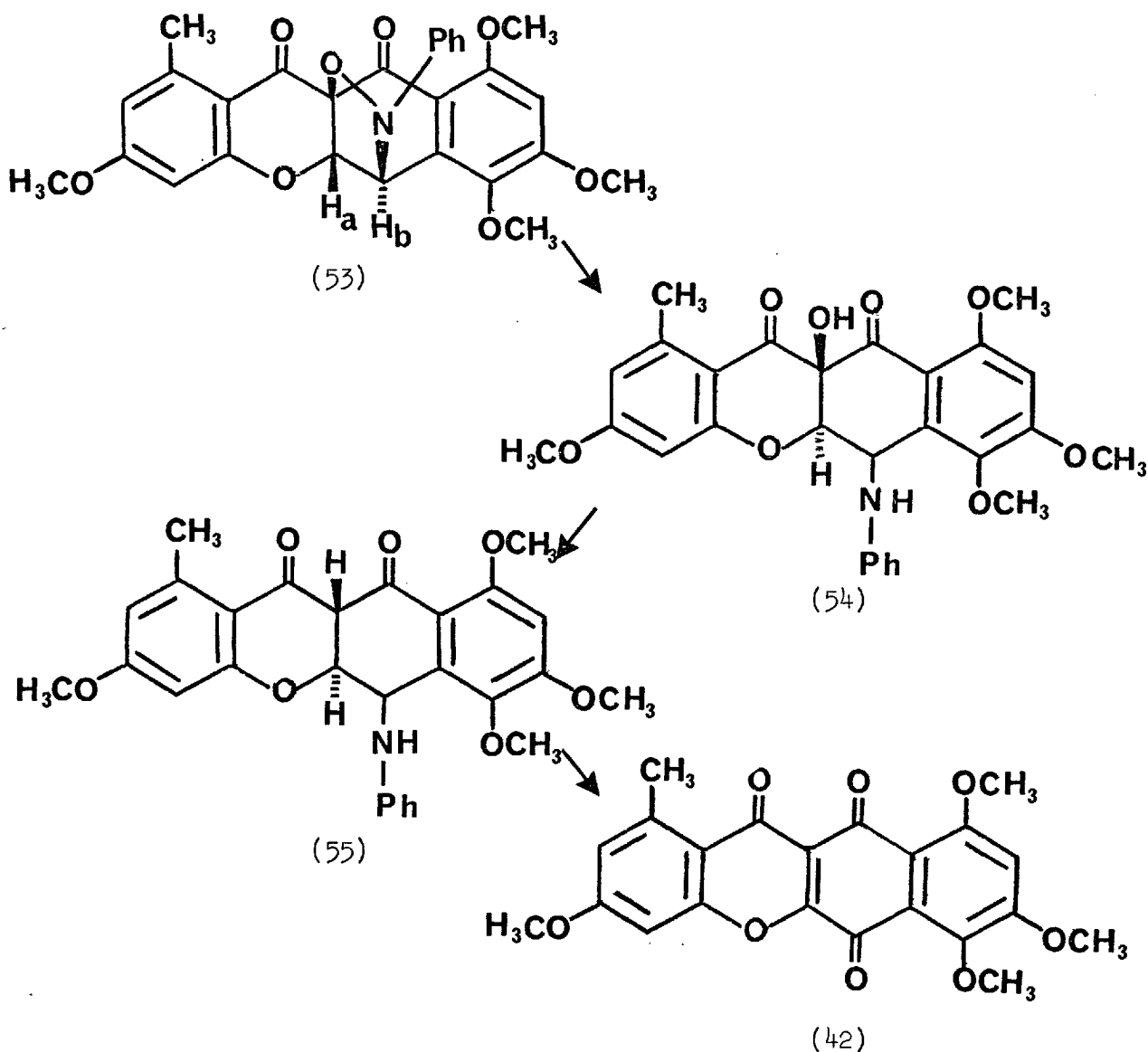
Scheme XI



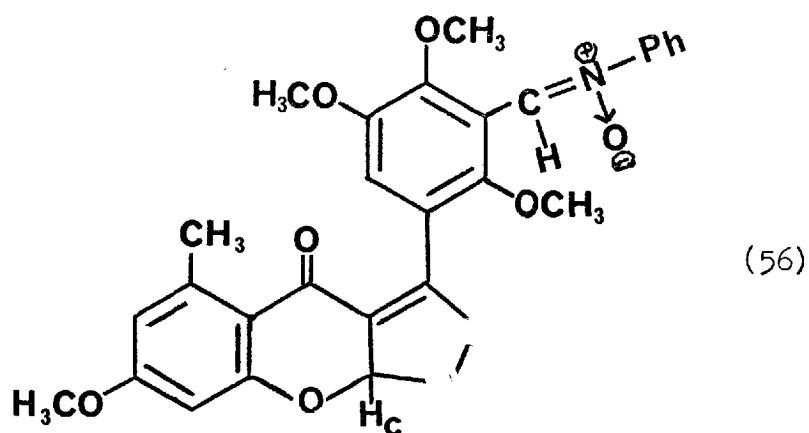
The aldehyde (52) was reacted with phenylhydroxylamine in ethanol to give yellowish needles (53) that showed an ultraviolet absorbance at λ_{max} 260, 300 nm. and had a m.p. of 185°C.

Reductive cleavage of the oxygen-nitrogen bond was expected to give a compound not far removed from the cyclic derivative we were aiming at. The ultimate goal was to find a convenient route to the diketone (42). Scheme XII

Scheme XII



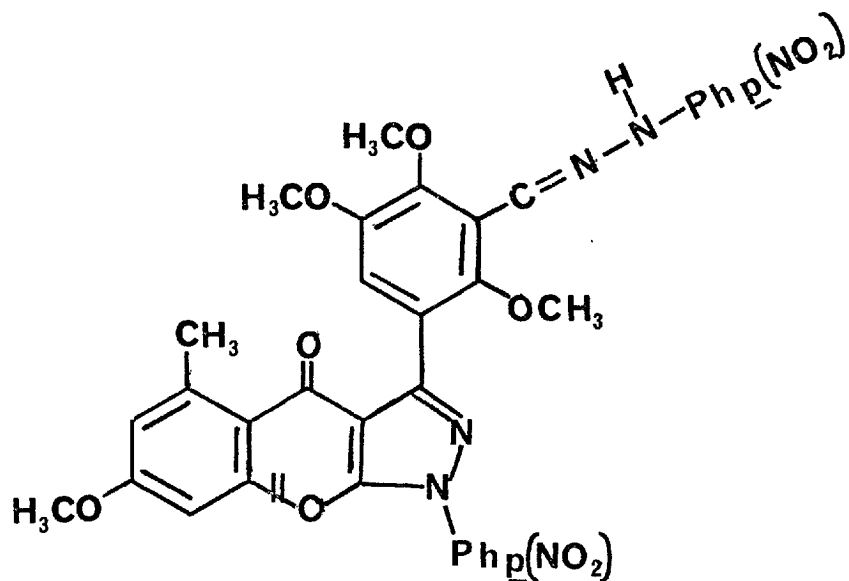
The compound isolated from the phenylhydroxylamine reaction was (56),



instead of compound (53) as shown by the n.m.r. spectrum where no peaks for the (Ha-Hb) protons (Scheme XI) appear but a singlet peak for Hc appears at 3.6 τ . It shows an absorbance at λ_{max} 362, 301 nm in the ultraviolet spectra and there is a disappearance of the benzoyl carbonyl in the infrared.

The reaction of the benzoyl chromone (52) with phenylhydrazine confirmed the structure of the ACD ring as compound (57) was obtained.

(over leaf)

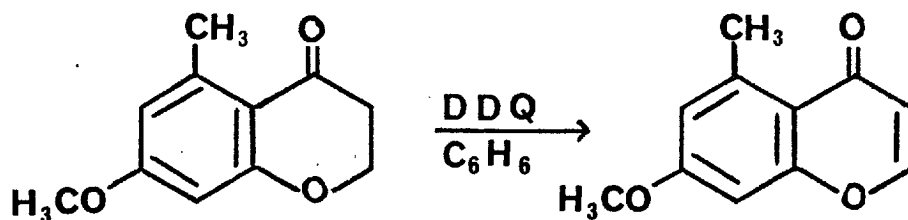


(57)

Which shows an ultraviolet absorbance at λ_{max} 295, 404 nm, and the benzoyl carbonyl band disappeared from the infrared spectrum.

These results confirmed that the aldehyde (23) has the wrong structure. In view of the problem this presents towards the cyclisation of ring B, it was thought that the cyclisation should be carried out by introducing an appropriate substituent on the 2 position of the chromanone.

To prepare this substituted compound the chromanone (2) was reacted with DDQ, ²⁵ to obtain the chromone (58).



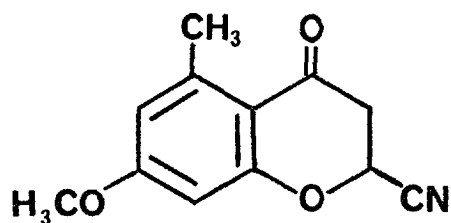
(2)

(58)

Compound (58) shows an ultraviolet absorbance λ_{max} 239, 248, 290 nm and n.m.r. scan shows a doublet at 2.45 τ ; J=4cps. and a doublet at 3.90 τ ; J=4cps.

The dehydrogenation also was tried with ortho and para - chloranil and selenium dioxide, to obtain no reaction in the first two cases and under 5% of the desired product (58) in the second instance.

The next step was the attempt of the addition of a nitrile group (59) to the olefin via Michael addition. The results are summarised in table V.



(59)

TABLE V

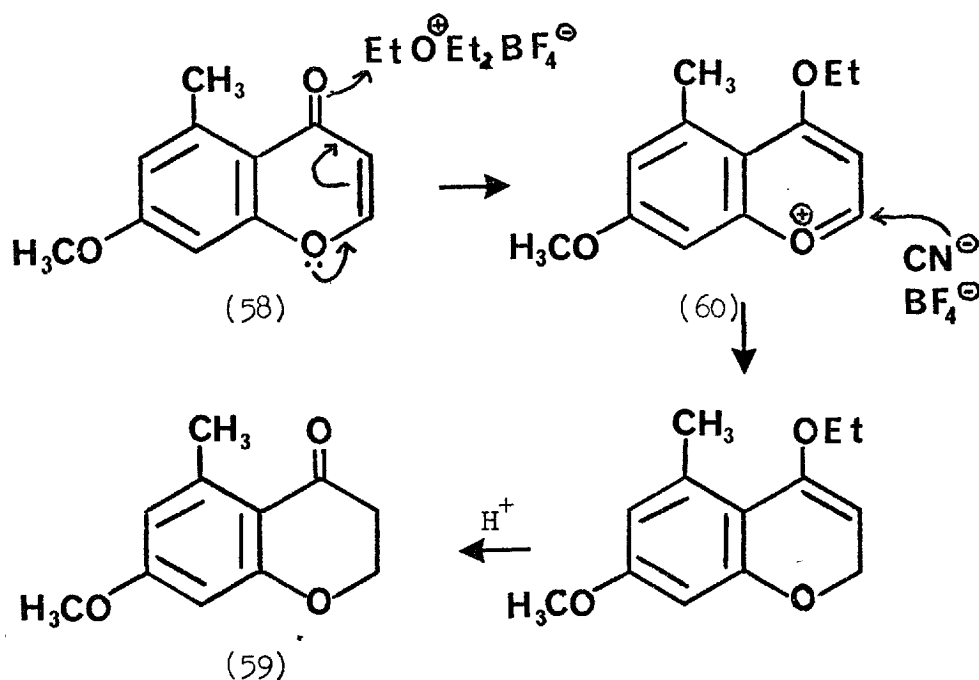
Solvent	chromome		time	neutral conditions	OH ⁻	H ⁺
DMF, H ₂ O	50 mg.	NaCN+NH ₄ Cl	12h.	n.r.	n.r.	n.r.
Glyme	50 mg.		12h.	n.r.	n.r.	n.r.
Acetone	45 mg.	excess	12h.	n.r.	n.r.	n.r.
Ethanol	50 mg.	NaCN	12h.	n.r.	n.r.	n.r.
DMSO	50 mg.	aqueous	12h.	n.r.	n.r.	n.r.
THF	60 mg.	solution	12h.	n.r.	n.r.	n.r.
in all cases.						

Note:- n.r. = no reaction.

As the reaction did not proceed under the neutral, basic or acid conditions, (table V) the reaction was abandoned.

The chromone (58) was reacted with Meervin Salt ³⁶ to prepare the oxonium derivative (60) and in situ react it with sodium cyanide (Scheme XIII)³⁷ to obtain compound (59).

Scheme XIII



This reaction to obtain the oxonium salt was unsuccessful as it did not go to completion even on large excess of $(\text{C}_2\text{H}_5)_3\text{O}^+\text{BF}_4^-$. The attempts to carry out the cyano group addition through the intermediate oxonium salt in situ by addition of t-butyl ammonium cyanide was also without success.

PART II b

2,3 Dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation

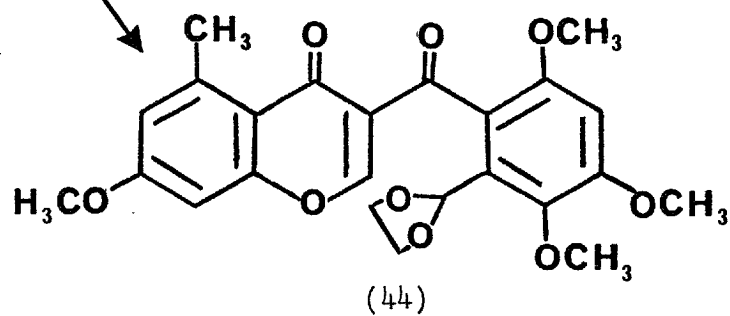
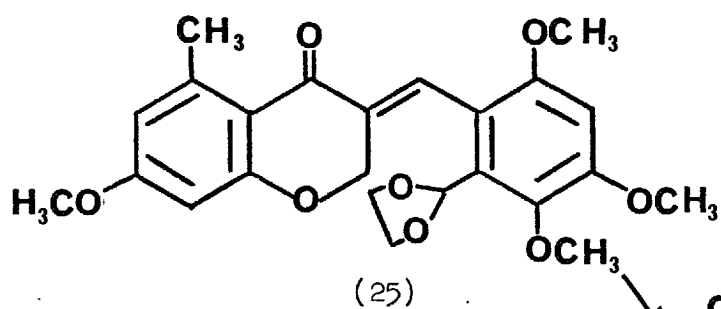
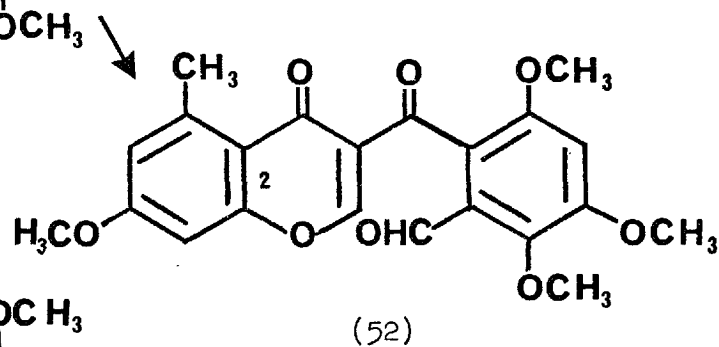
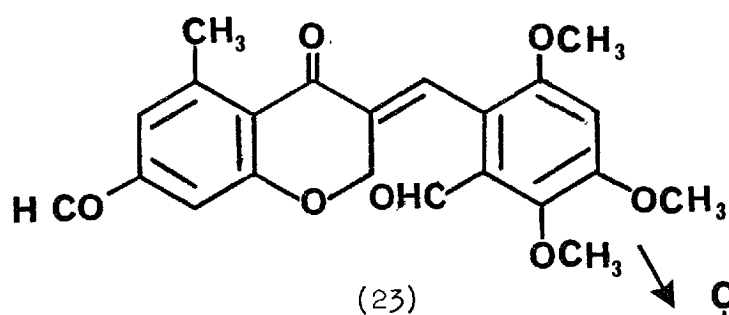
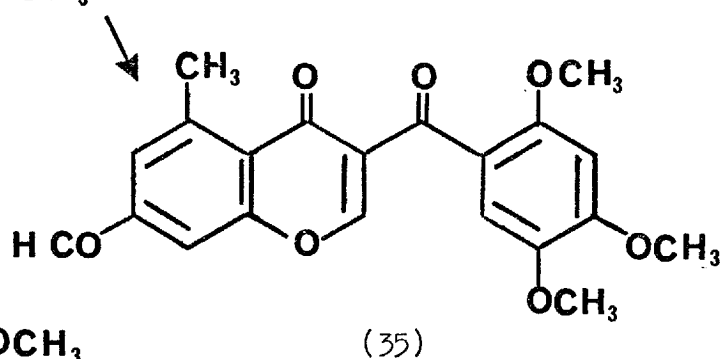
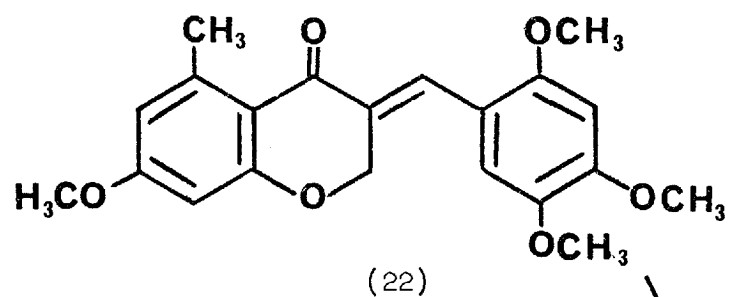
When the ACD dihydrochromanone compound (34) was treated with DDQ the expected simple dehydrogenation ^{39,40} did not take place (p.51). Instead, the only compound formed contained an extra oxygen function in the form of a carbonyl group, namely (35).

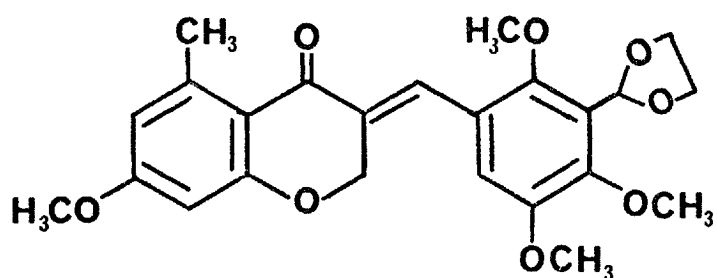
The dehydrogenation reactions of DDQ are well documented ^{25,41} however, only one previous report is found in the literature ⁴² where dehydrogenation results in the formation of a carbonyl compound in addition to, or instead of the desired product.

On the basis of the experimental result where compound (35) was obtained the possibilities of preparing the appropriate benzoyl-chromone system, which would be useful for photocyclisation became apparent. The applicability of the reaction to prepare benzoyl chromones is indicated in table VI.

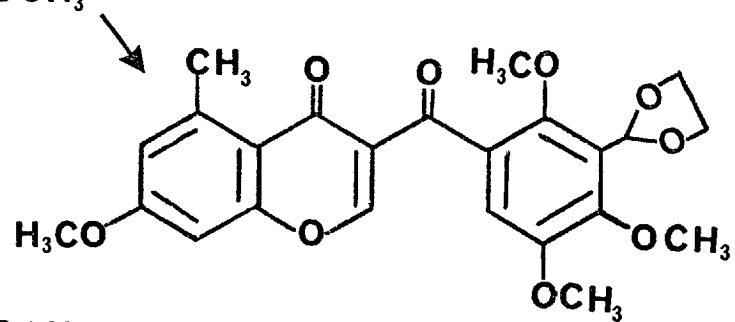
(table VI over leaf)

TABLE VI

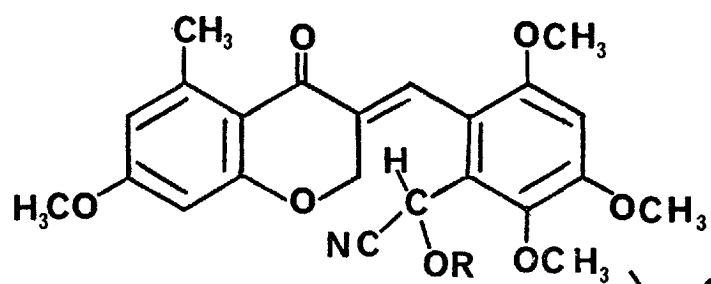




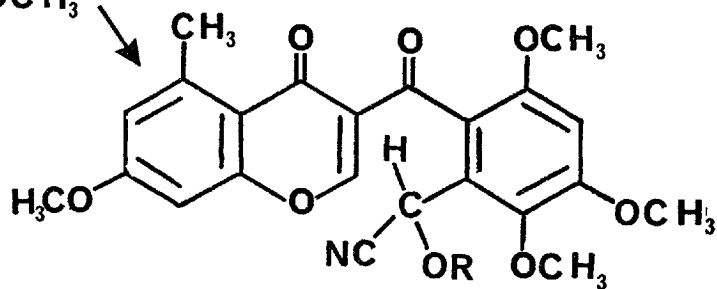
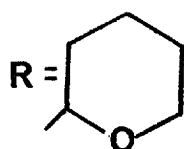
(26)



(46)

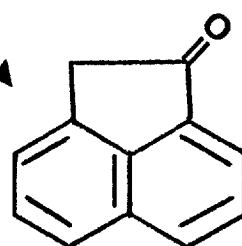
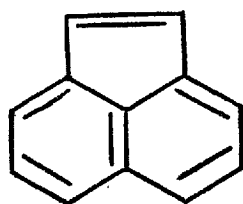


(48)



(49)

(63)



(64)

Studying the conditions of the reaction demonstrated that 2 molar equivalents of DDQ were needed for the reaction to go to completion. Table VII summarises the various conditions used for this reaction.

(table VII over leaf)

TABLE VII

Substrate	equivalent	temperature	time	observations
1. Chromenone(4)	1.0	r.t.	15h.	30% complete ¹
2. "	1.5	r.t.	15h.	40% complete
3. "	2.0	r.t.	12h.	50% complete
4.a "	1.0			80% complete for (c);
b "	1.5	40°C	12h.	less in the case of (a) and
c "	2.0			(b) but more than (1),(2),(3)
5.a "	1.0	70°C	12h.	starting material still
b "	1.5			present in both (a) and (b)
6. "	2.0	70°C	12h.	complete*
7. "	2.0	70°C	12h.	(in darkness) complete
8. "	2.0	70°C	12h.	(under nitrogen atmosphere)
				complete
9. "	2.0	70°C	12h.	(same conditions as in (8) but
				nitrogen flushed through the solvent ^未
				no reaction

Note: ¹ estimated on basis of starting material recovered.

* The reaction appears to be complete in about 2-3h. but the hydroquinone precipitates out of the solution slowly.

* * Nitrogen was flushed through the solution for 0.6h. before DDQ was added.

* * * In the early experiments benzene was used as solvent, but as it was determined that the reaction conditions improved with an increase in temperature, toluene proved to be a better solvent.

From table VII it can be seen that when the solution was thoroughly flushed with nitrogen and then the reaction carried out under a nitrogen atmosphere, no reaction takes place and the starting material is recovered.

The observations with regards to the reaction are similar to those of Sadler.³⁸ The reaction turns a deep colour, although in this case it was dark tan rather than greenish and fades to light tan as the reaction proceeds. The reaction was difficult to work-up as not all the hydroquinone precipitates out. Washing the solution with water, dilute acid ⁴² and evaporating under reduced pressure, turns it dark green, with decomposition of the benzoyl chromone.

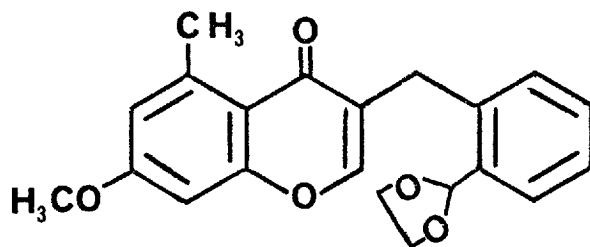
On chromatography on alumina the benzoyl chromone breaks up apparently cleaving off the A ring. Chromatography over silica also caused decomposition. The best conditions found to work-up the reaction were to filter the precipitated hydroquinone and evaporate under reduced pressure. Titration of the residue with acetone gives the benzoyl chromones in reasonable purity.

Ortho and para - chloranil reactions were also investigated but neither react.⁴² Table VIII summarises the alternative reactions attempted.

TABLE VIII

substrate	reagent	solvent	temp.	time	observations
chromanone	CeO ₂ (tech) 30% H ₂ O ₂	EtOH	60°	12h.	N ₂ , no reaction
"	CeO ₂ (tech) 30% H ₂ O ₂	t-ButOH	60°	12h.	N ₂ , no reaction
"	O ₂ , eosin (singlet oxygen)	Acetonitrile/MeOH pyridine	-15°	12h.	O ₂ , no reaction
"acetal	SeO ₂	C ₆ H ₄ Cl ₂	135°C	12h.	starting material dis- appears gives oil.
"	Jones reagent H ₂ CrO ₄ +H ₂ SO ₄	Acetone	r.t.	10min.	greenish precipitate decomposes on workup.
"	t-butyl chromate	CCl ₄	r.t.	4h.	no reaction
"	o-chloranil	toluene	70°	12h.	no reaction
"	p "	toluene	70°	12h.	no reaction

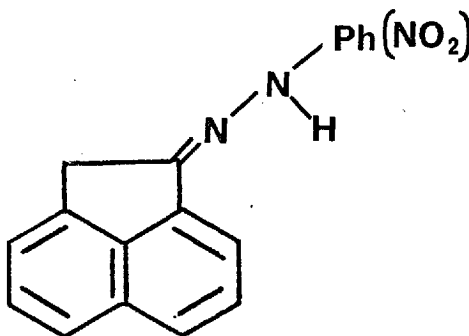
Attempts to carry out a DDQ incorporation of the oxygen function on the endocyclic compound (28)



(28)

failed to give the corresponding benzoyl chromone.

Acenaphthalene (63) was reacted with DDQ to give acenaphthenone (64) m.p. 118°, ν_{max} 1725 cm^{-1} ⁵⁰, M^+ 168. Compound (64) was converted to the 2;4-dinitrophenyl hydrazone derivative (65) m.p. 258°C⁵³

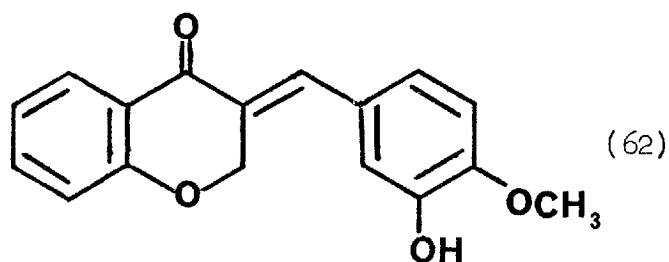
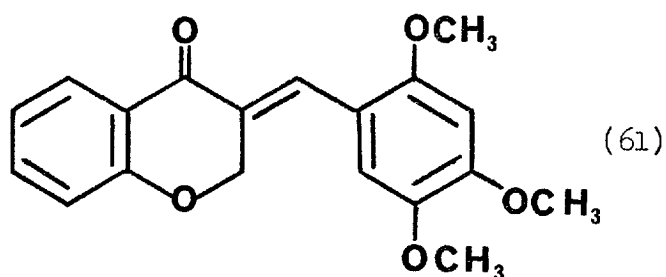


(65)

Condensation¹³ of the chroman-4-one (1) with isovanillin in ethanol-triethylamine mixture resulted in the formation of the exocyclic double bond compound (62), m.p. 188-190°C. Its ultraviolet spectra showed absorbance at λ_{max} 265, 390nm.

A condensation¹³ of the main series ring A (21) with the unsubstituted chromanone (1) was carried out in benzene-piperidine solution

to determine the position of the double bond. It resulted in an exocyclic double bond compound (61) m.p. 136-8°C, the absorbance in the ultraviolet spectrum showed a λ_{max} 272, 392nm, and the n.m.r. scan showed the benzylic proton as a doublet at 4.72 τ ; $J=3\text{cps}$.



From looking at the series of experiments carried out during this work, and the resulting compounds it can be observed that substitution on the D ring does not affect the orientation of the double bond, yielding the endocyclic chromones as condensation product. Meanwhile substitution on the A ring will cause the double bond to form exocyclic to the C ring.

CONCLUSION

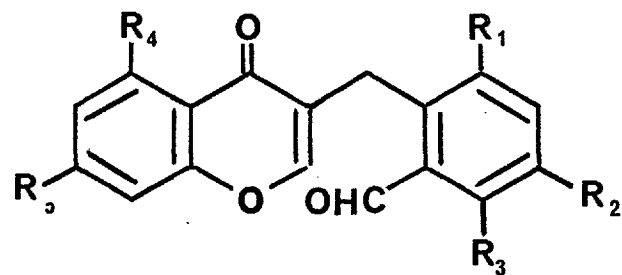
The conclusions that can be drawn from the work discussed in this thesis can be summed up as follows:

The intramolecular Houben-Hoesch ^{7,8,9} cyclisation presents a new method of preparing substituted chromanones using a simplified route with higher yields. It can presumably be used as an efficient cyclisation step for ortho substituted activating groups (OH, OCH₃, CH₃).

From the various ACD ring condensation experiments it can be stated that the presence of substituents on ring A causes the formation of the exocyclic bond system in the 2 position, while an unsubstituted ring A (except for the formyl group), allows the formation of the endocyclic double bond in ring C. This has been summarised in table IX.

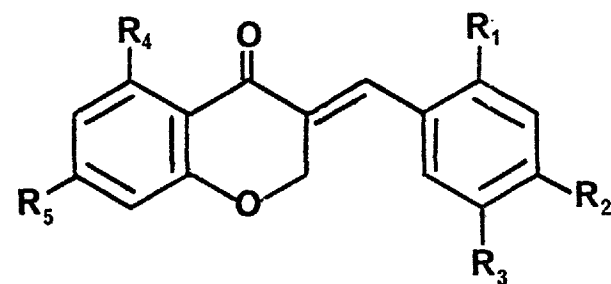
(table IX over leaf)

TABLE IX



1)¹³ $R_1=R_2=R_3=R_4=R_5=H$

2) $R_1=R_2=R_3=H; R_4=CH_3; R_5=OCH_3$



3) $R_1=H; R_2=OCH_3; R_3=OH; R_4=R_5=H$

4) $R_1=H; R_2=OCH_3; R_3=OH; R_4=CH_3; R_5=OCH_3$

5) $R_1=R_2=R_3=R_5=OCH_3; R_4=CH_3$

*6) $R_1=R_3=H; R_2=OCH_3; R_4=R_5=OH$

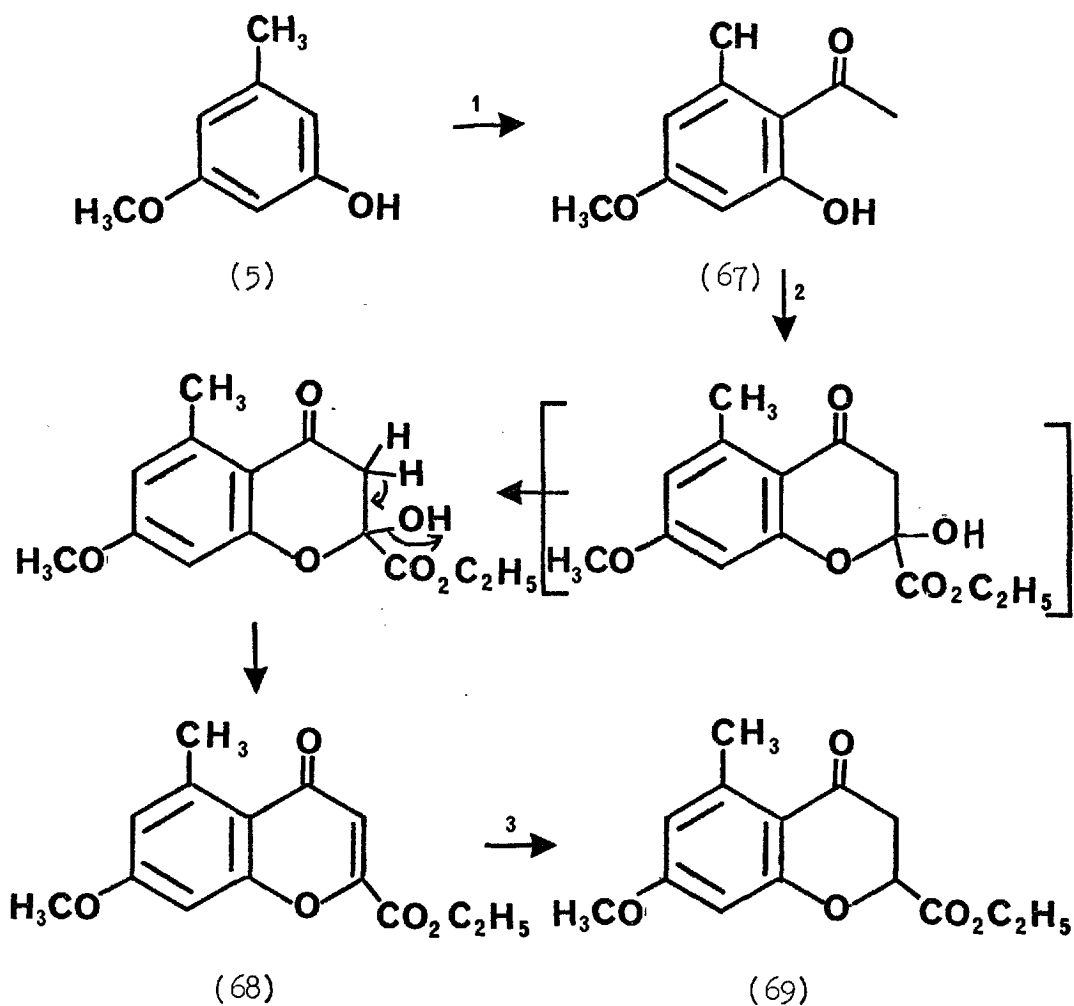
*7) $R_1=R_3=H; R_2=OCH_3; R_4=R_5=OAc$

*8) $R_1=R_3=H; R_2=OCH_3; R_4=R_5=PhCH_2O$

* ref. 43, 44.

The reason being presumably a higher degree of stabilisation due to the electron delocalisation of ring A and a steric compression caused by the presence of substituents in ring A. This leads us to contemplate that future work on the total synthesis of bikaverin should be approached by preparation of a suitable chromanone (69) substituted at the 2 position, Scheme XIV

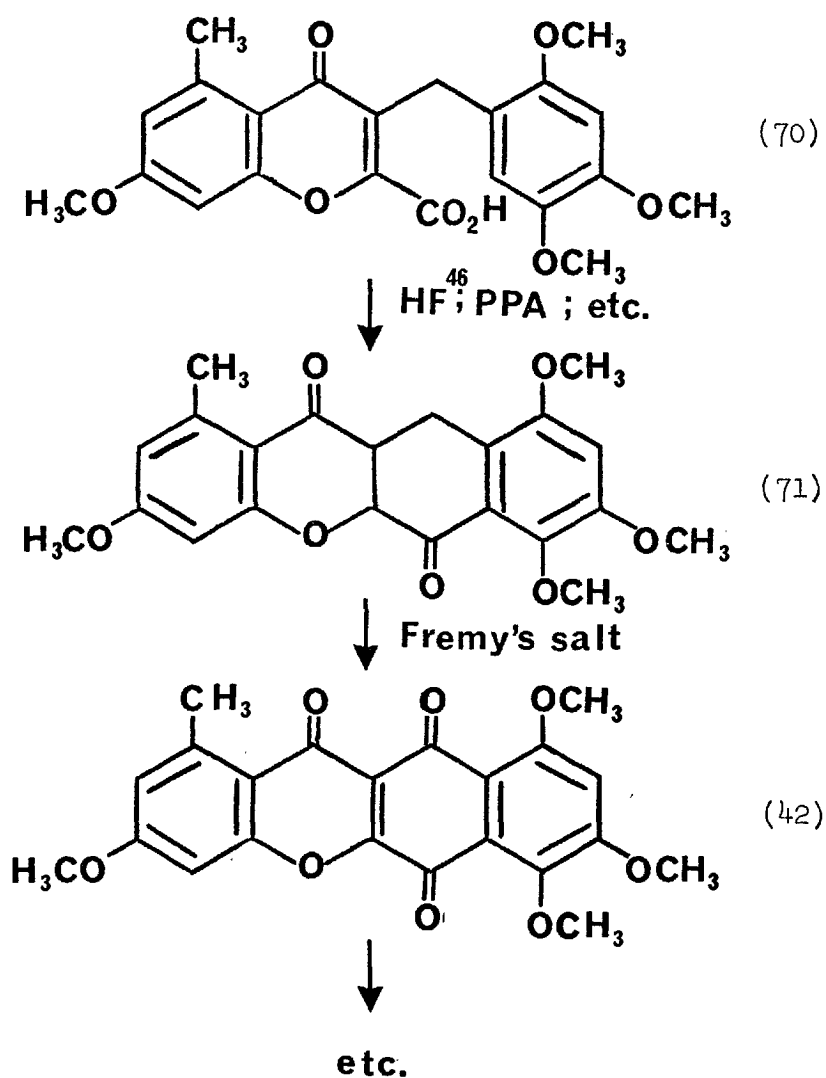
Scheme XIV



Reagents: 1. MeCOCl/AlCl₃, 2. NaH/THF/((COOC₂H₅)₂)⁴⁵ 3. H₂/Pd

to be condensed with a A ring, and the cyclisation carried out by an anion generated on the C-6 position upon an electrophilic centre at C-6a. Scheme XV

Scheme XV



EXPERIMENTAL

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

Infrared spectra were measured on a Unicam S.P. 200 or a Perkin Elmer 137 spectrometer.

Ultraviolet spectra were run on a Unicam S.P. 800 spectrometer.

Mass spectra were run on a A.E.I. MS 9 high resolution mass spectrometer.

Nuclear magnetic resonance spectra were determined on Varian A 60, Varian T60 or Varian HA100 spectrometers with tetramethyl silane as internal standard. The chemical shifts are given in τ values and the following abbreviations- (solvent CDCl_3 unless otherwise stated)

s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet

Alumina refers to neutral alumina grade 3.

Silica gel plates were made from Merck silical gel G 254.

Preparative layer plates (p.l.c. had a thickness of 1mm.)

Thin plates (t.l.c.) were developed by spraying with 6N sulphuric acid followed by heating over a hot block.

3,5-Dimethoxy toluene⁴ (4)

Orcinol (12.4g) in dry acetone (124ml) containing anhydrous potassium carbonate (55.2g) was treated with dimethyl sulphate (25.2g) in acetone (25ml). (Added dropwise over 45min) The mixture was stirred for 24h., and filtered. The mixture was exavaporated under reduced pressure and the residual oil was dissolved in ether. The ethereal solution was washed successively with water, aq. 5% NaOH(x2), concentrated amonium hydroxide (x2) and water. Finally dried (Na₂ SO₄ anhydrous).

The ether was removed and the residue was fractionated under reduced pressure to afford the dimethylether (4) as an oil b.p. 111-113°C/13mm. yield 95% τ ; (3Hs, 3.67)(6Hs, 6.26)(3Hs, 7.72).

3Hydroxy-5methoxy toluene⁴ (5)

Ethanethiol (10g.) in dry NN-dimethylformamide (DMF) (25ml.) was added with stirring, under nitrogen, to sodium hydride (5.5g. 60% dispersion in oil) in dry DMF (50ml.) over 1.5h.. The mixture was then stirred a further 0.75h., after which 3,5-dimethoxytoluene (4) (5g.) in dry DMF (10ml.) was added during 5 min. The mixture was heated under reflux for 3h., and allowed to cool. It was poured into a large volume of water, and extracted exhaustively with ether.

The extract was washed with 5% NaOH and discarded. The combined aqueous layers were acidified and extracted with ether. The extract was washed with brine and dried (anhydrous Na₂ SO₄). The ether was removed to give an oily product sufficiently pure for further transformations. Yield 94%, b.p. 89°C/0.1mm. τ ; 3.05 (1H,S); 3.81(3Hm); 6.39(3Hs); 7.84(3Hs).

Methyl 2-(3¹Methoxy-5¹methyl)phenoxy propionate (6)

3-Hydroxy 5methoxy toluene (5)(10g.) was dissolved in methyl acrylate (50ml.) to which an aqueous solution of triton B (2ml.) was added.⁶ The mixture was heated at reflux for 48h. until the mixture has completely reacted to give the ester (6)(t.l.c.) The ester (6) was dissolved in ether, evaporated under reduced pressure and distilled at 0.1 mm to give an oil that was pure enough to be used in further transformations. Yield 55%

ν max 1745, 1600cm⁻¹; λ max (EtOH) 223, 273, 279nm (ϵ 9,136; 2,122; 2,122). τ ; 3.58(3Hs), 5.76(2Ht; J=7cps); 6.26(6Hd; J=2cps); 7.23 (2Ht; J=7cps), 7.73(3Hs); M+224

Found: C, 64.3; H, 7.3; C₁₂H₁₆O₄ requires; C, 64.3; H, 7.2.

2-(3¹Methoxy-5methyl) phenoxy propionic acid (7)

The ester (6)(10g.) in MeOH⁶ (5ml.) and 6N HCl (100ml.) was heated at reflux for 24h.. The solution was cooled and colourless crystals precipitated out. The crystals were filtered and dissolved in a solution of 10% Na₂CO₃ with warming. The solution was filtered through cotton wool to obtain a clean solution to which concentrated HCl (50ml) was added.

The acid (7) was washed with distilled water until neutral and dried under vacuum. Yield 89%

m.p. 81°, max (nujol mull) 1708, 1605, 1164cm⁻¹; max 271, 278nm, (ϵ 2226, 2338). ; 3.68(3Hs); 5.74(2Ht; J=7cps); 6.25(3Hs); 7.22 (2Ht; J=7cps); 7.76(3Hs); M+210

Found; C, 62.8; H, 6.6; C₁₁H₁₄O₄ requires; C, 62.8; H, 6.7.

5-Methyl-7methoxy chroman-4-one (2)

A mixture of the aryloxypropionic acid (7) (5g.) and P_2O_5 ^{3,6} (10g.) in dry benzene (100ml) was heated at reflux for 1h. The solution was cooled and additional P_2O_5 (10g.) was added. The reaction mixture was refluxed for a further 20h.

The benzene solution was decanted and the solid residues thoroughly extracted with boiling benzene. The benzene solution was washed with aq. 5% NaOH with water and dried. (anhydrous Na_2SO_4). The solvent was evaporated under reduced pressure to give the chromanone (2) (Yield 72%). Recrystallised from benzene - light petrol ether.

m.p. $68^{\circ}C$; λ max 309, 273nm; (ϵ 4,992; 14,967); 234nm; (ϵ 11,096);
 ν max 1618, $1665cm^{-1}$. $M+192$. τ ; 3.67(2Hs); 5.55(2Ht; J=7cps); 6.21(3Hs); 7.29(2Ht; J=7cps); 7.39(3Hs).
Found: C, 68.7; H, 6.3; $C_{11}O_3H_{12}$ requires: C, 68.7; H, 6.3.

(3¹Methyl-5¹methoxy)-2)phenoxy propionitrile (8)

3-Hydroxy-5-methoxy toluene (5)(10g) was dissolved in excess acrylonitrile,⁴⁷ to which a catalytic amount of aqueous Triton B⁶ (2ml) had been added. The mixture was heated at reflux for 48h., cooled, extracted into ether, washed with water, dilute HCl, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a white solid.

The solid was recrystallised from benzene - light petrol ether giving fine colourless needles of the nitrile (8) Yield 92%.

m.p. $73-4^{\circ}C$. λ max 206nm, λ_{sh} 222nm; (ϵ 1722, 819). ν max (nujol) 2260, 1595, $1155cm^{-1}$. $M+191$.

τ ; 3.69(3Hs); 5.88(2Ht; J=7cps); 6.27(3Hs); 7.26(2Ht; J=7cps); 7.72(3hs)
Found: C, 69.2; H, 6.8; N, 7.3; $C_{11}H_{13}O_2N$ requires: C, 69.1; H, 6.8; N, 7.3.

5-Methyl-7methoxy chroman-4-one⁷ (2)

The nitrile (8)(5.0g.) was dissolved in anhydrous diethyl ether (50ml) at 0°C, to which anhydrous zinc chloride ^{8,9} (7.0g) was added with stirring over 10 min. The solution was allowed to stir with hydrogen chloride gas passing through the solution for two hours. The iminohydrochloride formed a white precipitate (9) which was filtered, and dissolved in boiling water. The solution was refluxed for 2h., allowed to cool, and the chroman-4-one (2) separated.

The product was recrystallised from benzene - light petrol ether. Yield 95%
m.p. 68°C; M+192. This compound has identical spectral properties as compound (2).

5-Methoxy-7methyl chroman-4-one (10)

The minor product from the intramolecular Houben-Hoesch cyclisation of the aryloxypropionitrile (8) was compound (10)
Yield 2-5%
m.p. 65-6°C. λ_{max} 222, 271, 326nm; (ϵ 15, 465; 15, 235; 4, 256);
 ν_{max} 1690, 1635, 1160cm⁻¹. M+192.
 τ 3.62(1Hs); 3.68(1Hs); 560(2Ht; J=7cps); 6.14(3Hs); 7.30(2Ht, J=7cps); 7.74(3Hs).
Found: C, 68.8; H, 6.1; C₁₁O₃H₁₂ requires: C, 68.7; H, 6.2.

2-Bromo isovanillin⁴⁸ (12)

A solution of isovanillin (11) (10g.) in acetic acid (60ml) was treated with bromine (10.7g.) in acetic acid (15ml.). After standing for 1.5h., the white crystals which had separated filtered off (4.6g.). Recrystallisation from alcohol furnished colourless needles.
m.p. 210°C.⁴⁹

3-(3¹Hydroxy-4methoxy benzylidene)
5methyl-7methoxy chroman-4-one (13)

Isovanillin (11)(0.5g.) was added to 5methyl-7methoxy chroman-4-one (2)(0.6g.) in absolute ethanol (5ml.) and triethylamine¹³ (5ml). The solution was heated at reflux for 20h. The water drained from the condenser, and a slow stream of nitrogen was allowed to sweep through the flask containing the reaction mixture while it is heated in an oil bath at 140°-170°C.

After 1h. a 1:1 mixture of ethanoltriethylamine (10ml.) was added to the reaction mixture and left in the oil bath for further 5h. (If at this stage t.l.c. shows more than one compound the treatment is repeated.) The mixture was allowed to cool to room temperature and dissolved in benzene. Elution through an alumina column (G3) gave the chromanone (13). It was recrystallised from benzene - light petrol ether. Yield 83% crude, 77% recrystallised. m.p. 180-181°C $\lambda_{\max}$ 246, λ_{sh} 308, $\lambda_{\max}$ 351 nm; (ϵ 11,636; 14, 996; 20,016). $\nu_{\max}$ 3560, 1680, 1627, 1278cm⁻¹ M+326 τ ; 2.20(1Hs); 2.64(1Hs); 3.06(2Hs); 3.60(2Hd; J=7cps); 4.65(2Hd; J=3cps); 6.02(3Hs); 6.11(3Hs); 7.24(3Hs). Found: C, 69.7; H, 5.6; C₁₉H₁₈O₅ requires: C69.9; H, 5.6.

3-(6¹-Formyl-3¹-hydroxy-4¹-methoxybenzylidene)
-5-methyl-7-methoxychromanone²⁰(15)

The chromanone (13)(0.5g.) in dry dichloromethane (30ml) and α,α -dichloromethyl methylether (0.5g.) was treated with aluminium trichloride (1.5g) at 0°C. After stirring at room temperature for 2.5h. the mixture was poured into ice-cold dilute hydrochloric acid (50ml.).

The organic phase was separated, dried (anhydrous Na₂SO₄) and evaporated under reduced pressure to give the chromanone (15).

Yield 72%

m.p. 96-8°C $\lambda_{\max}$ 208, 248, 350nm; (ϵ 5,400; 2,140; 1,930cm⁻¹. M+354.

τ ; 2.31(1Hs); 2.78(1Hs); 3.12(2Hs); 3.52(1Hs); 4.62(2Hd; J=3cps); 6.08(3Hs); 6.10(3Hs); 7.23(3Hs)
accurate mass measurement; Ratio 355/354=1002454; M(354)=354.1102;
C₂₀H₁₈O₆ call for 354.1103.

Malonate derivative (16)

The aldehyde (15)(0.1g.) was dissolved in pyridine (5 ml.) and (2eq.) diethyl malonate followed by piperidine (2 drops) was added. After heating the mixture at 90°-100°C for 1h. the cooled solution was extracted into ether, washed with water, neutralised with acid, dried (anhydrous Na₂SO₄) and evaporated under reduced pressure. The derivative (16) was recrystallised from benzene - petrol ether.

m.p. 72-4°C M+496 τ ; 2.7-3.6(4H); 4.6(1Hd; J=3cps); 5.6(2Hs); 5.83(4Hm); 6.62(6Hs); 7.23(3Hs); 8.7(6Ht; J=12cps)

1,2,4-Trimethoxybenzene (19)¹⁶

Prepared using method described in the literature.¹⁶

2,4,5-Trimethoxybenzaldehyde (21)⁵⁰

Prepared using method described in the literature.⁵⁰

3-(2¹,4¹,5¹-Trimethoxybenzenzylidene)-5-methyl-7-methoxy chroman-4-one (22)

2,4,5-Trimethoxybenzaldehyde (21)(1.0g.) was added to 5-methyl-7-methoxychroman-4-one (2) (1.0g.) in dry benzene (50ml.) and piperidine (1.5ml.). The solution was heated at reflux under nitrogen for 24h. after which it is heated to 130°C in an oil bath.

After 2h. benzene (30ml.) with a few drops of piperidine were added to the mixture and left for a further 2h. (If after this

stage t.l.c. shows more than one spot the treatment with benzene-piperidine is repeated until the reaction has gone to completion). The reaction is allowed to cool to room temperature. The residue was dissolved in benzene and eluted through a column of alumina (G3) to give the chromanone (22). Recrystallised from benzene - light petrol ether. Yield 86%

m.p. 130-2°C λ max 215, λ sh. 248, λ max 298, λ sh. 340nm; (ϵ 15,481; 10,126; 9,347; 8,763). ν max 1675, 1605, 1385cm⁻¹. M+370 τ ; 2.12(1Hs); 3.54(1Hs); 3.62(1Hs); 3.70 (1Hs); 4.93(2Hd; J=3cps); 6.10(3Hs); 6.20(9Hs); 7.23(3Hs).

Found: C, 68.0; H, 5.7; C₂₁H₂₂O₆ requires: C, 68.1; H, 6.0.

3-(2¹,4¹,5¹-Trimethoxy-6-formylbenzylidene)-5-methyl-7-methoxy-chroman-4-one (23)

The chromanone (22)(1g.) in dry dichloromethane (50ml) and α,α dichloromethyl methyl ether (1g.) was treated with aluminium trichloride (2g.) at 0°C. After stirring at room temperature for 1.5h. the mixture was poured onto ice cold dilute hydrochloric acid (50ml.).

The organic phase was separated, dried (anhydrous Na₂SO₄), evaporated under reduced pressure to give a brownish oil which was eluted through an alumina (G3) column with dichloromethane to give the aldehyde (23). Recrystallised from benzene - light petrol ether. Yield 78%

m.p. 112-4°C λ max 213, 264, 363nm; (ϵ 11,041; 9,757; 5,007) ν max 1695, 1675, 1385cm⁻¹. M+398. τ ; -0.33(1Hs); 2.09(1Hs); 2.74(1Hs); 3.37(1Hs); 3.42(1Hs); 4.85(2Hd; J=3cps); 6.06(3Hs) 6.10(3Hs); 6.18(6Hs); 7.24(3Hs)

Found: C, 66.6; H, 5.7; C₂₂H₂₂O₇ requires: C, 66.3; H, 5.6.

3-(2¹,4¹,5¹-Trimethoxy-3-formylbenzylidene)-
5-methyl-7-methoxychroman-4-one (24)

Is the minor product formed in the preparation of the aforementioned aldehyde (23)

$\lambda_{\max}$ 210, 274, 360nm; (ϵ 11,420; 9,932; 6,040)

$\nu_{\max}$ 1700, 1685, 1385cm⁻¹. M+398. m.p. 136-8°C.

τ ; -0.29(1Hs); 2.09(1Hs); 2.75(1Hs); 3.40(1Hs); 3.50(1Hs); 4.88 (2Hd; J=3cps); 6.08(3Hs); 6.10(3Hs); 6.16(6Hs); 7.23(3Hs).

Found: C, 66.3; H, 5.4; C₂₂H₂₂O₇ requires: C, 66.3; H, 5.6.

3-[2¹,4¹,5¹-Trimethoxy-6-(1,3 dioxanyl)]benzylidene-
5-methyl-7-methoxychroman-4-one (25)

The aldehyde (23)(0.6g), ethylene glycol (1.5ml) and *p*-toluene sulphonic acid (20mg.) in dry benzene (180ml) was heated at reflux, under nitrogen, for 5h. over calcium hydride in a soxhlet. The cooled solution was added with stirring to aqueous sodium carbonate (10%, 200ml). The aqueous layer was extracted with benzene and added to the organic layer. The combined benzene solution was dried (anhyd. Na₂SO₄).

Removal of the solvent under reduced pressure gave the acetal (25). Recrystallised from benzene - light petrol ether. Yield 77%.

m.p. 151-2°C $\lambda_{\max}$ 213, 256, 308, 376nm; (ϵ 28,021; 10,341; 10,007; 12,843). $\nu_{\max}$ 1670, 1603, 1125cm⁻¹. M+442

τ ; 2-3.6(5H); 4.9(2Hd; J=3cps); 6.1(4Ht, J=6cps); 6.2(12Hm); 7.2 (3Hs).

Found: C, 65.3; H, 5.8; C₂₄H₂₆O₈ requires C, 65.2; H, 5.9.

3-(2¹,4¹,5¹ Trimethoxy-6-(1,3-dioxanyl)benzylidene)-5-methyl-7-methoxychroman-4-one (26)

Prepared from the aldehyde (24) by the method described in the preceding experiment. Yield 74%
m.p. 169-171°C. λ max 213, λ sh. 233, λ max 253, 300, 375nm;
(ϵ 25,519; 11,243; 10,856; 9,692- 7,366). ν max 1670, 1603, 1120cm⁻¹
M+442
 τ ; 2-3.6(5H); 4.9(2Hd; J=3cps); 6.1(4Ht ; J=6cps); 6.2(12Hm); 7.2 (3Hs).
Found: C, 65.0; H, 5.8; C₂₄H₂₆O₈ requires C, 65.2; H, 5.9.

3-(2¹-formylbenzylidene)-5-methyl-7-methoxychroman-4-one (27)

Phthaldehyde (0.5g.) was added to the chromanone (2)(0.6g) in absolute ethanol (10ml) and triethylamine (10ml). The reaction mixture was heated at reflux for 15h. Water was drained from the condenser. A slow stream of nitrogen was then allowed to sweep through the flask containing the reaction mixture, while it was heated in an oil bath to 150-160°C. After 1h. a 1:1 mixture of ethanol and triethylamine was added to the reaction mixture and left for 6h., after which t.l.c. showed only one compound.

The mixture was cooled, dissolved in benzene and eluted through a column of alumina (G3) to give crystals of the aldehyde (27). Yield 75% m.p. 159-161°C

This compound proved extremely difficult to purify and thus was fully characterised as its acetal derivative (28). On reactions larger than 0.5g of substrate the yield decreases considerably. Also condensation in benzene-piperidine solution was attempted unsuccessfully as only starting material was recovered. Yield 54%

λ max 215, 243, 256, 285nm; (ϵ 17,089; 16,890; 16,691; 7153).
 ν max 1700, 1655, 1620, 1285cm⁻¹. M+308; C₁₉H₁₆O₄
 τ ; -0.30(1Hs); 2.14(1Hs); 2.48-3.37(6Hm); 5.86(2Hs); 6.14(3Hs); 7.18(3Hs)

3-[2-(1,3-diocanyl)benzylidene]-5-
methyl-7-methoxychroman-4-one (28)

Prepared from the aldehyde (27) by the method described in the preparation of compound (25)(p.85). Yield 81% m.p. 116-8°C. pale yellow plates. λ_{max} 222, 238, 246, 271, 283, 299nm; (ϵ 17,991; 18,871; 16,328; 7,724; 5,964; 6,062). ν_{max} 1740, 1655, 1190 cm^{-1} M+352. τ ; 2.35-3.60(6Hm); 4.04(1Hs); 5.99(2Hs); 6.04(4Ht; J=4cps); 6.16(3Hs); 7.13(3Hs). Found: C, 71.5; H, 5.7; $\text{C}_{21}\text{H}_{20}\text{O}_5$ requires: C, 71.6; H, 5.7.

Photolysis of 3-[2-(1,3-dioxanyl)benzylidene]-
5-methyl-7-methoxychroman-4-one (28)

Photolysis^{13,21} of (28) to give the hydroxanthone was achieved by using a medium pressure mercury arc lamp (MBW/U)125 watts supplied by A.E.I.

The solution to be photolysed was contained in a 3-neck flask equipped with a reflux condenser and an inlet tube through which a slow stream of nitrogen was introduced into the system. The reaction was followed by thin layer chromatography and ultraviolet spectroscopy.

(1-Methyl-3-methoxy)trans-5a,6,11,11a-ethylenedioxy-
5a,11,11a-tetrahydrobenzo[blxanthone (30)

The acetal (28)(40mg) was photolysed in dry benzene (10ml) containing o-dichlorobenzoic acid (0.2g). The solvent was removed from the combined reaction product and the residue chromatographed on a column of alumina (G3) with a 2:1 mixture of ethylacetate-60-80° petroleum ether.

On t.l.c. before elution there were two compounds, the cis-isomer (29) probably corresponding to the minor component of the mixture. On evaporation of the eluate only one spot (trans-isomer)

appeared. The tetrahydrobenzoxanthone (30) was recrystallised from benzene - light petrol ether. Yield 121-3°C. λ_{max} 241, 248, 282nm; (ϵ 4,928; 4,670; 1,967). ν_{max} 1695 and 1610cm⁻¹ M+352

τ : 2.15-3.20(6H); 5.62(1Hd); 5.95(4Hm); 6.12(3Hs); 6.96(2Hm); 7.11(3Hs); 7.30(1Hm).

Found: C, 71.8; H, 5.7; C₂₁H₂₀O₅ requires: C, 71.7; H, 5.7.

Reduction of the chroman-4-one (22)

3-(2¹,4¹,5¹-Trimethoxybenzyl)-5-methyl
-7-methoxychroman-4-one (34)

The chromanone (22)(0.2g) in ethanol (35ml) to which a catalytic amount of 10% palladium on carbon was added, was hydrogenated in the usual way. The solution was filtered through Celite 545 to give a clear solution, which was evaporated to give the chromanone (34). Recrystallised from ether - light petrol ether to yield colourless needles. Yield 75%
m.p. 95°C λ_{max} 225, 274, λ_{sh} 313nm (ϵ 13,861; 13,154; 4,526)
 ν_{max} 1675cm⁻¹ M+372

τ : 2.05(1H); 2.30(1h); 2.45(1H); 2.66(1H); 5.77(3Hm); 6.10(3Hs); 6.17(6Hs); 6.23(3Hs); 7.15(2Hm); 7.33(3Hs).

Found: C, 67.6; H, 6.4; C₂₁H₂₄O₆ requires C, 67.7; H, 6.5.

3-(2¹,4¹,5¹-Trimethoxy)benzoyl chromone (35)

Was prepared by the same procedure from both compounds (22) and (34).

The chromanone (22)(0.15g) in toluene (30ml) to which DDQ (2 equivalents) was added with stirring was heated at 80°C for 12h. The mixture was cooled to room temperature and the precipitated hydroquinone was filtered.

The solution was evaporated under reduced pressure using the least heating possible. The residue was dissolved in acetone

and the benzoyl chromone (35) separated as colourless crystals.

Yield 62%

m.p. 181°C $\lambda_{\max}$ 213, 250, λ_{sh} 286, $\lambda_{\max}$ 345nm; (ϵ 15,709;

18,520; 10,204; 4,430) $\nu_{\max}$ 1660, 1660 1610, 1390cm⁻¹ M+384

τ ; 2.00(1Hs); 2.70(1Hs); 3.33(2Hs); 3.61(1Hs); 6.15(6Hs); 6.17(3Hs); 6.43(3Hs); 7.30(3Hs)

Found: C, 65.5; H, 5.4; C₂₁H₂₀O₇ requires C, 65.6; H, 5.3.

An identical product was obtained from oxidation by DDQ of the chromanone (34). The only variation was the need to use 3 equivalents of DDQ.

Description of general experimental procedure
to prepare the benzoylchromones by DDQ oxidation
of chromanones

To the chromanone (0.15g) in toluene (30ml) DDQ (2 equivalents) was added and heated at 80° for 12h. Cooled to room temperature and the precipitated hydroquinone filtered. The solvent evaporated under reduced pressure (not to complete dryness) and the oily residue dissolved in a minimal amount of acetone, from which the colourless crystals of the benzoyl chromone separates.

These compounds were difficult to purify and partially decomposed on plate or column chromatography.

3-(2¹,4¹,5¹-Trimethoxy-6-formylbenzoyl)-
5-methyl-7-methoxychromone (52)

This compound (52) was prepared according to the general description given on the preparation of benzoylchromones (p. 89).

Yield 64%; m.p. 225-230° with decomposition.

λ 215, 237, 285, λ_{sh} 305, $\lambda_{\max}$ 345nm; (ϵ 15,450; 16,737; 9,012; 6,437; 5,471) $\nu_{\max}$ 1695, 1665, 1625cm⁻¹ M+412

τ ; -0.52(1Hs); 1.96(1Hs); 2.73(1Hs); 3.28(1Hs); 3.67(1Hs); 6.04(3Hs);

6.12(3Hs); 6.18(3Hs); 6.48(3Hs); 7.21(3Hs)

Found: C, 64.0; H, 4.9; $C_{22}H_{20}O_8$ requires: C, 63.8; H, 5.0
accurate mass measurement Ratio $412/414=1.004520$ $M(412)=412.1147$;
 $C_{22}H_{20}O_8$ calls for 412,1158

3-[2¹,4¹,5¹-Trimethoxy-3-(1¹,3-dioxanyl)]
benzoyl-5-methyl-7-methoxychromone (46)

Prepared by DDQ oxidation of the chromanone (26). Yield 57%
(22mg) m.p. 235°C with decomposition $M+456$ λ_{max} 208, 252, λ sh.
285, λ_{max} 340; (ϵ 15,824; 18,323; 10,827; 4,789). ν_{max} 1650, 1601,
1120 cm^{-1}

τ ; 2.45-3.60(5Hm); 5.95(4Hm); 6.12(6Hs); 6.17(3Hs); 6.40(3Hs); 7.15
(3Hs).

accurate mass measurement . Ratio $456/455=1.002570$; $M(456)=456.1421$;
 $C_{24}H_{24}O_9$ calls for 456.1420

Photolysis of 3-[2¹,4¹,5¹-Trimethoxy-6-(1¹,3-dioxanyl)
dioxymethylbenzoyl-5-methyl-7-methoxychromone (44)

The acetal (44)(50mg) was dissolved in dry benzene (20ml).
The solution was kept under a nitrogen atmosphere and irradiated
with a tungsten lamp for 4h. at reflux. The reaction was followed
by t.l.c. and ultraviolet spectra, and no change took place. On
addition of o-chlorobenzoic acid (1 equivalent) and further irradi-
ation no change occurs.

When the source of irradiation was replaced by a medium
pressure mercury arc lamp and irradiation continued for 15h. no
change could be observed on t.l.c.

Irradiation with a high pressure mercury arc lamp gave many
products, none of which appeared to be the tetrahydrobenzoxanthone
(45).

The same procedure using dry acetonitrile as solvent and
dichlorobenzoic acid was unsuccessful. In all cases starting mat-
erial was recovered, and no cyclisation occurred.

On irradiation of the acetal (46) no changes were observed.

3-(2¹,4¹,5¹-Trimethoxy-6¹-formylcyanohydrinbenzylidene)
5-methyl-7-methoxychroman-4-one (47)

The chromanone (23)(1g) in tetrahydrofuran (30ml) at 5°C was treated with a solution of sodium cyanide (0.27g) in water (10ml). The solution was neutralised with 0.5N sulphuric acid (11ml) over 20 min. The mixture was stirred at 0°C for 1h. then extracted into chloroform and the chloroform extract washed with water and dried (anhydrous Na₂SO₄). Evaporation of 2/3 of the solvent yielded yellow crystals of the cyanohydrin (47). Yield 89%
m.p. 142-5°C $\nu_{\max}$ 3350, 1660cm⁻¹

γ ; 2.7(1H); 3.1-3.7(3Hm); 4.8(2H); 6.1(12Hm); 7.2(3H).

It was not possible to purify the compound (47) sufficiently for analysis, thus it was characterised as its tetrahydropyranyl derivative (48).

3-(2¹,4¹,5¹-Trimethoxy-6¹-formylcyanohydrin
tetrahydropyranyl ether benzylidene)-5
-7-methoxychroman-4-one (48)

The cyanohydrin (47)(1g) in dry benzene (120ml) containing 2,3-dihydropyran (10ml) and conc. hydrochloric acid (10 drops) was heated at reflux for 2h. The mixture was cooled and poured into a saturated sodium bicarbonate solution (100ml). The organic phase was separated, washed with water and dried (anhydrous Na₂SO₄). The solvent was evaporated to give an oil which was chromatographed on a column of alumina (G3). The resulting product was recrystallised from benzene - light petrol ether to give yellow crystals of the cyanohydrin tetrahydropyranyl ether (48).
Yield 82%

m.p. 104-6°C $\lambda_{\max}$ 217, λ_{sh} 235, $\lambda_{\max}$ 280, 357nm; (ϵ 16,710;
10,993; 6,922; 5,936; 5,936) $\nu_{\max}$ 2400, 1660, 1050cm⁻¹ M+509

γ ; 2.05(1Hs); 3.32-3.60(4H); 3.91(1Hs); 4.01(1Hs); 4.75(2Hd; J=3cps);
6.03(6Hs); 6.15(6Hs); 7.23(3Hs); 8.18(8Hm).

Found: C, 66.1; H, 6.1; N, 2.9; $C_{28}H_{31}O_8$ requires: C, 66.0; H, 6.1; N, 2.8.

3-(2¹,4¹,5¹-Trimethoxy-6¹-formylcyanohydrin
tetrahydropyranyl ether)benzoyl-5-methyl-7-
methoxychromone (49)

Prepared by the general method (p. 89) for preparation of benzoylchromones by DDQ oxidation. The colourless crystals of the tetrahydropyranyl ether benzoylchromone (49) were obtained in (58% yield).

m.p. 255°-65 with decomposition. $\lambda_{\max}$. 213, 248, λ_{sh} . 305, $\lambda_{\max}$ 350nm (ϵ 17,392; 18,132; 6,167; 2,466) $\nu_{\max}$ 2230, 1660, 1600, 1120cm⁻¹

τ ; 2.15(1H); 2.78(1H); 2.91(1H); 3.32(1H); 3.70(1H); 6.20(6H); 6.26(3H); 6.61(3H); 7.13(1Hm); 7.31(3H); 8.50(8Hm)

Accurate mass measurement ratio 523/522=1.001914; M(523)=523.1833; $C_{28}H_{29}O_8N$ calls for 523.1842

Cyclisation of 3-(2¹,4¹,5¹-Trimethoxy-6¹-formyl
cyanohydrin tetrahydropyranyl ether)benzoyl
-5-methyl-7-methoxychromone (49)

Anhydrous sodium t-butoxide (1 molar equivalent in t-butanol) was added to a refluxing solution of the benzoylchromone (49)(50mg) in absolute ether (30ml). The reaction was heated at reflux for 1h. under an atmosphere of nitrogen. Poured into water and neutralised with carbon dioxide. The ethereal solution was dried (anhydrous Na_2SO_4) and evaporated to give a solid which was identified as the starting material (49) instead of the cyclised tetrahydrobenzo-xanthone (50).

3-(2¹,4¹,5¹-Trimethoxy-6¹-formyl)benzoyl-
5-methyl-7-methoxychromone (52)

The aldehyde was oxidized with DDQ by the method described (p. 89) for the preparation of benzoylchromones. The colourless crystals were recrystallised from ethyl acetate - petrol ether.

Yield 64%

m.p. 225-230°C λ max 215, 237, 285, λ sh. 305, λ max. 345nm;
(ϵ 15.450; 16, 737; 9,012; 6,437; 5,471) ν max 1695, 1665, 1625cm⁻¹

M+412

τ ; -0.52(1Hs); 1.96(1Hs); 2.73(1Hs); 3.28(1Hs); 3.67(1Hs); 6.04(3Hs);
6.12(3Hs); 6.18(3Hs); 6.48(3Hs); 7.21(3Hs).

Found: C, 64.0; H, 4.9; C₂₂H₂₀O₈ requires: C, 63.8; H, 5.0

Accurate mass measurement 412/414 = 1.004520

M(412) = 412.1147; C₂₂H₂₀O₈ calls for 412.1158

Reaction of 3-(2¹,4¹,5¹-trimethoxy-6¹-formyl)benzoyl
-5-methyl-7-methoxychromone (52) with sodium cyanide

The benzoylchromone (52) (40mg.) in t-butanol (10ml) at 45°C was treated with excess sodium cyanide. The mixture was stirred for 1.5h. under an atmosphere of nitrogen. The reaction was quenched in water, extracted into ethyl acetate, dried (anhyd. Na₂SO₄) and evaporated under reduced pressure. It gave an unstable compound which could not be isolated, and decomposes.

Preparation of the isoxazolidine derivative of

3-(2¹,4¹,5¹-Trimethoxy-6¹-formyl)benzoyl-

5-methyl-7-methoxychromone (56)

The aldehyde (52)(0.1g.) was suspended in absolute ethanol (25ml) and treated with phenylhydroxylamine (50mg.) which had been freshly prepared. The mixture was stirred at room temperature under an atmosphere of nitrogen. After 4h. the reaction was complete and the product precipitated from the solution.

It was filtered, washed with light petrol ether and recrystallised from benzene - petrol ether to give pale yellowish crystals of the nitrone (56). Yield 76%

m.p. 195°C $\lambda_{\max}$ 260, 300nm (ϵ 16,632; 13,806) $\nu_{\max}$, 1635, 1585, 1275cm⁻¹ M+594

; 2.22-3.66(15Hm); 6.20(6Hs); 6.28(3Hs); 6.42(3Hs); 7.33(3Hs)

Accurate mass measurement: Ratio 594/ 595= 1.004522; (M594)=594.2738

C₃₄H₃₀O₈ N₂ calls for 594.2766

Preparation of the p-nitrophenylhydrazine

derivative of 3-(2¹,4¹,5¹,-Trimethoxy-6¹-formyl)

benzoyl-5-methyl-7-methoxychromone (51)

The aldehyde (52)(0.1g.) was added to a solution of p-nitrophenylhydrazine (0.1g) and a few drops of glacial acetic acid in ethanol (10ml). The mixture was refluxed for 15min., cooled and few drops of petroleum ether were added, precipitating the p-nitrophenylhydrazone derivative (57). The orange crystals were recrystallised from benzene - light petrol ether. Yield 41%

m.p. 185°C M+682 $\lambda_{\max}$ 295,405nm; (ϵ 24,850; 26,600) $\nu_{\max}$ 3450, 1600cm⁻¹

; 2.2-3.5 (12Hm); 6.18 (6Hs); 6.23 (3Hs); 6.48 (3Hs); 7.1 (1H); 7.3 (3H)

Accurate mass measurement; 682/683=1.004138; M(682)=682.2032;

C₃₄H₃₀N₆O₁₀ calls for 682.2023

3-(2¹,4¹,5¹-Trimethoxybenzylidene)chroman-4-one (61)

Trimethoxybenzaldehyde (21)(1g.) was added to the chroman-4-one (1)(0.8g) in benzene (30ml) and piperidine (1ml). The solution was heated at reflux for 20h. the water drained from the condenser, and a slow stream of nitrogen was allowed to sweep through the flask containing the reaction mixture.

It was then heated to 130-135°C in an oil bath. After 1h. the addition of benzene/piperidine mixture was repeated and left in the oil bath for further 2h. (If at this stage t.l.c. shows more than one compound the treatment is repeated). It was allowed to cool to room temperature still under nitrogen. The solidified brown mass was dissolved with benzene and eluted with benzene through a column of alumina (G3) to give the chroman-4-one (61). Recrystallised from benzene - light petrol ether. Yield 84%
m.p. 136-8°C λ max 212, 272, 392nm (ϵ 16,911; 10,570; 8,011)

ν max. 1659, 1605cm⁻¹ M+326

τ ; 2-3.5(7H); 4.72(2Hd, J=3cps); 6.08(3Hs); 6.15(6Hs);

Found: C, 69.9%; H, 5.5% • C₁₉H₁₈O₅ requires: C, 69.9; H, 5.6.

5-Methyl-7-methoxychromone (58)

The chromanone (2)(1.0g.) was dissolved in benzene (50ml.), to which DDQ (1.1 equivalents) was added. The reaction was allowed to stir for 12h. at 60°C, cooled and the precipitate hydroquinone filtered. The solution evaporated under reduced pressure and eluted with benzene through a column of alumina (G3) to give colourless needles of the chromone (58). Recrystallised from benzene - light petrol ether. Yield 85%

m.p. 116-7°C λ max 209, 239, 248, 290nm; (ϵ 4,644; 4,143; 3,984; 2,111). ν max 1655, 1625cm⁻¹ M+190

τ ; 2.45(1Hd; J=8cps); 3.60(2Hs); 3.90(1Hd; J=8cps); 6.23(3Hs); 7.25(3Hs)

Found: C, 69.3; H, 5.3; C₁₁H₁₀O₃ requires: C, 69.5; H, 5.3.

3-(3¹-hydroxy-4¹-methoxy benzylidene)
chroman-4-one (62)

Isovanillin (1g) was added to chroman-4-one (1g) in absolute ethanol (7.5ml) and triethylamine (7.5ml). The reaction was allowed to reflux 15h. The water was drained from the condenser. A slow stream of nitrogen was allowed to sweep through the flask containing the reaction mixture while it was heated in an oil bath at 160-170°C. After 1h. a 1:1 mixture of ethanol (5ml) triethylamine (5ml) was added to the reaction mixture and left in the oil bath for further 5h. (If at this stage t.l.c. shows more than one compound treatment with ethanol triethylamine was repeated). It was allowed to cool to room temperature still under nitrogen. The mixture was eluted with benzene through a column of alumina (G3) to give the chroman-4-one (62). Yield 72%
m.p. 188-190°C λ_{max} 220, 265, λ_{sh} 318, λ_{max} 390nm; (ϵ 13,602; 12,938; 12,109; 6,635) ν_{max} 3450, 1605cm⁻¹ M+282
 τ ; 2.7-3.7(7Hm); 3.9(1Hs); 5.4(2Hd; J=3cps); 6.9(3Hs)
Found: C, 72.3; H, 5.1; C₁₇H₁₅O₄ requires C, 72.3; H, 5.0.

1-Acenaphthenone (64)

Acenaphthalene (63) was converted to acenaphthenone (64) by the method described (p. 89) for the oxidation with DDQ. (34%)
m.p. 118°C ν_{max} 1725cm⁻¹

2,4,-Dinitrophenylhydrozone derivate⁵²
of acenaphthenone (64)

To a solution obtained by warming (50mg) of 2:4-dinitrophenylhydrozine, conc. hydrochloric acid (0.2ml) and ethanol (3ml) the acenaphtholene (20mg) was added and heated to boiling. After cooling to room temperature, the crystalline product (65) was filtered. Recrystallised from ethanol. m.p. 256-8°C.⁵³

3- 2¹,4¹,5¹-Trimethoxy-6 (1¹,3¹-dioxanyl)
benzoyl-5-methyl-methoxy chromone (44)

Prepared by DDQ oxidation (p. 89) of the chromanone (25).

Yield 61%. m.p. 259-270°C with decomposition. M+ 456

max. 208, 250, 345 nm.; (16,271; 18,079; 3816). max. 1655,
1603, 1110 cm⁻¹.

; 2.52-3.56(5Hm); 5.92-6.17(13H); 6.38(3Hs); 7.13(3Hs)

Found: C, 63.4; H, 5.3; C₂₄H₂₄O₉ requires: C, 63.2; H, 5.3

accurate mass measurement: Ratio 456/455=1.002567 M(456)=456.1408;

C₂₄H₂₄O₉ calls for 456.1420

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